Increased Frailty in Individuals With Osteoarthritis and Rheumatoid Arthritis and the Influence of Comorbidity: An Analysis of the UK Biobank Cohort

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Objective. To determine the association between osteoarthritis (OA), rheumatoid arthritis (RA), and frailty and to determine whether comorbidities interact with OA and RA to further increase the likelihood of frailty.

Methods. Participants of the UK Biobank age 40–69 years at baseline were included. Demographic, lifestyle, and clinical data were collected at baseline and follow-up in a subset. Frailty was assessed using a frailty index (FI) (continuous) and a modified frailty phenotype (robust, pre-frail, frail). The association between RA and OA and frailty at baseline and follow-up was assessed using multiple regression models. We looked at whether comorbidities, including cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, and depression interacted additively with OA and RA to increase the likelihood of frailty.

Results. In total, 457,561 participants contributed data. Those with (versus without) RA (n = 4,894) and OA (n = 35,884), respectively, were more likely to be frail (adjusted relative risk ratio 10.7 [95% confidence interval (95% CI) 9.7, 11.7] and 3.4 [95% CI 3.3, 3.6]) and were more likely to have a higher FI at baseline. There was evidence of additive interaction between RA, OA, and common comorbidities increasing the occurrence of prevalent frailty. Among 25,163 participants included in longitudinal analysis, patients with RA (n = 202) and OA (n = 1,811) at baseline had an increased adjusted frailty incidence rate ratio (2.8 [95% CI 1.7, 4.6] and 1.7 [95% CI 1.3, 2.1], respectively) and also a higher FI during follow-up.

Conclusion. Individuals with RA and OA are more likely to have, or develop, frailty. Common comorbidities interact with OA and RA to further increase the likelihood of frailty.

INTRODUCTION

Frailty is a clinical state associated with dysregulation in multiple physiological systems and loss of homeostatic capacity, resulting in an increased risk of adverse health outcomes, including morbidity, disability, and death (1,2). The clinical phenotype of frailty is characterized by low physical activity, weakness, exhaustion, slowness, and loss of weight (3). Many of these features are seen also in patients with inflammatory arthritis, such as rheumatoid arthritis (RA), and noninflammatory arthritis, such as osteoarthritis (OA) (4–6). Identification of an association between OA/RA and frailty would be important, as it may help in targeting potential prevention measures to reduce frailty.

A small number of studies have demonstrated an increased risk of prevalent and incident frailty in individuals with OA compared to those without OA (7–10). Limited cross-sectional data have demonstrated an increased prevalence of frailty among individuals with RA compared to healthy controls (11,12), although there is a lack of prospective data. The mechanism by which these arthritides are linked with frailty is not fully understood, although pain (13), physical inactivity (14), and elevated inflammatory markers (15) have been linked with an increased risk of frailty and are features common among those with RA and OA. There is also evidence that comorbidity may play a role (16). Both OA and RA are linked with an increased risk of comorbid conditions (17,18), and previous research suggests that multimorbidity and...
SIGNIFICANCE & INNOVATIONS

- Osteoarthritis (OA) and rheumatoid arthritis (RA) are associated with increased prevalent and incident frailty.
- Common comorbidities are associated with increased prevalent frailty among individuals with OA and RA.
- Common comorbidities interact additively with OA and RA to increase the likelihood of frailty.

Subjects and methods

Study design and participants. The UK Biobank is a population-based prospective cohort of men and women in the UK (20,21). The purpose of UK Biobank is to provide a valuable resource for health researchers to better understand the genetic and environmental determinants of a wide range of diseases in middle and older age (20,21). Postal invitations to participate were sent to individuals ages 40–69 years who lived ~25 miles (40 km) from 1 of 22 assessment centers located throughout England, Wales, and Scotland (22).

