Understanding associations between rheumatoid arthritis and associated biomarkers with brain and psychological health in the UK Biobank

Ioana Stanciu
MA (Hons), MSc

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School of Health and Wellbeing
College of Medical, Veterinary and Life Sciences

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Abstract

Rheumatoid arthritis (RA) is the most prevalent chronic inflammatory condition affecting the joints, that if left untreated can result in permanent damage and reduced quality of life. The general focus of RA literature and treatment has been on pain, inflammation and maintaining joint function, with limited research on psychological factors such as mental health, sleep and cognition, and an almost complete gap for structural brain differences (vs. people without RA). Similarly, more research is needed to understand the role of rheumatoid factor (RF), an autoantibody that is used in the official classification criteria for RA. This thesis aimed to fill in these gaps in the literature, with the overall aim of investigating whether RA/RF positive (RF+) are associated with differences in mental health, sleep, cognition, and structural brain health.

This thesis used data from a relatively large cohort, the UK Biobank, covering approximately 500,000 people for the baseline visit and around 40,000 participants for the imaging visit to test for associations between RA/RF and mental health, sleep, and cognition in Chapter 3; associations between RA/RF and structural brain phenotypes in Chapter 4; and associations between increased polygenic risk for RF with structural brain and cognitive differences in Chapter 5. Compared to previous studies, the current thesis had the advantage of using a very large cohort that also enabled me to control for a variety of confounders that have largely been neglected in previous literature.

Chapter 3 provides evidence that self-reported RA is associated with higher neuroticism, worse sleep, and worse performance on cognitive tests for reaction time and fluid intelligence while RF+ status was associated with worse sleep. Chapter 4 suggested that self-reported RA

is associated with a higher volume of white matter lesions, higher volume of the caudate, and a smaller volume for the amygdala. Chapter 5 found that a polygenic risk score (PRS) for RF was associated with markers of healthier white matter, more specifically lower volume of lesions and lower mean diffusivity, and better performance on a cognitive test for visuo-spatial processing and short-term memory.

This thesis provided evidence that people with RA/RF+ status might present with differences in psychological and brain structure health that are currently unaddressed and untreated in the clinic despite being important contributors to overall health, as well as health-related quality of life. Considering that it is still unclear what exactly causes RA, as well as why some people respond well to treatments while others do not benefit from medication at all, this thesis suggests that future research should further aim for a better understanding of blood biomarkers, genetic risk factors, and psychological and brain health differences associated with RA. This could aid diagnosis, disease stratification, treatment, and health interventions, as well as a better understanding of comorbid risk factors.

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This thesis is dedicated to my parents to whom I owe everything!

Author’s Declaration

I declare that this thesis has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where stated otherwise by reference or acknowledgement, the work presented is entirely my own.

Ioana Stanciu

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Definitions/ Abbreviations

ACPA	Anti-Citrullinated Protein Antibody
ACR	American College of Rheumatology
AD	Alzheimer's Disease
BMI	Body Mass Index
CBT	Cognitive Behavioural Therapy
CCTCC	Cerebellar-thalamic-cortical circuit
CI	Confidence Interval
CRP	C-reactive Protein
CVD	Cardiovascular Disease
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
DSM	Diagnostic and Statistical Manual of Mental Health Disorders
DT-MRI	Diffusion tensor magnetic resonance imaging
DZ	Dizygotic (twins derived from two separate ova, and so not identical)
ESR	Erythrocyte Sedimentation Rate
EULAR	European Alliance of Associations for Rheumatology
FA	Fractional Anisotropy
FDR	False Discovery Rate
GM	Total Gray Matter Volume
GWAS	Genome-Wide Association Study
HADS	The Hospital Anxiety and Depression Scale
ICV	Intracranial Volume
MD	Mean Diffusivity
MDD	Major Depressive Disorder
Meta-SMR	Meta Standardized Mortality Rate
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MR	Mendelian Randomization
MRI	Magnetic Resonance Imaging
MZ	Monozygotic (twins derived from a single ovum, and so identical)
NHS	National Health Service
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratio
PHQ-9	Patient Health Questionnaire- Depression module
PRS	Polygenic Risk Score
PRT	Progressive Resistance Training
PSQI	Pittsburgh Sleep Quality Index
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RF	Rheumatoid Factor
SE	Standard Error
SNP	Single-Nucleotide Polymorphism
TBV	Total Brain Volume
ULN	Upper Limit of Normal
LLN	Lower Limit of Normal
WM	Total White Matter Volume
WMH	White Matter Hyperintensities

Publications and Conference Presentations or Abstracts

The following publications and conference presentations or abstracts have been submitted and accepted following research described in the current thesis.

Publications:

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Chapter 1: Introduction

1.1 Chapter overview

Despite being the most prevalent chronic inflammatory condition affecting the joints, there are currently significant gaps in the literature regarding the associations between RA and mental health, sleep, cognition, and structural brain differences, while in the clinic they go completely unaddressed. The limited number of studies that do investigate these factors suffer from a small sample size, not correcting for any confounders such as age, sex, ethnicity, deprivation, smoking status, or alcohol intake, while measurement instruments vary considerably. Similarly, the role of RF in general, as well as in the development of RA is not clearly understood. This thesis aims to fill in these gaps, highlighting the importance of addressing these factors to improve people's health and quality of life.

1.2 Rheumatoid arthritis

Rheumatoid arthritis (RA), the most prevalent chronic inflammatory condition affecting the joints, is characterized by pain, stiffness and swelling of peripheral joints, which if not controlled, can lead to permanent damage (Symmons, 2002). In the UK the estimated prevalence of RA in adults is 0.81%, with a higher prevalence for women (1.16%) than for men (0.44%) (Symmons et al., 2002). Based on these estimates there were around 387,000 people in the UK living with RA in the year 2000. On an individual level, people with RA have reduced physical function and quality of life (Smolen et al., 2016) and an increased risk of mortality due to comorbidities, most notably CVD (cardiovascular disease) (Aviña-Zubieta et al., 2008). From a socioeconomic viewpoint, work disability is a major concern for people with RA (Sokka et al., 2010). A systematic review published in 2000 on the economic burden of RA estimated that the mean annual cost per person was over £3,500 (Cooper, 2000). This can be split into

direct costs such as medication, hospitalisation, surgery, diagnostic tests, emergency room visits and indirect costs such as absenteeism, presenteeism and work disability (Hsieh et al., 2020). While in the past the costs associated with RA have been dominated by indirect costs, with the advent of effective but expensive therapies, drugs have become the main component of the cost burden, with a more recent systematic review estimating that medication accounts for up to 78% of direct costs (Hsieh et al., 2020).

The exact pathogenesis of RA is unknown but it is believed that genetic predisposition and environmental determinants play an important role in the onset and development of the disease (Symmons, 2002). One way to measure the proportion of variance in RA that is explained by genetic variation (i.e., heritability) is by comparing prevalence rates in monozygotic (MZ) and dizygotic (DZ) twins. While both types of twins have the same shared environment, the genetic contribution to covariance in DZ twins is half that of MZ twins (MacGregor et al., 2000). Using data from two previously published nationwide studies of twin populations in Finland and the UK, RA was identified in 73 MZ twins and 173 DZ twins in the Finnish cohort and 91 MZ twins and 112 DZ twins in the UK cohort, and using a variance components analysis, RA heritability was estimated around 60%, with no differences between groups for sex, age, disease onset age and disease severity (MacGregor et al., 2000). The Finnish population of this study was drawn from health registers linked through record linkage to information from a nationwide sickness insurance register, with date of birth used to approximate age at the time of the survey. In contrast, a study published in 2002 using two nationwide twin populations from the Danish Twin Register (MZ N = 13 and DZ N = 36, cohort 1 born between 1921 to 1940, cohort 2 born between 1953 to 1982) reported heritability as 0%, indicative of no genetic contribution to RA development (Svendsen et al., 2002). A revised

version of the study in 2013, using a larger sample (MZ N = 34; DZ same-sex N = 81; DZ opposite sex N = 47) gave an estimate of around 12% (Svendsen et al., 2013), highlighting the importance of sample size in these studies and providing an explanation for the observed discrepancy in heritability estimates between papers. In general, the most important limitation of twin studies is the very small sample size as there are relatively few pairs of twins with RA available to recruit (Viatte & Barton, 2017).

Using the familial aggregation method from the Swedish total population (RA N = 90,372), heritability was estimated to be around 50% for anti-citrullinated protein antibody (ACPA)-positive RA and approximately 20% for ACPA-negative RA (Frisell et al., 2013). Since the International HapMap Project mapped the entire human genome (Gibbs et al., 2003), genetic technology and statistical methods evolved rapidly leading to several genome-wide association studies (GWAS) for RA (Okada et al., 2019). For example, a genome-wide complex trait study estimated that RA heritability attributable to common single-nucleotide polymorphisms (SNPs) is approximately 19% (RA N = 8064; SE = 0.007) (Lee et al., 2015). These SNPs can then be used to estimate someone's PRS (genetic risk) for a particular disease or trait and potentially aid disease stratification and diagnosis. To our knowledge there is a complete gap in the literature for studies that generated a PRS for RF.

1.3 Characteristics and comorbidities

RA is an auto-immune condition that primarily involves the joints (Smolen et al., 2016) and a patient is currently classified as having RA if they have a score of ≥6/10 using the criteria in **Table 1.** below. A more detailed version of this table is available in the Appendices.

Table 1 The 2010 ACR American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria. Source: (Aletaha et al., 2010a)

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)	
2) with the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA)	
A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

The course of RA seems to vary considerably between patients resulting in a focus in research on identifying predictors of likelihood of disease such as age, sex, or biomarkers like RF and other autoantibodies (Scott & Steer, 2007). T-cells and B-cells are paramount to the development of RA, with the synovial tissue being an active site for the accumulation of B-cell activity, plasma cell differentiation and production of antibodies, making B-cells an excellent target for both management and immunosuppressive therapy improvement in RA (Nakken et al., 2011). A high number of B-cells in the synovial membrane produce RF, an autoantibody that is reported to be present in approximately 80% of people with RA and that can occur years before any clinical symptoms of RA (Nell et al., 2005). A prospective study of 9,712 people without RA suggested that higher levels of RF led to a 26-fold higher long term risk and up to 32% higher 10-year absolute risk of developing RA (Nielsen et al., 2012). This means that within 10 years from the blood analysis indicating positive RF, one in three patients will develop RA (Nielsen et al., 2012). RF might therefore play a pivotal role in the pathogenesis of RA. Patients with a positive RF can have worse outcomes and higher disease activity and radiographic progression, a more aggressive disease course, as well as higher morbidity and mortality than those with negative RF (Aletaha et al., 2013; Nakken et al., 2011; Scott et al., 1987).

However, RF is not specific to patients with RA and can be present in the general population (Van Schaardenburg et al., 1993) and other conditions too (Pasternack et al., 1990). It has been suggested that RF levels increase with age, but strong evidence for this is lacking (Nielsen et al., 2012), and the majority of papers investigating the role of RF in the development of RA are several decades old. For example, in the Van Schaardenburg et al. (1993) study, there was a significant gradual increase with age in the levels of lgG-RF ($p < 0.0001$), but a decrease in lgM-RF levels ($p < 0.0001$) and no change for lgA-RF levels

(p = 0.63). A better understanding of the specific genetic susceptibility of RF could have significant scientific and clinical value for early diagnosis and treatment.

The above ACR classification criteria (Aletaha et al., 2010a) (**Table 1**) is intended to increase specificity in research, making it problematic for a quick and early diagnosis in a clinical setting without assessing each individual situation-risks and cost-effectiveness (Mjaavatten & Bykerk, 2013; Smolen et al., 2005). Joint damage occurs early in the course of RA (Nell et al., 2005; O'Dell, 2004) so early treatment is essential for long-term benefits and to avoid irreversible damage (Quinn & Emery, 2003), especially in the first 3 months (Nell et al., 2004). Therefore, prompt diagnosis and follow-up treatment are paramount for RA management (Nell et al., 2004) but a gold standard test for fast diagnosis is lacking. If not treated optimally or early enough, RA can lead to several negative outcomes including increased mortality, hospitalization and work disability and decreased quality of life (Michaud & Wolfe, 2007). RA is also associated with other comorbidities such as CVD, diabetes and depression (Michaud & Wolfe, 2007). Among RA comorbidities, CVD has been studied most extensively and accounts for the majority of the increased mortality associated with RA. A meta-analysis indicated that people with RA have a 50% increased risk of CVD-related mortality compared to the general population (meta-SMR 1.50, 95% CI: 1.39 to 1.61), with no significant differences between men and women (meta-SMR for women 1.58, 95% CI 1.35 to 1.84, meta-SMR for men 1.45, 95% CI: 1.11 to 1.90) (Aviña-Zubieta et al., 2008). Even after accounting for traditional cardiovascular risk factors (54%), there is still a large proportion of heart failure (at the age of 80) left unexplained in RA patients (p < 0.01) (Crowson et al., 2005).

Risk factors: smoking status, alcohol intake and BMI

In a case-control study at the national level in Denmark that included 515 RA patients and 769 sex and age-matched controls (Pedersen et al., 2006), participants that reported being former or current smokers were more likely to be diagnosed with RA than people that never smoked (OR = 1.57 and OR = 1.80 respectively, $p < 0.001$). A meta-analysis of 16 studies further suggests that being a current or past smoker increases people's odds of having RA (Sugiyama et al., 2010), with an almost twice as high risk for male smokers and 1.3 as high risk for female smokers than non-smokers. No differences between females and males were noticed for heavy smokers. Moreover, for RF+ male smokers the odds were almost double. Similarly, in another study (Saag et al., 1997) involving 336 RA patients, those that reported smoking for over 25 years were 3.1 times more likely to be RF+, even after adjusting for covariates. Having a body mass index (BMI) over 30 was also associated with an increased risk of RA (RR = 1.25, 95% CI: 1.07 to 145) (Qin et al., 2015) and 40% lower odds of achieving remission (Liu et al., 2017). In contrast, overall alcohol consumption 10 years prior to the interview was inversely associated in a dose-response manner with the risk of developing RA ($p = 0.05$) (Pedersen et al., 2006). A 'protective' effect of alcohol for RA was reported in several other papers as well. A systematic review and meta-analysis of nine such studies reported that alcohol consumption was suggested to have a protective effect against RA when comparing drinkers and non-drinkers (OR = 0.78, 95% CI: 0.63 to 0.96, $p < 0.001$) (Scott et al., 2013). However, due to the observational nature of these studies the protective effect of alcohol on RA might be observed due to confounding or reverse causation. It is plausible that those with more severe RA simply drink less alcohol and that complete abstainers are a less healthy population than those that drink occasionally. Indeed a two-sample mendelian

randomization study did not support an inverse causal relationship between alcohol consumption and RA (β = -0.778, p = 0.42) (Bae & Lee, 2018).

1.4 Treatment of RA

Pharmacological treatment

There is currently no cure, and therefore treatment for RA has three main aims: (1) pain and inflammation reduction; (2) maintaining joint function and improving quality of life; and, (3) prevention of disease progression and/or joint function loss (Alam et al., 2017). There is an expanding range of immunomodulatory therapies available to help achieve these aims, incorporating: non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), biological agents (biologic DMARDs) and JAK inhibitors (for a comprehensive list of medication see **Table 2)** (Alam et al., 2017). However, there are still patients who do not respond to any therapy, while many who do respond only partially benefit from these treatments (Alam et al., 2017; Viatte & Barton, 2017). As for any pharmacological therapy, there can also be significant side effects associated with these therapies. While there are guidelines and treatment recommendations for RA, there is still no gold standard for diagnosis (Aletaha et al., 2010b). A better understanding of prognostic and theragnostic biomarkers (e.g., serological, genetic etc.) could enable a more stratified, precision medicine approach, which can have tremendous benefits for improving health and treatment costs in RA. For example, the synovial expression of tumor necrosis factor- α (TNF-α) is believed to be a response biomarker, while anti-cyclic citrullinated peptide antibody and rheumatoid factor positivity have been suggested to predict poor responses (Gibbons & Hyrich, 2009). Also, due to high levels of B-cell activating factor (BAFF) cytokine

only present in RF+ patients, pharmacological treatment such as Rituximab has been suggested to be less effective in RF- patients, whereby B-cells play a smaller role than in RF+ patients (Nakken et al., 2011). Indeed, major improvements have been made in RA patient treatments by classifying pharmacological options by mechanism of action, including TNF-α inhibitors, interleukin-6 inhibitors, T-cell costimulation inhibitors, B-cell modulation and JAK inhibitors (Strand et al., 2022).

Table 2 Pharmacological treatment used in RA. Source: (Alam et al., 2017)

NSAIDS	**Corticosteroids**	**DMARDS**	**Biologic Agents**	
			In used/Target	**In phase Trial/Target**
Ibuprofen	Methyl Prednisolone	Auranofin (oral gold)	Abatacept/	Canakinumab/ Human anti-IL1ß monoclonal antibody
Naproxen	Prednisolone	Azathioprine	T-cell costimulation blocker Adalimumab/	Sirukumab/ Human anti-IL-6 monoclonal antibody
Ketoprofen	Triamcinolone acetonide	Cyclosporin	TNF blocker Anakinara/	Secukinumab/ Human anti-IL-17A monoclonal antibody
Piroxicam	Triamcinolone hexaacetonide	D-Penicillamine	IL-1 receptor blockade Certilozumab Pegol/	Ofatumumab/ Human anti-CD20 monoclonal antibody
Diclofenac		Hydroxychloroquine	TNF blocker Etaneracept/	Atatcicept/ Inhibit B cell maturation by blocking the binding BLyS & APRIL
Celecoxib		Leflunomide	TNF blocker Golimumab/ TNF blocker Infliximab/	Denosumab/ Anti-RANK ligand antibody
		Methotrexate	TNF blocker Rituximab/	Tofacitinib/ Orally administered JAK inhibitor that selectively inhibits Janus kinase (JAK), JAK-1, JAK-2, JAK-3
		Mycophenolate mofetil (MMF)	B-cell depletion Toxilizumab/	Fostamatinib/ Spleen tyrosine kinase (Syk) inhibitors The Syk signalling pathway has an important role in the TNF alpha-induded expression of inflammatory cytokines.
		Sodium aurothiomalate	IL-6-receptor blockade	
		Sulfasalazine		
		Cyclophosphaminde		

Non-pharmacological treatment

Despite limited published research, there is accumulating evidence that RA patients might also benefit from non-pharmacological interventions, in addition to existing pharmacological therapies. Systematic reviews comparing psychological interventions, such as relaxation, biofeedback, cognitive-behavioural therapy (CBT) and stress management, to usual treatment (waiting list) for RA found a positive effect on pain, functional disability, depression, coping, self-efficacy, cognitive coping and appraisal and social role function (number of studies included 25, 31 and 25 respectively) (Astin et al., 2002; Dissanayake & Bertouch, 2010; Morley et al., 1999). A randomized controlled trial of CBT in RA indicated that delivering psychological treatment in the first two years of RA diagnosis (N = 53; Mean age = 55.06 ± 14.07) (Sharpe et al., 2001) is just as important as prompt physical treatment (Quinn & Emery, 2003) for delivering long-term benefits.

While in the past people with RA were often advised against physical activity due to perceived concerns about joint damage (Durcan et al., 2014), there is increasing evidence that it is in fact beneficial, a good alternative to pharmaceutical approaches aimed at improving sleep in RA and that its therapeutic effects have been underestimated (Baillet et al., 2010). Physical activity interventions positively affected several RA patient reported outcomes: function, quality of life, pain, stiffness, sleep quality, fatigue, disease activity and decreased radiologic damage (Baillet et al., 2010; Cairns & McVeigh, 2009; Durcan et al., 2014). As the biggest cause of mortality in RA is CVD (Aviña-Zubieta et al., 2008), aerobic exercise may prove to be particularly beneficial for this population in light of its known cardio-protective effects. Also, an RCT (N = 28) of high-intensity progressive resistance training (PRT) suggested that it is an effective and safe treatment for restoring muscle mass in RA ($p < 0.05$) (Lemmey et al., 2009).

1.5 RA and physical and mental health

1.5.1 Depression

Patients with RA are more likely to suffer from depression than the general population (N = 2,597; r = 0.21; 95% CI: 0.17 to 0.24; $p < 0.0001$), even after controlling for age and sex (N = 1,894; r = 0.19; 95% CI: 0.15 to 0.24; $p < 0.0001$) (Dickens et al., 2002). A cross-sectional study (Lok et al., 2010) recruited patients with RA (N = 200; 79% women; mean age = 51.4 ± 10.5 years) from an outpatient rheumatology clinic in Hong Kong, who were then assessed and diagnosed by a psychiatrist according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders). Depressive disorders were found to have a point prevalence of 14.5% and a lifetime prevalence of 39% in this RA sample. Four independent factors were found to predict depression: reduced social interaction (OR = 1.94, 95% CI: 1.14 to 3.31; $p < 0.05$), reduced perceived social support (OR = 0.96, 95% CI: 0.92 to 0.99; $p < 0.05$), increased pain intensity (OR = 1.05, 95% CI: 1.01 to 1.10; $p < 0.05$) and a family history of psychiatric disorders (OR = 19.93, 95% CI: 1.84 to 215.47; $p < 0.05$). The authors draw attention to the role of social support and suggest it can act as a buffer in the face of adverse events such as a chronic disease.

Prevalence rates for depression in RA vary significantly between studies. A systematic review reported that estimates for the prevalence of depression range from 16.8% (95% CI: 10% to 24%) using the gold standard of diagnostic criteria (i.e., DSM diagnostic criteria), 38.8% (95% CI: 34% to 43%) using the Patient Health Questionnaire depression module (PHQ-9) and between 14.8% (95% CI: 12% to 18%) and 48% (95% CI: 9% to 87%) using the Hospital Anxiety and Depression Scale (HADS) (Matcham et al., 2013a). Nevertheless, irrespective of what

measurement instrument was used, all the above prevalence rates are significantly higher than those for depression in the general population: 4.1% for 1-year estimates (95% CI: 2.4% to 6.2%) and 6.7% for lifetime prevalence (95% CI: 4.2% to 10.1%) (Waraich et al., 2004). Another issue with studies investigating depression in RA is that the two disorders share several symptoms (e.g., fatigue, sleep problems) that may be excluded from analysis (Nerurkar et al., 2019), so true prevalence rates of depression may be underestimated.

Tension (r = 0.73, $p < 0.01$), followed by self-esteem (r = 0.73, $p < 0.01$), RA impact (r = 0.58, $p < 0.01$), fatigue (r = 0.57, $p < 0.01$), pain (r = 0.55, $p < 0.01$), passive coping (r = 0.47, $p < 0.01$), and physical disability (r = 0.44, $p < 0.01$) are among the strongest predictors of depression reported in RA (Covic et al., 2006). Age and functional class were also found to be associated with depression in RA, with younger people and patients with greater functional impairment more likely to report depression (N = 495; r = 0.22; $p = 0.0001$), even after controlling for confounding variables ($p < 0.0001$) (Wright et al., 1998). The authors highlight the importance of future longitudinal studies to confirm the observation that younger people with RA appear more likely to suffer from depression. A genetic risk for major depressive disorder (MDD) can also impact depression in RA (N = 520; mean age = 54.7 ± 12.6; MDD wGRS = -1.21 (0.48); $p = 0.013$) (Euesden et al., 2017), suggesting that genetic risk increases the likelihood of poor mental health in the face of adverse environmental effects (e.g., chronic condition).

