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ORIGINAL RESEARCH

Relative importance of inflammation and cardiorespiratory fitness for all-cause mortality risk in persons with rheumatoid arthritis: the population-based Trøndelag Health Study

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ABSTRACT

Objective Inflammation and reduced cardiorespiratory fitness (CRF) are associated with increased mortality rates in rheumatoid arthritis (RA). We aimed at directly comparing the relative importance of inflammation and reduced CRF as mediators of all-cause mortality in persons with RA compared with controls, quantifying direct and indirect (mediated) effects.

Methods Persons with (n=223, cases) and without (n=31 684, controls) RA from the third survey of the Trøndelag Health Study (HUNT3, 2006–2008) were included. Inflammation was quantified using C reactive protein (CRP) and estimated CRF (eCRF) was calculated using published formulae. All-cause mortality was found by linkage to the Norwegian Cause of Death Registry, with follow-up from inclusion in HUNT3 until death or 31 December 2018. Data were analysed using standardised equation modelling, permitting complex correlations among variables.

Results Persons with RA had increased all-cause mortality rates (24.1% vs 9.9%, p<0.001). Both eCRF (p<0.001) and CRP ≥3 mg/L (p<0.001) were mediators of this excess mortality, rendering the direct effect of RA non-significant (p=0.19). The indirect effect of RA mediated by eCRF (standardised coefficient 0.006) was approximately three times higher than the indirect effect mediated by CRP (standardised coefficient 0.002) in a model adjusted for other mortality risk factors.

Conclusion Even with CRP concentrations <3 mg/L in all patients with RA, excess mortality mediated by low CRF would still play an important role. Improved inflammation control in RA does not necessarily lead to better CRF. Therefore, our study strongly supports recommendations for development and implementation of exercise programmes aimed at improving CRF in persons with RA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Both inflammation and low cardiorespiratory fitness are important mediators of mortality in persons with rheumatoid arthritis (RA).

WHAT THIS STUDY ADDS

⇒ By direct comparison, this study demonstrated that the negative effect on all-cause mortality of low cardiorespiratory fitness was approximately three times higher than that of inflammation indicated by C reactive protein concentrations ≥3 mg/L.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study supports that in addition to medication that provides inflammation control, care for patients with RA should strongly emphasise measures that help them improve their cardiorespiratory fitness. There is an urgent need for patient-centred exercise programmes to this end.

INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune inflammatory joint disease, affecting up to 1% of the population in most parts of the world.[1] Genetic and environmental factors contribute to pathogenesis.[1] Modern treatment guidelines advocate early treatment[2] and focus on a wide range of targets including achievement of minimal levels of joint and general inflammation. The guidelines include lifestyle interventions for smoking cessation, weight control and sufficient physical activity (PA), management of comorbidities and patient education.[2 3] New drugs and ambitious treatment targets have greatly reduced the risk of permanent joint damage. However, patients still suffer from several extra-articular symptoms including fatigue,[4] and comorbidities including cardiovascular disease (CVD), pulmonary disease, neurological manifestations, kidney disease and malignancies.[5 6]

CVD is an important cause of mortality in RA, and persons with RA have benefited from the general improvements in diagnostics and

treatment of CVD.[7] However, improvements with respect to other causes of death including respiratory diseases and cancer may not be as large,[7] which may be related to the immune dysregulation in RA, comorbidities and side effects of treatment.[6]

Several recent studies from different countries indicate that there is still a mortality gap when comparing individuals with RA with general populations.[8–11] The gap might be narrowing, but data so far are conflicting,[12–15] which may partly be due to varying RA treatment, patient selection criteria and follow-up duration.

Focus on modifiable risk factors where interventions may help reduce mortality rates in RA is therefore warranted. Physical inactivity has many detrimental effects and is linked to comorbidities including CVD, cancer and depression, as well as to increased mortality rates (extensively reviewed in 16). There is substantial evidence that increased cardiorespiratory fitness (CRF) may counteract such negative effects,[16] including in persons with RA.[17] CRF may be improved by suitable PA and exercise training.

