

## ORIGINAL ARTICLE

# Health-related quality of life and depression among participants in the Sjögren's International Collaborative Clinical Alliance registry

Annie Chou,<sup>1</sup> John A Gonzales,<sup>2</sup> Troy E Daniels,<sup>1</sup> Lindsey A Criswell,<sup>3</sup> Stephen C Shiboski,<sup>4</sup> Caroline H Shiboski<sup>1</sup>

**To cite:** Chou A, Gonzales JA, Daniels TE, *et al.* Health-related quality of life and depression among participants in the Sjögren's International Collaborative Clinical Alliance registry. *RMD Open* 2017;**3**:e000495. doi:10.1136/rmdopen-2017-000495

Received 11 May 2017

Revised 1 August 2017

Accepted 30 August 2017

## ABSTRACT

**Objective** To examine health-related quality of life (HRQoL) and depression among participants in an international Sjögren's syndrome (SS) registry, comparing those with and without SS.

**Methods** Cross-sectional study of participants in the Sjögren's International Collaborative Clinical Alliance (SICCA) registry. The 2016 American College of Rheumatology/European League Against Rheumatism SS classification criteria were used to determine disease status. HRQoL was assessed using the Short Form 12, version 2 Health Survey to derive scores for physical component summary (PCS) and mental component summary (MCS). Depression was assessed using the 9-Item Patient Health Questionnaire. Multivariate linear and logistic regression analyses were performed to identify predictors of HRQoL and depression while controlling for potential confounders.

**Results** Among 2401 SICCA participants who had symptoms of dry eyes and dry mouth, 1051 had SS (44%) and 1350 did not (56%). After controlling for confounders, when compared with non-SS participants, those with SS had better PCS ( $p < 0.001$ ,  $\beta = 2.43$ , 95% CI 1.57 to 3.29), MCS ( $p = 0.002$ ,  $\beta = 1.37$ , 95% CI 0.50 to 2.23) and lower adjusted odds of depression ( $p < 0.001$ , OR 0.67, 95% CI 0.55 to 0.81). Other significant predictors of HRQoL and depression included employment, country of residence and use of medication with anticholinergic effect or for management of SS-related signs and symptoms.

**Conclusion** Our results suggest that among symptomatic patients, having a diagnosis of SS may be associated with better emotional and psychological well-being compared with patients without a diagnosis. Having a definitive diagnosis of SS may encourage patients to obtain a better understanding of their disease and have coping mechanisms in place to better manage their symptoms.

## INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disorder characterized by salivary and lacrimal gland dysfunction due to chronic inflammation. In addition to autoantibody production, a wide variety of other systemic manifestations, such as cutaneous vasculitis

## Key messages

### What is already known about this subject?

- ▶ Sjögren's syndrome (SS) is associated with significant morbidity, so exploring health-related quality of life (HRQoL) and depression are important first steps in developing strategies to improve it.

### What does this study add?

- ▶ This study explored the association between HRQoL and depression among individuals who fulfilled the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for SS using the Short Form 12, version 2 and the 9-Item Patient Health Questionnaire, respectively, among a large, well-characterized cohort of adults participating in the Sjögren's International Collaborative Clinical Alliance (SICCA) registry.
- ▶ We found that symptomatic individuals with SS participating in the SICCA registry had higher perceived HRQoL and lower odds of depression compared with individuals in the registry without SS.

### How might this impact on clinical practice?

- ▶ This suggests that in a population of symptomatic patients, those who have an actual diagnosis of SS fare better, with respect to HRQoL and depression, than those who do not. This finding underscores the importance of being able to provide patients with a disease classification status so that they may pursue appropriate treatment and other alternatives.

and musculoskeletal pain, may also develop.<sup>1</sup> SS is estimated to affect 0.06% individuals worldwide and has a strong female predominance with an estimated female to male ratio of 9:1.<sup>2</sup> As a chronic disease, SS can become progressively disabling as increasing oral and ocular dryness may interfere with basic daily functions.<sup>3-8</sup> Currently available therapeutic options for SS are palliative, and limited



CrossMark

<sup>1</sup>Department of Orofacial Sciences, School of Dentistry, University of California, San Francisco, California, USA

<sup>2</sup>F.I. Proctor Foundation, Department of Ophthalmology, University of California, San Francisco, California, USA

<sup>3</sup>Department of Medicine, School of Medicine, University of California, San Francisco, California, USA

<sup>4</sup>Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco, California, USA

## Correspondence to

Dr Annie Chou;  
Annie.Chou@ucsf.edu

research has been done to assess the effects of systemic medications on exocrine and extraglandular damage. Therefore, assessing health-related quality of life (HRQoL) has emerged as an important clinical outcome of patient-centered care in SS.

HRQoL is a multidimensional concept that describes aspects of quality of life, including self-perceived well-being and functionality, relating specifically to a person's health.<sup>9</sup> Compared with healthy controls, individuals with SS report significantly poorer physical capacity,<sup>10 11</sup> reduced productivity<sup>12</sup> and more cognitive deficiencies.<sup>13</sup> Patients with SS also carry significant symptom burden, highlighted by studies that demonstrate dryness-related discomfort to be associated with HRQoL impairment, depression and anxiety.<sup>14–18</sup> While oral and ocular dryness are strong predictors of diminished HRQoL in SS, these symptoms may be exacerbated by factors unrelated to SS, such as medication use, anxiety and allergies, which complicate this relationship. Therefore, the impact of SS on HRQoL and depression independent of oral and ocular symptoms should be examined.