Pain might significantly affect the relationship between RA and depression, as effect sizes for depression appear to increase linearly in proportion to the effect sizes for pain (z = 2.67, $p = 0.006$) (Dickens et al., 2002). Furthermore, RA patients with depression also report higher subjective pain levels (N = 40) (Çakirbay et al., 2004). However, as other manifestations of RA,

such as physical disability, are also associated with pain, longitudinal studies are needed to understand the complex relationship between RA, mental health and pain (Dickens et al., 2002). The traditional causation model between pain, disability and mental health problems is currently being challenged, as a bidirectional relationship was also found (Lu et al., 2016) and evidence is growing that immunological pathways could directly influence both physical and mental health (Nerurkar et al., 2019)

Summary

Depression in RA remains largely undetected and unaddressed by rheumatologists (Rathbun et al., 2014). Growing evidence suggests that early psychological treatment in RA patients might be just as important as early physical treatment (Nell et al., 2004; Quinn & Emery, 2003; Sharpe et al., 2001; Sharpe, Sensky, Timberlake, et al., 2001). People with RA that were originally depressed, perceived their condition as 'serious' and had higher levels of disability were more likely be depressed after 15 or 21 months (N = 22, mean age = 55.06 ± 14.07) (Sharpe et al., 2001). A cognitive behavioural intervention delivered in the first two years of diagnosis showed significant improvements in depressive symptoms and joint involvement both at the 6-month follow-up and post-treatment time points (N = 53; mean age = 55.06 ± 14.07; F (1,41) = 6. 041; p = 0.018) (Sharpe et al., 2001). The relationship between age and mental health, coupled with increased life expectancy, suggest that the prevalence of depression in RA will likely increase in the future (Wright et al., 1998), so assessment and treatment of mental health issues should be a key component of RA management, especially since the presence of depression and anxiety may reduce the likelihood of achieving remission with RA treatments (N = 1326) (Michelsen et al., 2017).

1.5.2 Sleep

Health is significantly affected by sleep quality and quantity, although it can be difficult to attribute causality (vs. correlation) to that association. In the general population, short duration of sleep (≤ 5-6 hours per night), generally considered a marker of poorer health, was found to be associated with a greater risk of developing or dying from coronary heart disease (RR = 1.48, 95% CI: 1.22-1.80, $p < 0.0001$) and stroke (RR = 1.15, 95% CI: 1.00 to 1.31, $p = 0.047$) (Cappuccio et al., 2011), greater risk for obesity (OR = 1.55, 95% CI: 1.43 to 1.68, $p < 0.001$) (Cappuccio et al., 2008), and diabetes (RR = 1.28, 95% CI: 1.03 to 1.60, $p = 0.024$) (Cappuccio et al., 2010). Interestingly, long sleep duration (> 8-9 hours per night) was also associated with the risk of developing diabetes (RR = 1.48, 95% CI: 1.13 to 1.96, $p = 0.005$) (Cappuccio et al., 2010), coronary heart disease (RR = 1.38, 95% CI: 1.15 to 1.66, $p = 0.0005$), stroke (RR = 1.65, 95% CI: 1.45 to 1.87, $p < 0.0001$) and total CVD (RR = 1.41, 95% CI: 1.19 to 1.68, $p < 0.0001$) (Cappuccio et al., 2011). Lastly, both short (RR = 1.12, 95% CI: 1.06 to 1.18, $p < 0.01$) and long sleep duration were associated with a greater risk for all-cause mortality (RR = 1.30, 95% CI: 1.22 to 1.38, $p < 0.0001$) (Cappuccio et al., 2010).

Sleep disturbance is common in people with RA. Devins et al. (1993) noted that 70% of their RA sample (N = 110) reported having at least one episode of sleep disturbance in the past week, while 20% of the sample reported five to seven episodes. Other studies estimate sleep disturbance to occur in approximately 49% to 80% of patients with RA (Durcan et al., 2014; Goes et al., 2017; Guo et al., 2016). Regarding individual components of sleep, people with RA most often complain about impaired subjective sleep quality, sleep latency, habitual sleep efficiency, daytime dysfunction as a consequence of poor sleep, use of sleeping medication (Durcan et al., 2014; Guo et al., 2016) and sleep fragmentation (Mahowald et al.,

1989; Taylor-Gjevre et al., 2011). Kim et al. (2016) (N = 37,979) also suggest that there is a U-shaped relationship between sleep and RA where both short sleepers (≤ 6 hours/day) and long sleepers (≥ 9 hours/day) are at an increased risk for RA. While sleeping for a short amount of time may be detrimental to health, sleeping for too long could also be a potential indicator of illness, fatigue, worse RA or extra comorbidities.

Depression (Guo et al., 2016; Nicassio et al., 2012; Sarıyıldız, 2013), pain (Nicassio et al., 2012), disease activity (Guo et al., 2016; Sarıyıldız, 2013), and perceived stress at baseline (Treharne et al., 2007) have been reported among the most common predictors of impaired sleep. Worse fatigue, morning stiffness, impact of disability, reduced self-efficacy about fatigue and mood (Treharne et al., 2007) and sleep apnoea (Goes et al., 2017; Reading et al., 2009) have also been associated with disturbed sleep in people with RA. Experimentally induced sleep deprivation led to worse subjective fatigue [$F (1, 51.15) = 9.05$, $p < 0.005$], depression [$F (1,51.23) = 3.93$, $p = 0.05$] and anxiety [$F (1,51.43) = 7.45$, $p < 0.01$] in people with RA (N = 27) compared to the control group (N = 27) (Irwin et al., 2012). Those reporting poor sleep were also more likely to report excessive daytime sleepiness (Louie et al., 2011) and poorer health-related quality of life (Guo et al., 2016). The above-mentioned studies suggest that there are significant sleep problems in patients with RA that are probably largely unaddressed in routine clinical practice. Therefore, treatment for RA should investigate and address mood and sleep problems, in addition to the current focus on controlling inflammation and pain.

1.5.3 Cognition

Few studies have looked at cognition in RA. A recent systematic review of 15 studies involving 749 participants reported that a considerable number of RA patients may have impaired cognitive function but more research is needed to determine the prevalence and what cognitive domains are affected (Meade et al., 2018a). Appenzeller et al. (2004) reported cognitive impairment in 30% of RA patients (N = 40, mean age = 37.2 ± 3.2) compared to 7.5% in the control group (N = 40, mean age = 35.9 ± 2.9), with worse performance on semantic memory (p = 0.03), logical/episodic memory (p = 0.03) and short memory (p < 0.001) tests. Cognitive impairment in another study ranged from 8% in the semantic memory test to 29% in the design fluency test (both tests measuring higher-level thinking and cognitive flexibility), with 30% of RA patients displaying impairment in four or more tests (N = 122, Mean age = 58.4 ± 10.8) (Shin et al., 2013). Vitturi et al. (2019) observed significantly worse performance (p < 0.001) for the RA sample (N = 210) on tasks that tested attention, short-term memory and long-term memory. Other studies found that RA patients with a higher disease activity score were more likely to perform worse on cognitive tests compared to healthy controls and therefore suggested that treatment targeted at disease activity or remission might also positively target cognitive decline in RA (Katchamart et al., 2019; Lee et al., 2018). The specific domains in which RA patients showed poorer performance were semantic memory in the Lee at al. study (2018) and visuo-spatial memory, executive function (i.e., the ability to plan, focus attention, multitask and remember) and fluid intelligence (i.e., the ability to think abstractly and problem-solve independent of any previous knowledge) in the Kachamart et al. study (2019). Worse cognitive function has been observed in both RA patients with long-standing disease (between 5 and 16 years) (Katchamart et al., 2019) as well as newly diagnosed people

(within three years of receiving a diagnosis) (Simos et al., 2016) highlighting the importance of monitoring and addressing cognition throughout the disease course, including in the early disease.

Pain and depression were found to be negatively associated with performance on information-processing speed, reasoning, working memory and long-term memory (N = 121, mean age = 56.07 ± 12.74) (Brown et al., 2002). Chronic pain in RA might disrupt normal cognitive function, as current pain levels have been observed to be inversely related to cognition (N = 157, mean age = 54, r = -.24, p = 0.003). Other variables reported to be associated with impaired cognitive function in RA are disease activity, fatigue, medication (prednisone/steroids) and cardiovascular risk factors (Meade et al., 2018a; Shin et al., 2012). Comorbid risk factors such as hypertension, obesity or smoking status may also increase the risk of cognitive impairment in RA (N = 115, mean age = 58.6 ± 10.8) (Shin et al., 2012).

Previous studies have speculated that there is an inverse relationship between RA and Alzheimer's disease (AD), and a meta-analysis and systematic review of 10 studies (N = 6,346) reported that RA was indeed associated with a significantly reduced risk of AD (OR = 0.60, 95% CI: 0.46-0.77, p < 0.001) (Policicchio et al., 2017). However, a Mendelian Randomization (MR) analysis using summary statistics from the largest published RA GWAS to date (29,880 RA patients and 73,758 controls) (Okada et al., 2014) and summary data from the largest GWAS of AD to date- the International Genomics of Alzheimer's Project (IGAP) (17,008 AD patients and 37,154 controls) (Lambert et al., 2013), did not support the above inverse causal relationship (OR = 1.018, 95% CI: 0.98 to 1.06), with the authors suggesting previous observations were probably due to bias in observational studies over RA diagnosis,

medication, small sample sizes and biased selection (Policicchio et al., 2017). Rather than RA being protective, it has also been suggested that in fact the anti-inflammatory medication used to treat RA patients could have a protective effect against AD (Cunningham & Hennessy, 2015), as patients currently taking biologic therapies were less likely to be cognitively impaired according to the Mini-Mental State Examination (MMSE) (OR = 0.5, 95% CI: 0.3 to 0.9, N = 210, $p < 0.05$) (Vitturi et al., 2019). Conversely, the Montreal Cognitive Assessment (MoCA) showed significant associations with cognitive impairment ($p < 0.05$) only for patients taking oral glucocorticoids (OR = 7.0, 95% CI: 1.1 to 43.6) and those with positive RF (OR = 13.8, 95% CI: 1.5 to 126.8) (Vitturi et al., 2019).

Summary

Generally, the investigation into the effects of aging on cognition has become a priority for contemporary research and while more studies are needed, growing consensus has been reached that cognitive functions relating to verbal and numerical ability and general knowledge are largely unaffected by age while memory, executive functions, processing speed and reasoning are associated with a decline from middle age, with 'fluid' cognitive abilities typically most sensitive to ageing (Deary et al., 2009; Ritchie et al., 2015). Nevertheless, even after controlling for age in a mediation analysis in the Brown et al. (2002) study, depression still had a significant relationship with cognition in people with RA. This could have additional implications for RA as treatment for depression in this patient-population may also benefit their cognitive health (Brown et al., 2002). To sum up, cognitive function seems to be significantly affected in RA patients but the prevalence, severity and associations with pain, depression and medication require further study. The exact pathogenesis also warrants further study, with current studies suggesting that several

biological, clinical and psychological factors are at play, including cardiovascular comorbidities, chronic pain, autoantibodies, medication side effects, as well as genetic and psychological factors (Basile et al., 2021). At a clinical level, it may be warranted and necessary to assess and monitor cognition over time as part of the management of RA (Meade et al., 2018a). As RA is a chronic condition requiring significant self-management and input by the patient, intact cognition is essential for performing daily activities such as taking medication or planning the day to accommodate physical disability levels and healthcare appointments (Abeare et al., 2010).

1.5.4 The intersection of mental health, cognition, and sleep in RA

Depression is often found to be independently associated with sleep disturbance in RA (Devins et al., 1993; Goes et al., 2017; Guo et al., 2016; Nicassio et al., 2012; Nicassio & Wallston, 1992). The observational nature of most studies limits our understanding of the relationship between sleep and mental health in RA, especially the directionality of any observed association. It is equally plausible that the presence of sleep problems (especially in a chronic disease) can cause depression, or that disturbed sleep is a symptom of depression. Depressed patients may also have worse perceptions of the symptoms and limitations caused by RA (Luyster et al., 2011)

Experimentally induced partial sleep deprivation led to increases in self-reported fatigue [$F(1, 51.15) = 9.05$, $p < 0.005$], depression [$F(1,51.23) = 3.93$, $p = 0.05$] and anxiety [$F(1,51.43) = 7.45$, $p < 0.01$] in RA patients compared to the control group (Irwin et al., 2012). It was also suggested that depression accounts for more variance in sleep disturbance than pain (N = 106, Mean age= 56.2 ± 12.45) (Abeare et al., 2010; Nicassio et al., 2012).

Furthermore, Brown et al. (2002) suggest that the relationship between pain and cognition is mediated by depression. The authors propose a model where pain is directly associated with depression and depression is directly associated with cognition, leaving pain only indirectly related to cognition through its relationship with depression. The study was limited however, by the fact that it did not account for the possible effect of pain medication on cognition. Based on earlier studies the only medication they investigated was methotrexate (an immunosuppressive drug) but found no significant association with cognitive performance. Medication is rarely accounted for in studies investigating cognition in RA. Higher consumption of opioids has been associated in the literature with worse cognitive performance on tasks for attention, language, orientation and psychomotor function (Khera & Rangasamy, 2021), and therefore, more research into the relationship between pain medication and cognition is warranted. The relationship between depression and cognition in RA also warrants further investigation as many studies exclude participants based on depression scores or do not include a depression measure (Meade et al., 2018a).

1.6 RA and the brain

Structural brain differences, even in the absence of pathology like dementia, are a strong predictor for cognition in older age, even after controlling for past cognitive ability and sex, with similar effects for white and gray matter (Royle et al., 2013). For example longitudinal changes in the microstructure of white matter are associated with worse fluid intelligence scores, while white matter hyperintensities (WMH) (i.e. brain white matter lesions) are associated with worse cognitive performance, executive function and processing speed (Debette & Markus, 2010; Ritchie et al., 2015). However, the literature is very limited for the

potential effects of RA on the structure of the brain. On top of that, the majority of studies suffer from a small sample size (Hanspach et al., 2021; Marek et al., 2022). The first study to look into the association between RA and structural gray matter differences found differences mainly in the basal ganglia, a region responsible for executive function and motor control and associated with anticipation of pain, pain relief and movement planning as a consequence of pain, with the RA subsample having larger volumes of the caudate nucleus, putamen and nucleus accumbens (Wartolowska et al., 2012). RA patients are also more likely to present with hyperintensities or lesions of the white matter (Hamed et al., 2012; Phukan et al., 2022).

Even when reviewing the literature on chronic pain in general, a major symptom of RA (Aletaha et al., 2010b) the number of studies is still limited. The literature on structural brain differences in chronic pain is also mixed. Several brain clusters suggest a decrease in gray matter volume with a meta-analysis identifying 12 affected clusters (Smallwood et al., 2013). In contrast, an increase in gray matter volume was also noted in the right hippocampus and parahippocampal gyrus. Many of the brain regions identified in the Smallwood et al. (2013) meta-analysis were previously associated with pain perception but some are also thought to have functions outside of the “pain matrix” suggesting a connection to other features of chronic pain conditions such as fatigue, and cognitive and emotional processes. More research is therefore needed to fully understand the potential structural brain differences that come with chronic disease and aging, as well as specific disorders such as RA.

1.7 Key gaps in literature

1. The classification criteria for RA includes serology whereby being positive for RF or ACPA gives you a higher score. However, RF can be present in other conditions and the general population as well and prevalence rates in RA are mixed in the literature that is usually decades old. Therefore, there is currently a lack of a clear understanding of the role of RF in general, and in the development of RA.

2. There are significant knowledge gaps for the association between RA and/or RF and sleep, mental health, cognition, and structural brain differences, despite being important areas of unmet clinical need.

3. There is no understanding whether links between RA and poorer health may be due to common genetic factors (i.e., whether people with a high genetic risk for RF show poorer brain and cognitive health).

4. Most studies to date have been based on small sample sizes and measurement instruments vary between studies. They are also poorly controlled for confounders such as age, sex, ethnicity, deprivation, smoking status, BMI, or alcohol intake. The UK Biobank is a relatively large general population cohort that can provide a solution to these issues, having over 500,000 participants that are measured identically and being followed long-term.

1.8 Aims of thesis

1. To characterise patients with self-reported RA or RF status in the UK Biobank in terms of mental health, cognition, and sleep problems, as well as association analyses for self-reported RA/RF+. As RA in the UKB was based on self-report, we decided to test for associations with RF+ status (irrespective of RA status) and mental health, sleep, and cognition as well, due to its involvement in RA diagnosis and severity. We hypothesize that having RA and being RF+ will make participants more likely to suffer from poor mental health, worse sleep, and worse cognitive performance, based on previous literature and RF+ status' reported associations with worse RA outcomes and severity.

2. To identify associations between self-reported RA or RF status and structural brain phenotypes. We hypothesize we will see structural brain differences for self-reported RA in brain areas known to be associated with pain processing and motor planning due to common symptoms in RA like pain and stiffness, such as the basal ganglia and amygdala, as well as differences in white matter lesions due to the high prevalence of cardiovascular-related comorbidities in RA.

3. To test for associations between PRS for RF and structural brain phenotypes and separately performance on cognitive tests. Due to its associations with higher disease activity, worse radiographic progression, more aggressive disease course and higher morbidity and mortality we hypothesize that a genetic risk score for RF will be associated with worse structural brain health and worse cognition.

1.9 Importance of thesis

The above research aims have significant potential impact for RA in terms of prevention, risk stratification for precision medicine, diagnosis, and treatment. A better understanding of the underlying mechanisms of RF and the associations of RA with cognition, sleep, mental health, and structural brain differences could; (1) aid therapeutic targeting, (2) allow for stratification according to genetic risk and biomarkers (i.e., a precision medicine approach), and (3) indicate how 'environmental' and therefore how potentially modifiable these factors are, which would enable the development of evidence-based health interventions.

Chapter 2: Methodology

2.1 The UK Biobank, participants and ethical approval

Different factors are believed to affect the risk of developing certain diseases, as well as how severe they get, from genetic susceptibility to lifestyle and environmental factors. However, most studies to date have suffered from small sample sizes, incomplete or missing risk factors or confounders and are usually retrospective. The UK Biobank was aimed as a solution to these problems by including around 500,000 people living in the UK that had a variety of measures taken. Since the initial recruitment in 2006, participants had completed an extensive baseline questionnaire, had blood and urine samples collected which were later used for blood and genetic biomarkers, attended imaging visits for brain, heart and fully body scans, had physical activity data monitored, and had their data linked to a wide range of electronic health-related records including death, cancer, and hospital admissions. The overall aim was to aid our understanding of the causes of diseases as well as identify novel ways for prevention and treatment (Protocol available at: https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf). However, this cohort might not be representative of the sampling population as a whole, with participants more likely to be older, female, less deprived as well as less likely to be obese, to smoke, to drink alcohol and report health conditions (Fry et al., 2017), with accumulating evidence suggesting a 'healthy bias' in the UK Biobank (Lyall et al., 2022; Tyrrell et al., 2021).

Therefore, this thesis used the UK Biobank, a general population cohort of N = 502,649 participants. People aged between 40 and 69 years old that were registered with the National Health Service (NHS) and lived up to approximately 25 miles from one of the 22 UK Biobank assessment centers were invited to take part (Allen et al., 2012). The final number of

participants that agreed to take part was 502,649-equivalent to 5.47% of those invited - and recruitment took place between 2006 to 2010. The data was anonymized, all volunteers gave informed consent, and all methods were performed in accordance with the relevant guidance and regulations. The study was conducted under generic approval from the NHS National Research Ethics Service (approval letter dated 17th June 2021, Ref 11/NW/0382) and the work presented here under UK Biobank project approval 17689 (PI Lyall). The current thesis used data from two instances: instance 0 for the baseline visit (2006-2010) and instance 2 for the imaging visit that included body and MRI scans (2014+). It will be specified for each variable what instance was used.

2.2 Demographic and lifestyle data

At the baseline visit at the assessment centre, participants completed touchscreen questionnaires on their sociodemographic factors (such as age, sex, ethnicity, postcode of residence), lifestyle (e.g. smoking status, alcohol intake), medical history (including mental health and musculoskeletal problems) and had several physical measures taken and samples of blood, saliva and urine collected (Allen et al., 2012).

The age variable (Data field 21003) used for Chapter 3 was given by the participant at the baseline visit (Instance 0), while chapter 4 and 5 used the age reported by the participant at the imaging visit (Instance 2).

For all analytical chapters the sex (Data field 31) and deprivation variables (Data field 189) used were reported at the baseline visit as they were only recorded then (Instance 0). Area-

based socioeconomic deprivation was measured using Townsend scores derived from postcode of residence (Townsend, 1972). The Townsend scores were used to categorize participants into quintiles for the general population.

Two instances for smoking status (Data field 20116) and alcohol intake (Data field 1558) were used in the current thesis. For chapter 3, smoking status was reported at the initial assessment visit (Instance 0), while for chapter 4 and 5 that used data from the imaging visit we used the smoking status from Instance 2. Smoking status was recorded as "never", "previous" and "current". Those that answered "prefer not to answer" were recorded as NAs and the rest of the data treated as ordinal. Alcohol intake was treated as an ordinal variable and split into "daily or almost daily", "three or four times a week", "once or twice a week", "one to three times a month", "special occasions only" and "never". Participants' data that preferred not to answer on alcohol status was recoded as NA. Similarly, we used two instances for BMI data (Data field 21001), Instance 0 for chapter 3 and Instance 2 for chapters 4 and 5. BMI was derived from weight (kg)/(height (m) x height (m) measured at the time of these visits. The rationale for using different instances for these variables was based on the fact that the subsample and data used in chapter 3 consisted of those participants that attended the baseline visit (Instance 0), while the subsample and data used in chapters 4 and 5 covered only participants that came back for a repeat imaging visit. As the imaging visit could be 8 years after the baseline visit, we wanted to use the most relevant and up-to-date data regarding smoking, alcohol, and BMI. Unfortunately, we were limited to using baseline data for sex and deprivation as it was only recorded once.

The following variables were only used in chapter 3 and therefore only one instance of data was necessary: ethnic background (Data field 21000), hip circumference (Data field 49) and waist circumference (Data field 48). Ethnic background was recoded into a categorical variable with 3 levels: White British, Other and Missing. The physical activity score derived in chapter 3 was calculated using six variables: Total Physical Activity Score= Duration of walks (Data field 874) * Walking days per week (Data field 864)+ Duration of Moderate physical activity (Data field 894) * Moderate physical activity days per week (Data field 884) + Duration of Vigorous physical activity (Data field 914) * Vigorous physical activity days per week (Data field 904).

In all three analytical chapters, assessment centre (Data field 54) was used as a covariate (as a factor) using data from both the baseline visit (Instance 0) and imaging visit (Instance 2). For chapters 4 and 5 we controlled for assessment centre in all analyses while for chapter 3 we controlled for assessment centre after the original analyses as part of sensitivity analyses. This did not affect any of our significant analyses. For all chapters we excluded those with a BMI under 18 (due to frailty) and those participants whose doctor advised they stopped drinking alcohol (Data field 3859). The numeric memory cognitive test was removed from the current thesis due to very low completion rates.

