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Appraising causal risk and protective factors for rheumatoid arthritis

A SYSTEMATIC REVIEW AND META-ANALYSIS OF MENDELIAN RANDOMIZATION

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Aims

Mendelian randomization (MR) is considered to overcome the bias of observational studies, but there is no current meta-analysis of MR studies on rheumatoid arthritis (RA). The purpose of this study was to summarize the relationship between potential pathogenic factors and RA risk based on existing MR studies.

Methods

PubMed, Web of Science, and Embase were searched for MR studies on influencing factors in relation to RA up to October 2022. Meta-analyses of MR studies assessing correlations between various potential pathogenic factors and RA were conducted. Random-effect and fixed-effect models were used to synthesize the odds ratios of various pathogenic factors and RA. The quality of the study was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines.

Results

A total of 517 potentially relevant articles were screened, 35 studies were included in the systematic review, and 19 studies were eligible to be included in the meta-analysis. Pooled estimates of 19 included studies (causality between 15 different risk factors and RA) revealed that obesity, smoking, coffee intake, lower education attainment, and Graves' disease (GD) were related to the increased risk of RA. In contrast, the causality contribution from serum mineral levels (calcium, iron, copper, zinc, magnesium, selenium), alcohol intake, and chronic periodontitis to RA is not significant.

Conclusion

Obesity, smoking, education attainment, and GD have real causal effects on the occurrence and development of RA. These results may provide insights into the genetic susceptibility and potential biological pathways of RA.

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Keywords: Rheumatoid arthritis, Mendelian randomization, Risk factors

Article focus

- Many Mendelian randomization (MR) studies on rheumatoid arthritis (RA) have been performed, and the purpose of this study was to summarize the research progress.
- We conducted a systematic review and meta-analysis of MR studies on RA.

Key messages

- Our study provides phased review and synthesis of the causality evidence between various pathogenic factors and RA, based on our analysis of MR studies.
- Our study provides evidence of the association between RA and related risk

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factors, but the results still rely on modelling experiments and real-world evidence.

Strengths and limitations

- The main strength of this study was its comprehensive search protocol involving the largest medical research databases. This study is the first systematic review and meta-analysis of published MR studies on RA.
- The main limitation was the heterogeneity of the included studies, which may predispose the pooled causality estimates to some extent of bias.

Introduction

The comprehensive management of rheumatoid arthritis (RA) has made remarkable progress from physiopathology to diagnosis and treatment.[1-4] However, there are still a considerable number of patients whose clinical symptoms are not obvious, so they may be diagnosed with 'difficult-to-treat' RA.[5] If these patients are slow to be diagnosed, or treated inadequately, there will be cumulative joint injuries and irreversible disabilities, which may lead to a shortened life expectancy of three to 18 years.[6] This brings great challenges to the medical community.

Epidemiological studies have reported several potential influencing factors of RA, including obesity,[7] drinking,[8] smoking,[9] education,[10] and so on. However, these studies cannot determine the direct causal effects between aetiology and disease, and need more information to fill the evidence gap caused by unmeasured confounding or reverse causality. In recent years, to address the limitations of observational studies and randomized controlled trials, Mendelian randomization (MR) has become a new method to explore the causality between aetiology and disease. The principles and advantages of MR have been extensively discussed in numerous publications.[11,12] There are many MR studies on the causality between lifestyle, nutrition, disease status, and RA, but these studies differ in design, population, genetic instruments, and causal-effect estimation. These differences indicate that systematic evaluation and meta-analysis of these MR studies are essential.

Many systematic reviews of MR studies have been reported, such as osteoarthritis,[13] colorectal cancer,[14] and the relationship between smoking and various diseases.[15] To our knowledge, this is the first systematic review and meta-analysis of published MR studies on RA. We included the MR studies that evaluated the risk factors of RA. Then we quantitatively analyzed the estimated values of obesity-related indicators, life environment, serum minerals, disease status, and RA causal effects to provide phased carding and summary of the causality evidence between various pathogenic factors and RA (Figure 1).

Methods

Data sources and search strategy. The process of literature retrieval and inclusion-exclusion is shown in Figure 2. We searched the MR literature on RA published up to 1 October 2022 using PubMed, Embase, and Web of Science electronic databases, supplemented with manual searches of the included reference lists. The keywords used are as follows: subject words and free words related to "Mendelian randomization" or "genetic instrument" and "rheumatoid arthritis" (e.g. "Mendelian Randomization Analysis" [MeshSH], "Analysis, Mendelian Randomization [Title/Abstract]", "Mendelian Randomization [Title/Abstract]"). Detailed search strategies for each database are given in Supplementary Table i.

Study selection. All rertrieved articles were exported to the NoteExpress reference library, version 3.7 (Beijing Aegean Lezhi Technology, China), wherein duplicates were sought and removed. Two independent reviewers (PG, BP) evaluated the remaining articles, and only those that met the predefined criteria were selected. A third investigator (TL) was consulted to resolve any discrepancies. Initially, we selected the relevant articles according to the title and abstract, and then read the full text to confirm the relevance. The following criteria were used to select studies.

Inclusion criteria were: 1) original studies using MR analysis to investigate the causal relationship between any risk factor-related phenotype and RA; 2) any genome-wide or phenome-wide association studies (GWAS/PheWAS) that incorporated MR into their analysis; and 3) in cases where multiple studies have been published on the same study population or GWAS data, include the study with the largest number of cases or the largest number of instrumental variables (if sample sizes are equal).

Exclusion criteria were: 1) case reports, narrative reviews, letters, editorials, opinions, and conference abstracts; 2) studies for which complete English manuscripts or original data are not obtainable; and 3) studies that used genetic variants as proxies without employing an MR design.

Data extraction and quality assessment. The data extracted from each MR study included: the first author's last name; publication year; the alliances or consortium conducting RA genomics research; total number of participants; ancestry of the study population; exposure variables; and principal findings. In addition, we also extracted the relative risk estimate (odds ratio (OR)), the corresponding 95% confidence interval (CI) and sensitivity analysis results based on the inverse variance weighting (IVW) method, and the pleiotropic analysis results based on MR-Egger analysis. The adjusted effect was extracted and combined for the study of reporting crude effect and adjusted effect at the same time. Two researchers (PG, BP) independently extracted and cross-checked the relevant information. Disagreements were resolved by the third investigator (TL or DY).

