A bidirectional Mendelian randomisation study of the association between rheumatoid arthritis and frailty

S. Li[1], Y. Shi[1], W. Fang[2], Y. Feng[1]

[1]Chengdu University of Traditional Chinese Medicine, Chengdu, China;
[2]Meishan Hospital of Traditional Chinese Medicine, Meishan, China.

Abstract

Objective

Observational studies have linked rheumatoid arthritis and frailty, but confounding factors and reverse causality make it unclear if there is a causal relationship. The current study used bidirectional two-sample Mendelian randomisation (MR) to assess the bidirectional causation between rheumatoid arthritis and frailty.

Methods

The primary analysis used the latest GWAS data for rheumatoid arthritis and frailty index in pure Europeans from large genome-wide association studies. Validation analysis was done to verify the accuracy of the results. The appropriate instrumental variables (IVs) were selected based on the three MR assumptions. The MR methods used were MR-Egger, weighted median (WM), and inverse variance weighted (IVW). The effects of horizontal pleiotropy were examined using the MR-Egger intercept and the MR-PRESSO method. To avoid single SNP bias, a leave-one-out analysis was performed.

Results

Genetic predictions suggested that there is a significant association between rheumatoid arthritis and the increased prevalence of frailty (IVW OR=1.01; 95% CI=[1.01–1.02], p=2.47 E-06). It has been verified in validation analysis that rheumatoid arthritis is also associated with frailty (IVW OR=1.03, 95% CI=[1.02-1.04], p=3.30E-17). Notably, genetic predictions suggested that frailty may be associated with the onset or development of rheumatoid arthritis (IVW β=1.25, SE=0.44, 95% CI=[0.39–2.12], p=4.58E-03).

Conclusion

The present study provides evidence supporting the fact that rheumatoid arthritis can increase the prevalence of frailty. Frailty may be a risk factor for rheumatoid arthritis, and whether frailty is involved in triggering the onset or progression of rheumatoid arthritis needs further study.

Key words
frailty, frailty index, Mendelian randomisation, rheumatoid arthritis

Shuhan Li, BS
Yue Shi, BS
Wei Fang, MS
Yue Feng, PhD

Please address correspondence to:
Wei Fang
Chengdu University of Traditional Chinese Medicine, 610075 Chengdu, China.
E-mail: ms15983311710@163.com

and to:
Yue Feng: fengyue714@163.com

Received on July 23, 2023; accepted in revised form on September 21, 2023.

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a chronic disease characterised by inflammation, which causes joint inflammation (1). The condition can lead to fatigue, pain, and physical incapacity and is considered a serious illness (2). RA is known to increase the levels of C-reactive protein, interleukin-6, and tumour necrosis factor (3). It is the most common joint disease, affecting 1% of the world population, and it typically develops between the ages of 30 and 50 (4). However, 30% of cases occur in individuals over the age of 60. As life expectancy increases, it is likely that the number of older individuals with RA will also rise (5). The elderly RA population includes both geriatric-onset RA that appears after age 60 and individuals diagnosed with RA earlier in life who naturally become members of this group as they age (6). Elderly frailty is associated with increased health risks (7). The Fried criterion (8) and the frailty index (FI) (9) are commonly used to define frailty. In the Cardiovascular Health Study, Fried and his colleagues modified the phenotypic model to create three groups: frailty (three or more criteria), pre-frailty (one or two criteria), and no criteria (8). The frailty index is used to diagnose frailty in individuals aged 15–18 and ranges from 0 (no problems) to 1, with the boundaries of frailty being non-frail (0 to ≤0.12), mild (>0.12 to ≤0.24), moderate (>0.24 to ≤0.36), and severe (>0.36) (10). The frailty index is now considered to be the most useful vulnerability assessment methodology (11–14), with higher values of the index being associated with factors such as disability, mobility issues, chronic diseases, hospitalisation, and death (15–17). Frailty tends to increase with age, affecting 7% to 10% of individuals over 65 and 20% to 40% of those over 80 (8).

Frailty is characterised by weakness, fragility, slowness, and weight loss. Many of these symptoms are also present in people with RA (18–20). RA sufferers often experience muscle weakness, poor nutrition, and limited exercise, putting them at an increased risk for frailty (21–23). Cross-sectional research showed that 18.9% of Japanese RA patients were weak, while a systematic analysis found that 7.4% of older Japanese adults were frail (24, 25). As life expectancy increases and more people develop RA at an older age, there are more elderly RA patients. In Japan, it is expected that there will be 800,000 RA patients, with two-thirds of them being over 65 (26, 27). The mechanism between RA and frailty is not known, but factors such as pain, reduced physical activity, and inflammation may contribute (28–31). RA patients have greater circulating inflammatory markers than healthy individuals, which increases their risk of frailty (32, 33). However, despite evidence suggesting that RA patients are more likely to become frail (34), confounding factors and the possibility of reverse causation bias make the association between the two controversial.

Mendelian randomisation (MR) uses genetic variation as instrumental variables (IVs) to establish a strong causal inference between exposure and disease risk without involving potential confounders or reverse causality (35). To date, no MR analyses have investigated the possible causal relationship between RA and frailty. The research on the causal link between these two illnesses is significant because it will enhance our understanding of their causes and improve preventive and treatment strategies. In this study, a bidirectional MR analysis of RA and frailty was conducted to determine the bidirectional causal relationship between RA and frailty.

