The influence of social support, financial status and lifestyle on the disparity between inflammation and disability in rheumatoid arthritis

James M Gwinnutt PhD[1] – james.gwinnutt@manchester.ac.uk (ORCID: 0000-0002-1435-8797)

Sam Norton PhD[2,3] – sam.norton@kcl.ac.uk

Kimme L Hyrich PhD[1,4] – Kimme.hyrich@manchester.ac.uk (ORCID: 0000-0001-8242-9262)

Mark Lunt PhD[1] – mark.lunt@manchester.ac.uk (ORCID: 0000-0002-2391-5575)

Bernard Combe PhD[5] – bernard.combe@umontpellier.fr

Nathalie Rincheval MSc[6] – nathalie.rincheval@inserm.fr

Adeline Ruyssen-Witrand PhD[7, 8] - ruyssen-witrand.a@chu-toulouse.fr

Bruno Fautrel PhD[9, 10] - bruno.fautrel@aphp.fr

Daniel F McWilliams PhD[11, 12] – dan.mcwilliams@nottingham.ac.uk (ORCID: 0000-0002-0581-1895)

David A Walsh PhD[11, 12, 13] – david.walsh@nottingham.ac.uk

Elena Nikiphorou PhD[3,14] – enikiphorou@gmail.com (ORCID: 0000-0001-6847-3726)

Patrick DW Kiely PhD[15,16] - patrick.kiely@nhs.net (ORCID: 0000-0002-8091-2717)

Adam Young PhD[17] - adam.young@nhs.net

Jacqueline R Chipping MSc[18,19] – j.chipping@uea.ac.uk

Alex MacGregor PhD[18,19] – a.macgregor@uea.ac.uk

Suzanne MM Verstappen PhD[1,4] – Suzanne.verstappen@manchester.ac.uk (ORCID: 0000-0001-6181-0646)

[1] Centre for Epidemiology Versus Arthritis, Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK.
[2] Health Psychology section, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[3] Centre for Rheumatic Diseases, Department of Inflammation Biology, Faculty of Life Sciences and Medicine, King's College London, London, UK
[4] NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, UK
[5] University of Montpellier, Montpellier, France
[6] Laboratory of Biostatistics and Epidemiology, University of Montpellier, Montpellier, France
[7] Centre de Rhumatologie, Hôpital Purpan, Toulouse, France
[8] Faculté de Médecine, Université Toulouse III, Paul Sabatier University, Inserm UMR1027, Toulouse, France
[9] Sorbonne University – Assistance Publique Hôpitaux de Paris, Pitie Salpetriere Hospital, Department of Rheumatology, Paris, France.
[10] PEPITES team, Pierre Louis Institute of Epidemiology and Public Health, INSERM UMRS 1136, Paris France.
[11] Pain Centre Versus Arthritis, University of Nottingham, Nottingham, UK
[12] NIHR Nottingham Biomedical Research Centre, Nottingham, UK
[13] Department of Rheumatology, Sherwood Forest Hospitals NHS Foundation Trust, Sutton in Ashfield, UK
[14] Rheumatology Department, King's College Hospital, London, UK

[15] Department of Rheumatology, St George's University Hospitals NHS Foundation Trust, London, UK
[16] Institute of Medical and Biomedical Education, St George's University of London, London, UK
[17] Centre for Health Services and Clinical Research, Life and Medical Sciences, University of Hertfordshire, Hatfield, UK
[18] Norwich Medical School, University of East Anglia, Norwich, United Kingdom.
[19] Rheumatology Department, Norfolk and Norwich University Hospitals NHS Trust, Norwich, United Kingdom

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Corresponding author: James M Gwinnutt, Centre for Epidemiology Versus Arthritis, Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. James.gwinnutt@manchester.ac.uk

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COMPETING INTERESTS

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DATA ACCESS STATEMENT

The data underlying this article cannot be shared publicly for the privacy of individuals that participated in the study. The data will be shared on reasonable request to the principal investigators of each of the three datasets (NOAR: AM, ERAN: DAW, ESPOIR: BC).

Abstract

Objectives: To investigate how social support, financial status and lifestyle influence the development of excess disability in rheumatoid arthritis (RA).

Methods: Data came from the *Étude et Suivi des Polyarthrites Indifférenciées Récentes* (ESPOIR) cohort study of people with RA. A previous analysis identified groups with similar inflammation trajectories but markedly different disability over 10 years; those in the higher disability trajectory groups were defined as having "excess disability". Participants self-reported data on contextual factors (social support, financial situation, lifestyle) and completed patient reported outcome measures (PROMs; pain, fatigue, anxiety, depression) at baseline. The direct effect of the contextual factors on excess disability and the effect mediated by PROMs was assessed using structural equation models. Findings were validated within two independent datasets (Norfolk Arthritis Register [NOAR], Early Rheumatoid Arthritis Network [ERAN]).

Results: Of 538 included ESPOIR participants (mean age [standard deviation (SD)]: 48.3 [12.2] years, 79.2% women), 200 (37.2%) were in the excess disability group. Less social support (β 0.17 [95% CI 0.08, 0.26]), worse financial situation (β 0.24 [95% CI 0.14, 0.34]), less exercise (β 0.17 [95% CI 0.09, 0.25]) and less education (β 0.15 [95% CI 0.06, 0.23]) were associated with excess disability group membership; smoking, alcohol consumption and body mass index were not. Fatigue and depression mediated a small proportion of these effects. Similar results were seen in NOAR and ERAN.

Conclusions: Greater emphasis is needed on the economic and social context of people with RA at presentation; these factors might influence disability over the following decade.

Significance and Innovations

- Financial instability and lower social support, education and exercise were associated with disability in RA, independent of inflammation level.
- Patient reported outcomes (pain, fatigue, anxiety, depression) only mediated a small proportion of this effect.
- Social and economic factors play a key role in explaining the inflammation-disability gap evident in long-term outcomes in RA; potentially people at risk of excess disability would benefit from greater assessment (e.g. via remote technologies), signposting to community groups, and targeted non-pharmacological interventions (e.g. exercise).

Antecedent factors contribute to the progression of chronic illness. The Dahlgren and Whitehead model of health determinants highlights the multi-layered nature of these 'social determinants of health' whereby living and working conditions, including education, employment and housing (1) influence social and community networks (2), which in turn can influence individual lifestyle factors (e.g. smoking, exercise, weight and alcohol use). These individual, contextual and societal factors are important components determining the onset and progression of chronic illness (e.g. diabetes, cardiovascular disease) alongside biological determinants such as genetic factors, potentially by moderating long-term stress levels (3).

Rheumatoid arthritis (RA) is a chronic condition involving the inflammation of synovial joints, potentially leading to long-term pain and functional disability (4, 5). Improvements in available treatments for RA have meant that inflammation can be controlled at low levels into the long-term for the majority of people, but for many this is not accompanied by improvements in disability; the so-called "inflammation-disability gap" in RA (6, 7). Our previous analysis of three large-scale European cohorts of people with early RA has demonstrated there are trajectory groups that share similar inflammation trajectories over 10 years of follow-up, but have markedly different disability trajectories (8). The level of disability of these trajectory groups was relatively fixed from baseline, indicating that factors prior to the onset of RA may influence baseline disability and thus subsequent disability.

