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Systemic inflammation is associated with future risk of fatal infection: an observational cohort study

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Summary: Systemic inflammation assessed using C-reactive protein is common in many chronic diseases and is associated with increased long-term risk of fatal infection. This may contribute to the observed risks of fatal infection in recipients of anti-inflammatory therapies.

Conflict of interest statement: AWM has previously undertaken consultancy work on behalf of the University of Leeds in relation to giant cell arteritis for Roche, Chugai, GlaxoSmithKline, Sanofi, Regeneron Pharmaceuticals, Astra Zeneca and Vifor and has received research funding from UK National Institute of Health Research (NIHR) and Roche. MTK has received speaker fees from Merck and Novo Nordisk, and unrestricted research awards from Medtronic. KKW has: received research grants from the British Heart Foundation, the and NIHR Heart; undertaken consultancy work for Medtronic and Cardiac Dimensions; acted as an investigator and steering committee member for studies coordinated by Novartis, Medtronic; participated in data safety and monitoring board or advisory board for Microport and Boehringer Ingelheim; received speaker fees from Cardiac Dimensions, Medtronic, Microport, Abbott, Pfizer, Novartis, Boehringer Ingelheim and BMS; received payment for expert testimony from the UK National Health Service. MPR is currently employed by Union Chimique Belge (UCB) Biopharma. All other authors have no relevant disclosures.

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52 **Abstract**

53 *Background:* Many diseases are associated with chronic inflammation, resulting in
54 widening application of anti-inflammatory therapies. Whilst effective as disease
55 modifying agents, these increase the risk of serious infection; however, it remains
56 unknown if chronic systemic inflammation *per se* is also associated with fatal infection.
57 *Methods:* Using serum C-reactive protein (CRP) data from 461,052 UK Biobank
58 participants, we defined incidence rate ratios (IRR) for death from infection,
59 cardiovascular disease, or other causes, adjusted for comorbidities and the use of
60 anti-inflammatory therapies.
61 *Results:* Systemic inflammation, defined as CRP ≥2mg/L, was common in all
62 comorbidities considered. After adjusting for confounding factors, systemic
63 inflammation was associated with a higher IRR point estimate for infection death (1.70;
64 95% confidence interval 1.51-1.92) than cardiovascular (1.48; 1.40-1.57) or other
65 death (1.41; 1.37-1.45), although confidence intervals overlapped. CRP thresholds of
66 ≥5 and ≥10 mg/L yielded similar findings, as did analyses in people with ≥2, but not
67 <2, comorbidities.
68 *Conclusions:* Systemic inflammation *per se* identifies people at increased risk of
69 infection death, potentially contributing to the observed risks of anti-inflammatory
70 therapies in clinical trials. Future clinical trials of anti-inflammatory therapies should
71 carefully consider risks and benefits in target populations, guided by research into
72 mechanisms of infection risk.

73

74 **Key words:** Infection; inflammation; mortality; C-reactive protein

Background

Inflammation is a common pathological factor in many chronic diseases including atherosclerosis, arthritis, chronic lung disease, cancer, diabetes and obesity [1–5]; moreover, it is more common as multimorbidity accrues [6–8]. The success of anti-inflammatory therapies as disease modifying agents for inflammatory rheumatological, dermatological and gastrointestinal disorders has recently prompted phase 3 clinical trials in the context of atherosclerosis [9,10]. There is also hope that inflammation could represent a novel therapeutic target in diseases ranging from heart failure to cancer to depression [11–13]. However, canakinumab and colchicine failed to improve overall survival in people with advanced atherosclerosis, in spite of substantially reducing cardiovascular events, probably because of the increased risk of fatal infections [9,14]. This highlights the complexity of therapeutic modulation and suggests that future approaches will require nuance [15], perhaps informed by experience from more established indications for anti-inflammatory therapy [16]. However, in spite of a wealth of experience in therapeutically targeting inflammation, it remains unclear whether systemic inflammation *per se* is a risk factor for serious infection, perhaps by indicating individuals more likely to mount abnormal immune responses to pathogens. We set out to answer this question using the UK Biobank (UKB) cohort study, which provides detailed phenotyping of approximately 500,000 adults, including large numbers with diverse chronic inflammatory morbidities. Since clinical trials of anti-inflammatory therapies used serum C-reactive protein (CRP) ≥2 mg/L to include people with systemic inflammation [9,17], we used this threshold to define systemic inflammation in our analysis of UKB. Our primary objective was to define associations between CRP ≥2 mg/L and the risk of death from infection, cardiovascular disease or other causes, including stratification by chronic diseases

previously shown to be associated with increased risk of infection death [18]. We hypothesised that CRP ≥2 mg/L is associated with greater relative risk of death from infection than cardiovascular or other causes, and that this would be observed across chronic disease strata.