We have previously used data from the Trøndelag Health Study, a large open cohort study in Norway, to demonstrate that when studied separately, both inflammation[18] and reduced CRF levels[19] are important mediators of the observed mortality gap in RA. Thus, both these two risk factors are essential targets for intervention, but their relative importance has not previously been directly compared. We hypothesised that such comparison would shed light on whether interventions aimed at further reducing inflammation or improving CRF can be expected to provide larger gains with respect to mortality rate reductions in RA. The aim of the present study was therefore to evaluate the relative importance of inflammation and CRF as mediators of all-cause mortality in persons with RA compared with a large control group in a population-based study, including both direct and indirect (mediated) effects.

METHODS

The study used data from the third survey of the Trøndelag Health Study (HUNT3 2006–2008, participation rate ~54%). HUNT is a population-based open cohort study where all inhabitants ≥20 years of age in northern Trøndelag county are invited to participate.[20] Participants filled in questionnaires, measurements were taken and results from non-fasting blood samples were recorded.

Inclusion and exclusion to the study are shown in figure 1. Further comparisons of baseline characteristics between included and excluded participants are given in the online supplemental material 1. The 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria[21] were used to ascertain RA diagnoses for the **H**UNT **L**ongitudinal **A**nkylosing Spondylitis and **R**heumatoid **A**rthritis **S**tudy by case file review as previously detailed.[22] The remaining participants not fulfilling these diagnostic criteria were

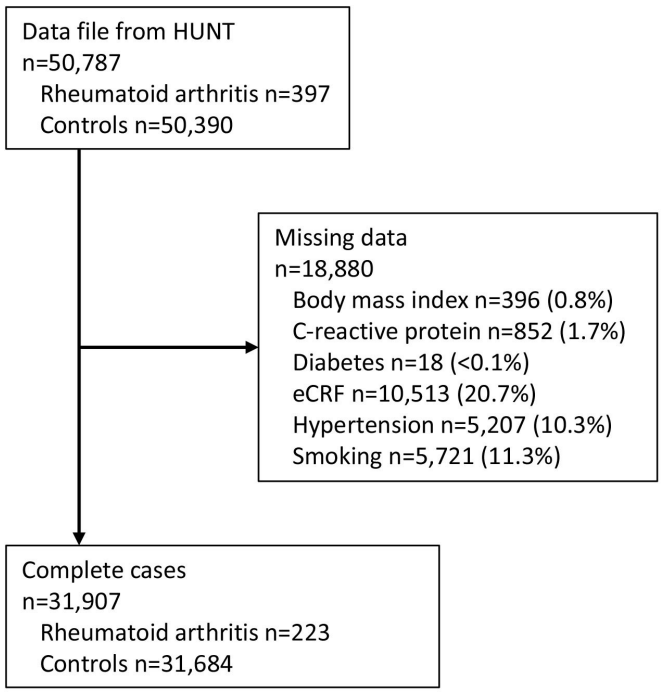


Figure 1 Participant inclusion and exclusion criteria. eCRF, estimated cardiorespiratory fitness.

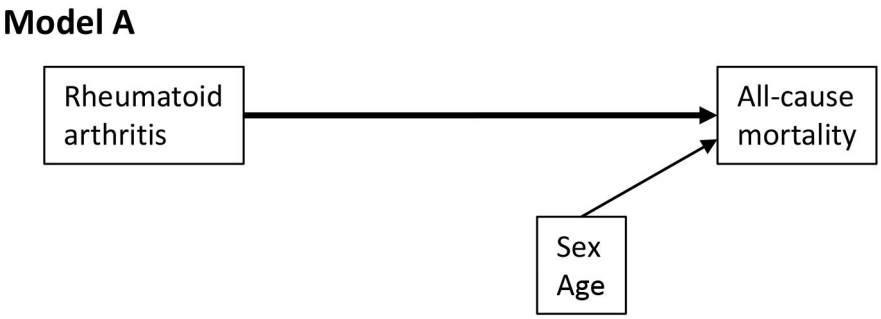
defined as controls. Due to incomplete information, persons with other forms of inflammatory arthritis were not excluded. Seropositivity for the patients with RA was defined as case file information of having IgM rheumatoid factor and/or antibodies to citrullinated proteins. Shortly after HUNT3 participation, the HUNT Research Centre analysed C-reactive protein (CRP) using the Vario high-sensitivity kit (measurement range: 0.1–160.1 mg/L) on an Architect ci8200 instrument (Abbott Clinical Chemistry, Lake Forest, Illinois, USA).

