RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Depression, anxiety and cognitive function in persons with inflammatory rheumatic diseases: cross-sectional results from the German National Cohort (NAKO)

Johanna Callhoff ,[1,2] Klaus Berger,[3] Katinka Albrecht ,[1] Anja Strangfeld ,[1,4] The NAKO Investigators

To cite: Callhoff J, Berger K, Albrecht K, *et al*. Depression, anxiety and cognitive function in persons with inflammatory rheumatic diseases: cross-sectional results from the German National Cohort (NAKO). *RMD Open* 2024;**10**:e004808. doi:10.1136/rmdopen-2024-004808

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/rmdopen-2024-004808).

Received 31 July 2024
Accepted 8 October 2024

For numbered affiliations see end of article.

Correspondence to
Dr Johanna Callhoff; Johanna.Callhoff@drfz.de

ABSTRACT

Objective To assess the presence of mental health disorders in persons with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE) and Sjögren's disease (SjD) (all: inflammatory rheumatic disease, iRMD) in a population-based cohort.

Methods Baseline data from 101 601 participants of the German National Cohort (NAKO) were analysed. Self-reported physician's diagnoses of depression and anxiety, the depression scale of the Patient Health Questionnaire (PHQ-9), the Generalised Anxiety Disorder Symptoms Scale (GAD-7), the depression section of the Mini-International Neuropsychiatric Interview (MINI) and cognitive tests on memory and executive functions were analysed. Results of participants with iRMD were compared with participants with osteoarthritis (OA), stratified by age and sex. Cognitive function was described for iRMD and OA using a linear regression model, adjusted for sex and education.

Results n=3257 participants (3.2%) had an iRMD (2.3% RA, 0.6% AS, 0.5% PsA, 0.2% SLE, 0.1% SjD) and n=24 030 (24%) had OA. Physicians' diagnoses of depression (26% vs 21%), anxiety (15% vs 11%), current depressive (PHQ-9 ≥10: 13% vs 9.0%) and anxiety symptoms (GAD-7 ≥10: 8.6% vs 5.8%) were more frequent in iRMDs compared with OA. In all age groups, women were more often affected than men. Linear regression models showed no differences in neuropsychological test results between iRMD and OA.

Conclusion Individuals with iRMD frequently experience mental disorders. The study provides an assessment of both self-report and test-based occurrences in this group. Depression and anxiety are more frequent in iRMD compared with OA, whereas levels of cognitive dysfunction were comparable.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ · Mental health disorders are common in persons with inflammatory rheumatic diseases (iRMDs).

WHAT THIS STUDY ADDS

⇒ · Depression and anxiety were more common in individuals with iRMD compared to those with osteoarthritis (OA). This particularly affected middle-aged women and persons with connective tissue diseases.

⇒ · Cognitive function was not different between persons with iRMD and OA within this population-based cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ · Supporting the patient's mental health should be an integral part of iRMD management.

INTRODUCTION

Mental health disorders are common in people with inflammatory rheumatic diseases (iRMDs). The occurrence of depression and anxiety in persons with iRMD is higher than in the population without iRMD. This is predominantly described for people with rheumatoid arthritis (RA)[1] but also for ankylosing spondylitis (AS), psoriatic arthritis (PsA) and connective tissue diseases such as systemic lupus erythematosus (SLE) and Sjögren's disease (SjD).[2–5]

Among the mental health conditions, depression is the most common in persons with RA.[6] A meta-analysis reported current major depression in 17% of patients with RA. The frequency of depressive symptoms above the scale cut-off for moderate to severe was 39% according to the Patient Health Questionnaire (PHQ)-9 (with a threshold of 10) and 15% (threshold of 11) to 34% (95% CI 25%, 44%; threshold of 8) according to the Hospital Anxiety and Depression Scale (HADS).[7] Depressive and anxiety symptoms

are also more common in persons with AS, PsA, SLE and SjD.[3–5 8 9]

Cognitive dysfunctions are less often studied. In persons with SLE, cognitive impairment is commonly reported with highly varying frequencies, depending on the test, the definition of impairment and comparator groups.[10 11] A recent metaregression showed moderate impairments across a range of cognitive domains in people with distinct iRMD.[12] This was the case for both SLE and RA compared with age-matched persons with osteoarthritis (OA). Another study found no association between RA and cognitive impairment.[13] Impairments only in the selective attention but not in episodic working memory have recently been described for persons with spondyloarthritis and PsA in Germany.[14] Besides age and education, disease activity, depression and chronic pain are associated with cognitive impairment.[15]

Chronic peripheral inflammation interferes with brain function, contributing to mental illness.[16] The substantial impact of mental health disorders on clinical outcomes and treatment success are well described.[9 17–22] Mental health comorbidities contribute substantially to a reduced quality of life[23 24] and to the development of a difficult to treat state of iRMD.[25]

Mental health aspects have received increasing attention in rheumatological research.[26] In clinical practice, however, mental health symptoms and conditions are often poorly recognised, and neuropsychological testing is rarely performed.[10] Psychiatric and neurological disorders are one of the main research areas within the German National Cohort (NAKO Gesundheitsstudie), being the largest population-based cohort study in Germany.[27] The aim of this study was to assess the presence of mental disorders and cognitive performance in persons with iRMD and to compare it to persons having the non-inflammatory musculoskeletal disease OA.

METHODS

Data source

NAKO is a prospective population-based cohort study to investigate the development and consequences of common chronic diseases in Germany.[28] A random sample of the general population aged 20–69 years was drawn by 18 regional study centres across Germany. Participants were recruited stratified for age and sex.[29] Baseline examinations were conducted between 2014 and 2019 and comprised physical examinations, standardised interviews and questionnaires at two levels. Level 1 examinations were performed in all participants and lasted on average 4 hours. A randomly selected subset of 28% of the Level 1 participants underwent a more detailed Level 2 assessment, lasting an additional 1.5 hours. All study centres' local ethics committees had given approval. The study was conducted in accordance with the Declaration of Helsinki. All participants had provided written consent for study participation. The current analysis is based on the baseline assessment of the first 101 601 participants (NAKO data freeze 100 000; application NAKO-603). Of all contacted persons for the 100k data freeze, 18% participated. Detailed information on participation in the different assessments were described by Schipf *et al*.[30]

Inclusion criteria

NAKO participants were asked in a face-to-face interview conducted by a trained study assistant, whether they had ever been diagnosed by a physician with RA, AS, PsA, SLE or SjD. If participants answered 'yes', the time of the first diagnosis (either age or calendar year) was assessed. All individuals who reported at least one of these iRMDs were included. Participants who reported OA (OA of the hip, knee or hand) among the musculoskeletal disorders but did not indicate an iRMD were considered as a comparison group. This group was chosen as a comparator, because people with OA experience many symptoms people with iRMD also experience but it does not have an inflammatory component.

Sociodemographic characteristics

Participants reported their sex, date of birth and highest level of education. Education was reported in years and additionally categorised according to the International Standard Classification of Education 97 (ISCED97)[31] into lower (ISCED97 level 1/2), intermediate (ISCED97 level 3/4) and higher (ISCED97 level 5/6) education level.[32] Smoking was categorised to current, former or never.

Instruments

Face-to-face interview

Other common chronic conditions, including hypertension, myocardial infarction, stroke, hyperlipidaemia, diabetes, reduced renal function, cancer, osteoporosis, anxiety disorder and depression, were also assessed as lifetime diagnoses by a physician. If depression was affirmed, participants were asked whether they had received antidepressant therapy (eg, psychotherapy, medication) by a physician or by a psychologist in the previous 12 months.