Two researchers assessed the quality of the research by adopting a modified version of the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines.[16] The guidelines were adapted based on articles reporting quality assessment approaches used to document MR

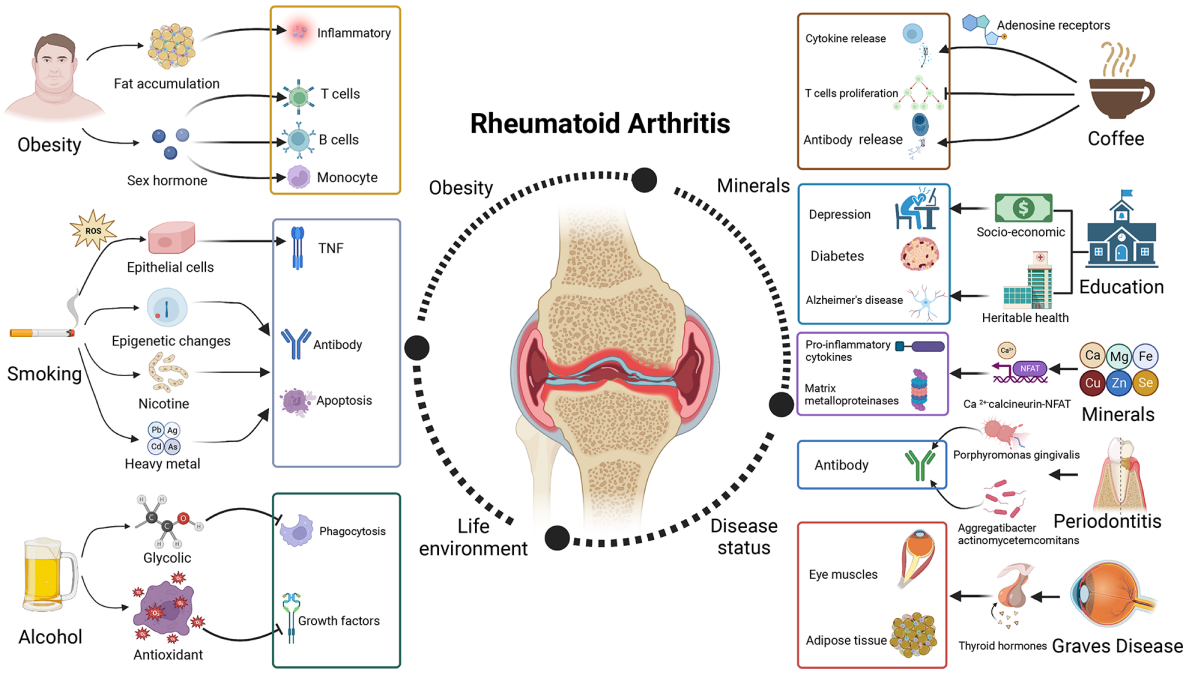

Fig. 1

Factors influencing rheumatoid arthritis (RA) in Mendelian randomization. Created with BioRender.com. TNF, tumour necrosis factor.

studies.[17,18] After converting the quality assessment score into a percentage, studies with > 85%, 75% to 85%, and < 75% were considered as high-, medium-, and low-quality, respectively.

Statistical analysis. When at least two independent studies/datasets were identified to assess the causality between pathogenic factors/genetic instruments and RA, the data were incorporated into the meta-analysis. Studies not included in the meta-analysis were still included in the qualitative analysis (systematic review). Fixed-effect and/or random-effect models were used to calculate the aggregate OR value of different factors on RA risk.[19] Cochran's Q test and Higgins I^2 test were used to judge heterogeneity. The combined results of fixed effect models were at I^2 < 50% and p > 0.1, otherwise, the heterogeneity between included studies was considered to be statistically significant. We conducted a sensitivity analysis by excluding one study at a time and comparing the results of the fixed-effect model. If the heterogeneity was eliminated, the results of the fixed-effect model were reported, and vice versa, the results of the random-effect model were reported. Visual examination of the funnel plot was performed to assess publication bias.[20]

The data of this study were analyzed by RevMan version 5.4.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020). A two-sided p-value less than 0.05 was considered to be statistically significant.

Results

Study selection. The pre-established database retrieval strategy produced 517 records. After excluding 219 duplicate and 130 non-Mendelian articles, 26 conference reports and correspondence articles were excluded according to the literature type. After thoroughly reviewing 121 articles, we excluded 86 articles that did not report RA as an outcome (including case reports, narrative reviews, meta-analyses, editorials, opinions, and conference abstracts). A total of 35 articles were included in this review (Figure 2).

Study characteristics and quality assessment. Overall, 35 MR studies were included in the systematic review.[21–55] These studies included RA participants recruited from multiple datasets, including European populations, East Asian populations,[39] and mixed populations (European + Asian).[32,34,41,48,52,53] The number of single nucleotide polymorphisms (SNPs) used in these studies ranged from two[33,34,36] to 1,265.[24] All MR studies used two or more data sources from the large GWAS meta-analyses alliances, IEU OpenGWAS Project, UK Biobank, FinnGen biobanks, and Biobank Japan. The characteristics of the included studies are shown in Table I.

A total of 19 MR studies were included in the meta-analysis.[21–39] The final quality assessment scores ranged from 85% to 100%, and 15 articles scored above 85% (high quality) (Supplementary Table ii). All studies indicated "Mendelian randomization" in the title or abstract, which provided information about the basic principles and related data sources for research and objectives. All studies reported information on the sample size of exposure and outcome. One study did not report the number of SNPs in the MR process,[21] while others used two to hundreds of SNPs as instrumental variables. Most MR studies used the strict critical value of linkage disequilibrium (R^2 < 0.001) to select independent SNPs