Just over 0.5 million men and women were recruited to the UK Biobank (20,21). Participants attended an assessment center between 2006 and 2010 and provided data about demographic characteristics, lifestyle, smoking status (never, past, or current), physical activity (International Physical Activity Questionnaire [IPAQ] [23]), medical history, and morbidities via a questionnaire completed on a touch-screen computer and in an interview with a research nurse. Some physical measures, including hand-grip strength, were also taken. Two follow-up assessments (one between 2009 and 2013, and one between 2014 and 2016) were carried out in different subsets of participants, where a repeat of the full baseline assessments was completed. Townsend scores were determined based on participants’ postcode and provide an area-specific measure of socioeconomic status based on the proceeding national census data (24,25). This study had ethics approval and is part of UK Biobank project 21082 (NHS National Research Ethics Service 16/NW/0274).

Ascertainment of arthritis and comorbidity. Participants were asked to indicate whether they had ever been diagnosed by a doctor with angina, stroke, high blood pressure, or heart attack using a touch-screen computer questionnaire. During administration of the touch-screen questionnaire, participants were also asked whether a doctor had ever told them that they have any other serious illnesses or disabilities (yes/no). Following the touch-screen questionnaire, participants were interviewed by a research nurse who asked, “In the touch-screen questionnaire, you selected that you have been told by a doctor that you have other serious illnesses or disabilities, could you now tell me what they are?” Illnesses or disabilities reported by the participant (including OA, RA, CHD, diabetes mellitus, COPD, and depression) were selected by the research nurse from a classification structure based loosely on International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. Specific conditions included in each of the comorbidities are shown in Supplementary Table 1, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24747. OA, RA, and comorbidities were determined at the baseline assessment (2006–2010).

Ascertainment of frailty. Frailty was assessed using a frailty index (FI) and a modified frailty phenotype, which are 2 of the most widely used and validated methods of assessing frailty in research studies (26) and have previously been applied in the UK Biobank (19,27). Frailty indices are determined as the ratio of age-related health deficits present in an individual to the total of a specified number of deficits measured (28). The UK Biobank FI comprises 49 deficits covering aspects of health, presence of diseases and disabilities, and mental well-being (27). The UK Biobank FI has been shown to increase with increasing age and to predict all-cause mortality independently of age (27). Components of the UK Biobank FI include RA, OA, hip pain, and knee pain; however, in our analyses, these components were removed, resulting in an FI comprising 45 deficits. The FI was defined as missing for participants who had missing data for ≥10 components. In participants who had missing data for <10 components, the denominator was the total number of nonmissing deficits. Further details of the FI used are shown in Supplementary Table 2, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24747.

We also used an adapted frailty phenotype, which comprises 5 components: low grip strength, slow walking speed, weight
loss, low physical activity, and exhaustion (3). The presence of none of these deficits indicates a robust individual; the presence of 1–2 of these deficits indicates a pre-frail individual; and the presence of ≥3 of these deficits indicates a frail individual. Details of the components of the frailty phenotype in the UK Biobank and comparison with the original frailty phenotype from the Cardiovascular Health Study are summarized in Supplementary Table 3, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24747.

**Statistical analysis.** Descriptive statistics were used to assess subject characteristics including the mean FI and also the occurrence of frailty. The FI was modeled as a continuous variable, and the frailty phenotype was modeled as a categorical variable (robust, pre-frail, frail). Since the FI had a right-skewed distribution and was overdispersed relative to the Poisson distribution, negative binomial regression was used to determine the association between the presence (versus absence) of OA and RA at baseline (independent variable) and the FI at baseline (dependent variable). Since negative binomial regression models outcomes with integer values, the FI was multiplied by 100. Multinomial logistic regression was used to determine the association between the presence (versus absence) of OA and RA at baseline (independent variable) and the frailty phenotype at baseline (“robust” was the reference group). Logistic regression was used to determine the association between each of the 5 components of the frailty phenotype and OA/RA at baseline. Subsequently, the association between RA and OA at baseline and the FI over time among participants with at least 2 assessments (maximum 3 assessments) was investigated. To account for correlation in repeated measurements of the FI within individuals, the association between OA and RA at baseline and the FI at follow-up assessments was determined using negative binomial random effects models (separate models for OA and RA). The presence (versus absence) of OA or RA at baseline was the independent variable, and the FI at each assessment was the dependent variable. To determine whether the rate of change of FI was different among individuals with (versus without) OA or RA at baseline, an interaction term between OA or RA and time (in years) since the baseline assessment was considered (separate models for OA and RA). Participants who were robust or pre-frail at baseline according to the frailty phenotype and frail at either follow-up assessment were indicated as incident cases of frailty. The frailty incidence rate ratio among individuals with OA (versus no OA) or RA (versus no RA) at baseline was determined using negative binomial regression.