Mini-International Neuropsychiatric Interview (MINI)

The MINI (V.5.0.0) is a structured interview containing different diagnostic modules for the diagnosis of psychiatric disorders.[33] For NAKO, the module for assessing a current episode of major depression disorder (MDD) was adapted to assess the occurrence of lifetime depressive episodes. Individuals who affirmed the initial question 'Have you had periods of 2 weeks or more during your life when you felt depressed or disinterested?', received the screening questions for the MDD module of the MINI, assessing cardinal depressive symptoms. Only Level 2 participants received the remaining questions from the depression module in case the screening was positive. Fulfilment of the NAKO MINI classification indicates a lifetime diagnosis for a MDD.[32]

Patient Health Questionnaire (PHQ-9)

PHQ-9 is the depression module of the Patient Health Questionnaire. It was developed for screening of

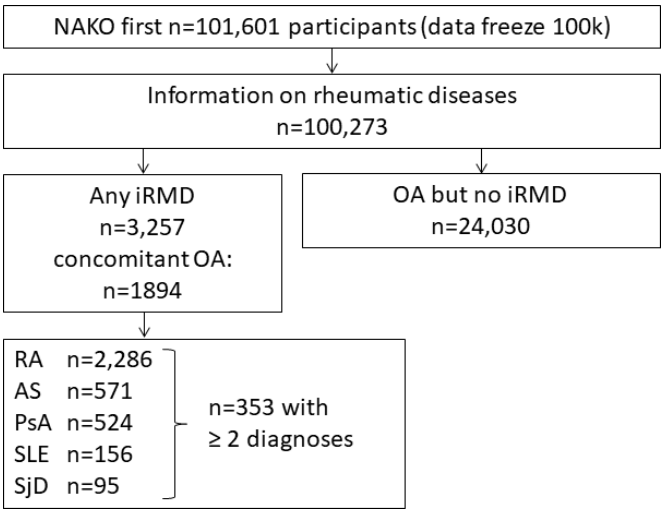

Figure 1 Flow chart. AS, ankylosing spondylitis; iRMD, inflammatory rheumatic disease; NAKO, German National Cohort; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SjD, Sjögren's disease; SLE, systemic lupus erythematosus.

depression and contains nine items related to the presence of symptoms in the last 2 weeks which can be answered on a scale of 0 (not at all) to 3 (almost every day). The items can be summarised into a score (possible range 0–27) representing depressive symptom severity. A cut-off score of ≥10 is commonly used to indicate the possible presence of a current depressive episode[32] and was applied in the present analysis for comparability with other studies. The PHQ-9 has been validated for depression screening in persons with RA with a sensitivity of 0.75 (95% CI 0.58, 0.88) and specificity of 0.75 (95% CI 0.49, 0.87) compared with the Montgomery-Asberg Depression Rating Scale (MADRS)[34] and a sensitivity of 0.87 (95% CI 0.62, 0.98) and specificity of 0.77 (95% CI 0.69, 0.84) compared with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Axis I Disorders (SCID-1).[35]

Generalised Anxiety Disorder Questionnaire (GAD-7)

The Generalised Anxiety Disorder seven-item scale (GAD-7) is part of the NAKO questionnaire implemented via touch screen.[36] It was developed and validated as a measure for evaluating the presence and severity of generalised anxiety disorders. It is a self-reported questionnaire measuring general anxiety symptoms related to the past 2 weeks, however, in the NAKO version the time frame was extended to 4 weeks. Response options are scored from 0 (not at all) to 3 (almost every day) for each question (possible range 0–21). A cut-off score of ≥10 is used to indicate the presence of GAD.[37] The GAD-7 has been validated to measure GAD in persons with RA with a sensitivity of 0.64 (95% CI 0.31, 0.89) and a specificity of 0.86 (95% CI 0.78, 0.91).[35]

Neuropsychological tests

A set of questions assessed subjective memory complaints and yielded case classifications of no memory complaints and those with complaints with and without worry.

The neuropsychological test battery included different tests to address the domains of memory and executive functions, tests for fine motor movements and attention as well as numerical reasoning.[27] The Level 1 examination included a word list with immediate and delayed recall to test verbal episodic memory (12 nouns), a verbal fluency test (animal names), a digit span backwards test of working memory and the Stroop interference task of selective attention.[38] A number series task was included in the extended Level 2 examination.[39]

In the word list recall tests 1–3, participants were asked three times, one delayed at the end of testing, to recall as many words as possible from a digitally recorded list of words (possible range 1–12). In the semantic fluency task, participants were asked to enumerate as many animal names as possible within 1 min (possible range 1–79). In the Stroop colour-word task, participants were first asked to name the colour of 36 differently coloured boxes (Stroop table 2) and second to name the colour of incongruent colour names (Stroop table 3). For the digit span backwards, participants were acoustically presented digitally recorded number sequences of increasing length, containing three to nine random single digits spoken at a rate of 1 s per number. Participants were instructed to recall each sequence in reverse order.[38] Scores from participants who experienced documented disturbances during the neuropsychological tests, for example, sudden noise or interruption, were not considered in the analyses.

Statistical analysis

We analysed these cross-sectional data descriptively. Participants with missing data were excluded from the regression models, those with missing data for education were excluded from the description of neuropsychological function stratified by education. The outcomes were reported stratified by self-reported disease (RA, AS, PsA, SLE, SjD, iRMD, OA but no iRMD). The frequency of a physician's diagnosis of depression was additionally stratified by sex and age group. Depression and anxiety measures as well as neuropsychological tests were stratified by education level.

To assess the relationship between neuropsychological function and iRMD status in an exploratory way, we fitted linear regression models. These were characterised as *Neuro-Score*=sex+iRMD_status+age+education with dependent variables immediate word recall, delayed word recall, semantic fluency (animal names), executive function (Stroop test), memory (digit span backwards) and independent variables sex, IRMD-status, age and education. One model was fitted for each neuropsychological test. We show the least square means for the age groups (20, 30, 40, 50, 60, 70 years) and iRMD, respectively, non-iRMD OA, describing the score for different

