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Patterns of multimorbidity and their effects on adverse outcomes in rheumatoid arthritis: a study of 5658 UK Biobank participants

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Abstract

Objective

To investigate how type and number of long-term conditions (LTCs) impact on all-cause mortality and major adverse cardiovascular events (MACE) in people with RA.

Design

Population-based cross-sectional cohort study.

Setting

UK Biobank.

Participants

UK Biobank participants (N=502,533) aged between 37 and 73 years old.

Primary outcome measures

Primary outcome measures were risk of all-cause mortality and MACE.

Methods

We examined the relationship between LTC count and individual comorbid LTCs (N=42) on adverse clinical outcomes in participants with self-reported RA (N=5658). Risk of all-cause mortality and MACE were compared using Cox's proportional hazard models adjusted for

lifestyle factors (smoking, alcohol intake, physical activity), demographic factors (sex, age, socioeconomic status), and rheumatoid factor.

Results

75.7% of participants with RA had multimorbidity and these individuals were at increased risk of all-cause mortality and MACE. RA and ≥4LTCs showed a three-fold increased risk of all-cause mortality (hazard ratio (HR) 3.30, 95% confidence interval (CI) 2.61-4.16), and MACE (HR 3.45, 95% CI 2.66-4.49) compared to those without LTCs. Of the comorbid LTCs studied, osteoporosis was most strongly associated with adverse outcomes in participants with RA compared to those without RA or LTCs: two-fold increased risk of all-cause mortality (HR 2.20, 95% CI 1.55-3.12) and three-fold increased risk of MACE (HR 3.17, 95% CI 2.27-4.64). These findings remained in a subset (N=3683) with RA diagnosis validated from clinical records or medication reports.

Conclusion

Those with RA and other LTCs, particularly comorbid osteoporosis, are at increased risk of adverse outcomes. These results are clinically relevant for the monitoring and management of RA across the healthcare system, and future clinical guidelines for RA should acknowledge the importance of multimorbidity.

Keywords

Rheumatoid arthritis, mortality, multimorbidity, comorbidity, cardiovascular

Strengths and limitations

- This is the first study to examine both comorbidity and multimorbidity in RA and the associations with mortality and major adverse cardiovascular events (MACE).
- We used data from 5658 participants in UK Biobank with RA, including detailed information on participant demographics, lifestyle factors and rheumatoid factor status to examine multimorbidity and comorbidity using 42 non-RA LTCs.
- These results provide crucial new information which should be incorporated into clinical guidelines and used to influence management of peoples with RA.
- This study was limited by lack of information on RA disease severity which may play a role in both outcomes measured.

Introduction

Rheumatoid arthritis (RA) is a debilitating, chronic autoimmune disease characterised by inflammation of the synovial joints. RA is associated with physical and socio-economic issues, including increased pain levels, reduced physical functioning, and early mortality[1-3]. Globally, whilst disability adjusted life years for RA have improved since 1990, age-standardised prevalence and incidence rates are increasing [4].

Between 60% and 75% of those with RA are reported to have multimorbidity – two or more long-term conditions (LTCs) - with higher number of LTCs reported with increasing age and disease activity [5 6]. Common comorbidities include cardiovascular conditions[7] such as coronary artery disease [8] and cardiac failure [9], as well as mental health conditions such as depression [10]. Cardiovascular disease (CVD) accounts for the majority of the excess mortality observed in RA, with raised inflammatory markers and shared risk factors implicated [11]. However, the effects of comorbidities in RA have generally been studied in isolation and less is known regarding the risks posed by multimorbidity when RA co-occurs with more than one other long-term physical or mental health LTC.

Through analysis of UK Biobank data, this paper aims to explore the effect of multimorbidity and a wide range of comorbid LTCs on all-cause mortality and major adverse cardiovascular events (MACE) in people with RA. Our objectives were to:

1. Compare the effect of LTC count on all-cause mortality in those with and without self-reported RA.

2. Compare the effect of LTC count on MACE in those with and without self-reported RA.

3. Evaluate the effect of individual co-morbid LTCs on the risk of all-cause mortality and MACE in participants with self-reported RA.

Patients and Methods

Study design and data collection

This study utilised data from UK Biobank, a longitudinal population-based cohort of 502533 participants, aged 37-73 years in Great Britain.[12] Data was collected between 2006-10 from recruitment centres in Scotland, England and Wales, and subsequently linked to mortality and hospitalisation outcomes. A subset of primary care data was available for 230105 participants. This study was covered by the generic ethics approval for UK Biobank studies from the NHS National Research Ethics Service (16/NW/0274).

Variables and outcome measures

UK Biobank collected information on a wide range of demographic, health-based lifestyle and self-reported LTC questions through self-administered touch screen questionnaire and nurse-led interview. These include age, sex, socioeconomic status (measured using Townsend score, a UK area-based measure of deprivation) [13], smoking status, frequency of alcohol intake, body mass index (BMI), level of physical activity and number of LTCs.

Age was categorised into bands of 37-49, 50-59 and 60-73 years. Sex was a binary categorical variable. Smoking status was categorised into "never" or "current or previous". Frequency of alcohol intake was categorised into four groups, "Never or special occasions only", "One to three times a month", "One to four times a week" or "Daily or almost daily". BMI was categorised into four groups based on WHO BMI guidelines [14]: "underweight <18.5", "normal weight 18.5-24.9", "overweight 25-29.9" and "obese ≥30". Level of physical activity was defined as "none", "low", "medium", or "high" using Metabolic Equivalent Task (MET) scores data based on International Physical Activity Questionnaire (IPAQ) scoring protocol (available from https://sites.google.com/site/theipaq/scoring-protocol).

Rheumatoid factor was ascertained through participant blood samples and categorised into positive and negative status, with rheumatoid factor <20IU/ml considered negative, and values above this considered positive (by manufacturer specification, available at https://www.beckmancoulter.com/wsrportal/techdocs?docname=/cis/988646/%%/RF_988646-%25%25_English.pdf). Participants whose rheumatoid factor was labelled as "not reportable at assay (too low)" were considered to be rheumatoid factor negative. Similarly, those labelled "not reportable at assay (too high)" were considered rheumatoid factor positive.

The list of 42 LTCs considered was based on previous work in UK Biobank [15 16], the number of LTCs reported, apart from RA, were summed and then categorised as 0, 1, 2-3 and ≥4 LTCs. RA and all LTCs in UK Biobank are based on self-report using a questionnaire and nurse-led interview asking for existing diagnoses.

All-cause mortality was calculated using data linkage to national mortality registers. MACE were calculated using stroke and myocardial infarction (MI) hospitalisation event data from UK Biobank, and using ICD-10 mortality codes: "I00-I78", "G45", "G451-G454", "G456", "G458", "G459", and "G460-G468". The median follow-up time of both outcome measures was nine years.

A sensitivity analysis of self-report RA by participants was performed by examining four other indicators of RA: any primary care RA Read code, any secondary care RA hospitalisation code, self-reporting of any common RA drugs or any primary care prescription record of RA drugs (as shown in Supplementary Table 2). Both prospective and retrospective data were used: primary care Read codes were available for a maximum period of January 1991 and December 2017, and primary care prescriptions were between January 1991 and December 2016; the time period for each participant varied, depending on records held. Participants were considered to have confirmed RA if they had a positive record for one or more of these indicators. This

analysis was performed on a subset (74%) of participants who self-reported RA for whom primary care data in UK Biobank was available (N=4196/5658).

Statistical methods

In line with previous UK Biobank studies, $\chi 2$ tests were utilised for both categorical data and ordinal data. Kruskal–Wallis tests were used for continuous data [17]. Similarly, we used $\chi 2$ testing to examine differences in proportion of individual LTCs between those with and without RA. Age-adjusted Cox's proportional hazards tests were used to examine the relationship between LTC count / type of LTCs with all-cause mortality and MACE as outcome variables in those with and without RA. The model was further adjusted for demographic and lifestyle factors as described above. Among those with RA, cumulative hazards-based Kaplan-Meier plots were used to display proportion of events (all-cause mortality or MACE) in participants with 0, 1, 2-3 and ≥4 co-morbid LTCs. To measure the contribution of individual index LTCs towards all-cause mortality and MACE in those with and without RA, we created a categorical variable that assigned participants to one of four groups: those with neither RA nor the index condition (reference group), those with RA but not the index LTC (RA only), those with no RA with the index LTC (index LTC only), and those with both RA and the index LTC. This variable was used as an outcome measure in an age-adjusted Cox's proportional hazards model controlling for demographic factors, lifestyle factors and rheumatoid factor status. To calculate the interaction between RA and each index LTC, we used an ANOVA to measure p values between two Cox's proportional hazards models: the first containing RA and the index LTC, and the second containing RA, the index LTC and an interaction term between RA and the index LTC. Interaction terms were considered significant when $p<0.01$.

Results

5658 UK Biobank participants (1.1%) reported having RA. Lifestyle and demographic characteristics of participants with and without self-reported RA are shown in Table 1. Participants with RA were significantly more likely to be older, female, have lower socioeconomic status, be current or previous smokers, have a lower frequency of alcohol intake, have a BMI ≥30, have lower levels of physical activity, and have larger numbers of co-morbid LTCs. $\chi 2$ testing showed participants with self-reported RA were significantly more likely to have rheumatoid factor positive status: 35.6% had rheumatoid factor levels of over 20 IU/ml – compared with 3.6 % in those without RA.

Prevalence of LTCs in people with RA

Proportions of number of LTCs in participants with and without RA are shown in Table 1. Reporting multiple long-term conditions was more common in those with RA: 34.5% had 2-3 LTCs (27.1% in those without RA), and 11.1% had ≥ 4 LTCs (4.9% in those without RA). Overall, 75.7% of people with RA were noted to be multimorbid. The difference in comorbidity experienced by those with and without RA is shown in Supplementary Table 1. Those with RA reported proportionately higher numbers of physical and mental health-based LTCs, namely: cardiovascular LTCs including hypertension, coronary heart disease, and stroke or transient ischemic attack; pulmonary LTCs including asthma, COPD and chronic bronchitis; digestive system LTCs including dyspepsia, irritable bowel syndrome and inflammatory bowel disease; musculoskeletal conditions including osteoporosis; and mental-health based LTCs including depression.

All-cause mortality and LTCs in people with RA

We examined the outcomes associated with different LTC counts in participants with RA using a Kaplan Meier plot (Supplementary Figure 1). There was an increased proportion of all-cause mortality in participants with RA concurrent with increasing multimorbidity counts: 4.2%

(N=58) in those with no additional LTCs, 5.3% (N=91) in those with 1 additional LTC, 9.9% (N=194) in those with 2-3 additional LTCs and 14.4% (N=90) in those with ≥4 additional LTCs during the follow up period (median 9 years).

To quantify the effect of LTC count on all-cause mortality, we performed a Cox's proportional hazards test controlling for lifestyle factors, demographic factors and rheumatoid factor in participants with and without self-reported RA using a stepwise model adjustment (Table 2). Participants with RA and no additional LTCs had a significant increase in all-cause mortality when using an age-adjusted Cox's proportional hazards model fully adjusting for additional lifestyle and demographic factors (Hazard Ratio (HR) 1.59, 95% confidence intervals (CI) 1.21-2.08) compared to those without RA or any LTCs. Whilst controlling additionally for rheumatoid factor status appeared to show some attenuation of all-cause mortality risk, a statistically significant risk for this group remained (HR 1.39, 95% CI 1.05-1.84) when compared to those without RA or any LTCs. When examining additional co-morbid LTCs alongside RA, there appeared to be a dose-based response all-cause mortality risk, with a 44% increased risk of all-cause mortality in those with RA and one other LTC (HR 1.44, 95% CI 1.14-1.81), an approximately two-and-a-half-fold increased risk for RA with 2-3 other LTCs (HR 2.48, 95% CI 2.12-2.90) and an over three-fold increased risk associated for RA with ≥4 other LTCs (HR 3.30, 95% CI 2.61-4.16) compared to those without RA or any LTCs in the fully adjusted models, which included rheumatoid factor. A dose-based response was also observed in the non-RA population: those with 1 LTC had a 39% increased risk of death (HR 1.39, 95% CI 1.33-1.46), and those with ≥4 were at a two-and-a-half-fold increased risk (HR 2.69 95% CI 2.54-2.85) compared with participants without RA or any LTCs.

MACE and LTCs in people with RA

We next investigated the effect of LTC count on MACE in participants with RA using a Kaplan Meier plot (Supplementary Figure 2). For RA and no additional LTCs, 3.3% (N=46) of participants had a recorded MACE event, compared with 4.6% of participants with RA and one additional LTC (N=78), 6.7% those with RA and 2-3 additional LTCS (N=131), and almost four times as many proportionately in participants with RA and ≥4 LTCs (11.7%, N=73 events) over the follow-up period.

Table 3 shows the risk of MACE for participants with and without RA using age-adjusted multivariate Cox's proportional hazards regression models. There was a 63% increased hazard of MACE for participants with RA and no other LTCs compared with participants without RA or any LTCs (HR 1.63, 95% CI 1.21-2.21) in a fully adjusted model including demographic factors, lifestyle factors and rheumatoid factor status. This remained significant for people with RA with increasing LTCs count, with a 86% increased risk of MACE in participants with one other co-occurring LTC (HR 1.86, 95% CI 1.31-2.15), an over two-fold increase in those with 2-3 co-occurring LTCs (HR 2.09, 95% CI 1.73-2.54) and an almost three-and-a-half-fold increase in MACE for those with ≥4 LTCs (HR 3.39, 95% CI 2.61-4.40), compared to those without RA or any LTCs. This relationship was similar but to a lesser degree for participants without RA, with those with 1 LTC at 24% increased risk (HR 1.24, 95% CI 1.19-1.31), those with 2-3 LTCs at a 66% increased risk (HR 1.66, 95% CI 1.59-1.74) and those with ≥4 LTCs at over two times risk (HR 2.37 95% CI 2.23-2.53) of MACE compared with those without LTCs.

Contribution of individual LTCs to all-cause mortality and MACE in people with RA

Using an age-adjusted Cox's proportional hazards model, adjusting for demographic factors, lifestyle factors and rheumatoid factor status, we investigated the role individual LTCs play in

risk of all-cause mortality and MACE, using participants with no RA and no index condition as the reference group (Table 4 and 5).

The presence of cardiovascular-based LTCs appeared to be a risk factor in those with RA for both all-cause mortality and MACE. Compared to those with no RA and no hypertension, RA with hypertension showing an over one-and-a-half-fold increased risk of all-cause mortality (HR 1.59, 95% CI 1.37-1.86) and an approximately two-fold increased risk of MACE (HR 2.07, 95% CI 1.64-2.33).

Similarly, heart disease was associated with an over two-fold increase for both all-cause mortality (HR 2.07, 95% CI 1.63-2.63) and MACE (HR 2.28 95% CI 1.76-2.98) in those with RA compared to those with no RA and no heart disease. However, there was no evidence of interaction between RA and either cardiovascular condition. Whilst thyroid disorders showed no significant increased risk of all-cause mortality, they displayed an over two-fold increased risk of MACE (HR 2.10, 95% CI 1.50-2.93) in those with RA compared to those without RA or thyroid disease but again there was no significant interaction between RA and thyroid disease and MACE event.

The co-occurrence of osteoporosis in participants with RA appeared to strongly influence both mortality and MACE; more than doubling all-cause mortality (HR 2.20, 95% CI 1.55-3.12), and resulting in an over three times higher risk of MACE (HR 3.17, 95% CI 2.17-4.64) compared to those without RA or osteoporosis. This increased risk in those with both RA and osteoporosis was greater than in those with RA but no osteoporosis or those with osteoporosis but no RA. Interaction terms for RA and osteoporosis showed no significant interaction with all-cause mortality ($p=0.10$) but displayed a significant interaction with MACE ($p<0.01$), suggesting a multiplicative effect in the association with MACE.