The association between each comorbidity and prevalent pre-frailty and frailty at baseline was determined using multinomial regression (robust was the reference group). To assess whether the effect of RA or OA plus comorbidity had a greater effect on the risk of pre-frailty and frailty at baseline over and above the expected risk due to RA or OA plus the morbidity considered individually, we looked at additive interaction between them and determined the attributable proportion (AP) of risk from interaction (29,30). For 2 exposures (in our case, OA and each morbidity considered), the AP of risk from interaction indicates the proportion of risk for a given outcome among patients with both exposures that is due to the additive interaction of exposures. The AP of risk from interaction is calculated as the relative excess risk from the (additive) interaction divided by the relative risk (RR) in persons with both exposures of interest: AP = [RR_{AB} - (RR_A + RR_B - 1)]/RR_{AB}, where A and B are 2 patient characteristics. An AP of 0 indicates no additive interaction, values >0 indicate positive interaction, and values <0 indicate negative interaction. Confidence intervals for the AP of risk from interaction were calculated using the method described by Horner and Lemeshow (31). Statistical models were carried out unadjusted and also adjusted for putative confounders: age at baseline, sex, smoking status (current smoker, former smoker, never smoked), body mass index (BMI), and Townsend deprivation score.

The data underlying this article were accessed from the UK Biobank under application number 21082. Analyses were carried out using Stata/MP, version 13.1.

**RESULTS**

**Cohort characteristics.** In total, 502,633 individuals participated in the UK Biobank. Participants with missing data for OA or RA (n = 9,680) or for whom either the FI or the frailty phenotype could not be determined at baseline due to missing data (n = 37,661) were excluded from the analyses. Of the 457,561 participants analyzed at baseline, 4,894 (1.1%) had RA, and 35,884 (7.8%) had OA. Five hundred thirteen (0.1% of the total study cohort) reported having both RA and OA at the baseline assessment, and these participants were included in both the RA cohort and also the OA cohort. Compared to the whole cohort, participants with RA and OA were older (mean ± SD age 59.2 ± 7.1 years and 60.7 ± 6.3 years, respectively, versus 56.5 ± 8.1 years), more likely to be female (69.2% and 64.6%, respectively, versus 54.2%), and to have a higher mean ± SD BMI (28.2 ± 5.4 kg/m² and 29.1 ± 5.4 kg/m² versus 27.4 ± 4.7 kg/m²) (Table 1). The mean ± SD FI at baseline among the whole cohort was 0.13 ± 0.08; among participants with RA, it was 0.18 ± 0.08; and among participants with OA, it was 0.17 ± 0.09 (Table 1). The prevalence of frailty based on the Fried phenotype in the whole cohort was 3.4% and was higher among those with RA and OA (18.6% and 10.0%, respectively) (Table 1). The mean FI increased with age in the whole cohort and was higher among women in each age group compared to men; however, there was no clear increase with age among people with RA or OA at baseline (see Supplementary Table 4, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24747). This was true
Association between OA, RA, and frailty at baseline.

The adjusted RR ratio for pre-frailty and frailty, respectively, at baseline was higher among those with (compared to those without) OA and RA: OA (versus no OA) adjusted RR ratio 1.58 (95% CI 1.54, 1.62) and 3.41 (95% CI 3.26, 3.56); and RA (versus no RA) adjusted RR ratio 2.79 (95% CI 2.61, 2.98) and 10.66 (95% CI 9.73, 11.69) (Table 2). Similar findings were observed for the individual components of the frailty phenotype model (Table 3). Similarly, the FI at baseline was greater among those with RA and OA according to an adjusted negative binomial model: RA (versus no RA) 32% (95% CI 30%, 35%) higher; OA (versus no OA) 23% (95% CI 23%, 24%) higher.