Methods

UK Biobank cohort: UKB is a population-based prospective cohort study that consists of 502,505 people aged between 37-73 years. The resource was developed using UK Government and biomedical research charity funding to improve understanding of disease and is an open access resource for all *bona fide* researchers. Full details of the study design and conduct are available from the UKB website (https://www.ukbiobank.ac.uk). Participants were recruited between 2006 and 2010 by approaching all adults living within 40 kilometres of 22 assessment centres across England, Scotland and Wales. Detailed analysis of differences between the UK population and UK Biobank cohort is provided by Fry and colleagues [19]. In brief, participation rates were higher in females than males (6.4% vs 5.1%); older people (9% in those aged ≥60 years and 3% in those aged 40–44 years); and in less socioeconomically deprived areas (8.3% among persons from the least deprived areas and 3.1% among persons from the most deprived areas). There was also possible under-representation of non-white ethnic groups. When compared with nationally representative data, Fry *et al* noted lower rates of self-reported disease and lower all-cause mortality in UK Biobank participants, overall consistent with a healthy volunteer effect. Whilst the cohort is not representative of the whole UK population relating to socio-economic deprivation (SED), some non-communicable diseases and ethnic minorities, it allows assessment of exposure-disease relationships [19].

Baseline biological measurements were recorded, and participants completed a touchscreen and nurse-led questionnaire, as described elsewhere [20]. UKB received ethical approval from the NHS Research Ethics Service (11/NW/0382); we conducted this analysis under application number 59585. All participants provided written informed consent.

Definitions of systemic inflammation and study covariates: Systemic inflammation was defined using serum C-reactive protein (CRP) data generated with a high sensitivity immunoturbidimetric assay (Beckman Coulter AU5800). UKB collected CRP data at study enrolment from 468,528 participants. Our primary analyses defined systemic inflammation as CRP ≥2mg/L, based upon prior clinical trials targeting anti-inflammatory agents to people above this threshold [9,17]. Potential confounding factors considered in the adjusted analyses were age, sex, ethnicity, SED, smoking status, comorbidity and anti-inflammatory medical therapy, all determined at study recruitment. Ethnicity was participant-classified within UKB-defined categories of white, mixed, Asian or British Asian, black or British black, Chinese or other ethnic group; due to the small number of people (and deaths) in each minority (non-white) ethnic group, these were pooled as 'non-white ethnicity'. Smoking status was self-reported as never, previous or current at the point of recruitment. SED was measured using the Townsend score, an area-based deprivation index, and categorised into quintiles. Obesity was classified using the World Health Organisation's categorisation according to body mass index: class 1 (30.0-34.9 kg/m^2), class 2 (35.0-39.9 kg/m^2), class 3 (≥40 kg/m^2). Self-reported medical disorders recorded solely at study recruitment during face-to-face interview with a nurse were used to classify morbidities (described in **Supplementary Table 1**). We used clinical consensus prior to our

analyses to select a range of morbidities that represent a broad spectrum of common disease groups: hypertension, chronic heart disease (ischaemic heart disease and heart failure), chronic respiratory disease, diabetes, prior cancer, chronic liver disease, chronic kidney disease, prior stroke or transient ischaemic attack (TIA), other neurological disease, psychiatric disease and chronic inflammatory and autoimmune rheumatic disease [18]. The number of these morbidities was calculated for each participant as an index of multimorbidity. Self-reported use of non-steroidal anti-inflammatory drugs (NSAID) or immunosuppressive agents (including disease-modifying anti-rheumatic drugs and oral glucocorticoids) was assessed at study enrolment as described in **Supplementary Table 2**. Missing data for comorbidities (n=863), body mass index (n=3,106), smoking (n=2,949), ethnicity (n=2,777), and SED (n=624), and loss to follow- up or withdrawal of consent (n=1,343), resulted in exclusion of 7,476 participants from our analyses (some participants with more than one variable missing), resulting in a study cohort of 461,052 participants.