In this analysis, we took advantage of the well-characterized Sjögren's International Collaborative Clinical Alliance (SICCA) dataset, which is the first international data registry that is geographically and socioeconomically diverse. It employs standardised questionnaires to collect data on a wide array of outcome measures, including HRQoL and depression. Therefore, the SICCA dataset provides unprecedented opportunity to evaluate HRQoL and depression among an international group of individuals with SS or with signs and symptoms suggestive of SS. The primary objective of this analysis is to compare HRQoL and depression scores of patients with SS to those without SS while exploring other relevant covariates and potential confounders. Furthermore, by focusing on symptomatic individuals with and without SS in this study, the association between SS and HRQoL and depression, unrelated to the effects of oral and ocular symptoms, is further explored.

## METHODS

### Study design and population

We conducted a cross-sectional study among participants in the SICCA registry. Enrolment occurred between 2004 and 2012 within nine academically based research sites located in seven countries (Argentina, China, Denmark, India, Japan, UK and the USA) and directed by investigators at the University of California San Francisco in the USA, where both the data coordinating center and biorepository are located. Details regarding the SICCA study design and population, including recruitment and eligibility criteria, have been previously described.<sup>19</sup> Additional information can also be found at <http://sicca-online.ucsf.edu>.

The present analysis involved all individuals enrolled in the SICCA registry for whom data relevant to the outcomes of interest were available. Individuals with

another concurrent autoimmune connective tissue disease diagnosis such as rheumatoid arthritis, systemic lupus erythematosus or sarcoidosis were excluded from the current study due to those disease associations with HRQoL and depression. Participants who reported either dry mouth or dry eyes (and not both) were also excluded from the study in order to establish uniform symptomatic and asymptomatic groups for our stratified analyses.

## Variables and measures

### Demographics

Information on gender, age, highest level of education (high school, college), employment (employed, unemployed), self-reported race/ethnicity (White, Hispanic, African American, Asian, Native American), country of residence (Argentina, China, Denmark, India, Japan, UK, USA), medication use with anticholinergic effects and systemic medication use for the management of SS-related symptoms (non-steroidal anti-inflammatory drugs (NSAIDs), cholinomimetic drugs, antimalarials and others (corticosteroids, alkylating agents, antineoplastic, tumour necrosis factor (TNF)-alpha inhibitors, disease-modifying antirheumatic drugs (DMARDs), anti-CD-20 and other immune-modifying biological agents)) were collected as part of the various questionnaires administered at the time of study entry. All of the aforementioned data were self-reported. In addition, trained SICCA team clinicians (including oral medicine specialists, ophthalmologists and rheumatologists) performed focused protocol-driven clinical evaluations, which assessed for oral, ocular and rheumatological features. All serological test results were obtained from the same Quest laboratory. SICCA questionnaires, data collection forms and protocols are available for review at <http://sicca-online.ucsf.edu>.

### HRQoL: SF-12v2 Health Survey

SICCA participants completed the Short Form 12, version 2 (SF-12v2) survey, which is a self-report health survey pertaining to the previous 4 weeks.<sup>20 21</sup> It is a validated alternative to its longer predecessor, the 36-Item Short Form (SF-36) health survey, and was created for studies with large sample sizes. This general health survey comprises 12 items representing eight subdomains of functional health and well-being: physical functioning (two items), role limitations due to physical problems (two items), bodily pain (one item), general health (one item), vitality (one item), social functioning (one item), role limitations due to emotional problems (two items) and mental health (two items). From these eight health subdomains, two summary scores can be derived: the physical component summary (PCS) and mental composite summary (MCS). Subscale and summary scores range from 0 to 100, with higher scores indicating better health. Generally, PCS and MCS are standardized to a mean of 50 and SD of 10 using a 2009 US general population normative sample provided by Quality Metric. For this analysis, we examined differences in PCS and MCS raw

scores between chosen characteristic subgroups (ie, age or SS classification) rather than the comparison of values to the US general population normative sample since this reference group would not serve as an adequate comparison group for this international study.

#### Depression: 9-Item Patient Health Questionnaire (PHQ-9)

Depressive symptoms were assessed using the PHQ-9.<sup>22</sup> Health professionals use the PHQ-9 to screen for major depressive disorders and to monitor treatment, with clinical symptoms measured over the previous 2 weeks. A cumulative PHQ-9 score is obtained through summation of responses from the nine questions, each of which take on values in the range of 0–3. The resulting score ranges between 0 and 27. The PHQ-9 yields an index of

depressive symptom severity with scores of 0–4 indicating no depression, 5–9 mild depression, 10–14 moderate depression, 15–19 moderately severe depression and 20–27 severe depression.

#### SS classification criteria

The 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) SS classification criteria<sup>23 24</sup> used in this study are based on the weighted sum of five items: anti-Sjögren-specific antibody A (SSA)SSA/Ro antibody positivity<sup>25</sup> and focal lymphocytic sialadenitis with a  $\geq 1$  focus/ $4\text{ mm}^2$  in a labial salivary gland biopsy,<sup>26</sup> each scoring 3; an abnormal ocular staining score of  $\geq 5$ ,<sup>27</sup> a Schirmer's test result of  $\leq 5\text{ mm}/5\text{ min}$  and an unstimulated salivary flow rate

**Table 1** Demographic characteristics by SS classification among 2527 SICCA\* participants

	SS participants n (%), (N=1117)	Non-SS participants n (%), (N=1410)	p Value
Age, median years (Q1–Q3)	52.4 (43–62)	53.5 (45–63)	0.03
Women	1049 (94)	1258 (89)	<0.001
Race/ethnicity			<0.001
African	33 (3)	35 (2)	
Asian/Pacific Islander	424 (38)	243 (17)	
White	508 (46)	903 (64)	
Hispanic	112 (10)	168 (12)	
American Indian	39 (3)	60 (4)	
Country of residence			<0.001
Argentina	122 (11)	202 (14)	
China	170 (15)	52 (4)	
Denmark	145 (13)	300 (21)	
India	48 (4)	30 (2)	
Japan	152 (14)	113 (8)	
UK	91 (8)	120 (9)	
USA	389 (35)	593 (42)	
College education	630 (58)	899 (64)	0.001
Employed	563 (50)	638 (45)	0.009
Anticholinergic medication†	253 (23)	549 (39)	<0.001
Medications‡			<0.001
NSAIDS	105 (9)	231 (16)	
Cholinomimetics	75 (7)	60 (4)	
Antimalarials	130 (12)	118 (8)	
Other immunosuppressants§	191 (17)	162 (11)	
None	616 (55)	839 (60)	

\*Participants from the Sjögren's International Collaborative Clinical Alliance registry.