Association between OA, RA, and change in frailty.

In total, 26,349 attended at least 1 follow-up assessment. The FI or frailty phenotype could not be determined at follow-up for 1,186 participants due to missing data. In total, 25,163 participants were therefore included in the longitudinal analysis; 202 (0.8%) had RA at baseline, and 1,811 (7.1%) had OA at baseline. The median (interquartile range) follow-up time was 5.1 (4.4–6.3) years. Overall, there were 554 incident cases of frailty during follow-up according to the frailty phenotype; 89 cases among those with OA at baseline, and 15 among those with RA at baseline. In

Table 1. Participant characteristics at baseline*

| Characteristic                        | Whole cohort (n = 457,561) | RA (n = 4,894) | OA (n = 35,884) |
|--------------------------------------|-----------------------------|----------------|-----------------|
| Age, mean ± SD years                 | 56.5 ± 8.1                  | 59.2 ± 7.1     | 60.7 ± 6.3      |
| BMI, mean ± SD kg/m²                 | 27.4 ± 4.7                  | 28.2 ± 5.4     | 29.1 ± 5.4      |
| FI, mean ± SD                        | 0.13 ± 0.08                 | 0.18 ± 0.08    | 0.17 ± 0.09     |
| Female                               | 247,737 (54.2)              | 3,384 (69.2)   | 23,174 (64.6)   |
| Hypertension                         | 123,640 (27.1)              | 1,749 (35.8)   | 13,279 (37.1)   |
| Coronary heart disease               | 20,334 (4.5)                | 392 (8.0)      | 2,494 (7.0)     |
| Diabetes mellitus                    | 23,230 (5.1)                | 375 (7.7)      | 2,484 (6.9)     |
| Stroke/transient ischemic attack     | 7,540 (1.7)                 | 148 (3.0)      | 830 (2.3)       |
| Chronic obstructive pulmonary disease| 8,042 (1.8)                 | 227 (4.6)      | 1,252 (3.5)     |
| Depression                           | 25,351 (5.5)                | 336 (6.9)      | 3,010 (8.4)     |
| Quintile of Townsend deprivation score |                                |                |                 |
| 1                                    | 91,558 (20.0)               | 867 (17.7)     | 6,450 (18.0)    |
| 2                                    | 91,199 (20.0)               | 852 (17.4)     | 6,896 (19.2)    |
| 3                                    | 91,383 (20.0)               | 958 (19.6)     | 7,139 (19.9)    |
| 4                                    | 91,378 (20.0)               | 975 (20.0)     | 7,063 (19.7)    |
| 5                                    | 91,369 (20.0)               | 1,235 (25.3)   | 8,292 (23.4)    |
| Smoking status                       |                             |                |                 |
| Current smoker                       | 46,854 (10.2)               | 602 (12.3)     | 3,490 (9.7)     |
| Former smoker                        | 226,307 (49.5)              | 2,508 (51.3)   | 18,839 (52.5)   |
| Never smoked                         | 184,400 (40.3)              | 1,784 (36.5)   | 13,555 (37.8)   |
| Frailty phenotype                    |                             |                |                 |
| Not frail                            | 271,430 (59.3)              | 1,406 (28.7)   | 15,203 (42.4)   |
| Pre-frail                            | 170,782 (37.3)              | 2,578 (52.7)   | 17,088 (47.6)   |
| Frail                                | 15,349 (3.4)                | 910 (18.6)     | 3,593 (10.0)    |
| Frailty phenotype component          |                             |                |                 |
| Exhaustion                           | 55,635 (12.2)               | 1,108 (22.6)   | 6,304 (17.6)    |
| Weight loss                          | 70,068 (15.3)               | 933 (19.1)     | 6,372 (17.8)    |
| Low physical activity                | 36,094 (7.9)                | 833 (17.0)     | 4,459 (12.4)    |
| Slow walking speed                   | 34,733 (7.6)                | 1,473 (30.1)   | 7,713 (21.5)    |
| Low grip strength                    | 63,239 (13.8)               | 2,341 (47.8)   | 9,733 (27.1)    |

* Values are the number (%) unless indicated otherwise. There are no missing data for the frailty phenotype, FI, or smoking status. For each of the other variables, data are missing for <0.03% of the cohort. BMI = body mass index; FI = frailty index; OA = osteoarthritis; RA = rheumatoid arthritis.