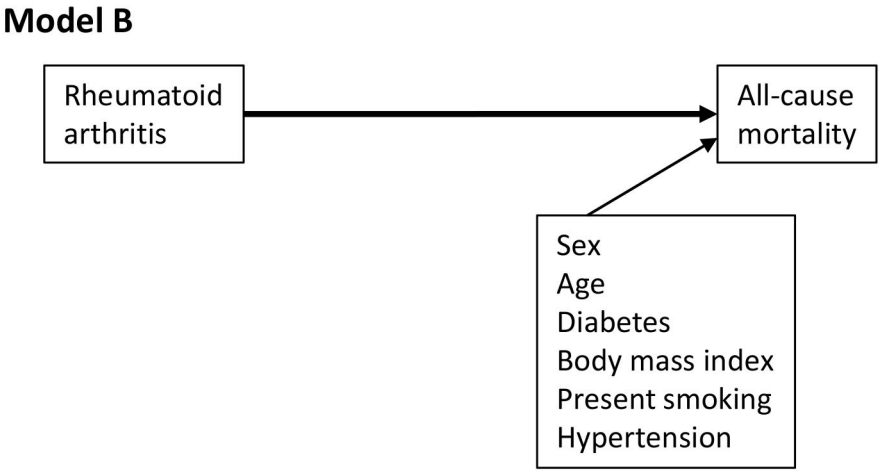
Estimated CRF (eCRF) was calculated using previously published formulae based on sex, age, body mass index (BMI) or waist circumference, smoking, physical activity (frequency, duration and intensity), resting heart rate and systolic blood pressure.[23 24] The formulae are given in the online supplemental material 2.

Linkage to the Norwegian Cause of Death Registry was used to find all-cause mortality data. The registry has >99% coverage for Norwegian citizens living in Norway or abroad. Follow-up was from the date of inclusion in HUNT3 until death or 31 December 2018, whichever came first.

Statistics

Stata (V.16.1, StataCorp, College Station, Texas, USA) was used for data analysis. Two-tailed p values of <0.05 were considered statistically significant. Due to non-normal distributions of most variables in histograms, descriptive statistics are given as median (25th and 75th percentiles), or as number (%). Patients with RA and controls were compared using the Mann-Whitney U test or X^2 test. To calculate 95% CIs for mortality rates, the binomial distribution was used. Observed mortality for persons with RA





Model	Effect	Standardized coefficient	P-value
Model A	RA direct effect →	0.016	0.002
Model B	RA direct effect →	0.015	0.003

