Results

(A) Metabolomics analysis

Author, Setting Year,	Study Group	Healthy Control (HC) or other	Diagnostic criteria for Sjögren's syndrome	Sample	Analytical Methods	Results
Piacenza Florezi et al. Brazil 2024 [1]	10 pSjS 8♀ 2♂ Average age 41	10 HC 9♀ 1♂ Average age 46.8	2002 AECG criteria	NWS	Ultra-high Performance Liquid Chromatograph Coupled Mass Spectrometry (UPLC MS)	↑ concentration in pSS ($p<0.05$.) Guanosine p= 0.011 L-Lactic acid p= 0.024 Malic acid p= 0.032 L-Arginine p= 0.010 L-Threonine p= 0.045 L-Valine p= 0.027 4-Hydroxyproline p= 0.003 L-Leucine p= 0.011 L-Methionine p= 0.032 L-Alanine p= 0.019 L-Isoleucine p= 0.005
Vyas et al. USA 2024 [2]	26-SjS 4♂ 22♀ Age 60 (± 10)	24-HC 14♂ 8♀ Age 60 (± 10) 22-RD (radiation therapy for head and neck cancers) 18♂ 4♀ Age 66 (± 9)	Not specified in the source article	NWS	Raman hyperspectroscopy, machine learning	SjS vs HC & RD Proline ↓ Tryptophan ↓
Alt-Holland et al. USA 2023 [3]	30 pSjS 28♀ 2♂ Age 62,2 +-10,2	30 HC 21♀ 9♂ Age 37,2 +-15,6	ACR/EULAR 2016 criteria	NWS	NMR spectroscopy	↑ pSjS: glucose (p= 0.0289) glycerol (p= 0.0302) lactate (p=0.0074) taurine (p=0.0001) ↓ pSjS: 5-ANP (p=0.0027) acetate (p=0.0043) butyrate (p=0.0048) fucose (p=0.0117) propionate (p=0.0027)
Alt-Holland et al. USA 2023 [3]	24 pSjS 22♀ 2♂ Age 60,5 (iqr 10,5)	14 HC 11♀ 3♂ Age 49,5 (iqr 28)	ACR/EULAR 2016 criteria	NWS	NMR spectroscopy	↑ pSjS: choline (p=0.0191) glucose (p= 0.0194) glycerol (p= 0.0148) lactate (p=0.0559) taurine (p=0.0041) fructose (p=0.0544) ↓ pSjS: 5-ANP (p=0.0034) acetate (p=0.0148) butyrate (p=0.0041) propionate (p=0.0003)
Bosman et al.	18 SjS ♀	22 HC ♀	2002 AECG criteria	NWS, SWS	LC-HRMS	pSjS vs HC Alanine (AUC): 0.873.

Author, Setting Year,	Study Group	Healthy Control (HC) or other	Diagnostic criteria for Sjögren's syndrome	Sample	Analytical Methods	Results
France, Brasil 2023 [4]	Age 35 to 82 years old (53.4 ± 12.1)	Age 55 to 72 years old (60.0 ± 4.5)				Succinic Acid: AUC: 0.906. Isovaleric Acid: AUC: 0.871 Amino acids or derivatives: Alanine, serine, threonine, leucine/isoleucine, lysine, phenylalanine, glutamic acid ↓ Purine derivatives: Hypoxanthine, uric acid ↓ Organic acids: Lactic acid, malic acid ↓ Carboxylic acids: Succinic acid, isovaleric acid ↓ SjS impact on metabolic pathways: Amino Acid Metabolism: glutamic acid and lysine ↓ Purine Metabolism: hypoxanthine and uric acid ↓ Citric Acid Cycle: succinic acid and malic acid ↓ Threitol ↓ D-α-Aminobutyric acid ↓ GABA ↓
Setti et al. Italy 2023 [5]	7 pSjS ♀	6 HC♀	ACR/EULAR 2016 criteria	NWS,	1D 1H-NMR CPMG NMR spectra, PCA, PLS-DA	50 metabolites SjS methylamine ↑ $p < 0.05$ HC proline ↑ $p < 0.05$
Li et al. 2022 China [6]	32 pSjS (test group 20, validation group 12)	38 HC (test group 25, validation group 13)	ACR/EULAR 2016 criteria	NWS	UPLC-HRMS	pSjS: Significant enrichment ($p < 0.05$) of metabolism of tryptophan, tyrosine, aspartate, asparagine and carbon fixation. Metabolites involved in metabolism of tryptophan, aspartate and asparagine were upregulated ↑ Metabolites derived from amino acids was upregulated ↑: phenylalanyl-alanine, tryptophyl-isoleucine, tyrosyl-phenylalanine, asparaginyl-valine,