Materials and methods

Study design

The bidirectional MR study method was used to measure the causal effect in both directions. Based on the three assumptions of MR, eligible single-nucleotide polymorphisms (SNPs)were selected as IVs, the IVs must have a strong correlation with exposure. Secondly, the IVs should not be associated with confounders related to the exposure or the outcome, particularly the outcome. Lastly, IVs must exclusively affect outcomes through exposure. The causation and reverse causation between RA and frailty were observed by using IVs. In other words, the forward MR study analysed the effect of RA on the increased preva-

lence of frailty, and then the reverse MR study analysed the impact of frailty on the onset or development of RA. In order to ensure the accuracy of the analysis results, the primary analysis and validation analysis were carried out in both the forward MR study and the reverse MR study. Each predicted direction was validated through three crucial processes: the selection of the appropriate genetic IVs, the utilisation of multiple MR techniques, and the analysis of the results. Different sensitivity analyses were performed to determine the robustness of the results. Figure 1 presents the bidirectional Mendelian randomisation design.

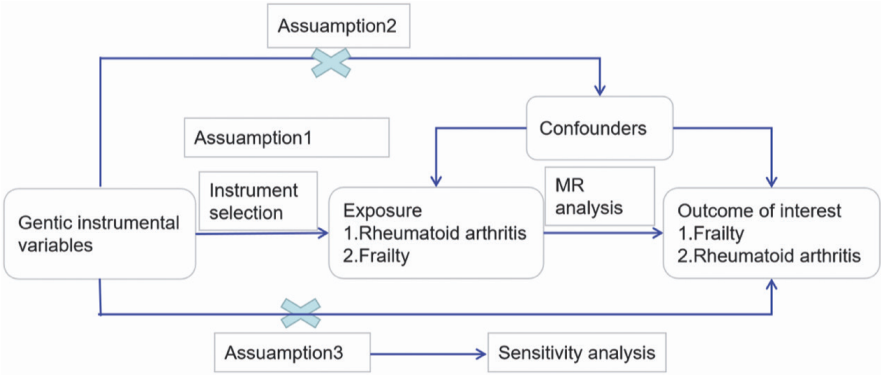

Fig. 1. The bidirectional Mendelian randomisation concept framework
Rheumatoid arthritis and frailty were studied using the bidirectional Mendelian randomisation method. Assumption 1: The IVs must demonstrate a statistically significant correlation with the exposure variable; Assumption 2: The IVs should not exhibit any correlation with confounding variables that affect both the exposure and outcome variables, especially the outcome variable; Assumption 3: The IVs should only affect the outcome variable through the exposure variable, without any direct influence.

Data source

One critical part of this MR analysis was choosing the suitable instrumental variables (IVs) from the genome-wide association study (GWAS) datasets that were available to the public. To prevent population stratification from having an impact, all SNPs and associated pooled data were obtained from European-ancestry groups. The primary analysis used the latest GWAS data for RA and frailty index in pure Europeans from large genome-wide association studies, including SNPs associated with RA from 97,173 people and SNPs associated with frailty index from 386,565 people. Meanwhile, an independent validation dataset was used for validation analysis. From IEU GWAS database (https://gwas.mrcieu.ac.uk/datasets/) to choose the appropriate SNPs, including RA from 58,284 European ancestry associated SNPs and frailty index from 175,226 European ancestry associated SNPs. The power calculation for this MR study was obtained via an online web tool (https://shiny.cnsgenomics.com/mRnd/). Table I provides information on the datasets used to assess the relationship between genetic polymorphisms, RA, and frailty, which were gathered from previously published studies. Previous studies of the statistics used have been ethically approved, and patient consent has been given; therefore, no additional ethical approval is required for this investigation.

Selection of instrumental variables

Genetic variation is used as instrumental variables (IVs) based on three assumptions of MR. To meet the first assumption, the entire genome was first scanned for single-nucleotide polymorphisms (SNPs) that were strongly correlated with exposure (p<5E-8). To exclude SNPs associated with a considerable linkage disequilibrium (LD), a clumping approach of R^2 <0.001 with a window size of 10,000 kb was used. The results of horizontal pleiotropy were corrected using Mendelian Randomisation Pleiotropy Residual Sum and Outlier (MR-PRESSO) approach. To avoid weak instrumental bias, F-statistics and variance (R^2) were used to assess the strength of the screened SNPs. The most recent and precise formula $F=R^2(N-K-1)/K(1-R^2)$ is used to determine the strength of the instrument (36). R^2 indicates the amount of exposure explained by each independent variable, and a device with an F value lower than 10 was considered weak when determining the strength of the instrument.