Table 2. Association between osteoarthritis (OA), rheumatoid arthritis (RA), and the frailty phenotype at baseline*

| Presence (vs. absence) of disease at baseline | Not frail | Unadjusted | Adjusted† |
|----------------------------------------------|-----------|------------|-----------|
|                                              |           | Pre-frail  | Frail     | Pre-frail | Frail     |
| RA                                           | Ref       | 2.94 (2.76, 3.14) | 12.10 (11.12, 13.18) | 2.79 (2.61, 2.98) | 10.66 (9.73, 11.69) |
| OA                                           | Ref       | 1.87 (1.83, 1.92) | 5.15 (4.95, 5.37) | 1.58 (1.54, 1.62) | 3.41 (3.26, 3.56) |

* Values are the relative risk ratio (95% confidence interval). Ref. = reference. Multinomial logistic regression model. Frailty phenotype at baseline is the dependent variable. Presence (vs. absence) of the indicated musculoskeletal condition at baseline is the independent variable.† Adjusted for age at baseline, sex, smoking status, body mass index at baseline, and Townsend score.
Table 3. Association between osteoarthritis (OA), rheumatoid arthritis (RA), and components of the frailty phenotype at baseline*

| Frailty phenotype component | OA (vs. no OA) | RA (vs. no RA) |
|-----------------------------|----------------|----------------|
|                             | Unadjusted     | Adjusted†      | Unadjusted     | Adjusted†      |
| Exhaustion                  | 1.61 (1.56, 1.66) | 1.59 (1.55, 1.64) | 2.14 (2.00, 2.29) | 2.04 (1.90, 2.19) |
| Weight loss                 | 1.21 (1.18, 1.25) | 1.19 (1.16, 1.23) | 1.31 (1.22, 1.40) | 1.28 (1.19, 1.38) |
| Low physical activity       | 1.75 (1.69, 1.81) | 1.42 (1.37, 1.47) | 2.43 (2.25, 2.62) | 2.08 (1.92, 2.25) |
| Slow walking speed          | 4.00 (3.89, 4.11) | 2.76 (2.67, 2.84) | 5.43 (5.10, 5.78) | 4.82 (4.50, 5.16) |
| Low grip strength           | 2.56 (2.50, 2.63) | 1.65 (1.61, 1.70) | 5.90 (5.57, 6.24) | 5.03 (4.74, 5.35) |

* Values are the odds ratio (95% confidence interval), logistic regression model. Component of the frailty phenotype at baseline is the dependent variable. Presence (vs. absence) of the indicated musculoskeletal condition at baseline is the independent variable.
† Adjusted for age at baseline, sex, smoking status, body mass index at baseline, and Townsend score.

Comorbidity and frailty. Within individuals with OA and RA, the presence (versus absence) of each of the individual comorbidities considered was associated with an increased RR of pre-frailty and frailty at baseline (Table 4). There was an additive interaction between each of the comorbidities considered and OA increasing the risk of pre-frailty at baseline, indicated by an AP of >0, which was statistically significant for all comorbidities other than depression (Table 5). There was significant additive interaction between the presence of RA and also OA and all of the individual comorbidities considered and the risk of frailty at baseline (Table 5). Considering interaction with RA, the AP between RA and stroke/TIA and the risk of frailty was highest (AP 0.60 [95% CI 0.38, 0.82]), followed by RA and depression (0.53 [95% CI 0.35, 0.70]), and RA and CHD (0.52 [95% CI 0.36, 0.68]) (Table 5). Considering interaction with OA, the AP between OA and diabetes mellitus and the risk of frailty was highest (AP 0.49 [95% CI 0.42, 0.55], followed by OA and CHD (0.48 [95% CI 0.41, 0.55]) and OA and depression (0.47 [95% CI 0.41, 0.53]).