In a previous analysis of two RA cohorts exploring longitudinal trajectories of functional impairment, lower socioeconomic status (defined using the United Kingdom's Index of Multiple Deprivation) predicted increased disability over time (9). A study from Texas reported that lower socioeconomic status (composite measure comprised of education, income, and occupation) was associated with increased disease activity, erosions and

functional disability (10). A study of Swedish mortality records reported lower education was associated with twofold increased risk of death in people with RA (11). Lifestyle factors, such as smoking, exercise, body weight and alcohol consumption have all been reported to influence outcomes in RA (12-14). Furthermore, lower social support is correlated with more depression, distress and disability in RA (15-17). Traumatic life events, such as the death of a spouse, may also influence outcomes (18). In summary, disparities in socioeconomic status, lifestyle and social support may explain part of the aforementioned inflammation-disability gap in RA. However, these factors are typically studied in isolation, meaning the relative contributions of economic, social and lifestyle factors on RA outcomes are unclear.

Therefore, the aim of this study was to determine the association between specific social determinants of health (rather than deprivation indices) and antecedent events prior to the onset of RA and inflammation-disability trajectory group membership (8). Furthermore, previous research has shown that pain, fatigue and depression are strongly associated with excess disability group membership (8). Therefore, a second objective was to explore the mediating effect of patient reported outcome measures (PROMs) on the relationship between these antecedent factors and excess disability in RA.

Patients and Methods

The data for this analysis came from the *Étude et Suivi des Polyarthrites Indifférenciées Récentes* (ESPOIR) study, a cohort of people with inflammatory arthritis recruited from 14 centres across France from 2002 to 2005 (ClinicalTrials.gov: NCT03666091). The inclusion criteria of ESPOIR were: >2 swollen joints for >6 weeks and <6 months, clinical diagnosis of RA as certain or possible, aged 18-70 years and no disease modifying anti-rheumatic drugs

(DMARDs) or glucocorticoids for >2 weeks (19). The ESPOIR cohort study was approved by the Ethics Committee of Montpellier (reference: 020307).

Social context, financial situation and lifestyle variables

Participants of ESPOIR answered several questions at baseline from the "Evaluation de la Précarité et des Inégalités de santé dans les Centres d'Examens de Santé" (EPICES) (20, 21) questionnaire related to availability of social support (yes/no), including whether participants felt they had someone to rely on for accommodation (accommodation help) or financial assistance (financial help), whether they were married or co-habiting compared with being single, divorced or widowed (married/co-habiting), and whether they had seen their family in the previous 6 months (family contact). Participants also reported the number of inhabitants of the town or city where they lived (<5000; 5000-20,000; 20,000-50,000; >50,000).

Participants' financial situation at baseline was assessed through questions asking participants to self-report their monthly family income (<€610; €610-€1220; €1220-€1830; €1830-2440; €2440-€2745; >€2745), personal income (same categories), and whether participants were homeowners (homeowner), had been to a show or the cinema in the previous 6 months (show/cinema), and had been on holiday in the previous 6 months (holiday). Participants also reported their working status (full-time; part-time; at home; disabled; student; retired; unemployed; long-term illness; other) and job level (coded into three levels: low-level = farmer, artisan/trader, worker/labourer, without profession; mid-level = employee, intermediate occupation; high-level = management, self-employed).

Baseline lifestyle data available in ESPOIR included smoking status (current smoker, yes/no), alcohol consumption (yes/no), body mass index (BMI; calculated from height and weight measured at baseline) and whether participants had played sports in the previous six months

(yes/no). Furthermore, participants reported their education level at baseline (primary; qualifications at 16 years; qualifications at 18 years; undergraduate degree; postgraduate). Lastly, participants reported whether they had experienced any traumatic events or the death of someone close in the six months prior to RA onset.

Clinical variables and patient reported outcome measures

At baseline, researchers completed 28 swollen and tender joint counts with each participant, and a blood sample was taken from which C-reactive protein (CRP) level was measured. Participants of ESPOIR also completed pain, fatigue and global assessment visual analogue scales (VAS, mm) and the French version of the Health Assessment Questionnaire (HAQ), a measure of functional disability (22). Anxiety and depression were assessed using five variables from the French version of the Arthritis Impact Measurement Scales-2 (AIMS-2) (23). The Disease Activity Score (DAS28), a composite measure of disease activity, was calculated from the participants' swollen and tender joint counts and CRP level (24). The two-component DAS28 (DAS28-2C), a composite measure of inflammation, was calculated from participants' swollen joint count and CRP level (25).

Excess disability group membership

Our previous analysis of three European cohort studies (including ESPOIR) analysing the trajectories of inflammation (measured using the DAS28-2C (25), chosen to isolate the influence of inflammation specifically [the target of pharmacological treatment in RA], as opposed to disease activity [which is likely influenced by inflammation level plus multiple other factors]) and disability (measured using the HAQ (22, 26)) over ten years identified five subgroups (i.e. one trajectory with very low inflammation and disability; two trajectories with similar low levels of inflammation but one with higher disability than the other; and two trajectories with similar

high levels of inflammation, again with one group having higher disability than the other [Supplementary Figure 1]). The people in these high-HAQ groups (i.e. the low inflammation-high HAQ group and the high inflammation-high HAQ group) were described as having "excess disability" in relation to their inflammation level (8). For the current analysis, the two subgroups characterised by excess disability were combined and compared with the groups who had similar inflammation over follow-up, but lower disability (i.e. the outcome for this analysis is excess disability compared with other people with RA with similar inflammation levels but lower disability).

Validation datasets

The Norfolk Arthritis Register (NOAR) (27) and the Early Rheumatoid Arthritis Network (ERAN) (28) datasets acted as validation datasets. In NOAR, data were collected on current employment status (categorised as: working = 'working'; not working = 'unemployed', 'off sick', 'house-person/parent', 'retired early – health grounds'; retired = 'retired') and job seniority level (categorised as: low = 'partly skilled', 'unskilled'; medium = 'non-manual skilled', 'manual skilled'; high = 'professional', 'managerial and technical'). In ERAN, employment status was available (same coding as NOAR), as were deciles of the 2007 Index of Multiple Deprivation (IMD), an area level index of deprivation combining: income deprivation; employment deprivation; health deprivation and disability; education deprivation; crime deprivation; barriers to housing and services deprivation; and living environment deprivation (29). Ethical approval for NOAR and ERAN came from the Cambridgeshire and Hertfordshire Research Ethics Committee (15/EE/0076) and the Trent Research Ethics Committee (01/4/047) respectively. Participants in all three cohorts gave written informed consent.