Author, Setting Year,	Study Group	Healthy Control (HC) or other	Diagnostic criteria for Sjögren's syndrome	Sample	Analytical Methods	Results
						aspartyl-isoleucine and tyrosyl-hydroxyproline. Purine metabolites: 8-hydroxyadenine and oxypurinol Metabolites involved in carbon fixation ↓ 38 metabolites diagnostic value, with an AUC above 0.7 30 metabolites diagnostic value, with an AUC above 0.8 Aspartyl-isoleucine ($p<0.001$) Phenylalanyl-alanine
Herrala et al. Finland 2021 [7]	14 ♀ pSjS (4x14=56 samples)	15 HC	2002 AECG criteria	SWS	proton nuclear magnetic resonance (1H-NMR) spectroscopy	pSjS: Choline ↑ (higher at each time: $p = 0.015, 0.023, 0.001, <0.001$) Taurine ↑ (higher at the three last points $p = 0.023, 0.002, 0.001$), Alanine ↑ (higher at the two last points ($P = 0.005$ and 0.001) Glycine ↑ (higher at the three last points ($p = 0.040, 0.032, 0.004$)
Tvarijonaviciute et al. 2019 Spain [8]	SjS 17♀ non-SS sicca group 19♀	13 HC ♀	2002 AECG criteria	NWS	ELISA	SjS: Salivary adiponectin ↑ SjS and non-SS sicca: Adenosine deaminase (ADA) ↑
Kageyama et al. Japan 2015 [9]	12♀ pSjS mean age 44.26±13.01	21 HC ♀ Age matched	2002 AECG criteria	NWS	Principal component analysis (PCA)	pSjS 88 metabolites were detected (41 ↓) pSjS glycine ↓ tyrosine ↓ uric acid ↓ fucose ↓

(B) Salivary Proteomics

Author, Setting Year,	Study Group	Healthy Control (HC) or other	Diagnostic criteria for Sjögren's syndrome	Sample	Analytical Methods	Results
Tian et al. China 2024 [10]	36 pSS Discovery 24(21♀) Age 41.1±10.9 Validation 12 (10♀) Age 40.6 ±12.8	38 HC Discovery 25(23♀) 41.4±12.2 Validation 13 (12♀), 44.1±127	ACR/EULAR 2016 criteria	NWS	Liquid chromatography mass spectrometry (LC- MS/MS) data- independent acquisition-mass spectrometry (DIA- MS) mode	19 proteins – potential biomarkers: Q13217, P01034, P07711, P09958, P28065, 043852, 043505, P25789, Q9UBX7, Q9NRI3, P35030, P12109, O75976, Q92743, P16870, P13798, P01011, P32320, P08670 Up-regulated in pSjS: CA-I the most up-regulated (fold change = 10) B2 microglobulin, S100 A8, S100A11.-(2- or 3-fold changes) HTRA-1 (Q92743) down-regulated in pSjS Kallikreins KLKs
Giorgi et al. 2022 Italy [11]	pSjS 11 preclinical SjS SSA+ 8	8 HC age,gender-matched	ACR/EULAR 2016 criteria	NWS , EVs	high-performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS)	pSjS 11and preclinical SjS SSA+ compared to HC MUC5B ↓ Prolactin-Inducible Protein (PIP) ↓ CST4 ↓ lipocalin 1 ↓
Finamore et al. 2021 Italy [12]	7 pSjS ♀ age 25–75	5 HC ♀ age 26–65	ACR/EULAR 2016 criteria	NWS, EVs	SWATH-MS	pSjS EVs vs NWS increase of: S100 protein family (S100A7, A8, A9, A11, A12), resistin (RETN), serpin peptidase inhibitors (SERPINB1, SEPINB5), azurocidin (AZU1), monocyte differentiation antigen (CD14) annexin A2 (ANXA2), cofilin-1 (CFL-1), plastin-2 (LCP1), macrophage migration inhibitory factor (MIF)