†Participants who reported that they were taking a medication with anticholinergic effect at the time of study entry, such as antianxiety, antihypertensive, antidepressant, antihistamine/antiemetic, antipsychotic, antiparkinson, antiacne, decongestant, bronchodilator and muscle relaxant drugs.

‡Patient-reported systemic medications used for the management of SS-related symptoms and currently received at study entry.

§Include corticosteroids, alkylating agents, antimetabolites, tumour necrosis factor- $\alpha$  inhibitors, disease-modifying antirheumatic drugs, anti-CD-20 and other immune-modifying biological agents.

NSAIDS, non-steroidal anti-inflammatory drugs; SS, Sjögren's syndrome.

**Table 2** Sjögren's syndrome (SS)-related characteristics stratified by SS classification and symptoms among 2527 SICCA\* participants

	Symptomatic participants (total=2401)			Asymptomatic participants (total=126)		
	SS (N=1051)	Non-SS (N=1350)	p Value†	SS (N=66)	Non-SS (N=60)	p Value†
Symptoms, median years (Q1–Q3)						
Reported duration of dry mouth symptoms	4.0 (1.7–9.7)	2.9 (1.0–7.3)	0.002	NA	NA	NA
Reported duration of dry eye symptoms	4.3 (1.8–9.8)	3.9 (1.4–9.1)	0.22	NA	NA	NA
SS-related findings, n (%)						
Labial salivary gland with FLS and FS $\geq 1$ foci/4 mm	852 (82)	49 (4)	<0.001	44 (67)	3 (5)	<0.001
Anti-SSA/Ro-positive	799 (76)	44 (3)	<0.001	60 (91)	8 (13)	<0.001
OSS $\geq 5$ in at least one eye	838 (80)	468 (35)	<0.001	49 (74)	16 (27)	<0.001
Schirmer's test $\leq 5$ mm/5 min in at least one eye	614 (58)	389 (29)	<0.001	20 (30)	10 (17)	0.08
UWS flow rate $\leq 0.1$ mL/min	748 (71)	582 (43)	<0.001	17 (26)	6 (10)	0.02

\*Participants from the Sjögren's International Collaborative Clinical Alliance registry.

†Kruskal-Wallis test and  $\chi^2$  test used to determine the relationship between SS and non-SS.

FLS, focal lymphocytic sialadenitis; FS, focus score; OSS, ocular staining score; NA, not applicable; UWS, unstimulated whole saliva.

of  $\leq 0.1$  mL/min, each scoring 1. Individuals with signs and/or symptoms suggestive of SS who have a total score of  $\geq 4$  for the above items meet the criteria for primary SS.

### Statistical analysis

We summarized baseline characteristics of our study sample using frequencies and percentages for categorical variables and median/quartiles for continuous variables. HRQoL scores for each of the eight SF-12v2 subdomains and the two component summary scores (PCS and MCS) were summarized using the mean and SD. We used the  $\chi^2$  test to evaluate associations between categorical variables and the Kruskal-Wallis test to assess differences in distribution of continuous outcome variables between groups defined by categorical predictors. Interaction was detected when HRQoL outcome variables were stratified by the presence of symptoms (ie, oral and ocular dryness) and SS classification. To manage this interaction, multivariate analyses presented are restricted to the symptomatic subgroup. We used linear regression to assess marginal associations between HRQoL component scores, SS classification and other selected variables. Logistic regression was used to evaluate marginal associations between depression (defined as having a PHQ-9 score of  $\geq 10$ ) and these variables. Multivariate linear and logistic regression models were also fitted to explore the effects of adjustment for potential confounding variables, including demographic and socioeconomic characteristics. Candidate adjustment variables were limited to those that were marginally associated with these outcomes at the 10% significance level. Variables were retained in the final model if they were found to be associated with the outcome at a significance level of at most 5% or if their removal resulted in a  $\geq 10\%$  change in estimated

coefficients for the remaining covariates. Age, gender and country of residence were adjusted for in all models, regardless of statistical significance level in the unadjusted analysis. Diagnostic analyses were conducted to assess linearity, normality of residuals, multicollinearity and presence of outliers. All analyses were conducted using Stata V.12.0.

## RESULTS

### Demographic and sample characteristics

This study included 2527 SICCA participants, which represents a subset of the SICCA cohort who do not have a coexisting autoimmune connective tissue disease diagnosis and who also report having both dry eyes and dry mouth (or neither). One thousand one hundred seventeen participants met the ACR/EULAR classification criteria for SS, and 1410 did not (table 1). As shown in table 1, participants who met SS criteria and those who did not differed with respect to a number of sociodemographic characteristics. Of note, the proportion of Asian/Pacific Islander participants was significantly higher among SS participants (38%) than among those who did not meet SS criteria (17%). Similarly, participants from the China site had a higher representation among the SS group (15%) than among the non-SS group (4%). Not surprisingly, a higher proportion of non-SS participants (39%) than those with SS (23%) were taking a medication with anticholinergic effect.