Table 1 Characteristics of NAKO participants with an iRMD and persons with OA

	RA	AS	PsA	SLE	SjD	iRMD total	OA	N missing
N	2286	571	524	156	95	3257	24 030	–
Female, %	73	46	59	81	94	67	59	0
Age in years, mean±SD	58±9.5	55±10	57±9.5	54±11	57±9.7	57±9.8	58±8.7	0
Age at onset, mean±SD	43±15	35±13	n.a.*	39±14	46±13	41±15	Hip: 44±15 Knee: 42±15 Hands: 50±10	
Education, ISCED-97 level,% (n)								2408
Lower	3.9 (88)	2.3 (13)	1.9 (10)	1.9 (3)	2.1 (2)	3.4 (109)	3.4 (869)	
Intermediate	42 (956)	39 (222)	42 (216)	42 (64)	38 (36)	41 (1321)	42 (10 953)	
Higher	43 (977)	48 (269)	47 (244)	48 (74)	46 (44)	45 (1453)	46 (11 800)	
Smoking, % (n)								1625
Never	39 (897)	33 (189)	33 (172)	38 (59)	51 (48)	38 (1232)	40 (9541)	
Current	17 (391)	21 (122)	16 (86)	22 (34)	13 (12)	18 (575)	17 (3987)	
Former	36 (819)	39 (223)	45 (233)	33 (52)	31 (29)	37 (1211)	38 (9110)	
Comorbidities, % (n)								
Hypertension	45 (1037)	40 (229)	48 (251)	42 (65)	35 (33)	44 (1444)	43 (10 334)	72
Hyperlipidaemia	41 (930)	35 (201)	38 (200)	29 (45)	38 (36)	39 (1261)	37 (8959)	260
Osteoporosis	14 (328)	9.6 (55)	11 (58)	14 (21)	20 (19)	13 (417)	7.5 (1802)	197
Cancer	12 (268)	9.8 (56)	11 (57)	12 (19)	14 (13)	12 (378)	12 (2794)	84
Diabetes	12 (277)	8.1 (46)	11 (59)	6.4 (10)	5.3 (5)	11 (356)	10 (2396)	42
Reduced renal function	5.6 (127)	6.0 (34)	4.8 (25)	17 (26)	15 (14)	5.6 (187)	3.5 (839)	90
Myocardial infarction	3.9 (90)	2.6 (15)	3.1 (16)	3.2 (5)	1.1 (1)	3.5 (115)	2.7 (650)	42
Stroke	2.7 (61)	2.6 (15)	2.3 (12)	3.8 (6)	4.2 (4)	2.7 (88)	2.7 (655)	62
OA	65 (1462)	48 (272)	56 (289)	47 (72)	57 (54)	59 (1894)	100 (24 030)	0

SD, based on NAKO data freeze 100 000; application NAKO-603.
*Age at onset only available for psoriasis, not for PsA.
AS, ankylosing spondylitis; iRMD, inflammatory rheumatic disease; ISCED-97, International Standard Classification of Education 97; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SjD, Sjögren's disease; SLE, systemic lupus erythematosus.

age groups and iRMD/non-iRMD OA while controlling for sex and education.

RESULTS

Of 100 273 NAKO participants from the first data freeze who answered the questions on rare diseases, n=3257 had any iRMD (3.2%), thereof n=2286 had RA (2.3%), n=571 AS (0.6%), n=524 PsA (0.5%), n=156 SLE (0.2%) and n=95 SjD (0.1%), including n=353 with more than one iRMD diagnosis. N=1894 (59% of those with iRMD) reported an iRMD and OA, n=24 030 (24%) had OA but no iRMD (figure 1).

The mean age of participants with iRMD ranged between 54 years (SLE) and 58 years (RA) with 46% (AS)–94% (SjD) being female. The majority of persons with an iRMD (97%) had an intermediate or high level of education and 38% were never smokers (table 1). Persons with OA were less often female compared with the iRMD group (59% in OA vs 67% in iRMD) and on average 1 year older (58 years in OA vs 57 in iRMD), while education and smoking status were comparable (iRMD and higher education: 45%, OA: 46%, iRMD never smokers: 38%, OA: 40%) .

Hypertension (44%) and hyperlipidaemia (39%) were the most common comorbidities in iRMD, followed by osteoporosis (13%), any cancer (12%) and diabetes (11%) (table 1). Osteoporosis was more frequent in iRMD compared with OA (7.5%), especially in SjD (20%).

Depression

A lifetime self-reported physician's diagnoses of depression was more frequent in SjD (37%) and SLE (33%) compared with AS (24%), PsA (26%) and RA (28%). Overall, depression was more frequent in iRMD (26%) compared with OA (21%). Of all persons with a self-reported lifetime depression, 53% (iRMD) and 48% (OA) had antidepressive therapy within the past 12 months (table 2).

The MINI screening was positive in 37% (AS)–49% (SjD) and in 34% of persons with OA. Of those who

Table 2 Frequency of mental health disorders for persons with iRMD and OA

	RA	AS	PsA	SLE	SjD	iRMD total	OA	N missing
Depression								
Depression, physician lifetime diagnosis, % (n)	28 (630)	24 (136)	26 (138)	33 (52)	37 (35)	26 (865)	21 (5095)	148
Percentage of those with depression treatment by physician or psychologist in the last 12 months (n)	54 (338)	50 (68)	47 (65)	65 (34)	49 (17)	53 (459)	48 (2449)	8
MINI screen positive, % (n)	40 (921)	37 (209)	41 (212)	41 (64)	49 (47)	39 1288)	34 (8051)	256
MDD MINI positive* % (n)	9.5 (215)	8.5 (48)	7.1 (40)	9.7 (15)	17 (16)	7.8 (287)	6.5 (1567)	24 933*
PHQ-9 sum score, mean±SD	5.4±4.7	4.9±3.7	5.4±4.6	6.8±5.2	5.4±4.3	5.2±4.6	4.4±4.0	2808
PHQ-9 ≥10, % (n)	13 (304)	12 (69)	13 (67)	24 (38)	12 (11)	13 (415)	9.0 (2173)	2808
Anxiety								
Anxiety disorder, physician lifetime diagnosis, % (n)	16 (369)	14 (77)	15 (76)	17 (26)	18 (17)	15 (493)	11 (2613)	86
GAD-7 sum score, mean±SD	4.3±4.1	3.8±3.8	4.3±3.9	5.3±4.3	4.4±4.0	4.1±4.0	3.5±3.5	2903
GAD-7 ≥10, % (n)	9.2 (210)	7.9 (45)	9.4 (49)	15 (23)	11 (10)	8.6 (281)	5.8 (1389)	2903

Based on NAKO data freeze 100 000; application NAKO-603.
*Only done for Level 2 examination participants with a positive MINI screen.
AS, ankylosing spondylitis; GAD-7, General Anxiety Disorder-7; iRMDs, inflammatory rheumatic diseases; MDD, major depressive disorder; MINI, Mini-International Neuropsychiatric Interview; NAKO, German National Cohort; OA, osteoarthritis; PHQ-9, Depression Scale of the Patient Health Questionnaire; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SjD, Sjögren's disease; SLE, systemic lupus erythematosus.

had a positive screen and a Level 2 examination, a lifetime depressive episode classified by the MINI was present in 287 persons with iRMD and 1567 persons with OA, corresponding to 7.8% versus 6.5% of the entire sample.

Individuals with iRMD had a mean±SD PHQ-9 of 5.2±4.6 versus. 4.4±4.0 in OA. Current depressive symptoms based on PHQ-9 ≥10 were more frequent in iRMD compared with OA (13% vs 9%) and most frequent in SLE (24%).

Association of depression with sex and age

For all age groups and across all iRMD and OA, women were more often affected by depression than men (figure 2). Compared with OA, those with iRMDs were particularly affected in middle age. Middle-aged (51–60 years old) women with SLE (47%), AS (45%) and PsA (40%) were most frequently affected by physician's diagnoses of depression, while current depressive episodes were also common in younger age groups.

Anxiety

A lifetime physician diagnosis of anxiety was reported by 14% (AS)–18% (SjD), overall in 15% (iRMDs) versus 11% in OA (table 2). Individuals with iRMD had a mean GAD-7 sum score of 4.1±4.0 versus 3.5±3.5 in OA. Current anxiety symptoms based on GAD-7 ≥10 were present in 8.6% (iRMD) versus 5.8% (OA) and most frequent in SLE (15%).

Cognitive performance

According to the subjective memory complaints, 29% (iRMD) versus 27% (OA) felt that their memory is getting worse, 20% versus 17% were concerned about it and 12% versus 9.6% had ever consulted a physician about their memory problems, most frequently in SjD (15%) and SLE (14%) (table 3).

Mean values from the word list recall tests, the semantic fluency task, the digit span backwards test and number series task were comparable across the individual iRMDs and in OA (table 3).