2.3 Rheumatoid factor

All UK Biobank participants had biomarker levels measured at baseline from serum and packed red blood cell samples. Results were excluded from analyses when no data was

returned or there was an error from the analysis (i.e., the values were outside the reportable range of the assay or there was an aliquot problem). In particular, oestradiol and RF had a high proportion of values below the lower reportable range (80% and 90% in ca respectively). Therefore, UK Biobank advised researchers to consider these values as 'naturally low' rather than 'missing'. More information about quality control applied to the assays, instrumentation and analysis methods can be found at:

https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/biomarker_issues.pdf

https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/serum_biochemistry.pdf

For the current thesis, very low levels of RF that were coded as 'missing' in the original data were recoded conservatively as the square root of the minimum stated detectable value if participants had data for a remaining biomarker and were not coded for missing reason as "no data returned" or having "unrecoverable aliquot problem" (Data field 30825) as in the Ferguson et al. (2020) paper. A new binary variable was then computed for RF category with variables over 14 IU/ml considered RF positive (RF+) (Sunar & Ataman, 2020). RF was measured in the UK Biobank on two instances: Instance 0 at the baseline visit (between 2006-2010 and covering 472,711 participants) and instance 1 at the first repeat assessment visit (between 2012-2013 and covering 18,551 participants) (Data field 30821). Because we had no data available for RF levels at the imaging visit, we performed a correlation (see **Figure 1**) between the two available instances to see whether RF values are generally stable ($r = 0.57$, $p < 0.001$). In order to see whether RF levels were significantly higher at the repeat visit, we performed a t-test which suggested that RF levels were higher at the repeat visit (Instance 1) than at the baseline visit (Instance 0), but this was not significant ($p = 0.10$). Because RF was very non-linearly distributed in the UK Biobank (essentially high in cases and otherwise not,

see **Figure 2**) we decided to test for associations in cases versus controls (RF- vs RF+) rather than use it as a continuous variable.

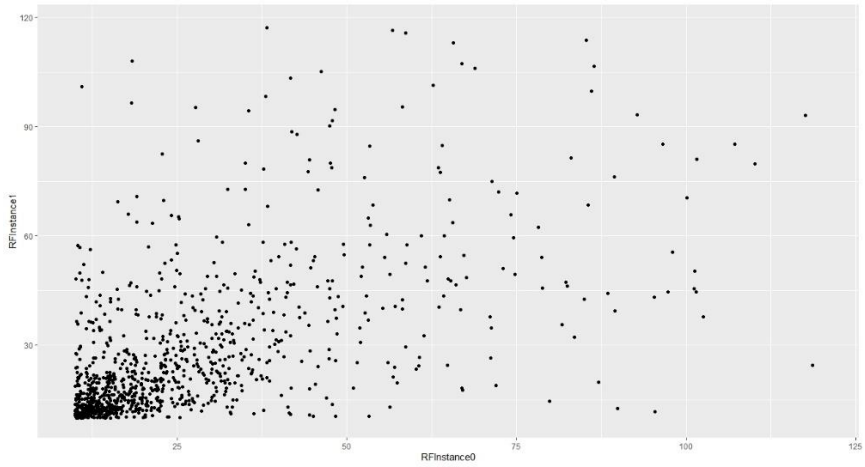

Figure 1 Scatterplot of the correlation between rheumatoid factor at Instance 0 and rheumatoid factor at Instance 1

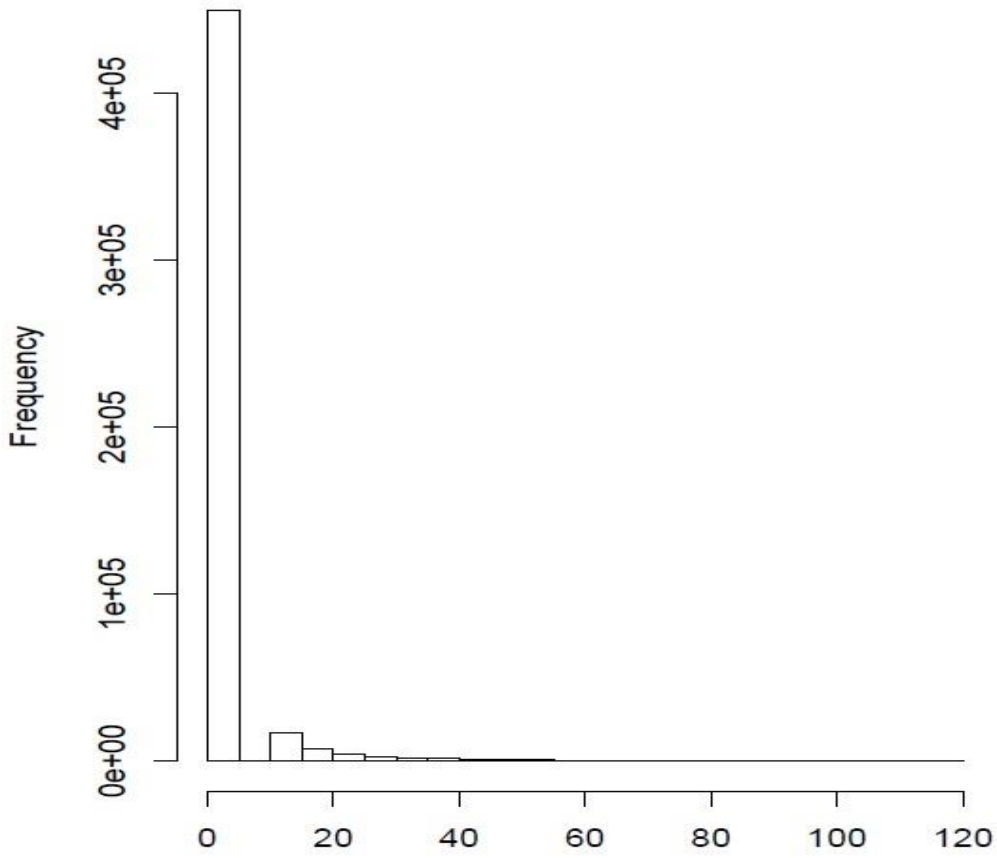

Figure 2 Distribution of rheumatoid factor values at Instance 0 in the UK Biobank

2.4 Self-reported rheumatoid arthritis, mental health and cardiometabolic conditions

The current thesis used self-reported mental health and cardiometabolic conditions. This was based on Data field 20002, non-cancer illness codes for self-reported illness. For the current thesis we were interested in RA, depression, anxiety/ panic attacks, diabetes, hypertension, angina, heart attack and stroke. Neuroticism is the only mental health feature that was not based on self-report but rather an externally derived scores based on 12 questions assessed at the baseline visit using a touchscreen questionnaire (Data field 20127).

2.5 Cognitive assessment

At the assessment centre, five cognitive tests were administered to participants via a touchscreen computer. It took approximately 15 minutes to complete all tests. We excluded from our analyses the numeric memory task due to low completion rates. The cognitive tests used in the current thesis were:

- **Reaction time (Data field 20023).** This assessment was based on 12 rounds of the card-game 'Snap'. The participant saw two cards at the same time; the participant was asked to press a button-box in front of them as fast as possible if both cards were the same. Mean time to correctly react was recorded in milliseconds (mean = 563.83, SD = 117.803). Data was available for 496,565 participants.

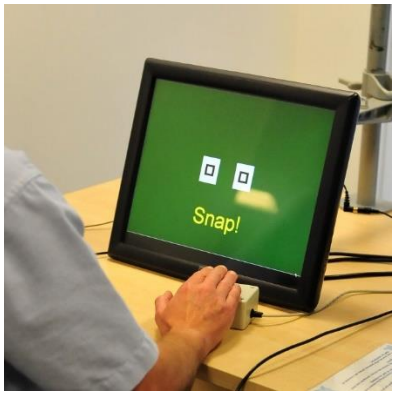

Figure 3 Screen showing reaction time task
Image from: https://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20023, resources tab.

- **Fluid intelligence score/ Reasoning (Data field 20016).** This touchscreen assessment was comprised of questions designed to assess the capacity to solve problems that require logic and reasoning ability, independent of acquired knowledge. The total score was derived from 13 questions that can be found at https://biobank.ndph.ox.ac.uk/ukb/refer.cgi?id=100231 and that covered numeric addition, identifying the largest number, word interpolation, positional arithmetic, family relationship calculation, conditional arithmetic, synonyms/antonyms, chained arithmetic, concept interpolation, arithmetic sequence recognition, square sequence recognition and subset inclusion logic. Participants had 2 minutes to answer as many questions as possible. The data available covered 165,417 participants and the unit of interest for this thesis was the overall score for each participant (mean = 5.97, SD = 2.15).

- **Prospective memory (Data field 20018).** At the beginning of touchscreen cognitive assessments participants were shown the following message: "At the end of the games we will show you four coloured shapes and ask you to touch the Blue Square.

However, to test your memory, we want you to actually touch the Orange Circle instead". The data used for the present analyses was dichotomized as correctly recalled on first attempt or not. The available data covered 171,504 participants.

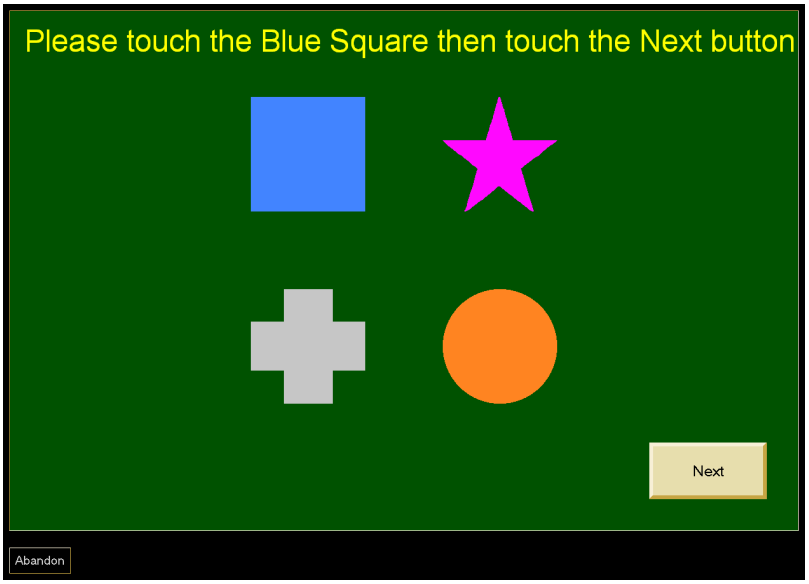

Figure 4 Screen showing prospective memory task

Image from: https://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20018, resources tab.

- **Pairs matching/ Short-term memory (Data field 20132).** For this category participants were shown several matching pairs of cards at different random positions that were later turned face down. The task was to touch as many pairs as possible as possible in the fewest tries. For this thesis the used variable was the number of errors made (mean =2.71, SD = 3.15). Data was available for 118,502 participants.

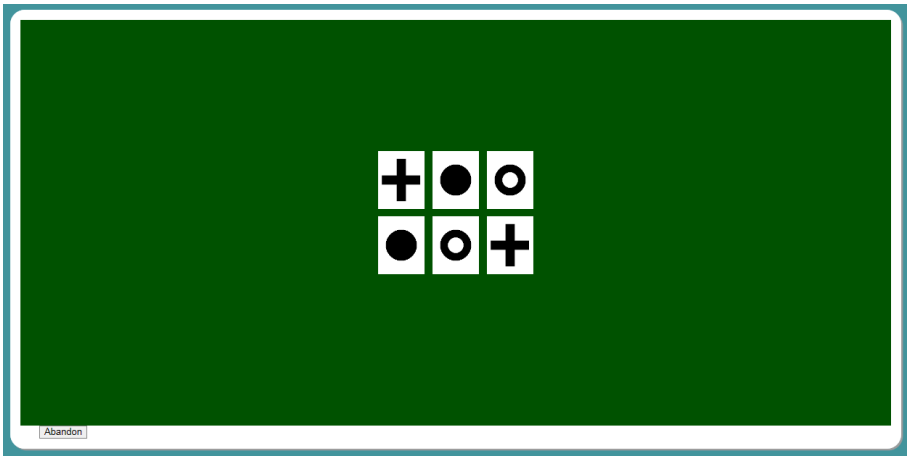

Figure 5 Screen showing snapshot of pairs matching task

Image from: https://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20132, resources tab.

2.6 Sleep features

At the assessment centre, participants completed touchscreen questionnaires about their lifestyle and environments, including sleep variables. For this thesis we were interested in sleep duration, nap during the day, getting up in the morning and insomnia. Sleep duration (Data field 1160) was a numeric variable recorded in self-reported hours/day (mean= 7.15, SD=1.1). Data was available for 501,500 participants. Participants were also asked whether they nap during the day with the possible answer options as "Never/rarely", "Sometimes" and "Usually" (Data field 1190). Available data covered 501,496 participants. For this thesis "prefer not to answer" was coded as missing. The questionnaire also asked how easy do the participants find getting up in the morning, with possible answers ranging from "Not at all easy" to "Very easy" (Data field 1170). Data was available for 497,730 subjects. Similar to the previous variable, "Prefer not to answer" and "Do not know" were recorded as missing in the analysis. Lastly, insomnia was assessed with the questions "Do you have trouble falling asleep

at night or do you wake up in the middle of the night?" and participants had to choose between "Never/rarely", "Sometimes" and "Usually" (Data field 1200). Data was available for 501,496 participants. "Prefer not to answer" was re-coded as missing in the analysis.

2.7 Brain imaging

After the original baseline assessment visit that took place between 2006 and 2010, a subset of UK Biobank volunteers were invited for a repeat visit where imaging data was collected on several organ systems including the brain. The current thesis, more specifically chapters 4 and 5, used imaging data that covered approximately 40,000 participants from January 2021. Information on the brain scan protocols and documentation regarding data acquisition and processing can be found at:

https://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977

https://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367

Total brain volume (TBV), total white matter volume (WM) and total gray matter volume (GM) were segmented automatically using T1 FMRIB's Automated Segmentation Tool (FAST https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf) and normalized for head size. Total white matter hyperintensities (WMH, lesions of the white matter) were derived from T1 and T2 fluid-attenuated inversion recovery (FLAIR) (Lyall et al., 2020), with the methodology described by Miller et al. (2016). Subcortical brain volumes were modelled using T1 FMRIB's Integrated Registration and Segmentation Tool (FIRST https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf).

The brain imaging phenotypes selected for the current thesis were: TBV normalized for head size (Data field 25009), GM normalized for head size (Data field 25005), WM normalized for head size (Data field 25007), WMH (Data field 25781), total accumbens volume (Data field 25023 and Data field 25024), total amygdala volume (Data field 25021 and Data field 25022), total caudate volume (Data field 25013 and Data field 25014), total hippocampus volume (Data field 25019 and Data field 25020), total pallidum volume (Data field 25017 and Data field 25018), total putamen volume (Data field 25015 and Data field 25016), and total thalamus volume (Data field 25011 and Data field 25012)- all measured in mm^3. While gray matter consists mainly of neuronal cell bodies and is responsible for processing information and releasing new information (i.e., enables individuals to control movement, memory, and emotions), the white matter is primarily composed of bundles of axons, coated with myelin in order to conduct and send neve signals. The above mentioned brain structure phenotypes were selected based on previous literature that suggested a potential association with RA or worse psychological/cognitive health (Bekkelund et al., 1995; Debette & Markus, 2010; Fuggle et al., 2014; Hamed et al., 2012; Penke et al., 2012; Phukan et al., 2022; Ritchie et al., 2015; Wartolowska et al., 2012). All MRI phenotypes were standardized before analyses to Z-scores (equivalent to standardized betas). Due to its skewed distribution, the WMH variable was log-transformed before analyses. For all subcortical volumes analyses we performed sensitivity analyses where we controlled for intracranial volume (ICV) and separately for total brain volume (TBV). The ICV variable was computed by summing up total gray matter volume, total white matter volume and total cerebrospinal fluid (Data field 25003).

We additionally used principal components analysis to construct general factors of white matter integrity: fractional anisotropy - gFA (eigenvalue = 12.28, 49% variance explained) and

mean diffusivity- gMD (eigenvalue = 13.37, 53% variance explained). FA and MD are measures of WM tract integrity used to describe the directional coherence and magnitude of the diffusion of water molecules (Lyall et al., 2020). Lower FA values and higher MD values represent worse/less 'healthy' white matter. We excluded participants that had incomplete MRI data (Data field 12188) and also excluded MRI variables that had values of 0 because they were not plausible.

2.8 Genotyping

One of the main goals of the UK Biobank was to provide a large cohort of genetic data covering every single participant. This would enable researchers to associate this genetic data with several medical, psychological and lifestyle phenotypes to better understand the onset and development of several diseases of interest. Genotyping and quality control measures are available to access at:

https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/genotyping_qc.pdf

https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/impute_ukb_v1.pdf

Approximately 450,000 UK Biobank participants were genotyped using the UK Biobank Axio array. The remaining ~50,000 subjects were genotyped using the UK BiLEVE array. Both SNP arrays are similar and share more than 95% common marker content. Around 150,000 samples using ~100,000 SNPs were used to conduct a principal component analysis by the UK Biobank in order to capture the population structure of this cohort. Principal components can be useful to identify individuals that share genetic ancestry before association studies. The current study used eight principal components as covariates as the majority of variance in

geographic population structure is explained by the top five principal components (Galinsky et al., 2016), while using eight is a common approach.

Polygenic risk score

With an increasing availability of large cohorts that include genetic data as well, such as the UK Biobank, studies that use a genetic risk score to establish associations with phenotypes of interest are becoming more and more widespread (Collister et al., 2022). A PRS estimates an individual's common genetic risk for a disease or trait of interest by combining several common variants that are associated with the disease or trait in question (Collister et al., 2022). After selecting SNPs generated from the GWAS output (on an independent, unrelated cohort), the PRS can be calculated by adding up all the trait-associated or trait-increasing alleles in each participant or by using a weighted sum where each selected SNP is weighted by its effect size (Chatterjee et al., 2016; Dudbridge, 2013). To avoid including correlated SNPs that do not have independent signals into the PRS, linkage disequilibrium (LD)-based pruning can be performed using software such as PLINK (Chatterjee et al., 2016). The sample in which the PRS is calculated should have no overlap with the cohort that is used to perform association analyses in order to avoid over-estimation of the predictive accuracy of genetic score (Choi et al., 2020).

Genetic risk scores have the potential to aid our understanding for a multitude of disease outcomes in the future including susceptibility to disease, disease progression, response to treatment and others (Igo Jr. et al., 2019). For example in the case of RA, despite the positive evolution and progression of medication for this patient-population, it is still unknown why

there are still patients that do not respond to medication or only partially benefit from it compared to others (Alam et al., 2017; Viatte & Barton, 2017). Identifying new biomarkers to target 'the right treatment to the right patient' would potentially benefit the patient and the healthcare system (Viatte & Barton, 2017).

For the current thesis, PRS were generated by a colleague (Dr. Joey Ward) using the PLINK software using summary statistics from a genome-wide analysis and using the 25 SNPs that reached genome-wide significance. Each individual score was calculated as the sum of the risk alleles for each SNP weighted by the effect size of each SNP. To avoid over-fitting and over-estimation UK Biobank participants that had available MRI data were excluded from the GWAS in order to be used for the following analyses. Genetic quality control was carried out to exclude participants of non-European ancestry, participants with a mismatch between genetic sex and self-reported sex, sex chromosome aneuploidy, as well as outlier values for heterozygosity. The generated PRS were then added to association analyses with brain MRI and cognitive phenotypes.

Summary

The UK Biobank is a very large prospective cohort of around 500,000 people that have a variety of health-related data available from psychological factors such as sleep, mental health, self-reported illnesses, and performance on cognitive tests, to demographic data like age, sex, deprivation, smoking status, and alcohol intake, as well as genetic, biomarker and imaging data. The large sample size of this cohort, coupled with the availability of various health-related measures helped me address the aims of my thesis by looking at self-reported RA and RF+ status and test for associations with mental health, sleep, cognition, and structural brain health. I was also able to investigate whether the observed differences in cognition and brain structure reported in the literature are due to a genetic risk score for RF. Lastly, I was able to control for a variety of confounders relevant to this patient-population such as age, sex, smoking status, alcohol intake, deprivation index, BMI and cardiometabolic diseases.

Chapter 3: Associations of mental health, sleep and cognition characteristics with rheumatoid arthritis and rheumatoid factor

A version of this chapter is published in Scientific Reports:

Stanciu, I., Anderson, J., Siebert, S., Mackay, D., & Lyall, D. M. (2022). Associations of rheumatoid arthritis and rheumatoid factor with mental health, sleep and cognition characteristics in the UK Biobank. *Scientific Reports*, *12*(1), 1-7.

ABSTRACT

Objectives: While previous rheumatoid arthritis (RA) studies have focussed on cardiometabolic and lifestyle factors, less research has focussed on psychological variables including mood and cognitive health, and sleep. This study reports observational, cross-sectional associations between self-reported RA, and positive rheumatoid factor (binary RF+ vs. not) prevalence with psychological/sleep data in UK Biobank.

Methods: Cross-sectional analyses tested for associations between RA and positive rheumatoid factor (RF+) vs. mental health (depression, anxiety, neuroticism), sleep variables and cognition scores in UK Biobank (total N = 484,064).

Results: Those RF+ were more likely to report longer sleep duration (β = 0.01, *SE* = 0.004, p < 0.01) and less likely to get up in the morning easily (OR = 0.95, 95% CI: 0.92-0.99, p = 0.01). Those reporting RA were more likely to score higher for neuroticism (β = 0.05, *SE* = 0.01, p < 0.001), to nap during the day (OR = 1.10, 95% CI: 1.06-1.14, p < 0.001), have insomnia (OR = 1.28, 95% CI: 1.22-1.35, p < 0.001), have slower reaction times (β = 0.02, *SE* = 0.008, p<0.005) and score lower for fluid intelligence (β = -0.03, *SE* = 0.01, p < 0.05) and less likely to get up easily (OR = 0.61, 95% CI: 0.58-0.64, p < 0.001).

Conclusion: The current study suggests that prevalent RA, and RF+ status itself are associated with differences in mental health, sleep, and cognition, highlighting the importance of addressing these aspects in clinical settings and future research.

INTRODUCTION

Rheumatoid arthritis (RA), the most prevalent chronic inflammatory condition affecting the joints (Symmons, 2002), is characterized by pain, stiffness and swelling, which if not controlled, can lead to permanent damage. The estimated prevalence for RA in UK adults is around 0.81%, with a higher prevalence for women (1.16%) than for men (0.44%) (Symmons et al., 2002). Rheumatoid factor (RF) is an autoantibody that is present in approximately 80% of people with RA and can occur years before any clinical symptoms (Nell et al., 2005). It can lead to worse outcomes, including higher disease activity and radiographic progression (Aletaha et al., 2013; Scott et al., 1987). However, it can also be present in the general population (Van Schaardenburg et al., 1993) including those with multimorbidity (i.e., the presence of two or more long-term health conditions) (Newkirk, 2002). If left untreated, RA can result in several negative outcomes including increased mortality, hospitalization, work disability and decreased quality of life (Michaud & Wolfe, 2007). RA can also be associated with other comorbidities, most notably CVD (Aviña-Zubieta et al., 2008), mental health, sleep and cognitive problems.

Mental health

Patients with RA are more likely to suffer from depression, even after controlling for age and sex (Dickens et al., 2002). Prevalence rates for depression in research studies vary considerably and can range between 0.04% and 66.3% depending on the instrument used for diagnosis (Matcham et al., 2013a). The overall quality of published papers is poor, with a median quality score of 3/10 and 82% of papers scoring 5/10 or lower (Matcham et al.,

2013a). An important issue with depression research in RA is that the two disorders share several symptoms such as fatigue and sleep disturbance that can often be excluded from analyses (Nerurkar et al., 2019) resulting in an underestimation of true prevalence rates. Nevertheless, even when the gold standard of diagnostic criteria for depression is used (i.e., DSM diagnostic criteria) prevalence rates for depression in RA are still high (16.8%) (Matcham et al., 2013a) compared to prevalence estimates for the general population (4.1% for 1-year estimates and 6.7% for lifetime prevalence) (Waraich et al., 2004). Anxiety in RA has received considerably less attention but prevalence rates between 13.5% and 70% have been reported (Covic et al., 2012; El-Miedany & El Rasheed, 2002; Isik et al., 2007). Also, a high neuroticism score at baseline was significantly associated ($p < 0.01$) with depression and anxiety at the 3 and 5-year follow up in RA patients, making it the most consistent and effective predictor of mental health in the study (Evers et al., 2002). While Isik et al. (2007) reported no significant differences in anxiety and depression between RF+ and RF- groups, in another study people that were RF- spent twice as much time being treated for depression and were more likely to need longer depression treatment as a result of a prolonged diagnosis delay (Tillmann et al., 2013). Ho et al. (2011) reported RF to be a significant predictor for severity of depression even after adjusting for confounding factors, while for anxiety, RF was a significant predictor only in the univariate analysis.