### Quality of life and depression scores by SS status, stratified by oral and ocular symptoms

Two thousand four hundred one participants reported symptoms of dry eyes and dry mouth, including 1051

**Table 3** Health-related quality of life scores for SF-12v2 dimensions and PHQ-9 depression status stratified by SS classification and symptoms among 2527 SICCA\* participants

	Symptomatic participants (total=2401)			Asymptomatic participants (total=126)		
	SS (N=1051)	Non-SS (N=1350)	p Value†	SS (N=66)	Non-SS (N=60)	p Value†
SF-12v2, mean±SD						
Physical function	46.0±10.7	42.6±11.5	<0.001	52.2±8.4	52.6±7.2	0.76
Physical role functioning	44.2±10.3	40.1±10.4	<0.001	51.3±9.5	50.4±8.2	0.54
Bodily pain	44.5±11.3	39.9±11.6	<0.001	50.6±10.3	49.6±9.6	0.57
General health	41.8±10.7	40.5±11.2	0.004	44.5±10.6	46.8±10.4	0.22
Vitality	47.0±11.2	43.6±10.8	<0.001	53.2±11.7	53.2±11.9	0.97
Social functioning	46.0±10.4	42.7±11.2	<0.001	49.9±10.3	49.8±8.8	0.95
Emotional role functioning	44.6±11.3	42.0±11.8	<0.001	50.5±10.0	50.2±8.5	0.85
Mental health	46.5±10.6	44.2±10.5	<0.001	52.7±9.0	50.3±10.6	0.16
Physical component measure (PCS)	44.2±10.3	40.5±11.4	<0.001	49.6±8.8	50.2±7.6	0.66
Mental component measure (MCS)	46.4±10.3	44.3±10.8	<0.001	51.7±9.2	50.3±10.6	0.43
PHQ-9, n (%)			<0.001			0.20
No depression	439 (42)	388 (29)		55 (83)	41 (68)	
Mild	289 (27)	396 (29)		7 (11)	11 (18)	
Moderate	159 (15)	276 (20)		2 (3)	6 (10)	
Moderately severe	76 (7)	163 (12)		0 (0)	1 (2)	
Severe	39 (4)	97 (7)		2 (3)	1 (2)	

\*Participants from the Sjögren's International Collaborative Clinical Alliance registry.

†Kruskal-Wallis test and  $\chi^2$  test used to determine the relationship between SS and non-SS participants.

MCS, mental component summary; PCS, physical component summary; PHQ-9, 9-Item Patient Health Questionnaire; SF-12v2, Short Form 12, version 2; SS, Sjögren's syndrome.

with SS (44%) and 1350 without SS (56%) (table 2). There were 126 asymptomatic individuals, of whom 66 met SS criteria (52%) and 60 did not (48%). Symptomatic patients with SS had longer median duration of dry mouth symptoms compared with those without SS (4.0 vs 2.9 years,  $p=0.002$ ). While a similarly high proportion of symptomatic and asymptomatic SS participants had an ocular staining score (OSS)  $\geq 5$ , half the percentage of asymptomatic SS participants (30%) had a positive Schirmer's test compared with those with symptoms (58%).

Symptomatic participants with SS had higher mean SF-12v2 scores in all eight HRQoL subdomains, including summary scores PCS and MCS, compared with non-SS symptomatic participants (table 3). Similarly, symptomatic individuals with SS had fewer reported symptoms of depression (26%) compared with those without SS (39%) ( $p<0.001$ ). These results indicate that SICCA participants with SS had better self-perceived HRQoL and less depression compared with those without SS. Among asymptomatic participants, there were no statistically significant differences in HRQoL or depression levels between those with and without SS. The difference in statistical significance of HRQoL and depression levels uncovered in the symptomatic subgroup compared with the asymptomatic group, where none was found, suggested an interaction

of symptoms on the HRQoL/depression and SS status association. Therefore, in the subsequent multivariate analysis, we restricted the analysis to symptomatic SS participants.

#### Quality of life and depression in symptomatic SICCA participants: multivariate analyses

Multivariate analyses included 2401 symptomatic participants. After controlling for confounders, SS participants had a significantly higher adjusted mean PCS (ie, better physical HRQoL) compared with non-SS participants (table 4). Individuals living in the UK and China had a significantly higher mean PCS compared with those living in the USA. All unadjusted and adjusted regression coefficients, confidence intervals and p values are reported in tables 4 and 5, thus not duplicated in the text. In contrast, participants living in India had a lower mean score compared with those in the USA. Comparisons between other recruitment sites and the USA were not statistically significantly different. Use of medications with anticholinergic effect, antimalarials and other immunosuppressants were associated with lower mean PCS compared with not taking any of these medications. Also, being employed in a full-time occupation was associated with a higher mean PCS compared with not being employed.

**Table 4** Associations of subject characteristics with mean SF-12v2 physical component scale scores among 2401 SICCA\* participants with symptoms of dry eyes and dry mouth

	Unadjusted $\beta$ (95% CI)	Unadjusted p	Multivariable adjusted $\beta$ † (95% CI)	Multivariable adjusted p†
Age	-0.04 (-0.08 to 0.01)	0.01	0.04 (0.01 to 0.08)	0.01
Gender, female	0.76 (-0.83 to 2.34)	0.35	0.54 (-0.95 to 2.03)	0.47
Country of residence				
Argentina	1.04 (-0.36 to 2.44)	0.14	0.16 (-1.15 to 1.47)	0.81
China	4.88 (3.20 to 6.56)	<0.001	1.99 (0.26 to 3.73)	0.02
Denmark	-0.54 (-1.77 to 0.70)	0.40	-1.14 (-2.34 to 0.06)	0.06
India	-0.23 (-2.53 to 2.06)	0.84	-4.04 (-6.45 to 1.64)	0.001
Japan	0.98 (-0.65 to 2.61)	0.24	-1.30 (-2.87 to 0.27)	0.11
UK	5.55 (4.01 to 7.09)	<0.001	2.73 (1.24 to 4.22)	<0.001
USA	Reference		Reference	
Education, college	0.27 (-0.64 to 1.19)	0.59		
Employed	5.66 (4.81 to 6.51)	<0.001	5.29 (4.41 to 6.17)	<0.001
Meeting SS criteria	3.68 (2.79 to 4.57)	<0.001	2.43 (1.57 to 3.29)	<0.001
Anticholinergic medication	-6.46 (-7.36 to 5.56)	<0.001	-4.61 (-5.55 to 3.67)	<0.001
Medications‡				
None	Reference			
NSAIDS	-5.89 (-7.18 to 4.60)	<0.001	-4.38 (-5.63 to 3.13)	<0.001
Cholinomimetics	-0.64 (-2.55 to 1.27)	0.51	-1.42 (-3.29 to 0.44)	0.14
Antimalarials	-4.27 (-5.75 to 2.80)	<0.001	-4.03 (-5.47 to 2.59)	<0.001
Other immunosuppressants§	-4.89 (-6.17 to 3.61)	<0.001	-4.33 (-5.58 to 3.07)	<0.001