Statistical analysis

All statistical analyses were performed using R v. 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). MR analyses were performed using the 'TwoSampleMR' and 'MRPRESSO'packages. When all instrumental variables (IVs) were accurate, complementary MR methods like inverse variance weighted (IVW), weighted median (WM), and Mendelian randomisation-Egger (MR-Egger) were used to get the most accurate results (37). The fixed-effect or random-effect IVW approach was used as the primary analysis for causal estimates. In the MR-Egger regression model, an intercept denoting the mean multiplicity bias was involved (38). The WM approach utilised the median MR estimate as the causal estimate (39), and the odds ratio (OR) and 95% confidence interval (CI) were employed to evaluate the relative risk associated with the target illness. The MR-PRESSO technique was used to identify and eliminate outliers while testing for possible horizontal pleiotropy. The IVW method and Egger regression were used to assess heterogeneity, and Cochran's Q statistic was used to quantify it. If heterogeneity (p<0.05) was observed, a random-effect IVW test was performed for a more cautious yet reliable estimate. Finally, a leave-one-out analysis was conducted to ensure consistency in the relationship between SNPs and exposure and to identify any significant impact of the SNPs.

Results

Effects of RA on frailty

Based on strict exclusion criteria, 61 SNPs associated with RA were included. The F-value for instrumental variables was greater than 10, indicating there was no bias of weak instrumental variables. The IVW method was used in the random-effect model, because the Cochran Q test showed heterogeneity (p<0.05). Using the IVW method, genetic predictions suggested that RA was associated with the increased prevalence of frailty in the primary analysis

Table I. Characteristics of data sources used in the Mendelian randomisation study.

Traits	Sample size	Year	PMID	population	GWAS ID	Source
RA[a]	97,173	2022	36333501	Europe	NA	36333501
Frailty[a]	386,565	2023	36928559	Europe	NA	36928559
RA[b]	58,284	2014	24390342	Europe	ieu-a-832	MRC-IEU
Frailty[b]	175,226	2021	34431594	Europe	ebi-a-GCST90020053	MRC-IEU

SNP: single-nucleotide polymorphism; RA: rheumatoid arthritis.
[a] data for rheumatoid arthritis and frailty were used for primary analysis.
[b] data for rheumatoid arthritis and frailty were used for validation analysis.

Table II. MR assessments of the causality of RA on frailty.

Exposures	Outcomes	nSNPs	Method	OR (95%CI)	*p*	F
RA[a]	Frailty[a]	61	IVW	1.01 (1.01-1.02)	2.47E-06	35.69
		61	MR-Egger	1.01 (1.00-1.02)	3.17E-03	
		61	WM	1.01 (1.00-1.02)	3.00E-03	
RA[b]	Frailty[b]	34	IVW	1.03 (1.02-1.04)	3.30E-17	34.59
		34	MR-Egger	1.03 (1.02-1.04)	4.32E-06	
		34	WM	1.03 (1.02-1.04)	4.50E-12	

MR: Mendelian randomisation; IVW: inverse variance weighted; WM: weighted median; OR: odds ratio; SNP, single-nucleotide polymorphism; nSNPs: number of SNPs used in MR; CI: confidence interval; RA: rheumatoid arthritis.
[a] data for rheumatoid arthritis and frailty were used for primary analysis.
[b] data for rheumatoid arthritis and frailty were used for validation analysis.

Table III. MR assessments of the causality of frailty on RA.

Exposures	Outcomes	nSNPs	Method	β	SE(95%CI)	*p*	F
Frailty[a]	RA[a]	28	IVW	0.49	0.28 (-0.06-1.04)	8.21E-02	39
		28	MR-Egger	-1.02	1.09 (-3.15-1.11)	3.57E-01	
		28	WM	0.33	0.36 (-0.39-1.04)	3.68E-01	
Frailty[b]	RA[b]	6	IVW	1.25	0.44 (0.39–2.12)	4.58E-03	13.48
		6	MR-Egger	1.87	4.76 (-7.45-11.19)	7.14E-01	
		6	WM	1.15	0.53 (0.10–2.19)	3.14E-02	

MR: Mendelian randomisation; IVW: inverse variance weighted; WM: weighted median; OR: odds ratio; SNP, single-nucleotide polymorphism; nSNPs: number of SNPs used in MR; CI: confidence interval; RA: rheumatoid arthritis.
[a] data for rheumatoid arthritis and frailty were used for primary analysis.
[b] data for rheumatoid arthritis and frailty were used for validation analysis.

Table IV. Sensitivity analyses of MR.

Outcomes	Heterogeneity test						Pleiotropy test		
	IVW			MR-Eggr			MR-Egger intercept		
	Q	Q_df	Q_pval	Q	Q_df	Q_pval	Intercept	SE	*p*
RA[a]	35.76	27	0.12	33.15	26	0.16	0.0203	0.014	0.16
Frailty[a]	109.57	60	9.82E-05	109.50	59	7.18E-05	-.0001	0.001	0.85
RA[b]	1.07	5	0.96	1.05	4	0.90	-0.0125	0.096	0.90
Frailty[b]	27.58	33	0.73	27.41	32	0.70	-0.0004	0.001	0.68

MR: Mendelian randomisation; IVW: inverse variance weighted; SE: standard error; RA: rheumatoid arthritis.
[a] data for rheumatoid arthritis and frailty were used for primary analysis.
[b] data for rheumatoid arthritis and frailty were used for validation analysis.