Association of depression, anxiety and cognitive performance with education

Overall, higher percentages of lifetime physicians' diagnoses of depression and anxiety as well as current depressive and anxiety symptoms were observed in persons with lower educational level (table 4). The cognitive function tests also had poorer outcomes with a lower level of education.

Cognitive performance in iRMD and OA: results from linear regression models

When the association between iRMD status and the neuropsychiatric scores was explored while controlling for sex and education, almost no differences were observed between iRMD and OA (figure 3) in all age groups. Numeric results are shown in online supplemental table 1.

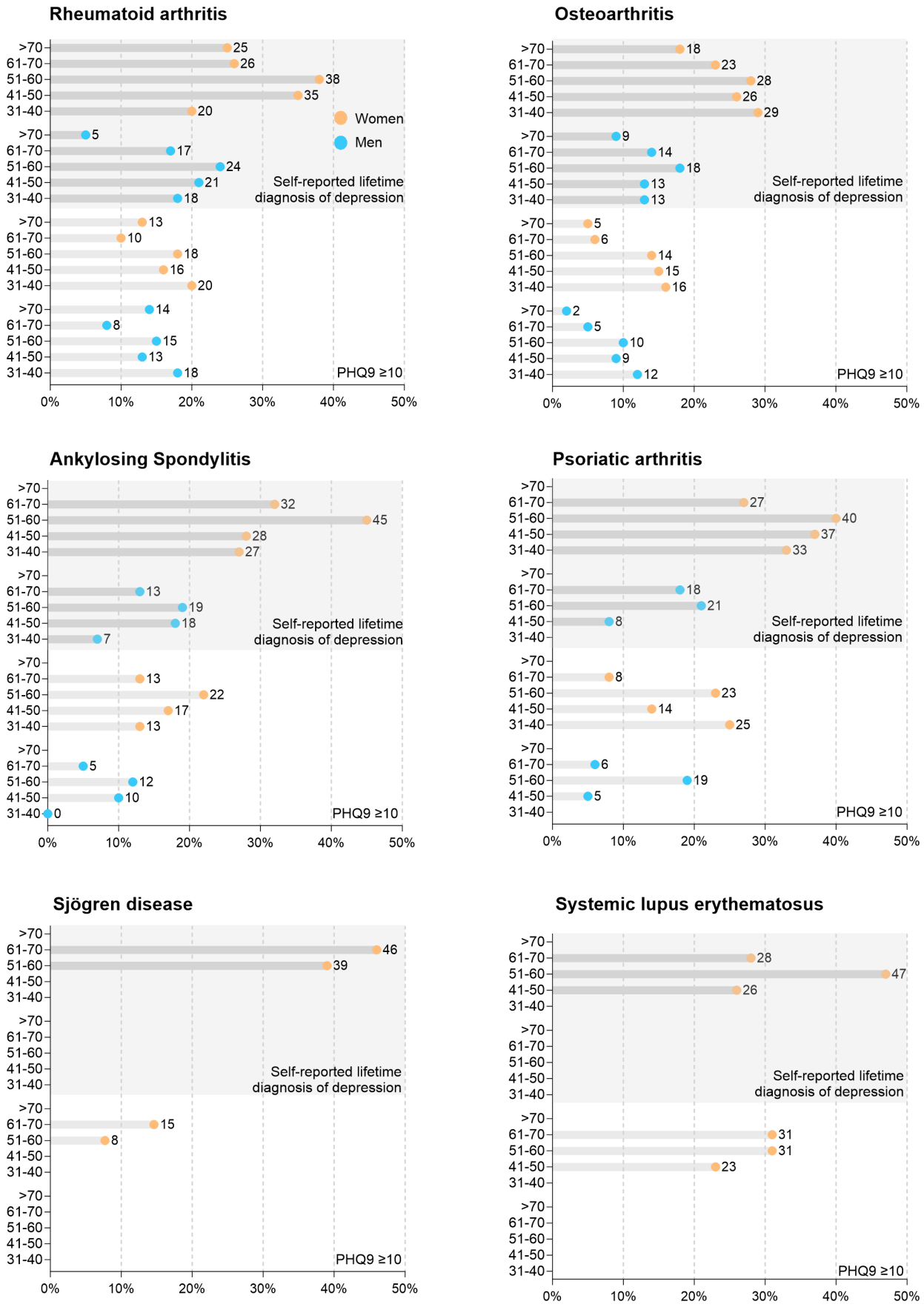

Figure 2 Depression diagnosis and symptoms by diagnosis. Percentage of persons with a self-reported lifetime diagnosis of depression and current depressive symptoms measured by the Patient Health Questionnaire (PHQ-9 ≥10) by age and sex. PHQ-9 Depression Scale of the Patient Health Questionnaire age groups with case numbers ≤10 are not shown.

Table 3 Cognitive performance

	RA	AS	PsA	SLE	SjD	iRMD total	OA	N missing
Subjective memory complaints								
Memory worse, % (n)*	31 (652)	24 (129)	25 (121)	32 (45)	33 (29)	29 (867)	27 (6119)	16283
Memory worse with concern about it, % (n)*	22 (455)	15 (77)	18 (82)	21 (31)	17 (15)	20 (580)	17 (3829)	19698
Memory worse with contact to a physician, % (n)*	13 (268)	8.8 (46)	9.0 (43)	14 (20)	15 (13)	12 (347)	9.6 (2139)	19719
Episodic memory domain								
Word list recall, immediate, mean±SD, range 1–12, (n)	6.5±1.8 (1942)	6.6±1.7 (495)	6.7±1.8 (456)	6.9±1.8 (132)	6.6±1.5 (80)	6.5±1.7 (2789)	6.5±1.7 (21 349)	1200
Word list recall, repeat, mean±SD, range 1–12 (n)	9.2±1.8 (1933)	9.3±1.8 (494)	9.3±1.8 (453)	9.6±1.8 (130)	9.4±1.6 (79)	9.3±1.8 (2773)	9.2±1.8 (21 204)	1250
Word list recall, delayed, mean±SD, range 1–12 (n)	7.8±2.3 (1933)	7.9±2.4 (494)	7.9±2.4 (453)	8.4±2.3 (130)	7.9±2.1 (79)	7.8±2.4 (2773)	7.7±2.4 (21 204)	1421
Executive function domain								
Semantic fluency (animal names), mean±SD, range 1–79, (n)	24±6.8 (1948)	25±7.1 (496)	25±6.7 (459)	25±6.9 (132)	26±6.9 (80)	25±6.9 (2798)	25±6.8 (21 403)	1100
Stroop task 1 (colour naming), mean±SD, range 11–422, (n)	22±5.1 (1942)	22±4.3 (494)	22±4.8 (456)	22±4.7 (131)	21±3.4 (80)	22±5.0 (2788)	22±4.7 (21 335)	1610
Stroop task 2 (incongruent condition), mean±SD, range 11–422, (n)	46±14 (1942)	44±14 (494)	46±15 (456)	43±14 (131)	44±13 (80)	45±14 (2788)	45±15 (21 335)	1622
Stroop effect (incongruent – colour naming), mean±SD, –250–360	24±12	22±12	24±13	21±11	23±11	23±12	23±13	1626
Digit span backwards, mean±SD, range 2–9, (n)	4.5±1.2 (1931)	4.6±1.2 (495)	4.6±1.2 (454)	4.7±1.4 (131)	4.7±1.2 (79)	4.6±1.2 (2777)	4.6±1.2 (21 273)	1321
Number series task only Level 2, (n)	502±21 (372)	500±22 (107)	505±19 (89)	502±22 (18)	507±24 (16)	502±21 (538)	502±21 (4110)	22140

NAKO, based on NAKO data freeze 100 000; application NAKO-603.
*Only for ≥45 year olds.
AS, ankylosing spondylitis; iRMD, inflammatory rheumatic disease; MDD, major depressive disorder; MINI, Mini-International Neuropsychiatric Interview; NAKO, German National Cohort; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SjD, Sjögren's disease; SLE, systemic lupus erythematosus.