\*Participants from the Sjögren's International Collaborative Clinical Alliance registry.

†All factors with a p value  $\leq 0.10$  on univariate analysis entered into multivariate model; p value  $\leq 0.05$  to remain in final multivariate model.

‡Systemic medications used for the management of SS-related symptoms and currently received at study entry.

§Including corticosteroids, alkylating agents, antimetabolites, tumour necrosis factor-alpha inhibitors, disease-modifying antirheumatic drugs, anti-CD-20 and other immune modifying biological agents.

$\beta$ , beta coefficient; NSAIDS, non-steroidal anti-inflammatory drugs; SF-12v2, Short Form 12, version 2; SS, Sjögren's syndrome.

After controlling for other confounders, SS participants had a significantly higher adjusted mean MCS, reflecting better mental HRQoL, compared with non-SS participants (table 5). We found that those living in China and Denmark had a higher mean MCS compared with participants living in the USA, whereas those living in the UK, Argentina and Japan had lower mean scores. Also, participants who were taking medications with anticholinergic effect had a lower mean MCS compared with those who were not using any anticholinergic medication. No significant associations were found between MCS and education, employment or use of other medications commonly used in the management of SS-related symptoms.

Similarly, SS participants also had significantly lower adjusted odds of developing depression compared with those participants without SS (table 6). All unadjusted and adjusted ORs, CIs, and p values are reported in table 6, thus not duplicated in the text. Individuals living in China or Denmark also had lower odds of depression compared with those living in the USA whereas participants living in Argentina and Japan had higher odds of depression. Also, participants using medications with

anticholinergic effect, NSAIDS and cholinomimetics had higher odds of depression compared with individuals not taking any of these medications. Being employed in a full-time occupation was associated with a lower adjusted odds of depression compared with not being employed.

## DISCUSSION

Contrary to our initial hypotheses, we found that symptomatic SICCA participants with SS had better physical and mental HRQoL, and lower depression scores than those without SS. While studies on HRQoL and depression in SS are limited, most have demonstrated reduced quality of life and depression in SS populations. For instance, in a large SS cohort in the USA, Segal *et al* found reduced physical and mental function in every domain of the SF-36 compared with their healthy control group.<sup>14</sup> However, our results demonstrated an inverse relationship between HRQoL and SS classification when comparing symptomatic SICCA participants with SS with those without SS. After controlling for country of residence and other covariates, we found that individuals with SS had better

**Table 5** Associations of subject characteristics with mean SF-12v2 mental component scale scores among 2401 SICCA\* participants with symptoms of dry eyes and dry mouth

	Unadjusted $\beta$ (95% CI)	Unadjusted p	Multivariable adjusted $\beta$ † (95% CI)	Multivariable adjusted p†
Age	0.10 (0.07 to 0.13)	<0.001	0.11 (0.08 to 0.15)	<0.001
Gender, female	-1.16 (-2.69 to 0.36)	0.14	-1.17 (-2.68 to 0.34)	0.13
Country of residence				
Argentina	-3.14 (-4.48 to 1.80)	<0.001	-3.11 (-4.43 to 1.79)	<0.001
China	5.72 (4.10 to 7.34)	<0.001	3.82 (2.10 to 5.53)	<0.001
Denmark	1.42 (0.23 to 2.60)	0.02	1.21 (0.03 to 2.38)	0.04
India	1.12 (-1.08 to 3.33)	0.32	0.09 (-2.31 to 2.49)	0.94
Japan	-0.63 (-2.20 to 0.93)	0.43	-1.65 (-3.23 to 0.06)	0.04
UK	-1.83 (-3.31 to 0.35)	0.02	-3.21 (-4.70 to 1.73)	<0.001
USA	Reference		Reference	
Education, college	0.27 (-0.64 to 1.19)	0.56		
Employed	0.28 (-0.56 to 1.13)	0.51		
Meeting SS criteria	2.17 (1.32 to 3.03)	<0.001	1.37 (0.50 to 2.23)	0.002
Anticholinergic medication	-3.73 (-4.62 to 2.84)	<0.001	-3.48 (-4.42 to 2.54)	<0.001
Medications‡				
None	Reference			
NSAIDS	-1.03 (-2.30 to 0.25)	0.11		
Cholinomimetic drugs	-0.85 (-2.73 to 1.04)	0.38		
Antimalarials	-1.44 (-2.90 to 0.02)	0.06		
Other immunosuppressants§	0.23 (-1.03 to 1.50)	0.72		

\*Participants from the Sjögren's International Collaborative Clinical Alliance registry.

†All factors with a p value  $\leq 0.10$  on univariate analysis entered into multivariate model; p value  $\leq 0.05$  to remain in model.

‡Systemic medications used for the management of SS-related symptoms and currently received at study entry.