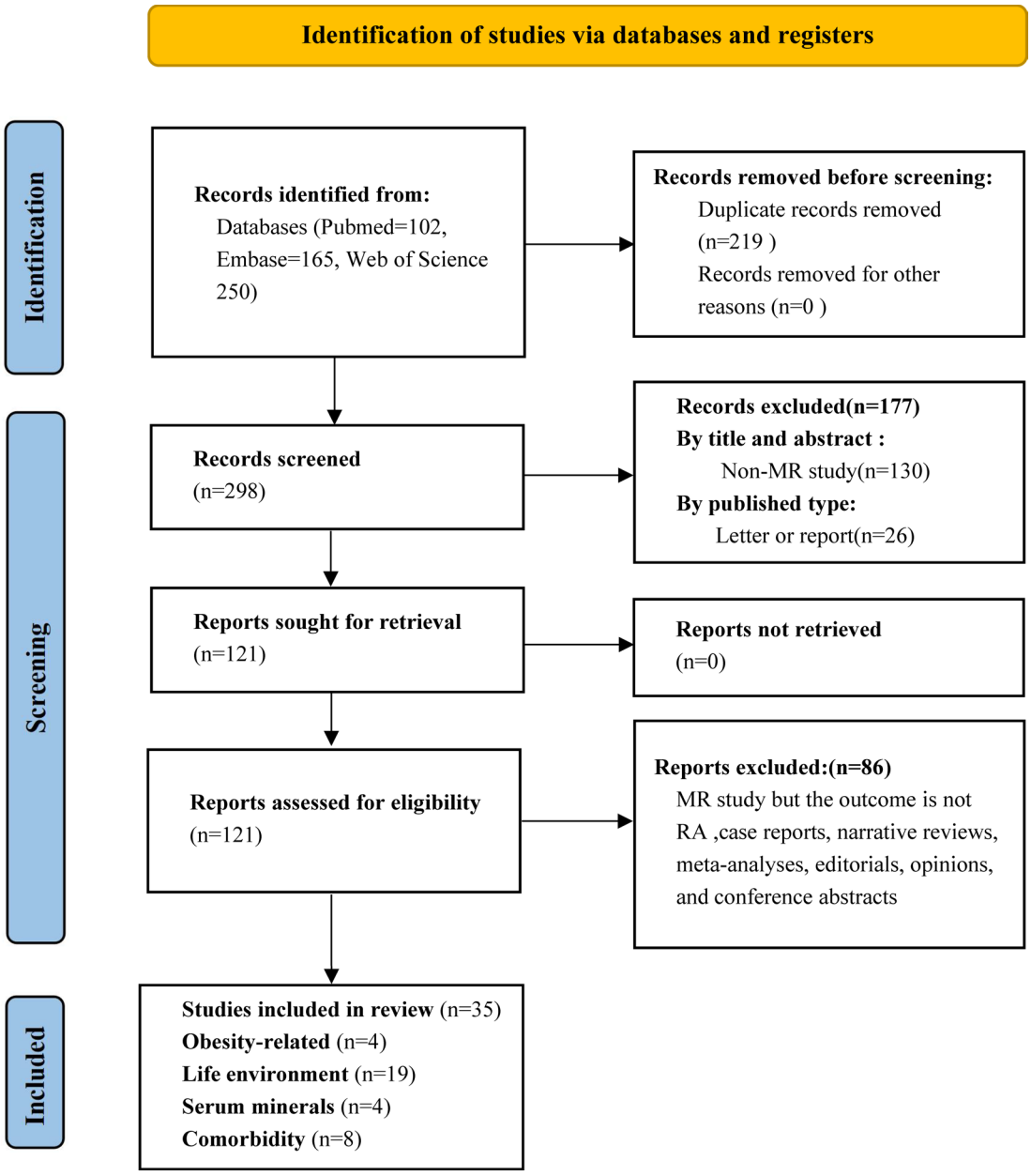

Fig. 2

Preferred Reporting Items for Systematic review and Meta-Analyses flow diagram. MR, Mendelian randomization; RA, rheumatoid arthritis.

as instrumental variables for exposure, but some studies selected all conditional independent SNPs identified in GWAS. All studies indicated the statistical analysis for MR analysis, and ten studies reported the sensitivity analysis results based on the robust MR method (IVW) and the horizontal pleiotropic results based on the MR-Egger method.[22,23,27–31,35,37,38] Visual examination of the funnel plot of obesity-related indicators showed a low study bias (Supplementary Figure a). Nevertheless, the funnel plot was not performed in other phenotypes because of the few included studies.

Meta-analysis results. A total of four studies (six datasets) for BMI,[21–24] one study (three datasets) for body fat percentage (BFP),[21] one study (three datasets) for favourable adiposity (FA),[21] one study (three datasets) for unfavourable adiposity (UFA),[21] two studies for lifetime smoking,[24,25] two studies for alcoholic drinks per week,[24,26] two studies for coffee intake,[28,29] four studies for educational attainment,[24,30–32] two studies for serum calcium (Ca),[33,34] three studies for serum iron,[33–35] two studies for serum copper,[33,34] two studies for serum magnesium,[33,34] two studies for serum zinc,[33,34] one study (two datasets) for serum selenium,[36] two studies for chronic periodontitis,[37,38] and one study (two datasets) for Graves' disease (GD)[39] were selected for quantitative analysis, on the basis that there were common risk factors among meta-analysis

Table I. Study characteristics of all 35 studies included for qualitative analysis.

Study	Year	Ethnicity	Cohort	Exposure (SNPs)	Sample size	Principal findings
Martin et al[21]	2022	European	IEU/FinnGen/UK Biobank	BMI,[56] BFP (696), FA,[36] UFA[38]	14,361 cases, 43,923 controls/4,701 cases, 121,222 controls/8,543 cases, 442,482 controls	Unfavourable effects of higher adiposity on RA.
Tang et al[22]	2021	European	IEU	BMI (793), WHR (372), and WHR adj BMI (445)	14,361 cases, 43,923 controls	BMI is causally associated with an increased risk of RA.
Bae & Lee[23]	2019	European	UK Biobank	BMI[57]	7,480 cases, 329,679 controls	BMI is causally associated with an increased risk of RA.
Zhao et al[24]	2022	European	IEU	Educational attainment (1,265), BMI (517), lifetime smoking exposure (124), alcoholic drinks per week,[35] number of days/week of vigorous physical activity,[11] dietary protein,[7] dietary fat,[5] dietary carbohydrate[12]	14,361 cases, 43,923 controls	Educational attainment is a protective effect on RA risk, and reducing smoking and excessive adiposity may reduce this risk.
Qian et al[25]	2020	European	IEU	Smoking initiation (378), lifetime smoking (126)	14,361 cases, 43,923 controls	Smoking is causally associated with an increased risk of RA.
Jiang et al[26]	2021	European	IEU	Drinks per week,[58] alcohol use disorder identification test consumption score[13]	14,361 cases, 43,923 controls	Excessive drinking did not appear to reduce the risk of RA.
Bae & Lee[27]	2019	European	IEU	Alcohol intake frequency[24]	5539 cases, 20,169 controls	The MR analysis does not support a causal inverse association between alcohol intake and RA occurrence.
Pu et al[28]	2022	European	IEU	Coffee intake[30]	14,361 cases, 43,923 controls	The study did not support a causal association between coffee intake and RA.
Bae & Lee[29]	2018	European	IEU	Coffee intake[4]	5539 cases, 20,169 controls	MR analysis results do not support causal associations between coffee consumption and RA.
Huang et al[30]	2021	European	IEU	Educational attainment (393)	14,361 cases, 43,923 controls	Educational attainment is causally associated with reduced risk of RA.
Bae & Lee[31]	2019	European	IEU	Years of education[49]	5,539 cases, 20,169 controls	Educational attainment is causally associated with reduced risk of RA.
Yuan et al[32]	2021	European + Asian	IEU	Educational attainment (1,217), intelligence (205)	29,880 cases, 73,758 controls	Higher education level adjusted for intelligence was associated with a lower risk of RA.
Zhou et al[33]	2021	European	Conall M. O'Seaghdha, GWAS[59]	Iron,[3] copper,[2] zinc,[2] calcium,[8] and magnesium[6]	2,547 cases, 308,452 controls	Five minerals concentrations not causally associated with the risk of RA.
Cheng et al[34]	2019	European + Asian	IEU	Iron,[14] copper,[2] zinc,[3] calcium,[8] and magnesium[5]	29,880 cases, 73,758 controls	Magnesium has a causal relationship with the increased risk of RA.
Yuan & Larsson[35]	2020	European	IEU	Serum iron,[5] transferrin saturation,[5] ferritin,[6] transferrin[8]	14,361 cases, 43,923 controls	Four iron biomarkers' high iron status was positively associated with RA.
Ye et al[36]	2021	European	IEU	Selenium (12 and 2)	14,361 cases, 43,923 controls	Selenium concentrations not causally associated with the risk of RA.
Bae & Lee[37]	2020	European	IEU	Chronic periodontitis[20]	5,539 cases, 20,169 controls	A weak causal association between periodontitis and RA.
Yin et al[38]	2022	European	IEU	Periodontitis,[18] aggressive periodontitis,[13] chronic periodontitis[22]	14,361 cases, 43,923 controls	Non-causal association of PD with RA.
Wu et al[39]	2021	East Asian	BBJ	Graves' disease[13]	4,873 cases, 17,642 controls/ 4,199 cases, 208,254 controls	A bidirectional causal effect between GD and RA in an Asian population.