Definition of outcomes: Mortality information provided by UKB was derived from linked national death registry data from NHS Digital for participants in England & Wales and from the NHS Central Register, part of the National Records of Scotland, for participants in Scotland. In the present analysis, we censored follow-up and only considered deaths until 31st December 2019 to ensure this was before the first reported case of COVID-19 in the United Kingdom [21]. As we have previously described, deaths were classified using ICD-10 codes for the main cause of death as infection-related [18], cardiovascular [22], or other causes; specific codes are described in **Supplementary Table 3**. Infection death was our primary study outcome.

Cardiovascular death was a secondary outcome given the wealth of data causally linking systemic inflammation to adverse cardiovascular outcomes [1,9,10,15].

Statistical analysis: Continuous variables are presented as mean (standard deviation) or median (inter-quartile range) if non-normally distributed, and categorical variables as number (percentage). Characteristics of participants with and without systemic inflammation were not formally statistically compared as these are descriptive data, rather than pertaining to a tested hypothesis. Adjusted cause-specific mortality incidence rate ratios (IRR) were estimated using Poisson regression with exposure time modelled. Time-varying covariates were not used, and the calendar year of recruitment was not included in models due to the narrow recruitment era. Unless specified otherwise, models were adjusted for all of the following covariates: age, sex, SED, smoking status, obesity, hypertension, chronic heart disease, chronic respiratory disease, diabetes, cancer, chronic liver disease, chronic kidney disease, prior stroke/TIA, other neurological disease, psychiatric disorder, autoimmune rheumatological disease, NSAID and immunosuppressive agent use. CRP was dichotomised as <2 or ≥2 mg/L in our primary analyses since this threshold has been applied in clinical trials of anti-inflammatory therapy [9,14]. When addressing multimorbidity, we separately modelled the number of comorbidities (i.e. number of comorbidities present at baseline, amongst those considered for adjustment, categorised as 1, 2, and 3 or more, since few participants had 4 or more) in place of the individual comorbidity variables (obesity, hypertension, chronic heart disease, chronic respiratory disease, diabetes, cancer, chronic liver disease, chronic kidney disease, prior stroke/TIA, other neurological disease, psychiatric disorder and rheumatological disease). When stratifying the population by specific morbidities, or

the number of comorbidities, the stratifying factor was excluded from the model. Correlation matrices of Poisson model's coefficients were used to confirm absence of correlation between covariates (defined as >0.3 or <-0.3). As previously described [18], age was modelled using restricted cubic splines with 5 knots for infection death analyses and 4 knots for non-infection death analyses, since these provided the best fit as assessed by the Akaike and the Bayesian Criterion (models including categorical, linear, cubic splines with 3, 4 and 5 knots and first and second degree fractional polynomials were compared). As the proportion of participants with missing covariate data is modest (1.6%), we did not impute missing data. Secondary analyses included: 1) assessment of age/sex adjusted, age/sex/socio-demographic factor/comorbidity adjusted and fully adjusted models; 2) sub-group analyses stratified by specific disease states or multimorbidity categories. Sensitivity analyses included: 1) assessment of alternate CRP thresholds of ≥5mg/L and ≥10mg/L; and 2) exclusion of participants who died during the first 6 months of follow-up, to reduce bias from reverse causality since elevated CRP could denote acute infection. All tests were 2-sided and statistical significance was defined as $p<0.05$. All statistical analyses were performed using Stata/MP (StataCorp LP, College Station, USA; version 16.1).

Results

Within a study population of 461,052 people, 35.2% (n=162,419) had serum CRP ≥2mg/L (characteristics of participants without CRP data are presented in **Supplementary Table 4**). In relation to people with CRP <2mg/L, a higher proportion of those with CRP ≥2mg/L were older, female, socio-economically deprived, current smokers, and multimorbid (**Table 1**). Similar observations resulted from analyses of people with CRP ≥5mg/L (11.6%; n=53,468) and ≥10mg/L (4.1%; n=19,024), as

shown in **Supplementary Tables 5-6**. Notably, CRP ≥2mg/L was highly prevalent in all of the chronic diseases studied, ranging from 39.6% of people with cancer, to 85.6% of people with class 3 obesity, and was more prevalent in people with greater multimorbidity (**Figure 1**).