Table 4 Depression and anxiety measures by ISCED-97 educational level in all persons with iRMD and information on education (n=2883)

			Education level		
	n	n missing	Lower	Intermediate	Higher
Number of participants with an inflammatory rheumatic disease*	2883	0	115	1313	1438
Physician's lifetime diagnosis of depression, %	2866	17	39	27	23
Depression treatment last 12 months, % of those with physician's diagnosis of depression	738	0	56	53	53
MINI screen positive, %	2841	24	44	39	38
MINI classification positive, % of positive screened and with Level 2	291	2586	92	85	89
PHQ-9 ≥10, %	2535	348	27	16	12
PHQ-9 sum score, mean±SD	2535	348	7.2±5.4	5.4±4.6	4.9±4.4
Physician's lifetime diagnosis of anxiety, %	2873	10	31	16	13
GAD-7 sum score, mean±SD	2525	358	5.6±4.5	4.2±4.1	3.9±3.8
GAD-7 ≥10, %	2525	358	21	11	8.2
Stroop effect, mean±SD	2671	212	27±15	24±13	21±10
Semantic fluency (animal names), mean±SD	2733	150	21±5.8	24±6.7	26±6.8
Digit span backwards, mean±SD, range 2–9	2712	171	4.2±1.0	4.5±1.2	4.8±1.3

Based on NAKO data freeze 100 000.
*Includes self-reported physician diagnosis of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, systemic lupus erythematosus or Sjögren disease.
GAD-7, General Anxiety Disorder-7 Scale; iRMD, inflammatory rheumatic disease; ISCED-9, International Standard Classification of Education 97; MINI, Mini International Neurospsychiatric Interview; PHQ-9, Depression Scale of the Patient Health Questionnaire.

DISCUSSION

The comparison of people with inflammatory and non-inflammatory rheumatic musculoskeletal diseases within this large population-based NAKO cohort shows that more people with iRMDs have depression and anxiety compared with persons with OA. No or marginal differences were observed in the cognitive performance tests.

The observed frequencies of current depressive episodes, self-reports of a physician diagnosis and treated depression are in line with the existing literature.[7] A previous German study used the PHQ-9 and the Beck-Depression Inventory II to assess the extent of depressive symptoms in patients with RA,[40] so that frequencies cannot be directly compared with this study. The proportion of patients with antidepressant therapy was lower in the VADERAII (validation of depression-questionnaires for patients with rheumatoid arthritis) study (12% of patients classified as having depressive symptoms) compared with this study. Another study on patients with PsA used the PHQ-2 to identify depressive symptoms.[41] The results complement each other in that a frequent occurrence of depressive symptoms is confirmed both in patients with RA and PsA undergoing rheumatological care and in people with iRMDs in the general population.

Anxiety symptoms and/or diagnoses are less often reported. Within population-based data from Canada, anxiety disorders were also elevated in RA compared with a cohort without RA matched by year of birth, sex and region of residence.[1] In a study from an early arthritis consultation at the Charité–Universitätsmedizin Berlin, Germany, the frequent occurrence of anxious symptoms, measured by the HADS, was noteworthy.[42] It is however remarkable that those symptoms were as frequently present in persons without an inflammatory disease who consulted the early arthritis clinic (mean disease duration 4 months).[42] This differs from our finding that depressive and anxious symptoms are less common in people with OA than those with iRMDs. The mean disease duration of the NAKO iRMD population is 16 years which is a possible reason for this difference to the early arthritis study population in the Charité study.

The proportion of a lifetime diagnosis of anxiety among people with iRMDs in this study was twice that of the total NAKO cohort (7.8%).[36] In line with previous reports, anxiety was associated with educational status.[1 36]

A new aspect of the NAKO evaluation is the comparison with the occurrence in people with the non-inflammatory musculoskeletal disease OA. Individuals with OA were selected as a comparison to differentiate the possible influence of chronic inflammatory activity from impairments caused by pain and functional limitations. The comparison group was very similar in most parameters such as age, comorbidity and education. This comparison is valuable because elevated levels of depression with pain and functional limitations occur in OA.[43] The even higher frequency across various iRMD indicates that the inflammatory process may additionally contribute to the development of depressive and anxiety symptoms. The