Sensitivity analysis of RA self-report

To investigate sensitivity of self-report by participants with RA, was examined the proportion of people with any primary care RA Read code, any secondary care RA hospitalisation code, self-reporting of any common RA drugs and any primary care prescription record of RA drugs (see supplementary table 2) for participants who had self-reported RA and had available primary care data available in UK Biobank (N=4196). Medications used here were previously reported by Siebert et al.[17] Using this method, we were able to identify RA medications, hospitalisations or primary care Read code in 3683 (87.8%) participants (Supplementary Table 3). Analysis performed in this study was repeated in these participants and showed the same relationships as those reported above in N=5658 with self-report RA, with only small changes in HR observed (Supplementary Tables 4-8).

Discussion

Within UK Biobank, multiple LTCs was common in participants with RA, with approximately 75.7% reporting multimorbidity and 45% of participants reporting two or more additional LTCs alongside RA. In our fully adjusted modes, increasing LTC count was associated with increased mortality and MACE in people with RA. When examining individual LTCs, we observed hypertension, heart disease, osteoporosis and thyroid disorders to increase risk of adverse outcomes. Of these, osteoporosis was associated with one of the largest increases in both adverse outcomes measured: participants with both RA and osteoporosis were at over three times the risk of all-cause mortality and two times the risk of compared to those with neither LTC. The negative effect of having both RA and osteoporosis was particularly evident in MACE outcomes, for which there was a significant interaction between RA and osteoporosis, suggesting a multiplicative effect on MACE of having both these conditions together. The presence of hypertension or heart disease alongside RA increased the risk of mortality and MACE, in keeping with previous literature [18] [19], but there was no evidence of statistical interaction.

To the best of our knowledge, this paper is the first to compare LTC count and type of comorbid LTCs and their association with all-cause mortality and MACE in men and women with RA after adjusting for a wide range of sociodemographic and lifestyle variables along with rheumatoid factor status. In our study, increasing LTC count resulted in adverse outcomes in participants with RA, with an increased rate of all-cause mortality and MACE.

We have shown that multimorbidity is common in participants with RA, with around 75% of participants with RA reporting one or more additional LTCs. This is in agreement with reported comorbidity rates of between 60% and 75% in those with RA [5 6], although these studies typically examined a smaller number of LTCs than in this study. We have shown participants with RA and 2-3 other LTCs were at over twice the risk of all-cause mortality, whilst those with ≥ 4 more were over three times the risk compared to participants with no LTCs. This data provides evidence for the first time the increased risk of all-cause mortality in men and women with RA and multimorbidity. While previous work has highlighted an increased risk of mortality in RA patients [20 21], or specific comorbidities alongside RA – for example in COPD [22] and depression [10] – these studies did not examine the effect of LTC count. One matched cohort study used a multimorbidity weighted index to study the effect of multimorbidity on mortality, but only examined effects in women [23]. Another examined LTCs using the Charlson comorbidity index [24] , however this measure uses only 19 LTCs and the study examined only all-cause mortality outcomes. Our study is the first study of its type to link multimorbidity in RA with MACE outcomes. Existing research has highlighted that RA increases the risk of cardiovascular events, and that individual LTCs such as diabetes and hypertension are risk factors [25], however, to date, no study has shown an association between multimorbidity and MACE outcomes in people with RA. Collectively, the results presented here report for the first time the magnitude of adverse outcomes associated with multimorbidity in those with RA.

In keeping with previous studies,[26] we have shown that osteoporosis prevalence is increased in those with RA compared to those without RA. The results presented in this paper, however, are the first to link osteoporosis in those with RA to increased risk of adverse outcomes and the first to show significant interaction between both conditions and MACE outcomes. The reasons for this association are not clear and cannot be extrapolated from the available data, which does not include factors such as disease severity or duration. One possibility may be that corticosteroids and RA disease activity play a role: corticosteroids are associated with increased prevalence of osteoporosis; people with RA with higher levels of disease activity are more likely to receive corticosteroids; both corticosteroid use and increased RA disease activity are reported to be associated with worse outcomes in mortality and MACE [27 28].

Our study therefore has several strong clinical implications. Current NICE guidelines for RA suggest annual checks for the development of hypertension, ischemic heart disease, osteoporosis and depression in RA [29], but do not highlight the increased risk of the co-occurrence of these LTCs with RA nor the risk posed by multimorbidity in general. In addition, we have shown a greatly increased risk of adverse outcomes in people with osteoporosis and RA that merits further investigation.

Our study has several key strengths: UK Biobank is a large population-based study with several thousand participants reporting RA; the study setting encompasses three countries within the UK (Scotland, England and Wales); it includes details of participant demographic and lifestyle factors as well as rheumatoid factor levels, which allowed us to adjust for variables, which have not been explored in previous studies.

Our study is limited by self-reporting of RA and LTCs by these participants; however, recent studies have shown that self-report is a reliable method for reporting RA [30] and in this study we additionally used four RA indicators (any primary care RA Read code, any secondary care

RA hospitalisation code, self-reporting of any common RA drugs and any primary care prescription record of RA drugs) to validate self-reported RA. We performed a sensitivity analysis using the subset of participants who had validated RA. Using this validation approach, we found a positive verification rate (participants self-reporting RA with further RA indicators) of 87.8% (N=3683). Re-analysis of the subset of participants with RA (Supplementary Tables 4-8) who had a validated RA report (N=3683) showed only small changes to Cox's proportional hazards models, and observed effects were in agreement with the population who self-reported RA. This provides confidence in our findings that we are examining a true RA population. Furthermore, we were unable to determine the severity or duration of RA in participants, or their previous medications.

Rheumatoid factor positive status in those self-reporting RA (35.6%) was lower than expected, however still a significantly higher proportion than in the UK Biobank population who did not report RA (3.6%). Analysis of rheumatoid factor in those who had RA primary care Read codes, prescriptions or hospitalisations (described above) showed an increased proportion of positive rheumatoid factor (47.6%), but this level remained below previously reported proportions in RA populations. However, our validation of self-report RA suggests that we can be confident that we have a high level of true RA included, regardless of rheumatoid factor levels.

Participants in UK Biobank are known to be less deprived than the wider UK population [31], suggesting that the level of multimorbidity reported here; and resulting associations are likely to be conservative in nature.

Conclusions

Multimorbidity is common in people with RA and is associated with increased risk of all-cause mortality and MACE. Certain comorbidities such as osteoporosis merit specific attention, in

view of their association with adverse outcomes; it will be important to test whether this association is replicated in other datasets and if so, to explore the underpinning mechanisms. As multimorbidity has been shown here to influence outcomes for those with RA, forthcoming work will examine which clusters of LTCs most strongly drive this increased risk of poor outcomes. Future clinical guidelines for RA should acknowledge the importance of multimorbidity when considering management planning and patient outcomes.

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Ethical approval

All participants gave informed consent for data provision and linkage. UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274).

Competing interests

None declared.

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Data sharing statement

The data used in this study are available via a direct application to UK Biobank.

Author contributions

This study was conceived by BN, FSM, SS, BJ and CM. The analysis was conducted by RM, BN and BJ. All authors (RM, BJ, BN, JC, SM, CM, JN, SB, FSM, SS) contributed to design, interpretation and discussion of all analysis. RM wrote this manuscript. All authors (RM, BJ, BN, JC, SM, CM, JN, SB, FSM, SS) edited, reviewed and commented on all versions of this manuscript. All authors read the manuscript draft and approved the final submission.

Patient and Public Involvement

The study was supported by a patient advisory group which provided input to the programme of research. This patient advisory group met on a regular basis for the duration of the study. Patients partnered with us and helped design research questions.

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Figure legends

Supplementary figure 1 – Kaplan-Meier plot of proportion of all-cause mortality during the follow-up period (median 108 months) for participants with RA and no LTCS (black line), RA and 1 LTC (red line), RA and 2-3 LTCs (green line) and RA and ≥4 LTCs (blue line).

Supplementary figure 1 – Kaplan-Meier plot of proportion of MACE during the follow-up period (median 108 months) for participants with RA and no LTCS (black line), RA and 1 LTC (red line), RA and 2-3 LTCs (green line) and RA and ≥4 LTCs (blue line).

Tables

Table 1 – Demographic factors, lifestyle factors, number of long-term conditions and rheumatoid factor status in patients with and without rheumatoid arthritis. Unless indicated, $p<0.01$. $\chi 2$ test was used for categorical variables, Kruskal-Wallis test was used for continuous variables. SD = standard deviation.

	Participants with RA (%) (N=5658)	**Participants without RA (%) (N=496882)**
Mean Age (years (SD)); missing values =0 (0%)	59.3 (7.1)	56.5 (8.1)
Age (years); missing values = 0 (0%)		
37-49	675 (11.9%)	117209 (23.6%)
50-59	1800 (31.8%)	165359 (33.3%)
60-73	3183 (56.3%)	214314 (43.1%)
Sex; missing values = 0 (0%)		
Female	3952 (69.8%)	269452 (54.2%)
Male	1706 (30.2%)	227430 (45.8%)
Townsend score; missing values = 623 (0.12%)		
0-20 (least deprived)	998 (17.7%)	99665 (20.1%)
20-40	980 (17.4%)	99117 (20%)
40-60	1087 (19.2%)	99311 (20%)
60-80	1154 (20.4%)	99224 (20%)
80-100 (most deprived)	1429 (25.3%)	98952 (19.9%)
Smoking status; missing values = 2950 (0.59 %)		
Never	2625 (46.8%)	270916 (54.8%)
Current or Previous	2983 (53.2%)	223066 (45.2%)
Frequency of alcohol intake; missing values = 1502 (0.30 %)		
Never or special occasions only	1830 (32.4%)	96832 (19.5%)
One to three times a month	690 (12.2%)	55170 (11.1%)
One to four times a week	2315	242428

	(41%)	(48.9%)
Daily or almost daily	811 (14.4%)	100962 (20.4%)
BMI (kg/m²); missing values = 5820 (1.15 %)		
underweight <18.5	50 (0.9%)	2576 (0.5%)
normal weight 18.5-24.9	1543 (27.9%)	155896 (31.7%)
overweight 25-29.9	2194 (39.6%)	212032 (43.2%)
obese ≥30	1750 (31.6%)	120679 (24.6%)
Physical activity; missing values = 7156 (1.42 %)		
none	814 (14.8%)	32035 (6.5%)
low	409 (7.4%)	18531 (3.8%)
medium	4111 (74.5%)	389412 (79.5%)
high	182 (3.3%)	49890 (10.2%)
Number of long-term conditions; missing values = 1845 (0.36 %)		
0	1369 (24.3%)	173846 (35.1%)
1	1690 (30.0%)	162657 (32.9%)
2-3	1943 (34.5%)	134403 (27.1%)
≥4	623 (11.1%)	24157 (4.9%)
Rheumatoid Factor (IU/ml); missing values = 33,066 (6.6 %)		
<20	3396 (64.4%)	447472 (96.4%)
>20	1879 (35.6%)	16720 (3.6%)

Table 2 Relationship between long term conditions and all-cause mortality in participants with and without self-reported RA using age-adjusted multivariate Cox's proportional hazards regression analysis. Unless otherwise shown, Cox's proportional hazards p<0.01.

		Risk of all-cause mortality				
Comorbidity status (reference: *No RA and no other long-term conditions*)		**Adjusted for sex and Townsend score HR (95% CI)**	**Adjusted for sex, Townsend score, alcohol status and smoking status HR (95% CI)**	**Adjusted for sex, Townsend score, alcohol status, smoking status, BMI and physical activity HR (95% CI)**	**Adjusted for sex, Townsend score, alcohol status, smoking status, BMI, physical activity and rheumatoid factor status HR (95% CI)**	**Number of deaths (%)**
No other long-term conditions	**RA**	1.84 (1.42-2.38)	1.72 (1.32-2.2)	1.59 (1.21-2.08)	1.39 (1.05-1.84)	58 (4.2%)
1 other long-term condition	**No RA**	1.45 (1.39-1.51)	1.42 (1.36-1.48)	1.40 (1.34-1.47)	1.39 (1.33-1.46)	5785 (3.6%)
	RA	2.01 (1.64-2.48)	1.88 (1.53-2.32)	1.72 (1.38-2.14)	1.44 (1.14-1.81)	91 (5.4%)
2-3 other long-term conditions	**No RA**	2.03 (1.95-2.11)	1.92 (1.84-2.00)	1.84 (1.77-1.92)	1.83 (1.75-1.91)	7914 (5.9%)
	RA	3.32 (2.87-3.84)	2.99 (2.59-3.46)	2.79 (2.40-3.24)	2.48 (2.12-2.90)	194 (10.0%)
≥4 other long-term conditions	**No RA**	3.39 (3.22-3.57)	3.04 (2.88-3.20)	2.71 (2.56-2.86)	2.69 (2.54-2.85)	2605 (10.8%)
	RA	4.68 (3.80-5.78)	3.95 (3.19-4.89)	3.52 (2.81-4.40)	3.30 (2.61-4.16)	90 (14.4%)

Table 3 Relationship between long term conditions and major adverse cardiovascular events in participants with and without self-reported RA using age-adjusted multivariate Cox's proportional hazards regression analysis. Unless otherwise shown, Cox's proportional hazards p<0.01.

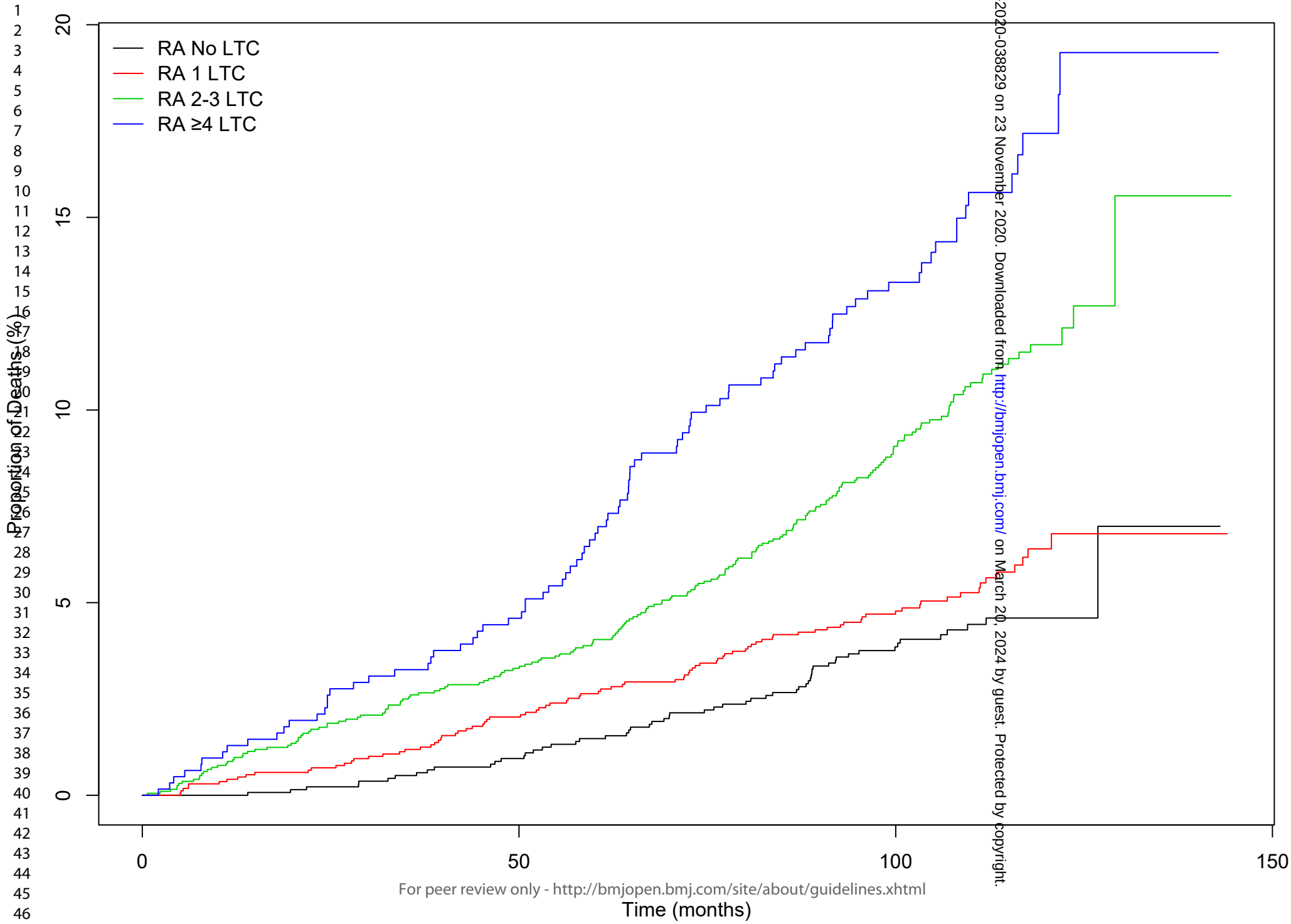
Risk of MACE						
Comorbidity status (reference: *No RA and no other long-term conditions*)		**Adjusted for sex and Townsend score HR (95% CI)**	**Adjusted for sex, Townsend score, alcohol status and smoking status HR (95% CI)**	**Adjusted for sex, Townsend score, alcohol status, smoking status, BMI, and physical activity HR (95% CI)**	**Adjusted for sex, Townsend score, alcohol status, smoking status, BMI, physical activity and rheumatoid factor status HR (95% CI)**	**Number of MACE (%)**
No other long-term conditions	**RA**	1.79 (1.33-2.39)	1.69 (1.26-2.27)	1.64 (1.21-2.20)	1.63 (1.21-2.21)	46 (3.4%)
1 other long-term condition	**No RA**	1.30 (1.24-1.36)	1.28 (1.22-1.34)	1.26 (1.20-1.320	1.24 (1.19-1.31)	4512 (2.8%)
	RA	2.08 (1.66-2.61)	1.91 (1.52-2.41)	1.87 (1.48-2.35)	1.68 (1.31-2.15)	78 (4.6%)
2-3 other long-term conditions	**No RA**	1.86 (1.78-1.94)	1.78 (1.70-1.86)	1.67 (1.60-1.75)	1.66 (1.59-1.74)	6208 (4.6%)
	RA	2.72 (2.28-3.24)	2.49 (2.09-2.98)	2.19 (1.82-2.64)	2.09 (1.73-2.54)	131 (6.7%)
≥4 other long-term conditions	**No RA**	3.04 (2.87-3.22)	2.76 (2.60-2.93)	2.40 (2.26-2.56)	2.37 (2.23-2.53)	1980 (8.2%)
	RA	4.79 (3.79-6.04)	4.07 (3.21-5.16)	3.52 (2.73-4.52)	3.39 (2.61-4.40)	73 (11.7%)