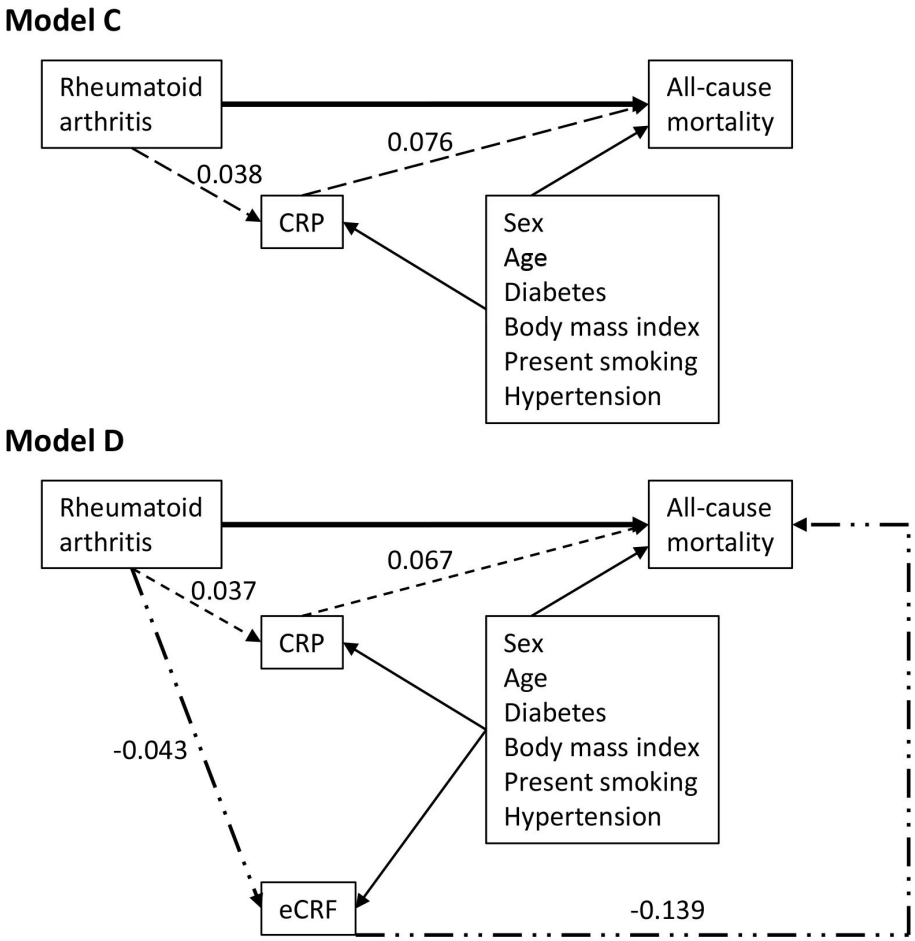
Figure 2 Proposed models for direct effects of rheumatoid arthritis (RA) on all-cause mortality. Model A and model B assume independent effects of RA and the adjustment variables on all-cause mortality. Fit indices for model A: root mean squared error of approximation (RMSEA)=0.00; Tucker-Lewis index (TLI)=1.00, Comparative Fit Index (CFI)=1.00, standardised root mean square residual (SRMR)=0.000. Fit indices for model B: RMSEA=0.00; TLI=1.00, CFI=1.00, SRMR=0.000.

and controls was analysed using a Kaplan-Meier plot and compared with the log-rank test.

Structural equation modelling (SEM) is a statistical method that can handle complex relationships with correlated explanatory variables and mediation effects, as in the present study. Using SEM, a path diagram is first drawn, depicting a model of the hypothesised relationships among the explanatory variables and an endpoint (examples in figure 2). The observed data are then compared with the model. Only if a series of common fit indices indicate little deviation between the observed data and the proposed explanatory model, the model is accepted.[25]

Data in the present study were analysed using SEM with maximum likelihood estimation. We employed the following fit indices: the X^2 test (fit vs perfect model, p>0.05 indicates good fit; too sensitive test in large studies), root mean squared error of approximation (RMSEA, compares observed and proposed covariance matrices; p<0.05 indicates excellent fit), Tucker-Lewis Index (TLI, compares proposed model with model with no correlations, adjusts for model complexity; TLI >0.95 indicates excellent fit), Comparative Fit Index (CFI, compares proposed model with model with no correlations, adjusts for model df; CFI >0.95 indicates excellent fit), standardised root mean square residual (SRMR, evaluates residuals between observed data and proposed model; SRMR <0.10 indicates good fit). The coefficient of determination of a model shows which percentage of the variation in the data it explains, akin to R^2 in linear regression models.

The proposed models are shown in figures 2 and 3. Model A investigated the association of RA with all-cause mortality, with adjustment for sex and age. Model B



Model	Effect	Standardized coefficient	P-value
Model C	RA direct effect ——▶	0.012	0.016
	RA indirect effect via CRP - - - -▶	0.003	<0.001
	RA total effect	0.015	0.003
Model D	RA direct effect ——▶	0.007	0.19
	RA indirect effect via CRP - - - -▶	0.002	<0.001
	RA indirect effect via eCRF —··—▶	0.006	<0.001
	RA total effect	0.015	0.003