§Include corticosteroids, alkylating agents, antimetabolites, tumour necrosis factor- $\alpha$  inhibitors, disease-modifying antirheumatic drugs, anti-CD-20 and other immune-modifying biological agents.

$\beta$ , beta coefficient; NSAIDS, non-steroidal anti-inflammatory drugs; SF-12v2, Short Form 12, version 2; SS, Sjögren's syndrome.

HRQoL and less depression than those without SS. This counterintuitive finding is likely the result of the heterogeneous makeup of the SICCA cohort, specifically our comparison (non-SS) group. Having symptoms of dry eyes and dry mouth in a non-SS setting can be associated with having other conditions such as anxiety, depression and/or other systemic diseases such as fibromyalgia.<sup>28-31</sup>

In fact, the non-SS group had a higher reported prevalence of moderate to severe depression (39% vs 26%,  $p < 0.001$ ) and reported higher use of anticholinergic medication (39% vs 23%,  $p < 0.001$ ) than SS participants. Anticholinergic agents are a broad class of medications that include antidepressants, anxiolytics, antipsychotics, sleep aids and antihistamines/antiemetics, which themselves can produce sicca symptoms as well. Thus, when compared with this distinct subgroup of non-SS individuals, it may not be surprising to find that individuals with SS have better HRQoL and reduced depression levels.

Our results may also suggest that having a disease diagnosis may positively influence HRQoL while having symptoms without a known diagnosis may negatively impact it. Because many SICCA participants were recruited from

existing SS clinics or from rheumatology offices, many individuals who met the ACR/EULAR classification criteria in our study had previously received a clinical diagnosis of SS. However, there was a subset of individuals who presented with symptoms suggestive of SS, such as dry eyes and dry mouth, with no known disease diagnosis and who did not meet the classification criteria of SS. Because many autoimmune rheumatic diseases have overlapping disease profiles, individuals may not be easily categorized into an established clinical entity like SS. According to a study by Jones *et al*, at least 40% of patients in general practice do not have a diagnostic label, leaving most patients psychologically and emotionally vulnerable.<sup>32</sup> Without a known diagnosis, symptoms are difficult to manage long term. Among our SS subgroup, 36% of individuals had their disease managed with medications for SS such as cholinomimetics, antimalarials, corticosteroids, DMARDs and other immunomodulating agents compared with 23% of the non-SS subgroup. With the emergence of new biological agents, patients with a diagnosis of SS may also seek alternative treatments for SS through clinical trials. Furthermore, having a diagnosis

of SS enables patients to seek emotional and psychological support from other patients with SS in support groups. Therefore, having a definitive diagnosis of SS may encourage patients to obtain a better understanding of their disease and have coping mechanisms in place to better manage their symptoms. Healthcare providers must carefully evaluate disease phenotypic features so that they may provide patients with a disease classification status to allow patients to develop effective coping and disease management strategies.

Several demographic and socioeconomic factors were also associated with HRQoL and depression in our analysis. We found that older age was associated with higher mental HRQoL and lower odds of depression. It is well established in the literature that ageing is associated with a reduction in anxiety and depression over time. A meta-analysis by Jorm *et al* examined the occurrence of anxiety, depression and general distress across the adult life span and found that there was an initial rise across age groups, which was then followed by a significant drop in anxiety and depression.<sup>33</sup> We also found that country

of residence was associated with specific varying HRQoL and depression scores. This is likely explained by differences in psychological and cultural factors that may affect perceptions of HRQoL within each country. Our observation that recruitment from China was positively associated with PCS and MCS and negatively associated with depression could be impacted by the fact that prevalence of SS was higher among participants from that country relative to other registry sites, although controlling for country of residence in our multivariate analysis should address this. Furthermore, we found that employment is associated with better health outcomes, such as better physical health and less depression in our study population. Perhaps having job security promotes income stability thereby stimulating better physical and mental health.

A unique strength of this study was the use of the well-characterized SICCA registry, which is an international database consisting of geographically and socio-economically diverse individuals with SS or signs and/or symptoms suggestive of SS. Because of the suggested

**Table 6** Associations of subject characteristics with depression (PHQ-9 score  $\geq$  moderate depression) among 2401 SICCA\* participants with symptoms of dry eyes and dry mouth

	Unadjusted OR (95% CI)	Unadjusted p	Multivariable adjusted OR† (95% CI)	Multivariable adjusted p†
Age	0.99 (0.98 to 0.99)	<0.001	0.98 (0.97 to 0.98)	<0.001
Gender, female	0.79 (0.58 to 1.08)	0.14	0.85 (0.61 to 1.20)	0.37
Country of residence				
Argentina	1.49 (1.15 to 1.93)	0.003	1.64 (1.25 to 2.15)	<0.001
China	0.13 (0.08 to 0.23)	<0.001	0.24 (0.14 to 0.43)	<0.001
Denmark	0.68 (0.53 to 0.86)	0.002	0.72 (0.55 to 0.95)	0.02
India‡	NA		NA	
Japan	1.07 (0.79 to 1.46)	0.64	1.47 (1.05 to 2.04)	0.02
UK	0.70 (0.52 to 0.95)	0.02	1.00 (0.72 to 1.39)	0.99
US	Reference		Reference	
Education, college	1.06 (0.89 to 1.26)	0.52		
Employed	0.79 (0.67 to 0.94)	0.007	0.63 (0.52 to 0.76)	<0.001
Meeting SS criteria	0.54 (0.45 to 0.64)	<0.001	0.67 (0.55 to 0.81)	<0.001
Anticholinergic medication	2.70 (2.26 to 3.22)	<0.001	2.05 (1.68 to 2.50)	<0.001
Medications§				
None	Reference			
NSAIDs	2.03 (1.59 to 2.59)	<0.001	1.58 (1.21 to 2.05)	0.001
Cholinomimetics	1.76 (1.23 to 2.53)	0.002	1.62 (1.09 to 2.41)	0.02
Antimalarials	1.78 (1.34 to 2.35)	<0.001	1.35 (0.99 to 1.83)	0.06
Other immunosuppressants¶	1.16 (0.89 to 1.49)	0.27	1.08 (0.81 to 1.44)	0.59

\*Participants from the Sjögren's International Collaborative Clinical Alliance registry.