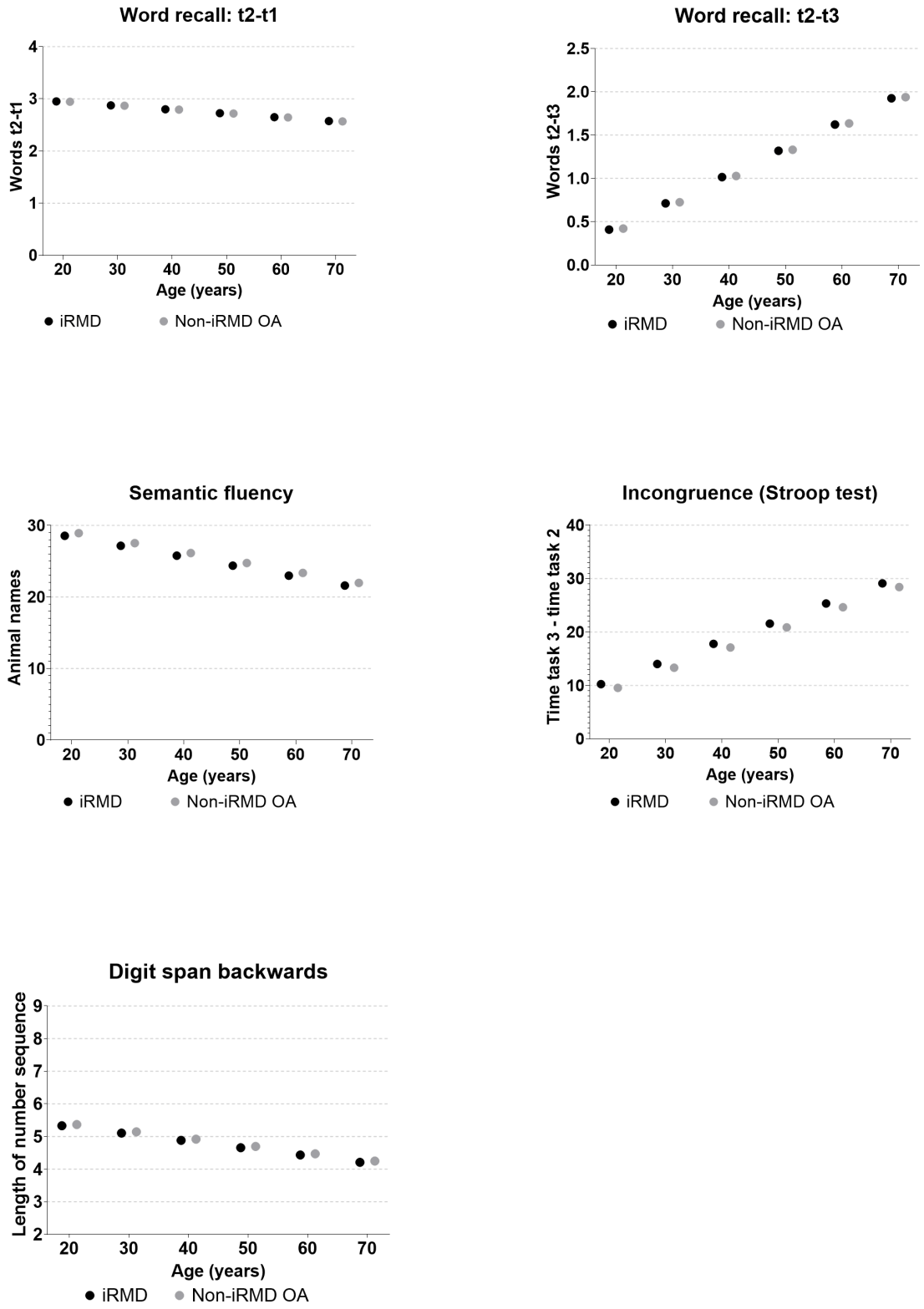

Figure 3 Cognitive performance in iRMD and OA. Results (least square means for ages 20, 30, 40, 50, 60 and 70) from linear regression models with iRMD status, sex, age and education as covariates. Immediate word recall: difference between recalled words (range 0–12) at t1 and t2 (immediate recall). Delayed word recall: difference between words at t2 (immediate recall) and t3 (delayed recall). iRMD, inflammatory rheumatic disease; OA, osteoarthritis.

results support assumptions about an interplay between chronic peripheral inflammation and alterations in the brain function[16] or, respectively, in the development of a competitive situation between the brain and a chronically activated immune system for the energy supply. The constraint energy expenditure can manifest, among other symptoms such as fatigue or sleeping disorders, also as depression and anxiety.[44]

In contrast to our results, a systematic review with a meta-analysis recently published by Gwinnutt *et al*[12] showed a clinically relevant cognitive impairment of n=3141 people from 62 studies with iRMDs compared with age-matched controls. Most of the iRMD population in this meta-analysis had SLE, and also 96% of the RA population was female. In a subgroup analysis of studies that adjusted for education, age and sex, the differences in cognitive abilities between the iRMD population and controls were still present: the standardised mean difference in overall cognition was −0.6 (95% CI −0.74, −0.45) for iRMD compared with controls and −0.64 (95% CI -0.9, −0.37) for complex attention/executive function. This meta-analysis did not include data from Germany. One reason for the different results might be the different recruitment of the iRMD population and the approaches to define comparison or control groups. While the meta-analysis mainly comprises patients recruited in specialised rheumatological care, the NAKO cohort is based on the general population. Thus, disease severity is likely to be different since mild forms of iRMDs are included in NAKO. In addition, the NAKO examinations are complex and long (4–6 hours) and the participants were contacted at home (via mail or telephone) and not at the doctor's office.[30] Both factors might contribute to further selection towards a higher education level and the exclusion of individuals with severe forms of iRMDs. There is no data on disease activity or severity available. A possible relation between inflammation and cognitive disorders most certainly depends on the degree of severity which may be one reason that we do not map any impairments.

In a letter referring to the meta-analysis by Gwinnutt *et al*, Recio-Barbero *et al* point out the lack of standardisation in cognitive assessments with a wide range from general screening tools to neurocognitive batteries.[45] In fact, in most of the studies, the screening scale Mini-Mental State Exam was used, which limits to estimate the degree of involvement and impact. However, cognitive impairment was also found in the studies that used test batteries.[12] A recent German study examined cognitive abilities in 101 patients with axial spondyloarthritis and 117 patients with PsA who were recruited from two rheumatology centres.[14] Using the Memory and Attention Test subscores, they found significant impairments in selective attention but no differences in episodic working memory compared with healthy volunteers.

The comparison with data from the OA group also showed no difference in the cognitive function tests. This is confirmed by comparison with the previously published NAKO data on cognitive test results.[38 39]

Limitations and strengths

The study provides an assessment based on self-reports and test results and enables comparison to OA covering 16 areas of Germany. The strengths of the study are the large sample size and the assessment of depression, anxiety and cognitive disorders using a set of validated instruments. The population-based design enabled comparison with age-stratified and sex-stratified groups of people without iRMD and comparison of distinct iRMDs with each other. One limitation is the non-representative sampling for Germany. The reported frequencies cannot be used as prevalence estimates for the German general iRMD and OA population. A second limitation is the self-report of physician's diagnoses without validation, no clinical examination confirmed the presence of iRMDs. The frequency of self-reported diagnoses on RA and SLE is higher in the NAKO (RA: 1.85%, SLE: 0.14%)[46] compared with a recent prevalence estimate for Germany (RA: 0.8%–1.2%, SLE: 0.056%)[47] which may be related to misclassification of hand OA as RA and cutaneous lupus as SLE in some cases. The participants prevalence of AS and SjD is comparable to other data.[46 48] For future analyses with the NAKO data it will be possible to link the self-reported diagnoses to claims data from the statutory health insurance. Due to the prospective design of the NAKO with planned follow-up surveys every 5 years, the age at inclusion into the study was limited to 70 years.

CONCLUSION

Mental disorders are common comorbidities in iRMD. The frequent findings of depression and anxiety within this population based sample of persons with various iRMDs should increase the awareness for mental disorders and help to target patients for possible limitations and symptoms. No evidence was found in this study to support any clinically meaningfully increased cognitive impairment in persons with iRMD.

Author affiliations
[1]Epidemiology and Health Services Research, German Rheumatism Research Center Berlin, Berlin, Germany
[2]Institute of Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Berlin, Germany
[3]Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany
[4]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany

X Johanna Callhoff @callhoffj

Acknowledgements We thank all participants who took part in the NAKO study, the staff in this research program, the data management and integration centre and the NAKO head office. We thank our research partners Peter Böhm and Julius Wiegand in the TARISMA project for dedicating their time to add the patient view to this project.

Collaborators The Nako Investigators: Prof Dr Annette Peters (Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health (GmbH), Neuherberg, Germany, Chair of Epidemiology, Institute for Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-Universität München, München, Germany, German Center for Diabetes Research (DZD), Neuherberg, Germany, Munich Heart Alliance, German Center for Cardiovascular Research (DZHK), Munich, Germany, German Center for Mental Health (DZPG), partner site Munich, Munich), Prof Dr Thomas Keil (Institute of Social Medicine, Epidemiology and Health Economics, Charité – Universitätsmedizin Berlin, Berlin, Germany, Institute of Clinical Epidemiology and Biometry, University of Wuerzburg, Wuerzburg, Germany, State Institute of Health I, Bavarian Health and Food Safety Authority, Erlangen, Germany), Prof Dr Stefan Willich (Institute of Social Medicine, Epidemiology and Health Economics, Charité – Universitätsmedizin Berlin, Berlin, Germany), Prof Dr Tobias Pischon (Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Molecular Epidemiology, Research Group, Berlin, Germany, Berlin-Buch, Germany, Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Biobank Technology Platform, Berlin,