Statistical analysis

The baseline characteristics of the cohorts were described using descriptive statistics. The associations between each antecedent social support, financial situation and lifestyle variable and membership of the excess disability subgroup were assessed using logistic regression, controlling for age and gender. However, many of these variables were correlated. Therefore a structural equation modelling (SEM) approach was used. Using SEM has several advantages: multiple indicators of an underlying, potentially unmeasurable concept (e.g. social support) can be combined to produce latent variables (closer approximations of these underlying constructs). Furthermore, the effect of these latent variables on excess disability can be decomposed into direct effects and indirect effects where antecedent factors influence disability via intermediary variables (i.e. mediation analysis), allowing a greater understanding of the pathways leading from these antecedent factors to excess disability in RA.

Initially, latent variables were constructed summarising participants' social support (measured using the accommodation help, financial help, family contact, and married/co-habiting variables) and participants' financial situation (measured using the family income, personal income, homeowner, show/cinema, holiday, working status, and job level variables); these latent variables were assessed using confirmatory factor analysis (maximum likelihood estimator), with model fit assessed using the Tucker-Lewis Index (TLI; good fit >0.9) and the Root Mean Square Error of Approximation (RMSEA; good fit <0.08). Several of the ordinal variables were dichotomised to aid model convergence: family income (≥€1830 vs <€1830; dichotomised at middle category), personal income (≥€1830 vs <€1830) and working status (full-time & part-time vs other categories). The total effects on membership of the excess HAQ group of each of these latent variables, plus lifestyle variables (smoking, alcohol, BMI,

exercise) and education were assessed using SEM (four models in total). To investigate the mediating effect of pain, fatigue, anxiety and depression on the relationship between the antecedent factors and excess disability group membership, path analysis was carried out using SEM. All models also included adjustment for age, and gender. In sensitivity analysis, inflammation dyad was also adjusted for (i.e. whether each participant was in the "low inflammation" or in the "high inflammation" dyad; Supplementary Table 1). Continuous variables with high variance (age, pain VAS, fatigue VAS, BMI) were standardised. All reported coefficients from the SEM analyses are from fully standardised models to allow direct comparison. The data available in the validation datasets were analysed using the same strategy.

As 93% of the participants in ESPOIR had no missing data, complete case analysis was performed across all analyses (comparison of those included vs excluded in Supplementary Table 2). The confirmatory factor analysis and structural equation models were fit using the lavaan (30) package in R version 3.6.0. The function "modindices" was used to improve the definition of the latent variables until a good model fit was achieved (see above). Whilst there are advantages to performing the mediation analysis within a SEM framework (see above), there is the potential for traditional mediation analysis to be biased beyond simple linear models (31). Therefore, in sensitivity analysis, the mediation analysis was also conducted within a causal mediation framework using the mediation package (32). Other packages used in this analysis were: tidyverse, psych, and haven.

Results

In total, 538 people with RA from the ESPOIR cohort were included, of which 200 (37.2%) were in the group characterised by excess disability over the subsequent 10 years. People in

the excess disability group were older at baseline (mean [SD]: 50.4 [10.7] vs. 47.0 [12.8] years), had a higher proportion of women (87.0% vs. 74.6%), the same inflammation level (mean [SD] DAS28-2C: 4.04 [1.28] vs. 3.99 [1.34]); as well as higher disability (mean [SD] HAQ: 1.39 [0.64] vs. 0.93 [0.61]), more pain, more fatigue, and more anxiety and depression compared with the no excess disability group (Table 1).

Social support, financial situation and lifestyle at baseline

Participants in the excess disability group had lower education on average compared with the lower disability group (Table 2). Participants in the excess disability group were less likely to have performed sport in the previous 6 months prior to baseline (sport vs no sport: OR 0.44 [95% CI 0.30, 0.64]), but did not differ in terms of smoking status, alcohol consumption or BMI (Table 2). In terms of social support, people who reported having accommodation support (OR 0.53 [95% CI 0.33, 0.81]), financial support (OR 0.56 [95% CI 0.38, 0.82]) and contact with family (OR 0.55 [95% CI 0.34, 0.90]) were less likely to be in the excess disability group, but being married or co-habiting compared with being single, divorced or widowed was not associated with group membership (OR 1.24 [95% CI 0.82, 1.89]) (Table 2).

Regarding personal financial situation at baseline, not working (at home, unemployed, student, disabled, long-term illness) was associated with higher odds of being in the excess disability group compared with working full- or part-time (OR 1.49 [95% CI 0.95, 2.33]). Baseline higher job level was associated with lower odds of being in the excess disability group (low vs medium: OR 1.40 [95% CI 0.91, 2.16]; high vs medium: OR 0.33 [0.15, 0.69]). Baseline higher personal and family income was also associated with lower odds of being in the excess disability group, as was being a home-owner (OR 0.77 [95% CI 0.52, 1.13]), being able to go to a show or the cinema (OR 0.53 [95% CI 0.37, 0.77]) and being able to go on holiday at

baseline (OR 0.50 [95% CI 0.35, 0.72]) (Table 2). Lastly, a traumatic event or the death of someone close in the six months preceding baseline were associated with 50% increased odds of being in the excess disability group, as was living in a rural as opposed to an urban environment (although the confidence intervals overlapped 1) (Table 2).

Definition of latent variables

Many of the social support, financial and lifestyle variables are correlated. Therefore, latent variables were constructed to summarise these correlated variables (Figure 1). Confirmatory factor analysis indicated good model fit, supporting these latent variables fit the data (Social support: TLI = 0.996, RMSEA = 0.020; Financial situation: TLI = 0.892, RMSEA = 0.054). Sport, smoking, alcohol consumption and BMI were analysed as individual components within a SEM, as no latent variables combining these indicators had satisfactory model fit (Figure 1c).

Relationship between latent variables and excess disability group membership

Less social support (β 0.17 [95% CI 0.08, 0.26]), worse financial situation (β 0.24 [95% CI 0.14, 0.34]), less sport in the previous six months (β 0.17 [95% CI 0.09, 0.25]) and less education (β 0.15 [95% CI 0.06, 0.23]) were all associated with excess disability group membership (Table 3 and Figure 1). However, smoking (β 0.05 [95% CI -0.03, 0.14]), alcohol consumption (β -0.04 [95% CI -0.12, 0.04]) and BMI (β 0.04 [95% CI -0.05, 0.12]) were not associated with excess disability group membership.

Regarding the mediating effect of the PROMs, pain and anxiety did not mediate the effect of any of the social, economic or lifestyle factors (Table 3). However, fatigue and depression each mediated between 10% and 17% of the effect of these factors (Table 3 and Figure 2).

These findings were confirmed when using a causal mediation analysis framework (Supplementary Tables 3 & 4).

Validation analyses – NOAR and ERAN

In total, 416 people had complete data and were included in the NOAR analysis (excess disability = 166 [39.9%], lower disability = 250 [60.1%]) (Supplementary Table 5 for baseline characteristics). Not working and having a lower job status at baseline were associated with increased odds of being in the excess disability group (Supplementary Table 6). The total effect of working status was β 0.18 (95% CI 0.07, 0.29; adjusted for age and gender), of which 49% was a direct effect, with the remaining effect mediated through pain, fatigue and depression (Supplementary Table 7). A similar relationship was observed for job status (Supplementary Table 7).