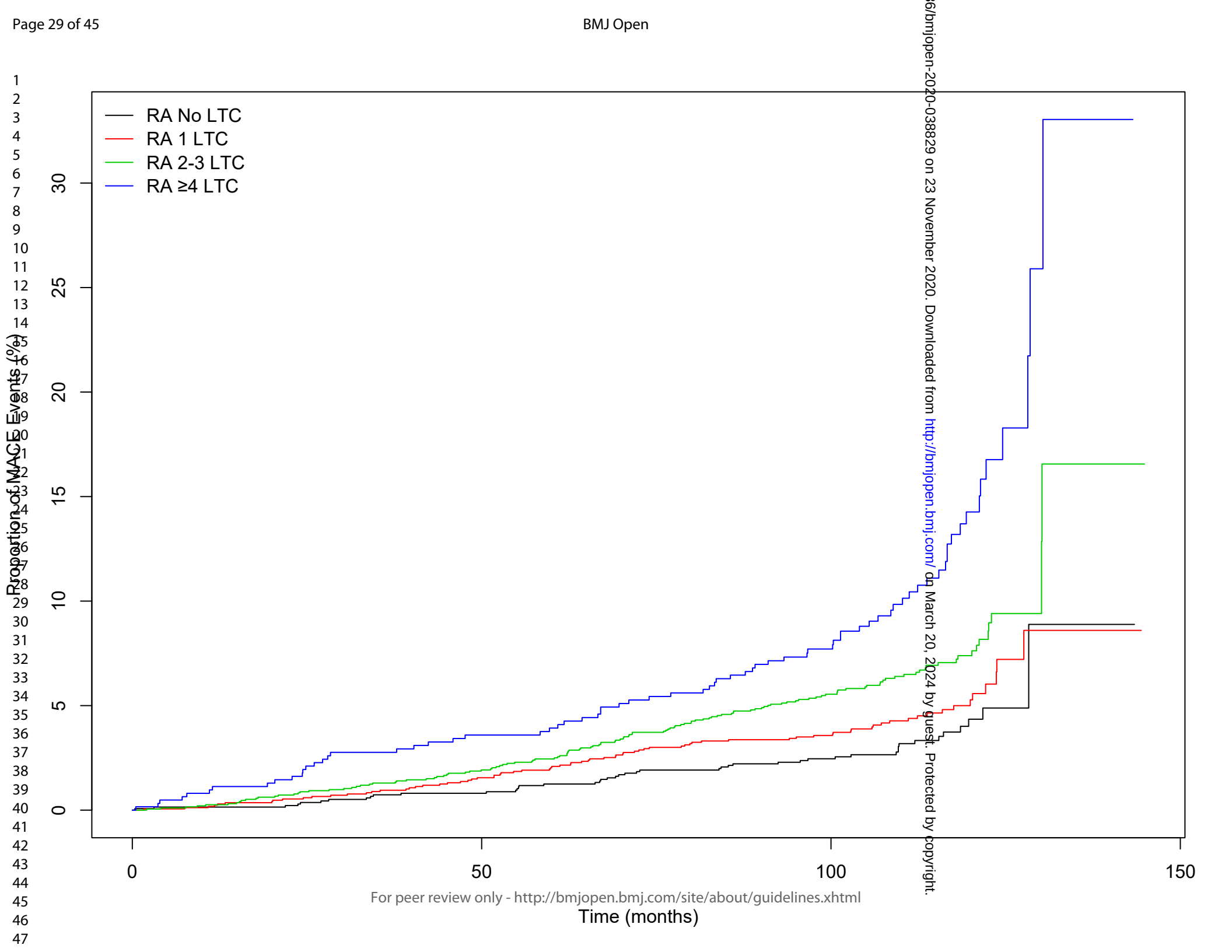
Table 4 Risk of all-cause mortality for individual index conditions in patients with RA and no index condition, RA with index condition, RA with no index condition and RA and index condition. Age-adjusted Cox's proportional hazards models were adjusted for sex, Townsend score, smoking status, alcohol intake frequency, BMI, physical activity level and rheumatoid factor status. Unless otherwise shown, Cox's proportional hazards p<0.01. Index conditions labelled * have interaction term p>0.01

	Risk of all-cause mortality			
Index condition	**No RA, no index condition HR, (95% CI), p**	**No RA, with index condition HR, (95% CI), p**	**RA, no index condition HR, (95% CI), p**	**RA and index condition HR, (95% CI), p**
Hypertension	1	1.24 1.21-1.28	1.29 1.11-1.48	1.59 1.37-1.86
Coronary heart disease	1	1.57 1.50-1.65	1.26 1.12-1.42	2.07 1.63-2.63
Diabetes	1	1.68 1.60-1.75	1.33 1.18-1.48	1.83 1.37-2.44
Asthma	1	1.10 1.05-1.15	1.27 1.13-1.42	1.56 1.22-2.00
Dyspepsia	1	1.01 0.97-1.06 p=0.47	1.27 1.14-1.43	1.45 1.10-1.90
Cancer	1	2.50 2.41-2.59	1.35 1.20-1.52	3.04 2.39-3.86
Depression	1	1.27 1.20-1.35	1.29 1.15-1.44	1.71 1.21-2.42
Thyroid disorder	1	1.05 0.98-1.12 p=0.11	1.32 1.18-1.47	1.14 0.80-1.62 p=0.46
COPD	1	2.11 1.98-2.49	1.26 1.13-1.42	2.68 2.00-3.58
Epilepsy	1	1.81 1.42-1.82	1.29 1.15-1.43	2.86 1.43-5.73
Migraine	1	0.85 0.76-0.94	1.29 1.16-1.44	1.09 0.55-2.19 p=0.79
Psoriasis /Eczema	1	1.05 0.98-1.14 p=0.16	1.27 1.14-1.42	1.88 1.20-2.95
Prostate disease	1	0.83 0.76-0.90	1.30 1.17-1.45	0.90 0.43-1.90 p=0.79
Osteoporosis	1	1.26 1.14-1.39	1.25 1.12-1.40	2.20 1.55-3.12
Atrial fibrillation	1	1.40 1.45-1.57	1.30 1.17-1.45	1.32 0.50-3.52 p=0.58
Anxiety	1	1.22 1.10-1.35	1.30 1.16-1.44	1.48 0.67-3.30 p=0.34
Inflammatory bowel disease	1	1.37 1.20-1.57	1.30 1.17-1.44	1.30 0.54-3.11 p=0.56
Heart failure	1	2.69 2.22-3.25	1.29 1.16-1.43	5.14 2.14-12.38

Table 5 Risk of MACE for individual index conditions in patients with RA and no index condition, RA with index condition, RA with no index condition and RA and index condition. Age-adjusted Cox's proportional hazards models were adjusted for sex, Townsend score, smoking status, alcohol intake frequency, BMI, physical activity level and rheumatoid factor status. Unless otherwise shown, p<0.01. Index conditions labelled * have interaction term p>0.01

	Risk of MACE			
	No RA, no index condition HR, (95% CI), p	**No RA, with index condition HR, (95% CI), p**	**RA, no index condition HR, (95% CI), p**	**RA and index condition HR, (95% CI), p**
Index condition				
Hypertension	1	1.50 1.44-1.55	1.48 1.25-1.75	1.97 1.66-2.33
Coronary heart disease	1	1.89 1.80-1.98	1.43 1.45-1.63	2.28 1.76-2.98
Diabetes	1	1.67 1.58-1.75	1.49 1.31-1.69	1.69 1.19-2.39
Asthma	1	1.12 1.06-1.18	1.43 1.25-1.63	1.47 1.09-1.98
Dyspepsia	1	1.14 1.08-1.20	1.39 1.22- 1.58	1.85 1.30-2.34
Cancer	1	1.11 1.04-1.17	1.43 1.26-1.62	1.44 0.98-2.11 p=0.07
Depression	1	1.25 1.17-1.34	1.39 1.22-1.58	2.06 1.41-3.00
Thyroid disorder	1	1.14 1.03-1.23	1.37 1.20-1.55	2.10 1.50-2.93
COPD	1	1.49 1.37-1.62	1.40 1.24-1.59	1.97 1.33-2.92
Epilepsy	1	1.50 1.30-1.73	1.41 1.21-1.60	2.21 0.83-5.88 p=0.11
Migraine	1	0.99 0.89-1.12 p=0.97	1.40 1.23-1.58	2.08 1.12-3.87
Psoriasis /Eczema	1	1.05 0.96-1.14 p=0.25	1.42 1.26-1.61	1.23 0.64-2.37 p=0.53
Prostate disease	1	0.92 0.83-1.00 p=0.07	1.41 1.25-1.60	1.27 0.64-2.54 p=0.50
Osteoporosis*	1	1.34 1.18-1.53	1.25 1.10-1.41	3.17 2.17-4.64
Atrial fibrillation	1	1.41 1.25-1.60	1.72 1.53-1.93	2.67 1.99-5.95
Anxiety	1	1.28 1.14-1.43	1.40 1.24-1.59	2.73 1.30-5.72
Inflammatory bowel disease	1	1.09 0.92-1.29 p=0.32	1.42 1.26-1.60	1.11 0.36-3.44 p=0.85
Heart failure	1	2.64 2.15-3.24	1.41 1.25-1.59	3.45 1.11-10.70 p=0.03





Tables

Supplementary table 1 – Proportion of long term conditions in participants with and without RA. P value determined using $\chi 2$ testing.

Condition	Prevalence in RA participants (%)	Prevalence in non-RA participants (%)	p value
Hypertension	**35·6**	**26·4**	**<0·01**
Asthma	**15·4**	**11·6**	**<0·01**
Dyspepsia	**11·3**	**7·7**	**<0·01**
Thyroid disorder	**9·5**	**5·8**	**<0·01**
Cancer	**8·7**	**7·7**	**<0·01**
Coronary heart disease	**8·2**	**4·5**	**<0·01**
Diabetes	**7·6**	**5·0**	**<0·01**
Depression	**7·0**	**5·6**	**<0·01**
Osteoporosis	**4·9**	**1·5**	**<0·01**
Chronic obstructive pulmonary disease	**4·4**	**1·6**	**<0·01**
Psoriasis/eczema	4·1	3·5	0·03
IBS	**3·3**	**2·3**	**<0·01**
Migraine	3·2	2·9	0·04
Stroke/TIA	**3·1**	**1·7**	**<0·01**
Diverticular disease	**2·2**	**1·1**	**<0·01**
Anxiety	1·7	1·8	0·47
IBD	**1·4**	**0·8**	**<0·01**
Prostate disease	1·3	1·6	0·06
Pernicious anaemia	**1·2**	**0·3**	**<0·01**
Glaucoma	1·2	1·1	0·26
Epilepsy	1·2	0·8	0·38
Endometriosis	0·9	0·8	0·39
Atrial fibrillation	0·9	0·7	0·14
Peripheral vascular disease	**0·9**	**0·3**	**<0·01**
Chronic bronchitis	**0·8**	**0·3**	**<0·01**
Chronic sinusitis	0·8	0·6	0·34
Meniere's disease	**0·7**	**0·3**	**<0·01**
Chronic kidney disease	0·5	0·3	0·01
Chronic liver disease	**0·4**	**0·2**	**<0·01**
Schizophrenia	0·4	0·4	0·68
Chronic fatigue syndrome	0·4	0·4	0·42
Alcohol problems	0·4	0·2	0·02
Viral hepatitis	0·3	0·3	0·91
Heart failure	0·3	0·2	0·18
Polycystic ovary syndrome	0·2	0·1	0·08
Multiple sclerosis	0·2	0·4	0·03
Parkinson's disease	0·1	0·2	0·71
Constipation	0·1	0·1	0·81
Dementia	0·1	0·02	0·17
Anorexia/bulimia	0·1	0·1	0·80

Psychoactive substance misuse	0·03	0·02	0·30

Supplementary table 2 –Medications, primary care read codes and hospitalisation codes used for RA self-report verification

Medications	Primary care read codes	Hospitalisation ICD-10 codes
Depomedrone	14G1	M05
Triamcinilone	F3712	M06
Methylprednisolone	F3964	
Prednisolone	G5yA.	
Prednisone	G5y8.	
Auranofin	H570.	
Azathioprine	N04..	
Hydroxychloroquine	N040.	
leflunomide	N0400	
Methotrexate	N0401	
Myocrisin	N0402	
Penicillamine	N0403	
Sulfasalazine	N0404	
Abatacept	N0405	
Adalimumab	N0406	
Certolizumab	N0407	
Etanercept	N0408	
Golimumab	N0409	
Infliximab	N040A	
Rituximab	N040B	
Tocilizumab	N040C	
	N040D	
	N040E	
	N040F	
	N040G	
	N040H	
	N040J	
	N040K	
	N040L	
	N040M	
	N040N	
	N040P	
	N040Q	
	N040R	
	N040S	
	N040T	
	N041.	
	N042.	
	N0421	
	N0422	
	N042z	
	N043.	
	N0430	

N0431
N0432
N0433
N043z
N047.
N04X.
N04y2
N0455
Nyu10
Nyu11
Nyu12
Nyu1G

Supplementary table 3 – Proportion of rheumatoid arthritis related hospitalisation, medication or primary care read code in participants who self-report rheumatoid arthritis.

Rheumatoid arthritis self-report	*Any rheumatoid arthritis hospitalisation, medication or primary care read code*		***Total***
	No	Yes	
No	141152 74.4 %	48634 25.6 %	189786 100 %
Yes	513 12.2 %	3683 87.8 %	4196 100 %
Total	141665 73 %	52317 27 %	193982 100 %

Supplementary table 4 – Demographic factors, lifestyle factors, number of long-term conditions and rheumatoid factor status in patients with and without RA. Unless indicated, p<0·01. Chi squared test used for categorical variables, Kruskal-Wallis test used for continuous variables. SD = standard deviation. RA defined here as RA self-report plus hospitalisation, medication or primary care read code related to rheumatoid arthritis.