Continued

Table I. Continued

Study	Year	Ethnicity	Cohort	Exposure (SNPs)	Sample size	Principal findings
Liu et al[40]	2021	European	Elsworth et al, GWAS[60]	Heel (342), forearm,[3] femoral neck,[14] lumbar spine,[14] and total body[50] BMD	1,523 cases, 461,487 controls	BMD/OP did not appear to reduce the risk of RA.
Luo et al[41]	2022	European + Asian	IEU	Soluble receptor for advanced glycation end products[4]	29,880 cases, 73,758 controls	Soluble receptor for advanced glycation end products (sRAGE) has a causal relationship with RA.
Huang et al[42]	2022	European	IEU	Leisure television watching (145), computer use,[36] and driving[4]	14,361 cases, 43,923 controls	Provides evidence supporting the protective effects of computer use and RA and unfavourable effects of leisure television watching on RA.
Gao et al[43]	2022	European	IEU	Short sleep duration,[27] frequent insomnia,[61] any insomnia,[61] sleep duration,[53] getting up,[62] morningness (274), snoring[42]	14,361 cases, 43,923 controls	Short sleep duration is causally linked to an increased risk of RA.
Chen et al[44]	2022	European	IEU	Beef intake[7]	14,361 cases, 43,923 controls	Beef intake was associated with an increased risk of RA.
Chen et al[45]	2022	European	IEU	Tea consumption[22]	14,361 cases, 43,923 controls	Tea consumption did not appear to reduce the risk of RA.
Sun et al[46]	2021	European	IEU	Palmitoleic acid[5] and oleic acid[1]	14,361 cases, 43,923 controls	A causal relationship between higher genetically predicted dietary monounsaturated fatty acids levels and lower risks of RA.
Sun et al[47]	2021	European	IEU	Average acceleration PA,[6] moderate-to-vigorous PA,[17] vigorous PA[6]	14,361 cases, 43,923 controls	No significant association of PA with RA.
Inamo et al[48]	2020	European + Asian	IEU, BBJ	T2DM (267 and 167)	14,361 cases, 43,923 controls/n = 433,540 (Asia)	There is a significant protective effect of T2DM on RA.
Zhu et al[49]	2022	European	IEU	Plasma omega-3 fatty acids[52]	14,361 cases, 43,923 controls	Unfavourable effects of plasma omega-3 on RA in populations with European ancestry.
Meisinger & Freuer[50]	2022	European	IEU	Inflammatory bowel disease,[63] Crohn's disease,[52] and ulcerative colitis[37]	29,880 cases, 73,758 controls	IBD as a whole and both subtypes were unrelated to RA.
Cai et al[51]	2018	European	IEU	Alzheimer's disease[21]	14,361 cases, 43,923 controls	No significant association of AD with RA.
Zhao et al[52]	2022	European + Asian	Ishigaki et al, GWAS[64]	Childhood (313) and adult body size (580)	22,350 cases, 74,823 controls	Body size did not appear to reduce the risk of RA.
Yu et al[53]	2022	European + Asian	IEU	Urticaria[11]	29,880 cases, 73,758 controls	Unfavourable effects of urticaria on RA.
Bae & Lee[54]	2018	European	IEU	Vitamin D[3]	5,539 cases, 20,169 controls	MR analysis does not support a causal association between vitamin D level and RA.
Zhu et al[55]	2021	European	IEU	Age at menarche (340), age at natural menopause,[54] age at first birth[10]	14,361 cases, 43,923 controls	No significant association between age at menarche, age at natural menopause, age at first birth with RA.

AD, Alzheimer's disease; BBJ, BioBank Japan; BFP, body fat percentage; BMD, bone mineral density; FA, favourable adiposity; GD, Graves' disease; IBD, inflammatory bowel disease; MR, Mendelian randomization; OP, osteoporosis; PA, physical activity; PD, periodontitis; RA, rheumatoid arthritis; SNP, single nucleotide polymorphism; T2DM, type 2 diabetes; UFA, unfavourable adiposity; WHR, waist-hip ratio.