Sleep

Poor sleep in RA is estimated to be present in at least 49% of patient cohorts, with many studies reporting figures as high as 80% for the RA subsample (Devins et al., 1993; Durcan et al., 2014; Goes et al., 2017; Guo et al., 2016). Zhang et al. (2020) undertook the first meta-

analysis (N = 1,143) evaluating poor sleep in RA as measured by the Pittsburgh Sleep Quality Index (PSQI) and suggested that RA patients scored higher (indicative of worse sleep) than the healthy control group in every domain of the questionnaire (i.e., subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, presence of sleep disorders, use of sleeping medication and daytime dysfunction as a consequence of poor sleep) and in the total PSQI score. When comparing between poor sleepers with RA and good sleepers with RA, poor sleepers are more likely to have higher disease activity scores, worse night pain and total pain and higher rates for depression and anxiety, while the good sleep RA subsample reported using significantly more synthetic DMARDs (Guo et al., 2016). In contrast, RF status did not significantly differ between poor and good sleepers with RA (Goes et al., 2017; Guo et al., 2016).

Cognition

A recent systematic review including 15 papers and 749 participants has suggested that the RA patient-population might exhibit cognitive differences that could warrant attention in clinical and research settings, but more studies are needed to better understand prevalence rates and what specific cognitive domains are impaired (Meade et al., 2018). RA patients either had worse performances than healthy controls on average or performed at a level that was below their age-related norms. Considering that some of the studies included in this review also had other comparison clinical groups (i.e., fibromyalgia, systemic lupus erythematosus, Sjögren's syndrome) that also had worse performances at cognitive tasks, the authors suggest that cognitive impairment may be present in other chronic, inflammatory, or autoimmune conditions involving pain. Cognitive impairment on a range of cognitive tests

ranged from 8% in the semantic memory (recall test) to 29% in the design fluency test (both measures of higher-level reasoning and cognitive flexibility), with 30% of RA patients displaying impairment in four or more tests (N = 122, mean age = 58.4 ± 10.8) (Shin et al., 2013). In the multivariable analyses, use of glucocorticoids and cumulative number of CVD factors were independently associated with cognitive impairment in this patient population. Regarding individual components of cognition, Vitturi et al. (2019) observed significantly worse performance ($p < 0.001$) in RA for tests that measured attention, short-term memory and long-term memory. Those using biologics were less likely to be classified as cognitively impaired using the MMSE ($p = 0.05$), while those receiving glucocorticoids and those that were RF+ were more likely to be classified as cognitively impaired, according to the MoCA ($p = 0.01$ and $p = 0.05$ respectively).

Sleep, mental health, and cognition have been largely neglected in the RA literature, despite being important contributors to quality of life. Most studies to date had a sample size of under 1000 people and use a variety of instruments to test these associations, without properly controlling for covariates. As the systematic review carried out by Matcham et al. (2013) indicated depression was defined and measured in 40 different ways leading to different prevalence rates and an overall poor quality of published papers. Similarly, there is a lack of understanding and a significant gap in the literature about the associations of RF positivity (RF+) with these domains. We aim to provide a solution to these problems by using a large population cohort of around 500,000 participants assessed using uniform, standardized methods to evaluate associations with both self-reported RA and RF status. In conclusion, the aim of the current study was to characterize mental health, cognition, and sleep variables in

people with RA and to compare associations with these factors in people with positive RF (RF+) and negative RF (RF-) in a large population cohort.

METHODS

Participants and procedure

At the baseline visit at the assessment centre, participants completed touchscreen questionnaires on their sociodemographic factors (such as age, sex, ethnicity, postcode of residence), lifestyle (e.g. smoking status, alcohol intake), medical history (including mental health and musculoskeletal problems) and had several physical measures taken and samples of blood, saliva and urine collected (Allen et al., 2012). Area-based socioeconomic deprivation was measured using Townsend scores derived from postcode of residence (Townsend, 1972). In the current chapter RA, depression, anxiety and cardiometabolic diseases are based on self-report. All UK Biobank participants had biomarker levels measured at baseline from serum and packed red blood cell samples. For the current study, very low levels of RF that were coded as 'missing' in the original data were recoded conservatively as the square root of the minimum stated detectable value if participants had data for a remaining biomarker (Ferguson et al., 2020). A new binary variable was then computed for RF category with variables over 14 IU/ml considered rheumatoid factor positive (RF+) (Sunar & Ataman, 2020). We removed those that failed biomarker quality control (coded as 'no data returned' or logged as having unrecoverable aliquot problems).

At the assessment centre, five cognitive tests were administered to participants via a touchscreen computer. It took approximately 15 minutes to complete all tests (numeric

memory excluded in the present study due to low completion rates (Lyall et al., 2016). For reaction time (N = 496,771), mean response time (milliseconds) was recorded to matching pairs of visual stimuli. The fluid intelligence/verbal-numeric reasoning touchscreen assessment (N = 209,473) was comprised of questions designed to assess the capacity to solve problems that require logic and reasoning ability, independent of acquired knowledge. Prospective memory (N = 216,124) tested the ability for the participant to remember and follow instructions given before a task. The data used for the present analyses was dichotomized as correctly recalled on first attempt or not. The pairs matching task (N = 498,748) assessed visuo-spatial memory. For this paper, the used variable was the number of errors made.

At the assessment centre participants also completed touchscreen questionnaires about their lifestyle and environment, including mental health (depression, anxiety, derived summary score of neuroticism based on 12 neurotic behaviour domains) and sleep variables such as sleep duration (hours/day), frequency of napping during the day (ordinal with four options), ease of getting up in the morning (ordinal with 6 options) and insomnia frequency (ordinal with four options). Multi-level ordinal variables were dichotomized for the current study: ever nap during the day (No/Yes), ease of getting up in the morning (Not easy/Easy) and insomnia (No/Yes).

Statistical analyses

We used baseline data from the UK Biobank cohort (N = 502,506) to cross-sectionally compare people with and without RA, and people that are RF+ versus RF- on a variety of sociodemographic, lifestyle, illness-related factors and mental health, performance on cognitive tests and sleep-related factors. We performed logistic and linear regression analyses to determine whether RF+ status (i.e., seropositivity) or RA diagnosis were associated with mental health, cognition, and sleep variables. More specifically, we performed linear regression models for the neuroticism, sleep duration, reaction time, fluid intelligence and pairs matching variables and logistic regressions for the depression, anxiety, nap during the day, getting up in the morning, insomnia, and prospective memory variables. We adjusted for the covariates of age, sex, self-reported ethnicity, deprivation index, smoking status, BMI, and alcohol intake (frequency). We removed those that were advised by their doctor to stop drinking alcohol and recorded those with a BMI under 18 as missing. For sleep analyses we also controlled for cardiometabolic diseases. False Discovery Rate (FDR) was applied using the 'p.adjust' function in R, to correct for multiple testing, but this did not affect any of our significant results.

RESULTS

Demographics

Of the approximately 500,000 baseline UK Biobank participants, 5,722 (1.18%) self-reported having RA and 25,772 (5%) were RF+. Out of those that self-reported RA 74% were RF- and 26% were RF+. For the current study we have split the baseline sample between self-report RA and non-RA and RF+ versus RF- to compare any differences between these subsamples.

The baseline characteristics of the groups are shown in **Table 3**. Participants that reported RA were older and more likely to be female (69% of RA patients compared to 31% for males). The RA subsample was more likely to report being a current or previous smoker but more likely to drink alcohol less frequently. They were also more likely to have higher values for BMI, hip circumference, and waist circumference. Participants with RF+ were also older and more likely to be female (56% compared to 44% males). There were also significant differences between RF- and RF+ for ethnicity, smoking status, alcohol intake, deprivation index and physical activity score.

Table 3 Characteristics of participants with/without rheumatoid arthritis and by rheumatoid factor seropositivity

	No rheumatoid arthritis N = 484,064	Self-reported rheumatoid arthritis N = 5,722	p-value	Negative rheumatoid factor (RF-) N = 463,415	Positive rheumatoid factor (RF+) N = 25,772	p-value
Age [a, c]	58 (50-63)	61 (55-65)	**<0.001**	58 (50-63)	60 (53-64)	**<0.001**
Sex [b, d]						
Female	261,960 (54%)	3,829 (69%)		251,476 (54%)	14,413 (56%)	
Male	222,104 (46%)	1,793 (31%)	**<0.001**	212,495 (46%)	11,402 (44%)	**<0.001**
Ethnicity [b,d]						
White British	456,123 (94.3%)	5,394 (94.4%)		437,102 (94.3%)	24,415 (94.7%)	
Other	21,321 (4.4%)	251 (4.4%)		10,497 (2.2%)	574 (2.2%)	
Missing	6,110 (1.2%)	67 (1.1%)	0.8	5,875 (1.3%)	302 (1.2%)	**0.05**
Smoking [b,d]						
Never	264,224 (55%)	2,691 (47%)		253,343 (55%)	13,572 (53%)	
Previous	166,767 (35%)	2,273 (40%)		159,593 (35%)	9,447 (37%)	
Current	50,625 (11%)	710 (13%)	**<0.001**	48,675 (10.5%)	2,660 (10%)	**<0.001**
Alcohol [b,d]						
Daily/almost daily	98,894 (20.4%)	840 (14.5%)		93,984 (20.3%)	5,750 (22.3%)	
3-4 times/week	112,175 (23.2%)	967 (16.8%)		107,269 (23.1%)	5,873 (22.7%)	
1-2 times/week	124,962 (25.8%)	1,429 (25%)		120,020 (25.9%)	6,371 (24.7%)	
1-3 times/month	53,834 (11.1%)	689 (12%)		51,795 (11.2%)	2,728 (10.6%)	
Special occasions	55,442 (11.5%)	945 (16.5%)		53,447 (11.5%)	2,940 (11.4%)	
Never	37,682 (7.8%)	839 (14.6%)	**<0.001**	36,418 (7.8%)	2,103 (8.1%)	**<0.001**
BMI [a,c]	26.74 (24.2-29.9)	27.5 (24.5-31.1)	**<0.001**	26.7 (24.2-29.9)	26.7 (24.1-29.9)	0.4
Hip circumference [a,c]	102 (97-108)	103 (98-110)	**<0.001**	102 (97-108)	102 (97-108)	0.6
Waist circumference [a,c]	90 (80-99)	91 (81-101)	**<0.001**	90 (80-99)	90 (80-99)	0.1
Deprivation quintile [b,d]						
1 (least deprived)	167,073 (34.5%)	1,736 (30.1%)		159,717 (34.4%)	9,092 (35.2%)	
2	103,801 (21.4%)	1,160 (20.3%)		99,359 (21.4%)	5,602 (21.7%)	
3	80,312 (16.6%)	906 (15.9%)		76,975 (16.6%)	4,243 (16.5%)	
4	73,770 (15.3%)	1,001 (17.5%)		70,891 (15.3%)	3,880 (15.1%)	
5 (most deprived)	58,519 (12.1%)	909 (15.9%)	**<0.001**	56,473 (12.2%)	2,955 (11.5%)	**0.001**
Physical activity score [a,c]	520 (270-1020)	550 (270-1080)	0.1	520 (270-1020)	510 (267-990)	**0.02**

[a] Kruskal-Wallis test
[b] Pearson χ^2 test
[c] Median (IQR)
[d] N (%)
Values in bold indicate significant tests.

Regarding comorbidities (see **Table 4**), people that self-reported RA were more likely to self-report depression and score higher for neuroticism, while those RF+ were less likely to report depression. People that reported RA were also more likely to self-report other comorbidities including diabetes, hypertension, heart attack and stroke. Participants with RF+ were more likely to report hypertension and heart attack.

Table 4 Frequency of self-reported comorbid conditions between participants with/without rheumatoid arthritis and by rheumatoid factor seropositivity

	No rheumatoid arthritis N = 484,064	**Self-reported rheumatoid arthritis N = 5,722**	**p-value**	**Negative rheumatoid factor (RF-) N = 463,415**	**Positive rheumatoid factor (RF+) N = 25,772**	**p-value**
Depression (self-report) [b,d]	27,379 (5.7%)	396 (6.9%)	**<0.001**	26,379 (5.7%)	1,396 (5.4%)	0.06
Anxiety (self-report) [b,d]	6,725 (1.4%)	67 (1.1%)	0.16	6,459 (1.4%)	333 (1.3%)	0.17
Neuroticism score [a,c]	4 (1-6)	4 (2-7)	**<0.001**	4 (1-6)	4 (1-6)	**0.002**
Diabetes [b,d]	20,866 (4.3%)	364 (6.4%)	**<0.001**	20,128 (4.3%)	1,102 (4.2%)	0.5
Hypertension [b,d]	125,782 (26%)	1,973 (34.5%)	**<0.001**	120,295 (26%)	7,460 (29%)	**<0.001**
Heart attack [b,d]	11,171 (2.3%)	225 (4%)	**<0.001**	10,738 (2.3%)	658 (2.5%)	**0.01**
Stroke [b,d]	6,508 (1.3%)	143 (2.5%)	**<0.001**	6,266 (1.3%)	385 (1.5%)	**0.05**

[a] Kruskal-Wallis test
[b] Pearson χ^2 test
[c] Median (IQR)
[d] N (%)
Values in bold indicate significant tests.

Association analyses

Mental Health

In the unadjusted regression models, people that reported RA were more likely to have depression (OR = 1.16, 95% CI: 1.08 to 1.25, p < 0.001) and score higher for neuroticism (β = 0.08, *SE* = 0.01, p < 0.001) (see **Table 5**), while people RF+ were more likely to score less for neuroticism (β = -0.01, *SE* = 0.005, p < 0.001) (see **Table 6**). After adjusting for age, sex, ethnicity, deprivation, smoking status, BMI, and alcohol intake, those that reported RA were still more likely to score high for neuroticism (β = 0.05, *SE* = 0.01, p < 0.001) but less likely to report anxiety (OR = 0.80, 95% CI: 0.67 to 0.95, p < 0.01), but the associations between RF status and neuroticism was no longer significant.

Table 5 Regression models for the association between RA and mental health

	Unadjusted Model			Fully adjusted model [c]		
	β / OR	95% CI	P value	β / OR	95% CI	P value
Depression [a]	1.16	1.08-1.25	**<0.001**	1.03	0.95-1.10	0.4
Anxiety [a]	0.88	0.74-1.04	0.16	0.80	0.67-0.95	**0.01**
Neuroticism [b]	0.08 (0.01)	0.06-0.10	**<0.001**	0.05 (0.01)	0.03-0.07	**<0.001**

[a] Logistic regression with OR
[b] Linear regression with standardized betas and *SE*
[c] *Adjusted for the covariates of age, sex, ethnicity (White British vs Other), deprivation index, smoking status, BMI and alcohol intake*
Values in bold indicate significant tests.

Table 6 Regression models for the association between RF-/RF+ and mental health

	Unadjusted Model			Fully adjusted model [c]		
	β/ OR	95% CI	P value	β/ OR	95% CI	P value
Depression [a]	0.96	0.92-1.00	0.06	0.97	0.93-1.01	0.2
Anxiety [a]	0.94	0.87-1.02	0.172	0.95	0.88-1.03	0.2
Neuroticism [b]	-0.01 (0.005)	-0.09- -0.02	**<0.001**	-0.006 (0.004)	-0.01-0.002	0.16

[a] Logistic regression with OR
[b] Linear regression with standardized betas and *SE*
[c] *Adjusted for the covariates of age, sex, ethnicity (White British vs Other), deprivation index, smoking status, BMI and alcohol intake*
Values in bold indicate significant tests.

Sleep

Regarding sleep, those that self-reported RA were more likely to nap during the day (OR = 1.21, 95% CI: 1.17 to 1.26, p < 0.001), less likely to get up in the morning with ease (OR = 0.61, 95% CI: 0.59 to 0.63, p < 0.001) and more likely to have insomnia (OR = 1.48, 95% CI: 1.41 to 1.56, p < 0.001) (see **Table 7**), while those RF+ were more likely to report longer sleep durations (β = 0.01, *SE* = 0.004, p < 0.001), more likely to nap during the day (OR = 1.06, 95% CI: 1.03 to 1.09, p < 0.001), and more likely to have insomnia (OR = 1.06, 95% CI: 1.03 to 1.10, p < 0.001) (see **Table 8**). After adjusting for covariates, those self-reporting having RA were more likely to nap during the day (OR = 1.10, 95% CI: 1.06 to 1.14, p < 0.001), less likely

to get up with ease (OR = 0.61, 95% CI: 0.58 to 0.64, p < 0.001) and more likely to suffer from insomnia (OR = 1.28, 95% CI: 1.22 to 1.35, p < 0.001). Those RF+ were more likely to report longer sleep duration (β = 0.01, *SE*=0.004, p < 0.01) and less likely to get up in the morning easily (OR = 0.95, 95% CI: 0.92 to 0.99, p = 0.01).

Table 7 Regression models for the association between RA and sleep

		Unadjusted model			Fully adjusted model [c]	
	β/ OR	95% CI	P value	β/ OR	95% CI	P value
Sleep duration [b]	0.01 (0.009)	-0.02-0.007	0.2	-0.01 (0.009)	-0.03- 0.001	0.06
Nap during the day [a]	1.21	1.17-1.26	**<0.001**	1.10	1.06-1.14	**<0.001**
Getting up in the morning [a]	0.61	0.59-0.63	**<0.001**	0.61	0.58-0.64	**<0.001**
Insomnia [a]	1.48	1.41-1.56	**<0.001**	1.28	1.22-1.35	**<0.001**

[a] Logistic regression with OR
[b] Linear regression with standardized betas and *SE*
[c] *Adjusted for the covariates of age, sex, ethnicity (White British vs Other), deprivation index, smoking status, BMI, alcohol intake and cardiometabolic diseases*
Values in bold indicate significant tests.

Table 8 Regression models for the association between RF-/RF+ and sleep

	Unadjusted model			Fully adjusted model [c]		
	β/ OR	95% CI	P value	β/ OR	95% CI	P value
Sleep duration [b]	0.01 (0.004)	0.01-0.02	**<0.001**	0.01 (0.004)	0.003-0.020	**0.008**
Nap during the day [a]	1.06	1.03-1.09	**<0.001**	1.01	0.98-1.04	0.2
Getting up in the morning [a]	1.02	0.99-1.06	0.09	0.95	0.92-0.99	**0.01**
Insomnia [a]	1.06	1.03-1.10	**<0.001**	1.01	0.98-1.04	0.4

[a] Logistic regression with OR

[b] Linear regression with standardized betas and *SE*

[c] *Adjusted for the covariates of age, sex, ethnicity (White British vs Other), deprivation index, smoking status, BMI, alcohol intake and cardiometabolic diseases*

Values in bold indicate significant tests.

Cognition

For cognition, those that self-reported having RA were also more likely to score higher for reaction time (i.e. slower reaction/ worse performance) (β = 0.13, *SE* = 0.009, p < 0.001), more likely to score less for fluid intelligence (worse performance) (β = -0.10, *SE* = 0.01, p < 0.001) and less likely to perform well on the prospective memory task (OR = 0.87, 95% CI: 0.81 to 0.94, p < 0.001) (see **Table 9**). Those RF+ were more likely to score higher for reaction time (i.e., slower reaction/worse performance) (β = 0.03, *SE* = 0.004, p < 0.001) (see **Table 10**). After adjusting for covariates, reaction time (β = 0.02, *SE* = 0.008, p < 0.005) and fluid intelligence (β = -0.03, *SE* = 0.01, p < 0.05) remained significant for RA, indicative of worse performance.

Table 9 Regression models for the association between RA and cognition

	Unadjusted model			Fully adjusted model [c]		
	β/ OR	95% CI	P value	β/ OR	95% CI	P value
Reaction time [b]	0.13 (0.009)	0.11-0.14	**<0.001**	0.02 (0.008)	0.009- 0.04	**0.002**
Fluid intelligence [b]	-0.10 (0.01)	-0.13- -0.07	**<0.001**	-0.03 (0.01)	-0.07- -0.004	**0.02**
Pairs matching [b]	0.008 (0.02)	-0.03- 0.05	0.7	-0.02 (0.021)	-0.06- 0.01	0.2
Prospective memory [a]	0.87	0.81- 0.94	**<0.001**	0.97	0.90- 1.05	0.5

[a] Logistic regression with OR
[b] Linear regression with standardized betas and *SE*
[c] *Adjusted for the covariates of age, sex, ethnicity (White British vs Other), deprivation index, smoking status, BMI and alcohol intake*
Values in bold indicate significant tests.

Table 10 Regression models for the association between RF-/RF+ and cognition

	Unadjusted model			Fully adjusted model [c]		
	β/ OR	95% CI	P value	β/ OR	95% CI	P value
Reaction time [b]	0.03 (0.004)	0.03-0.04	**<0.001**	0.001 (0.004)	-0.006- 0.009	0.7
Fluid intelligence [b]	0.005 (0.007)	-0.01- 0.02	0.5	0.01 (0.007)	-0.003- 0.02	0.1
Pairs matching [b]	0.002 (0.009)	-0.016- 0.02	0.8	-0.01 (0.009)	-0.03-0.003	0.1
Prospective memory [a]	0.98	0.95-1.02	0.4	1.01	0.97-1.05	0.4

[a] Logistic regression with OR

[b] Linear regression with standardized betas and *SE*

[c] *Adjusted for the covariates of age, sex, ethnicity (White British vs Other), deprivation index, smoking status, BMI and alcohol intake*

Values in bold indicate significant tests.

DISCUSSION

The prevalence of self-report RA within the UK Biobank baseline sample was 1.18%, out of which 69% were female and 31% were males. This is similar to other estimates in the literature that suggest around 0.81% of people in the UK suffer from RA, with a higher prevalence for women than men (Symmons et al., 2002). Out of the 5,722 participants that reported RA, 74% were RF- and 26% were RF+. This was much lower than other estimates of 80% RF+ (Nell et al., 2005) and it could be due to differences in measurement, measurement error or changes in RF levels compared to previous population recorded values. RA patients were more likely to report being a current or previous smoker, in line with previous literature suggesting smoking is a risk factor for developing RA (Sugiyama et al., 2010). There were also significant differences between RF+ and RF- people regarding smoking as Sugiyama et al. (2010) suggested that odds of having RA are almost double for RF+ male smokers. The RA subsample was more likely to drink alcohol less frequently. Observational studies often suggest a 'protective' effect of alcohol for RA but this can be due to confounding recall bias (Scott et al., 2013). It is possible that those with more severe RA drink less alcohol or that those that completely abstain from drinking do so due to medical reasons and are less healthy overall compared to those that drink occasionally. Indeed, MR analyses generally do not support the inverse causal relationship between alcohol and RA (Bae & Lee, 2018). The RA subsample was also more likely to have higher values for BMI, hip circumference, and waist circumference. Having a BMI over 30 was associated in the literature with an increased risk of developing RA (RR = 1.25, 95% CI: 1.07-145) (Qin et al., 2015) and 40% lower odds of achieving remission (Liu et al., 2017). To our knowledge there is a gap in the literature

comparing people RF- and RF+ but we found significant differences for age, sex, ethnicity, smoking status, alcohol intake, deprivation, and physical activity score (but not BMI).