	Participants with RA (%) (N=3683)	**Participants without RA (%) (N=498857)**
Mean Age (years (SD)); missing values =0 (0%)	59.2 (7.1)	56.5 (8.1)
Age (years); missing values = 0 (0%)		
37-49	413 11.2 %	117470 23.5 %
50-59	1161 31.5 %	165992 33.3 %
60-73	2109 57.3 %	215388 43.2 %
Sex; missing values = 0 (0%)		
Female	2672 72.5 %	270729 54.3 %
Male	1011 27.5 %	228121 45.7 %
Townsend score; missing values = 623 (0·12%)		
0-20	672 18.3 %	99991 20.1 %
20-40	666 18.1 %	99430 20 %
40-60	735 20 %	99663 20 %
60-80	760 20.7 %	99615 20 %
80-100	847 23 %	99531 20 %
Smoking status; missing values = 2950 (0·59%)		
Never	1679 46 %	271857 54.8 %
Current or Previous	1973 54 %	224074 45.2 %
Frequency of alcohol intake; missing values = 1502 (0·30%)		
Never or special occasions only	1218 33.1 %	97442 19.6 %
One to three times a month	453 12.3 %	55405 11.1 %
One to four times a week	1504 40.9 %	243237 48.9 %
Daily or almost daily	504 13.7 %	101268 20.4 %
BMI (kg/m^2); missing values = 5820 (1·15%)		
underweight <18.5	34 0.9 %	2592 0.5 %

normal weight 18.5-24.9	1084 30 %	156353 31.7 %
overweight 25-29.9	1425 39.5 %	212799 43.2 %
obese >=30s	1067 29.6 %	121359 24.6 %
Physical activity; missing values = 7156 (1·42%)		
none	595 16.6 %	32254 6.6 %
low	286 8 %	18652 3.8 %
medium	2596 72.4 %	390922 79.5 %
high	107 3 %	49965 10.2 %
Number of long-term conditions; missing values = 1845 (0·36%)		
0	922 25.2 %	174293 35.1 %
1	1103 30.1 %	163244 32.8 %
2-3	1255 34.3 %	135091 27.2 %
≥4	379 10.4 %	24401 4.9 %
Rheumatoid Factor (IU/ml); missing values = 33,066 (6·6%)		
<20	1801 52.4 %	449067 96.4 %
≥20	1639 47.6 %	16960 3.6 %

Supplementary Table 5 – Relationship between long term conditions and all-cause mortality in participants with and without RA using age-adjusted multivariate Cox's proportional hazards regression analysis. Unless otherwise shown, Cox's proportional hazards p<0·01. RA defined here as RA self-report plus hospitalisation, medication or primary care read code related to rheumatoid arthritis.

		Risk of all-cause mortality	
Comorbidity status (reference: *No RA and no other long-term conditions*)		**Adjusted for sex, Townsend score, alcohol status, smoking status, BMI, physical activity and rheumatoid factor status HR (95% CI)**	**Number of deaths (%)**
No other long-term conditions	**RA**	1.50 (1.09 – 2.07)	44 (4.8%)
1 other long-term condition	**No RA**	1.39 (1.33 - 1.46)	5810 (3.6%)
	RA	1.42 (1.07 - 1.88)	66 (5.9%)
2-3 other long-term conditions	**No RA**	1.83 (1.75 - 1.91)	7966 (5.9%)
	RA	2.75 (2.29 - 3.30)	142 (11.3%)
≥4 other long-term conditions	**No RA**	2.70 (2.55 - 2.86)	2461 (10.8%)
	RA	2.98 (2.19 - 4.04)	54 (14.2%)

Supplementary Table 6 – Relationship between long term conditions and major adverse cardiovascular events in participants with and without RA using age-adjusted multivariate Cox's proportional hazards regression analysis. Unless otherwise shown, Cox's proportional hazards p<0·01. RA defined here as RA self-report plus hospitalisation, medication or primary care read code related to rheumatoid arthritis.

		Risk of MACE	
Comorbidity status (reference: *No RA and no other long-term conditions*)		**Adjusted for sex, Townsend score, alcohol status, smoking status, BMI, physical activity and rheumatoid factor status HR (95% CI)**	**Number of MACE (%)**
No other long-term conditions	**RA**	1.63 (1.13 - 2.36)	32 (3.5%)
1 other long-term condition	**No RA**	1.24 (1.18 - 1.30)	4530 (2.8%)
	RA	1.95 (1.46 - 2.59)	60 (5.4%)
2-3 other long-term conditions	**No RA**	1.66 (1.58 - 1.74)	6244 (4.6%)
	RA	2.50 (2.00 - 3.12)	95 (7.6%)
≥4 other long-term conditions	**No RA**	2.38 (2.23 - 2.54)	2007 (8.2%)
	RA	3.30 (2.36 - 4.61)	46 (12.1%)

Supplementary Table 7 – Table 4 Risk of all-cause mortality for individual index conditions in patients with RA and no index condition, RA with index condition, RA with no index condition or RA and index condition. Age-adjusted Cox's proportional hazards models were adjusted for sex, Townsend score, smoking status, alcohol intake frequency, BMI, physical activity level and level of rheumatoid factor. Unless otherwise shown, Cox's proportional hazards p<0·01. Index conditions labelled * have interaction term p>0.01. RA defined here as RA self-report plus hospitalisation, medication or primary care read code related to rheumatoid arthritis.

	Risk of all-cause mortality			
Index condition	**No RA, no index condition HR, (95% CI), p**	**No RA, with index condition HR, (95% CI), p**	**RA, no index condition HR, (95% CI), p**	**RA and index condition HR, (95% CI), p**
Hypertension	1	1.24 1.20-1.28	1.27 1.07-1.52	1.69 1.41-2.02
Coronary heart disease	1	1.58 1.50-1.65	1.30 1.13-1.50	2.08 1.55-2.79
Diabetes	1	1.68 1.60-1.76	1.37 1.20-1.57	1.76 1.22-2.54
Asthma	1	1.10 1.05-1.15	1.32 1.14-1.52	1.48 1.10-2.00
Dyspepsia	1	1.02 0.97-1.07 p=0.42	1.31 1.15-1.50	1.46 1.04-2.06
Cancer	1	2.50 2.41-2.60	1.43 1.25-1.65	2.72 1.99-3.70
Depression	1	1.28 1.20-1.35	1.32 1.16-1.51	1.79 1.17-2.75
Thyroid disorder	1	1.05 0.99-1.12 p=0.12	1.36 1.19-1.55	1.14 0.76-1.72 p=0.53
COPD	1	2.12 1.98-2.26	1.32 1.15-1.50	2.53 1.77-3.63
Epilepsy	1	1.62 1.43-1.84	1.33 1.17-1.51	2.15 0.80-5.72 p=0.13
Migraine	1	0.85 0.76-0.94	1.33 1.17-1.51	1.02 0.38-2.71 p=0.97
Psoriasis /Eczema	1	1.06 0.94-1.14 p=0.15	1.30 1.14-1.49	2.08 1.23-3.50
Prostate disease	1	0.83 0.75-0.90	1.32 1.16-1.51	1.33 0.55-3.19 p=0.52
Osteoporosis	1	1.27 1.16-1.40	1.29 1.13-1.48	2.09 1.38-3.14
Atrial fibrillation	1	1.40 1.25-1.58	1.34 1.18-1.52	0.99 0.25-3.98 p=0.99
Anxiety	1	1.23 1.11-1.36	1.34 1.18-1.53	0.72 0.18-2.89 p=0.64
Inflammatory bowel disease	1	1.38 1.21-1.58	1.35 1.18-1.53	0.63 0.16-2.51 p=0.51
Heart failure	1	2.71 2.25-3.28	1.32 1.16-1.51	4.34 1.39-13.43

Supplementary Table 8 – Risk of MACE for individual index conditions in patients with RA and no index condition, RA with index condition, RA with no index condition or RA and index condition. Age-adjusted Cox's proportional hazards models were adjusted for sex, Townsend score, smoking status, alcohol intake frequency, BMI, physical activity level and level of rheumatoid factor. Unless otherwise shown, p<0·01. Index conditions labelled * have interaction term p>0.01. RA defined here as RA self-report plus hospitalisation, medication or primary care read code related to rheumatoid arthritis.

	Risk of MACE			
Index condition	**No RA, no index condition HR, (95% CI), p**	**No RA, with index condition HR, (95% CI), p**	**RA, no index condition HR, (95% CI), p**	**RA and index condition HR, (95% CI), p**
Hypertension	1	1.49 1.44-1.55	1.55 1.26-1.90	2.26 1.85-2.76
Coronary heart disease	1	1.89 1.80-1.98	1.60 1.37-1.88	2.31 1.65-3.22
Diabetes	1	1.66 1.58-1.75	1.62 1.39-1.90	1.66 1.58-1.75
Asthma	1	1.12 1.06-1.17	1.57 1.34-1.84	1.67 1.19-2.36
Dyspepsia	1	1.14 1.08-1.20	1.55 1.33-1.82	1.80 1.23-2.64
Cancer	1	1.11 1.05-1.17	1.59 1.37-1.85	1.42 0.87-2.33 p=0.16
Depression	1	1.25 1.17-1.34	1.53 1.31-1.78	2.38 1.52-3.74
Thyroid disorder	1	1.14 1.06-1.23	1.50 1.28-1.75	2.32 1.59-3.36
COPD	1	1.50 1.38-1.63	1.58 1.36-1.84	1.81 1.09-3.00
Epilepsy	1	1.50 1.31-1.74	1.56 1.35-1.81	1.74 0.44-6.97 p=0.43
Migraine	1	1.00 0.90-1.12 p=0.96	1.54 1.33-1.79	2.41 1.08-5.37
Psoriasis /Eczema	1	1.05 0.96-1.14 p=0.29	1.56 1.34-1.80	1.72 0.86-3.44 p=0.12
Prostate disease	1	0.91 0.83-1.00 p=0.05	1.53 1.32-1.78	2.53 1.20-5.31 p=0.01
Osteoporosis*	1	1.27 1.12-1.43	1.48 1.28-1.73	3.15 2.03-4.90
Atrial fibrillation	1	1.72 1.53-1.93	1.56 1.35-1.81	2.78 1.04-7.43 p=0.04
Anxiety	1	1.29 1.15-1.44	1.56 1.35-1.81	2.29 0.86-6.10 p=0.09
Inflammatory bowel disease	1	1.09 0.92-1.29 p=0.30	1.57 1.36-1.82	0.90 0.23-3.63 p=0.89
Heart failure	1	2.67 2.18-3.28	1.57 1.35-1.81	1.71 1.35-12.17 p=0.59

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2

Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	n/a (data collected by UK Biobank)
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6-7

Bias	#9	Describe any efforts to address potential sources of bias	n/a (data collected by UK Biobank)
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6-7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	8
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	8
Statistical methods	#12e	Describe any sensitivity analyses	8
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing	9

		follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	n/a (not applicable here)
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	9
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	10-13
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
Main results	#16b	Report category boundaries when continuous variables were categorized	10-13

Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-13
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	#18	Summarise key results with reference to study objectives	13
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	15
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	14
Generalisability	#21	Discuss the generalisability (external validity) of the study results	16-17
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

Notes:

- 6a: n/a (data collected by UK Biobank)
- 9: n/a (data collected by UK Biobank)

- 13c: n/a (not applicable here) The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 25. March 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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Patterns of multimorbidity and their effects on adverse outcomes in rheumatoid arthritis: a study of 5658 UK Biobank participants

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Patterns of multimorbidity and their effects on adverse outcomes in rheumatoid arthritis: a study of 5658 UK Biobank participants

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Abstract

Objective

To investigate how type and number of long-term conditions (LTCs) impact on all-cause mortality and major adverse cardiovascular events (MACE) in people with rheumatoid arthritis (RA).

Design

Population-based longitudinal cohort study.

Setting

UK Biobank.

Participants

UK Biobank participants (N=502,533) aged between 37 and 73 years old.

Primary outcome measures

Primary outcome measures were risk of all-cause mortality and MACE.

Methods

We examined the relationship between LTC count and individual comorbid LTCs (N=42) on adverse clinical outcomes in participants with self-reported RA (N=5658). Risk of all-cause mortality and MACE were compared using Cox's proportional hazard models adjusted for

lifestyle factors (smoking, alcohol intake, physical activity), demographic factors (sex, age, socioeconomic status), and rheumatoid factor.

Results

75.7% of participants with RA had multimorbidity and these individuals were at increased risk of all-cause mortality and MACE. RA and ≥4LTCs showed a three-fold increased risk of all-cause mortality (hazard ratio (HR) 3.30, 95% confidence interval (CI) 2.61-4.16), and MACE (HR 3.45, 95% CI 2.66-4.49) compared to those without LTCs. Of the comorbid LTCs studied, osteoporosis was most strongly associated with adverse outcomes in participants with RA compared to those without RA or LTCs: two-fold increased risk of all-cause mortality (HR 2.20, 95% CI 1.55-3.12) and three-fold increased risk of MACE (HR 3.17, 95% CI 2.27-4.64). These findings remained in a subset (N=3683) with RA diagnosis validated from clinical records or medication reports.

Conclusion

Those with RA and other LTCs, particularly comorbid osteoporosis, are at increased risk of adverse outcomes, although the role of corticosteroids could not be evaluated in this study. These results are clinically relevant for the monitoring and management of RA across the healthcare system, and future clinical guidelines for RA should acknowledge the importance of multimorbidity.

Keywords

Rheumatoid arthritis, mortality, multimorbidity, comorbidity, cardiovascular

Strengths and limitations

- This is the first study to examine both comorbidity and multimorbidity in RA and the associations with mortality and major adverse cardiovascular events (MACE).
- We used data from 5658 participants in UK Biobank with RA, including detailed information on participant demographics, lifestyle factors and rheumatoid factor status to examine multimorbidity and comorbidity using 42 non-RA LTCs.
- These results provide crucial new information which should be incorporated into clinical guidelines and used to influence management of peoples with RA.
- This study was limited by lack of information on RA disease severity which may play a role in both outcomes measured.

Introduction

Rheumatoid arthritis (RA) is a debilitating, chronic autoimmune disease characterised by inflammation of the synovial joints. RA is associated with physical and socio-economic issues, including increased pain levels, reduced physical functioning, and early mortality.[1-4] Globally, whilst disability adjusted life years for RA have improved since 1990, age-standardised prevalence and incidence rates are increasing.[5]

Between 60% and 75% of those with RA are reported to have multimorbidity – two or more long-term conditions (LTCs) - with higher number of LTCs reported with increasing age and disease activity.[6-8] Common comorbidities include cardiovascular conditions[9] such as coronary artery disease[10] and cardiac failure,[11] as well as mental health conditions such as depression.[12] Cardiovascular disease (CVD) accounts for the majority of the excess mortality observed in RA, with raised inflammatory markers and shared risk factors implicated.[13] However, the effects of comorbidities in RA have generally been studied in isolation and less is known regarding the risks posed by multimorbidity when RA co-occurs with more than one other long-term physical or mental health LTC.

Through analysis of UK Biobank data, this paper aims to explore the effect of multimorbidity and a wide range of comorbid LTCs on all-cause mortality and major adverse cardiovascular events (MACE) in people with RA. Our objectives were to:

1. Compare the effect of LTC count on all-cause mortality in those with and without self-reported RA.

2. Compare the effect of LTC count on MACE in those with and without self-reported RA.

3. Evaluate the effect of individual co-morbid LTCs on the risk of all-cause mortality and MACE in participants with self-reported RA.

Patients and Methods

Study design and data collection

This study utilised data from UK Biobank, a longitudinal population-based cohort of 502533 participants, aged 37-73 years in Great Britain[14]. UK Biobank baseline data was collected between 2006-10 from recruitment centres in Scotland, England and Wales, and subsequently linked to mortality and hospitalisation outcomes from external routine data registries over a median follow-up period of 9 years. A subset of primary care data was available for 230105 participants. This study was covered by the generic ethics approval for UK Biobank studies from the NHS National Research Ethics Service (16/NW/0274).