Author, Setting Year,	Study Group	Healthy Control (HC) or other	Diagnostic criteria for Sjögren's syndrome	Sample	Analytical Methods	Results
Aqrawi et al. Norway 2020 [13]	27 pSjS	32 HC age- and gender matched	2002 AECG criteria	SWS, EVs	LC-MS	pSjS ↑ Neutrophil gelatinase-associated lipocalin (NGAL)
Chen et al. Norway 2019 [14]	pSjS 29 ♀ age 56.8 ± 13.0 years 20 non-SjS (sicca control) age 51.7 ± 10.6 years	17 HC ♀ age 45.4 ± 10.9 years	2002 AECG criteria	NWS, SWS	immunoassay technology (Bio-Plex XMap; Bio-Rad Laboratories, Inc., Hercules, CA, USA)	pSjS ↑ IP-10 pSjS, non-SjS ↑ MIP-1α
Cecchettini et al. 2019 Italy [15]	SjS 20	20 HC age- and sex-matched	2002 AECG criteria	NWS	nano-HPLC-SWATH-MS, ELISA	203(proteins differently expressed in pSjS) SjS: prolactin-inducible protein PIP protein ↓ proline-rich proteins (PRPs) ↓ cystatins ↓ (except for cystatin A and B) carboanhydrase VI ↓ cathepsin family ↑ S100A proteins ↑
Aqrawi et al. Norway 2019 [16]	10 pSjS ♀ 15 non-SjS sicca	10 HC	2002 AECG criteria	SWS, EVs	LC-MS	SWS Non-SS vs. pSS↑ peptidyl-prolyl cis-trans isomerase FKBP1A (FKBP1A) ↑ CD44 antigen (CD44) ↑ Beta-2-microglobulin ↑ SWS HC vs. pSS↑ Beta-2-microglobulin ↑ Secreted Ly-6/uPAR-related protein 1 SLUR1 ↑ Clusterin CLUS ↑ EVs SWS Non-SS vs. pSS↑ CD44 CD44 antigen ↑ MVP Major vault protein ↑ NGAL Neutrophil gelatinase-associated lipocalin ↑ EVs SWS HC vs. pSS↑ FCN1 Ficolin-1 ↑ CD44 CD44 antigen ↑ ANXA4 Annexin A4 ↑

Author, Setting Year,	Study Group	Healthy Control (HC) or other	Diagnostic criteria for Sjögren's syndrome	Sample	Analytical Methods	Results
Garza-García et al. Mexico 2017 [17]	71 ♀pSjS age 53.05 ± 12.19 years PASS(Patient-Acceptable Symptom State) (n = 28)	non-PASS groups (n = 43)	2002 AECG criteria	NWS	Not specified in the source article	↑ β2-microglobulin correlation with ↑ ESSPRI (EULAR Sjögren's syndrome Patient Reported Index)
Aqrawi et al. Norway 2017 [18]	27 pSjS	32 HC age- and gender matched	AECG criteria 2002	SWS, EVs	LC-MS Liquid chromatography-mass spectrometry and size exclusion chromatography	SWS pSjS ↑ LCN2 GRN CALM NPC2 CALML5 EVs pSjS ↑ APMAP GNA13 WDR1 SIRPA LSP1
Delaleu et al. Switzerland 2016 [19]	48 ♀ pSjS 24 Hyposalivation 24 Normal GC (ectopic germinal centers) + 34 GC - 14	------	2002 AECG criteria	NWS	Human Discovery MAP 1.0.	Hyposalivation: uromodulin UMOD ↓ secreted phosphoprotein 1 (SPP1) ↓ GC + pregnancy-associated plasma protein A (PAPPA) p=6.795x10 $^{-08}$ ↑ Thrombospondin 1 THBS1 p=5.178 x10 $^{-04}$ ↑ uromodulin UMOD p=2.194x 10 $^{-05}$ ↓ IL5 p=1.959 x 10 $^{-04}$ ↓
Deutsch et al. Israel, Finland, USA 2014 [20]	18 SjS ♀ Age: 55.5 years (s.d. 15.3)	18 HC ♀ [52.1 years (s.d. 7.2)	2002 AECG criteria	NWS	LC-MS/MS	79 biomarker candidates pSjS strongly differentially: profilin↑ Histone H2B ↑ Carcinoembryonic antigen ↑ MMP 9 ↑ MPO precursor ↑ CA-I ↓