DISCUSSION

We found that participants with RA and OA were more likely to have prevalent frailty as defined by the frailty phenotype and also a higher FI compared to participants without these diseases. During follow-up, those with (versus without) OA and RA were more likely also to develop incident frailty and have a higher FI over time. Individuals with (versus without) OA at baseline had a higher longitudinal analysis, the presence (versus absence) of RA and OA, respectively, at baseline was associated with an increased incidence rate ratio for frailty according to the frailty phenotype: RA unadjusted 3.78 (95% CI 2.31, 6.19); RA adjusted 2.82 (95% CI 1.73, 4.59); OA unadjusted 2.72 (95% CI 2.18, 3.39); OA adjusted 1.66 (95% CI 1.32, 2.09).

An adjusted negative binomial random effects model including individuals with at least 1 follow-up assessment showed that among those with (versus without) OA at baseline, the FI was 21.0% (95% CI 17.4%, 24.7%) higher at baseline. The rate of increase of FI over time was greater among individuals with OA at baseline compared to those without OA at baseline. Among individuals without OA at baseline, the FI increased by 3.1% (95% CI 2.9%, 3.2%) per year, and among individuals with OA at baseline, the FI increased by 3.7% (95% CI 3.4%, 4.1%) per year. Among individuals with (versus without) RA at baseline, the FI was 35.2% (95% CI 24.1%, 47.2%) higher at baseline. There was no significant difference in the rate of change of FI over time among individuals with RA at baseline compared to those without RA at baseline. The FI increased by 3.0% per year among individuals with RA at baseline and also among those without RA at baseline (95% CI among those with RA at baseline: 2.0%, 4.1% per year; 95% CI among those without RA at baseline: 2.9%, 3.2% per year).

Table 4. Association between morbidity and the frailty phenotype at baseline among individuals with rheumatoid arthritis (RA) and osteoarthritis (OA) at baseline*

| Presence (vs. absence) of comorbidity | Among participants with RA at baseline | Among participants with OA at baseline |
|---------------------------------------|---------------------------------------|---------------------------------------|
|                                       | Pre-frail     | Frail            | Pre-frail     | Frail            |
| Hypertension                          | 1.22 (1.05, 1.42) | 1.68 (1.39, 2.03) | 1.31 (1.24, 1.38) | 1.99 (1.84, 2.16) |
| Coronary heart disease                 | 1.84 (1.36, 2.48) | 3.01 (2.15, 4.21) | 1.71 (1.54, 1.89) | 3.86 (3.39, 4.41) |
| Diabetes mellitus                      | 1.69 (1.22, 2.32) | 2.99 (2.11, 4.23) | 1.93 (1.73, 2.16) | 3.98 (3.47, 4.55) |
| Stroke/transient ischemic attack       | 1.97 (1.18, 3.29) | 3.64 (2.11, 6.29) | 1.83 (1.53, 2.17) | 3.71 (2.99, 4.61) |
| Chronic obstructive pulmonary disease  | 1.72 (1.18, 2.50) | 2.45 (1.60, 3.75) | 2.09 (1.80, 2.42) | 4.45 (3.71, 5.33) |
| Depression                             | 1.76 (1.28, 2.42) | 2.74 (1.92, 3.92) | 1.68 (1.53, 1.84) | 3.40 (3.02, 3.84) |

* Values are the adjusted relative risk ratio (95% confidence interval), adjusted for age, sex, smoking, deprivation (Townsend score), and body mass index. Multinomial logistic regression model. “Not frail” is the reference group.
Fl at baseline and higher rate of change of FI over time. Those with (versus without) RA at baseline had a higher FI at baseline and a higher FI throughout the follow-up, although the rate of change in FI was not higher. There was evidence also of additive interaction between RA and OA and a number of comorbidities that are common in these rheumatic disorders, with an increased likelihood of frailty beyond that expected from the additivity of risk due to the presence of RA or OA and comorbidity. As the number of comorbidities increased, the likelihood of frailty increased nonlinearly and was higher among patients with RA, and to a lesser extent, in patients with OA compared to those without these diseases, and elevated inflammatory markers were increased among patients with RA, to a lesser extent, in OA compared to those without these diseases, and elevated inflammatory markers are associated with an increased risk of frailty.