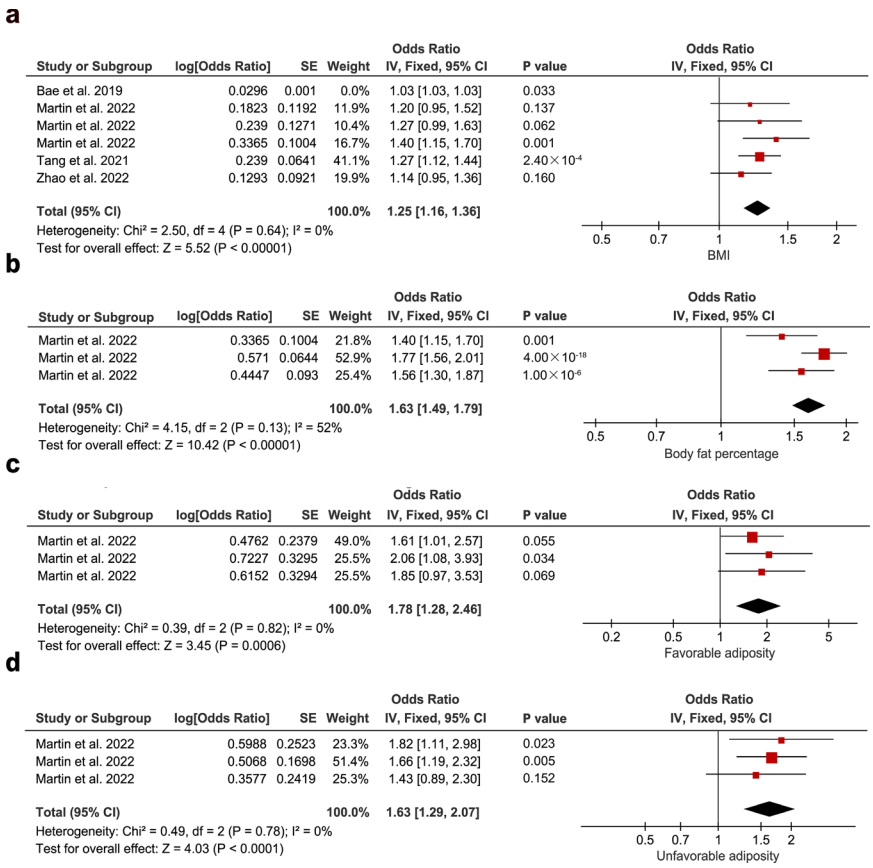

Fig. 3

Meta-analysis results of the association between genetic liability to obesity-related indicators and risk of rheumatoid arthritis (RA). Estimates are odds ratios (ORs) with 95% confidence intervals (CIs) for a one-standard deviation increase in genetic liability to obesity-related indicators. a) Forest plot of causal relationship between BMI genetic susceptibility and RA risk. b) Forest plot of causal relationship between body fat percentage (BFP) genetic susceptibility and RA risk. c) Forest plot of causal relationship between favourable adiposity (FA) genetic susceptibility and RA risk. d) Forest plot of causal relationship between unfavourable adiposity (UFA) genetic susceptibility and RA risk. IV, inverse variance; SE, standard error.

studies. Detailed information of the included studies and the results of meta-analysis is shown in Supplementary Table iii.

Obesity-related indicators. Genetic susceptibility of four obesity-related indicators is related to the increased risk of RA (Figure 3; Supplementary Table iii). Genetically predicted BMI led to higher relative OR of RA (25% higher for every additional 4.8 kg/m^2 of BMI). Each standard deviation (SD) increase in BFP (OR 1.63, 95% CI 1.49 to 1.79), FA (OR 1.78, 95% CI 1.28 to 2.46), and UFA (OR 1.63, 95% CI 1.29 to 2.07) led to a higher relative OR of RA.

The Higgins I^2 test (I^2 = 88%, p < 0.1) indicates significant heterogeneity among the BMI. Considering the different populations included in the meta-analysis, we removed the mixed population study,[23] then the heterogeneity disappeared (Figure 3; Supplementary Figure b). Slight heterogeneity between BFP and RA was observed (I^2 = 52%, p = 0.130). Since BFP was based on three different populations in the same study, we believed that slight heterogeneity could be ignored, and the results used a fixed-effect model. A comparative diagram of the random-effect and fixed-effect models is shown in Supplementary Figure c.

Phenotypes of life environment. We used the values obtained by the IVW method to evaluate the overall causal effects of four phenotypes of life environment on RA. Each 1-SD increase in lifetime smoking increased the odds of RA by 68% (p < 0.001). Each 1-SD (one cup/day) increase in coffee intake increased the odds of RA by 82% (p < 0.001). Each 1-SD (4.2 years) increase in educational attainment decreased the odds of RA by 57% (p < 0.001). However, no correlation was observed between alcoholic drinks per week and RA (p = 0.590). The Higgins I^2 test (I^2 = 58%, p = 0.100) indicates significant heterogeneity among the educational attainment, but we still chose the random-effect model to evaluate due to the lack of included studies (Figure 4; Supplementary Figure d). No heterogeneity was found in other analyses. Therefore, we used the fixed-effect model as the primary method (Figure 4).

Serum minerals. Genetically predicted six serum mineral levels were not associated with RA risk (Figure 5; Supplementary Table iii). There is no causality between serum Ca, iron, copper, magnesium, zinc, selenium, and the risk of RA (p = 0.790 (IVW method and random-effect model), p = 0.130, p = 0.740, p = 0.990, p = 0.450, and p