Author, Setting Year,	Study Group	Healthy Control (HC) or other	Diagnostic criteria for Sjögren's syndrome	Sample	Analytical Methods	Results
						bacterial permeability increasing (BPI) protein ↓

(C) Molecular Biomarkers

Author, Setting Year,	Study Group	Healthy Control (HC) or other	Diagnostic criteria for Sjögren's syndrome	Sample	Analytical Methods	Results
Cross et al. Norway 2023 [21]	pSjS 11♀ mean age of 55	11 HC ♀ mean age of 55	ACR/EULAR 2016 criteria	SWS, EVs	Qiagen exoRNeasy Midi Kit, Affymetrix Clariom D™ microarrays	1475 transcripts (notable difference in abundance between the pSjS and HC) pSjS tRNAs ↓ tRNA-Ile-AAT-2-1 (biomarker candidate)
Karagianni et al. Greece 2020 [22]	16 SjS patients age = 63·2, mean ± standard deviation (s.d.) = 8·8	10 sicca controls with negative MSG biopsy age = 57·2, mean ± s.d. = 13·7	2002 AECG criteria	NWS	PCR	Statistically significant reduction in H19 ICR methylation in SjS patients' saliva vs. sicca controls Significant negative correlation between C4 serum levels and H19 ICR methylation
Sembler-Møller et al. Denmark 2020 [23]	pSjS 24 22♀ 2♂ age 55 ± 11	16 non-Sjögren's sicca patients 14♀ 2♂ age 53 ± 16	ACR/EULAR 2016 criteria	NWS, SWS	miRCURY LNA™ Universal RT miRNA PCR, Polyadenylation, cDNA synthesis kit (Exiqon)	pSjS 14 miRNAs differed significantly let-7i-5p ↑ p=0.00006 miR-17-5p ↓ p=0.00003 miR-328-3p ↓ p= 0.00024 miR-7-5p ↓ p=0.00149 miR-30c-5p ↓ p=0.00173 miR-191-5p ↓ p=0.00199 miR-106a-5p ↓ p=0.00202 miR-222-3p ↑ p=0.00203 miR-154-5p ↓ p=0.00206 miR-215-5p ↓ p=0.00207 miR-106b-5p ↓ p=0.00229 let-7e-5p ↑ p=0.0023 miR-409-3p ↓ p=0.00297 miR-20b-5p ↓ p=0.00359

(D) Autoimmune Biomarker Panel

Author, Setting Year,	Study Group	Healthy Control (HC) or other	Diagnostic criteria for Sjögren's syndrome	Sample	Analytical Methods	Results
Chiang et al. USA, Denmark, Korea	♀ 94% 34 pSjS mean age (± SD)	41 HC	ACR Criteria 2012	NWS	Electric Field-Induced Release and	pSjS↑ anti- SSA/Ro52 isotypes IgG/M/A, IgG, IgA, IgA1, IgA2