After 4,927,012 person-years of follow-up (median 10.9 [IQR 10.1 – 11.6] years per participant), 25,619 deaths (5.6% of participants) occurred. Of these, 1,274 (5.0%) were attributed to infection, 5,202 (20.3%) to cardiovascular events, and 19,143 (74.7%) to other causes. IRRs for the association between CRP ≥2mg/L and these three categories of death are shown in **Figure 2**. Results from secondary analyses presenting IRRs from unadjusted, age/sex adjusted, and other models are also presented in **Supplementary Table 7**. To exclude the possibility that deaths occurring early during follow-up were related to undiagnosed acute infection at the time of enrolment, we repeated analyses after excluding all deaths during the first 6-months and derived similar IRRs (**Supplementary Table 8**). These data illustrate that CRP ≥2mg/L is associated with increased risk of the three categories of death. Point estimates for relative risk of infection death were higher than for cardiovascular or other death, although some confidence intervals overlapped. Sensitivity analyses using higher CRP thresholds of ≥5mg/L and ≥10mg/L yield broadly the same conclusion, although differences in point estimates of relative risk between infection death and cardiovascular or other death were higher than for the ≥2mg/L threshold (**Figure 2)**. However, in spite of higher relative risk of infection death, it is important to emphasise that the absolute rate of infection death was lower than those of cardiovascular and other death, even in people with CRP ≥10mg/L (**Supplementary Table 9**).

We also assessed whether the association between systemic inflammation and cause-specific mortality was consistent in subgroups with specific morbidities or accumulating multimorbidity. Again, CRP ≥2mg/L was associated with increased risk of all categories of death, but nominally higher IRRs were observed for infection death than cardiovascular or other death in all morbidities except 'other neurological diseases' (**Figure 3**). The same conclusion was reached irrespective of the number of comorbid diseases, although the IRR for infection death was nominally lower than that for cardiovascular death in people without disease (**Figure 4**). Sensitivity analyses applying higher CRP thresholds of ≥5mg/L and ≥10mg/L yielded similar conclusions (**Supplementary Tables 10-13**).

Discussion

Our analysis provides a novel exploration of the association between systemic inflammation and infection death and has important implications for future research and clinical practice. We show that elevated CRP is highly prevalent in many morbidities and is associated with a greater relative risk of infection death than cardiovascular or other causes of death, irrespective of the CRP threshold chosen. This observation was consistent in stratified analyses across the vast majority of diseases we studied, suggesting that it is broadly relevant to people with diverse diseases, or combinations of diseases. In the context of broadening clinical use of anti-inflammatory therapies, our data caution that people identified as candidates based on elevated CRP are already predisposed to fatal infection before initiating treatment. This suggests that careful balancing of risks and benefits of such therapies is

essential, which is likely to require greater understanding of how perturbed inflammation contributes to chronic diseases in order to personalise therapy.

Our findings may be particularly pertinent to recent clinical trials, which targeted canakinumab or colchicine to people with advanced atherosclerotic cardiovascular disease [9,10]. Inflammation is a key driver of atherosclerosis [1,15], and these trials demonstrated clinically important reductions in adverse cardiovascular events, yet without improving overall mortality [9,10]. Serious infection events are also substantially increased by these agents [9,14], which may underpin their failure to improve overall survival in people with advanced atherosclerosis; this represents a major hurdle to routine clinical adoption. Whilst these trials only recruited people after myocardial infarction, data from people with other cardiovascular diseases demonstrate that adverse infection events are frequent causes of death [22–25], suggesting that safely targeting inflammation will be challenging. However, in our study, whilst we consistently observed that elevated CRP was associated with a greater relative risk of infection than cardiovascular death, absolute rates of infection death were still appreciably lower, suggesting that safer anti-inflammatory approaches could offer overall benefit. Indeed, the targeting of Rosuvastatin to people at high cardiovascular risk with CRP ≥2mg/L was shown to reduce inflammation, along with improving cardiovascular events *and* all-cause mortality [17].

Beyond cardiovascular disease, our observations have much broader relevance since inflammation is causally implicated in many disease processes [1–8]. We observed that elevated CRP was common across diseases, and in disease- or multimorbidity-stratified analyses was almost uniformly associated with greater IRR for infection