Germany, Berlin-Buch, Germany, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany), Dr Ilais Moreno Velásquez (Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Molecular Epidemiology), Prof Dr Matthias Bernd Schulze (Institute of Nutritional Science, University of Potsdam, Nuthetal, Germany, NAKO Study Center, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany), Dr Sylvia Gastell (NAKO Study Center, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany), Prof Dr Wolfgang Ahrens (Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany), Dr Kathrin Günther (Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany), Dr Johanna Mucke (Department of Rheumatology, University Hospital Düsseldorf, Medical Faculty of Heinrich Heine University, Düsseldorf, and Hiller Research Center, University Hospital Düsseldorf, Medical Faculty of Heinrich Heine University, Düsseldorf, Germany), Nina Ebert (Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany), Dr Tamara Schikowski (IUF - Leibniz Research Institute for Environmental Medicine, Düsseldorf, Düsseldorf, Germany), Prof Dr Börge Schmidt (Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany), Prof Dr Andreas Stang (Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany), Dr Stefanie Jaskulski (Institute for Prevention and Cancer Epidemiology, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany), Prof Dr Rafael Mikolajczyk (Institute of Medical Epidemiology, Biometrics and Informatics, Medical Faculty of the Martin-Luther University Halle-Wittenberg, Halle (Saale), Germany, German Center for Mental Health (DZPG), partner site Halle-Jena-Magdeburg, Halle), Janka Massag (Institute of Medical Epidemiology, Biometrics and Informatics, Medical Faculty of the Martin-Luther University Halle-Wittenberg, Halle (Saale), Germany), Prof Dr Volker Harth (Institute for Occupational and Maritime Medicine Hamburg (ZfAM), University Medical Centre Hamburg-Eppendorf (UKE), Hamburg, Germany), Dr Nadia Obi (Institute for Occupational and Maritime Medicine Hamburg (ZfAM), University Medical Centre Hamburg-Eppendorf (UKE), Hamburg, Germany), Dr Stefanie Castell (Department for Epidemiology, Helmholtz Centre for Infection Research (HZI), Braunschweig, Germany), Jana-Kristin Heise (Department for Epidemiology, Helmholtz Centre for Infection Research (HZI), Braunschweig, Germany), Prof. Dr. Wolfgang Lieb (Institute of Epidemiology, Kiel University, Kiel, Germany), Dr Cara Övermöhle (Institute of Epidemiology, Kiel University, Kiel, Germany), Prof Dr Markus Löffler (Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany), PD Dr Kerstin Wirkner (LIFE - Leipzig Research Centre for Civilization Diseases, University of Leipzig, Leipzig, Germany), Prof Dr Rudolf Kaaks (Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany), Dr Verena Katzke (Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany), Prof Dr Till Bärnighausen (Heidelberg Institute of GlobalHealth, University Hospital Heidelberg, Heidelberg, Germany, Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, USA, Africa Health Research Institute (AHRI), Somkhele and Durban, South Africa), Prof Dr André Karch (Institute of Epidemiology and Social Medicine, University of Münster, Germany), Prof Dr Carsten Oliver Schmidt (Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany), Dr Claudia Meinke-Franze (Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany), Prof Dr Michael Leitzmann (Institute for Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany), Dr Beate Fischer (Institute for Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany), Prof Dr Hermann Brenner (Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ)), Dr Lena Koch-Gallenkamp (Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ)), PD Dr Bernd Holleczek (Saarland Cancer Registry, Saarbrücken, Germany), Dr Karin Greiser (Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany), Dr Barbara Bohn (NAKO e.V., Heidelberg, Germany).

Contributors JC is responsible for the overall content as guarantor. JC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JC, KB and KA developed the research questions. JC prepared the data for analyses and conducted the data analyses. KA, KB and AS advised on data analysis and interpretation. All authors except JC, KA and AS were involved in data collection of the NAKO. JC and KA drafted the manuscript. JC, JB, KA and AS contributed to the interpretation of the data. All authors and collaborators contributed to the article and approved the submitted version.

Funding The study was supported by the Federal Ministry of Education and Research within the network TARISMA (01EC1902A). The project was conducted with data from the German National Cohort (NAKO Gesundheitsstudie, www.nako.de). The NAKO is funded by the Federal Ministry of Education and Research (BMBF) (project funding reference numbers: 01ER1301A/B/C, 01ER1511D and 01ER1801A/B/C/D), federal states of Germany and the Helmholtz Association, the participating universities and the institutes of the Leibniz Association.

Competing interests JC: speaker fees—Janssen, Pfizer, Idorsia. AS: Lecture honoraria from AbbVie, Amgen, BMS, Celltrion, MSD, Lilly, Pfizer, Roche, UCB. All others: none declared.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the ethics committee of the Charité-Universitätsmedizin Berlin (EA2/233/22) and all other local ethics committees of the study centres. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Access to and use of NAKO data and biosamples can be obtained via an electronic application portal (https:// transfer.nako.de).

ORCID iDs
Johanna Callhoff http://orcid.org/0000-0002-3923-2728
Katinka Albrecht http://orcid.org/0000-0003-0886-0294
Anja Strangfeld http://orcid.org/0000-0002-6233-022X

REFERENCES

1 Marrie RA, Hitchon CA, Walld R, *et al*. Increased Burden of Psychiatric Disorders in Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)* 2018;70:970–8.
2 Omar M, Ben-Shabat N, Tsur AM, *et al*. The association between ankylosing spondylitis and psychiatric disorders: Insights from a population based cross-sectional database. *J Affect Disord* 2023;323:788–92.
3 Zusman EZ, Howren AM, Park JYE, *et al*. Epidemiology of depression and anxiety in patients with psoriatic arthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2020;50:1481–8.
4 León-Suárez P, Rúa-Figueroa I, González Martín J, *et al*. Depression and anxiety in systemic lupus erythematosus: A case-control study on prevalence and associated factors in a single-center cohort. *Lupus (Los Angel)* 2023;32:827–32.
5 Westhoff G, Dorner T, Zink A. Fatigue and depression predict physician visits and work disability in women with primary Sjogren's syndrome: results from a cohort study. *Rheumatol Sunnyvale* 2012;51:262–9.
6 Lwin MN, Serhal L, Holroyd C, *et al*. Rheumatoid Arthritis: The Impact of Mental Health on Disease: A Narrative Review. *Rheumatol Ther* 2020;7:457–71.
7 Matcham F, Rayner L, Steer S, *et al*. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatol (Oxford)* 2013;52:2136–48.
8 Redeker I, Hoffmann F, Callhoff J, *et al*. Determinants of psychological well-being in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. *Ann Rheum Dis* 2018;77:1017–24.
9 Zhao S, Thong D, Miller N, *et al*. The prevalence of depression in axial spondyloarthritis and its association with disease activity: a systematic review and meta-analysis. *Arthritis Res Ther* 2018;20:140.
10 Raghunath S, Glikmann-Johnston Y, Vincent FB, *et al*. Patterns and prevalence of cognitive dysfunction in systemic lupus erythematosus. *J Int Neuropsychol Soc* 2023;29:421–30.
11 Rayes HA, Tani C, Kwan A, *et al*. What is the prevalence of cognitive impairment in lupus and which instruments are used to measure