Our results are in agreement with previous studies also showing a higher prevalence and incidence of frailty among individuals with OA compared to those without OA (7–10). Castell et al, in a cross-sectional study of 2,455 men and women (mean ± SD age 74.0 ± 5.0 years) from 6 European countries looked at the association between clinical OA and frailty, defined using a modified frailty phenotype (7). The odds ratio (OR) for pre-frailty and frailty, respectively, among participants with OA (any site) versus those without OA was 1.54 (95% CI 1.24, 1.91) and 2.96 (95% CI 2.11, 4.16). Despite the participants in the study by Castell et al being slightly older than those in our study, these estimates are broadly similar to those found in our study.

Wise et al, in a study of 4,130 community-dwelling men age ≥65 years, found that men with radiographic hip OA or total hip replacement (THR) (versus no radiographic hip OA and no THR) were more likely to be frail or intermediate frail (versus robust) in cross-sectional analysis (OR 1.45 [95% CI 1.18, 1.78]) (8). Participants with radiographic hip OA or THR were also more likely to experience worsening frailty, defined using a modified frailty phenotype, during a mean ± SD follow-up of 2.3 ± 0.36 years (OR 1.27 [95% CI 1.19, 1.38]) (8).

In a longitudinal study of 2,980 men and women age ≥60 years from the US, Misra et al defined frailty using a modified frailty phenotype (9). Participants with radiographic knee OA and symptomatic knee OA at baseline, respectively, were more likely to develop frailty during a follow-up period of up to 30 months compared to participants who did not have radiographic or symptomatic knee OA (adjusted RR ratio 1.45 [95% CI 0.91, 2.30] and 1.66 [95% CI 1.11, 2.48]), similar to the estimates reported in our study.

Last, using data from the MOST study, Bindawa et al analyzed data from 3,053 non-frail men and women ages 45–79 years from the US (10). Participants with unilateral knee pain at baseline were more likely to become pre-frail or frail (defined using the Fried frailty phenotype), respectively, over a 6 year follow-up compared to participants who did not have knee pain (OR 1.16 [95% CI 1.01, 1.31] and 1.90 [95% CI 1.37, 2.63]). Those with bilateral knee pain (versus no knee pain) were also more likely to become pre-frail or frail, respectively, during follow-up (OR 1.40 [95% CI 1.23, 1.60] and 2.20 [95% CI 1.62, 3.00]).

The mechanisms linking RA, OA, and frailty are not fully understood, although the occurrence of pain and reduced physical activity may potentially contribute (10, 14, 32, 33). Inflammation may also play a role; elevated circulating inflammatory markers are increased among patients with RA, and to a lesser extent, in OA (34), compared to those without these diseases, and elevated inflammatory markers are associated with an increased risk of frailty (15).

We found evidence of additive interaction between OA, RA, and common comorbidities increasing the risk of frailty. Studies have suggested that the likelihood of frailty increases nonlinearly with increasing number of abnormal physiological systems (35). This may occur because of the interrelationship between physiological systems, and dysregulation in one system may potentially adversely impact on feedforward and feedback mechanisms, resulting in dysregulation in another system, with a consequent increase in likelihood of frailty (35).