The ERAN analysis included 386 people (excess disability = 198 [51.3%], lower disability = 188 [48.7%]) (Supplementary Table 5 for baseline characteristics). In ERAN, higher deprivation was weakly associated with increased odds of being in the high HAQ group and the confidence interval contained the null (OR per decile increase in deprivation [IMD]: 1.06 [95% CI 0.97, 1.15]) (Supplementary Table 6). As the effect of IMD was weak and the sample size was small, the confidence intervals from the path analysis were wide (Supplementary Table 7).

Discussion

This analysis of a large cohort of people with RA illustrates the importance of social and financial factors and lifestyle behaviours in influencing excess disability occurring in RA, independent of inflammation level. People who had excess disability over ten years with respect to their inflammation levels were more likely to have less social support, poorer

financial status (less disposable income, less likely to be home owners, working in lower level occupations), lower education and perform less exercise at baseline. Previous research highlighted the role pain, fatigue and depression may play in driving this excess disability in RA (8). The current analysis illustrates that, whilst some of the effect of the aforementioned antecedent social and financial factors was mediated through fatigue and depression in the ESPOIR cohort, a significant proportion was not explained by these PROMs. Therefore, social inequality is potentially an important factor influencing long-term disability in RA, alongside inflammation, pain, fatigue and depression. Tackling this clear social inequality gradient in RA outcomes should be addressed more prominently in RA management strategies and guidelines.

Social and economic factors have been shown to correlate with RA outcomes in previous studies. Cross-sectional and short-term follow-up studies have reported associations between social support and depression (15), and psychological distress (17), as well as relationships between income and disability (33-36). Furthermore, physical activity is an established intervention that improves disability in RA (12, 37, 38), and people with early RA and lower socioeconomic status are less likely to perform physical activity in the early phases of RA (39). The current analysis extends these cross-sectional and short-term follow-up studies to show that social support, financial factors and exercise prior to RA onset predict outcome trajectories over ten years following symptom onset.

Social support is a potentially vital resource for dealing with a wide variety of stressors, such as RA and the disability that may follow (the “buffering” hypothesis (40)) (41), whereas social isolation is associated with poor health and greater risk of mortality (2). This social support may influence disability in two ways: (a) health facilitating function (e.g. encouragement,

motivation), and (b) stress reducing function (e.g. facilitating cognitive and practical adjustment) (42). RA can also have significant economic implications (43), and people with higher disability earn even less in the years after diagnosis (44). Potentially greater economic reserves mean patients are better able to adapt to RA onset and thus experience lower disability (45) as well as potentially being able to access advanced therapies in certain healthcare settings (46, 47), or perhaps higher economic level and more education and health literacy allow people with RA greater autonomy in terms of positive health behaviours and seeking support (48). Therefore, rheumatology teams may need to identify people with these characteristics for enhanced follow-up, potentially through digital modalities, or referral to additional non-pharmacological interventions (e.g. physical activity, psychological or self-management interventions (49, 50)). Signposting to patient organisations may also be beneficial in order to tackle social isolation. Furthermore, greater macro-level changes need to be implemented to reduce the social gradients of RA outcomes observed in these analyses.

This study has several strengths. The ESPOIR cohort is large, and the multicentre design means the population is representative of French regional variation, with extensive data on social and economic factors. Furthermore, whilst identical analyses could not be performed in NOAR and ERAN due to differences in available data on antecedent social and economic factors, a similar interpretation of the results from analyses of these datasets was made (i.e. that antecedent economic factors are associated with excess disability in RA), in part substantiating the generalisability of the findings. The reported level of alcohol consumption was low, potentially indicating social desirability bias. The use of "traditional" mediation analysis can be biased in situations with non-linear effects (31). However, sensitivity analysis using a causal mediation approach showed similar results, indicating minimal bias. Attempts to include all the exposure variables within a single SEM were unsuccessful due to problems with model convergence (perhaps due to

limitations in statistical power). As there could potentially be some correlation between the latent variables in this analysis, a hypothetical model that included all the antecedent variables within this paper may deliver attenuated effect estimates of the associations between each factor and excess disability, compared with the separate models within this paper. Future analyses with larger sample sizes should aim to combine all these antecedent factors into single models to separate out the individual effects. There was a higher proportion of missing data in the validation datasets compared with ESPOIR. Whilst a sensitivity analysis from a previous analysis illustrated minimal bias from these missing data (8), the validation analyses of the current paper may be susceptible to some missing data bias.

In conclusion, social support, personal financial situation, education and exercise were associated with membership of groups characterised by excess disability over 10 years following the onset of symptoms. These effects were largely independent of baseline PROMs. This indicates the pivotal importance social and economic factors play in explaining the inflammation-disability gap evident in the long-term outcomes of people with RA, and these factors require greater prominence in RA management strategies and guidelines.

References

1. Lewer D, Jayatunga W, Aldridge RW, Edge C, Marmot M, Story A, et al. Premature mortality attributable to socioeconomic inequality in England between 2003 and 2018: an observational study. The Lancet Public health. 2020;5(1):e33-e41.
2. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS medicine. 2010;7(7):e1000316.
3. Palmer RC, Ismond D, Rodriquez EJ, Kaufman JS. Social Determinants of Health: Future Directions for Health Disparities Research. American journal of public health. 2019;109(S1):S70-s1.
4. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nat Rev Dis Primers. 2018;4:18001.
5. Gwinnutt JM, Symmons DPM, Macgregor AJ, Chipping JR, Marshall T, Lunt M, et al. Twenty-Year Outcome and Association Between Early Treatment and Mortality and Disability in an Inception Cohort of Patients With Rheumatoid Arthritis: Results From the Norfolk Arthritis Register. Arthritis Rheumatol. 2017;69(8):1566-75.
6. Gwinnutt JM, Symmons DPM, Macgregor AJ, Chipping JR, Marshall T, Lunt M, et al. Have the 10-year outcomes of patients with early inflammatory arthritis improved in the new millennium