(IVW OR = 1.01, 95% CI=[1.01–1.20], *p*=2.47E-6). The analysis results of the WM and MR-Egger methods are consistent with the findings of IVW (WM OR=1.01, 95% CI=[1.00–1.02], *p*=3.00 E-03; MR-Egger OR=1.01, 95% CI=[1.00–1.02], *p*=3.17 E-03). All three MR analysis methods showed a significant causal relationship between RA and frailty. In the validation analysis, 34 SNPs associated with RA were included according to strict exclusion criteria, with an F-value greater than 10 for the instrument variable, indicating no bias for the weak instrument variables. The results of the validation analysis also suggested that RA was associated with the increased prevalence of frailty (IVW OR=1.03, 95% CI=[1.02–1.04], *p*=3.30E-17). Table II summarises the results of MR analyses of the effects of RA on frailty.

Effects of frailty on RA

The reverse MR study was used to investigate the causal relationship between frailty as an exposure factor and RA. 28 SNPs associated with the frailty index were included according to stringent exclusion criteria. The F-value for instrumental variables was greater than 10, indicating there was no bias of weak instrumental variables. The IVW method was used in fixed-effect model, because the Cochran Q test showed no heterogeneity ($p>0.05$). Using the IVW method, genetic predictions suggested that frailty was not associated with RA in the primary analysis (IVW β=0.49, SE=0.28, 95% CI=[-0.06–1.04], p=0.082). The analysis results of the WM and MR-Egger methods are consistent with the findings of IVW (WM β=0.33, SE=0.36, 95% CI=[-0.39–1.04], p=0.368; MR-Egger β= -1.02, SE=1.09, 95% CI=[-3.15–1.11], p=0.357). However, genetic predictions suggested that frailty may be associated with the onset or development of RA in the validation analysis (IVW β=1.25, SE=0.44, 95% CI=[0.39–2.12], p=4.58E-03). Table III summarises the results of MR Analyses of the effects of frailty on RA.

All MR-Egger regressions produced negative outcomes ($p>0.05$), suggesting an absence of horizontal pleiotropy. For additional details on heterogeneity and pleiotropy, please see Table IV. To enhance the clarity and comprehensibility of the study findings, scatter plots, funnel plots, leave-one-out plots, and forest plots were employed (see online Supplementary file).

Discussion

The present MR study assessed the bidirectional causal link between RA and

frailty by analysing pooled GWAS data. The findings suggest a significant association between RA and the increased prevalence of frailty. Notably, genetic predictions suggest a possible association between frailty and the onset or development of RA.

The present forward MR study has analysed the causal relationship between RA and the increased prevalence of frailty. Previous research has indicated that frailty or pre-frailty is common in patients with RA. First, a logistic regression analysis assessed the effect of RA on frailty. The results showed that the degree of frailty in RA patients was linked to age (OR [95% CI]=1.12 [1.07–1.17]), comorbidities (OR [95% CI]=1.51 [1.01–2.27]), and high disease activity (OR [95% CI]=1.10 [1.04–1.16]) (40). Meanwhile, in a recent meta-analysis of frailty and pre-frailty in patients with RA, the results showed a pooled prevalence of 52.8% (95% CI= 42.7–62.8; I=99%) for pre-frailty and 24.0% (95% CI=19.4–28.6; I2=96%) for frailty (41). The results of the present MR study confirmed the findings of these earlier observational studies. The results of both the primary analysis and the validation analysis suggest that RA is associated with an increased prevalence of frailty; this is consistent with the results of observational studies, and the present study validated the observational findings using the GWAS data of RA and the frailty index, which enhances the robustness of causality. The underlying mechanism of the association between RA and frailty is still under investigation. Previous studies have suggested that systemic inflammation is linked to frailty (42), with elevated levels of pro-inflammatory cytokines associated with fatigue, reduced functional capacity, and decreased activity (43). Experimental evidence also supports a direct influence of cytokines on the central nervous system, which could contribute to exhaustion (44). Notably, IL-6, a pro-inflammatory cytokine, has been shown to cross the blood-brain barrier and affect neurons, while high levels of IL-6 and TNF have been linked to decreased muscle mass and strength (45, 46). Pain is another symptom that may indicate frailty, highlighting the importance of pain management to prevent vulnerability and mortality (47). Depression is a particularly prevalent comorbidity in RA patients, with up to 16.7% fulfilling diagnostic criteria for severe depression (48). Co-morbid depression can have a significant negative impact on patients' health-related quality of life, physical function, mental function, mortality, pain experience, and symptom severity (49). Depressive symptoms may also be a risk factor for frailty, as they could be associated with changes in behaviours and activities that lead to greater impairment and frailty (50). A long-term connection between pain and depressive symptoms suggests, on the other hand, that depressive symptoms might be early indicators of frailty (51). This connection is unaffected by visit duration, age, or disabling disease and has been referred to as the depression-pain binary model (52). More older people are developing RA, and the death rate has increased. The management of older RA patients is more challenging because a robust therapeutic targeting approach must be balanced against adverse events caused by increased comorbidities in older age (6). Frailty is becoming increasingly recognised as a sign of aging and is linked to an increased risk of falls, injuries, and mortality. There is a growing need to recognise frailty as a significant issue in the management of RA. A greater understanding of the link between RA and frailty is needed to develop targeted preventive measures.