Variables and outcome measures

UK Biobank collected information on a wide range of demographic, health-based lifestyle and self-reported LTC questions through self-administered touch screen questionnaire and nurse-led interview. These include age, sex, socioeconomic status (measured using Townsend score, a UK area-based measure of deprivation),[15] smoking status, frequency of alcohol intake, body mass index (BMI), level of physical activity and number of LTCs.

The age range of the study population was 37-73 years and was categorised into groups: 37-49, 50-59 and 60-73 years. Sex was a binary categorical variable. Smoking status was categorised into “never” or “current or previous”. Frequency of alcohol intake was categorised into four groups, “Never or special occasions only”, “One to three times a month”, “One to four times a week” or “Daily or almost daily”. BMI was categorised into four groups based on WHO BMI guidelines [16]: "underweight <18.5", "normal weight 18.5-24.9", "overweight 25-29.9" and "obese ≥30". Level of physical activity was defined as “none”,

"low", "medium", or "high" using Metabolic Equivalent Task (MET) scores data based on International Physical Activity Questionnaire (IPAQ) scoring protocol (available from https://sites.google.com/site/theipaq/scoring-protocol) which has shown moderate to good validity and reliability in adults in UK settings.[17, 18]

Rheumatoid factor was ascertained, as part of a predefined biomarker panel, for all participants in UK Biobank, regardless of diagnosis, and categorised into positive and negative status, with rheumatoid factor <20IU/ml considered negative, and values above this considered positive (by manufacturer specification, available at https://www.beckmancoulter.com/wsrportal/techdocs?docname=/cis/988646/%%/RF_988646-%25%25_English.pdf). Participants whose rheumatoid factor was labelled as "not reportable at assay (too low)" were considered to be rheumatoid factor negative. Similarly, those labelled "not reportable at assay (too high)" were considered rheumatoid factor positive.

The list of 42 LTCs considered was based on previous work in UK Biobank,[19, 20] the number of LTCs reported, apart from RA, were summed and then categorised as 0, 1, 2-3 and ≥4 LTCs. RA and all LTCs in UK Biobank are based on self-report using a questionnaire and nurse-led interview asking for existing diagnoses.

All-cause mortality was calculated using data linkage to national mortality registers. MACE were calculated using stroke and myocardial infarction (MI) hospitalisation event data from UK Biobank, and using ICD-10 mortality codes: "I00-I78", "G45", "G451-G454", "G456", "G458", "G459", and "G460-G468". The median follow-up time for both morality and MACE was nine years; the length of follow-up for each participant varied as follow-up continued until an event occurred (death or MACE) or until the mortality the linkage was carried out.

A sensitivity analysis of self-report RA by participants was performed by examining four other indicators of RA: any primary care RA Read code, any secondary care RA hospitalisation code, self-reporting of any common RA drugs or any primary care prescription record of RA drugs (as shown in Supplementary Table 1). Both prospective and retrospective data were used: primary care Read codes were available for a maximum period of January 1991 and December 2017, and primary care prescriptions were between January 1991 and December 2016; the time period for each participant varied, depending on records held. Participants were considered to have confirmed RA if they had a positive record for one or more of these indicators. This analysis was performed on a subset (74%) of participants who self-reported RA for whom primary care data in UK Biobank was available (N=4196/5658).

Statistical methods

In line with previous UK Biobank studies, $\chi 2$ tests were utilised for both categorical data and ordinal data. Kruskal–Wallis tests were used for continuous data.[21] Similarly, we used $\chi 2$ testing to examine differences in proportion of individual LTCs between those with and without RA. Age-adjusted Cox's proportional hazards tests were used to examine the relationship between LTC count / type of LTCs with all-cause mortality and MACE as outcome variables in those with and without RA. The model was further adjusted for demographic, lifestyle and biological factors (sex, Townsend score, alcohol status, smoking status, BMI, physical activity and rheumatoid factor status) as described above. Among those with RA, cumulative hazards-based Kaplan-Meier plots were used to display proportion of events (all-cause mortality or MACE) in participants with 0, 1, 2-3 and ≥4 co-morbid LTCs. To measure the contribution of individual index LTCs towards all-cause mortality and MACE in those with and without RA, we created a categorical variable that assigned participants to one of four groups: those with neither RA nor the index condition (reference

group), those with RA but not the index LTC (RA only), those with no RA with the index LTC (index LTC only), and those with both RA and the index LTC. This variable was used as an outcome measure in an age-adjusted Cox's proportional hazards model controlling for demographic factors, lifestyle factors and rheumatoid factor status. To calculate whether there was a multiplicative or synergistic effect between RA and each index LTC, we used an ANOVA to compare the p-values between two Cox's proportional hazards models: the first contained RA and the index LTC, and the second contained RA, the index LTC and a statistical interaction term between RA and the index LTC. A statistical interaction was considered significant when the ANOVA test has a $p<0.01$.

Results

5658 UK Biobank participants (1.1%) reported having RA. Lifestyle and demographic characteristics of participants with and without self-reported RA are shown in Table 1. Participants with RA were significantly more likely to be older, female, have lower socioeconomic status, be current or previous smokers, have a lower frequency of alcohol intake, have a BMI ≥30, have lower levels of physical activity, and have larger numbers of co-morbid LTCs. $\chi 2$ testing showed participants with self-reported RA were significantly more likely to have rheumatoid factor positive status: 35.6% had rheumatoid factor levels of over 20 IU/ml – compared with 3.6 % in those without RA.

Prevalence of LTCs in people with RA

Proportions of number of LTCs in participants with and without RA are shown in Table 1. Reporting multiple long-term conditions was more common in those with RA: 34.5% had 2-3 LTCs (27.1% in those without RA), and 11.1% had ≥ 4 LTCs (4.9% in those without RA). Overall, 75.7% of people with RA were noted to be multimorbid. The difference in comorbidity experienced by those with and without RA is shown in Supplementary Table 2.

Those with RA reported proportionately higher numbers of physical and mental health-based LTCs, namely: cardiovascular LTCs including hypertension, coronary heart disease, and stroke or transient ischemic attack; pulmonary LTCs including asthma, COPD and chronic bronchitis; digestive system LTCs including dyspepsia, irritable bowel syndrome and inflammatory bowel disease; musculoskeletal conditions including osteoporosis; and mental-health based LTCs including depression.

All-cause mortality and LTCs in people with RA

We examined the outcomes associated with different LTC counts in participants with RA using a Kaplan Meier plot (Supplementary Figure 1). There was an increased proportion of all-cause mortality in participants with RA concurrent with increasing multimorbidity counts: 4.2% (N=58) in those with no additional LTCs, 5.3% (N=91) in those with 1 additional LTC, 9.9% (N=194) in those with 2-3 additional LTCs and 14.4% (N=90) in those with ≥4 additional LTCs during the follow up period (median 9 years).

To quantify the effect of LTC count on all-cause mortality, we performed a Cox's proportional hazards test controlling for lifestyle factors, demographic factors and rheumatoid factor in participants with and without self-reported RA using a stepwise model adjustment (Table 2). Participants with RA and no additional LTCs had a significant increase in all-cause mortality when using an age-adjusted Cox's proportional hazards model fully adjusting for additional lifestyle and demographic factors (Hazard Ratio (HR) 1.59, 95% confidence intervals (CI) 1.21-2.08) compared to those without RA or any LTCs. Whilst controlling additionally for rheumatoid factor status appeared to show some attenuation of all-cause mortality risk, a statistically significant risk for this group remained (HR 1.39, 95% CI 1.05-1.84) when compared to those without RA or any LTCs. When examining additional co-morbid LTCs alongside RA, there appeared to be a dose-based response all-cause mortality

risk, with a 44% increased risk of all-cause mortality in those with RA and one other LTC (HR 1.44, 95% CI 1.14-1.81), an approximately two-and-a-half-fold increased risk for RA with 2-3 other LTCs (HR 2.48, 95% CI 2.12-2.90) and an over three-fold increased risk associated for RA with ≥4 other LTCs (HR 3.30, 95% CI 2.61-4.16) compared to those without RA or any LTCs in the fully adjusted models, which included rheumatoid factor. A dose-based response was also observed in the non-RA population: those with 1 LTC had a 39% increased risk of death (HR 1.39, 95% CI 1.33-1.46), and those with ≥4 were at a two-and-a-half-fold increased risk (HR 2.69 95% CI 2.54-2.85) compared with participants without RA or any LTCs.

MACE and LTCs in people with RA

We next investigated the effect of LTC count on MACE in participants with RA using a Kaplan Meier plot (Supplementary Figure 2). For RA and no additional LTCs, 3.3% (N=46) of participants had a recorded MACE event, compared with 4.6% of participants with RA and one additional LTC (N=78), 6.7% those with RA and 2-3 additional LTCS (N=131), and almost four times as many proportionately in participants with RA and ≥4 LTCs (11.7%, N=73 events) over the follow-up period.

Table 3 shows the risk of MACE for participants with and without RA using age-adjusted multivariate Cox's proportional hazards regression models. There was a 63% increased hazard of MACE for participants with RA and no other LTCs compared with participants without RA or any LTCs (HR 1.63, 95% CI 1.21-2.21) in a fully adjusted model including demographic factors, lifestyle factors and rheumatoid factor status. This remained significant for people with RA with increasing LTCs count, with a 86% increased risk of MACE in participants with one other co-occurring LTC (HR 1.86, 95% CI 1.31-2.15), an over two-fold increase in those with 2-3 co-occurring LTCs (HR 2.09, 95% CI 1.73-2.54) and an almost three-and-a-

half-fold increase in MACE for those with ≥4 LTCs (HR 3.39, 95% CI 2.61-4.40), compared to those without RA or any LTCs. This relationship was similar but to a lesser degree for participants without RA, with those with 1 LTC at 24% increased risk (HR 1.24, 95% CI 1.19-1.31), those with 2-3 LTCs at a 66% increased risk (HR 1.66, 95% CI 1.59-1.74) and those with ≥4 LTCs at over two times risk (HR 2.37 95% CI 2.23-2.53) of MACE compared with those without LTCs.

A similar pattern was observed for the relationship between LTC count and mortality/MACE for the group without RA (Supplementary Figures 3 and 4).

Contribution of individual LTCs to all-cause mortality and MACE in people with RA

Using an age-adjusted Cox's proportional hazards model, adjusting for demographic factors, lifestyle factors and rheumatoid factor status, we investigated the role individual LTCs play in risk of all-cause mortality and MACE, using participants with no RA and no index condition as the reference group (Table 4 and 5).

The presence of cardiovascular-based LTCs appeared to be a risk factor in those with RA for both all-cause mortality and MACE. Compared to those with no RA and no hypertension, RA with hypertension showing an over one-and-a-half-fold increased risk of all-cause mortality (HR 1.59, 95% CI 1.37-1.86) and an approximately two-fold increased risk of MACE (HR 2.07, 95% CI 1.64-2.33).

Similarly, heart disease was associated with an over two-fold increase for both all-cause mortality (HR 2.07, 95% CI 1.63-2.63) and MACE (HR 2.28 95% CI 1.76-2.98) in those with RA compared to those with no RA and no heart disease. However, there was no evidence of interaction between RA and either cardiovascular condition. Whilst thyroid disorders showed no significant increased risk of all-cause mortality, they displayed an over two-fold increased

risk of MACE (HR 2.10, 95% CI 1.50-2.93) in those with RA compared to those without RA or thyroid disease but again there was no significant interaction between RA and thyroid disease and MACE event.

The co-occurrence of osteoporosis in participants with RA appeared to strongly influence both mortality and MACE; more than doubling all-cause mortality (HR 2.20, 95% CI 1.55-3.12), and resulting in an over three times higher risk of MACE (HR 3.17, 95% CI 2.17-4.64) compared to those without RA or osteoporosis. This increased risk in those with both RA and osteoporosis was greater than in those with RA but no osteoporosis or those with osteoporosis but no RA. Interaction terms for RA and osteoporosis showed no significant interaction with all-cause mortality ($p=0.10$), suggesting an additive effect only, but displayed a significant interaction with MACE ($p<0.01$), suggesting a multiplicative or synergistic effect in the association with MACE.

Sensitivity analysis of RA self-report

To investigate sensitivity of self-report by participants with RA, we examined the proportion of people with any primary care RA Read code, any secondary care RA hospitalisation code, self-reporting of any common RA drugs and any primary care prescription record of RA drugs (see supplementary table 1) for participants who had self-reported RA and had available primary care data available in UK Biobank (N=4196). Medications used here were previously reported by Siebert et al.[21] Using this method, we were able to identify RA medications, hospitalisations or primary care Read code in 3683 (87.8%) participants (Supplementary Table 3). Analysis performed in this study was repeated in these participants and showed the same relationships as those reported above in N=5658 with self-report RA, with only small changes in HR observed (Supplementary Tables 4-8).

Discussion

Within UK Biobank, multiple LTCs was common in participants with RA, with approximately 75.7% reporting multimorbidity and 45% of participants reporting two or more additional LTCs alongside RA. In our fully adjusted modes, increasing LTC count was associated with increased mortality and MACE in people with RA. When examining individual LTCs, we observed hypertension, heart disease, osteoporosis and thyroid disorders to increase risk of adverse outcomes. Of these, osteoporosis was associated with one of the largest increases in both adverse outcomes measured: participants with both RA and osteoporosis were at over three times the risk of all-cause mortality and two times the risk of compared to those with neither LTC. The negative effect of having both RA and osteoporosis was particularly evident in MACE outcomes, for which there was a significant interaction between RA and osteoporosis, suggesting a multiplicative or synergistic effect on MACE of having both these conditions together. The presence of hypertension or heart disease alongside RA increased the risk of mortality and MACE, in keeping with previous literature,[22, 23] but there was no evidence of a synergistic effect.

To the best of our knowledge, this paper is the first to compare LTC count and type of comorbid LTCs and their association with all-cause mortality and MACE in men and women with RA after adjusting for a wide range of sociodemographic and lifestyle variables along with rheumatoid factor status. In our study, increasing LTC count resulted in adverse outcomes in participants with RA, with an increased rate of all-cause mortality and MACE.

We have shown that multimorbidity is common in participants with RA, with around 75% of participants with RA reporting one or more additional LTCs. This is in agreement with reported comorbidity rates of between 60% and 75% in those with RA,[6-8] although these studies typically examined a smaller number of LTCs than in this study. We have shown participants with RA and 2-3 other LTCs were at over twice the risk of all-cause mortality, whilst those with ≥ 4 more were over three times the risk compared to participants with no

LTCs. This data provides evidence for the first time the increased risk of all-cause mortality in men and women with RA and multimorbidity. While previous work has highlighted an increased risk of mortality in RA patients,[24, 25] or specific comorbidities alongside RA – for example in COPD[26] and depression[27] – these studies did not examine the effect of LTC count. One matched cohort study used a multimorbidity weighted index to study the effect of multimorbidity on mortality, but only examined effects in women.[28] Another examined LTCs using the Charlson comorbidity index,[29] however this measure uses only 19 LTCs and the study examined only all-cause mortality outcomes. Our study is the first study of its type to link multimorbidity in RA with MACE outcomes. Existing research has highlighted that RA increases the risk of cardiovascular events, and that individual LTCs such as diabetes and hypertension are risk factors,[30] however, to date, no study has shown an association between multimorbidity and MACE outcomes in people with RA. Collectively, the results presented here report for the first time the magnitude of adverse outcomes associated with multimorbidity in those with RA.

In keeping with previous studies,[8, 31] we have shown that osteoporosis prevalence is increased in those with RA compared to those without RA. The results presented in this paper, however, are the first to link osteoporosis in those with RA to increased risk of adverse outcomes and the first to show significant interaction between both conditions and MACE outcomes. The reasons for this association are not clear and cannot be extrapolated from the available data, which does not include factors such as disease severity or duration. One possibility may be that corticosteroids and RA disease activity play a role: corticosteroids are associated with increased prevalence of osteoporosis[32]; people with RA with higher levels of disease activity are more likely to receive corticosteroids; both corticosteroid use and increased RA disease activity are reported to be associated with worse outcomes in mortality and MACE.[33, 34]

Our study therefore has several strong clinical implications. Current NICE guidelines for RA suggest annual checks for the development of hypertension, ischemic heart disease, osteoporosis and depression in RA,[35] but do not highlight the increased risk of the co-occurrence of these LTCs with RA nor the risk posed by multimorbidity in general. In addition, we have shown a greatly increased risk of adverse outcomes in people with osteoporosis and RA that merits further investigation.