298 death than for cardiovascular death. Previously, we have shown that multimorbidity
299 and some morbidities (class 3 obesity, hypertension, chronic respiratory disease,
300 chronic kidney disease, psychiatric disease, chronic inflammatory and autoimmune
301 rheumatological disease), along with advancing age and increasing SED, were
302 associated with greater risk of infection death than other causes of death [18]. Since
303 elevated CRP was still associated with greater risk of infection death than other causes
304 of death in these subgroups, it is possible that the combination of elevated CRP and
305 these diseases identifies people particularly predisposed to infection death.
306
307 An important question arising from our observations is which factors mediate the
308 association between systemic inflammation and infection death. Since elevated CRP
309 was more strongly associated with infection death than cardiovascular or other causes
310 of death in all but one of the morbidities we studied, a common mechanism (or
311 mechanisms) seems the most plausible explanation. One possibility is that elevated
312 CRP is a marker of frailty and reduced physiological reserve, and the substantial
313 reduction in IRR between crude and age-sex adjusted models (**Supplementary Table**
314 **7**) may support this possibility. However, the persistent association between elevated
315 CRP and infection death in our 'fully adjusted' models suggests that factors beyond
316 frailty and comorbidity are relevant. Another possibility is that elevated CRP is a
317 biomarker of more broadly perturbed immune responses, as observed with ageing,
318 and characterised by persistent systemic inflammation and impaired adaptive immune
319 responses to pathogens and vaccines [26–28]. Notably, recent data have suggested
320 that clonal haematopoiesis of indeterminate potential (CHIP), a disorder arising from
321 somatic mutations that promote over-representation of pro-inflammatory myeloid
322 clones (and elevated CRP) [29,30], is associated with increased risk of diverse

infections [31]. Therefore, it will be important for future research to better profile the immune milieu in at risk populations, both in periods of usual health and during episodes of infection. These data may help to identify elements of the immune response whose perturbation may predispose to infection, which may act as a useful biomarker and even define safer avenues for anti-inflammatory therapy or strategies to reduce infection risk.

It is also important to interpret our work in the context of some limitations. First, the observational design precludes us from inferring causality in the association between systemic inflammation and infection death. Second, we have no data on the use of immunosuppressive anti-inflammatory therapies beyond the point of study enrolment, or indeed the lifetime doses of these. This is important since some people with undiagnosed inflammatory disorders, either at baseline or emerging during follow-up, may have later commenced these therapies, which are known to increase the risk of infection death. Moreover, lifetime dose of some immuno-suppressive agents is associated with increased risk of infection and cardiovascular events [16,32]. Hence, our adjusted IRR data may overestimate the association between elevated CRP and some causes of death. However, a relatively small proportion of the general population is prescribed such therapy, so our inability to account for incident use is unlikely to substantially diminish our estimates. Our analysis is similarly limited by only having access to CRP and covariate data at baseline. Finally, it is important to note that CRP defines only one facet of inflammation and may not be the optimal biomarker to define or understand this issue; hence, future studies should explore other markers.

In conclusion, we show that elevated CRP is common in people with diverse chronic diseases and accumulates with multimorbidity. Irrespective of the threshold chosen, CRP defines a group of people at particularly increased relative risk of infection death. Moreover, this observation persisted in analyses restricted to the majority of comorbidities we studied, indicating that it is broadly relevant. This suggests that using CRP as a biomarker to identify people who may benefit from potent anti-inflammatory therapies also selects a population at increased risk of fatal infection, in keeping with recent clinical trial data in people with atherosclerosis [9]. This raises the question of whether more could be done to prevent infection, for example by improving suboptimal uptake of existing vaccination strategies [16], before commencing anti-inflammatory therapy. Future research should aim to understand the immune responses to pathogens in people with systemic inflammation, which may help to develop safer anti-inflammatory therapies for chronic disease and target their use to people most likely to obtain net benefit.

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Figure Legends

Figure 1: Prevalence of elevated CRP in chronic morbidity or multimorbidity groups

Stacked bar chart illustrating the percentage of people in specified chronic disease and multimorbidity groups with CRP ≥2mg/L, ≥5mg/L and ≥10mg/L. CRP – C-reactive protein; TIA – transient ischaemic attack.

Figure 2: Adjusted incidence rate ratios of cause-specific mortality according to CRP category

Forest plot illustrating adjusted incidence rate ratios (IRR) and their 95% confidence intervals (CI) for specified modes of death in people with CRP ≥2mg/L, ≥5mg/L and ≥10mg/L (versus below these thresholds). The adjusted model includes the following factors in addition to CRP categories: age, sex, SED, smoking status, obesity, hypertension, chronic heart disease, chronic respiratory disease, diabetes, cancer, chronic liver disease, chronic kidney disease, prior stroke/TIA, other neurological disease, psychiatric disorder, autoimmune rheumatological disease, self-reported NSAID prescription and self-reported immunosuppressive agent prescription. CV – cardiovascular.