The present reverse MR study was conducted to analyse the causal effect of frailty on RA and also to explore potential risk factors for RA. The aetiology of RA remains unclear, but great progress has been made in identifying risk factors for RA in recent years. Genetic susceptibility factors for RA have been known for many years; the most prevalent and strongly associated region remains the HLA-DRB1 region, with a 3-fold increased risk of RA (53). The best-defined environmental and behavioral risk factor for seropositive RA is smoking (54). Other factors such as obesity, hormonal factors, drug use, alcohol consumption, an unhealthy diet, periodontitis, and low socioeconomic status may also affect susceptibility to RA (55). Notably, the interaction of genetic, environmental, and behavioural risk factors leads to a breakdown of immune tolerance and an autoimmune process that begins with the first symptoms of non-clinical arthritis and ends with arthritis. Frailty is a poor clinical condition that can lead to many adverse outcomes, such as the development of new diseases or the hindering of recovery from existing diseases. Musculoskeletal function is a key component in quantifying frailty, and in patients with frailty, sarcopenia is often observed, which can lead to joint instability and increase the likelihood of biomechanical damage (56). In addition, higher levels of pro-inflammatory cytokines, such as IL-116, CRP, and TNF, are present in frail subjects. These mediators may accumulate in the joints, induce local low-grade inflammation and cartilage destruction, and lead to catabolic changes in joint structure. The proinflammatory state may impair the ability of joints to repair themselves (57). It can be seen that frailty is closely related to musculoskeletal health. Osteoarthritis and RA are both musculoskeletal disorders. Studies have shown that frailty and osteoarthritis disease interact, and frailty is one of the risk factors for osteoarthritis. Musculoskeletal pain, swelling, and stiffness are common symptoms of RA, and RA patients are at high risk of sarcopenia (greater than 25% prevalence), with varying degrees of loss of skeletal muscle strength and mass (58). The results of the reverse MR study suggest that frailty may be related to the occurrence or development of RA. Such results have suggestive clinical significance because there are no observational studies on the effect of frailty on RA, and such results are also worth exploring. There are several possible reasons for such results. First, frailty is a poor clinical health condition, and frailty is closely related to musculoskeletal health. Patients with frailty may be prone to some musculoskeletal problems. When recognised risk factors for RA such as autoimmune disease, genetics, infection, or smoking are present, patients with frailty are more likely to develop RA relative to non-frailty patients. Second, as with many autoimmune diseases, the

cause of RA is multifactorial, and in the exploratory stage, frailty may be a risk factor for RA. Finally, if frailty interacts with RA, frailty may promote the onset or progression of RA, and when frailty is already present in patients with RA, frailty may be associated with an accelerated progression of RA.

The study offers several significant benefits. First, this is an analysis of bidirectional causal relationships between RA and frailty using pooled GWAS data. Some previous cross-sectional studies have controlled for confounding factors, but there may still be bias that hasn't been found. Reverse causality has no impact on the association between genotype and disease for the genes used as IVs in the MR Study, and there is very little chance that these genes are associated with environmental confounders. Second, the MR analysis method is accurate enough, especially the IVW method, to detect causal effects when all IVs are valid and to produce consistent estimates using different MR techniques. At the same time, sensitivity analysis is performed in this study to check the robustness of the analysis results. Finally, the bidirectional analysis ensured causal inferences about RA and frailty in both directions. The present study provided strong evidence to support a causal relationship between RA and frailty from a genetic perspective. Notably, the results suggest that frailty may be associated with the onset or development of RA, which has clinical implications for further exploration of potential risk factors for RA in the future. However, some limitations of this study should be noted. First, the present study was limited to a European population, so additional research is warranted to determine if the current study can be extended to other populations. Second, because demographic data for all GWAS participants was not available, no MR analysis was performed based on the gender of the participants. Finally, there may be overlapping participants in exposure and outcome studies, but assessing the extent of sample overlap is challenging, and it is reassuring that the strong IVs (F statistic greater than 10) used in this study minimise potential bias in sample overlap.

In conclusion, the present study provides evidence supporting a significant association between RA and the increased prevalence of frailty, suggesting a causal link between RA and frailty. Interestingly, the results of the reverse MR study predict that frailty may be associated with the onset or development of RA. The influence of frailty on RA has been rarely studied in the past, so the present results have suggestive significance for future research on the relationship between frailty and RA. The results suggest that frailty may be an unexplored risk factor for RA, that frailty may affect the onset or development of RA, and that if RA and frailty interact, their severity may change over time. It is recommended that disease activity in RA be regularly evaluated and treatment adjusted accordingly, and frailty should also be regularly evaluated. Because there is now no clear evidence that frailty has an effect on RA, further research is needed in the future to determine whether frailty is involved in triggering the onset or progression of RA.

Acknowledgment

The authors appreciate the public datasets provided by the research or consortiums cited and included in this study.