it? A systematic review and meta-analysis. *Semin Arthritis Rheum* 2018;48:240–55.
12 Gwinnutt JM, Toyoda T, Barraclough M, *et al*. Cognitive impairment in the immune-mediated inflammatory diseases compared with age-matched controls: Systematic review and meta-regression. *Semin Arthritis Rheum* 2023;58:152131.
13 Booth MJ, Janevic MR, Kobayashi LC, *et al*. No association between rheumatoid arthritis and cognitive impairment in a cross-sectional national sample of older U.S. adults. *BMC Rheumatol* 2021;5:24.
14 Kleinert S, Schuch F, Rapp P, *et al*. Impairment in cognitive function in patients with axial spondyloarthritis and psoriatic arthritis. *Rheumatol Int* 2023;43:89–97.
15 Meade T, Manolios N, Cumming SR, *et al*. Cognitive Impairment in Rheumatoid Arthritis: A Systematic Review. *Arthritis Care Res (Hoboken)* 2018;70:39–52.
16 Straub RH, Cutolo M. Psychoneuroimmunology-developments in stress research. *Wien Med Wochenschr* 2018;168:76–84.
17 de Sousa DC, Sobreira EST, Feitosa WLQ, *et al*. Cognitive dysfunction in systemic lupus erythematosus is associated with disease activity and oxidative stress: a comparative study with rheumatoid arthritis for identifying biomarkers. *BMC Neurosci* 2023;24:66.
18 Louati K, Berenbaum F. Fatigue in chronic inflammation - a link to pain pathways. *Arthritis Res Ther* 2015;17:254.
19 Katz G, Ogdie A, Baker JF, *et al*. Association between depression, anxiety, chronic pain, or opioid use and tumor necrosis factor inhibitor persistence in inflammatory arthritis. *Clin Rheumatol* 2022;41:1323–31.
20 Matcham F, Norton S, Scott DL, *et al*. Symptoms of depression and anxiety predict treatment response and long-term physical health outcomes in rheumatoid arthritis: secondary analysis of a randomized controlled trial. *Rheumatology (Oxford)* 2016;55:268–78.
21 Michelsen B, Kristianslund EK, Sexton J, *et al*. Do depression and anxiety reduce the likelihood of remission in rheumatoid arthritis and psoriatic arthritis? Data from the prospective multicentre NOR-DMARD study. *Ann Rheum Dis* 2017;76:1906–10.
22 Pedersen JK, Wang L, Risbo N, *et al*. Mortality in patients with incident rheumatoid arthritis and depression: a Danish cohort study of 11071 patients and 55355 comparators. *Rheumatol (Oxford)* 2024;63:680–8.
23 Anyfanti P, Triantafyllou A, Panagopoulos P, *et al*. Predictors of impaired quality of life in patients with rheumatic diseases. *Clin Rheumatol* 2016;35:1705–11.
23 Anyfanti P, Gavriilaki E, Pyrpasopoulou A, *et al*. Depression, anxiety, and quality of life in a large cohort of patients with rheumatic diseases: common, yet undertreated. *Clin Rheumatol* 2016;35:733–9.
25 Dey M, Nagy G, Nikiphorou E. Comorbidities and extra-articular manifestations in difficult-to-treat rheumatoid arthritis: different sides of the same coin? *Rheumatology (Oxford)* 2023;62:1773–9.
26 Doumen M, Pazmino S, Verschueren P, *et al*. Viewpoint: Supporting mental health in the current management of rheumatoid arthritis: time to act! *Rheumatology (Oxford)* 2023;62:SI274–81.
27 Berger K, Rietschel M, Rujescu D. The value of “mega cohorts” for psychiatric research. *World J Biol Psychiatry* 2023;24:860–4.
28 German National Cohort C. The German National Cohort: aims, study design and organization. *Eur J Epidemiol* 2014;29:371–82.
29 Peters A, Peters A, Greiser KH, *et al*. Framework and baseline examination of the German National Cohort (NAKO). *Eur J Epidemiol* 2022;37:1107–24.
30 Schipf S, Schone G, Schmidt B, *et al*. [The baseline assessment of the German National Cohort (NAKO Gesundheitsstudie): participation in the examination modules, quality assurance, and the use of secondary data]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2020;63:254–66.
31 Dragano N, Reuter M, Greiser KH, *et al*. Soziodemografische und erwerbsbezogene Merkmale in der NAKO Gesundheitsstudie. *Bundesgesundheitsbl* 2020;63:267–78.
32 Streit F, Zillich L, Frank J, *et al*. Lifetime and current depression in the German National Cohort (NAKO). *World J Biol Psychiatry* 2023;24:865–80.
33 Sheehan DV, Lecrubier Y, Sheehan KH, *et al*. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59 Suppl 20:22–33.
34 Englbrecht M, Alten R, Aringer M, *et al*. Validation of Standardized Questionnaires Evaluating Symptoms of Depression in Rheumatoid Arthritis Patients: Approaches to Screening for a Frequent Yet Underrated Challenge. *Arthritis Care Res (Hoboken)* 2017;69:58–66.
35 Hitchon CA, Zhang L, Peschken CA, *et al*. Validity and Reliability of Screening Measures for Depression and Anxiety Disorders in Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)* 2020;72:1130–9.
36 Erhardt A, Gelbrich G, Klinger-König J, *et al*. Generalised anxiety and panic symptoms in the German National Cohort (NAKO). *World J Biol Psychiatry* 2023;24:881–96.
37 Spitzer RL, Kroenke K, Williams JBW, *et al*. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166:1092–7.
38 Kleineidam L, Stark M, Riedel-Heller SG, *et al*. The assessment of cognitive function in the German National Cohort (NAKO) – Associations of demographics and psychiatric symptoms with cognitive test performance. *World J Biol Psychiatry* 2023;24:909–23.
39 Schmiedek F, Kroehne U, Goldhammer F, *et al*. General cognitive ability assessment in the German National Cohort (NAKO) – The block-adaptive number series task. *World J Biol Psychiatry* 2023;24:924–35.
40 Englbrecht M, Alten R, Aringer M, *et al*. New insights into the prevalence of depressive symptoms and depression in rheumatoid arthritis - Implications from the prospective multicenter VADERA II study. *PLoS One* 2019;14:e0217412.
41 Englbrecht M, Bartz-Bazzanella P, Decken C, *et al*. Prevalence of Depressive Symptoms in Patients With Psoriatic Arthritis: Have Numbers Changed During the COVID-19 Pandemic? *Front Med (Lausanne)* 2021;8:748262.
42 Freier D, Englbrecht M, Höhne-Zimmer V. Höhere Prävalenz von depressiven und ängstlichen Symptomen bei Früharthritispatienten im Vergleich zur Normalbevölkerung. [Higher prevalence of depressive and anxiety symptoms in early arthritis patients in comparison to the normal population]. *Z Rheumatol* 2019;78:820–31.
43 Callhoff J, Albrecht K, Redeker I, *et al*. Disease Burden of Patients With Osteoarthritis: Results of a Cross-Sectional Survey Linked to Claims Data. *Arthritis Care Res (Hoboken)* 2020;72:193–200.
44 Straub RH, Pongratz G, Buttgereit F, *et al*. [Energy metabolism of the immune system: Consequences in chronic inflammation]. *Z Rheumatol* 2023;82:479–90.
45 Recio-Barbero M, Segarra R, Perez-Arbide E, *et al*. Letter to the editor: Gwinnutt JM, Toyoda T, Barraclough M, Verstappen SMM, Hornberger M, MacGregor A. Cognitive impairment in the immune-mediated inflammatory diseases compared with age-matched controls: Systematic review and meta-regression. *Semin Arthritis Rheum* 2023;62:152236.
46 Schmidt CO, Günther K-P, Goronzy J, *et al*. Frequencies of musculoskeletal symptoms and disorders in the population-based German National Cohort (GNC). *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2020;63:415–25.
47 Albrecht K, Binder S, Minden K, *et al*. Systematic review to estimate the prevalence of inflammatory rheumatic diseases in Germany. *Z Rheumatol* 2024;83:20–30.
48 Qin B, Wang J, Yang Z, *et al*. Epidemiology of primary Sjögren’s syndrome: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:1983–9.