We observed a higher rate of change in FI over time among individuals with (versus without) OA, although not with RA. The reason for this is not clear, although the number of those with

| Comorbidity                        | Pre-frail       | Frail           |
|------------------------------------|-----------------|-----------------|
| Hypertension                        | OA 0.10 (0.06, 0.14) | RA 0.06 (0.07, 0.19) | OA 0.33 (0.28, 0.38) | RA 0.26 (0.12, 0.39) |
| Coronary heart disease              | OA 0.17 (0.09, 0.26) | RA 0.30 (0.09, 0.50) | OA 0.48 (0.41, 0.55) | RA 0.52 (0.36, 0.68) |
| Diabetes mellitus                   | OA 0.13 (0.04, 0.23) | RA 0.11 (0.17, 0.39) | OA 0.49 (0.42, 0.55) | RA 0.48 (0.30, 0.66) |
| Stroke/transient ischemic attack    | OA 0.21 (0.07, 0.35) | RA 0.34 (0.003, 0.68) | OA 0.41 (0.28, 0.54) | RA 0.60 (0.38, 0.82) |
| Chronic obstructive pulmonary disease | OA 0.23 (0.12, 0.35) | RA 0.20 (0.10, 0.50) | OA 0.44 (0.34, 0.54) | RA 0.36 (0.09, 0.64) |
| Depression                          | OA 0.07 (0.02, 0.15) | RA 0.23 (0.02, 0.47) | OA 0.47 (0.41, 0.53) | RA 0.53 (0.35, 0.70) |

* Values are the AP (95% confidence interval). The AP is calculated from a multinomial logistic regression model adjusted for age, sex, smoking, Townsend score, and body mass index.

We found evidence of additive interaction between OA, RA, and common comorbidities increasing the risk of frailty. Studies have suggested that the likelihood of frailty increases nonlinearly with increasing number of abnormal physiological systems (35). This may occur because of the interrelationship between physiological systems, and dysregulation in one system may potentially adversely impact on feedforward and feedback mechanisms, resulting in dysregulation in another system, with a consequent increase in likelihood of frailty (35). We observed a higher rate of change in FI over time among individuals with (versus without) OA, although not with RA. The reason for this is not clear, although the number of those with
RA was smaller compared to OA, with less precise estimates for the rate of change in Fl, which did not preclude a higher rate of change in RA (versus no RA). Strengths of our study include the large sample size and standardized methods of data collection. We were also able to look at frailty using 2 instruments. There are some limitations, however, that need to be considered in interpreting the data. The response rate for the UK Biobank study was low (5.5%), and participants are older, more likely to be female, and less likely to live in socioeconomically deprived areas compared to nonparticipants (22). This may potentially influence the occurrence of frailty and underlying comorbidities; however, given that our analysis was based on an internal comparison of responders, it is unlikely that any factors influencing participation would have influenced the strength of the underlying biological associations observed. Indeed, in a previous study using the cohort, it was shown that risk factor associations within the UK Biobank cohort are likely to be generalizable (36).

In our study, ascertainment of OA and RA was by self-report and is subject therefore to misclassification. Peeters et al in a systematic review of studies looking at self-report of both RA and OA in population studies reported a pooled sensitivity and specificity for OA of 0.75 and 0.89, respectively; while for RA, the pooled sensitivity was 0.88 and specificity 0.93 (37). These data are consistent, at least for RA, in the UK Biobank, where 87.8% of cases of self-reported RA had evidence of an RA code in linked electronic medical records (38). The effect of such misclassification would tend, if anything, to reduce the chance of finding significant associations and to bias any observed associations towards the null and to underestimate the magnitude of any association between arthritis and frailty. We were also unable to stratify by the site of the arthritis, as this was not included in the self-reported data.

In conclusion, we have shown that individuals with OA and RA are more likely to have frailty and more likely also to develop frailty. We also found that common comorbidities including cardiovascular disease and diabetes mellitus interact with both OA and RA to further increase the likelihood of frailty. Our data indicate that those with arthritis and these comorbidities are at higher risk of frailty and underscore the importance of targeted interventions to prevent and manage such comorbidities in these patients.

ACKNOWLEDGMENTS

The authors thank the participants of the UK Biobank study. The authors acknowledge the assistance given by IT Services and the use of the Computational Shared Facility at the University of Manchester.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. O’Neill had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Cook, Lunt, O’Neill.

Acquisition of data. Cook, Versstappen, Lunt, O’Neill.

Analysis and interpretation of data. Cook, Versstappen, Lunt, O’Neill.

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