Among RA comorbidities, cardiovascular-related disease was studied most extensively as it is believed that RA patients have a 50% increased risk of CVD-related mortality compared to the general population (meta-SMR 1.50, 95% CI: 1.39-1.61). Even after accounting for traditional cardiovascular risk factors, there is still a large proportion of heart failure (at the age of 80) left unexplained in RA patients ($p < 0.01$) (Crowson et al., 2005). The RA subsample in the current study was also more likely to report diabetes, hypertension, heart attack and stroke, while RF+ people were more likely to report hypertension, heart attack and stroke.

Regarding mental health, there were significant differences between RA and non-RA groups for a number of domains. The prevalence rate for depression in RA was 6.9% and for anxiety was 1.1%. Prevalence rates for depression in the literature range between 0.04% and 66.3% depending on the instrument used for diagnosis (Matcham et al., 2013a). The current study was limited to using self-report depression and anxiety. After adjusting for covariates, people with RA were less likely to report anxiety. RA was associated with higher neuroticism in our analyses, even after adjusting for covariates. This is likely important for mental health in RA as Evers et al. (2002) suggested neuroticism is the most consistent and effective predictor of mental health issues in RA at 3 and 5 years follow up. Regarding sleep, previous studies estimated that between 49%-80% of RA patients report poor sleep (Devins et al., 1993; Durcan et al., 2014; Goes et al., 2017; Guo et al., 2016). Those that reported having RA were more likely to nap during the day, less likely to get up with ease in the morning (also a feature of joint inflammation in RA) and more likely to suffer from insomnia even after adjusting for

covariates. For cognition, a systematic review suggested that people with RA might have cognitive impairment but more research is needed to better understand what specific domains are affected (Meade et al., 2018b). In the unadjusted regressions those that reported having RA were more likely to have slower reaction times and perform worse for the fluid intelligence (reasoning/logic) and the prospective memory tasks. After adjusting for covariates, worse performance for the reaction time and fluid intelligence tasks remained significant predictors. Considering that RA is a disease that can cause joint stiffness and pain, we believe a reaction time task can be severely impacted by this, unveiling a problem with mobility rather than cognition. Lastly, our study extended the evaluation to RF status as well, regardless of whether participants had RA or not. In our study, those RF+ were more likely to report longer sleep duration and less likely to get up in the morning with ease, even after adjusting for covariates. RF+ people were also more likely to score lower for neuroticism and have slower reaction times, were more likely to nap during the day and have insomnia only in the unadjusted regression analyses.

The UK Biobank has the advantage of being a relatively large cohort with around half a million people recruited, tested, and measured in the same, standardised way. However, it might not be representative of the wider population for lifestyle risk factors and disease, particularly relating to age, ethnicity and deprivation status; there is a well-established 'healthy bias' in the UK Biobank and some evidence this may meaningfully and significantly bias analyses towards type 1/2 errors (Keyes & Westreich, 2019; Lyall et al., 2021). It is also possible that those with less severe RA or mental health are more likely to take part in research studies. The current study was also limited to using self-reported illnesses (e.g., depression, anxiety, and RA). As in a previous study by Siebert et al. (2016) this meant that we could not

differentiate between participants that preferred not to report or did not remember their diseases, and those that were actually healthy and hence had nothing to report. However, our self-report RA prevalence was similar to previous estimates.

We believe that the 'getting up in the morning' question could have been phrased differently as it does not differentiate between difficulties waking up and difficulties getting out of bed due to mobility or other issues. People with RA suffer from joint stiffness, especially in the morning, which could make it more difficult for them to get out of bed and therefore influence their response to this question intended to enquire about sleep quality. Additionally, fatigue is a main symptom of RA and other chronic inflammatory conditions (Nikolaus et al., 2013), and therefore daytime symptoms (i.e., tiredness/needing a nap) may relate to this rather than poor sleep. It is essential to understand the prevalence and causes of both sleep and fatigue problems in RA as management of these components may differ. Dedicated sleep assessments and surveys in RA cohorts may help identify the relative contribution of impaired sleep to morning symptoms. Similarly, we observed an association with RF+ and poorer sleep; the exact mediating mechanisms underlying this are unclear. It is possible that RF+ status may be associated with some subclinical changes that impact on these aspects, without manifesting as clinical disease. In our study, those RF+ were more likely to report longer sleep duration and more likely to have insomnia which may appear contradictory. The UK Biobank insomnia question was based on self-report and asked participants to include naps as well. We believe that naps should have been excluded from this question as they can give the impression of a long sleep duration at night when in fact quite the opposite could be true- a person could suffer from insomnia which would make them more likely to need a nap throughout the day. Future research should also investigate this further based on more objective sleep measures. The cross-sectional nature of the

current study means that we could not establish causal relationships or rule out confounding and reverse causation. It is unclear whether mental health, sleep and cognition predate or are caused by RA. By only using a single measurement of RF we were also unable to investigate whether levels fluctuate over time or whether they are stable. Future research could benefit from using primary care and hospital admissions diagnoses and genetic or longitudinal analyses for causal relationships. Main symptoms of RA like pain, fatigue and disease activity can fluctuate and change over time highlighting the importance of longitudinal studies compared to those that test a single point in time.

Despite being important areas of RA patients' overall quality of life, mental health, sleep, and cognition are often overlooked in the literature and in the clinic, where the focus is on controlling inflammation and disease activity. Similarly, we need a better understanding about the role RF plays on these domains, as well as investigating the possible underlying mechanisms. The current study suggests that self-reported RA and RF status are associated with differences in all three domains and provide substantial support and novelty in the case of RF to previous literature, highlighting the importance of addressing these aspects in clinical settings and future research.

Chapter 4: Associations between self-reported rheumatoid arthritis, rheumatoid factor positivity and structural brain phenotypes

A version of this chapter is published as a preprint:

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ABSTRACT

Objectives: The literature on structural brain health in people with rheumatoid arthritis (RA) is very limited. Our aim was to investigate whether there are any brain phenotype differences between people with self-reported RA and/or those that are positive rheumatoid factor (RF+) regardless of RA status, compared with people who do not report RA or are RF negative ('control group'), respectively.

Methods: We tested for cross-sectional associations between RA and/or RF+ vs. several relevant MRI brain volume variables in the UK Biobank (N = 37,379 participants, out of which 432 reported RA and 1,833 were RF+). We adjusted for age, sex, and assessment centre in the partially adjusted models, while in the fully adjusted models we additionally controlled for deprivation, smoking and cardiometabolic conditions.

Results: Those that self-reported RA were more likely to have increased white matter hyperintensity volumes (WMH standardised β = 0.08, 95% CI: 0.021 to 0.14, p = 0.008), and smaller volumes of the amygdala (β = -0.09, 95% CI: -0.16 to -0.02, p = 0.006) in the partially adjusted analyses. In the fully adjusted model RA remained significantly associated with amygdala volume (β = -0.09, 95% CI: -0.16 to -0.02, p = 0.008). We found no significant associations with RF+ status.

Conclusion: Our study provides evidence for differences in structural brain volumes that are known to be related to psychological and cognitive health in those with vs. without RA. Previous literature suggests a potential role for the amygdala in pain modulation and mental health, and an increased risk for stroke associated with WMH, so our findings may be of clinical importance in people with RA. Further research is necessary to confirm these associations and asses their functional implications.

INTRODUCTION

More research is needed to understand the potential brain structure differences that come with chronic disease and aging. It is essential to investigate and monitor the role of cognition and brain phenotype differences that come with age as these can be associated with later-life neurodegenerative disease. For example, it has been suggested that mild cognitive impairment, as seen through poorer performance on cognitive tests, is associated with an increased risk of future dementia (Calvin et al., 2019; Swaddiwudhipong et al., 2022). Differences in brain structure, even in the absence of dementia, strongly predict cognitive performance with age (even after controlling for past cognitive ability) with similar effects for both white and gray matter and for both males and females (Royle et al., 2013). For example a study by Ritchie et al. (2015) that used diffusion tensor MRI and cognitive tests for fluid intelligence, processing speed and memory in a large sample of older adults (mean age of 73 years at baseline and 76 years at follow-up) showed that there are longitudinal changes in the microstructure of white matter that were associated with changes in fluid intelligence scores. Similarly, WMH are associated with worse overall cognitive performance, executive function and speed of processing, as well as an increased risk of dementia and CVD (Debette & Markus, 2010). White matter tract integrity has also been shown to be associated with processing speed and general cognition (Penke et al., 2012). Fundamentally, structural brain phenotypes are a key and potentially early indicator of cognitive and psychological health (Ferguson et al., 2020; Zhu et al., 2021).

There is very limited research into potential effects of RA on the brain. Compared to other disorders with an inflammatory or neurodegenerative component, far fewer studies have

investigated brain differences in RA using neuroimaging (Fuggle et al., 2014). Moreover, the majority of MRI studies suffer from a small sample size, with a median sample size reported in review papers between N = 6 to 25 (Hanspach et al., 2021; Marek et al., 2022). The first and to our knowledge only study that looked into structural brain differences in cortical and subcortical gray matter in RA patients versus healthy controls was conducted by Wartolowska et al. (2012). 31 participants with RA and 25 healthy age- and sex-matched controls underwent MRI scans. In the analyses adjusted for ICV, age and sex, RA patients had larger volumes of the caudate nucleus (right hemisphere $F[1, 51] = 8.5$, $p = 0.005$, left hemisphere $F[1,51] = 5.9$, $p = 0.02$) and a larger volume of the putamen in the left hemisphere ($F[1, 51] = 4.6$, $p = 0.04$) as well as larger right nucleus accumbens volume ($F[1,51] = 5.5$, $p = 0.02$). As the observed differences in the adjusted analyses were mainly in the basal ganglia, a region associated with anticipation of pain, pain relief and movement planning as a consequence of pain, these findings could be indicative of an altered function of the basal ganglia in RA as well as compensatory pain and movement responses (Wartolowska et al., 2012). The authors conclude that their RA sample did not exhibit extensive or localized differences in cortical gray matter structure despite the chronic elements of pain and inflammation. Hamed et al. (2012) also investigated cross-sectionally whether there are any central nervous system differences in RA (N = 55 female participants but no controls). Only seven out of the 55 patients presented abnormal hyperintense signals (i.e., lesions) in subcortical white matter and at the intersection between gray and white matter that are typical signs of vasculitis, ischemic brain lesions or demyelination dots. Moreover, all seven of these subjects had higher serum levels of the S100B protein, a marker of inflammation and neurodegeneration. Those with higher levels of this biomarker were also more likely to perform more poorly on cognitive tests. Another study that looked at hyperintensities in nine RA patients compared to 15 control

subjects (Bekkelund et al., 1995) found no differences in atrophy levels and no associations between RF status and brain changes in the RA patients. However, when looking specifically at patients with longstanding disease (RA for more than 15 years), they were more likely to show significant brain atrophy that may suggest long-term neurodegenerative changes caused by RA (Fuggle et al., 2014). It is important to note that a limitation of this study is that it is unclear whether they corrected for age in the subsample of those with longstanding RA. Similarly, Phukan et al. (2022) found cerebral hyperintense lesions as well as altered white matter integrity in their RA subsample compared to the healthy control group. In RA patients with neuropsychiatric symptoms in particular (i.e., headaches, blurry vision, insomnia, limb weakness etc.), there was an increased diffusion coefficient and radial diffusivity ($p < 0.05$) and a decreased fractional anisotropy coefficient and axial diffusivity ($p < 0.05$), indicative of less healthy white matter. The authors suggest that this could be due to the central nervous system vasculitis that is sometimes present in RA which can result in tissue hypoxia, disruption of the blood-brain barrier and ultimately degeneration of axons, neuronal cells, and the myelin in the white matter fibers.

Current study

There is little to no research on structural brain differences in RA and all studies to date have a relatively small sample ($N < 56$) and/or fail to control for important potential confounders like deprivation, smoking status or cardiometabolic diseases. For RF+ status (regardless of RA diagnosis) there is a complete gap in the literature. Previous literature suggests there might be a cerebrovascular component in RA but more research is needed to see if this can be detected through routine MRI scans (Fuggle et al., 2014). As RA is characterized by systemic inflammation and pain, we were interested to see whether this correlates with

neuroinflammation and structural brain differences. The constant chronic inflammation can lead to persistent stimulation of nociceptor and afferent neurons and therefore, we were interested whether brain areas that are known to have a role in pain/conditioned fear such as the amygdala, or a role in mediating nociceptive inputs to the brain such as the thalamus, will be associated with RA (Davis, 1992; Fuggle et al., 2014; Neugebauer et al., 2004; Oosterman et al., 2006; Simons et al., 2014). As the biggest risk for morbidity and mortality in RA is due to CVD (Aviña-Zubieta et al., 2008) we were particularly interested in investigating whether RA is associated with a higher volume of WMH, a marker of cerebrovascular health.

Brain imaging phenotypes are important because they are early markers of brain differences which may then manifest as psychiatric and/or neurodegenerative pathologies (Swaddiwudhipong et al., 2022). The aim of this cross-sectional study was to test for associations between self-reported RA or RF positivity and several brain volume and white matter tract integrity measures derived using MRI in the UK Biobank (N = 37,379). In particular, we looked for differences in phenotypes considered to be relevant to cognitive and psychological health based on previous literature described above (Debette & Markus, 2010; Penke et al., 2012; Ritchie et al., 2015; Royle et al., 2013) including TBV, GM, WM, total volume of WMH (a marker of cerebrovascular health), subcortical volumes and measures of white matter tract integrity (fractional anisotropy and mean diffusivity).

METHODS

Participants and procedure

The UK Biobank is a large cohort of participants aged 40 to 69 years old that were recruited between 2006 and 2010 (Allen et al., 2012). The cohort is described in detail in the methods chapter. Informed consent was collected from all participants and the study was conducted under generic approval from the NHS National Research Ethics Service and under UK Biobank project approval 17689 (PI Lyall). At the baseline visit participants attended one of the 22 assessment centres and completed touchscreen questionnaires on various sociodemographic and lifestyle factors and also had physical measures taken (e.g., weight, height) and blood, saliva and urine samples (Allen et al., 2012).

Independent variables

For the current study we were interested in self-reported RA and RF biomarker levels that were derived from serum and packed red blood cell samples. We used both baseline visit and imaging visit data for self-reported RA (i.e., reported at either) and baseline visit data for RF (because it is not repeated/performed for imaging visits). We recorded very low levels of RF that were coded as 'missing' due to being under the minimum detectable value as the square root of the minimum stated detectable value if participants had data for a remaining biomarker as previously described in another study (Ferguson et al., 2020). Following that, we derived a new binary variable with values over 14 IU/ml considered rheumatoid factor positive (RF+) and values under being considered rheumatoid factor negative (RF-) (Sunar &

Ataman, 2020). Given the gap between the baseline visit where RF levels were measured and the imaging visit, we performed a correlation analysis between baseline RF values versus first repeat assessment visit RF values for the ~18,000 participants that had repeat data available and found a $r = 0.57$ ($p < 0.001$) correlation for RF values across the 5 years.

Covariates

Our covariates for the current chapter were age, sex, assessment centre at baseline and imaging visit, Townsend deprivation index, smoking history at imaging visit (never/previous/current smoker), alcohol intake, BMI and cardiometabolic conditions based on non-cancer self-report (diabetes, hypertension, angina, heart attack, stroke). Townsend scores derived from postcode of residence were used in the current chapter to categorize people into socioeconomic deprivation quintiles (Townsend, 1972). In the current chapter cardiometabolic conditions (diabetes, hypertension, angina, heart attack, stroke) were based on self-report at both the baseline visit (2006-2010) and the imaging visit (2014+). We used baseline visit data for deprivation index, sex, and imaging visit data for smoking status, alcohol intake, BMI, and age.

Outcome variables-MRI measures

After the initial recruitment phase between 2006 and 2010, a subset of UK Biobank participants was invited to attend an imaging visit and undertake brain MRI. The current study used brain MRI data that consists of approximately 40,000 participants captured around January 2021. Even though limited, previous research focused on gray matter volume,

subcortical volumes and WMH (a marker of cerebrovascular health) and integrity when studying RA and chronic pain conditions. Therefore, we selected brain structures that had *a priori* evidence to be potentially associated with RA or worse cognitive health.

The MRI variables used in the current study are: TBV, GM, WM, WMH, total accumbens volume, total amygdala volume, total caudate volume, total hippocampus volume, total pallidum volume, total putamen volume, and total thalamus volume (all measured in mm^3). We also used principal components analysis to construct general factors of white matter integrity: fractional anisotropy - gFA (eigenvalue = 12.28, 49% variance explained) and mean diffusivity- gMD (eigenvalue = 13.37, 53% variance explained). FA and MD are measures of white matter tract integrity used to describe the directional coherence and magnitude of the diffusion of water molecules (Lyall et al., 2020). Lower FA values and higher MD values represent worse/less 'healthy' white matter.

More information about data acquisition and processing including the primary brain image documentation can be found at: https://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977 and for the brain scan protocol at: https://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367. TBV, WM and GM were segmented automatically using T1 FMRIB's Automated Segmentation Tool (FAST https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf) and normalized for head size, while total WMH were derived from T1 and T2 fluid-attenuated inversion recovery (FLAIR) (Lyall et al., 2020), with the methodology described by Miller et al. (2016). Due to its skewed distribution, the WMH variable was log-transformed. Subcortical brain volumes were modelled using T1 FMRIB's Integrated Registration and Segmentation Tool (FIRST https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf). All numeric variables were standardized to Z-scores before analyses.

Statistical analyses

We excluded data from participants that had failed biomarker quality control, had incomplete MRI data, had a BMI under 18 (i.e., frailty) or who were advised by the doctor to quit alcohol. We also excluded MRI variables that had values of 0. This cross-sectional study used data from the UK Biobank imaging visit to compare structural brain differences in people with and without self-reported RA, and separately for participants that were RF+ versus RF-. We performed linear regressions to determine whether there are any associations between RA/RF+ and selected structural cortical and subcortical brain measures.

The partially adjusted models were adjusted for age, sex, and assessment centre, while in the fully adjusted models we also controlled for deprivation index, smoking status, alcohol intake and BMI and cardiometabolic conditions (diabetes, hypertension, angina, heart attack, stroke). We performed sensitivity analyses for subcortical volumes where we additionally controlled for ICV and separately for TBV. False Discovery Rate (FDR) was applied using the 'p.adjust' function in R, to correct for multiple testing.

RESULTS

After exclusions our sample had 37,379 participants, out of which 432 (1.15%) self-reported having RA and 1,833 (4.9%) were RF+ based on baseline biomarker values (See **Table 11**). Those that self-reported having RA were more likely to be older, female and have a higher BMI value (see **Table 12** for descriptive statistics). Those who were RF+ were also more likely to be older.

Table 11 Crosstab of RF seropositivity status for those with/without RA

No RA	**Self-reported RA**
95% are RF-	76% are RF-
5% are RF+	24% are RF+

Table 12 Descriptive statistics of participants with/without RA and RF+/RF- from the MRI imaging sample

	No rheumatoid arthritis N = 36,947 (98.8%)	Self-reported rheumatoid arthritis N = 432 (1.15%)	P value	Negative rheumatoid factor (RF-) N = 35,546 (95%)	Positive rheumatoid factor (RF+) N = 1,833 (4.9%)	P value
Age [a, c]	63.8 (7.68)	65.2 (7.22)	**<0.001**	63.8 (7.69)	65 (7.23)	**<0.001**
Sex [b,d]						
Female	19,168 (52%)	268 (62%)	**<0.001**	18,476 (52%)	960 (52%)	0.74
Male	17,779 (48%)	164 (38%)		17,070 (48%)	873 (48%)	
BMI [a, c]	26.5 (4.3)	27.3 (4.95)	**0.004**	26.5 (4.32)	26.7 (4.27)	**0.04**
Normalised total brain volume (mm^3) [a, c]	1,496,276 (72878)	1,491,047 (70189)	0.188	1,496,531 (72809)	1,490,062 (73371)	**0.001**
Normalised gray mater volume (mm^3) [a, c]	793,705 (47804)	792,983 (44322)	0.749	793,901 (47747)	789,696 (47936)	**0.003**
Normalised white matter volume (mm^3) [a, c]	702,571 (40807)	698,063 (40367)	**0.03**	702,630 (40799)	700,367 (40865)	**0.02**
Volume white matter hyperintensities (mm^3) (before log-transform) [a, c]	4,855 (6337)	5,712 (7534)	**<0.001**	4,861 (6360)	4,924 (6201)	0.2
Subcortical volumes						
Total accumbens volume (mm^3) [a, c]	887 (209)	855 (215)	**0.003**	886 (209)	881 (209)	0.3
Total amygdala volume (mm^3) [a, c]	2,493 (438)	2,399 (410)	**<0.001**	2,493 (439)	2,487 (421)	0.9
Total caudate volume (mm^3) [a, c]	6,951 (847)	6,901 (816)	0.29	6,951 (847)	6,938 (840)	0.6
Total hippocampus volume (mm^3) [a, c]	7,690 (882)	7,512 (838)	**<0.001**	7,689 (882)	7,663 (888)	0.2
Total pallidum volume (mm^3) [a, c]	3,562 (462)	3,466 (450)	**<0.001**	3,560 (460)	3,563 (491)	0.6
Total putamen volume (mm^3) [a, c]	9,610 (1156)	9,410 (1129)	**<0.001**	9,609 (1155)	9,577 (1159)	0.3
Total thalamus volume (mm^3) [a, c]	15,342 (1484)	14,958 (1492)	**<0.001**	15,341 (1485)	15,269 (1476)	0.1

[a] Kruskal-Wallis test
[b] Pearson χ^2 test
[c] Mean (SD)
[d] N (%)
Values in bold indicate significant tests.

Association analyses: partially-adjusted

In the regression models partially adjusted for age, sex and assessment centre, those that self-reported having RA were more likely to have a higher volume of WMH (β = 0.08, 95% CI: 0.021 to 0.14, p = 0.008), a smaller amygdala volume (β = -0.09, 95% CI: -0.16 to -0.02, p = 0.006), a smaller pallidum volume (β = -0.07, 95% CI: -0.13 to -0.005, p = 0.03) and a smaller thalamus volume (β = -0.06, 95% CI: -0.12 to -0.01, p = 0.02) (see **Table 13**). The significant results for the pallidum and thalamus did not survive FDR correction or the sensitivity analyses where we controlled for ICV. After controlling for ICV, the association with the caudate became significant (β = 0.07, 95% CI: 0.01 to 0.13, p = 0.01). There were no significant associations for total brain volume, gray matter volume, white matter volume, gFA, gMD, the accumbens, the caudate, the hippocampus, and the putamen (all p>0.05). We found no significant associations with RF+ status (see **Table 14**).