Figure 3 Proposed models for total effects of rheumatoid arthritis (RA) on all-cause mortality. Model C permits indirect effects of the adjustment variables on CRP in addition to their direct effects on all-cause mortality. Fit indices for model C: root mean squared error of approximation (RMSEA)=0.014; Tucker-Lewis index (TLI)=0.99, Comparative Fit Index (CFI)=1.00, standardised root mean square residual (SRMR)=0.001. Model D permits indirect effects of the adjustment variables on CRP and on eCRF in addition to their direct effects on all-cause mortality. Fit indices for model C: RMSEA=0.008; TLI=1.00, CFI=1.00, SRMR=0.001. Numbers indicate standardised coefficients for indirect paths from RA via CRP and eCRF, respectively. CRP, C-reactive protein ≥3 mg/L; eCRF, estimated cardiorespiratory fitness.

included further adjustments for diabetes, BMI, present smoking and hypertension, which are well-known mortality risk factors that often differ between patients with RA and controls. Model C added CRP ≥3 mg/L as a mediator of the association of RA with all-cause mortality. It also permitted associations with the mentioned adjustment variables and the CRP level. This cut-off was chosen because it is often used clinically. Model D added eCRF as a second mediator of the association of RA with all-cause mortality, again permitting associations between the adjustment variables and eCRF. Due to few missing values for most variables (figure 1), the models included complete cases (n=31 907).

The models were standardised, meaning that the measurement unit for all variables was SD. The coefficients thus become directly comparable, which would not be the case when, for example, RA was measured as a yes/no variable and eCRF was measured in $mL \times min^{-1} \times kg^{-1}$. Because eCRF was included as a continuous variable, linearity of the association was checked in a modified model D using quintiles of eCRF instead.

Three sensitivity analyses were included, all modifying model D. In the first two, CRP was coded as ≥5 mg/L or ≥10 mg/L, respectively, instead of ≥3 mg/L, because these cut-offs are used clinically as indicating 'moderately elevated' and 'markedly elevated' CRP. In the third sensitivity analysis, model D was run on all possible participants in the file from HUNT (n=50 787) using estimation with maximum likelihood for missing values, to evaluate whether the findings were biased because the study excluded cases with missing data.

RESULTS

Participants with RA were more often women, were older, had higher BMI and had less favourable risk factor profiles (diabetes, hypertension, smoking) than the controls (table 1). Their level of inflammation measured as CRP was higher, and their fitness level (eCRF) was lower. They also had higher mortality rates (24.1% vs 9.9%, p<0.001), in accordance with previous studies in HUNT.[19 26] Figure 4 shows the Kaplan-Meier survival estimates for persons with RA and controls, which were

Table 1 Participant characteristics*

Variable	Patients with RA (n=223)	Controls (n=31 684)	P value
Women, n	139 (62%)	17 615 (57%)	0.044
Age, years	65 (58, 72)	54 (42, 64)	<0.001
Body mass index, kg/m^2	27.4 (24.5, 30.5)	26.6 (24.1, 29.5)	0.015
Total cholesterol, mmol/L	5.6 (4.7, 6.3)	5.4 (4.7, 6.2)	0.30
HDL cholesterol, mmol/L	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)	0.11
Creatinine, µmol/L	84 (74, 94)	82 (73, 92)	0.15
Diabetes, n	18 (8%)	1335 (4%)	0.004
Hypertension, n	138 (62%)	12 757 (40%)	<0.001
Smoking			<0.001
Never smoker	79 (35%)	15 638 (49%)	
Previous smoker	97 (44%)	10 033 (32%)	
Present smoker	47 (21%)	6013 (19%)	
C-reactive protein, mg/L	2.4 (1.2, 6.5)	1.2 (0.6, 2.6)	<0.001
C-reactive protein ≥3.0 mg/L, n	98 (44%)	6867 (22%)	<0.001
C-reactive protein ≥5.0 mg/L, n	66 (30%)	3767 (12%)	<0.001
eCRF, $mL \times min^{-1} \times kg^{-1}$	26.1 (20.1, 30.8)	35.1 (35.0, 35.2)	<0.001
Mortality, n	54	3124	<0.001
Mortality, %†	24.1 (18.1, 31.6)	9.9 (9.5, 10.2)	
Age at RA diagnosis, years	55 (46, 63)	NA	
Years with RA at HUNT3	5 (9, 16)	NA	
Seropositive‡	157 (70%)	NA	

*Data are given as number (%) or median (25th,75th percentile). Patients with RA and controls were compared using the X^2 test or Mann-Whitney U test.
†95% CIs in parentheses, calculated using the binomial distribution.
‡Seropositive: positive for IgM rheumatoid factor and/or anti-citrullinated protein antibodies.
eCRF, estimated cardiorespiratory fitness; HDL, high-density lipoprotein; HUNT3, third survey of the Trøndelag Health Study; NA, not applicable; RA, rheumatoid arthritis.