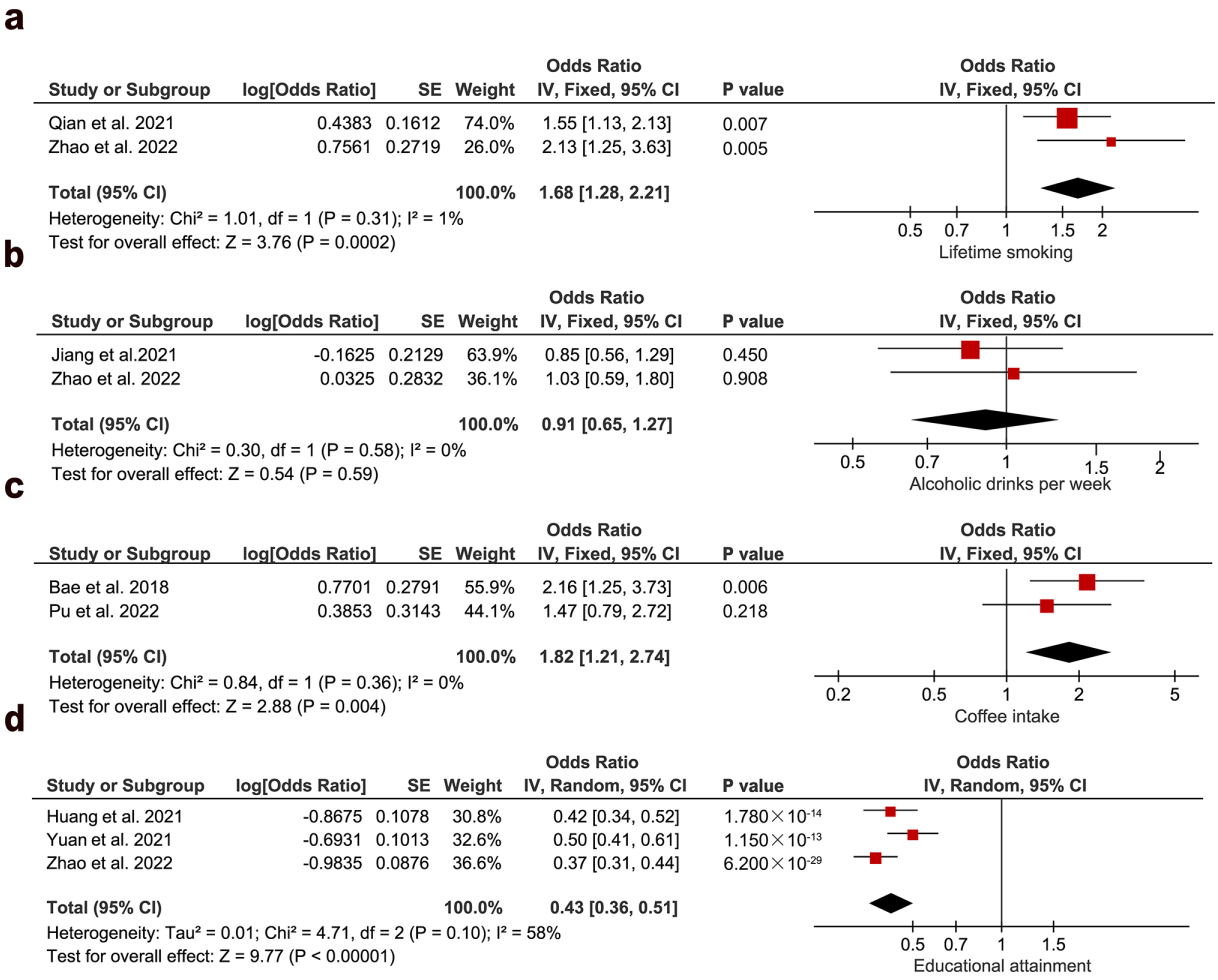

Fig. 4

Meta-analysis results of the association between genetic liability to phenotype of life environment and risk of rheumatoid arthritis (RA). Estimates are odds ratios (ORs) with 95% confidence intervals (CIs) for a one-standard deviation increase in genetic liability to phenotype of life environment. a) Forest plot of causal relationship between lifetime smoking genetic susceptibility and RA risk. b) Forest plot of causal relationship between alcoholic drinks genetic susceptibility and RA risk. c) Forest plot of causal relationship between coffee intake genetic susceptibility and RA risk. d) Forest plot of causal relationship between educational attainment genetic susceptibility and RA risk. IV, inverse variance; SE, standard error.

= 0.450 (all IVW method and fixed-effect model), respectively). Although high heterogeneity was observed in the combination of serum Ca, we still chose the random-effect model to evaluate due to the lack of included studies. A comparative diagram of the random-effect and fixed-effect models is shown in Supplementary Figure e.

Disease status. The existence of GD may increase the risk of RA by 32% (OR 1.32, 95% CI 1.04 to 1.68; p = 0.020; IVW method and fixed-effects model). However, chronic periodontitis was not associated with an increased risk of RA (OR 1.08, 95% CI 0.94 to 1.24; p = 0.300; IVW method and random-effect model) (Figure 6; Supplementary Table iii). Supplementary Figure f shows a comparative diagram of random-effect and fixed-effect models of chronic periodontitis.

Discussion

This review includes a meta-analysis of the published MR results. Genetic evidence shows that BMI, BFP, FA, UFA, lifetime smoking, coffee intake, and GD are associated with an increased risk of RA; educational attainment is associated with a decreased risk of RA. In contrast, serum minerals (Ca, iron, magnesium, copper, zinc, and selenium), alcoholic drinks per week, and chronic periodontitis were not observed to be related to the risk of RA. These results are consistent with the quantitative analysis results of the 19 articles we included.

Obesity-related indicators. The essence of obesity is an abnormal or excessive fat accumulation that can lead to health damage. Adipose tissue is positively related to inflammation and immunity. It can secrete pro-inflammatory and anti-inflammatory cytokines, hormone active substances, and chemokines.[65]

Our meta-analysis showed that obesity-related indicators (BMI, BFP, FA, and UFA) are risk factors for RA. These results are consistent with the conclusions from the articles included in our systematic review. Obesity-induced increased risk of RA may be associated with the low-grade