Association analyses: fully-adjusted

In the fully adjusted model for age, sex, deprivation index, smoking status, alcohol intake, BMI and cardiometabolic diseases, those that self-reported RA were more likely to have a smaller amygdala volume (β = -0.09, 95% CI: -0.16 to -0.02, p = 0.008) (see **Table 13**). After our sensitivity analyses where we controlled for ICV, the association with the caudate became significant (β = 0.07, 95% CI: 0.02 to 0.1, p = 0.006). There were no significant associations for TBV, GM, WM, WMH, gFA (fractional anisotropy), gMD (mean diffusivity), the accumbens, the caudate, the hippocampus, the pallidum, the putamen, and the thalamus. We found no significant associations with RF+ status (see **Table 14**)

Table 13 Multiple linear regressions between self-reported RA and brain MRI variables with standardized betas and standard errors

	Partially adjusted model (Age, Sex and Assessment Centre)			**Fully adjusted model** (Age, Sex, Assessment Centre, **Deprivation, BMI, Alcohol intake, Smoking and Cardiometabolic Diseases**)		
	β (SE)	**95% CI**	**p value**	**β (SE)**	**95% CI**	**p value**
Total brain volume (mm^3)	-0.0004 (0.029)	-0.05- 0.05	0.9	0.005 (0.03)	-0.05- 0.06	0.8
Gray matter volume (mm^3)	0.01 (0.02)	-0.03- 0.07	0.5	0.03 (0.02)	-0.02- 0.08	0.2
White matter volume (mm^3)	-0.02 (0.03)	-0.08- 0.04	0.5	-0.02 (0.03)	-0.09- 0.04	0.4
Volume WM hyperintensities (mm^3)	**0.08 (0.03)**	**0.021- 0.14**	**0.008**	0.05 (0.03)	-0.005- 0.12	0.07
gFA: fractional anisotropy	-0.04 (0.03)	-0.11- 0.02	0.2	-0.01 (0.03)	-0.09- 0.05	0.5
gMD: mean diffusivity	0.01 (0.03)	-0.04- 0.08	0.6	-0.007 (0.03)	-0.07- 0.05	0.8
Subcortical volumes						
Total accumbens volume (mm^3)	-0.02 (0.03)	-0.08- 0.04	0.5	-0.004 (0.03)	-0.06- 0.06	0.8
Total amygdala volume (mm^3)	**-0.09 (0.03)**	**-0.16 - -0.02**	**0.006**	**-0.09 (0.03)**	**-0.16- -0.02**	**0.008**
Total caudate volume (mm^3)	0.03 (0.03)	-0.03- 0.09	0.3	0.04 (0.03)	-0.02- 0.11	0.2
Total hippocampus volume (mm^3)	-0.06 (0.03)	-0.12- 0.004	0.06	-0.04 (0.03)	-0.11- 0.01	0.1
Total pallidum volume (mm^3)	**-0.07 (0.03)**	**-0.13- -0.004**	**0.03**	-0.05 (0.03)	-0.12- 0.01	0.1
Total putamen volume (mm^3)	-0.008 (0.03)	-0.06- 0.05	0.7	-0.001 (0.03)	-0.06- 0.06	0.9
Total thalamus volume (mm^3)	**-0.06 (0.03)**	**-0.12- -0.007**	**0.02**	-0.04 (0.03)	-0.10- 0.01	0.1

Values in bold indicate significant tests.

Table 14 Multiple linear regressions between RF status and brain MRI variables with standardized betas and standard errors

	Partially adjusted model (Age, Sex and Assessment Centre)			**Fully adjusted model** (Age, Sex, Assessment Centre, **Deprivation, BMI, Alcohol intake, Smoking and Cardiometabolic Diseases**)		
	β (SE)	**95% CI**	**p value**	**β (SE)**	**95% CI**	**p value**
Total brain volume (mm^3)	-0.005 (0.01)	-0.03- 0.02	0.6	-0.003 (0.01)	-0.03- 0.02	0.7
Gray matter volume (mm^3)	-0.003 (0.01)	-0.03- 0.02	0.7	-0.003 (0.01)	-0.02- 0.02	0.8
White matter volume (mm^3)	-0.005 (0.01)	-0.03- 0.02	0.7	-0.01 (0.01)	-0.04- 0.02	0.5
Volume WM hyperintensities (mm^3)	-0.02 (0.01)	-0.05- 0.005	0.11	-0.02 (0.01)	-0.06- -0.001	0.06
gFA: fractional anisotropy	-0.01 (0.01)	-0.05- 0.01	0.3	-0.008 (0.01)	-0.04- 0.02	0.6
gMD: mean diffusivity	-0.009 (0.1)	-0.04- 0.02	0.5	-0.01 (0.01)	-0.05- 0.01	0.2
Subcortical volumes						
Total accumbens volume (mm^3)	0.02 (0.01)	-0.008- 0.05	0.1	0.02 (0.01)	-0.005- 0.05	0.1
Total amygdala volume (mm^3)	-0.006 (0.01)	-0.04- 0.02	0.6	-0.009 (0.01)	-0.04- 0.02	0.5
Total caudate volume (mm^3)	0.001 (0.01)	-0.03- 0.03	0.9	0.001 (0.01)	-0.03- 0.03	0.9
Total hippocampus volume (mm^3)	0.008 (0.01)	-0.02- 0.04	0.5	0.006 (0.01)	-0.02- 0.04	0.6
Total pallidum volume (mm^3)	0.02 (0.01)	-0.01- 0.05	0.2	0.02 (0.01)	-0.007- 0.05	0.1
Total putamen volume (mm^3)	0.01 (0.01)	-0.01- 0.04	0.4	0.01 (0.01)	-0.01- 0.04	0.4
Total thalamus volume (mm^3)	0.001 (0.01)	-0.02- 0.03	0.9	-0.001 (0.01)	-0.03- 0.02	0.9

Values in bold indicate significant tests.

DISCUSSION

Overview and implications

In the current MRI sub-study, the prevalence of self-reported RA was 1.15%. These estimates are similar to those in the literature that suggest approximately 0.81% of UK residents suffer from RA. In the descriptive analyses the self-report RA subsample was more likely to have significantly smaller average white matter volume, a higher volume of WMH (i.e., worse cerebrovascular health), and smaller volumes for all subcortical volumes except for the caudate (i.e., accumbens, amygdala, hippocampus, pallidum, putamen, thalamus). To further test these associations, we carried out partially adjusted (for age and sex) and fully adjusted (age, sex, deprivation, smoking status, alcohol intake, BMI and cardiometabolic diseases) multiple linear regression models. In the partially adjusted models, people that self-reported having RA were more likely to have a higher volume of WMH, a smaller volume for the amygdala and a higher volume of the caudate (after the sensitivity analyses where we additionally controlled for ICV). In the fully adjusted models, the RA subsample was still more likely to have a smaller amygdala volume and a higher caudate volume (after the sensitivity analyses where we additionally controlled for ICV). To our knowledge there is a lack of studies that investigate differences in brain volumes between people that are RF- and RF+; in our descriptive analyses those RF+ were more likely to have a significantly smaller average total brain volume, gray matter volume and white matter volume. No significant associations were found for RF biomarker status.

Wartolowska et al. (2012) found no differences in cortical gray matter between the RA and control samples. In our study, those that self-reported RA or were RF+ did not differ significantly in total gray matter, white matter, or total brain volume. While Bekkelund et al.

(1995) found no differences in WMH for RA, in Hamed et al.'s (2012) study 7 out of the 55 RA patients presented WMH and lesions at the intersection between gray and white matter. These patients with WMH were more likely to perform worse on cognitive tasks and also had higher levels of the S100B protein that serves as a signal of both higher inflammation and worse brain degeneration. Our RA subsample was more likely to show a higher volume of WMH when adjusting just for age and sex. A significant relationship between WMH and pain affect has also been suggested (Oosterman et al., 2006), which may be relevant in the people with RA in our cohort. WMH are of clinical importance as they can be indicative of a higher risk of stroke, cognitive decline, dementia and death (Debette & Markus, 2010). Moreover, both white matter and gray matter lesion volumes are associated with later-life depression (Taylor et al., 2005). Many of these issues are increased in people with RA.

Basal ganglia

While Wartolowska et al. (2012) found no differences in cortical gray matter between RA subjects and healthy controls, they observed significant increases in subcortical basal ganglia structures, especially the nucleus accumbens and caudate nucleus. We also observed differences in the basal ganglia structure in our study, with the RA subsample more likely to show an increased caudate volume after controlling for ICV in the sensitivity analyses. These results may be indicative of differences in pain processing (Fuggle et al., 2014) and altered motor control (Wartolowska et al., 2012) in this patient population. Our results also suggested that those that self-reported RA were more likely to show a decreased pallidum volume (before FDR correction). Basal ganglia atrophy has been reported in other conditions as well. For example putamen volumes loss was associated with early and advanced Parkinson's

disease (PD) ($p < 0.05$), while a smaller pallidum volume was only noticed in advanced PD ($p = 0.023$) (Geng et al., 2006). More research is needed to understand whether differences in motor control and pain processing are associated with differences in the basal ganglia, as well as implications, as these are common symptoms in RA.

Thalamus

A smaller thalamus volume was observed in our RA subsample in the partially adjusted analyses, before FDR correction or sensitivity analyses with ICV. A decrease in gray matter density in the right anterior thalamus has also been reported in chronic back pain (Apkarian et al., 2004). The thalamus plays an important role in mediating nociceptive inputs (noxious) to the brain (Oosterman et al., 2006) and could be related to nociceptive pain in RA that is caused by joint damage. Putamen and thalamus atrophy has also been reported in patients with probable AD, with the reduced brain volumes associated with worse cognitive performance (De Jong et al., 2008). These results suggest that deep gray matter atrophy may also be present in AD which may contribute to the well-documented cognitive decline. Thalamic atrophy was also noticed in patients with first-episode or chronic schizophrenia (Adriano et al., 2010). According to the authors these results might suggest a defect in the cerebellar-thalamic-cortical circuit (CCTCC) that is responsible for motor control, as well as information processing and prioritization. This could be of clinical importance to RA patients who often need to adjust motor planning to accommodate stiffness and pain.

Amygdala

The amygdala was the only brain structure to show significant association with RA in our study after controlling for age, sex, deprivation, smoking status and cardiometabolic diseases. A coordinate-based meta-analysis looking at both experimentally induced pain studies and clinical pain studies supported the role of amygdala in pain processing (Simons et al., 2014). The authors further suggest the presence of enhanced cognitive and emotional processes in chronic pain. The amygdala may play an essential role in the formation and expression of conditioned fear (i.e., an elicited fear response paired with an originally neutral stimulus) (Davis, 1992). Indeed, a reciprocal relationship exists between chronic pain and negative emotional states such as fear, anxiety and depression, with accumulating evidence suggesting that the amygdala is essential in modulating this association (Neugebauer et al., 2004). As indicated in chapter three, 6.9% of people in the UK Biobank with RA reported having depression, compared with 5.7% in controls ($p < 0.001$). There is a possibility that existing comorbidities like depression and anxiety are associated with differences in brain volumes. For example, a study by Sheline et al. (1998) reported smaller amygdala core nuclei volumes for those with a history of recurrent major depression compared to the healthy control group. In contrast, a study by Frodl et al. (2002) suggested that patients with major depression have a significantly larger amygdala compared to the healthy control group [$F(1,55) = 9.4$; $p = 0.003$]. Therefore, it is possible that the amygdala differences in the RA cohort in our study relate to chronic pain and depression.

Strengths and limitations

Compared to previous studies that investigated brain differences in relatively small samples, the current study used the UK Biobank, a relatively large cohort that has imaging data for approximately 40,000 people. However, similar to other studies it is likely that those with less severe disease and comorbidities, as well as fewer financial difficulties (i.e., higher socioeconomic status) take part in research studies. Indeed, there is a recognized healthy bias in the UK Biobank, which increases the risk of type 1 and 2 errors (Keyes & Westreich, 2019; Lyall et al., 2021). The current study is also limited to using self-report illness (i.e., RA and cardiometabolic diseases). Note that the biomarker data were from baseline assessment; while we show good stability in ~20k participants with repeat biomarker data across an average of 5 years, it is possible some of the sample have developed higher RF in the period between baseline and imaging. RF+ levels in the current cohort were also lower than previous estimates which could potentially be due to measurement error. Therefore, our RF+ vs. RF- analyses are possibly an underestimate of effect.

The cross-sectional nature of the study means we cannot establish causality between the observed brain differences and RA. Smaller volumes for brain structures and higher burden of brain lesions could be clinically different for RA patients compared to healthy controls as a consequence of disease but could also predate the diagnosis and indicate a different genetic profile or environmental differences (Wartolowska et al., 2012). It is also impossible to pinpoint what specific RA trait would affect these observed brain differences as these could be a result of the pain itself, medication or chronic illness in general (Buckalew et al., 2008). The current cohort was limited by not having access to information relevant to RA such as

disease activity score and had incomplete treatment data (i.e., medication such as biologics would not show on primary care prescriptions as they are currently not prescribed by general practitioner practices), information that could affect the observed associations.

Conclusion

In comparison to other inflammatory or chronic disorders, the literature on structural brain differences in RA is extremely limited (Fuggle et al., 2014).The current study suggests that self-reported RA is associated with differences in the volume of white matter lesions, the volume of the amygdala and the volume of the caudate. As the observed differences have been previously associated with general cognition, pain processing and a higher risk of comorbidities it is essential that they are addressed in future research. There were no significant differences associated with RF status in the current chapter, supporting that the observed differences may relate to disease-associated symptoms, most notably pain, rather than just the presence of RF.

Chapter 5: Associations between polygenic risk score for rheumatoid factor and brain and cognitive health

ABSTRACT

Introduction: Previous chapters have shown that people with RA may present with differences in cognition and brain structure and thus we were interested if these were related to underlying genetic factors, more specifically RF, independently of the clinical manifestations of RA. There is a gap in the literature evaluating the association between a PRS for RF and structural brain and cognitive differences that could be relevant to the quality of life of those living with RA.

Methods: We tested for associations between PRS-RF and several MRI brain volumes and cognitive tests variables using the UK Biobank imaging sample (N = 37,379 participants). In the partially adjusted models, we controlled for genotype array, first 8 principal components, age, sex, and assessment centre, while in the fully adjusted models we additionally controlled for BMI, deprivation index, alcohol intake and smoking status.

Results: In the partially adjusted models, PRS-RF was associated with a lower volume of WMH (β = - 0.01, 95% CI: -0.029 to -0.006, p = 0.001 per SD of PRS-RF), higher gFA (β = 0.01, 95% CI: 0.0006 to 0.02, p < 0.05), lower gMD (β = -0.01, 95% CI: -0.02 to -0.004, p < 0.005) and lower scores for the pairs matching task (β = -0.021, 95% CI: -0.03 to -0.006, p < 0.005). In the fully adjusted models, PRS for RF was still associated with lower volume of WMH (β = -0.01, 95% CI: -0.02 to -0.006, p < 0.005), lower gMD (β= -0.01, 95% CI: -0.02 to -0.002, p<0.05) and lower score for the pairs matching task (β = -0.02, 95% CI: -0.03 to 0.005, p < 0.05). No significant associations were found for any of the subcortical volumes in either the partially adjusted or fully adjusted models.

Discussion: This is the first study, to our knowledge, that used a PRS for RF to investigate differences in brain and cognitive health that could be essential for the health and quality of life of people with RA. The findings of this chapter were unexpectedly in the protective direction, considering the increased association of the cognitive and mental health issues with RA. However, the effect sizes were very small, and there may be issues with RF measures in UK Biobank, so future studies are needed to understand and validate these analyses while also looking at longitudinal changes and comorbid risk factors and illnesses that are relevant to RA.

INTRODUCTION

Rheumatoid arthritis (RA) is the most prevalent chronic inflammatory disorder affecting the joints with the exact cause is still unknown but believed to be a mix of both environmental and genetic components leading to systemic and joint inflammation (Symmons, 2002). Using twin data to quantify the genetic contribution to RA, a study estimated the heritability to be between 53% (UK cohort) and 65% (Finnish cohort) (MacGregor et al., 2000). The rapid evolution of new genetic technologies and statistical methods has revealed that multiple genes and common genetic risk factors contribute to the onset and progression of RA and other autoimmune diseases (McAllister et al., 2011). Genetic susceptibility loci have been identified through three main methods: candidate gene studies, linkage studies and GWAS, the latter having identified 34 RA risk loci by 2011 and over 100 susceptibility loci by 2017 (Kim et al., 2017), with the majority of RA genetic risk factors having been identified in autoantibody positive RA patients, more specifically cohorts positive for ACPA (McAllister et al., 2011). However, it is believed that more than 50% of genetic heritability to RA is still unknown and therefore, a better understanding of the genetic mechanism involved in RA could potentially lead to better diagnosis methods and new treatments in the future (McAllister et al., 2011). Since the International HapMap Project mapped the entire human genome sequence variations (Gibbs et al., 2003), several large-scale GWAS for RA were carried out (Okada et al., 2019). When genome-wide studies investigate seropositive RA patients in particular, the focus in the literature is usually on ACPA (De Rooy et al., 2015; Plenge et al., 2007; Plenge et al., 2007). In contrast, RF+ status received much less attention. In one GWAS study of 5,539 “autoantibody-positive individuals” with RA versus 20,169 controls of European ancestry the authors defined “autoantibody positive individuals” as

having being either RF or anti-cyclic citrullinated peptide (anti-CCP) autoantibody positive (Stahl et al., 2010). After removing RA risk alleles that were already confirmed in previous studies, 34 independent SNPs were selected for a replication GWAS, the results of which identified seven new RA risk alleles at genome-wide significance ($p < 5 \times 10^{-8}$) near genes known to be related to immune function or previously involved in other autoimmune diseases (Stahl et al., 2010). The first GWAS to specifically test for associations with RF positivity was the one carried out by Julia et al. (2016) using a Spanish cohort of 937 RF+ and 323 RF- RA patients. Their findings suggested that RF status is associated with 10 confirmed RA risk loci. Nevertheless, on top of the very limited literature for RF+ GWAS, the sample sizes are also quite small and replication is needed with a larger cohort like the UK Biobank.

To our knowledge there are no studies that compute a PRS for RF. A PRS represents a person's genetic risk for a particular disorder or trait in the form of a quantitative score (Brown & Li, 2021). Clinically, PRS could potentially aid RA's disease stratification and prediction due to their stability throughout life. For diseases such as RA that usually develop later in life, PRS could have a great predictive ability due to their independence from the development of the disease (Brown & Li, 2021). Stahl et al. (2012) used an RA PRS derived from a GWAS to infer the amount of heritability explained by GWAS SNPs and estimated that on top of known RA associated loci, an extra 20% risk of seropositive RA can likely be explained by thousands of common variants. Honda et al. (2022) aimed to use a PRS for RA to predict radiographic progression severity over the first 5 years since assessment. Those with higher risk scores were at a higher risk of severe RA progression (OR = 1.90, p= 0.002). Additionally, those participants that were diagnosed at an earlier age had an even higher risk of radiographic progression (OR = 5.06, p = 0.0003).

Current study

Previous chapters have shown that RA is associated with negative outcomes such as worse performance on cognitive tests and structural brain differences. However, it is unclear whether these predate or are caused by RA. By using a genetic risk score that is set at birth we can investigate whether the observed differences are due to RF and predate RA or whether higher genetic susceptibility on its own is not enough and other lifestyle factors such as inflammation, pain, multimorbidity and medication might influence the psychological and brain health of RA patients. To our knowledge no studies have generated a PRS for RF and therefore, there are no association studies between genetic risk for RF and brain structure or cognition. This could help indicate whether the underlying genetic risk for RF is driving at least some of the RA cognitive/brain health effects – rather than the clinical onset and symptoms per se. For most PRS studies for rheumatological diseases, the sample size has been small for the discovery sets, and larger ones are needed for a better predictive performance (Brown & Li, 2021). The current chapter used a PRS generated from a large cohort, the UK Biobank (N = 380,501), to test for associations using the imaging visit data (N = 37,379) between PRS for RF and structural brain phenotypes, as well as cognitive tests. More specifically we were interested whether there are any associated differences in cognitive performance and brain structure known to be associated with cognitive and psychological health as previously described in the literature (Debette & Markus, 2010; Penke et al., 2012; Ritchie et al., 2015; Royle et al., 2013) as well as suggested to be associated with RA in previous chapters. These included reaction time, fluid intelligence, pairs matching, prospective memory, TBV, GM, WM, subcortical volumes and measures of white matter tract integrity-fractional anisotropy and mean diffusivity.

METHODS

Participants and procedure

The UK Biobank is a large, deeply-phenotyped cohort of around 500,000 people studied prospectively. The current chapter used data from the imaging visit where approximately 40,000 were recruited to take part in a repeat assessment visit. After exclusions the total sample used for the current chapter was N = 37,379. More information on this sample can be found in Chapters 2 and 4.

Polygenic risk score generation

A GWAS was carried out and a PRS was generated by a colleague with expertise in this (Dr Joey Ward). Genetic quality control was carried to exclude participants of non-European ancestry, those that had a mismatch between self-reported and genetic sex, sex chromosome aneuploidy, as well as outlier values for heterozygosity. To avoid over-fitting and over-estimation, participants that had imaging data available and those that failed quality control were excluded from the GWAS. The final GWAS sample covered 380,501 participants, out of which 20,208 were RF+ (See **Table 15**). The GWAS was conducted for RF both as a continuous variable and as a categorical variable (RF+/RF-) and both analyses yielded similar results, therefore the current thesis only discussed the case/control analysis due to the fact that RF was non-linearly distributed even after log-transforming and due to previous papers also investigating RF as categorical. A training set was created to obtain the LD structure using 1000 unrelated UK Biobank participants that passed genetic quality control but were excluded from the GWAS (because they didn't have imaging data). This training data was later used to

generate PRS for RF in the UK Biobank subsample that had MRI data available. The PRS was generated using a weighted sum of the 25 genome-wide significant hits using the PLINK software (-- score flag command). Following this, association analyses were conducted between PRS and imaging phenotypes and separately, performance on cognitive tests (N = 37,379).

Table 15 GWAS sample descriptive statistics

	RF+ cases, N = 20,208	RF controls, N = 360,293	Full sample, N = 380,501
Age in years, mean (standard deviation)	58 (7.7)	56.5 (8.14)	56.6 (8.13)
Age range (years)	40-71	37-73	37-73
Female, N (%)	8,894 (44)	165,603 (46)	174,497 (45.9)

Note: no imaging participants were included in this stage of analysis (GWAS discovery)

Outcome variables-brain MRI phenotypes and cognitive phenotypes

Information about MRI data acquisition and processing can be found in chapters 2 and 4. MRI outcome measures used in the current chapter were TBV, GM, WM, WMH, total accumbens volume, total amygdala volume, total caudate volume, total hippocampus volume, total pallidum volume, total putamen volume, and total thalamus volume (all measured in mm^3). We also used principal component analysis to construct general factors for fractional anisotropy - gFA (eigenvalue = 12.28, 49% variance explained) and mean diffusivity- gMD (eigenvalue = 13.37, 53% variance explained). Fractional anisotropy and mean diffusivity are measures of white matter tract integrity that describe the directional coherence and

magnitude of the diffusion of water molecules (Lyall et al., 2020). Lower FA values and higher MD values represent worse/less 'healthy' white matter. For total white matter and total gray matter we used the variables normalized for head size. All numeric variables were standardized. Due to its skewed distribution, the WMH variable was log-transformed.

The cognitive tests used in the current chapter were reaction time (mean response time in milliseconds), fluid intelligence, pairs matching (number of errors made) and prospective memory (correctly recalled on first attempt versus not). These tests were administered at the baseline visit, taking approximately 15 minutes to complete all tests. More information about these variables can be found in Chapter 2 and Chapter 3.

Covariates

Models in the current chapter were adjusted for genotype array, the first eight principal components, age at imaging visit, sex, Townsend deprivation index, assessment centre at baseline and imaging visit, smoking history, alcohol intake, and BMI. We used postcode of residence to derive Townsend scores and categorize participants into deprivation quintiles.

Statistical analyses

The exclusion criteria before any association analyses were carried out included incomplete MRI data, having MRI values of 0, having a BMI value under 18 and being advised by their doctor to quit alcohol. We then performed regression analyses between a PRS for RF status and structural brain variables. We also performed regression analyses separately to test the associations between a PRS for RF seropositivity and performance on cognitive tests. We ran

a multiple linear regression for TBV, GM, WM, WMH, gFA, gMD, all subcortical volumes, reaction time, fluid intelligence and pairs matching and a logistic regression for prospective memory. In the partially adjusted models, we controlled for genotype array, the first eight principal components, age, sex, and assessment centre. In the fully adjusted models, we controlled for genotype array, first eight principal components, age, sex, deprivation index, assessment centre, BMI, alcohol intake and smoking. We performed sensitivity analyses for all subcortical measures where we separately controlled for intracranial volume (ICV) and total brain volume (TBV). We also performed sensitivity analyses where we controlled for self-reported RA as a binary variable, and this did not affect our analyses. False Discovery Rate (FDR) was applied using the 'p.adjust' function in R, to correct for multiple testing.