compared with the decade before? Results from the Norfolk Arthritis Register. Ann Rheum Dis. 2018;77(6):848-54.
7. Kapetanovic MC, Lindqvist E, Nilsson JA, Geborek P, Saxne T, Eberhardt K. Development of functional impairment and disability in rheumatoid arthritis patients followed for 20 years: relation to disease activity, joint damage, and comorbidity. Arthritis Care Res (Hoboken). 2015;67(3):340-8.
8. Gwinnutt J, Norton S, Hyrich K, Lunt M, Combe B, Rincheval N, et al. Exploring the disparity between inflammation and disability in the ten year outcomes of people with rheumatoid arthritis. Rheumatology (Oxford). 2022;Online ahead of print.
9. Norton S, Fu B, Scott DL, Deighton C, Symmons DP, Wailoo AJ, et al. Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. Semin Arthritis Rheum. 2014;44(2):131-44.
10. Molina E, Del Rincon I, Restrepo JF, Battafarano DF, Escalante A. Association of socioeconomic status with treatment delays, disease activity, joint damage, and disability in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2015;67(7):940-6.
11. Kiadaliri AA, Petersson IF, Englund M. Educational inequalities in mortality associated with rheumatoid arthritis and other musculoskeletal disorders in Sweden. BMC Musculoskelet Disord. 2019;20(1):83.
12. Gwinnutt JM, Verstappen SM, Humphreys JH. The impact of lifestyle behaviours, physical activity and smoking on morbidity and mortality in patients with rheumatoid arthritis. Best practice & research Clinical rheumatology. 2020:101562.
13. Gwinnutt JM, Wieczorek M, Cavalli G, Balanescu A, Bischoff-Ferrari HA, Boonen A, et al. Effects of physical exercise and body weight on disease-specific outcomes of people with rheumatic and musculoskeletal diseases (RMDs): systematic reviews and meta-analyses informing the 2021 EULAR recommendations for lifestyle improvements in people with RMDs. RMD Open. 2022;Accepted / In press.
14. Wieczorek M, Gwinnutt JM, Ransay M, Balanescu A, Bischoff-Ferrari HA, Boonen A, et al. Smoking, alcohol consumption and disease-specific outcomes in rheumatic and musculoskeletal diseases (RMDs): systematic reviews informing the 2021 EULAR recommendations for lifestyle improvements in people with RMDs. RMD Open. 2022;(Under review).
15. Brandstetter S, Riedelbeck G, Steinmann M, Ehrenstein B, Loss J, Apfelbacher C. Pain, social support and depressive symptoms in patients with rheumatoid arthritis: testing the stress-buffering hypothesis. Rheumatol Int. 2017;37(6):931-6.
16. Strating MM, Suurmeijer TP, van Schuur WH. Disability, social support, and distress in rheumatoid arthritis: results from a thirteen-year prospective study. Arthritis Rheum. 2006;55(5):736-44.
17. Benka J, Nagyova I, Rosenberger J, Calfova A, Macejova Z, Middel B, et al. Social support and psychological distress in rheumatoid arthritis: a 4-year prospective study. Disabil Rehabil. 2012;34(9):754-61.
18. Lin KC, Chen PC, Twisk JW, Lee HL, Chi LY. Time-varying nature of risk factors for the longitudinal development of disability in older adults with arthritis. J Epidemiol. 2010;20(6):460-7.
19. Combe B, Benessiano J, Berenbaum F, Cantagrel A, Daurès JP, Dougados M, et al. The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. Joint Bone Spine. 2007;74(5):440-5.
20. Sass C, Moulin JJ, Guéguen R. Le score Epices: Un score individuel de précarité. Construction du score et mesure des relations avec des données de santé, dans une population de 197 389 personnes. Bull Epidemiol Hebd. 2006;14(14):93-6.
21. Labbe E, Blanquet M, Gerbaud L, Poirier G, Sass C, Vendittelli F, et al. A new reliable index to measure individual deprivation: the EPICES score. European journal of public health. 2015;25(4):604-9.

22. Guillemin F, Braincon S, Pourel J. [Measurement of the functional capacity in rheumatoid polyarthritis: a French adaptation of the Health Assessment Questionnaire (HAQ)]. Rev Rhum Mal Osteoartic. 1991;58(6):459-65.
23. Pouchot J, Guillemin F, Coste J, Brégeon C, Sany J. Validity, reliability, and sensitivity to change of a French version of the arthritis impact measurement scales 2 (AIMS2) in patients with rheumatoid arthritis treated with methotrexate. J Rheumatol. 1996;23(1):52-60.
24. Fransen J, Welsing P, de Keijzer R, van Riel P. Disease Activity scores using C-reactive protein: CRP may replace ESR in the assessment of RA disease activity [abstract]. Ann Rheum Dis. 2004;62(Suppl 1):151.
25. Hensor EMA, McKeigue P, Ling SF, Colombo M, Barrett JH, Nam JL, et al. Validity of a two-component imaging-derived disease activity score for improved assessment of synovitis in early rheumatoid arthritis. Rheumatology (Oxford). 2019.
26. Kirwan JR, Reeback JS. Stanford Health Assessment Questionnaire modified to assess disability in British patients with rheumatoid arthritis. Br J Rheumatol. 1986;25(2):206-9.
27. Symmons DP, Barrett EM, Bankhead CR, Scott DG, Silman AJ. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. Br J Rheumatol. 1994;33(8):735-9.
28. Garwood W. The Early Rheumatoid Arthritis Network (ERAN). Musculoskeletal Care. 2004;2(4):240-4.
29. Ministry of Housing CaLG. Index of Multiple Deprivation Score, 2007 2015 [Available from: https://data.gov.uk/dataset/5ceb7e93-bc1a-48cf-80fd-fbdd15909640/index-of-multiple-deprivation-score-2007.
30. Rosseel Y. lavaan: An R Package for Structural Equation Modeling. Journal of Statistical Software. 2012;48(2):1 - 36.
31. Lange T, Vansteelandt S, Bekaert M. A simple unified approach for estimating natural direct and indirect effects. Am J Epidemiol. 2012;176(3):190-5.
32. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. mediation: R Package for Causal Mediation Analysis. Journal of Statistical Software. 2014;59(5):1-38.
33. Zhao S, Chen Y, Chen H. Sociodemographic factors associated with functional disability in outpatients with rheumatoid arthritis in Southwest China. Clinical rheumatology. 2015;34(5):845-51.
34. Alarcón AM, Muñoz S, Kaufman JS, Martínez C, Riedemann P, Kaliski S. Contribution of ethnic group and socioeconomic status to degree of disability in rheumatoid arthritis in Chilean patients. Rheumatol Int. 2015;35(4):685-9.
35. Callhoff J, Luque Ramos A, Zink A, Hoffmann F, Albrecht K. The Association of Low Income with Functional Status and Disease Burden in German Patients with Rheumatoid Arthritis: Results of a Cross-sectional Questionnaire Survey Based on Claims Data. J Rheumatol. 2017;44(6):766-72.
36. Yang G, Bykerk VP, Boire G, Hitchon CA, Thorne JC, Tin D, et al. Does socioeconomic status affect outcomes in early inflammatory arthritis? Data from a canadian multisite suspected rheumatoid arthritis inception cohort. J Rheumatol. 2015;42(1):46-54.
37. Baillet A, Vaillant M, Guinot M, Juvin R, Gaudin P. Efficacy of resistance exercises in rheumatoid arthritis: meta-analysis of randomized controlled trials. Rheumatology (Oxford). 2012;51(3):519-27.
38. Baillet A, Zeboulon N, Gossec L, Combescure C, Bodin LA, Juvin R, et al. Efficacy of cardiorespiratory aerobic exercise in rheumatoid arthritis: meta-analysis of randomized controlled trials. Arthritis Care Res (Hoboken). 2010;62(7):984-92.
39. Gwinnutt JM, Alsafar H, Hyrich KL, Lunt M, Barton A, Mm Verstappen S. Do people with rheumatoid arthritis maintain their physical activity level at treatment onset over the first year of methotrexate therapy? Rheumatology (Oxford). 2021.
40. Cohen S, Wills TA. Stress, social support, and the buffering hypothesis. Psychological bulletin. 1985;98(2):310-57.