Our study has several key strengths: UK Biobank is a large population-based study with several thousand participants reporting RA; the study setting encompasses three countries within the UK (Scotland, England and Wales); it includes details of participant demographic and lifestyle factors as well as rheumatoid factor levels, which allowed us to adjust for variables, which have not been explored in previous studies.

Our study is limited by self-reporting of RA and LTCs by these participants; however, recent studies have shown that self-report is a reliable method for reporting RA[36]. Inthis study we additionally used four RA indicators (any primary care RA Read code, any secondary care RA hospitalisation code, self-reporting of any common RA drugs and any primary care prescription record of RA drugs) to validate self-reported RA. Using this validation approach, we found a positive verification rate (participants self-reporting RA with further RA indicators) of 87.8% (N=3683). Re-analysis of the subset of participants with RA (Supplementary Tables 4-8) who had a validated RA report showed only small changes to Cox's proportional hazards models, and observed effects were in agreement with the population who self-reported RA. This provides confidence in our findings that we are examining a true RA population. Rheumatoid factor positive status in those self-reporting RA (35.6%) was lower than expected, however still a significantly higher proportion than in the UK Biobank population who did not report RA (3.6%). Analysis of rheumatoid factor in those who had a validated RA report showed an increased proportion of positive rheumatoid

factor (47.6%), but this level remained below previously reported proportions in RA populations. We were unable to determine the severity or duration of RA in participants, or their previous medications. Participants in UK Biobank are known to be less deprived than the wider UK population,[37] suggesting that the level of multimorbidity reported here; and resulting associations are likely to be conservative in nature. Future work will examine potential clusters of LTCs that are associated with poor health-related outcomes in people with RA to try to inform clinical management of patients with RA and multiple LTCs.

Conclusions

Multimorbidity is common in people with RA and is associated with increased risk of all-cause mortality and MACE. Certain comorbidities such as osteoporosis merit specific attention, in view of their association with adverse outcomes; it will be important to test whether this association is replicated in other datasets and if so, to explore the underpinning mechanisms. As multimorbidity has been shown here to influence outcomes for those with RA, forthcoming work will examine which clusters of LTCs most strongly drive this increased risk of poor outcomes. Future clinical guidelines for RA should acknowledge the importance of multimorbidity when considering management planning and patient outcomes.

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Ethical approval

All participants gave informed consent for data provision and linkage. UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274).

Competing interests

None declared.

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Data sharing statement

The data used in this study are available via a direct application to UK Biobank.

Author contributions

This study was conceived by BN, FSM, SS, BJ and CM. The analysis was conducted by RM, BN and BJ. All authors (RM, BJ, BN, JC, SM, CM, JN, SB, FSM, SS) contributed to design, interpretation and discussion of all analysis. RM wrote this manuscript. All authors (RM, BJ, BN, JC, SM, CM, JN, SB, FSM, SS) edited, reviewed and commented on all versions of this manuscript. All authors read the manuscript draft and approved the final submission.

Patient and Public Involvement

The study was supported by a patient advisory group which provided input to the programme of research. This patient advisory group met on a regular basis for the duration of the study. Patients partnered with us and helped design research questions.

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Figure legends

Supplementary figure 1 – Kaplan-Meier plot of proportion of all-cause mortality during the follow-up period (median 108 months) for participants with RA and no LTCS (black line), RA and 1 LTC (red line), RA and 2-3 LTCs (green line) and RA and ≥4 LTCs (blue line).

Supplementary figure 2 – Kaplan-Meier plot of proportion of MACE during the follow-up period (median 108 months) for participants with RA and no LTCS (black line), RA and 1 LTC (red line), RA and 2-3 LTCs (green line) and RA and ≥4 LTCs (blue line).

Supplementary figure 3 – Kaplan-Meier plot of proportion of all-cause mortality during the follow-up period (median 108 months) for participants no RA and no LTCS (black line), RA no RA and 1 LTC (red line), no RA and 2-3 LTCs (green line) and no RA and ≥4 LTCs (blue line).

Supplementary figure 4 – Kaplan-Meier plot of proportion of MACE during the follow-up period (median 108 months) for participants no RA and no LTCS (black line), RA no RA and 1 LTC (red line), no RA and 2-3 LTCs (green line) and no RA and ≥4 LTCs (blue line).

Tables

Table 1 – Demographic factors, lifestyle factors, number of long-term conditions and rheumatoid factor status in patients with and without rheumatoid arthritis. Unless indicated, $p<0.01$. $\chi 2$ test was used for categorical variables, Kruskal-Wallis test was used for continuous variables. SD = standard deviation. Unless otherwise indicated, all results are shown as number (%).

	Participants with RA (N=5658)	**Participants without RA (N=496882)**
Mean Age (years (SD)); missing values =0 (0%)	59.3 (7.1)	56.5 (8.1)
Age (years); missing values = 0 (0%)		

37-49	675 (11.9%)	117209 (23.6%)
50-59	1800 (31.8%)	165359 (33.3%)
60-73	3183 (56.3%)	214314 (43.1%)
Sex; missing values = 0 (0%)		
Female	3952 (69.8%)	269452 (54.2%)
Male	1706 (30.2%)	227430 (45.8%)
Townsend score; missing values = 623 (0.12%)		
0-20 (least deprived)	998 (17.7%)	99665 (20.1%)
20-40	980 (17.4%)	99117 (20%)
40-60	1087 (19.2%)	99311 (20%)
60-80	1154 (20.4%)	99224 (20%)
80-100 (most deprived)	1429 (25.3%)	98952 (19.9%)
Smoking status; missing values = 2950 (0.59 %)		
Never	2625 (46.8%)	270916 (54.8%)
Current or Previous	2983 (53.2%)	223066 (45.2%)
Frequency of alcohol intake; missing values = 1502 (0.30 %)		
Never or special occasions only	1830 (32.4%)	96832 (19.5%)
One to three times a month	690 (12.2%)	55170 (11.1%)
One to four times a week	2315 (41%)	242428 (48.9%)
Daily or almost daily	811 (14.4%)	100962 (20.4%)
BMI (kg/m^2); missing values = 5820 (1.15 %)		
underweight <18.5	50 (0.9%)	2576 (0.5%)
normal weight 18.5-24.9	1543 (27.9%)	155896 (31.7%)
overweight 25-29.9	2194 (39.6%)	212032 (43.2%)
obese ≥30	1750 (31.6%)	120679 (24.6%)
Physical activity; missing values = 7156 (1.42 %)		
none	814 (14.8%)	32035 (6.5%)
low	409 (7.4%)	18531 (3.8%)
medium	4111 (74.5%)	389412 (79.5%)
high	182 (3.3%)	49890 (10.2%)
Number of long-term conditions; missing values = 1845 (0.36 %)		
0	1369 (24.3%)	173846 (35.1%)
1	1690 (30.0%)	162657 (32.9%)
2-3	1943 (34.5%)	134403 (27.1%)
≥4	623 (11.1%)	24157 (4.9%)
Rheumatoid Factor (IU/ml); missing values = 33,066 (6.6 %)		
<20	3396 (64.4%)	447472 (96.4%)
>20	1879 (35.6%)	16720 (3.6%)

Table 2 - Relationship between long term conditions and all-cause mortality in participants with and without self-reported RA using age-adjusted multivariate Cox's proportional hazards regression analysis. Unless otherwise shown, Cox's proportional hazards p<0.01.

	Risk of all-cause mortality					
Comorbidity status (reference: *No RA and no other long-term conditions*)	**Adjusted for sex and Townsend score HR (95% CI)**	**Adjusted for sex, Townsend score, alcohol status and smoking status**	**Adjusted for sex, Townsend score, alcohol status, smoking status, BMI**	**Adjusted for sex, Townsend score, alcohol status, smoking status, BMI, physical**	**Number of deaths (%)**

			HR (95% CI)	and physical activity HR (95% CI)	activity and rheumatoid factor status HR (95% CI)	
No other long-term conditions	**RA**	1.84 (1.42-2.38)	1.72 (1.32-2.2)	1.59 (1.21-2.08)	1.39 (1.05-1.84)	58 (4.2%)
1 other long-term condition	**No RA**	1.45 (1.39-1.51)	1.42 (1.36-1.48)	1.40 (1.34-1.47)	1.39 (1.33-1.46)	5785 (3.6%)
	RA	2.01 (1.64-2.48)	1.88 (1.53-2.32)	1.72 (1.38-2.14)	1.44 (1.14-1.81)	91 (5.4%)
2-3 other long-term conditions	**No RA**	2.03 (1.95-2.11)	1.92 (1.84-2.00)	1.84 (1.77-1.92)	1.83 (1.75-1.91)	7914 (5.9%)
	RA	3.32 (2.87-3.84)	2.99 (2.59-3.46)	2.79 (2.40-3.24)	2.48 (2.12-2.90)	194 (10.0%)
≥4 other long-term conditions	**No RA**	3.39 (3.22-3.57)	3.04 (2.88-3.20)	2.71 (2.56-2.86)	2.69 (2.54-2.85)	2605 (10.8%)
	RA	4.68 (3.80-5.78)	3.95 (3.19-4.89)	3.52 (2.81-4.40)	3.30 (2.61-4.16)	90 (14.4%)

Table 3 Relationship between long term conditions and major adverse cardiovascular events in participants with and without self-reported RA using age-adjusted multivariate Cox's proportional hazards regression analysis. Unless otherwise shown, Cox's proportional hazards p<0.01.

	Risk of MACE				
Comorbidity status (reference: *No RA and no other long-term conditions*)	**Adjusted for sex and Townsend score**	**Adjusted for sex, Townsend score,**	**Adjusted for sex, Townsend score,**	**Adjusted for sex, Townsend score,**	**Number of MACE (%)**

		HR (95% CI)	alcohol status and smoking status HR (95% CI)	alcohol status, smoking status, BMI, and physical activity HR (95% CI)	alcohol status, smoking status, BMI, physical activity and rheumatoid factor status HR (95% CI)	
No other long-term conditions	**RA**	1.79 (1.33-2.39)	1.69 (1.26-2.27)	1.64 (1.21-2.20)	1.63 (1.21-2.21)	46 (3.4%)
1 other long-term condition	**No RA**	1.30 (1.24-1.36)	1.28 (1.22-1.34)	1.26 (1.20-1.320	1.24 (1.19-1.31)	4512 (2.8%)
	RA	2.08 (1.66-2.61)	1.91 (1.52-2.41)	1.87 (1.48-2.35)	1.68 (1.31-2.15)	78 (4.6%)
2-3 other long-term conditions	**No RA**	1.86 (1.78-1.94)	1.78 (1.70-1.86)	1.67 (1.60-1.75)	1.66 (1.59-1.74)	6208 (4.6%)
	RA	2.72 (2.28-3.24)	2.49 (2.09-2.98)	2.19 (1.82-2.64)	2.09 (1.73-2.54)	131 (6.7%)
≥4 other long-term conditions	**No RA**	3.04 (2.87-3.22)	2.76 (2.60-2.93)	2.40 (2.26-2.56)	2.37 (2.23-2.53)	1980 (8.2%)
	RA	4.79 (3.79-6.04)	4.07 (3.21-5.16)	3.52 (2.73-4.52)	3.39 (2.61-4.40)	73 (11.7%)

Table 4 Risk of all-cause mortality for individual index conditions in patients with RA and no index condition, RA with index condition, RA with no index condition and RA and index condition. Age-adjusted Cox's proportional hazards models were adjusted for sex, Townsend score, smoking status, alcohol intake frequency, BMI, physical activity level and rheumatoid factor status. Cox's proportional hazards p<0·01, except for those labelled with + indicating p>0.01. Index conditions labelled * have interaction term p<0.01

	Risk of all-cause mortality			
	No RA, no index condition	**No RA, with index condition HR, (95% CI)**	**RA, no index condition HR, (95% CI)**	**RA and index condition HR, (95% CI)**

Index condition				
Hypertension	1	1.24 (1.21-1.28)	1.29 (1.11-1.48)	1.59 (1.37-1.86)
Coronary heart disease	1	1.57 (1.50-1.65)	1.26 (1.12-1.42)	2.07 (1.63-2.63)
Diabetes	1	1.68 (1.60-1.75)	1.33 (1.18-1.48)	1.83 (1.37-2.44)
Asthma	1	1.10 (1.05-1.15)	1.27 (1.13-1.42)	1.56 (1.22-2.00)
Dyspepsia	1	1.01 (0.97-1.06)$^{+}$	1.27 (1.14-1.43)	1.45 (1.10-1.90)
Cancer	1	2.50 (2.41-2.59)	1.35 (1.20-1.52)	3.04 (2.39-3.86)
Depression	1	1.27 (1.20-1.35)	1.29 (1.15-1.44)	1.71 (1.21-2.42)
Thyroid disorder	1	1.05 (0.98-1.12)$^{+}$	1.32 (1.18-1.47)	1.14 (0.80-1.62)$^{+}$
COPD	1	2.11 (1.98-2.49)	1.26 (1.13-1.42)	2.68 (2.00-3.58)
Epilepsy	1	1.81 (1.42-1.82)	1.29 (1.15-1.43)	2.86 (1.43-5.73)
Migraine	1	0.85 (0.76-0.94)	1.29 (1.16-1.44)	1.09 (0.55-2.19)$^{+}$
Psoriasis/Eczema	1	1.05 (0.98-1.14)$^{+}$	1.27 (1.14-1.42)	1.88 (1.20-2.95)
Prostate disease	1	0.83 (0.76-0.90)	1.30 (1.17-1.45)	0.90 (0.43-1.90)$^{+}$
Osteoporosis	1	1.26 (1.14-1.39)	1.25 (1.12-1.40)	2.20 (1.55-3.12)
Atrial fibrillation	1	1.40 (1.45-1.57)	1.30 (1.17-1.45)	1.32 (0.50-3.52)$^{+}$
Anxiety	1	1.22 (1.10-1.35)	1.30 (1.16-1.44)	1.48 (0.67-3.30)$^{+}$
Inflammatory bowel disease	1	1.37 (1.20-1.57)	1.30 (1.17-1.44)	1.30 (0.54-3.11)$^{+}$
Heart failure	1	2.69 (2.22-3.25)	1.29 (1.16-1.43)	5.14 (2.14-12.38)

Table 5 Risk of MACE for individual index conditions in patients with RA and no index condition, RA with index condition, RA with no index condition and RA and index condition. Age-adjusted Cox's proportional hazards models were adjusted for sex, Townsend score, smoking status, alcohol intake frequency, BMI, physical activity level and rheumatoid factor status. Cox's proportional hazards p<0·01, except for those labelled with $^{+}$ indicating p>0.01. Index conditions labelled * have interaction term p<0.01

	Risk of MACE		
No RA, no index condition	**No RA, with index condition HR, (95% CI)**	**RA, no index condition HR, (95% CI)**	**RA and index condition HR, (95% CI)**