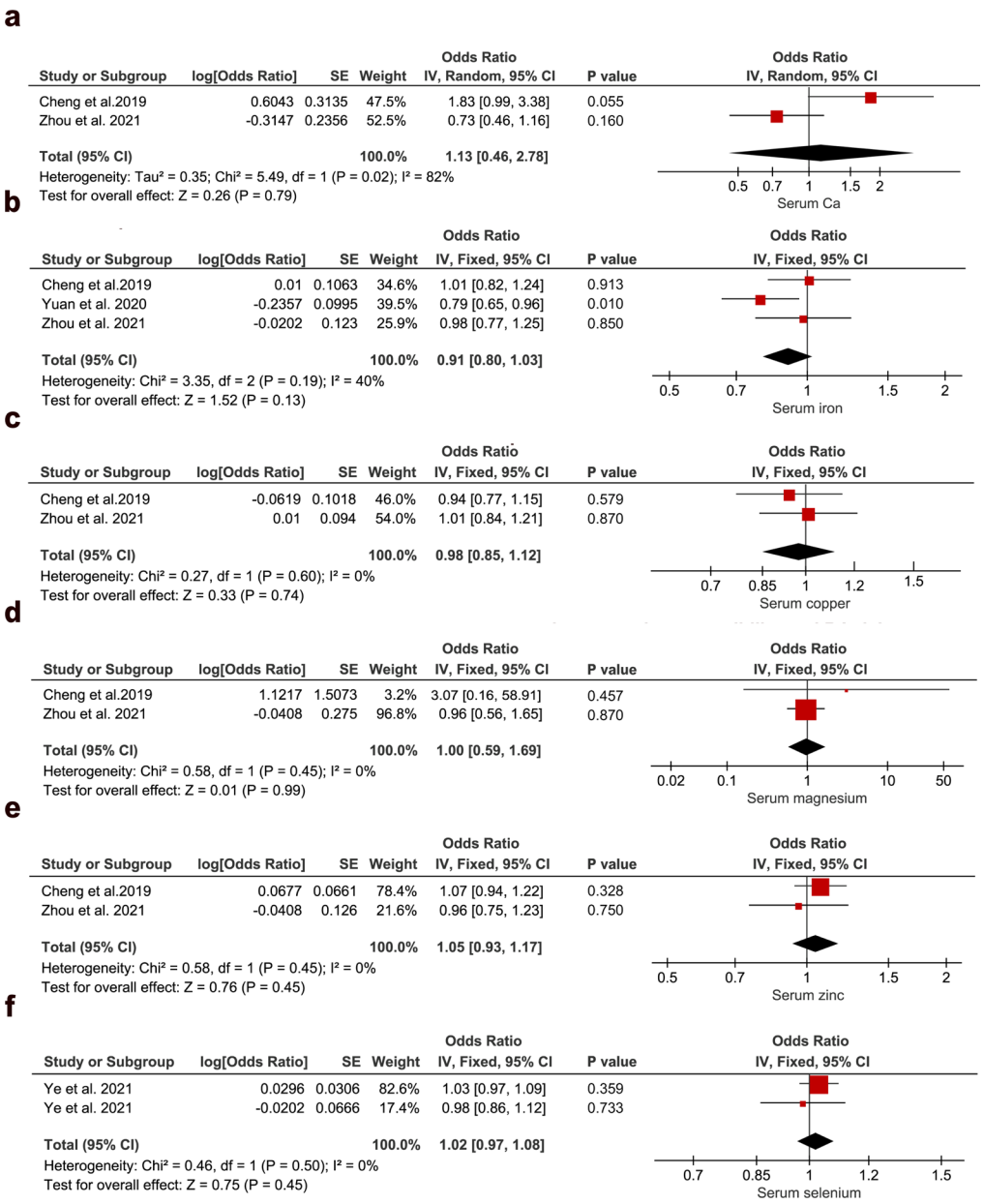

Fig. 5

Meta-analysis results of the association between genetic liability to serum minerals and risk of rheumatoid arthritis (RA). Estimates are odds ratios (ORs) with 95% confidence intervals (CIs) for a one-standard deviation increase in genetic liability to serum minerals. a) Forest plot of causal relationship between serum Ca genetic susceptibility and RA risk. b) Forest plot of causal relationship between serum iron genetic susceptibility and RA risk. c) Forest plot of causal relationship between serum copper genetic susceptibility and RA risk. d) Forest plot of causal relationship between serum magnesium genetic susceptibility and RA risk. e) Forest plot of causal relationship between serum zinc genetic susceptibility and RA risk. f) Forest plot of causal relationship between serum selenium genetic susceptibility and RA risk. IV, inverse variance; SE, standard error.

systemic inflammation triggered by obesity and the subsequent elevation of inflammatory cytokines.[61,66] FA and UFA may potentially contribute to the augmented risk of RA and systemic inflammatory cytokine levels through the enhancement of adipocyte gene expression, promotion of obesity accumulation, and interference with the production and expression of pro-inflammatory cytokines.[63,67–69]

Phenotypes of life environment. The results of our meta-analysis and observational studies all indicate that lifetime smoking increases the risk of RA.[70,71] Cigarette burning produces reactive oxygen species, which can activate the signalling cascades in epithelial cells, leading to the activation of inflammatory genes. Systemic inflammation and related inflammatory markers are associated with an increased risk of RA.[72,73] In addition, epigenetic changes, increased toxicity of nicotine and heavy metals,[74] apoptosis of immune cells, and changes in autoantibodies will also lead to the increased risk of RA.[57]

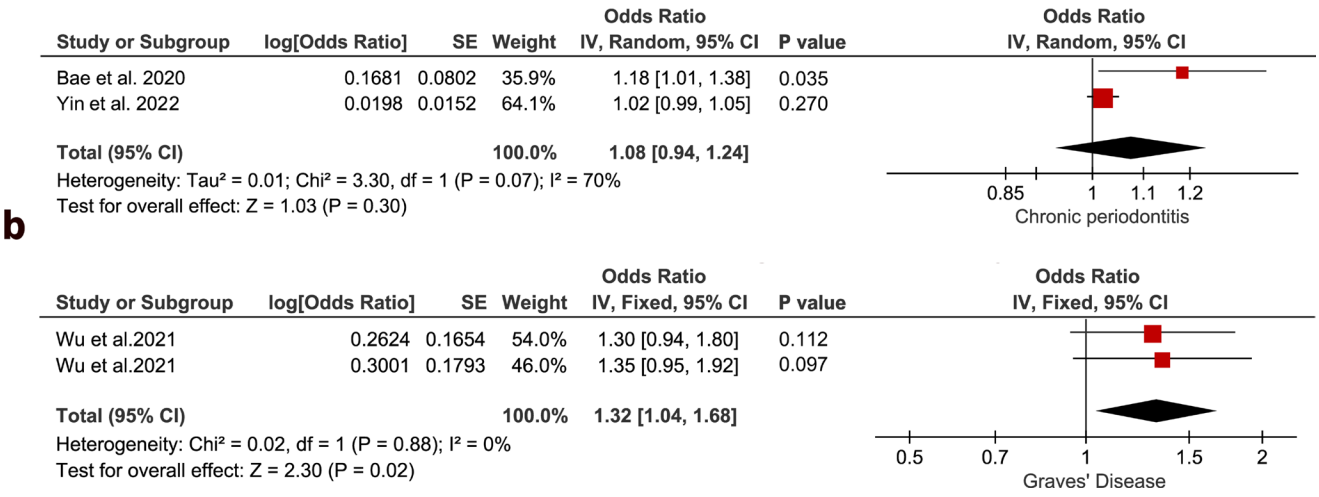

Fig. 6

Meta-analysis results of the association between genetic liability to disease status and risk of rheumatoid arthritis (RA). Estimates are odds ratios (ORs) with 95% confidence intervals (CIs). a) Forest plot of causal relationship between chronic periodontitis genetic susceptibility and RA risk. b) Forest plot of causal relationship between Graves' disease genetic susceptibility and RA risk. IV, inverse variance; SE, standard error.

The results of our meta-analysis and the studies included in the systematic review all suggest no definite evidence to support the causality between alcoholic drinks per week and RA. Prospective studies by Sundström et al[75] and Cerhan et al[62] also support our results. However, a meta-analysis by Turk et al[76] found that alcohol consumption was associated with decreased physical activity in patients with RA. Lu et al[8] conducted a prospective study of 662 patients with RA and found that moderate drinking was associated with a better functional status of RA. The contradictory results of previous studies may be related to different alcohol intakes. Alcohol, which contains ethanol and antioxidants, is considered to be a complex regulator of the immune system.[77] Intake of moderate doses of alcohol can enhance cell phagocytosis and immune function, reduce the production of inflammatory cytokines, and thus reduce the risk of RA. However, long-term intake of large doses of alcohol or alcohol abuse inhibits cell phagocytosis, growth factor production, and immune function, which increases the risk of RA.[26]

Our meta-analysis suggests that coffee intake is a risk factor for RA. This may be due to the inhibitory effects of caffeine on anti-inflammatory actions, immune function, and T cell proliferation, as well as its impact on antibody production.[56,78,79] Coffee constituents such as antioxidants, including polyphenols, cafestol, and melanoidins, play important roles in scavenging free radicals, inducing DNA repair, and influencing the progression of autoimmune diseases.[80–82] While some studies have observed a positive association between coffee consumption and RA,[29] other cross-sectional and MR studies have not found a causal relationship.[28] Due to conflicting findings and a lack of standardized descriptions of coffee intake, further research on the effects of coffee types and preparation methods on RA is crucial.