†All factors with a p value  $\leq$  0.10 on univariate analysis entered into multivariate model; p value  $\leq$  0.05 to remain in final model.

‡Item Personal Health Questionnaire (PHQ-9) was not administered to individuals recruited from India.

§Systemic medications used for the management of SS-related symptoms and currently received at study entry.

¶Include corticosteroids, alkylating agents, antimetabolites, tumour necrosis factor- $\alpha$  inhibitors, disease-modifying antirheumatic drugs, anti-CD-20 and other immune-modifying biological agents.

NA, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; SS, Sjögren's syndrome.



interaction of symptoms on the HRQoL/depression and SS status relationship, and because of the small number of asymptomatic non-SS individuals, we limited our multivariate analysis to symptomatic individuals. Although this may not have allowed us to thoroughly explore the association of symptom burden of SS with respect to HRQoL and depression, it allowed us to explore this relationship independent of the effect of oral and ocular symptoms. The main limitation of our study is the absence of a healthy control group. Even among the 60 asymptomatic non-SS individuals in the SICCA cohort, 13% were positive for anti-SSA/Ro antibody, and 27% had OSS  $\geq 5$ , suggesting some disease activity in this small group. Furthermore, because of the cross-sectional nature of the study, it is unclear if depression and poor HRQoL are a consequence or a cause of ocular and oral symptoms in the non-SS subgroup.

In conclusion, our focus on symptomatic individuals for the multivariate analysis allowed us to demonstrate the relationship between SS with respect to HRQoL and depression independent of oral and ocular dryness. Our findings suggest that obtaining a proper diagnosis is important for patient management so that appropriate treatment may be rendered to improve patient's overall HRQoL.

**Acknowledgements** We would like to express our gratitude to all the participants in the Sjögren's International Collaborative Clinical Alliance.

**Collaborators** In addition to the listed authors, many other professional collaborators in the Sjögren's International Collaborative Clinical Alliance have been essential to the conduct of this project. Their names and roles follow: University of California, San Francisco, USA—Oral Pathology: D Cox, R Jordan, JS Greenspan; Rheumatology: D Lee, K Sack; Ophthalmology: J Whitcher, T Lietman, N McNamara; Oral Medicine: A Wu; Operations Director: Y DeSouza; Clinical Coordinator/Phlebotomy: D Drury; Clinical Coordinator: A Do; Clinical Assistant: L Scott; Statistician/Programmer: M Lam; Data Manager: J Nespeco; Finance Director: J Whiteford; Administrative Assistant: M Margaret. University of Buenos Aires and German Hospital, Buenos Aires, Argentina—Stomatology: HE Lanfranchi, I Adler, AC Smith, AM Bisio, MS Gandolfo; Ophthalmology: AM Heidenreich; Rheumatology: CF Vollenweider; Oral Pathology: AM Chirife, A Keszler; Specimen Processing: S Daverio; Group Coordinator: V Kambo. Peking Union Medical College Hospital, Beijing, China—Rheumatology: Y Jiang, D Xu, J Su, Y Zhao, Y Dong; Stomatology/Pathology: D Du; Stomatology/LSG biopsies: H Wang, Z Li, J Xiao; Specimens/Rheumatology: Q Wu; Phlebotomy: C Zhang, W Meng; Project Assistant: J Zhang. Copenhagen University Hospital, Glostrup, Denmark—Ophthalmology: S Johansen, S Hamann, J Lindegaard; Oral Medicine: M Schiødt, J Schiødt, H Holm; Rheumatology: P Helin; Oral Pathology: P Ibsen; Group Coordinators/Specimen Handling: AM Manniche, SP Kreuztmann. Kanazawa Medical University, Ishikawa, Japan—Rheumatology: H Umehara, Y Masaki, T Sakai, S Sugai; Ophthalmology: K Kitagawa, N Shibata; Stomatology: M Honjo; Oral Pathology: N Kurose, T Nojima; Specimen Processing: T Kawanami; Hematology/Immunology: T Sawaki; Group Coordinator: K Fujimoto. King's College London, UK—Rheumatology: B Kirkham; Ophthalmology: G Larkin; Pathology: E Odell, P Morgan; Specimen Processing: L Fernandes-Naglik; Oral Medicine: S Challacombe, P Shirlaw, B Varghese-Jacob. University of Pennsylvania, Philadelphia, Pennsylvania, USA—Rheumatology: FB Vivino, S Seghal, R Mishra; Ophthalmology: V Bunya, M Massaro-Giordano; Otolaryngology: SK Abboud; Oral Medicine: A Pinto, YW Sia; Group Coordinator: K. Dow. Johns Hopkins University, Baltimore, Maryland, USA—Rheumatology: AN Bear; Ophthalmology: S Ingridi; Oral Medicine: W Henderson; Otolaryngology: C Gourin; Group Coordinator: A Keyes. Aravind Eye Hospital, Madurai, India—Co-Directors: M Srinivasan, J Mascarenhas, M Das, A Kumar; Ophthalmology: Pallavi Joshi; Physician: R Banushree; Surgeon: U Kim; Oral Medicine: B Babu; Administration: A Ram, Saravanan, Kannappan; Group Coordinator: N Kalyani.

**Contributors** All authors and coauthors contributed to the design, acquisition, analysis and interpretation for the work; drafting the work and revising it; final approval of this version; and agreement to be accountable for the work.