Index condition				
Hypertension	1	1.50 (1.44-1.55)	1.48 (1.25-1.75)	1.97 (1.66-2.33)
Coronary heart disease	1	1.89 (1.80-1.98)	1.43 (1.45-1.63)	2.28 (1.76-2.98)
Diabetes	1	1.67 (1.58-1.75)	1.49 (1.31-1.69)	1.69 (1.19-2.39)
Asthma	1	1.12 (1.06-1.18)	1.43 (1.25-1.63)	1.47 (1.09-1.98)
Dyspepsia	1	1.14 (1.08-1.20)	1.39 (1.22- 1.58)	1.85 (1.30-2.34)
Cancer	1	1.11 (1.04-1.17)	1.43 (1.26-1.62)	1.44 (0.98-2.11)$^{+}$
Depression	1	1.25 (1.17-1.34)	1.39 (1.22-1.58)	2.06 (1.41-3.00)
Thyroid disorder	1	1.14 (1.03-1.23)	1.37 (1.20-1.55)	2.10 (1.50-2.93)
COPD	1	1.49 (1.37-1.62)	1.40 (1.24-1.59)	1.97 (1.33-2.92)
Epilepsy	1	1.50 (1.30-1.73)	1.41 (1.21-1.60)	2.21 (0.83-5.88)$^{+}$
Migraine	1	0.99 (0.89-1.12)$^{+}$	1.40 (1.23-1.58)	2.08 (1.12-3.87)
Psoriasis/Eczema	1	1.05 (0.96-1.14)$^{+}$	1.42 (1.26-1.61)	1.23 (0.64-2.37)$^{+}$
Prostate disease	1	0.92 (0.83-1.00)$^{+}$	1.41 (1.25-1.60)	1.27 (0.64-2.54)$^{+}$
Osteoporosis*	1	1.34 (1.18-1.53)	1.25 (1.10-1.41)	3.17 (2.17-4.64)
Atrial fibrillation	1	1.41 (1.25-1.60)	1.72 (1.53-1.93)	2.67 (1.99-5.95)
Anxiety	1	1.28 (1.14-1.43)	1.40 (1.24-1.59)	2.73 (1.30-5.72)
Inflammatory bowel disease	1	1.09 (0.92-1.29)$^{+}$	1.42 (1.26-1.60)	1.11 (0.36-3.44)$^{+}$
Heart failure	1	2.64 (2.15-3.24)	1.41 (1.25-1.59)	3.45 (1.11-10.70)$^{+}$

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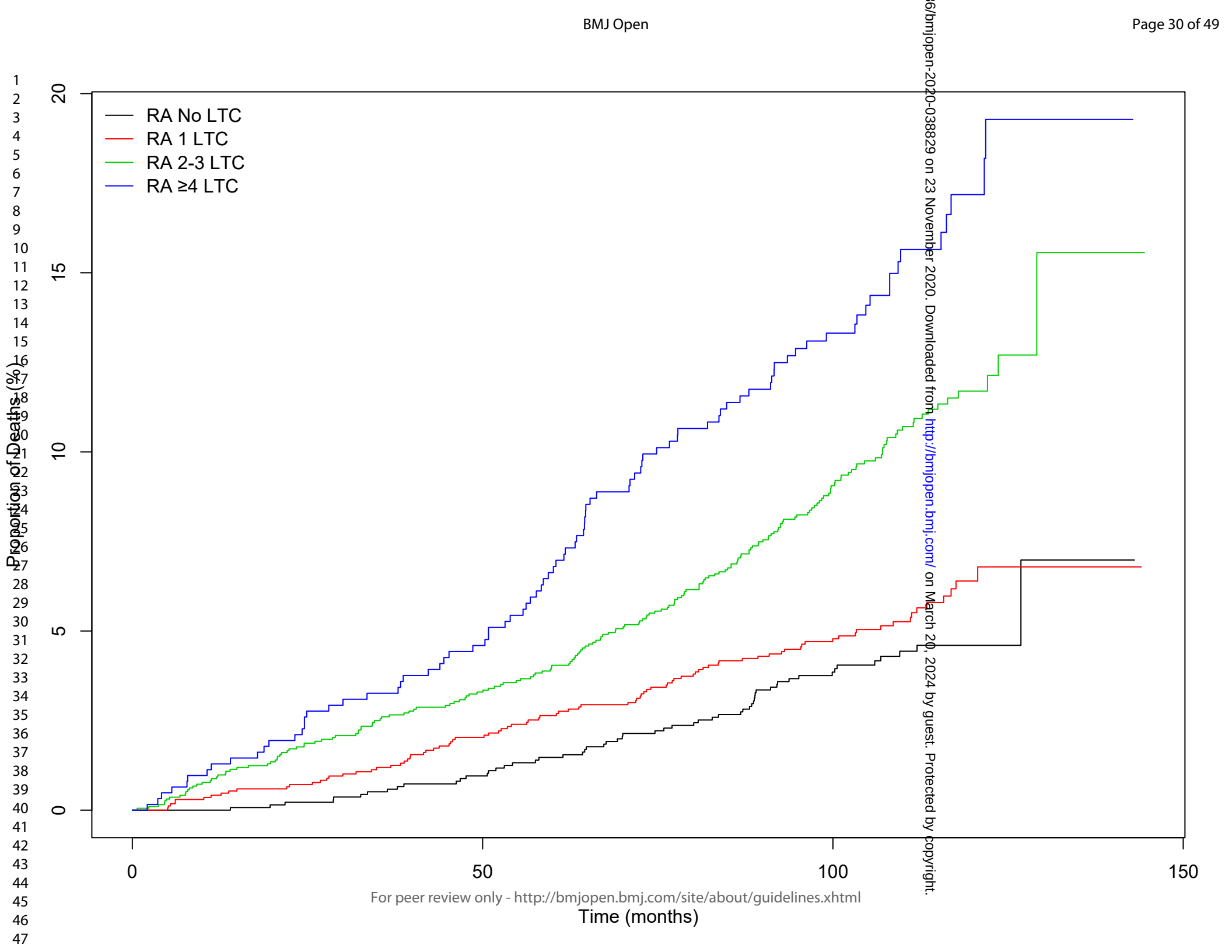

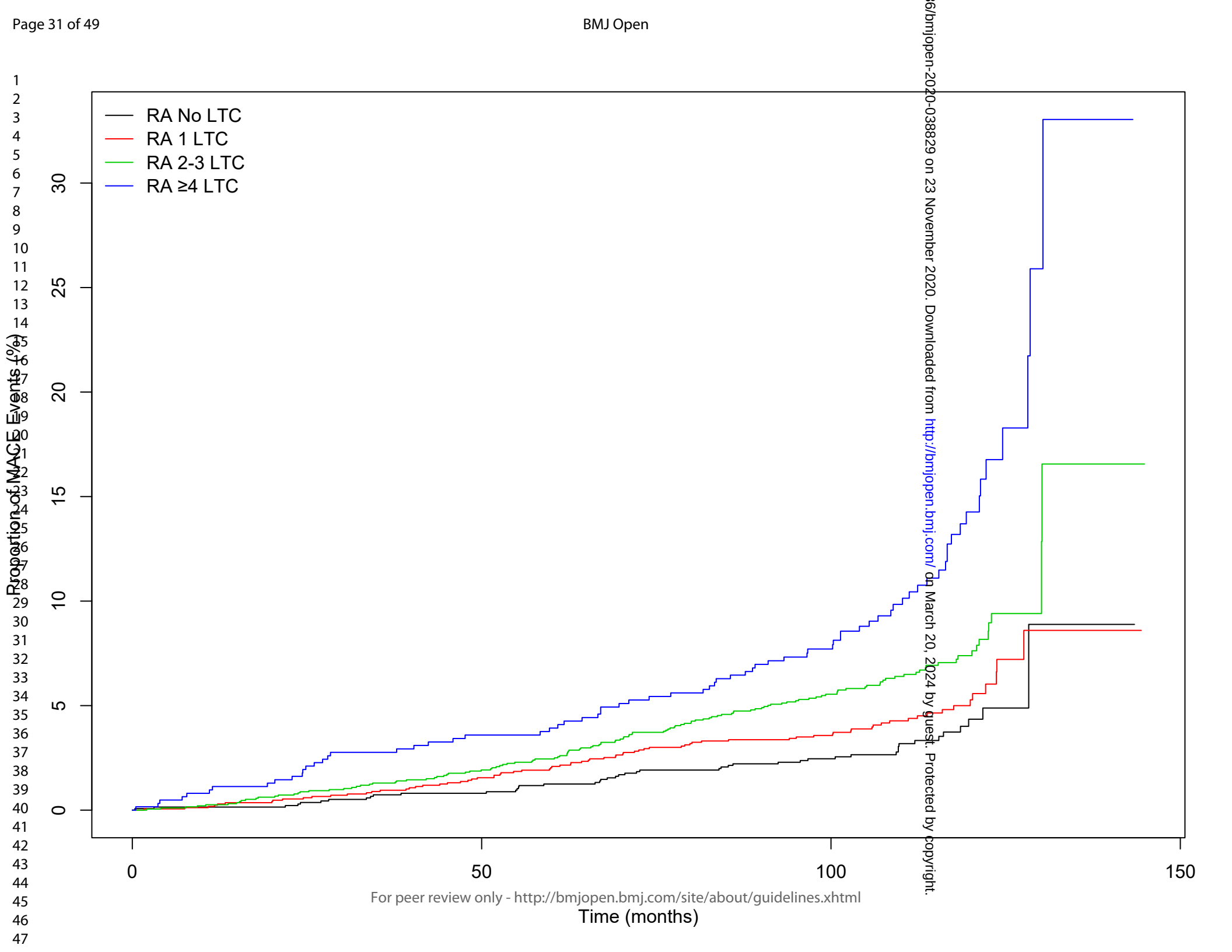

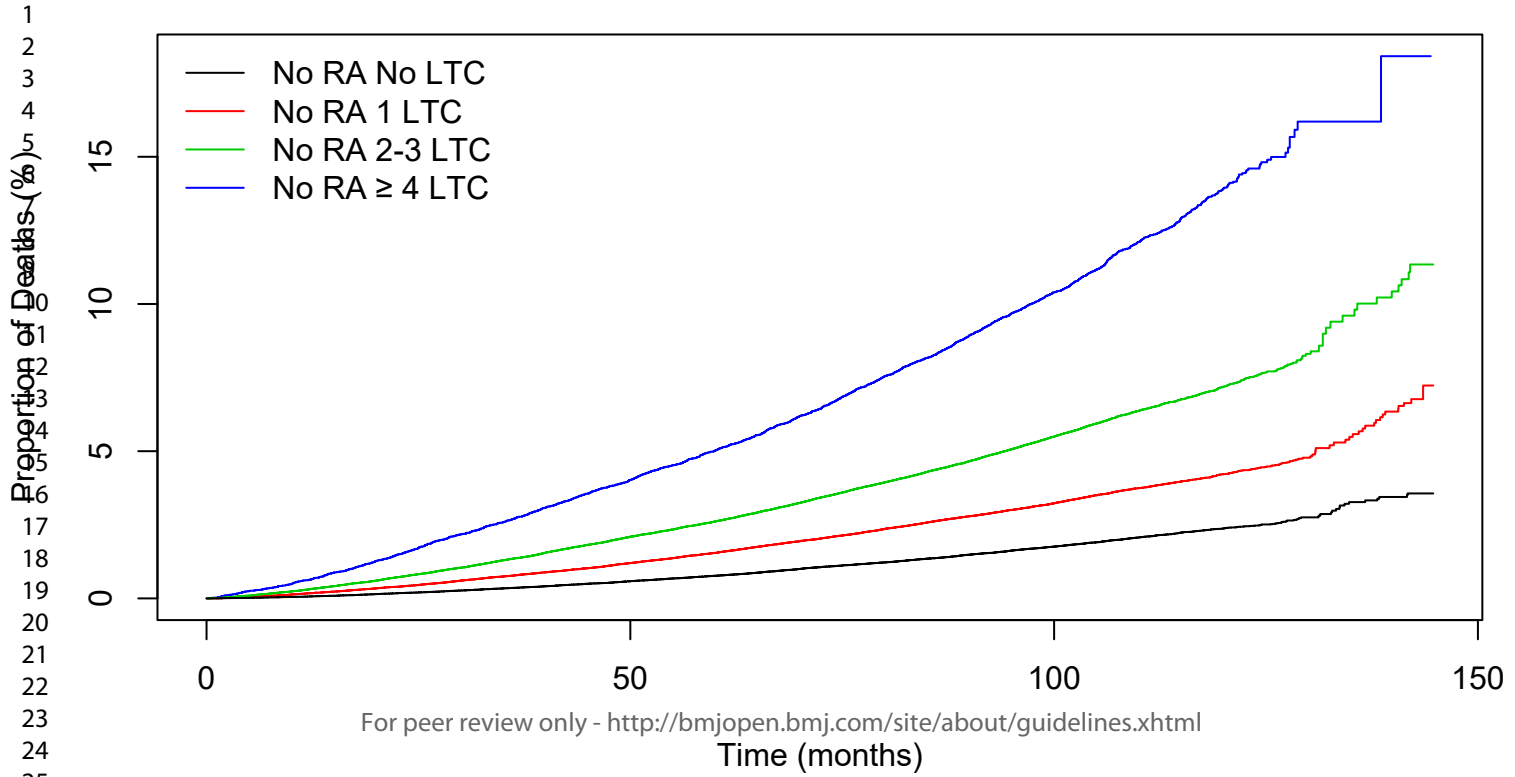

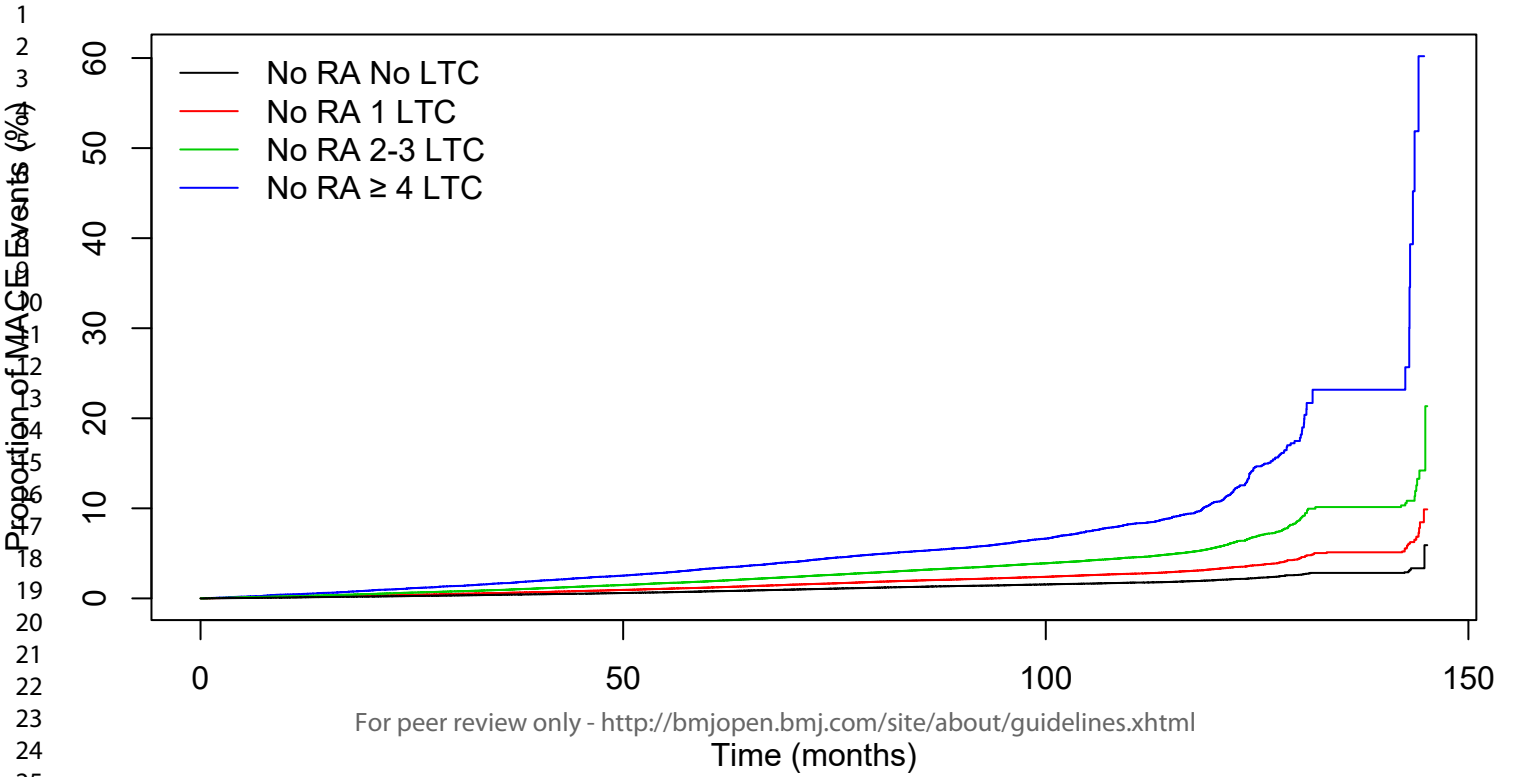

Tables

Supplementary table 1 – Proportion of long term conditions in participants with and without RA. P value determined using $\chi 2$ testing.