RESULTS

We tried to determine whether the PRS for RF was associated with continuous log RF scores in the subsample of those excluded from the GWAS. We adjusted for genotype chip, the first eight genetic principal components, age, and sex. The association between PRS for RF and RF scores was significant (β = 0.05, 95% CI: 0.04 to 0.06, $p < 0.001$). We were also interested to assess whether PRS for RF was associated with self-reported RA. After adjusting for the first eight genetic principal components, age and sex, the relationship was not significant (OR = 1.06, 95% CI: 0.96 to 1.17, p = 0.2).

PRS and brain MRI association analyses

In the analyses partially adjusted for genotype array, first eight principal components, age, sex, and assessment centre greater genetic risk score for RF was associated with lower volume of WMH (β = -0.01, 95% CI: -0.029 to -0.006, p = 0.001), higher FA (β = 0.01, 95% CI: 0.0007 to 0.02, p = 0.03) and lower MD (β = -0.01, 95% CI: -0.02 to -0.004, p = 0.004) (see **Table 16**). The significant association with FA did not survive FDR correction. After additionally adjusting for BMI, deprivation index, alcohol intake and smoking status, greater genetic risk score for RF was still associated with lower volume of WMH (β = -0.01, 95% CI: -0.02 to -0.006, p = 0.002) and lower MD (β = -0.01, 95% CI: -0.02 to -0.002, p = 0.02). The significant associations for MD did not survive FDR correction. No significant associations were found for any of the subcortical volumes in either the partially adjusted or fully adjusted models. We performed sensitivity analyses where we additionally controlled for ICV and separately for TBV for all subcortical volumes. After controlling for ICV, the association between PRS for RF and the caudate volume became significant (β = -0.009, 95% CI: -0.01 to -0.0002, p = 0.04).

PRS and cognition associations analyses

We were also interested whether RF PRS was associated with performance on cognitive tests. In the partially adjusted analyses (genotype chip, first eight principal components, age, sex, and assessment centre), higher genetic risk score for RF was associated with lower scores for the pairs matching task (β = -0.021, 95% CI: -0.03 to -0.006, p = 0.004) (see **Table 17**). After additionally controlling for BMI, deprivation index, alcohol intake and smoking, the

relationship with pairs matching remained significant (β = -0.02, 95% CI: -0.03 to 0.005, p = 0.007), but did not survive FDR correction.

Table 16 Multiple linear regressions between PRS RF and brain MRI variables

	Partially adjusted model (Genotype Array, first 8 principal components, Age, Sex and Assessment Centre)			**Fully adjusted model** (Genotype Array, first 8 principal components, Age, Sex, Assessment Centre, **Deprivation, BMI, Alcohol intake and Smoking**)		
	β (SE)	**95% CI**	**p value**	**β (SE)**	**95% CI**	**p value**
Total brain volume (mm^3)	-0.004 (0.004)	-0.01- 0.005	0.3	-0.004 (0.004)	-0.01- 0.005	0.4
Gray matter volume (mm^3)	-0.00006 (0.004)	-0.009-0.008	0.9	0.00008 (0.004)	-0.008- 0.009	0.9
White matter volume (mm^3)	-0.007 (0.005)	-0.01- 0.003	0.1	-0.007 (0.2)	-0.01- 0.003	0.2
Volume WM hyperintensities (mm^3)	**-0.01 (0.005)**	**-0.029- -0.006**	**0.001**	**-0.01 (0.005)**	**-0.02- -0.006**	**0.002**
gFA: fractional anisotropy	**0.01 (0.005)**	**0.0007- 0.02**	**0.03**	0.009 (0.006)	-0.002- 0.02	0.1
gMD: mean diffusivity	**-0.01 (0.005)**	**-0.02- -0.004**	**0.004**	**-0.01 (0.005)**	**-0.02- -0.002**	**0.02**
Subcortical volumes						
Total accumbens volume (mm^3)	-0.003 (0.005)	-0.01- 0.007	0.5	-0.004 (0.005)	-0.01- 0.006	0.4
Total amygdala volume (mm^3)	-0.001 (0.005)	-0.01- 0.009	0.7	-0.002 (0.005)	-0.01- 0.009	0.7
Total caudate volume (mm^3)	-0.007 (0.005)	-0.01- 0.003	0.1	-0.007 (0.005)	-0.01- 0.004	0.2
Total hippocampus volume (mm^3)	-0.007 (0.005)	-0.01- 0.003	0.1	-0.008 (0.005)	-0.01- 0.002	0.1
Total pallidum volume (mm^3)	0.002 (0.005)	-0.008- 0.01	0.5	0.003 (0.005)	-0.008- 0.01	0.5
Total putamen volume (mm^3)	0.001 (0.005)	-0.008- 0.01	0.8	0.0009 (0.005)	-0.009- 0.01	0.8
Total thalamus volume (mm^3)	0.001 (0.005)	-0.009- 0.01	0.8	0.001 (0.005)	-0.009- 0.08	0.8

Values in bold indicate significant tests.

Table 17 Multiple linear and logistic regressions between PRS RF and cognitive tests

	Partially adjusted model (Genotype Array, first 8 principal components, Age, Sex and Assessment Centre)			**Fully adjusted model** (Genotype Array, first 8 principal components, Age, Sex, Assessment Centre, **Deprivation, BMI, Alcohol intake and Smoking**)		
	β (SE)/ OR	**95% CI**	**p value**	**β (SE)**	**95% CI**	**p value**
Reaction time [b]	0.001 (0.005)	-0.008- 0.01	0.7	0.001 (0.005)	-0.009- 0.01	0.8
Fluid intelligence [b]	0.01 (0.009)	-0.003- 0.03	0.11	0.01 (0.009)	-0.006- 0.03	0.1
Pairs matching [b]	**-0.021 (0.007)**	**-0.03- -0.006**	**0.004**	**-0.02 (0.007)**	**-0.03- -0.005**	**0.007**
Prospective memory [a]	0.9	0.9- 1.05	0.9	1.00	0.94-1.06	0.9

[a] Logistic regression with OR

[b] Linear regression with standardized betas and *SE*

Values in bold indicate significant tests.

DISCUSSION

Overview and implications

In the current chapter we aimed to determine whether a genetic risk score for RF (PRS-RF) is associated with differences in brain volumes and performance on cognitive tests, in a general population sample (i.e., not purely RA/RF+ cases). In the partially adjusted analyses, the PRS for RF was associated with lower volume of lesions/WMH, higher fractional anisotropy and lower mean diffusivity, all markers of healthier white matter. After adjusting for additional covariates PRF for RF was still significantly associated with a lower volume of WMH and lower MD. After sensitivity analyses where we controlled for ICV, PRS for RF became significantly associated with a lower volume for the caudate volume. Additionally, PRS for RF was significantly associated with lower scores on the pairs matching tests, which signified fewer errors made, and hence better performance on this test. To our knowledge this is the first study to use a PRS for RF to test for associations with structural brain phenotypes and cognitive measures. While, RA in general has received more attention with several GWAS studies conducted to identify RA risk loci (Okada et al., 2019), to our knowledge no study has investigated whether a genetic risk score for RA is associated with brain and cognitive health. We found associations in the protective direction in both imaging and cognition analyses, which was unexpected, although effect sizes were very small.

GWAS results

The GWAS carried out by my colleague generated 25 genome-wide significant hits. Here I will discuss variants that were significant in our study that are also known to be relevant to other conditions in the literature. Variant rs2230624 has been identified in previous literature as a risk variant for asthma, having the greatest effect among all the identified genetic risk variants (Han et al., 2019, 2020; Liang et al., 2023). A meta-analysis estimating the association between variant rs1801274 and the susceptibility to autoimmune diseases suggested that associations have been reported in the literature with systemic lupus erythematosus, Kawasaki disease, diabetes, autoimmune thyroid disease, ulcerative colitis, Crohn's disease and RA (Liang et al., 2023). In another study, patients with the rs1801274-AA genotype showed better responses to Abatacept treatment, a biologic/immunosuppressant that is currently prescribed for RA (Márquez Pete et al., 2021). Both rs116446171 and rs10806425 have been associated in the literature with B-cell lymphoma and tumorigenesis (i.e., the formation of cancer whereby normal cells turn into cancer cells) (Bassig et al., 2015; Cerhan et al., 2014; Labreche et al., 2019), with the latter also being suggested as a risk variant for celiac disease, a chronic inflammatory condition (Dubois et al., 2010). Lastly, rs11650354 was previously associated with an increased risk of systemic sclerosis, leading to altered cytokine balance and immune dysregulation (Gourh et al., 2009).

White matter hyperintensities

One study that investigated WMH in RA using nine patients with RA and 15 controls found no difference in atrophy levels and no relationship between RF and structural brain differences

(Bekkelund et al., 1995). However, when looking specifically at participants with long-term RA, defined as more than 15 years, this subsample was more likely to show significant brain atrophy that could suggest RA may cause long-term neurodegenerative changes (Fuggle et al., 2014).

A study that investigated the volume of WMH in 144 healthy adults, aged 44-77 years, found that a genetic risk for increased inflammation was associated with an increased volume of WMH (Raz et al., 2012). Considering that the current chapter found that a genetic risk for RF was associated with lower volumes of WMH, it could be that it is not the genetic risk for RF that increases a person's likelihood to develop brain white matter lesions but rather the inflammation that comes with RA, which a delayed diagnosis or sub-optimally treated RA may exacerbate. A systematic review of 30 studies investigating the relationship between WMH and depression suggested that lesions of the white matter are more common and severe in people with late life and/or late onset depression compared to healthy controls (Herrmann et al., 2008). Larger WMH volumes were also found to be associated with older age, hypertension and high levels of C-reactive protein (CRP), a blood biomarker for inflammation. It could be possible that the studies that did find an association between RA and a larger volumes of WMH did so because of confounders like depression and hypertension, which have been shown to be more prevalent in RA patients than in healthy controls (Dickens et al., 2002; Michaud & Wolfe, 2007). Another potential confounder is medication. The literature suggests that the main risk factor contributing to increased mortality in RA is related to CVD like stroke, heart attack and hypertension (Aviña-Zubieta et al., 2008; Michaud & Wolfe, 2007) and that patients that are on antihypertensive medication appear to show slower progression of lesions/WMH (van Middelaar et al., 2018), while the effect of drugs used for the treatment

of RA is unknown. A possible reason for the mixed literature on WMH in RA could be that treatment for hypertension comorbidity can have a protective effect on the brain.

White matter tract integrity: gFA and gMD

White matter tract integrity variables measure the health of white matter by quantifying the degree of diffusion of water molecules in the brain- more directionally restricted is indicative of highly structured axons and therefore considered as healthier (Penke et al., 2012). A more restricted diffusion of water molecules means axons are more tightly and closely aligned and therefore, brain electrical signals are transmitted more efficiently. Diffusion tensor MRI (DT-MRI) can be used to measure white matter tract integrity with measures of FA and MD (Lyall et al., 2020). Lower FA values and higher MD values represent worse/less 'healthy' white matter. Additionally, these markers of white matter tract integrity have been associated with general cognitive ability and performance on a processing speed task (Penke et al., 2012). To our knowledge there are no studies investigating associations between white matter tract integrity and genetic risk score for RF or RF in general.

When specifically investigating RA participants with neuropsychiatric symptoms in particular (i.e., headaches, blurry vision, insomnia, limb weakness etc.), Phukan et al. (2022) suggested there was an increased diffusion coefficient and radial diffusivity ($p < 0.05$) and a decreased FA coefficient and axial diffusivity ($p < 0.05$), indicative of less healthy white matter. This may suggest that it is not RA itself that may be associated with worse white matter tract integrity but rather multimorbidity or symptoms associated with the disease. Damoiseaux et al. (2009) used DT-MRI to investigate differences in white matter integrity between participants with AD or with mild cognitive impairment versus healthy young and healthy old

participants. Their results suggested that there are differences between groups not only in measures of white matter tract integrity but also regarding what specific brain areas are affected. When comparing healthy older subjects to healthy younger ones, there were lower FA values noted in the frontal, parietal, and subcortical brain areas, while for AD participants the observed differences were in the left anterior temporal lobe. Future studies are needed to replicate the findings of the current chapter and should also consider looking into what specific white matter tracts are affected.

Cognitive health: pairs matching

There is a gap in the literature on the association between RF and cognition (reported in Chapter 3), and similarly the association between genetic risk for RF and cognition. A systematic review of 15 studies highlighted that the RA patient population might indeed have impaired cognitive function but the authors suggested that more research is needed in order to determine prevalence and what specific cognitive domains are affected (Meade et al., 2018a). In chapter 3 we found that RF+ status was associated with reaction time only in the unadjusted model and that self-reported RA was associated with worse performance on the reaction time, fluid intelligence and prospective memory tests in the unadjusted models and worse performance on the reaction time and fluid intelligence tests in the fully adjusted model.

In the current chapter, a PRS for RF was associated with fewer errors on the pairs matching task, a test for visuo-spatial processing and short-term memory, in both the partially adjusted and fully adjusted models. While the standardized beta values were quite small and need

further replication, it may also suggest that any differences in cognition in RA that were reported in the literature and a previous chapter of this thesis could be due to other factors such as underlying genetic risk, or comorbidities. For example, pain and depression were also found to be negatively associated with cognition on tests of information-processing speed, reasoning, working memory and long-term memory (Brown et al., 2002), while comorbid risk factors like hypertension, obesity and smoking status could also increase the risk of cognitive impairment (Shin et al., 2012). Previous studies have also suggested that medication that is often prescribed for RA can also have an effect on cognition with opioids and glucocorticoids having a potential negative effect on performance (Chau et al., 2008; Khera & Rangasamy, 2021; Labianca et al., 2012; Vitturi et al., 2019), while participants on biologics being less likely to show cognitive deficits (Vitturi et al., 2019). Unfortunately, we did not have access to this information for the imaging visit, while information for biologics medication in the UK Biobank was generally missing due to the fact that it is not prescribed in primary care.

We observed associations with the RF PRS in a protective direction. These were unexpected and could reflect issues in the original discovery set, or the imaging sample. Specifically, RF was very non-linearly distributed (essentially high in cases and otherwise not) in UK Biobank, which could lead to skewed PRS values. Previous studies in UK Biobank have suggested that protective effects for other measures in the unexpected direction could reflect 'healthy bias' in the sense that only relatively healthy participants without significant burden of illness attend (Cullen et al., 2019). In terms of the imaging sample, Lyall et al. (2022) showed that examining only the imaging sample can lead to significantly affected estimates of association.

Strengths and limitations

To our knowledge this is the first study to use a PRS for RF to investigate whether it is associated with structural brain differences or performance on cognitive tasks, in a relatively large sample of approximately 40,000 people. A PRS for RF was significantly associated with RF (but not self-reported RA). The effect size was however small which could reflect that the PRS has limited predictive value for non-linear phenotypes. Our results also suggested that a higher genetic risk for RF is associated with lower volume of WMH, higher fractional anisotropy and lower mean diffusivity, all markers of healthier white matter, as well as lower scores on the pairs matching tests, equivalent to fewer errors made. While our standardized betas were very small and should be interpreted with caution, we also discussed above other reasons why we might have found these unexpected results that suggest a protective effect for a genetic risk for RF. It could be that the differences in brain structure and cognition reported in the RA literature are not due to a genetic risk for RF or being RF positive but rather due to having chronic RA (Bekkelund et al., 1995; Fuggle et al., 2014), with associated symptoms of the disease, inflammation, pain, treatments or comorbidities like pain and hypertension (Brown et al., 2002; Herrmann et al., 2008; Raz et al., 2012). Similarly, our results could be due to RF measurement issues in the current sample and therefore future replication is required. Future studies would benefit from a longitudinal design as it is unclear whether RF levels change with time or if they are stable. A longitudinal study in 1984, that used a Norwegian blood sample of 8,807 people found that after 3.5 years 81% of RF+ individuals converted to being RF-, the authors suggesting that it is not RF itself that can lead to more severe RA but rather the host's rection to the autoantibody (Gran et al., 1984). Future research should try to replicate these findings longitudinally while also investigating

differences between healthy RF+ participants and RF+ people that go on to develop RA. A good resource for further testing would be to use the summary statistics of GWAS studies that mapped genetic variation in regional brain volumes (Bryant et al., 2013; Zhao et al., 2019) to investigate whether RA or RF positivity share genetic architecture with variants that influence brain volumes and whether these are similar to the structural brain differences observed in the literature and chapter 4.

Conclusion

It is still unclear what exactly causes RA but a mix of genetic and environmental factors are believed to contribute to both the onset and the development of this disease (Symmons, 2002). It is also unclear why some RA patients respond very well to treatment while others benefit only partially or do not respond to any medication at all (Alam et al., 2017; Viatte & Barton, 2017). With more and more large datasets available that include genetic data as well, genetic risk scores can be used to better understand conditions like RA and associated biomarkers like RF and aid our understanding of disease risk factors, disease onset and progression, as well as response to treatment (Igo Jr. et al., 2019). The current chapter was the first study to our knowledge to investigate whether there are any associations between a higher genetic risk for RF versus structural brain volumes and cognitive tests scores. Our results suggested that a PRS for RF is associated with better brain health (i.e., lower volume of WMH, higher FA and lower MD) and better performance on a test for visuo-spatial processing and short-term memory. (i.e., number of errors on a pairs matching task). Future research should try to replicate the current chapter's methodology while also incorporating a longitudinal design and taking into account potential confounders like age, sex, deprivation, BMI, alcohol intake and smoking status.

Chapter 6: Thesis overview and discussion

6.1 Review of background and aims

RA affects around 0.81% of adults in the UK (Symmons et al., 2002) making it the most prevalent chronic inflammatory illness affecting the joints. Those suffering from RA can have reduced physical function and quality of life (Smolen et al., 2016) and are also at an increased risk of comorbidities and mortality, most notably due to CVD (Aviña-Zubieta et al., 2008). RF is an autoantibody that can be present in a significant proportion of people with RA, often years before any clinical symptoms, while not all people who are RF positive develop RA (Nell et al., 2005).

The focus of RA research and treatment has been mainly on reduction of inflammation, easing of pain and maintaining joint function (Alam et al., 2017). There is more limited research on RF itself. Similarly, there are significant knowledge gaps for mental health, sleep, cognition, and structural brain differences in RA despite being important contributors to quality of life. While the UK Biobank has the advantage of being a relatively large population-based cohort, using self-report RA had limitations and therefore we used both RA based on self-report and RF status as alternative phenotypes to address questions relating to these factors. The current thesis used the UK Biobank, a large prospective cohort to examine the following aims:

1. To determine whether RA and RF+ are associated with differences in mental health, sleep, cognition, and brain structure.
2. To determine whether a genetic risk score for RF+ is associated with differences in brain structure and performance on cognitive tests in predominantly non-RA participants.

3. Contribute to the understanding of the overlap between RF+ status and self-reported RA.

6.1.1 Chapter-specific contributions

Chapter 3. *Associations of rheumatoid arthritis and rheumatoid factor with mental health, sleep, and cognition characteristics*

Gap: While the focus in research and medical settings for RA has traditionally been on inflammation, pain and associated cardiometabolic factors, psychological factors like mental health, cognition and sleep have been largely ignored. However, RA patients are more likely to suffer from depression (Dickens et al., 2002), anxiety (Covic et al., 2012; El-Miedany & El Rasheed, 2002; Isik et al., 2007), have poorer sleep (Devins et al., 1993; Durcan et al., 2014; Goes et al., 2017; Guo et al., 2016), and perform worse on cognitive tests (Meade et al., 2018b), all factors which can have a significant impact on a person's quality of life.

Most studies to date in these areas suffer from small sample sizes and wide range of instruments, often not validated to test mental health, sleep and cognition leading to large variation in prevalence rates and information about which specific domains may be affected. The majority of studies were also poorly controlled for important sociodemographic and confounding variables. For RF+ status there is almost a complete gap in the literature regarding these psychological phenotypes.

Contribution: Chapter 3 tested for cross-sectional associations between self-reported RA, and separately for RF+ status, with mental health (depression, anxiety, neuroticism), sleep (duration, nap behaviour, ease of getting up in the morning, insomnia) and cognition (reaction time, fluid intelligence, pairs matching, prospective memory). After adjusting for age, sex,

ethnicity, deprivation, smoking status, BMI, and alcohol intake those that self-reported RA were more likely to score higher for neuroticism, more likely to nap during the day, less likely to get up with ease in the morning, more likely to suffer from insomnia, more likely to score higher for the reaction time cognitive test and more likely to score less for the fluid intelligence task (indicative of worse performance). In the fully adjusted analyses those RF+ were more likely to report longer sleep durations and more likely to get up in the morning with difficulty. This chapter used a large cohort of participants all tested using the same instruments to highlight that even after controlling for sociodemographic confounders, people with RA or those that are RF+ might present with worse mental health, sleep, and cognition, issues that are probably largely unaddressed in clinical settings despite being important contributors to quality of life.

Chapter 4. *Associations between self-reported rheumatoid arthritis, rheumatoid factor positivity and structural brain phenotypes*

Gap: Chapter 4 focused on structural brain health in people with RA and those that are RF+. The literature on brain structure differences in RA is very limited and to our knowledge, there is an almost complete gap for studies that investigated differences in brain phenotypes associated with RF+ status. Moreover, the majority of studies have a very small sample size (Hanspach et al., 2021; Marek et al., 2022). The first study to investigate structural gray matter differences in RA suggested that this patient sample had larger volumes of the caudate nucleus, putamen and nucleus accumbens (Wartolowska et al., 2012). Other studies suggested that people suffering from RA might be more likely to have WMH or lesions (Hamed et al., 2012; Phukan et al., 2022).

Contribution: Chapter 4 investigated cross-sectionally whether those that self-reported RA or that were RF+ had structural brain differences in key areas known to be associated with cognitive ability or previously reported to be associated with RA, when compared to non-RA and RF- using a relatively large sample of around 40,000 participants in the UK Biobank. After adjusting for age, sex, and assessment centre, those that self-reported RA were more likely to have a higher volume of WMH (lesions), and smaller volumes of the amygdala, pallidum, and thalamus. After additionally adjusting for deprivation, smoking, alcohol intake, BMI and cardiometabolic diseases, the association with the amygdala remained significant. After controlling for ICV in the sensitivity analyses, the association with the caudate became significant both in the partially adjusted and fully adjusted models. We found no significant associations with RF status. These brain phenotypes have been associated with general cognitive ability, processing of pain and a higher risk of comorbidities in previous studies, suggesting they may be important in RA and are worthy of further study in future research.

Chapter 5. *Associations between polygenic risk score for rheumatoid factor and structural brain phenotypes and performance on cognitive tests in the UK Biobank*

Gap: The cause of RA involves a combination of genetic susceptibility factors and environmental exposures believed to affect both the onset and development of the disease (Symmons, 2002). There have been major advances in genetic technologies and understanding , although, to our knowledge, the focus of genetic studies has been mainly on RA disease in general and ACPA positive RA, with less attention on the genetics of RF status and the cognitive aspects of RA.The rapid evolution of new technology and analysis methods

such as GWAS enabled us to understand that several common genes contribute to both the cause and development of RA (McAllister et al., 2011). While the focus for genetic studies has been on RA in general or ACPA positive RA, RF+ status received much less attention, with an almost complete gap. To our knowledge there is no study that has generated a PRS for RF+ and used this to investigate whether this is associated with structural brain and cognitive phenotypes.