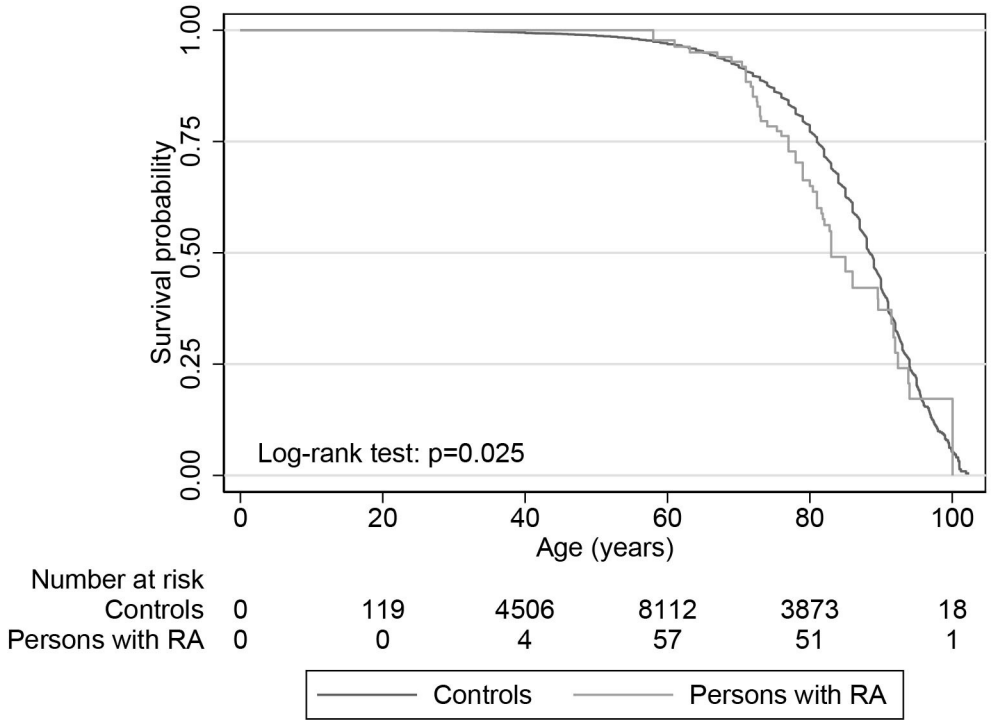


Figure 4 Kaplan-Meier survival estimates for persons with RA and controls. RA, rheumatoid arthritis.

significantly different by the log-rank test (p=0.025). Median observation time for all participants was 11.2 (10.8, 11.7) years.

The main results from the SEM analysis of mortality are shown in figures 2 and 3. The total effect of RA on all-cause mortality was similar (standardised coefficient 0.015–0.016, p=0.002–0.003) in all models, independent of inclusion of other risk factors. In other words, the adjustment variables only explained a minimal part of the association of RA with all-cause mortality, even if their total effects were significant in all models (p<0.001 for all).

In model C including CRP and adjustments, a significant part of the total effect of RA was mediated by CRP ≥3.0 mg/L (0.003, p<0.001), but there was still a remaining significant direct effect of RA (0.012, p=0.016, figure 3). In model D including CRP, eCRF and adjustments, a significant part of the total effect of RA was mediated by eCRF (0.006, p<0.001) and the indirect effect of CRP was maintained (0.002, p<0.001). The remaining direct effect of RA was no longer significant in model D (0.007, p=0.19, figure 3). The indirect effect of RA mediated by eCRF (0.006, p<0.001) was approximately three times higher than the indirect effect mediated by CRP ≥3 mg/L (0.002, p<0.001) in the fully adjusted model.