Condition	Prevalence in RA participants (%)	Prevalence in non-RA participants (%)	p value
Hypertension	**35·6**	**26·4**	**<0·01**
Asthma	**15·4**	**11·6**	**<0·01**
Dyspepsia	**11·3**	**7·7**	**<0·01**
Thyroid disorder	**9·5**	**5·8**	**<0·01**
Cancer	**8·7**	**7·7**	**<0·01**
Coronary heart disease	**8·2**	**4·5**	**<0·01**
Diabetes	**7·6**	**5·0**	**<0·01**
Depression	**7·0**	**5·6**	**<0·01**
Osteoporosis	**4·9**	**1·5**	**<0·01**
Chronic obstructive pulmonary disease	**4·4**	**1·6**	**<0·01**
Psoriasis/eczema	4·1	3·5	0·03
IBS	**3·3**	**2·3**	**<0·01**
Migraine	3·2	2·9	0·04
Stroke/TIA	**3·1**	**1·7**	**<0·01**
Diverticular disease	**2·2**	**1·1**	**<0·01**
Anxiety	1·7	1·8	0·47
IBD	**1·4**	**0·8**	**<0·01**
Prostate disease	1·3	1·6	0·06
Pernicious anaemia	**1·2**	**0·3**	**<0·01**
Glaucoma	1·2	1·1	0·26
Epilepsy	1·2	0·8	0·38
Endometriosis	0·9	0·8	0·39
Atrial fibrillation	0·9	0·7	0·14
Peripheral vascular disease	**0·9**	**0·3**	**<0·01**
Chronic bronchitis	**0·8**	**0·3**	**<0·01**
Chronic sinusitis	0·8	0·6	0·34
Meniere's disease	**0·7**	**0·3**	**<0·01**
Chronic kidney disease	0·5	0·3	0·01
Chronic liver disease	**0·4**	**0·2**	**<0·01**
Schizophrenia	0·4	0·4	0·68
Chronic fatigue syndrome	0·4	0·4	0·42
Alcohol problems	0·4	0·2	0·02
Viral hepatitis	0·3	0·3	0·91
Heart failure	0·3	0·2	0·18
Polycystic ovary syndrome	0·2	0·1	0·08
Multiple sclerosis	0·2	0·4	0·03
Parkinson's disease	0·1	0·2	0·71
Constipation	0·1	0·1	0·81
Dementia	0·1	0·02	0·17
Anorexia/bulimia	0·1	0·1	0·80

Psychoactive substance misuse	0·03	0·02	0·30

Supplementary table 2 –Medications, primary care read codes and hospitalisation codes used for RA self-report verification

Medications	Primary care read codes	Hospitalisation ICD-10 codes
Depomedrone	14G1	M05
Triamcinilone	F3712	M06
Methylprednisolone	F3964	
Prednisolone	G5yA.	
Prednisone	G5y8.	
Auranofin	H570.	
Azathioprine	N04..	
Hydroxychloroquine	N040.	
leflunomide	N0400	
Methotrexate	N0401	
Myocrisin	N0402	
Penicillamine	N0403	
Sulfasalazine	N0404	
Abatacept	N0405	
Adalimumab	N0406	
Certolizumab	N0407	
Etanercept	N0408	
Golimumab	N0409	
Infliximab	N040A	
Rituximab	N040B	
Tocilizumab	N040C	
	N040D	
	N040E	
	N040F	
	N040G	
	N040H	
	N040J	
	N040K	
	N040L	
	N040M	
	N040N	
	N040P	
	N040Q	
	N040R	
	N040S	
	N040T	
	N041.	
	N042.	
	N0421	
	N0422	
	N042z	
	N043.	
	N0430	

N0431
N0432
N0433
N043z
N047.
N04X.
N04y2
N0455
Nyu10
Nyu11
Nyu12
Nyu1G

Supplementary table 3 – Proportion of rheumatoid arthritis related hospitalisation, medication or primary care read code in participants who self-report rheumatoid arthritis.

Rheumatoid arthritis self-report	*Any rheumatoid arthritis hospitalisation, medication or primary care read code*		***Total***
	No	Yes	
No	141152 74.4 %	48634 25.6 %	189786 100 %
Yes	513 12.2 %	3683 87.8 %	4196 100 %
Total	141665 73 %	52317 27 %	193982 100 %

Supplementary table 4 – Demographic factors, lifestyle factors, number of long-term conditions and rheumatoid factor status in patients with and without RA. Unless indicated, p<0·01. Chi squared test used for categorical variables, Kruskal-Wallis test used for continuous variables. SD = standard deviation. RA defined here as RA self-report plus hospitalisation, medication or primary care read code related to rheumatoid arthritis.

	Participants with RA (%) (N=3683)	**Participants without RA (%) (N=498857)**
Mean Age (years (SD)); missing values =0 (0%)	59.2 (7.1)	56.5 (8.1)
Age (years); missing values = 0 (0%)		
37-49	413 11.2 %	117470 23.5 %
50-59	1161 31.5 %	165992 33.3 %
60-73	2109 57.3 %	215388 43.2 %
Sex; missing values = 0 (0%)		
Female	2672 72.5 %	270729 54.3 %
Male	1011 27.5 %	228121 45.7 %
Townsend score; missing values = 623 (0·12%)		
0-20	672 18.3 %	99991 20.1 %
20-40	666 18.1 %	99430 20 %
40-60	735 20 %	99663 20 %
60-80	760 20.7 %	99615 20 %
80-100	847 23 %	99531 20 %
Smoking status; missing values = 2950 (0·59%)		
Never	1679 46 %	271857 54.8 %
Current or Previous	1973 54 %	224074 45.2 %
Frequency of alcohol intake; missing values = 1502 (0·30%)		
Never or special occasions only	1218 33.1 %	97442 19.6 %
One to three times a month	453 12.3 %	55405 11.1 %
One to four times a week	1504 40.9 %	243237 48.9 %
Daily or almost daily	504 13.7 %	101268 20.4 %
BMI (kg/m^2); missing values = 5820 (1·15%)		
underweight <18.5	34 0.9 %	2592 0.5 %

normal weight 18.5-24.9	1084 30 %	156353 31.7 %
overweight 25-29.9	1425 39.5 %	212799 43.2 %
obese >=30s	1067 29.6 %	121359 24.6 %
Physical activity; missing values = 7156 (1·42%)		
none	595 16.6 %	32254 6.6 %
low	286 8 %	18652 3.8 %
medium	2596 72.4 %	390922 79.5 %
high	107 3 %	49965 10.2 %
Number of long-term conditions; missing values = 1845 (0·36%)		
0	922 25.2 %	174293 35.1 %
1	1103 30.1 %	163244 32.8 %
2-3	1255 34.3 %	135091 27.2 %
≥4	379 10.4 %	24401 4.9 %
Rheumatoid Factor (IU/ml); missing values = 33,066 (6·6%)		
<20	1801 52.4 %	449067 96.4 %
≥20	1639 47.6 %	16960 3.6 %

Supplementary Table 5 – Relationship between long term conditions and all-cause mortality in participants with and without RA using age-adjusted multivariate Cox's proportional hazards regression analysis. Unless otherwise shown, Cox's proportional hazards p<0·01. RA defined here as RA self-report plus hospitalisation, medication or primary care read code related to rheumatoid arthritis.

		Risk of all-cause mortality	
Comorbidity status (reference: *No RA and no other long-term conditions*)		**Adjusted for sex, Townsend score, alcohol status, smoking status, BMI, physical activity and rheumatoid factor status HR (95% CI)**	**Number of deaths (%)**
No other long-term conditions	**RA**	1.50 (1.09 – 2.07)	44 (4.8%)
1 other long-term condition	**No RA**	1.39 (1.33 - 1.46)	5810 (3.6%)
	RA	1.42 (1.07 - 1.88)	66 (5.9%)
2-3 other long-term conditions	**No RA**	1.83 (1.75 - 1.91)	7966 (5.9%)
	RA	2.75 (2.29 - 3.30)	142 (11.3%)
≥4 other long-term conditions	**No RA**	2.70 (2.55 - 2.86)	2461 (10.8%)
	RA	2.98 (2.19 - 4.04)	54 (14.2%)

Supplementary Table 6 – Relationship between long term conditions and major adverse cardiovascular events in participants with and without RA using age-adjusted multivariate Cox's proportional hazards regression analysis. Unless otherwise shown, Cox's proportional hazards p<0·01. RA defined here as RA self-report plus hospitalisation, medication or primary care read code related to rheumatoid arthritis.

		Risk of MACE	
Comorbidity status (reference: *No RA and no other long-term conditions*)		**Adjusted for sex, Townsend score, alcohol status, smoking status, BMI, physical activity and rheumatoid factor status HR (95% CI)**	**Number of MACE (%)**
No other long-term conditions	**RA**	1.63 (1.13 - 2.36)	32 (3.5%)
1 other long-term condition	**No RA**	1.24 (1.18 - 1.30)	4530 (2.8%)
	RA	1.95 (1.46 - 2.59)	60 (5.4%)
2-3 other long-term conditions	**No RA**	1.66 (1.58 - 1.74)	6244 (4.6%)
	RA	2.50 (2.00 - 3.12)	95 (7.6%)
≥4 other long-term conditions	**No RA**	2.38 (2.23 - 2.54)	2007 (8.2%)
	RA	3.30 (2.36 - 4.61)	46 (12.1%)

Supplementary Table 7 – Table 4 Risk of all-cause mortality for individual index conditions in patients with RA and no index condition, RA with index condition, RA with no index condition or RA and index condition. Age-adjusted Cox's proportional hazards models were adjusted for sex, Townsend score, smoking status, alcohol intake frequency, BMI, physical activity level and level of rheumatoid factor. Unless otherwise shown, Cox's proportional hazards p<0·01. Index conditions labelled * have interaction term p>0.01. RA defined here as RA self-report plus hospitalisation, medication or primary care read code related to rheumatoid arthritis.

	Risk of all-cause mortality			
Index condition	**No RA, no index condition HR, (95% CI), p**	**No RA, with index condition HR, (95% CI), p**	**RA, no index condition HR, (95% CI), p**	**RA and index condition HR, (95% CI), p**
Hypertension	1	1.24 1.20-1.28	1.27 1.07-1.52	1.69 1.41-2.02
Coronary heart disease	1	1.58 1.50-1.65	1.30 1.13-1.50	2.08 1.55-2.79
Diabetes	1	1.68 1.60-1.76	1.37 1.20-1.57	1.76 1.22-2.54
Asthma	1	1.10 1.05-1.15	1.32 1.14-1.52	1.48 1.10-2.00
Dyspepsia	1	1.02 0.97-1.07 p=0.42	1.31 1.15-1.50	1.46 1.04-2.06
Cancer	1	2.50 2.41-2.60	1.43 1.25-1.65	2.72 1.99-3.70
Depression	1	1.28 1.20-1.35	1.32 1.16-1.51	1.79 1.17-2.75
Thyroid disorder	1	1.05 0.99-1.12 p=0.12	1.36 1.19-1.55	1.14 0.76-1.72 p=0.53
COPD	1	2.12 1.98-2.26	1.32 1.15-1.50	2.53 1.77-3.63
Epilepsy	1	1.62 1.43-1.84	1.33 1.17-1.51	2.15 0.80-5.72 p=0.13
Migraine	1	0.85 0.76-0.94	1.33 1.17-1.51	1.02 0.38-2.71 p=0.97
Psoriasis /Eczema	1	1.06 0.94-1.14 p=0.15	1.30 1.14-1.49	2.08 1.23-3.50
Prostate disease	1	0.83 0.75-0.90	1.32 1.16-1.51	1.33 0.55-3.19 p=0.52
Osteoporosis	1	1.27 1.16-1.40	1.29 1.13-1.48	2.09 1.38-3.14
Atrial fibrillation	1	1.40 1.25-1.58	1.34 1.18-1.52	0.99 0.25-3.98 p=0.99
Anxiety	1	1.23 1.11-1.36	1.34 1.18-1.53	0.72 0.18-2.89 p=0.64
Inflammatory bowel disease	1	1.38 1.21-1.58	1.35 1.18-1.53	0.63 0.16-2.51 p=0.51
Heart failure	1	2.71 2.25-3.28	1.32 1.16-1.51	4.34 1.39-13.43

Supplementary Table 8 – Risk of MACE for individual index conditions in patients with RA and no index condition, RA with index condition, RA with no index condition or RA and index condition. Age-adjusted Cox's proportional hazards models were adjusted for sex, Townsend score, smoking status, alcohol intake frequency, BMI, physical activity level and level of rheumatoid factor. Unless otherwise shown, p<0·01. Index conditions labelled * have interaction term p>0.01. RA defined here as RA self-report plus hospitalisation, medication or primary care read code related to rheumatoid arthritis.

	Risk of MACE			
Index condition	**No RA, no index condition HR, (95% CI), p**	**No RA, with index condition HR, (95% CI), p**	**RA, no index condition HR, (95% CI), p**	**RA and index condition HR, (95% CI), p**
Hypertension	1	1.49 1.44-1.55	1.55 1.26-1.90	2.26 1.85-2.76
Coronary heart disease	1	1.89 1.80-1.98	1.60 1.37-1.88	2.31 1.65-3.22
Diabetes	1	1.66 1.58-1.75	1.62 1.39-1.90	1.66 1.58-1.75
Asthma	1	1.12 1.06-1.17	1.57 1.34-1.84	1.67 1.19-2.36
Dyspepsia	1	1.14 1.08-1.20	1.55 1.33-1.82	1.80 1.23-2.64
Cancer	1	1.11 1.05-1.17	1.59 1.37-1.85	1.42 0.87-2.33 p=0.16
Depression	1	1.25 1.17-1.34	1.53 1.31-1.78	2.38 1.52-3.74
Thyroid disorder	1	1.14 1.06-1.23	1.50 1.28-1.75	2.32 1.59-3.36
COPD	1	1.50 1.38-1.63	1.58 1.36-1.84	1.81 1.09-3.00
Epilepsy	1	1.50 1.31-1.74	1.56 1.35-1.81	1.74 0.44-6.97 p=0.43
Migraine	1	1.00 0.90-1.12 p=0.96	1.54 1.33-1.79	2.41 1.08-5.37
Psoriasis /Eczema	1	1.05 0.96-1.14 p=0.29	1.56 1.34-1.80	1.72 0.86-3.44 p=0.12
Prostate disease	1	0.91 0.83-1.00 p=0.05	1.53 1.32-1.78	2.53 1.20-5.31 p=0.01
Osteoporosis*	1	1.27 1.12-1.43	1.48 1.28-1.73	3.15 2.03-4.90
Atrial fibrillation	1	1.72 1.53-1.93	1.56 1.35-1.81	2.78 1.04-7.43 p=0.04
Anxiety	1	1.29 1.15-1.44	1.56 1.35-1.81	2.29 0.86-6.10 p=0.09
Inflammatory bowel disease	1	1.09 0.92-1.29 p=0.30	1.57 1.36-1.82	0.90 0.23-3.63 p=0.89
Heart failure	1	2.67 2.18-3.28	1.57 1.35-1.81	1.71 1.35-12.17 p=0.59

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2

Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	n/a (data collected by UK Biobank)
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6-7

Bias	#9	Describe any efforts to address potential sources of bias	n/a (data collected by UK Biobank)
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6-7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	8
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	8
Statistical methods	#12e	Describe any sensitivity analyses	8
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing	9

		follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	n/a (not applicable here)
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	9
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	9
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	10-13
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
Main results	#16b	Report category boundaries when continuous variables were categorized	10-13

Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-13
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	#18	Summarise key results with reference to study objectives	13
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	15
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	14
Generalisability	#21	Discuss the generalisability (external validity) of the study results	16-17
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

Notes:

- 6a: n/a (data collected by UK Biobank)
- 9: n/a (data collected by UK Biobank)

- 13c: n/a (not applicable here) The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 25. March 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai