HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2021 September 01.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2020 September ; 72(9): 1315–1322. doi:10.1002/acr.24014.

Sjögren's Syndrome is Associated With Reduced Lifetime Sex Hormone Exposure: A Case-Control Study

Sara S. McCoy, MD[1], **Emmanuel Sampene, PhD**[2], **Alan N. Baer, MD**[3]

[1]Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI;

[2]Department of Biostatistics, University of Wisconsin School of Medicine and Public Health Madison, Wisconsin.

[3]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

Abstract

Objective: To test whether cumulative estrogen exposure, as determined by age at menarche, age at menopause, female hormone use, hysterectomy, and parity, has an effect on the development of primary Sjögren's syndrome (pSS).

Methods: We performed a case-control study of 2680 women from the Sjögren's International Collaborative Clinical Alliance (SICCA) registry, including 1320 pSS and 1360 participants with sicca symptoms but no key features of pSS ("sicca controls"). Composite estrogen score (CES) was calculated by point assignment for early menarche (≤ 10 years), high parity (>3 pregnancies), hysterectomy, use of hormone therapy, and late menopause (≥53 years). Cumulative menstrual cycling (CMC) was calculated as years menstruating minus time pregnant.

Results: Using a regression model adjusting for age, recruitment site, ethnicity, education, employment status, and smoking, we observed a progressive inverse trend between pSS and CES. The odds ratio (OR) and 95% confidence interval (CI) were as follows for the sicca control group: CES1, OR 0.8[95% CI, 0.67–0.99]; CES 2, OR 0.7[95% CI, 0.57–0.97]; CES 3, OR 0.5[95% CI, 0.30–0.86]. This finding was corroborated by analysis of CMC. At the highest level of CMC within the postmenopausal group there was a 24% reduction in cumulative sex hormone exposure among pSS registrants relative to controls.

Conclusions: Women with pSS have lower estrogen exposure and CMC compared to a sicca control. Increasing estrogen exposure was negatively associated with development of pSS. Further longitudinal studies of sex hormone exposure in pSS are needed to confirm these findings.

Corresponding author: Sara McCoy, MD, University of Wisconsin, School of Medicine and Public Health, 1685 Highland Avenue, Madison, WI 53705-2281, ssmccoy@medicine.wisc.edu.

Conflicts of interest statement:The authors of this paper have no current financial support or other benefits from commercial sources for the reported work, or any other financial interests which could create a potential conflict of interest or appearance of a conflict of interest with regard to the work.

Introduction

Primary Sjögren's syndrome (pSS) is a disease characterized clinically by oral and ocular sicca and pathologically by lymphocytic infiltration of the lacrimal and salivary glands. Females are affected 10 times more often than males, making pSS the most female-predominant autoimmune disease (1). Of further interest, the age of onset of pSS typically occurs around the time of menopause when female sex hormones decrease precipitously (1). Both the female predominance and the perimenopausal time of disease onset implicate a role for sex hormones in the pathogenesis of pSS.

Various sex hormones may play a role in the pathogenesis of pSS, including dehydroepiandrosterone (DHEA), prolactin, and estrogen (2–4). However, few epidemiologic studies have examined reproductive or menstrual history and development of pSS. Small observational studies have failed to demonstrate an association of pSS with age of menarche or menopause (5, 6).

We sought to investigate a pathogenic role for sex hormone exposure in pSS through an analysis of the Sjögren's International Collaborative Clinical Alliance (SICCA) registry, an NIH-funded international project with more than 3,500 registrants (7). We examined reproductive and menstrual factors and pSS prevalence in 1320 female pSS compared to 1360 female registrants who did not have pSS. This study represents the largest study to date evaluating sex hormone exposure with the primary aim to investigate whether reproductive or menstrual history is associated first with the development of pSS and second with specific pSS phenotypic features.

Methods

Study population

SICCA is an NIH-funded international registry, based at the University of California, San Francisco, that enrolled individuals with suspected or established pSS from 2003 to 2012 (7). Participants were enrolled from nine international research institutions. Inclusion criteria included sicca symptoms, multiple dental caries without other risk factors, a previous diagnosis of pSS, bilateral parotid enlargement, or abnormal serology (antinuclear antibody (ANA), rheumatoid factor (RF), anti-SSA antibody, or anti-SSB antibody). To be eligible, participants had to be at least 21 years old and capable of signing informed consent. They were also excluded if they had known hepatitis C, human immunodeficiency virus, past head and neck radiation, graft-versus-host-disease, active tuberculosis, amyloidosis, sarcoidosis, current treatment with daily glaucoma eye drops, vision corrective corneal surgery in the last five years, cosmetic eyelid surgery, or a physical or mental condition that would impede study participation. As per the Helsinki Declaration, informed consent was provided by all participants.

Once enrolled in the registry, all participants completed an initial visit that included an interview and questionnaires, physical examination, blood, tear, and saliva collection, and labial salivary gland biopsy. All examinations and data collection were performed adhering to a uniform protocol at each SICCA site. Evaluation for other autoimmune disease

including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) was performed on all registrants with subsequent classification as SLE or RA if they met American College of Rheumatology (ACR) criteria. Details of enrollment procedures are provided at http://sicca.ucsf.edu/ and previously described in the literature (8, 9).

The current study included female registrants who fulfilled the ACR/European League Against Rheumatism (EULAR) 2016 criteria for pSS (10) who did not have another autoimmune disease. The control group was defined by the presence of at least one objective sicca sign but lacked both an anti-SSA antibody and a biopsy showing focal lymphocytic sialadenitis with a focus score of ≥1. Sicca signs were defined as unstimulated whole salivary flow (UWS) ≤0.1ml/minute, maximum ocular staining score (OSS) ≥5, and Schirmer's test ≤5mm/5 min for baseline mean Schirmer's of both eyes.

Data/Outcome collection

Menstrual and reproductive history.—Menstrual history included age of menarche (<12, 12, 13, ≥14 years), age of menarche ≤10 years (binary variable with age cut off at 10 years), age of menopause (<46, 46–50, 51–52, 53–55, ≥56 years), and age of menopause ≥ 53 years (binary variable with age cut off of 53 years). Reproductive history included number of pregnancies, number of full term pregnancies, number of pregnancies resulting in miscarriage (1^{st}, 2^{nd} and 3^{rd} term), use of female hormones at the time of enrollment (birth control pills, estrogen/progestin as pills, patches or injections), and hysterectomy history (no information was available on oophorectomy history).

Composite and cumulative scores.—To calculate composite estrogen score (CES), one point was assigned for each of the following variables: early menarche (≤ 10 years), high parity (>3 pregnancies), hysterectomy, use of hormone therapy, and late menopause (≥53 years) (11). CES total score ranged from zero to five. Hysterectomy is most commonly indicated for fibroids, a benign tumor dependent on estrogen presence (12, 13). Thus, hysterectomy without oophorectomy serves as a surrogate marker of estrogen exposure and was included in the CES as in previous similar composite scores (11, 14). The diagnosis date of pSS frequently lags behind onset of this disease; thus, we utilized onset of sicca symptoms as an indicator of date of onset of pSS. Cumulative menstrual cycling (CMC) years for premenopausal registrants were calculated as the age of the registrant minus years since first sicca symptom onset, menarche age, and time pregnant (15–17). For each live-born child, 0.75 years (nine months) were subtracted and for each miscarriage/stillborn, 0.25 years (three months) were subtracted (18). CMC years for postmenopausal women was calculated as age of menopause or date of onset of sicca symptoms (whichever was first) minus age of menarche and time pregnant. CMC was reported in quartiles or quintiles based on population distribution.

Variables related to pSS and disease severity.—Phenotypic characteristics of pSS including OSS, UWS, Schirmer's test score, arthritis (joint stiffness>1 hour, joint pain or swelling, or synovitis on examination), RF, anti-SSA antibody, focus score ≥1, and germinal center presence on labial gland biopsy. Germinal center presence was assessed only on tissue sections stained with Haemotoxylin and Eosin (H&E). Additional pSS variables included

presence of lymphadenopathy, parotid/submandibular gland swelling, or a history of lymphoma, cutaneous vasculitis, interstitial lung disease (ILD), glomerulonephritis, renal tubular acidosis, interstitial nephritis, anemia, thrombocytopenia, lymphopenia, and neutropenia. The top ten most prevalent phenotypic features of pSS were selected for analysis of association with pSS. Less frequent phenotype features were present in such low numbers that a meaningful association could not be established.

Data Analysis

This is a case-control study of women from the SICCA registry. Covariates included age, referral source, race, education level, employment status, smoking status, and recruitment site. Since all patients were women, there was no need to account for sex in the model. Differences in baseline characteristics by pSS and controls groups were compared via Chi-square test for categorical variables and t-test for continuous variables. Multivariable logistic regression was used for outcomes against the predictors of interest and all results are interpreted in terms of odds ratios. CMC was divided into quartiles, with the lowest quartile as reference group. We used Spearman's rho correlation coefficient to analyze the correlation between CES and CMC. Statistical analyses were performed using STATA software, version 15 (Stata Company, College Station, Texas).

Results:

Demographic Characteristics

2680 women were included in the study, resulting in a case-control study of 1320 pSS and 1360 sicca-control registrants. Demographic characteristics of the pSS and the sicca control group are presented in Table 1. The mean ages (±standard deviation [SD]) of the pSS and the sicca control group were 52.04±13.45 and 54.04±12.93 years, respectively. Referral source was similar between sicca-control and pSS; however, age, ethnicity, tobacco use, education, employment, and recruitment site varied between the two groups (Table 1).

Association between pSS *and menstrual/reproductive history*

Statistical analyses are reported for CES categories of 1 to ≥3, given the paucity of registrants with CES levels of four or higher. pSS registrants had significantly reduced cumulative estrogen exposure, when compared to controls, as measured by CES1 to CES≥3 (Table 2). This risk reduction increased progressively from the CES1 to CES≥3 strata in the sicca control group. pSS registrants were half as likely to have had CES≥3 compared to sicca controls (OR 0.5 [95% CI, 0.30–0.86]). This finding was corroborated by the analysis of CMC, after adjusting for covariates (Table 2). pSS was associated with lower CMC compared to sicca controls. In the premenopausal group there was significant reduction in risk within the 2nd and 3rd quartile (3rd quartile OR 0.49 [95% CI 0.30–0.80]) but this trend did not reach significance in the 4th quartile (OR 0.69 [95% CI 0.38–1.26]). Similarly, there was a trend toward reduced CMC in pSS compared to sicca control in the post-menopausal group, although statistical significance was not achieved (4th quartile OR 0.76 [95% CI 0.56–1.04]).

When individual components of reproductive and menstrual history were compared between pSS and sicca control, the latter had lower odds of hysterectomy (OR 0.71 [95% CI 0.57–0.89]), younger age of menarche (p=<0.00001), and more registrants currently taking female hormones (p<0.001) (Table 3). pSS had a trend toward young age of menarche (≤10 years) that did not reach significance (p=0.059). The age of menarche followed a Gaussian distribution. There was no clear association between pSS and other individual components of menstrual and reproductive history including pregnancies, miscarriages, and menopause. There was weak positive association between CES and premenopausal CMC (Spearman's rho=0.22, p<0.0001) and no association between CES and postmenopausal CMC (Spearman's rho=−0.01, p=0.61).

Association between reproductive history and phenotypic characteristics of pSS

Statistical analyses are reported for CES levels of 1–3, given the paucity of registrants with CES levels of four or higher. Among pSS registrants with CES levels of three compared to those with CES levels of zero, there was a statistically significant reduced risk of abnormal OSS, hypergammaglobulinemia, RF, and anti-SSA antibodies and increased risk of arthritis (Table 4). There was no association between CES and UWS, Schirmer's test score, germinal center-like structures, anemia, focus score, or RF. These findings were not corroborated by an analysis of CMC. Indeed, greater CMC was inversely associated with inflammatory arthritis. CMC was associated with abnormal UWS in premenopausal and postmenopausal groups, whereas CMC was inversely associated with abnormal Schirmer's test score and OSS in the premenopausal group. No association was seen between CMC and labial gland biopsy germinal center-like structures, anemia, hypergammaglobulinemia, focus score, RF, or anti-SSA antibody.

Discussion

This case-control study utilizing data from the SICCA registry demonstrates an inverse association between risk of pSS and both CMC and CES. This relationship was progressive in CES, suggesting a dose-response between pSS and historical reproductive hormone exposure. We adopted accepted measures of systemic sex hormone exposure widely used in epidemiologic studies, the CES and CMC, for use with data available in the SICCA registry (11, 15–21).

Although the CES and CMC both showed reduced odds of pSS with greater systemic sex hormone exposure, the CMC did not parallel the same dose-response that CES demonstrated. The discordance between CES and CMC might be explained by several factors. First, the CES is a composite score of multiple factors associated with greater female sex hormone exposure whereas the CMC evaluates only duration of menstruation as a sex hormone exposure event. Thus, the CES might have greater power to detect a difference in odds of pSS based on the higher number of female sex hormone exposure events included in this composite score. Second, the other individual components of the CES might have a greater influence on pSS than duration of menstruation included in the CMC. The CES includes both hysterectomy and hormone use, both factors that are significant when evaluated individually. Finally, CMC could also play a role in the development of dry eye or

mouth symptoms, reducing the ability to detect a difference between the pSS and control population.

Previous observational studies examined the relationship between pSS and reproductive and menstrual factors. One such study identified a possible increased risk of pSS with ≥1 pregnancy (5), but we could not confirm this finding. Additionally, previous studies did not find significant association between reproductive and menstrual history and pSS (5, 6). However, these studies were smaller than the current reported case-control study.

Our findings are consistent with previously reported studies that show greater reproductive hormone exposure prior to clinical onset of disease might protect against the development of pSS. This would also be consistent with the epidemiology of pSS in which the onset is typically in the perimenopausal time-period, upon estrogen and progesterone withdrawal. In humans, breast cancer patients treated with aromatase inhibitors develop pSS at increased frequency (4). Mouse models provide additional support for the protective effect of estrogen. Mice lacking aromatase have destruction of acinar cells of the major salivary glands with age (22) and normal mice who undergo ovariectomy develop apoptosis of the salivary gland epithelial cells (23). Additionally, retinoblastoma-associated protein 48 induces apoptosis within exocrine glands, creating autoimmune lesions similar to those found in pSS, and this process is dependent on estrogen absence (24). In another mouse model, ovariectomy in predisposed mice leads to accelerated onset of a pSS-like syndrome (25).

Although experimental evidence favors a protective role for estrogen, less is known about other female systemic hormones involved in menstruation and reproduction such as progesterone and prolactin. Prolactin levels may be higher in pSS patients; it is unclear if there is any relationship to systemic manifestations of pSS (26, 27). Progesterone may be present at lower levels compared to estrogen or prolactin in pSS patients compared to control (28), but no correlation with pSS activity has been studied. DHEA conversion to estrogen and dihydrotestosterone is impaired intracellularly within the salivary gland and this is suspected to contribute to the pathogenesis of pSS (29).

pSS and many other autoimmune diseases share a marked female predominance, but pSS is distinctive in exhibiting a peak onset of symptomatic disease around the age of menopause, despite the presence of autoantibodies up to 20 years earlier (30). Many factors have been postulated to account for the female predominance of autoimmune disease, including X-chromosome gene dosing, enhanced female hormone exposure, and environmental differences (31–33). The prevalence of trisomy X (XXX) is 2.9 times higher than in women with XX, a higher reported rate than that of systemic lupus erythematosus (34). Identified X-linked genes that might play a role in pSS-related autoimmunity include X-linked ectodermal dysplasia receptor and Foxp3 mutation (33, 35). X-chromosome-related sex hormone expression also influences autoimmunity as discussed above. Finally, environmental exposures such as gut microbiota may also explain sexual dimorphism. Male and female non-obese diabetic (NOD) mice develop type 1 diabetes a varying rates, this process is dependent on gut microbiota, which in turn regulates sex hormone levels and risk for autoimmunity (36–39). It is this complex interplay between different genetic, environmental, and estrogen exposures that might contribute to the variable and more severe

phenotype of younger onset pSS compared to later onset pSS (40–43). Our findings suggest cumulative estrogen exposure may have a modulating effect on factors that predispose women to autoimmune disease. In the case of pSS, lower cumulative estrogen exposure appears to augment the clinical expression of disease.

We also demonstrated potential relationships between pSS phenotype and reproductive and menstrual hormone exposure. However, these findings were not consistent across CES and CMC score. For example, inflammatory arthritis was associated with increasing risk with increased CES, whereas it appeared to be associated with reduced CMC score. It is possible this difference could be attributed to CES providing a measurement of estrogen exposure, whereas CMC measures overall menstrual cycling. Estrogen exposure and other sex hormones involved in menstruation may differentially influence features of pSS. UWS was associated with greater CES and CMC, whereas OSS, hypergammaglobulinemia, focus score, and rheumatoid factor were inversely associated with CES and CMC. Because germinal centers were identified by H&E, a method that has low sensitivity for germinal center detection, it is possible that specimens were falsely reported as negative. These findings indicate that menstrual and reproductive factors might influence pSS phenotype; however, additional larger studies are needed to evaluate this possibility adequately.

Strengths of this study include the large sample size and broadly representative population. The SICCA registry includes participants from across the world and from a multitude of recruitment sources including rheumatology, ophthalmology, dentistry, and local organizations. The variety of participants and locations included in the SICCA registry helps to mitigate selection bias and make the findings of this study more generalizable.

The findings of this study must be interpreted in the context of the limitations of a case-control study. Case-control studies identify association and we cannot confirm a causative effect of reproductive or menstrual factors on pSS. Certain confounders known to impact reproductive and menstrual factors were not available to include as covariates in our model, including body mass index, alcohol use, and physical activity (44). Another significant limitation to this study is the lack of information available through the SICCA registry detailing menstrual cycling and reproductive factors. No data are available describing menstrual regularity or lactation, both factors known to influence hormone-dependent disease outcomes (45). No details are available on the type, duration, or time-period of exogenous hormone or oral contraceptive use. Another limitation of this study is that the control population was not a standard healthy control as nearly all individuals recruited to the registry who did not have pSS had ocular or oral sicca. It is possible that the sicca-control group represent an incomplete form of pSS. However, this might actually strengthen our results, as a more similar control group would reduce the chances of the significant findings we report. Although a limitation, the use of a sicca-control population has some advantage in that most individuals seen in clinic for the question of pSS have some form of sicca, making sicca-control a clinically relevant control group. The SICCA registry included self-reported past reproductive and menstrual history, and such retrospective information may be subject to recall bias. Another potential concern is the accuracy of pSS diagnosis given that pSS patients might be misdiagnosed as RA or SLE (46). However, the SICCA registry performed a rigorous and standardized assessment of all patients using ACR and

EULAR criteria to minimize this risk. Finally, survival bias may affect the findings of this registry-based study.

Conclusion

Women with pSS have lower estrogen exposure and cumulative menstrual cycling compared to a sicca control group. As estrogen exposure increased, there was a trend toward decreased risk of pSS. Reproductive and menstrual factors might influence pSS phenotype, but this finding was not as compelling. Further longitudinal studies of sex hormone exposure in pSS are needed to confirm these findings

Acknowledgements

Data and specimens used in this manuscript are from the Sjögren's International Collaborative Clinical Alliance (SICCA) Biorepository, funded under contract #HHSN26S201300057C by the National Institute of Dental and Craniofacial Research. This manuscript/presentation was prepared using a publicly available SICCA data set and does not necessarily reflect the opinions or views of the SICCA investigators or NIDCR. The project described was supported by the Clinical and Translational Science Award (CTSA) program, through the NIH National Center for Advancing Translational Sciences (NCATS), grant UL1TR002373. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH

References

1. Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F, et al. Epidemiology of primary Sjogren's syndrome: a systematic review and meta-analysis. Annals of the rheumatic diseases. 2015;74(11):1983–9. [PubMed: 24938285]
2. Valtysdottir ST, Wide L, Hallgren R. Low serum dehydroepiandrosterone sulfate in women with primary Sjogren's syndrome as an isolated sign of impaired HPA axis function. The Journal of rheumatology. 2001;28(6):1259–65. [PubMed: 11409117]
3. Gutierrez MA, Anaya JM, Scopelitis E, Citera G, Silveira L, Espinoza LR. Hyperprolactinaemia in primary Sjogren's syndrome. Annals of the rheumatic diseases. 1994;53(6):425.
4. Laroche M, Borg S, Lassoued S, De Lafontan B, Roche H. Joint pain with aromatase inhibitors: abnormal frequency of Sjogren's syndrome. The Journal of rheumatology. 2007;34(11):2259–63. [PubMed: 17937464]
5. Priori R, Medda E, Conti F, Cassara EA, Sabbadini MG, Antonioli CM, et al. Risk factors for Sjogren's syndrome: a case-control study. Clinical and experimental rheumatology. 2007;25(3):378–84. [PubMed: 17631733]
6. Skopouli FN, Papanikolaou S, Malamou-Mitsi V, Papanikolaou N, Moutsopoulos HM. Obstetric and gynaecological profile in patients with primary Sjogren's syndrome. Annals of the rheumatic diseases. 1994;53(9):569–73. [PubMed: 7979594]
7. Daniels TE, Cox D, Shiboski CH, Schiodt M, Wu A, Lanfranchi H, et al. Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjogren's syndrome among 1,726 registry participants. Arthritis and rheumatism. 2011;63(7):2021–30. [PubMed: 21480190]
8. Daniels TE, Criswell LA, Shiboski C, Shiboski S, Lanfranchi H, Dong Y, et al. An early view of the international Sjogren's syndrome registry. Arthritis and rheumatism. 2009;61(5):711–4. [PubMed: 19405009]
9. Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, et al. American College of Rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance cohort. Arthritis care & research. 2012;64(4):475–87. [PubMed: 22563590]
10. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome: A consensus and data-driven methodology involving three

international patient cohorts. Annals of the rheumatic diseases. 2017;76(1):9–16. [PubMed: 27789466]

11. Gatto NM, Deapen D, Stoyanoff S, Pinder R, Narayan S, Bordelon Y, et al. Lifetime exposure to estrogens and Parkinson's disease in California teachers. Parkinsonism & related disorders. 2014;20(11):1149–56. [PubMed: 25179495]
12. Stewart EA. Uterine fibroids. Lancet (London, England). 2001;357(9252):293–8.
13. Bulun SE. Uterine fibroids. The New England journal of medicine. 2013;369(14):1344–55. [PubMed: 24088094]
14. Park HK, Ilango S, Charriez CM, Checkoway H, Riley D, Standaert DG, et al. Lifetime exposure to estrogen and progressive supranuclear palsy: Environmental and Genetic PSP study. Movement disorders : official journal of the Movement Disorder Society. 2018;33(3):468–72. [PubMed: 29460982]
15. Clavel-Chapelon F Cumulative number of menstrual cycles and breast cancer risk: results from the E3N cohort study of French women. Cancer causes & control : CCC. 2002;13(9):831–8. [PubMed: 12462548]
16. Duell EJ, Travier N, Lujan-Barroso L, Boutron-Ruault MC, Clavel-Chapelon F, Palli D, et al. Menstrual and reproductive factors, exogenous hormone use, and gastric cancer risk in a cohort of women from the European Prospective Investigation Into Cancer and Nutrition. American journal of epidemiology. 2010;172(12):1384–93. [PubMed: 21051447]
17. Chavez-MacGregor M, Elias SG, Onland-Moret NC, van der Schouw YT, Van Gils CH, Monninkhof E, et al. Postmenopausal breast cancer risk and cumulative number of menstrual cycles. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2005;14(4):799–804.
18. de Kleijn MJ, van der Schouw YT, Verbeek AL, Peeters PH, Banga JD, van der Graaf Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. American journal of epidemiology. 2002;155(4):339–45. [PubMed: 11836198]
19. Cao X, Zhou J, Yuan H, Chen Z. Cumulative effect of reproductive factors on ideal cardiovascular health in postmenopausal women: a cross-sectional study in central south China. BMC cardiovascular disorders. 2015;15:176. [PubMed: 26691526]
20. Laakkonen EK, Kulmala J, Aukee P, Hakonen H, Kujala UM, Lowe DA, et al. Female reproductive factors are associated with objectively measured physical activity in middle-aged women. PloS one. 2017;12(2):e0172054. [PubMed: 28225786]
21. Fox M, Berzuini C, Knapp LA. Cumulative estrogen exposure, number of menstrual cycles, and Alzheimer's risk in a cohort of British women. Psychoneuroendocrinology. 2013;38(12):2973–82. [PubMed: 24064221]
22. Shim GJ, Warner M, Kim HJ, Andersson S, Liu L, Ekman J, et al. Aromatase-deficient mice spontaneously develop a lymphoproliferative autoimmune disease resembling Sjogren's syndrome. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(34):12628–33. [PubMed: 15314222]
23. Ishimaru N, Arakaki R, Watanabe M, Kobayashi M, Miyazaki K, Hayashi Y. Development of autoimmune exocrinopathy resembling Sjogren's syndrome in estrogen-deficient mice of healthy background. The American journal of pathology. 2003;163(4):1481–90. [PubMed: 14507655]
24. Ishimaru N, Arakaki R, Yoshida S, Yamada A, Noji S, Hayashi Y. Expression of the retinoblastoma protein RbAp48 in exocrine glands leads to Sjogren's syndrome-like autoimmune exocrinopathy. The Journal of experimental medicine. 2008;205(12):2915 [PubMed: 19015307]
25. Czerwinski S, Mostafa S, Rowan VS, Azzarolo AM. Time course of cytokine upregulation in the lacrimal gland and presence of autoantibodies in a predisposed mouse model of Sjogren's Syndrome: the influence of sex hormones and genetic background. Experimental eye research. 2014;128:15–22. [PubMed: 25218176]
26. El Miedany YM, Ahmed I, Moustafa H, El Baddini M. Hyperprolactinemia in Sjogren's syndrome: a patient subset or a disease manifestation? Joint, bone, spine : revue du rhumatisme. 2004;71(3):203–8.

27. Haga HJ, Rygh T. The prevalence of hyperprolactinemia in patients with primary Sjogren's syndrome. The Journal of rheumatology. 1999;26(6):1291–5. [PubMed: 10381045]
28. Taiym S, Haghighat N, Al-Hashimi I. A comparison of the hormone levels in patients with Sjogren's syndrome and healthy controls. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics. 2004;97(5):579–83.
29. Spaan M, Porola P, Laine M, Rozman B, Azuma M, Konttinen YT. Healthy human salivary glands contain a DHEA-sulphate processing intracrine machinery, which is deranged in primary Sjogren's syndrome. Journal of cellular and molecular medicine. 2009;13(7):1261–70. [PubMed: 19298523]
30. Theander E, Jonsson R, Sjostrom B, Brokstad K, Olsson P, Henriksson G. Prediction of Sjogren's Syndrome Years Before Diagnosis and Identification of Patients With Early Onset and Severe Disease Course by Autoantibody Profiling. Arthritis & rheumatology (Hoboken, NJ). 2015;67(9):2427–36.
31. Scofield RH, Bruner GR, Namjou B, Kimberly RP, Ramsey-Goldman R, Petri M, et al. Klinefelter's syndrome (47,XXY) in male systemic lupus erythematosus patients: support for the notion of a gene-dose effect from the X chromosome. Arthritis and rheumatism. 2008;58(8):2511–7. [PubMed: 18668569]
32. Rubtsova K, Marrack P, Rubtsov AV. Sexual dimorphism in autoimmunity. The Journal of clinical investigation. 2015;125(6):2187–93. [PubMed: 25915581]
33. Sharma R, Deshmukh US, Zheng L, Fu SM, Ju ST. X-linked Foxp3 (Scurfy) mutation dominantly inhibits submandibular gland development and inflammation respectively through adaptive and innate immune mechanisms. Journal of immunology (Baltimore, Md : 1950). 2009;183(5):3212–8.
34. Liu K, Kurien BT, Zimmerman SL, Kaufman KM, Taft DH, Kottyan LC, et al. X Chromosome Dose and Sex Bias in Autoimmune Diseases: Increased Prevalence of 47,XXX in Systemic Lupus Erythematosus and Sjogren's Syndrome. Arthritis & rheumatology (Hoboken, NJ). 2016;68(5):1290–300.
35. Sisto M, Lorusso L, Lisi S. X-linked ectodermal dysplasia receptor (XEDAR) gene silencing prevents caspase-3-mediated apoptosis in Sjogren's syndrome. Clinical and experimental medicine. 2017;17(1):111–9. [PubMed: 26659383]
36. Pozzilli P, Signore A, Williams AJ, Beales PE. NOD mouse colonies around the world--recent facts and figures. Immunology today. 1993;14(5):193–6. [PubMed: 8517916]
37. Wen L, Ley RE, Volchkov PY, Stranges PB, Avanesyan L, Stonebraker AC, et al. Innate immunity and intestinal microbiota in the development of Type 1 diabetes. Nature. 2008;455(7216):1109–13. [PubMed: 18806780]
38. Markle JG, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, Rolle-Kampczyk U, et al. Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. Science (New York, NY). 2013;339(6123):1084–8.
39. Yurkovetskiy L, Burrows M, Khan AA, Graham L, Volchkov P, Becker L, et al. Gender bias in autoimmunity is influenced by microbiota. Immunity. 2013;39(2):400–12. [PubMed: 23973225]
40. Anquetil C, Hachulla E, Machuron F, Mariette X, Le Guern V, Vittecoq O, et al. Is early-onset primary Sjogren's syndrome a worse prognosis form of the disease? Rheumatology. 2018.
41. Ramos-Casals M, Brito-Zeron P, Solans R, Camps MT, Casanovas A, Sopena B, et al. Systemic involvement in primary Sjogren's syndrome evaluated by the EULAR-SS disease activity index: analysis of 921 Spanish patients (GEAS-SS Registry). Rheumatology. 2014;53(2):321–31. [PubMed: 24162151]
42. Garcia-Carrasco M, Ramos-Casals M, Rosas J, Pallares L, Calvo-Alen J, Cervera R, et al. Primary Sjogren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore). 2002;81(4):270–80. [PubMed: 12169882]
43. Ramos-Casals M, Cervera R, Font J, Garcia-Carrasco M, Espinosa G, Reino S, et al. Young onset of primary Sjogren's syndrome: clinical and immunological characteristics. Lupus. 1998;7(3):202–6. [PubMed: 9607645]
44. Liu Y, Gold EB, Lasley BL, Johnson WO. Factors affecting menstrual cycle characteristics. American journal of epidemiology. 2004;160(2):131–40. [PubMed: 15234934]

45. Karlson EW, Mandl LA, Hankinson SE, Grodstein F. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. Arthritis and rheumatism. 2004;50(11):3458–67. [PubMed: 15529351]

46. Rasmussen A, Radfar L, Lewis D, Grundahl K, Stone DU, Kaufman CE, et al. Previous diagnosis of Sjogren's Syndrome as rheumatoid arthritis or systemic lupus erythematosus. Rheumatology. 2016;55(7):1195–201. [PubMed: 26998859]

Significance & Innovation

- Female sex hormones might be protective in primary Sjögren's syndrome.
- The finding that female sex hormones might be protective in primary Sjögren's syndrome provides insight into potential novel mechanisms of pathogenesis in this disease.

Table 1.

Demographic characteristics of female SS and sicca controls from the SICCA registry

		SS	Sicca Control	p
		n=1320	**n=1360**	
Age (mean, SD)		52.04(13.5)	54.04(12.93)	0.0001
		n(%)	n(%)	
Age (Years)	18–39	254(19)	199(15)	0.01
	40–59	648(49)	678(50)	
	60–79	401(30)	461(34)	
	80+	17(1)	20(1)	
Ethnicity *	Caucasian/Middle eastern	569(43)	879(65)	<0.001
	Hispanic/Latino	141(11)	171(13)	
	Native American	37(3)	52(4)	
	Asian/Pacific Islander	530(40)	222(16)	
	African Column	42(3)	34(3)	
Tobacco *	Ever	366(29)	366(40)	<0.0001
	Never	895(71)	895(60)	
Education	None	22(2)	13(1)	<0.0001
	Primary/grammar school	168(13)	199(15)	
	Some high school	117(9)	77(6)	
	Graduate from high school	271(21)	206(15)	
	Some college/university	234(18)	316(23)	
	Complete college/university	508(38)	549(40)	
Employment *	Full-time	480(36)	394(29)	<0.0001
	Part-time	185(14)	189(14)	
	Homemaker full time	216(16)	178(13)	
	Retired	274(21)	320(24)	
	Student	20(2)	17(1)	
	Temporarily not working	45(3)	46(3)	
	Disability	99(8)	215(16)	
Recruitment Site	Argentina	154(12)	208(15)	<0.0001
	China	233(18)	53(4)	
	Denmark	161(12)	284(21)	
	India	50(4)	22(2)	
	Japan	182(14)	110(8)	
	US	421(32)	563(41)	
	UK	119(9)	120(9)	
Referral Source *	Sjögren's clinic	331(25)	310(23)	0.10
	Dentist	111(8)	127(9)	
	Rheumatologist	376(29)	378(28)	
	Ophthalmologist	95(7)	100(7)	
	Other doctor	47(4)	73(5)	

	SS	Sicca Control	p
	n=1320	n=1360	
Website	145(11)	144(11)	
Advertisement	48(4)	46(3)	
Support Group	72(5)	57(4)	
Friend/Relative	41(3)	55(4)	
Other	50(4)	65(5)	

* Data missing for ethnicity (n=3), smoking (n=251), employment (n=2), referral source (n=9) categories

Table 2.

Association between CES and CMC and SS

		SS	Sicca Control			
		n=1320 (49%)	**n=1360 (51%)**	**P**	**OR**	**95% CI**
CES	0	667(51)	528(39)	<0.001	ref	
	1	462(35)	546(40)		0.81	0.67–0.99
	2	164(12)	233(17)		0.74	0.57–0.97
	≥3	27(2)	53(4)		0.50	0.30–0.86
CMC*						
Premenopausal	Q1	154	95	0.01	ref	
	Q2	136	114		0.64	0.41–0.98
	Q3	122	123		0.49	0.30–0.80
	Q4	121	127		0.69	0.38–1.26
Postmenopausal	Q1	203	213	0.4	ref	
	Q2	208	215		0.89	0.66–1.21
	Q3	191	226		0.82	0.60–1.12
	Q4	176	224		0.76	0.56–1.04

CES: Composite estrogen score; CMC: cumulative menstrual cycling; Q: Quartile;

*Missing data for SS CMC (n=9) and for sicca control (n=23) due to unavailable dates of menarche or menopause.