Figure 3 also shows the coefficients for the two parts of the indirect effects of RA mediated by CRP ≥3.0 mg/L and eCRF, respectively. For eCRF, these associations had negative coefficients, confirming that RA was associated with lower eCRF and that higher eCRF was associated with lower mortality rates.

All models had good fit according to the RMSEA, CFI, TLI and SRMR indices (details in legends in figures 2 and 3). However, the X^2 tests for model A (p<0.001), model B (p<0.001) and model C (p=0.006) indicated that they deviated significantly from a perfect model. This was supported by their coefficients of determination (0.17, 0.18 and 0.23, respectively), showing that they only explained a small part of the variation in the data. On the other hand, the X^2 test for model D was not significant (p=0.09) and the coefficient of determination was 0.83. Thus, model D fit the data very well and explained a large proportion of the variation in the data. This finding underscores the substantial importance of CRF as a risk factor for all-cause mortality. The model including quintiles of eCRF instead of the continuous variable confirmed good linearity of the effect.

The sensitivity analyses including CRP ≥5 mg/L or CRP ≥10 mg/L in model D, instead of CRP ≥3 mg/L, gave virtually identical findings. The sensitivity analysis including all possible participants (n=50 787) and estimating model D with maximum likelihood for missing values did not alter the conclusions of the study. The direct effect of RA was 0.004 (p=0.28), the indirect effect of RA via CRP ≥3 mg/L was 0.003 (p<0.001), the indirect effect of RA via eCRF was 0.007 (p<0.001) and total effect of RA was 0.014 (p<0.001).

DISCUSSION

The present study showed that there was a significant association between RA and increased all-cause mortality, independent of adjustment for other risk factors. When eCRF and CRP ≥3 mg/L were included as mediators, there was no longer a direct effect of RA, and the indirect effect of RA mediated by eCRF was approximately three

times higher than the indirect effect mediated by CRP in the fully adjusted model.

Adequate medication is a cornerstone in modern RA treatment.[3] By reducing symptoms and maintaining joint function, medication may also facilitate PA. However, both changing lifestyle habits and maintaining them are hard, especially in patients who may still experience pain and fatigue and lack the knowledge about the excellent safety and beneficial effects of PA.[27] The present study has clear clinical implications by underscoring that among the potential treatment aims, increasing CRF should be an important target because low CRF is a strong mortality risk factor in RA. Patients may not be aware of this association. Mortality may also be a sensitive topic for healthcare providers to raise, and both they and the patients may rather be most concerned about the present situation. From this perspective, it is important to be mindful of inactivity and low CRF as factors which also reduce well-being, restrict daily activities and predispose to loss of independency in the elderly.[27–29] PA may help reduce important symptoms like pain and fatigue[27 30 31] and have positive effects on cognition, depression and anxiety.[28 30–32]

Furthermore, rheumatologists may not have time or expertise to give advice on suitable training programmes. Therefore, the study also supports the current recommendation of establishing interdisciplinary RA treatment teams and referring patients to exercise physiologists or patient organisations offering suitable training programmes.[3] In cardiac rehabilitation, establishment of home-based exercise training programmes as a supplement to centre-based programmes has proven successful.[33] Similar programmes aimed specifically at persons with RA may prove useful in the future.

It could be argued that many patients in the present study were diagnosed before biological disease-modifying antirheumatic drugs (bDMARDs) became available. bDMARD treatment reduces the mortality gap compared with the pre-bDMARD era, but a gap still remains.[11] This is in accordance with our results, which indicated that even if all patients with RA had CRP levels <3 mg/L so that inflammation was no longer a risk factor, excess mortality mediated by low eCRF would still play an important role.

Given the recent stronger focus on PA as part of the RA treatment plan, CRF might be higher in present patients with RA than when HUNT3 was performed. Unfortunately, this does not seem to be the case: in a study our group performed in 2017/2018 testing fitness in patients with RA using a treadmill-based cardiopulmonary exercise test (CPET), only ~30% of the participants fulfilled current PA recommendations.[34]

The present study has both strengths and limitations. As in all case–control studies, RA-specific data such as diagnosis year and seropositivity could not be included in the models because there are no such data for controls, which would have led to multicollinearity. Repeated measurements of CRP over time would give a better description of fluctuations in inflammation. However, including variables obtained after the start of the observation time in the present study would be a design flaw, and it would be logistically and economically challenging to perform repeated CRP quantification in such a large study population.