41. Tough H, Siegrist J, Fekete C. Social relationships, mental health and wellbeing in physical disability: a systematic review. BMC Public Health. 2017;17(1):414.
42. Krol B, Sanderman R, Suurmeijer TP. Social support, rheumatoid arthritis and quality of life: concepts, measurement and research. Patient education and counseling. 1993;20(2-3):101-20.
43. Furneri G, Mantovani LG, Belisari A, Mosca M, Cristiani M, Bellelli S, et al. Systematic literature review on economic implications and pharmacoeconomic issues of rheumatoid arthritis. Clin Exp Rheumatol. 2012;30(4 Suppl 73):S72-84.
44. Wolfe F, Michaud K, Choi HK, Williams R. Household income and earnings losses among 6,396 persons with rheumatoid arthritis. J Rheumatol. 2005;32(10):1875-83.
45. Rojas M, Rodriguez Y, Pacheco Y, Zapata E, Monsalve DM, Mantilla RD, et al. Resilience in women with autoimmune rheumatic diseases. Joint Bone Spine. 2018;85(6):715-20.
46. DeWitt EM, Lin L, Glick HA, Anstrom KJ, Schulman KA, Reed SD. Pattern and predictors of the initiation of biologic agents for the treatment of rheumatoid arthritis in the United States: an analysis using a large observational data bank. Clinical therapeutics. 2009;31(8):1871-80; discussion 58.
47. Yelin E, Tonner C, Kim SC, Katz JN, Ayanian JZ, Brookhart MA, et al. Sociodemographic, disease, health system, and contextual factors affecting the initiation of biologic agents in rheumatoid arthritis: a longitudinal study. Arthritis Care Res (Hoboken). 2014;66(7):980-9.
48. Caplan L, Wolfe F, Michaud K, Quinzanos I, Hirsh JM. Strong association of health literacy with functional status among rheumatoid arthritis patients: a cross-sectional study. Arthritis Care Res (Hoboken). 2014;66(4):508-14.
49. Nagy G, Roodenrijs NMT, Welsing PMJ, Kedves M, Hamar A, van der Goes MC, et al. EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis. 2022;81(1):20-33.
50. Nikiphorou E, Santos EJF, Marques A, Böhm P, Bijlsma JW, Daien CI, et al. 2021 EULAR recommendations for the implementation of self-management strategies in patients with inflammatory arthritis. Ann Rheum Dis. 2021;80(10):1278-85.

Table 1 – Baseline demographic and clinical characteristics of the ESPOIR cohort, stratified by excess disability group status

Variable	Total ESPOIR cohort, Mean (SD) / N (%)	Excess disability, Mean (SD) / N (%)	No excess disability, Mean (SD) / N (%)	p
N	538	200	338	
Demographics				
Age, years	48.3 (12.2)	50.4 (10.7)	47.0 (12.8)	0.0012†
Women, N(%)	426 (79.2%)	174 (87.0%)	252 (74.6%)	<0.001‡
Symptom duration, months	3.46 (1.78)	3.63 (2.02)	3.36 (1.62)	0.11†
PROMs				
Pain VAS (0-100)	40.7 (27.5)	47.1 (27.4)	37.0 (26.9)	<0.001†
Fatigue VAS (0-100)	51.2 (27.4)	59.3 (27.2)	46.5 (26.5)	<0.001†
AIMS anxiety (0-10)	5.04 (2.30)	5.61 (2.25)	4.71 (2.27)	<0.001†
AIMS depression (0-10)	3.84 (2.13)	4.47 (2.24)	3.47 (1.97)	<0.001†
HAQ (0-3)	1.10 (0.67)	1.39 (0.64)	0.93 (0.62)	<0.001†
Disease activity				
DAS28	4.58 (1.15)	4.73 (1.07)	4.48 (1.19)	0.013†
DAS28 categories, N (%):				
Remission (DAS28 <2.6)	25 (4.7%)	4 (2.0%)	21 (6.2%)	0.011‡
Low (DAS28 ≥2.6 & <3.2)	37 (6.9%)	9 (4.5%)	28 (8.3%)	
Moderate (DAS28 ≥3.2 & ≤5.1)	308 (57.2%)	120 (60.0%)	188 (55.6%)	
High (DAS28 >5.1)	168 (31.2%)	67 (33.5%)	101 (29.9%)	
DAS28-2C	4.01 (1.31)	4.04 (1.28)	3.99 (1.34)	0.698†
Swollen joint count 28	7.3 (5.4)	7.4 (5.3)	7.3 (5.5)	0.801†
Tender joint count 28	9.0 (7.2)	10.3 (7.5)	8.3 (7.0)	0.003†
CRP, mg/l	22.2 (34.0)	22.4 (32.6)	22.1 (34.9)	0.931†
Patient global VAS (0-100)	62.1 (24.5)	69.3 (22.2)	57.9 (24.9)	<0.001†

† t-test. ‡ chi² test

AIMS = Arthritis Impact Measurement Scales, CRP = C-reactive protein, DAS28 = Disease Activity Score 28, DAS28-2C = two-component Disease Activity Score, ESPOIR = Étude et Suivi des Polyarthrites Indifférenciées Récentes, HAQ = Health Assessment Questionnaire, N = number, PROMS = patient reported outcome measures, SD = standard deviation, VAS = visual analogue scale

Table 2 - Social context, economic factors, education, and lifestyle at baseline, stratified by excess disability group