Table 3.

Association between individual reproductive and menstrual factors and SS

		SS n=1320	Sicca Control n=1360			
		n(%)	n(%)	P	OR	95% CI
Menarche age (mean, SD)		13.1(1.7)	12.8(1.7)	<0.00001		
Menarche ≤ 10 yrs (n)		53	70	0.06		
Pregnancies *	0	229(17)	217(16)	0.29	ref	
	1	159(12)	161(12)		0.8	0.60–1.15
	2	319(24)	332(24)		0.9	0.65–1.14
	3	289(22)	295(22)		0.8	0.62–1.11
	>3	322(24)	352(26)		0.8	0.63–1.12
Hormone Use *	No	1135(86)	1074(79)	<0.001	ref	0.68–1.08
	Yes	185(14)	285(21)		0.86	
Hysterectomy *	No	1117(85)	1037(76)	<0.001	ref	
	Yes	203(15)	322(24)		0.7	0.57–0.89
Menopause (mean, SD)		47.4(5.8)	47.2	0.55		
Menopause ≥ 53		105	134	0.39		

* Data missing for pregnancies (n=5), hormone use (n=1), and hysterectomy (n=1) categories

Table 4.

Association between phenotypic features of Sjogren's Syndrome and menstrual/reproductive history

		Arthritis (702)	UWS (625)	Schirmer's (322)	OSS (666)	Hyper-GG (368)	RF (431)	anti-SSA (489)
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
CES	0	ref	ref	ref	ref	ref	ref	ref
	1	1.2 (1.0–1.5)	1.3 (1.1–1.6)	0.9 (0.7–1.1)	0.8 (0.6–0.9)	0.8 (0.7–1.0)	0.9 (0.8–1.1)	1.0 (0.7–1.0)
	2	1.3 (1.0–1.7)	1.2 (0.9–1.6)	0.9 (0.7–1.2)	0.8 (0.6–1.0)	0.8 (0.6–1.1)	0.9 (0.7–1.1)	0.7 (0.6–1.0)
	3	2.5 (1.3–5.0)	1.1 (0.6–1.8)	1.0 (0.5–1.7)	0.4 (0.2–0.7)	0.3 (0.1–0.8)	0.5 (0.2–0.9)	0.5 (0.3–0.9)
Premenopausal CMC	Q1	ref	ref	ref	ref	ref	ref	ref
	Q2	0.7 (0.5–1.2)	1.8 (1.1–2.8)	0.8 (0.5–1.4)	0.8 (0.5–1.3)	0.9 (0.6–1.5)	0.8 (0.5–1.2)	0.8 (0.5–1.2)
	Q3	0.9 (0.5–1.4)	2.1 (1.3–3.3)	0.9 (0.5–1.5)	0.7 (0.4–1.1)	1.0 (0.6–1.8)	1.0 (0.6–1.7)	0.8 (0.5–1.3)
	Q4	0.7 (0.4–1.2)	3.5 (2.0–6.0)	0.5 (0.3–0.9)	0.6 (0.3–1.0)	0.5 (0.3–0.9)	0.5 (0.3–0.9)	0.5 (0.3–0.9)
	Q5	0.5 (0.2–1.0)	4.1 (2.1–7.9)	0.4 (0.2–0.9)	0.5 (0.3–1.0)	0.5 (0.2–1.0)	0.8 (0.4–1.5)	0.7 (0.4–1.5)
Postmenopausal CMC	Q1	ref	ref	ref	ref	ref	ref	ref
	Q2	0.8 (0.5–1.1)	1.0 (0.7–1.4)	0.7 (0.5–1.1)	0.9 (0.6–1.2)	0.8 (0.5–1.2)	1.0 (0.7–1.5)	1.0 (0.7–1.3)
	Q3	0.7 (0.5–0.9)	1.3 (0.9–1.8)	0.78 (0.5–1.1)	1.1 (0.8–1.6)	0.9 (0.6–1.4)	1.0 (0.7–1.4	0.9 (0.7–1.3)
	Q4	0.6 (0.4–0.9)	1.3 (0.9–1.9)	0.7 (0.5–1.0)	1.1 (0.8–1.5)	0.8 (0.5–1.3)	0.9 (0.6–1.2)	0.8 (0.5–1.1)
	Q5	0.6 (0.4–0.9)	1.5 (1.1–2.2)	0.9 (0.6–1.3)	1.0 (0.7–1.4)	0.8 (0.6–1.3)	0.9 (0.6–1.3)	0.7 (0.5–1.1)

CES: Composite estrogen score; CMC: cumulative menstrual cycling; Q: Quintile; UWS: unstimulated whole salivary flow; OSS: ocular staining score; Hyper-GG: Hypergammaglobulinemia; RF: Rheumatoid Factor