The use of SEM permitted analysis of models with mediated effects and correlated variables. For analysis of mortality risk factors, Cox regression is a common and very useful method. However, it would not have been appropriate for the present study. The included risk factors in Cox regression should not be too closely correlated, which would result in multicollinearity issues. The mortality risk factors related to RA are interwoven and partly overlapping. For example, inflammation is not only a central characteristic of RA, but is associated with adiposity, diabetes, smoking and reduced levels of PA, and may also mediate the effects on mortality of other risk factors. Furthermore, because the formulae for eCRF included some of the adjustment variables in the models, eCRF was correlated with these variables. These issues were overcome using SEM, and model D had good fit and explained a substantial part of the variation in the data.

Ideally, CRF should be measured using the gold-standard method, that is, quantifying maximal oxygen uptake in a CPET on a treadmill or bicycle ergometer. This is resource-intensive and therefore practically and economically impossible in a large population-based study like HUNT. Calculation of eCRF is a simple and inexpensive alternative, less prone to selection bias due to participants who are not able or willing to perform a maximal test, although less accurate. The eCRF formula for controls was developed in 4367 healthy HUNT participants who performed a CPET[24] and was recommended for routine clinical practice by the American Heart Association.[35] We have previously shown that it overestimates fitness in persons with RA having the lowest maximal oxygen uptake values and that the alternative formula employed in the present study agreed better with CPET results in persons with RA.[23] We therefore consider the employed eCRF formulae to be good choices for the present study.

Standardisation rendered the size of the coefficients for RA, CRP and CRF directly comparable. In the models, observation time could not be analysed as in Cox models, and the fact that a SEM model has good fit does not exclude that other models could also fit the data. The study shows associations and not causation. HUNT is a population-based study, so a large number of controls from the same population could be included even if the RA case number was limited by the population frequency. Data for separate analysis of cardiovascular mortality were not available. However, the number of RA cases in HUNT3 was probably too low for sufficient power to analyse this endpoint. Using HUNT data, we also had access to important confounders that are often not available in registry-based studies. RA diagnoses were ascertained by case file review covering all three hospitals in the

HUNT catchment area. There are no privately practising rheumatologists in Trøndelag. We cannot exclude that participation bias in HUNT or confounders not adjusted for may have biased the results. The present study shows association and thereby does not verify that improving fitness reduces mortality rates. However, another study from HUNT investigating mortality related to changes in PA habits over a period of 11–22 years has shown that maintaining PA at the recommended levels or increasing from lower to recommended levels was associated with lower mortality rates.[36]

In conclusion, the present study indicated that as treatment of inflammation in RA has advanced, low CRF has emerged as a strong mediator of excess mortality. Even with CRP concentrations <3 mg/L in all patients, excess mortality mediated by low eCRF would still play an important role. Our study strongly supports recommendations for development of exercise programmes aimed at improving CRF in persons with RA.

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Contributors VV–substantial contributions to the conception and design of the work, the acquisition, analysis and interpretation of data for the work; and drafting the work and revising it critically for important intellectual content. MHL–substantial contributions to the interpretation of data for the work and revising the work critically for important intellectual content. MH–substantial contributions to the conception of the work and interpretation of data for the work and revising the work critically for important intellectual content. All authors have approved the final version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. VV acts as the guarantor of the study.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The present study complies with the Declaration of Helsinki, and participants provided informed consent when participating in HUNT. The Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics (#26264) approved the present study as part of the HuLARS Project (HUNT Longitudinal Ankylosing Spondylitis and Rheumatoid Arthritis Study).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data from the HUNT Study are available upon reasonable request from the HUNT Research Centre (https://www.ntnu.edu/hunt/data), following approval from the Regional Research Ethics Committee. However, restrictions apply to the availability of the data for the present paper, which were used under license for the current study and are not publicly available, in accordance with Norwegian law.

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