Additionally, our meta-analysis revealed a significant correlation between higher education level and a lower risk of RA. Education level may exert its influence on disease occurrence through socioeconomic and health-related factors such as wealth, lifestyle, and quality of life.[83–86] Studies have indicated that smoking and BMI mediate the relationship between education level and RA.[32,52] However, further research is needed to explore the biological pathways through which education level reduces the risk of RA.

Finally, minerals are essential nutrients for the human body, but are closely related to various diseases. Ca, iron, copper, magnesium, zinc, selenium, and other minerals usually play a role in autoimmune diseases through different immunomodulatory mechanisms.[87]

Ca signalling plays a central role in immune cell proliferation, differentiation, and apoptosis. The chronic inflammatory process of RA is related to the upregulation of the Ca^{2+}-calcineurin-nuclear factor of activated T cells (NFAT) axis in various synovitis inflammatory cells.[88,89] There is a complex interaction between iron homeostasis, inflammatory response, and immune function.[90] Studies have pointed out that iron is essential for the proliferation of immune cells, especially lymphocytes, in dealing with infection.[91] Copper has antioxidant properties and participates in the central nervous system's metabolic process and redox reaction of the central nervous system.[92] In addition, because copper deficiency damages the metabolism of iron, copper is essential for the absorption of iron.[93] Magnesium is closely related to oxidative stress and inflammation. Magnesium deficiency can trigger systemic inflammation through the induction of oxidative

stress in inflammatory cells, activation of phagocytic cells, and reduction of anti-inflammatory mediators.[94] In addition, magnesium transporter (MagT1) plays a vital role in the immune response activated by T cells.[95] Zinc deficiency can lead to increased oxidative stress and the production of pro-inflammatory cytokines,[96,97] affecting immune cells' survival, proliferation, and maturation.[87]

Selenium plays an essential role in the activation, differentiation, and proliferation of immune cells. Selenium can also reduce the expression of pro-inflammatory mediators and regulate excessive immune response and chronic inflammation.[98,99] Although the role of minerals in autoimmune diseases has been confirmed, the current MR studies and our meta-analysis results do not support the causal role of these minerals in the development of RA.

Disease status. Chronic periodontitis can cause severe oral inflammation, leading to gingivitis and tooth loss.[100] It may trigger or worsen RA due to the presence of anticitrullinated protein antibodies and rheumatoid factors in patients.[58,101,102] Gingival bacteria and *Actinobacillus actinomycetemcomitans* induce citrullination reactions, which stimulate the immune system to produce antibodies and initiate joint inflammation.[103–105] RA and periodontitis share common mediators, such as shared epitopes of the HLA-DRB1 gene and proteases.[106] Studies have found that chronic periodontitis may increase the risk of RA,[37] but bidirectional studies have not established a causal relationship between the two diseases.[38] Further large-scale research is needed to confirm the association between periodontitis and RA.

GD is an autoimmune thyroid disease characterized by exophthalmos, eye pain, diplopia, photosensitivity, and difficulty closing the eyes.[107] RA accounts for approximately 3% to 5% of GD patients.[108] Ferrari et al[109] found RA to be a common autoimmune comorbidity in GD. Cui et al[110] observed increased levels of IGF-1R in GD and RA patients, which plays an important role in inflammation. Bidirectional MR studies showed that GD may increase the risk of RA by 30%, and RA may increase the risk of GD by 39%.[39] Further research is needed to confirm the causal relationship between GD and RA.

Clinical implications and future research. Given that obesity and smoking can increase the risk of RA, we suggest that increasing fitness awareness and healthy food accessibility, promoting physical activity, and enforcing smoking cessation programmes should be used as primary prevention and non-drug therapies. Similarly, due to the increase in educational attainment that can reduce the risk of RA, we call for improving the general population's educational attainment and literacy to prevent RA. Although we found that coffee intake has a negative causal effect on RA, we were skeptical about this result. Therefore, we do not recommend eliminating coffee as a means of preventing RA.

This review summarized the current MR studies on the risk factors of RA, but several issues must be considered in future studies. Firstly, it is crucial to incorporate more of the latest SNPs as instrumental variables in assessing the risk factors' influence on the development of RA. By using these contemporary genetic markers, a more precise evaluation of the impact of these risk factors on the disease can be achieved. Additionally, in order to enhance our understanding of the characteristics of RA risk factors, future studies should expand beyond a solely European population and include mixed populations exposed to diverse environmental factors for a more comprehensive analysis. Undoubtedly, in addition to providing a perfect complement to epidemiological studies, MR methods have also begun to improve our understanding of the pathophysiology and drug mechanisms of complex diseases such as RA. The next step is to promote this tool for prevention, optimizing treatment strategies, and reducing drug side effects.

Our meta-analysis has several limitations as follows. Firstly, due to the few MR studies available on RA, we cannot evaluate the publication bias by observing the symmetry of the funnel plot (except obesity-related indicators) and conducting Egger and Begg tests. Furthermore, we also cannot conduct subgroup analysis based on age, sex, and region to explore the impact of these variables on the outcome of the merger. Secondly, the substantial heterogeneity of several included studies is high, so we interpreted the results with caution. However, this heterogeneity was anticipated, given the variation in study methods, participants, and localities. Finally, although MR methods have several advantages compared with traditional meta-analysis methods, and can provide evidence for the association between RA and related risk factors, the results still rely on modelling experiments and real-world evidence.

In conclusion, this study indicates that obesity, smoking, and GD are risk factors of RA, while education is the protective factor. Therefore, reducing smoking, controlling weight, targeting treatment of GD, and improving access to education may greatly reduce the risk of RA. This is particularly relevant for those with a high risk of RA (e.g. those with strong family history of the disease).

Supplementary material

Tables showing search strategy used in each database searched, Quality Assessment tool conducted based on adherence to the STROBE-MR Guidelines for all 19 studies included in the meta-analysis, and Mendelian randomization studies included in the meta-analyses of genetically predicted obesity-related indicators, life environment, serum minerals, and disease status in relation to rheumatoid arthritis. Figures showing funnel plot of the included studies on obesity-related indicators, forest plot before and after the removal of heterogeneity of BMI, and forest plots of body fat percentage, educational attainment, serum calcium, and chronic periodontitis.

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