References

1. RADU AF, BUNGAU SG: Management of rheumatoid arthritis: an overview. *Cells* 2021; 10(11): 2857. https://doi.org/10.3390/cells10112857
2. ROODENRIJS NMT, VAN DER GOES MC, WELSING PMJ *et al*.: Difficult-to-treat rheumatoid arthritis: contributing factors and burden of disease. *Rheumatology* (Oxford) 2021; 60(8), 3778-88. https://doi.org/10.1093/rheumatology/keaa860
3. EKDAHL, C, BROMAN G: (1992). Muscle strength, endurance, and aerobic capacity in rheumatoid arthritis: a comparative study with healthy subjects. *Ann Rheum Dis* 1992; 51(1): 35-40. https://doi.org/10.1136/ard.51.1.35
4. SCHERER HU, HÄUPL T, BURMESTER G: The etiology of rheumatoid arthritis. *J Autoimmun* 2020; 110: 102400. https://doi.org/10.1016/j.jaut.2019.102400
5. WU J, YANG F, MA X, LIN J, CHEN W: Elderly-onset rheumatoid arthritis vs. polymyalgia rheumatica: differences in pathogenesis. *Front Med* 2023; 9: 1083879. https://doi.org/10.3389/fmed.2022.1083879
6. SERHAL L, LWIN MN, HOLROYD C, EDWARDS CJ: Rheumatoid arthritis in the elderly: characteristics and treatment considerations. *Autoimmun Rev* 2020; 19(6): 102528. https://doi.org/10.1016/j.autrev.2020.102528
7. PILOTTO A, CUSTODERO C, MAGGI S, POLIDORI MC, VERONESE N, FERRUCCI L: A multidimensional approach to frailty in older people. *Ageing Res Rev* 2020; 60: 101047. https://doi.org/10.1016/j.arr.2020.101047
8. FRIED LP, TANGEN CM, WALSTON J *et al*.; CARDIOVASCULAR HEALTH STUDY COLLABORATIVE RESEARCH GROUP (2001). Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56(3): M146-M156. https://doi.org/10.1093/gerona/56.3
9. MOORHOUSE P, ROCKWOOD K: Frailty and its quantitative clinical evaluation. *J R Coll Physicians Edinb* 2012; 42(4), 333-40. https://doi.org/10.4997/jrcpe.2012.412
10. CLEGG A, BATES C, YOUNG J *et al*.: Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing* 2018; 47(2): 319. https://doi.org/10.1093/ageing/afx001
11. LI G, PAPAIOANNOU A, THABANE L, CHENG J, ADACHI JD: Frailty change and major osteoporotic fracture in the elderly: data from the global longitudinal study of osteoporosis in women 3-year Hamilton cohort. *J Bone Miner Res* 2016; 31(4): 718-24. https://doi.org/10.1002/jbmr.2739
12. DE VRIES NM, STAAL JB, VAN RAVENSBERG CD, HOBBELEN JS, OLDE RIKKERT MG, NIJHUIS-VAN DER SANDEN MW: Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev*,2011; 10(1): 104-14. https://doi.org/10.1016/j.arr.2010.09.001.
13. ROCKWOOD K, MITNITSKI A: Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clin Geriatr Med* 2011; *27*(1): 17-26. https://doi.org/10.1016/j.cger.2010.08.008
14. PIALOUX T, GOYARD J, LESOURD B: Screening tools for frailty in primary health care: a systematic review. *Geriatr Gerontol Int* 2012; 12(2): 189-97. https://doi.org/10.1111/j.1447-0594.2011.00797.x
15. WILLIAMS DM, JYLHÄVÄ J, PEDERSEN NL, HÄGG S: A Frailty Index for UK Biobank participants. *J Gerontol A Biol Sci Med Sci* 2019; 74(4): 582-87. https://doi.org/10.1093/gerona/gly094
16. KOJIMA G: Frailty defined by FRAIL scale as a predictor of mortality: a systematic review and meta-analysis. *J Am Med Dir Assoc* 2018; 19(6): 480-83. https://doi.org/10.1016/j.jamda.2018.04.006
17. VERMEIREN S, VELLA-AZZOPARDI R, BECKWÉE D *et al*.; GERONTOPOLE BRUSSELS STUDY GROUP: Frailty and the prediction of negative health outcomes: a meta-analysis. *J Am Med Dir Assoc* 2016; 17(12): 1163.e1-1163.e17. https://doi.org/10.1016/j.jamda.2016.09.010.
18. STUBBS B, BINNEKADE TT, SOUNDY A, SCHOFIELD P, HUIJNEN IP, EGGERMONT LH: Are older adults with chronic musculoskeletal pain less active than older adults without pain? A systematic review and meta-analysis. *Pain Med* 2013; 14(9): 1316-31. https://doi.org/10.1111/pme.12154
19. VLIETSTRA L, STEBBINGS S, MEREDITH-JONES K, ABBOTT JH, TREHARNE GJ, WATERS DL: Sarcopenia in osteoarthritis and rheumatoid arthritis: the association with self-reported fatigue, physical function and obesity. *PloS One* 2019; 14(6): e0217462. https://doi.org/10.1371/journal.pone.0217462
20. OVERMAN CL, KOOL MB, DA SILVA JA,