**Funding** National Institutes of Health (National Institute for Dental and Craniofacial Research (NIDCR), National Eye Institute, and Office of Research on Women's Health) contract N01 DE32636 and NIDCR contract HHSN268201300057C.

**Competing interests** None declared.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

## REFERENCES

- Malladi AS, Sack KE, Shiboski SC, *et al.* Primary Sjögren. *Arthritis Care Res* 2012;64:911–8.
- Patel R, Shahane A. The epidemiology of Sjögren. *Clin Epidemiol* 2014;6:247–55.
- Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. *Arch Intern Med* 2004;164:1275–84.
- Ergun S, Cekici A, Topcuoglu N, *et al.* Oral status and Candida colonization in patients with Sjögren's Syndrome. *Med Oral Patol Oral Cir Bucal* 2010;15:e310–e315.
- Kruszka P, O'Brian RJ. Diagnosis and management of Sjögren syndrome. *Am Fam Physician* 2009;79:465–70.
- Fox PC, Bowman SJ, Segal B, *et al.* Oral involvement in primary Sjögren syndrome. *J Am Dent Assoc* 2008;139:1592–601.
- Carr AJ, W f n, Figueiredo F, *et al.* *Br Dent J* 2012;213:353–7.
- Liu KC, Huynh K, Grubbs J, *et al.* Autoimmunity in the pathogenesis and treatment of keratoconjunctivitis sicca. *Curr Allergy Asthma Rep* 2014;14:403.
- Zack MM; Centers for Disease Control and Prevention (CDC). Health-related quality of life—United States, 2006 and 2010. *MMWR Suppl* 2013;62:105–11.
- Bowman SJ, Booth DA, Platts RG. Measurement of fatigue and discomfort in primary Sjogren. *Rheumatology* 2004;43:758–64.
- Strömbeck B, Ek Dahl C, Manthorpe R, *et al.* Physical capacity in women with primary Sjögren. *Arthritis Rheum* 2003;49:681–8.
- Hackett KL, Newton JL, Frith J, *et al.* Impaired functional status in primary Sjögren's syndrome. *Arthritis Care Res* 2012;64:1760–4.
- Segal BM, Pogatchnik B, Holker E, *et al.* Primary Sjogren. *Acta Neurol Scand* 2012;125:272–8.
- Segal B, Bowman SJ, Fox PC, *et al.* Primary Sjögren. *Health Qual Life Outcomes* 2009;7:46.
- Kotsis K, Voulgari P V, Tsifetaki N, *et al.* Illness perceptions and psychological distress associated with physical health-related quality of life in primary Sjögren. *Rheumatol Int* 2014;34:1671–81.
- Segal B, Thomas W, Rogers T, *et al.* Prevalence, severity, and predictors of fatigue in subjects with primary Sjögren's syndrome. *Arthritis Rheum* 2008;59:1780–7.
- Rostron J, Rogers S, Longman L, *et al.* Health-related quality of life in patients with primary Sjögren. *Gerodontology* 2002;19:53–9.
- Westhoff G, Dörner T, Zink A. Fatigue and depression predict physician visits and work disability in women with primary Sjögren. *Rheumatology* 2012;51:262–9.
- Daniels TE, Criswell LA, Shiboski C, *et al.* An early view of the international Sjögren. *Arthritis Rheum* 2009;61:711–4.
- Maruish ME. *User's manual for the SF-12v2 Health Survey*. 3<sup>rd</sup> ed. Lincoln, RI: Quality Metric Incorporated, 2012.
- Ware JE, Kosinski M, Bjorner JB, *et al.* *How to score version 2 of the SF-12 health survey (with a supplement documenting version 1)*. Lincoln, RI: Quality Metric Incorporated, 2002.
- Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.
- Shiboski CH, Shiboski SC, Seror R, *et al.* 2016 American College of Rheumatology/European League against Rheumatism classification criteria for primary Sjögren's syndrome. *Ann Rheum Dis* 2017;76:9–16;76:9–16.
- Shiboski CH, Shiboski SC, Seror R, *et al.* American College of Rheumatology/European League against Rheumatism classification criteria for primary Sjögren. *Arthritis Rheum* 2016;76:9–16;76:9–16.

25. Baer AN, McAdams DeMarco M, Shiboski SC, *et al.* The SSB-positive/SSA-negative antibody profile is not associated with key phenotypic features of Sjögren's syndrome. *Ann Rheum Dis* 2015;74:1557–61.
26. Daniels TE, Cox D, Shiboski CH, *et al.* Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren. *Arthritis Rheum* 2011;63:2021–30.
27. Witcher JP, Shiboski CH, Shiboski SC, *et al.* Daniels T E. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren. *Am J Ophthalmol* 2010;149:405–15.
28. Castrejón-Pérez RC, Borges-Yáñez SA, Irigoyen-Camacho ME, *et al.* Negative impact of oral health conditions on oral health related quality of life of community dwelling elders in Mexico city, a population based study. *Geriatr Gerontol Int* 2017;17:744–52.
29. Locker D, status D. Dental status, xerostomia and the oral health-related quality of life of an elderly institutionalized population. *Spec Care Dentist* 2003;23:86–93.
30. Sheiham A. Oral health, general health and quality of life. World Health Organization. *Bull World Health Organ* 2005;83:644.
31. Ayaki M, Kawashima M, Negishi K, *et al.* Sleep and mood disorders in dry eye disease and allied irritating ocular diseases. *Sci Rep* 2016;6:22480.
32. Jones R, Barraclough K, Dowrick C. When no diagnostic label is applied. *BMJ* 2010;340:c2683.
33. Jorm AF. Does old age reduce the risk of anxiety and depression? A review of epidemiological studies across the adult life span. *Psychol Med* 2000;30:11–22.