Figure 3: Adjusted incidence rate ratios of cause-specific mortality in people with CRP ≥2mg/L stratified by chronic disease group

Forest plot illustrating adjusted incidence rate ratios (IRR) and their 95% confidence intervals (CI) for specified modes of death in people with CRP ≥2mg/L versus CRP <2mgL stratified by chronic disease group. The adjusted model includes the following

factors in addition to CRP status within chronic disease group strata: age, sex, SED, smoking status, comorbidity beyond defined strata (including obesity, hypertension, chronic heart disease, chronic respiratory disease, diabetes, cancer, chronic liver disease, chronic kidney disease, prior stroke/TIA, other neurological disease, psychiatric disorder) autoimmune rheumatological disease), self-reported NSAID prescription and self-reported immunosuppressive agent prescription. CV – cardiovascular; TIA – transient ischaemic attack.

Figure 4: Adjusted incidence rate ratios of cause-specific mortality in people with CRP ≥2mg/L stratified by number of morbidities

Forest plot illustrating adjusted incidence rate ratios (IRR) and their 95% confidence intervals (CI) for specified modes of death in people with CRP ≥2mg/L versus CRP <2mgL stratified by the extent of multimorbidity. The adjusted model includes the following factors in addition to CRP status within multimorbidity strata: age, sex, SED, smoking status, self-reported NSAID prescription and self-reported immunosuppressive agent prescription. CV – cardiovascular.

Table 1: Characteristics of people with CRP <2mg/L and ≥2mg/L

	CRP<2	CRP ≥2
	n=298,633	n=162,419
Age (Years)		
<45	33,864 (11.3)	13,466 (8.3)
45 to <50	42,303 (14.2)	18,272 (11.2)
50 to <55	46,603 (15.6)	23,418 (14.4)
55 to <60	54,047 (18.1)	29,363 (18.1)
60 to <65	69,635 (23.3)	42,099 (25.9)
65+	52,181 (17.5)	35,801 (22.0)
Sex		
Female	157,308 (52.7)	93,127 (57.3)
Male	141,325 (47.3)	69,292 (42.7)
Ethnicity		
White	283,469 (94.9)	153,602 (94.6)
Non-white	15,164 (5.1)	8,817 (5.4)
SED quintile		
1 (least deprived)	63,123 (21.1)	29,166 (18.0)
2	61,832 (20.7)	30,302 (18.7)
3	60,578 (20.3)	31,641 (19.5)
4	58,928 (19.7)	33,273 (20.5)
5 (most deprived)	54,172 (18.1)	38,037 (23.4)
Smoking		
Never	171,359 (57.4)	81,086 (49.9)
Former	100,953 (33.8)	59,200 (36.4)
Current	26,321 (8.8)	22,133 (13.6)
Obesity		
Not obese	253,639 (84.9)	94,204 (58)
Class 1	37,404 (12.5)	43,938 (27.1)
Class 2	6,312 (2.1)	16,703 (10.3)

Class 3	1,278 (0.4)	7,574 (4.7)
Hypertension	67,259 (22.5)	54,842 (33.8)
Chronic cardiac disease	12,864 (4.3)	8,933 (5.5)
Chronic respiratory disease	33,773 (11.3)	25,814 (15.9)
Diabetes	12,259 (4.1)	10,733 (6.6)
Cancer	22,846 (7.7)	14,975 (9.2)
Chronic liver disease	464 (0.2)	439 (0.3)
Chronic kidney disease	583 (0.2)	592 (0.4)
Prior stroke/TIA	4,496 (1.5)	3,483 (2.1)
Other neurological disease	3,541 (1.2)	2,547 (1.6)
Psychiatric disorder	15,755 (5.3)	12,004 (7.4)
Rheumatological disease	4,501 (1.5)	5,894 (3.6)
NSAID use	44,525 (14.9)	30,648 (18.9)
Immunosuppressant use	5,609 (1.9)	6,572 (4.0)
Number of chronic diseases		
0	149,909 (50.2)	45,502 (28.0)
1	94,988 (31.8)	56,652 (34.9)
2	37,770 (12.6)	37,566 (23.1)
3+	15,966 (5.3)	22,699 (14.0)

Legend: CRP – C-reactive protein; NSAID – non-steroidal anti-inflammatory drug; SED – socio-economic deprivation; TIA – transient ischaemic attack