GEENEN R: The prevalence of severe fatigue in rheumatic diseases: an international study. *Clin Rheumatol* 2016; 35(2): 409-15. https://doi.org/10.1007/s10067-015-3035-6
21. BAKER JF, VON FELDT J, MOSTOUFI-MOA S *et al*.: Deficits in muscle mass, muscle density, and modified associations with fat in rheumatoid arthritis. *Arthritis Care Res* 2014; 66(11): 1612-18. https://doi.org/10.1002/acr.22328
22. VERHOEVEN F, TORDI N, PRATI C, DEMOUGEOT C, MOUGIN F, WENDLING D: Physical activity in patients with rheumatoid arthritis. *Joint Bone Spine* 2016; 83(3): 265-70. https://doi.org/10.1016/j.jbspin.2015.10.002
23. GIOIA C, LUCCHINO B, TARSITANO MG, IANNUCCELLI C, DI FRANCO M: Dietary habits and nutrition in rheumatoid arthritis: can diet influence disease development and clinical manifestations? *Nutrients* 2020; 12(5): 1456. https://doi.org/10.3390/nu12051456
24. TADA M, YAMADA Y, MANDAI K, HIDAKA N: Correlation between frailty and disease activity in patients with rheumatoid arthritis: data from the CHIKARA study. *Geriatr Gerontol Int* 2019; 19(12): 1220-25. https://doi.org/10.1111/ggi.13795
25. KOJIMA G, ILIFFE S, TANIGUCHI Y, SHIMADA H, RAKUGI H, WALTERS K: (2017). Prevalence of frailty in Japan: a systematic review and meta-analysis. *J Epidemiol* 2017; 27(8): 347-53. https://doi.org/10.1016/j.je.2016.09.008
26. KOJIMA M, NAKAYAMA T, TSUTANI K *et al*.: Epidemiological characteristics of rheumatoid arthritis in Japan: Prevalence estimates using a nationwide population-based questionnaire survey. *Mod Rheumatol* 2020; 30(6): 941-47. https://doi.org/10.1080/14397595.2019.1682776.
27. BOOTS AM, MAIER AB, STINISSEN P, MASSON P, LORIES RJ, DE KEYSER F: The influence of ageing on the development and management of rheumatoid arthritis. *Nat Rev Rheumatol* 2013; 9(10): 604-13. https://doi.org/10.1038/nrrheum.2013.92
28. BINDAWAS SM, VENNU V, STUBBS B: Longitudinal relationship between knee pain status and incident frailty: data from the Osteoarthritis Initiative. *Pain Med* 2018; 19(11): 2146-53. https://doi.org/10.1093/pm/pnx296
29. KEHLER DS, CLARA I, HIEBERT B *et al*.: The association between patterns of physical activity and sedentary time with frailty in relation to cardiovascular disease. *Aging Med* (Milton) 2019; 2(1): 18-26. https://doi.org/10.1002/agm2.12059
30. DE GROOT IB, BUSSMANN JB, STAM HJ, VERHAAR JA: Actual everyday physical activity in patients with end-stage hip or knee osteoarthritis compared with healthy controls. *Osteoarthritis Cartilage* 2008; 16(4): 436-42. https://doi.org/10.1016/j.joca.2007.08.010
31. VERONESE N, MAGGI S, TREVISAN CG *et al*.: pain increases the risk of developing frailty in older adults with osteoarthritis. *Pain Med* 2017; 18(3): 414-27. https://doi.org/10.1093/pm/pnw163.
32. LEONG DP, TEO KK: Predicting cardiovascular disease from handgrip strength: the potential clinical implications. *Expert Rev Cardiovasc Ther* 2015; 13(12): 1277-79. https://doi.org/10.1586/14779072.2015.1101342
33. SOYSAL P, STUBBS B, LUCATO P *et al*.: (2017). Corrigendum to "Inflammation and frailty in the elderly: a systematic review and meta-analysis" [*Ageing Res Rev* 2016; 31: 1-8]. *Ageing Res Rev* 2017; 35: 364-65. https://doi.org/10.1016/j.arr.2016.12.007
34. COOK MJ, VERSTAPPEN SMM, LUNT M, O'NEILL TW: Increased frailty in individuals with osteoarthritis and rheumatoid arthritis and the influence of comorbidity: an analysis of the UK Biobank Cohort. *Arthritis Care Res* 2022; 74(12): 1989-96. https://doi.org/10.1002/acr.24747
35. BOCHUD M, ROUSSON V: Usefulness of Mendelian randomization in observational epidemiology. *Int J Environ Res Public health*, 2010; 7(3): 711-28. https://doi.org/10.3390/ijerph7030711
36. DAVIES NM, VON HINKE KESSLER SCHOLDER S, FARBMACHER H, BURGESS S, WINDMEIJER F, SMITH GD: The many weak instruments problem and Mendelian randomization. *Stat Med* 2015; 34(3): 454-68. https://doi.org/10.1002/sim.6358
37. BURGESS S, DAVEY SMITH G, DAVIES NM *et al*.: (2023). Guidelines for performing Mendelian randomization investigations: update for summer 2023. *Wellcome Open Res* 2023; 4: 186. https://doi.org/10.12688/wellcomeopenres.15555.3