Baseline Variable	Total ESPOIR cohort, Mean (SD) / N (%)	Excess disability, Mean (SD) / N (%)	No excess disability, Mean (SD) / N (%)	OR of excess disability group membership (95% CI)§
Education				
Highest educational attainment, N(%):				
Primary	71 (13.2%)	30 (15.0%)	41 (12.1%)	Ref.
Qualifications at 16 years	190 (35.3%)	89 (44.5%)	101 (29.9%)	1.44 (0.81, 2.57)
Qualifications at 18 years	123 (22.9%)	45 (22.5%)	78 (23.1%)	0.90 (0.48, 1.70)
Undergraduate	83 (15.4%)	17 (8.5%)	66 (19.5%)	0.44 (0.20, 0.92)
Postgraduate	71 (13.2%)	19 (9.5%)	52 (15.4%)	0.60 (0.28, 1.24)
Lifestyle				
Current smoker, N(%)	265 (49.3%)	100 (50.0%)	165 (48.8%)	1.35 (0.93, 1.96) [Ref. not smoking]
Alcohol consumption, N(%)	102 (19.0%)	32 (16.0%)	70 (20.7%)	0.77 (0.47, 1.24) [Ref. no consumption]
Sport in previous 6 months, N(%)	213 (39.6%)	55 (27.5%)	158 (46.7%)	0.44 (0.30, 0.64) [Ref. no sport]
BMI	25.6 (4.8)	26.1 (5.1)	25.3 (4.6)	1.03 (0.99, 1.07) †
Social support				
Accommodation support available, N(%)	434 (80.7%)	147 (73.5%)	287 (84.9%)	0.52 (0.33, 0.81) [Ref. no support]
Financial support available, N(%)	385 (71.6%)	127 (63.5%)	258 (76.3%)	0.56 (0.38, 0.82) [Ref. no support]
Contact with family, N(%)	455 (84.6%)	158 (79.0%)	297 (87.9%)	0.55 (0.34, 0.90) [Ref. no contact]
Married / co-habiting, N(%)	396 (73.6%)	151 (75.5%)	245 (72.5%)	1.24 (0.82, 1.89) [Ref. single, divorced or widowed]
Personal economic situation				
Family income:				
<€610	22 (4.1%)	11 (5.5%)	11 (3.3%)	2.29 (0.89, 5.91)
€610-€1220	94 (17.5%)	41 (20.5%)	53 (15.7%)	1.51 (0.87, 2.60)
€1220-€1830	119 (22.1%)	50 (25.0%)	69 (20.4%)	1.57 (0.94, 2.64)
€1830-€2440	108 (20.1%)	32 (16.0%)	76 (22.5%)	0.88 (0.51, 1.52)
€2440-€2745	48 (8.9%)	17 (8.5%)	31 (9.2%)	1.19 (0.58, 2.38)
>€2745	147 (27.3%)	49 (24.5%)	98 (29.0%)	Ref.
Personal income:				
<€610	110 (20.4%)	52 (26.0%)	58 (17.2%)	4.10 (1.51, 13.18)
€610-€1220	185 (34.4%)	72 (36.0%)	113 (33.4%)	3.12 (1.20, 9.76)
€1220-€1830	138 (25.7%)	48 (24.0%)	90 (26.6%)	2.77 (1.05, 8.73)
€1830-€2440	65 (12.1%)	21 (10.5%)	44 (13.0%)	2.41 (0.84, 8.04)
€2440-€2745	10 (1.9%)	2 (1.0%)	8 (2.4%)	1.28 (0.16, 7.55)
>€2745	30 (5.6%)	5 (2.5%)	25 (7.4%)	Ref.
Home-owner, N(%)	329 (61.2%)	120 (60.0%)	209 (61.8%)	0.77 (0.52, 1.13) [Ref. not home owner]
Show / cinema visit, N(%)	322 (59.9%)	101 (50.5%)	221 (65.4%)	0.53 (0.37, 0.77) [Ref. no show / cinema visits]
Holiday, N(%)	293 (54.5%)	90 (45.0%)	203 (60.1%)	0.50 (0.35, 0.72) [Ref. no holidays]
Job status:				
Working (full-time / part-time), N(%)	319 (59.3%)	107 (53.5%)	212 (62.7%)	Ref.
Not working (at home, unemployed, student, disabled, long-term illness), N(%)	118 (21.9%)	54 (27.0%)	64 (18.9%)	1.49 (0.95, 2.33)
Retired, N(%)	101 (18.8%)	39 (19.5%)	62 (18.3%)	0.64 (0.36, 1.14)
Job level				
Low, N(%)	134 (24.9%)	57 (28.5%)	77 (22.8%)	1.40 (0.91, 2.16)
Medium, N(%)	348 (64.7%)	134 (67.0%)	214 (63.3%)	Ref.
High, N(%)	56 (10.4%)	9 (4.5%)	47 (13.9%)	0.33 (0.15, 0.69)
Rural / urban dwelling				
Participant's town: <5,000 inhabitants	188 (34.9%)	76 (38.0%)	112 (33.1%)	Ref.
5,000 - 20,000	95 (17.7%)	39 (19.5%)	56 (16.6%)	1.08 (0.64, 1.81)
20,000 – 50,000	109 (20.3%)	35 (17.5%)	74 (21.9%)	0.69 (0.41, 1.14)
>50,000	146 (27.1%)	50 (25.0%)	96 (28.4%)	0.79 (0.50, 1.25)
Life events				
Traumatic event in previous 6 months, N(%)	59 (11.0%)	29 (14.5%)	30 (8.8%)	1.51 (0.86, 2.65) [Ref. no event]
Death of someone close in previous 6 months, N(%)	64 (11.9%)	30 (15.0%)	34 (10.1%)	1.47 (0.86, 2.51) [Ref. no event]

§ odds ratios from logistic regression – each factor tested in separate models (rather than a single multivariable model), each model was adjusted for age and gender

† analysed as a continuous scale

BMI = body mass index, ESPOIR = Étude et Suivi des Polyarthrites Indifférenciées Récentes, N = Number, OR = odds ratio, Ref. = reference category, SD = standard deviation,

Table 3 – Results from Structural Equation Models testing the relationships between latent variables, exercise and education with excess disability

Mediation SEM	Social Support Standardised β (95% CI)	Financial Status Standardised β (95% CI)	Exercise Standardised β (95% CI)	Education Standardised β (95% CI)
Total Effect on high HAQ membership	0.168 (0.076, 0.260)	0.237 (0.138, 0.335)	0.173 (0.093, 0.254)	0.149 (0.064, 0.233)
Direct effect	0.132 (0.041, 0.223)	0.141 (0.025, 0.257)	0.124 (0.043, 0.205)	0.082 (-0.004, 0.168)
Proportion of total effect unexplained by PROMs	79% (41, 98)	59% (18, 82)	71% (42, 87)	55% (2, 77)
Indirect effect through pain	0.003 (-0.006, 0.012)	0.017 (-0.010, 0.044)	0.006 (-0.003, 0.016)	0.015 (-0.004, 0.035)
Proportion mediated through pain	2% (-6, 10)	7% (-4, 23)	3% (-1, 12)	10% (-2, 33)
Indirect effect through fatigue	0.014 (-0.001, 0.028)	0.032 (0.006, 0.057)	0.020 (0.002, 0.038)	0.022 (0.004, 0.041)
Proportion mediated through fatigue	8% (0, 25)	13% (3, 30)	12% (2, 29)	15% (4, 39)
Indirect effect through depression	0.017 (-0.001, 0.034)	0.041 (0.003, 0.078)	0.020 (0.002, 0.039)	0.025 (0.004, 0.047)
Proportion mediated through depression	10% (0, 32)	17% (0, 43)	12% (2, 28)	17% (3, 45)
Indirect effect through anxiety	0.002 (-0.006, 0.011)	0.006 (-0.018, 0.031)	0.003 (-0.012, 0.019)	0.003 (-0.008, 0.015)
Proportion mediated through anxiety	1% (-5, 10)	3% (-9, 16)	2% (-7, 14)	2% (-5, 15)