Contribution: Chapter 5 used a relatively large cohort of around 40,000 people to test whether a genetic risk score for the RF+ biomarker generated using the top hits from a large GWAS, means this population is more likely to show differences in brain structure or cognitive performance. After adjusting for age, sex, assessment centre, genotype array and first eight principal components, a genetic risk for RF was associated with a lower volume of WMH, higher value for fractional anisotropy, lower value for mean diffusivity and lower scores for the pairs matching task (number of errors). We additionally performed sensitivity analyses with ICV, after which the relationship between PRS for RF and the caudate became significant. After additionally adjusting for deprivation, BMI, alcohol intake and smoking, the associations with WMH, mean diffusivity and pairs matching test remained significant. This is the first study to use a PRS for RF to investigate associations with structural brain and cognitive health. While all standardized beta values were quite small and need to be interpreted with caution, unexpectedly all significant associations we found were indicative of better brain or cognitive health. Future studies are needed to confirm and understand these findings and to take into account further potential confounders like age, sex, deprivation, BMI, alcohol intake and smoking status.

Multiple approaches to studying RA: RF Biomarker

Due to the fact that self-reported conditions can be biased we used a biomarker-based measure (RF) as well (irrespective of RA status). This thesis focused on the RF biomarker, that is widely used in clinical practice for RA (see **Table 1**) (Aletaha et al., 2010a). Due to very low numbers we were unable to additionally look at self-reported RA that were RF+ versus RF-. Due to the fact that RA can vary considerably between patients, this thesis also wanted to add to the literature aiming to identify predictors of likelihood of disease such as age, sex and biomarkers like RF (Scott & Steer, 2007). RF is an autoantibody that has been reported to be present in approximately 80% of people with RA in previous literature (Nell et al., 2005) but that can also be present in other conditions and the general population as well (Pasternack et al., 1990; Van Schaardenburg et al., 1993). In our study, the prevalence rate for RF+ in the RA subsample was much lower (26%) than previously reported. One possibility is that this reflects an issue with self-report of RA in UK Biobank; however, the prevalence rates in UK Biobank (unadjusted for age) were similar to previous population estimates that used strict ACR criteria(Siebert et al., 2016). It has also been proposed that RA is becoming milder in developed nations (Uhlig & Kvien, 2005; Welsing et al., 2005) so it is possible that the proportion of RF positive RA has changed compared to previous population estimates as the majority of papers are decades old. It is also unclear whether RF levels are stable throughout life or whether they increase with age (Nielsen et al., 2012). For example, one longitudinal study from 1984 reported that after 3.5 years, 81% of their RF+ sample converted to RF- (Gran et al., 1984), while in another study from 1993 there was a significant increase with age in levels of lgG-RF but a decrease in lgM-RF (Van Schaardenburg et al., 1993), so newer studies with a longitudinal design are needed to evaluate this. Lastly, and most likely, the lower

prevalence rates in this thesis could be due to measurement error as RF and oestradiol were identified as the only two UK Biobank biomarkers that had many 'missing' values that were probably not missing but below the minimum stated detectable value for the assay used. UK Biobank has advised researchers not to treat these values as "missing", so we recoded them conservatively as the square root of the minimum stated detectable value if participants had data for a remaining biomarker as per Ferguson et al. (2020). A solution to the potential issues with RF in the current cohort could be data linkage in the future with routinely collected laboratory results. We also believe that future studies should aim to evaluate both RF status and ACPA status, which was not available in the UK Biobank.

6.1.2 Contributions to the literature

- Chapter 3 provides evidence that RA patients, and people that are RF+, might present with differences in mental health, sleep and cognition that are currently unaddressed, including in the clinic for RA and need to be studied further in order to better understand these and help improve the treatment and quality of life of people with RA.
- Chapter 4 indicates that RA might be associated with differences in brain structure that are known to be important for psychological and cognitive health. No significant associations for RF were found with these brain structures.
- Chapter 5 found that a PRS for RF is nominally associated with differences in brain structure and cognition but due to the very small standardized betas these should be interpreted with caution and we suggest that there is no link between PRS for RF and

structural brain and cognitive phenotypes, implying that other factors, such as the presence of clinical disease, treatments or comorbidities are likely contributing to the brain differences in RA observed in the literature and chapter 4, rather than underlying genetics or RF itself.

- Several associations in the current thesis survived correction for various lifestyle/demographic covariates suggesting that we observed true associations between RA/RF+ and mental health, sleep, cognition, and differences in brain structure, independent of the associations between RA/RF+ and various comorbid risk factors.

6.1.3 Implications

This thesis highlights the importance of studying and addressing mental health, sleep, and cognition in chronic conditions like RA, as well as incorporating evaluation of structural brain changes and genetic contributions. Chapter 1 highlighted that psychological factors like mental health, sleep and cognition suffer from a limited literature with poor methodology in research and are largely unaddressed in the clinic (Bair et al., 2003; Rathbun et al., 2014). For example, a better understanding of the prevalence and causes of depression in RA could lead to clinicians being more likely to enquire about depression and the underlying factors relating to this, and address this in their management strategies, with some studies suggesting that treating depression with anti-depressants might result in an improvement in a patient's pain levels (Bair et al., 2003). Not addressing depression and anxiety has also been linked with reduced chances of achieving remission with RA treatments (Michelsen et al., 2017). When looking specifically at people from more socio-economic deprived groups in UK Biobank,

symptoms of depression appear to be the primary mediator of poor sleep (Fatima et al., 2020), while a longitudinal study suggested that optimal sleep may have a protective effect against depression symptoms over the long term (Sarris et al., 2020).

People with RA in our study showed higher neuroticism, which is a risk factor for mental health (Evers et al., 2002). This could be a specifically targeted variable in the clinic for the monitoring and preservation of good mental health. Chapter 3 suggested that even after controlling for a range of covariates, people with RA are significantly more likely to have a high neuroticism score. This finding should be evaluated further in a different cohort as Evers et al. (2002) indicate that neuroticism is the most consistent and effective predictor in RA of depression and anxiety 3 to 5 years later. Similarly, a systematic review of 23 studies concluded that self-reported sleep quality is significantly associated with quality of life in older people (Sella et al., 2021), which further highlights the need for psychological factors to be a crucial component of RA treatment. Cognitive decline in RA should also be monitored as it can be related to both clinical manifestations such as pain and fatigue as well as psychological factors like mental health and impaired sleep, while also being vital for this patient population for independent living, self-care and adherence to medication (Meade et al., 2018b).

It is essential to understand whether this patient population presents with differences in brain structure as these can predict cognitive performance with age (Royle et al., 2013). In the current thesis, we observed differences in white matter lesions and the amygdala, two structures that have been reported to be associated with pain processing and the affective component of pain (Oosterman et al., 2006; Simons et al., 2014). Previous imaging studies have suggested a reorganization of brain activity in chronic pain conditions whereby the

processing and representation of pain moves from sensory systems to emotional structures in the limbic system, especially the amygdala (Khera & Rangasamy, 2021), so it is possible that some of the differences we see reflect this.

A better understanding of the prevalence and severity of mental health, sleep, cognition, and structural brain differences in RA could also support the evaluation of non-pharmacological treatments that address these components of the disease. For example, systematic reviews of psychological interventions such as relaxation, biofeedback, CBT and stress management suggest a positive effect not only on pain and functional disability in RA but also depression, self-efficacy and cognitive coping (Astin et al., 2002; Dissanayake & Bertouch, 2010; Morley et al., 1999). Similarly, physical activity interventions in people with RA have been associated with improvements in pain, stiffness, radiologic damage and function but also sleep, fatigue and quality of life (Baillet et al., 2010; Cairns & McVeigh, 2009; Durcan et al., 2014). There is also accumulating evidence from meta-analyses of longitudinal studies that engaging in physical activity is associated with a reduced risk of cognitive problems later in life as well as larger volumes of gray matter in the frontal cortex, hippocampus and caudate nucleus in the general population (Erickson et al., 2015). Cardiorespiratory exercise have also been associated in the literature with greater white matter integrity for several tracts linking frontal and subcortical areas (Erickson et al., 2015). As the biggest cause of mortality in RA is due to CVD (Aviña-Zubieta et al., 2008), aerobic exercise could have additional beneficial cardio-protective effects. However, the results of a systematic review of sixteen studies suggested that physical activity levels in RA are reduced compared to the general population (Tierney et al., 2012).

The increasing availability of large datasets that also include blood biomarkers and genetic data could aid our knowledge regarding risk factors, disease onset and progression as well as response to treatments (Igo Jr. et al., 2019; McAllister et al., 2011). Despite being the most prevalent chronic inflammatory disease affecting the joints it is still unclear what exactly causes RA but it is believed to involve a combination of environmental and genetic components (Symmons, 2002). While medication to treat RA has evolved, it is still unknown why some patients only partially benefit from treatment or do not respond to medication at all (Alam et al., 2017; Viatte & Barton, 2017). Biomarkers could be used to ensure that each individual patient gets the best treatment option and could avoid high healthcare costs and the detrimental effects of untreated RA that affect the patient's quality of life, making RA a great candidate for such a precision medicine approach (Viatte & Barton, 2017). The current thesis focused on the RF blood biomarker and tried to establish in Chapter 5 if a genetic risk score for RF is associated with differences in brain and cognitive health that have been reported in the RA literature as well as Chapters 3 and 4. Our findings were in the opposite direction to what we hypothesized, with the PRS for RF being associated with healthier white matter and better performance on a cognitive test of visuo-spatial/short-term memory. Our standardized betas (i.e., effect sizes) were very small suggestive of no real link between PRS for RF and structural brain and cognitive differences, that could have been due to blood biomarker measurement error in the current cohort, which means our findings require further replication. It was interesting to note that despite the fact that PRS for RF and RF+ status were significantly associated, the effect size was very small in the imaging subsample, suggestive of a poor correlation. However, these findings could also mean that 1) there were changes in RF levels compared to previous population recorded values considering the majority of RF prevalence papers discussed in the current thesis are decades old; 2) RF levels

fluctuate with time; 3) The reported differences in RA literature regarding brain and cognitive differences are not due to RF but rather risk factors, symptoms and comorbidities that were discussed in Chapter 5 such as inflammation, pain, depression, CVD as well as medication used to treat RA or the chronicity of this disorder, especially if diagnosis and treatment are delayed. It could also be that a higher genetic risk for RF is not enough on its own but combined with other environmental factors it can lead to RA and its associated comorbidities. For example, smoking increases the risk of developing RA with an almost twice as high risk for males and 1.3 as high risk for females, and even higher odds for male smokers that are RF+ (Sugiyama et al., 2010), suggesting gene-environment interactions.

6.2 Thesis strengths and limitations

Medication

Limitation: One of the limitations of the current thesis was that we did not or were not able to take medication for RA into account in any of our associations, especially when investigating performance on cognitive tests. We did not include medications for a number of pragmatic reasons that suggested that the available records in UK Biobank were unlikely to be of value for this analysis. Firstly, our group has shown that very few people with RA in UK Biobank are receiving biologic therapies (119 people equivalent to 2.1% of the sample) (Siebert et al., 2016). While this may reflect the well-recognized healthy bias in UK Biobank, these numbers are unlikely to be correct based on UK clinical practice at that time. This underreporting in UK Biobank likely reflects the fact that in the UK, biologic therapies for RA are initiated and prescribed directly by rheumatologists in the hospital, so do not appear on primary care prescriptions that were used to capture medication use in UK Biobank. Similarly,

corticosteroids are often used during RA flare ups as intramuscular injections, often administered by rheumatology departments, so would also not be captured in UK Biobank. Even oral corticosteroids are typically prescribed as short courses rather than chronic prescriptions. Finally, the drug data in UK Biobank was captured at the baseline visit and not at the time of the imaging visit, which could be eight years later than the baseline visit and therefore not applicable at the time of the imaging/cognitive tests.

Future studies should evaluate medications as it is likely these may have had a significant effect on the outcomes evaluated in our study. Vitturi et al. (2019) reported that RA participants that were treated with biologics were less likely to show cognitive deficits when tested using the MMSE ($p = 0.05$), while the RA subjects that were treated with glucocorticoids were more likely to show cognitive deficits when tested using the MoCA. Furthermore, opioid medications, powerful analgesic used to treat moderate and severe chronic pain, can also include effects on the central nervous system such as sedation and mild cognitive impairment (Chau et al., 2008; Labianca et al., 2012) with higher mean consumption of opioids shown to be associated with worse performance on attention, language, orientation and psychomotor function (Khera & Rangasamy, 2021). Multimorbidity and taking multiple medications is therefore something that should be considered for both RA patients and older population samples. On top of the existing sedative effects of opioids, taking antidepressants as well could have additive sedative effects (Chau et al., 2008). A study conducted on a Finnish population over 75 years old suggested that taking 10 drugs or more was associated with a decline in cognition and functional ability (Jyrkkä et al., 2011).

Cognitive tests

Limitation: The cognitive tasks administered to UK Biobank participants at the assessment centre visit suffer from the fact that they were relatively short and administered unsupervised with participants using just the touchscreen questionnaire compared to more robust tests and studies. There were also cognitive abilities we were unable to look at due to their lack of availability in the UK Biobank, such as crystallized intelligence and long-term memory.

Strength: Nevertheless, the UK Biobank cognitive tests correlate moderately-to-strongly with other well-validated tests while a computed measure of general cognition using UK Biobank tests also correlates highly with a measure of overall cognitive ability computed using standard tests and therefore, the majority of cognitive tests show good test-retest reliability (Fawns-Ritchieid & Deary, 2020).

Self-report of conditions and sleep

Limitation: The current thesis was limited to using self-reporting conditions such RA, depression, anxiety and cardiometabolic conditions. The official 2010 ACR classification criteria for RA that this thesis discussed in the first chapter (Aletaha et al., 2010a) includes joint involvement, swelling, serology, acute-phase reactants and duration of symptoms-information that was limited or missing in the current cohort meaning we were not able to confirm whether the people that self-reported RA met the classification criteria. Therefore, we could not differentiate between participants that were genuinely healthy and did not have that specific disease and those that chose not to report it or did not remember (Siebert et al., 2016).

Strength: Nevertheless, our prevalence estimates for RA were similar to previous estimates in the literature. However, a systematic review and meta-analysis on the relationship between quality of sleep and quality of life in older people suggested that self-reported sleep quality but not objective sleep quality was significantly associated with quality of life (Sella et al., 2021), highlighting the importance of considering subjective psychological factors as well.

Limitation: Sleep measures were reported using subjective methods rather than more objectives ones like actigraphy. We also believe that the phrasing of the 'getting up in the morning' question did not allow differentiation between people that have difficulties waking up in the morning (due to poor sleep/tiredness) versus people that have difficulties getting out of bed for physical/other reasons. This is particularly important when studying people with RA as stiffness of the joints in the morning is a common and characteristic symptom of the condition, and which in turn could make it more difficult for them to get out of bed in the morning. Similarly, the UK Biobank sleep duration question asked participants to include naps as well. We also have concerns about the inclusion of naps in this question as we could not differentiate between people that have a good night's sleep and those that have poor/short sleep or suffer from insomnia and therefore are more likely to need a nap throughout the day. Furthermore, fatigue is a characteristic feature of RA and most chronic inflammatory conditions (Nikolaus et al., 2013) so these people may be more likely to take daytime naps, regardless of the quality or duration of their nocturnal sleep, making this a poor measure of sleep quality.

Correction for multiple testing

Strength: The current thesis corrected for multiple testing using FDR and the p.adjust function in R. It has become increasingly common for researchers to collect and analyze large datasets and therefore, correcting for multiple testing is advised to account for the increased probability of reporting false positive results (Glickman et al., 2014). There are a number of approaches used to control for erroneous scientific conclusions, with one of the most commonly used ones being the Bonferroni correction (Glickman et al., 2014). This method adjusts for the false positive rate, i.e., the probability of rejecting the null hypothesis when it is in fact true. A less conservative way is to use FDR, which represents the probability that a null hypothesis is true when it was rejected. However, if the association tests are not completely independent of one another this can make correction for multiple testing overly conservative (Williams &Haines, 2011). Therefore, the current thesis used the FDR approach to correct for multiple testing but also discussed those that did not survive the correction in order to avoid overly conservative correction and Type 2 errors. As a consequence, the results of this thesis need to be replicated using a large sample.

6.3 Future research

More diverse and representative cohorts

While the UK Biobank has the advantages of being a very large cohort of around 500,000 people all measured in a standardized way it might not be representative of the sampling population as a whole. A study that compared health and demographic data of UK Biobank responders with data from nationally representative cohorts found that UK Biobank participants are more likely to be older, female, and less deprived but less likely to be obese, to smoke and to drink alcohol as well as report health conditions (Fry et al., 2017). There is accumulating evidence pointing towards a 'healthy bias' in the UK Biobank which can significantly bias analyses towards type 1 and 2 errors (Lyall et al., 2022; Tyrrell et al., 2021). The affected domains include psychological factors, with this cohort being more likely to report depression less and have a lower neuroticism score, better performance on cognitive tests for memory, reasoning and information speed, as well as "better" demographic and disease risk factors (Lyall et al., 2022). Nevertheless, associations with risk factors and between exposures and health conditions in the UK Biobank appear to be generalizable (Batty et al., 2020; Fry et al., 2017). For genetic databases, one of the main limitations is that they are mainly comprised of participants of European ancestry, which renders most GWAS results non-transferable to other populations (Mills & Rahal, 2020). Due to the fact that PRS can be influenced by a variety of environmental factors such as country of origin and socioeconomic status, more diverse and representative samples are required in the future before making any clinical decisions based on genetic risk scores, in order to avoid aggravating existing health inequalities (Mills & Rahal, 2020)

Longitudinal design/Mendelian randomization

The cross-sectional nature of the current thesis means we could not test for causal relationships and rule out confounders or reverse causation. It is also unclear whether the observed differences in this thesis predate or are a consequence of RA and what proportion of those who are RF+ go on to develop RA. Similarly, it would be helpful to investigate whether RF status is stable in the long-term or whether people that are RF- become RF+ and vice versa. A good example of a potential confounder relevant to the current thesis is a study that used UK Biobank participants that had attended two imaging visits for brain scans, which suggested that those that have been infected with SARS-CoV-2 between scans showed differences in brain structure as well as greater cognitive decline (Douaud et al., 2022). One solution to these problems would be to conduct a longitudinal study. A longitudinal design would also help assess risk factors that contribute to RA. For example, in one longitudinal study the most effective and strong predictor of depression and anxiety in RA patients 3 and 5 years later was a high neuroticism score (Evers et al., 2002). In the current thesis, RA patients were more likely to score high for neuroticism than the healthy control group ($p < 0.001$) even after controlling for age, sex, ethnicity, deprivation index, smoking status, BMI and alcohol intake which suggests that a longitudinal study replicating Evers et al.'s findings would highlight the need to monitor the mental health of RA patients long term. However, longitudinal cohorts can be expensive to set up and run and can encounter difficulties in getting a large enough cohort of people developing the outcome of interest. Another solution to the problem of causality and confounders would be for future studies to conduct an MR analysis using genetic variants. This method tests the relationship between genetic variation and an outcome of interest by testing if and by how much an exposure of interest influences the outcome, with

the conditions that the genetic variant is independent of the outcome and confounders (Sanderson et al., 2022).

Linkage to primary care/hospital data

Primary care data was made available for approximately 230,000 UK Biobank participants in 2019, as well as hospital inpatient data for the full cohort. As a consequence, the UK Biobank has derived a new set of variables called "first occurrences data" by combining information from primary care, hospital inpatient admissions, death records and self-reported medical conditions. This data could provide a more objective measure than the self-reported illnesses used in the current thesis as we could not differentiate between participants that did not remember their disease, did not want to disclose their disease and those that were genuinely healthy and had nothing to report. This method may also be useful for assessing the longer-term outcomes associated with sleep, cognitive and structural brain changes.

Comorbidities and multimorbidity

Future research may investigate the possibility that joint deformities, higher chronic pain and other comorbidities may contribute to the observed associations and should also consider multimorbidity in order to ensure that the observed associations are in fact due to RA/RF+ and exclude the effect of other confounders, particularly comorbidities. For example, chapters 1 and 3 have discussed that prevalence rates of depression in RA are higher compared to estimates for the general population, making depression a potentially common comorbidity (Matcham et al., 2013b; Waraich et al., 2004). Regarding structural brain health,

previous studies have suggested a relationship between depression and the amygdala (Frodl et al., 2002; Sheline et al., 1998) and between white matter lesions and late onset depression (Herrmann et al., 2008). In the current thesis, the amygdala was the only brain phenotype to remain significantly associated with RA even after controlling for extra confounders (i.e., deprivation, smoking status and cardiometabolic diseases). Additionally, RA was also positively associated with WMH but a genetic risk score for RF was negatively associated with WMH, highlighting the need for further studies to investigate what exactly causes the higher rates of depression in RA. Similarly, WMH are more prevalent and severe in patients with CVD and cardiovascular risk factors (Debette & Markus, 2010), while CVD-related mortality is approximately 50% higher in RA, accounting for the majority of increased mortality in RA (Aviña-Zubieta et al., 2008). Given the potential relationship between WMH/amygdala and depression and between WMH and CVD we believe future research should address depression as well as other comorbidities when studying structural brain health in RA. In the UK Biobank cohort alone, which has an established 'healthy bias' (Keyes & Westreich, 2019; Lyall et al., 2022), around a fifth of all participants have two or more chronic conditions (Zemedikun et al., 2018). Therefore, future health-related research should consider and account for multimorbidity as well, considering the potential detrimental impact it might have on health, with a systematic review of 41 studies suggesting it is associated with worse disability and functional decline, poorer quality of life and higher healthcare costs (Marengoni et al., 2011).

6.4 Summary

The current thesis investigated differences in psychological and structural brain health in people with self-reported RA and people positive for the associated biomarker RF. The existing literature on these topics is relatively limited, with small sample sizes, high heterogeneity in testing methods and without controlling for relevant confounders. The current thesis' methodology aimed to address these problems and knowledge gaps, with our findings providing evidence for differences in mental health, sleep, cognition, and brain health relevant to this patient population that are likely going unaddressed in the clinic and in research.

This thesis suggests that:

1. Self-reported RA and RF+ status are associated with differences in mental health, sleep and cognition that need to be addressed in future research and strategies to improve the quality of life of this patient population.

2. Having RA is associated with differences in structural brain volumes, more specifically white matter lesions and the amygdala that could be extremely important to those suffering from this disorder due to their potential implication in pain modulation, mental health, and increased risk of cardiovascular disease.

3. A genetic risk score for RF is associated with better white matter health and fewer errors on a visuo-spatial memory task, which could imply that the structural brain and

cognitive differences observed in RA in the literature and previous chapters are not related to underlying genetics and could be due to other comorbidities, risk factors and/or explicit onset of the disease. The effect sizes were however very small, suggesting this association may be nominally but not clinically significant.

4. Self-report RA and RF positivity largely overlap, and while either variable is useful for clinical research, there are instances of unique and complementary contributions to understanding from each of the two.

5. Future research should investigate diverse, longitudinal samples, and the role of potentially modifiable factors in preserving psychological health (e.g., neuroticism).

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Appendices

Supplementary Table S1 The 2010 American College of Rheumatology/ European League Against Rheumatism classification criteria. Source: (Aletaha et al., 2010a)

	Score
Target population (Who should be tested?): Patients who	
3) have at least 1 joint with definite clinical synovitis (swelling)*	
4) with the synovitis not better explained by another disease †	
Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
E. Joint involvement§	
1 large joint¶	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)#	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
F. Serology (at least 1 test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
G. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
H. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

*The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfilment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

†Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed, and the criteria might be fulfilled cumulatively over time.

§Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint

distribution are classified according to the location and number of involved joints, with placement into highest category possible based on the pattern of joint involvement.

¶" Large joints" refers to shoulders, elbows, hips, knees, and ankles.

#" Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

††Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤ 3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody.

‡‡Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR=erythrocyte sedimentation rate.

§§Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.