38. BOWDEN J, DAVEY SMITH G, BURGESS S: Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015; 44(2): 512-25. https://doi.org/10.1093/ije/dyv080
39. BOWDEN J, DAVEY SMITH G, HAYCOCK PC, BURGESS S: Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol* 2016; 40(4): 304-14. https://doi.org/10.1002/gepi.21965
40. SALAFFI F, DI CARLO M, FARAH S, DI DONATO E, CAROTTI M: Prevalence of frailty and its associated factors in patients with rheumatoid arthritis: a cross-sectional analysis. *Clin Rheumatol*,2019; 38(7): 1823-30. https://doi.org/10.1007/s10067-019-04486-5
41. GERMONPRÉ S, MULIER S, FALZON L, BOONEN A, VAN ONNA M: Prevalence of frailty and pre-frailty in patients with rheumatoid arthritis: a systematic literature review and meta-analysis. *Clin Exp Rheumatol* 2023; 41(7): 1443-50. https://doi.org/10.55563/clinexprheumatol/1kr7bs
42. FRANCESCHI C, GARAGNANI P, PARINI P, GIULIANI C, SANTORO A: Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol* 2018; 14(10): 576-90. https://doi.org/10.1038/s41574-018-0059-4
43. LANGMANN GA, PERERA S, FERCHAK MA, NACE DA, RESNICK NM, GREENSPAN SL: Inflammatory markers and frailty in long-term care residents. *J Am Geriatr Soc* 2017; 65(8): 1777-83. https://doi.org/10.1111/jgs.14876
44. BANKS WA: Blood-brain barrier transport of cytokines: a mechanism for neuropathology. *Curr Pharm Des* 2005; 11(8): 973-84. https://doi.org/10.2174/1381612053381684
45. DANTZER R, KELLEY KW: Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun* 2007; 21(2): 153-60. https://doi.org/10.1016/j.bbi.2006.09.006
46. LENG S, CHAVES P, KOENIG K, WALSTON J: Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: a pilot study. *J Am Geriatr Soc* 2002; 50(7): 1268-71. https://doi.org/10.1046/j.1532-5415.2002.50315.x
47. COELHO T, PAÚL C, GOBBENS RJJ, FERNANDES L: Multidimensional frailty and pain in community dwelling elderly. *Pain Med* 2017; *18*(4): 693-701. https://doi.org/10.1111/pme.12746
48. MATCHAM F, RAYNER L, STEER S, HOTOPF M: The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology* (Oxford) 2013; 52(12): 2136-48. https://doi.org/10.1093/rheumatology/ket169
49. LI N, CHAN E, PETERSON S: The economic burden of depression among adults with rheumatoid arthritis in the United States. *J Med Econ* 2019; 22(4): 372-78. https://doi.org/10.1080/13696998.2019.1572015
50. APRAHAMIAN I, SUEMOTO CK, LIN SM *et al*.: Depression is associated with self-rated frailty in older adults from an outpatient clinic: a prospective study. *Int Psychogeriatr* 2019; 31(3): 425-34. https://doi.org/10.1017/s104161021800100x
51. SANDERS JB, COMIJS HC, BREMMER MA, DEEG DJ, BEEKMAN AT: A 13-year prospective cohort study on the effects of aging and frailty on the depression-pain relationship in older adults. *Int J Geriatr Psychiatr* 2015; 30(7): 751-57. https://doi.org/10.1002/gps.4224
52. BAIR MJ, ROBINSON RL, KATON W, KROENKE K: Depression and pain comorbidity: a literature review. *Arch Intern Med* 2003; 163(20): 2433-45. https://doi.org/10.1001/archinte.163.20.2433
53. GREGERSEN PK, SILVER J, WINCHESTER RJ: The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* 1987; 30(11): 1205-13. https://doi.org/10.1002/art.1780301102.
54. SUGIYAMA D, NISHIMURA K, TAMAKI K *et al*.: Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2010; 69(1), 70-81. https://doi.org/10.1136/ard.2008.096487
55. PETROVSKÁ N, PRAJZLEROVÁ K, VENCOVSKÝ J, ŠENOLT L, FILKOVÁ M: The pre-clinical phase of rheumatoid arthritis: From risk factors to prevention of arthritis. *Autoimmun Rev* 2021; 20(5): 102797. https://doi.org/10.1016/j.autrev.2021.102797
56. O'BRIEN MS, MCDOUGALL JJ: Age and frailty as risk factors for the development of osteoarthritis. *Mech Ageing Dev* 2019; 180: 21-28. https://doi.org/10.1016/j.mad.2019.03.003
57. WISE BL, PARIMI N, ZHANG Y *et al*.; OSTEOPOROTIC FRACTURES IN MEN (MROS) GROUP: Frailty and hip osteoarthritis in men in the MrOS cohort. *J Gerontol A Biol Sci Med Sci* 2014; 69(5): 602-8. https://doi.org/10.1093/gerona/glt126
58. BENNETT JL, PRATT AG, DODDS R, SAYER AA, ISAACS JD: Rheumatoid sarcopenia: loss of skeletal muscle strength and mass in rheumatoid arthritis. *Nat Rev Rheumatol* 2023; 19(4): 239-51. https://doi.org/10.1038/s41584-023-00921-9