Analyses also adjusted for age and gender

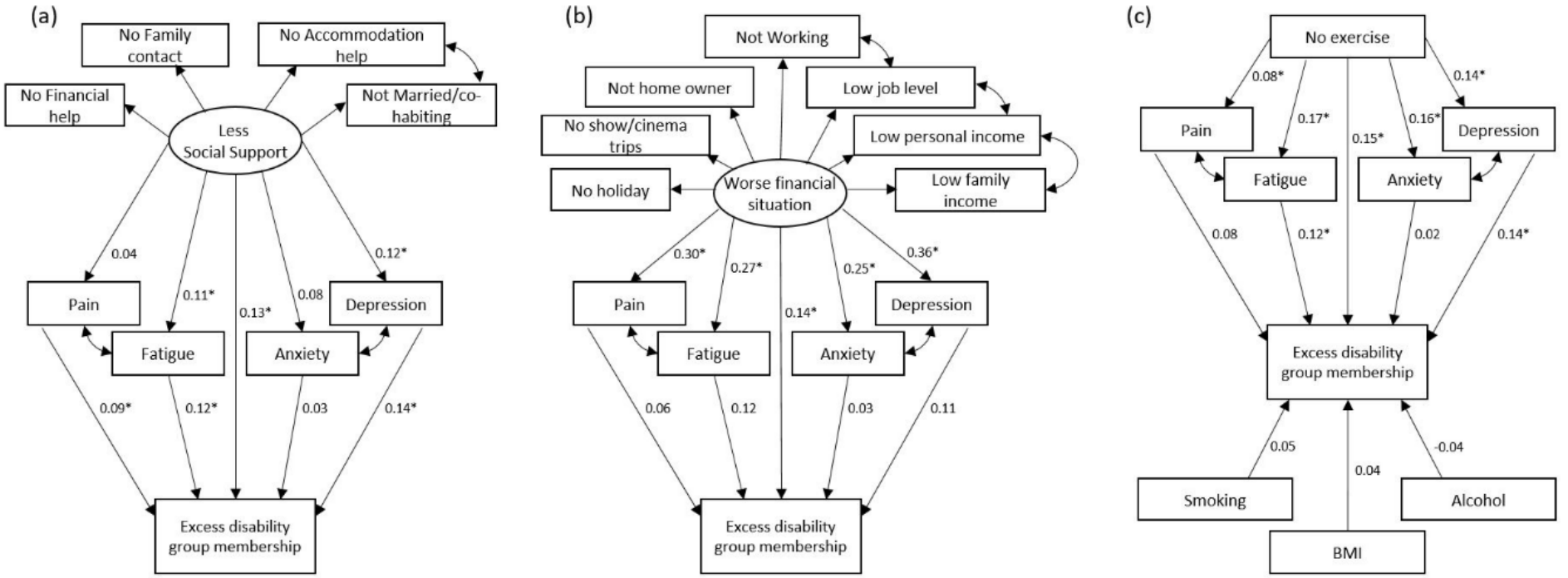

Figure 1 – SEM diagrams of direct and mediating paths between baseline latent variables (a) less social support, (b) worse financial situation as well as (c) lifestyle factors and excess disability group membership

All models also adjusted for age and gender

Ovals represent latent constructs, rectangles observed variables. The total effects referred to in the rest of the paper combine both the direct effect from the latent constructs to the outcome (excess disability), and the indirect effects through the PROMs. For example, the total effect of social support on excess disability (panel a) was 0.17, calculated as the direct effect (0.13) plus the indirect effects through the PROMs ([0.04 x 0.09] + [0.11 x 0.12] + [0.08 x 0.03] + [0.12 x 0.14]). Proportion mediated by the PROMs is the indirect effect divided by the total effect.

*BMI = body mass index, SEM = structural equation model, * indicates statistical significance*

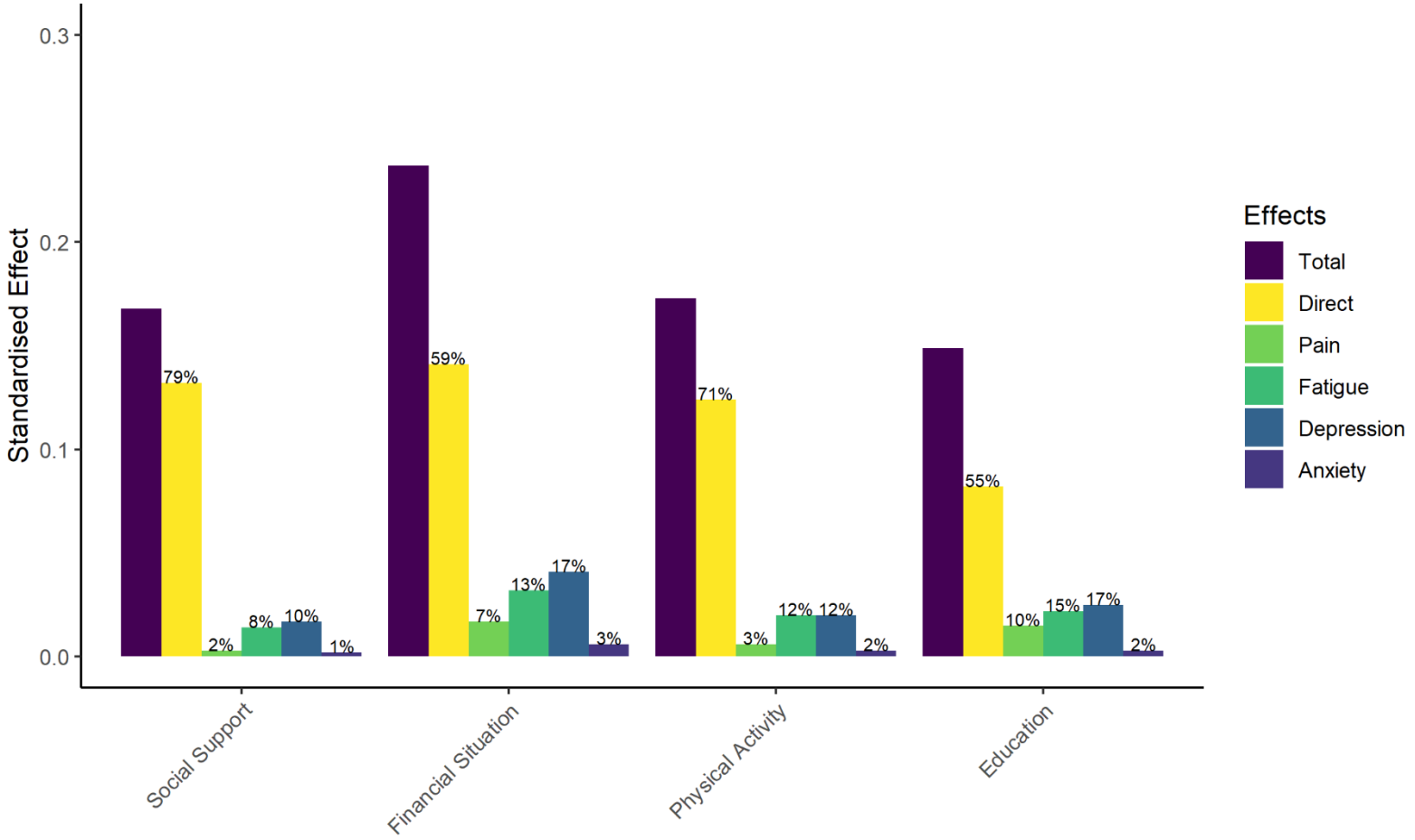

Figure 2 – Bar chart illustrating the total effect of each antecedent factor on excess disability, and how these total effects are decomposed into direct and indirect effects

Percentage labels on the top of the bars represent the proportion of each direct and indirect effect on the total effect – e.g. the total effect of social support is made up of 79% "direct effect", 2% of the effect is mediated through pain, 8% through fatigue, 10% through depression and 1% through anxiety