Author, Setting Year,	Study Group	Healthy Control (HC) or other	Diagnostic criteria for Sjögren's syndrome	Sample	Analytical Methods	Results
2024 [24]	54.6±10.5 years 35 patients with Sicca mean age 57.3±14.5 years				Measurement (EFIRM) immunoassay	SICCA>pSJS mIgA1 SICCA<pSJS pIgA1
Li et al. 2022 China [25]	95 pSjS ♀ 48.82±1.33	65 HC ♀ 47.31±1.425	ACR/EULAR 2016 criteria	NWS	ELISA	↑ pSjS: ICOS (Inducible T Cell Co-Stimulator)
Moreno-Quispe et al. Spain, Peru 2020 [26]	36 pSjS♀ age of 56.58 ± 12.35	35 HC ♀ age of 54.40 ± 9.16	2002 AECG criteria	NWS, SWS	high-sensitivity multiplex map human immunoassays HSTCMAG-28SK	pSjS ↑ IL-6 p = 0.0001
Jin et al. China 2019 [27]	12 pSjS	24 HC	2002 AECG criteria ACR Criteria 2012	NWS	ELISA	pSjS Saliva anti-CA6 IgG ↑ Saliva anti-SP1 IgG ↑ Saliva anti-PSP IgG ↑
Lee et al. Korea 2019 [28]	170 pSjS validation cohort 45 pSjS	25 HC 78 non SjS sicca patients 43 patients with systemic lupus erythematosus (SLE) validation cohort 45 non SS sicca patients	2002 AECG criteria Validation cohort ACR/EULAR 2016 criteria	NWS	ELISA	siglec-5 p=0.001 significantly higher in pSjS ↑ validation cohort siglec-5 higher in pSjS ↑
Sandhya et al. India 2017 [29]	15 pSjS 13♀ 2♂ age 30–43	15 HC	2002 AECG criteria ACR Criteria 2012	NWS	FREELITETM Human Kappa and Lambda Free Kit	pSjS salivary kappa (κ) Free Light Chains ↑ salivary Lambda (λ) Free Light Chains ↑

(E) Enzymatic Markers in Saliva

Author, Setting Year,	Study Group	Healthy Control (HC) or other	Diagnostic criteria for Sjögren's syndrome	Sample	Analytical Methods	Results
Garreto et al. Brazil 2021 [30]	10 pSjS 10 sSjS 19♀ 1♂	20 HC 19♀ 1♂	ACR/EULAR 2016 criteria	SWS	Invitrogen Qubit® 2.0 Fluorometer, Invitrogen™ Qubit™ Protein Assay	pSjS: dipeptidyl peptidase-4/CD26 (DPP4/ CD26) ↑ sSjS Matrix Metalloproteinase-9 (MMP9) ↑

Author, Setting Year,	Study Group	Healthy Control (HC) or other	Diagnostic criteria for Sjögren's syndrome	Sample	Analytical Methods	Results
					Kit, ELISA, LC-MS/MS	SjS: Neutrophil Elastase (ELANE) ↑ Cathepsin G (CTSG) ↑ Myeloblastin (PRTN3) ↑
Wei et al. China 2020 [31]	10 pSjS	10 HC	2002 AECG criteria	Not specified in the source article	LC-MS/MS, Western blot analysis	α-enolase ↑ fold change 4,21 in pSjS vs HC

Table S3. (A-E). Summary of salivary biomarkers investigated for the diagnosis of primary Sjögren's syndrome (pSjS), grouped by biomarker category (A–E). For each study, details include author, country, year, diagnostic criteria, saliva type, analytical methods, and key findings. Abbreviations are listed below.

Abbreviations used in Table S3A-E:

♂- male; ♀-female; ↑- increase; ↓- decrease; ACR - American College of Rheumatology; ADA - Adenosine Deaminase; ANXA2 - Annexin A2; ANXA4 - Annexin A4; APMAP - Adipocyte Plasma Membrane-Associated Protein; AUC - Area Under the Curve; AZU1 - Azurocidin 1; BPI - Bacterial Permeability-Increasing Protein; CA-I - Carbonic Anhydrase I; CA6 - Carbonic Anhydrase 6; CALM - Calmodulin; CALML5 - Calmodulin-Like 5; CD4+ T - Subpopulation of T-helper lymphocytes; CD14 - Cluster of Differentiation 14; CD44 - CD44 antigen; CEA - Carcinoembryonic Antigen; CFL-1 - Cofilin-1; CLUS - Clusterin; CST4 - Cystatin-S; DIA-MS - Data-Independent Acquisition Mass Spectrometry; DPP4/CD26 - Dipeptidyl Peptidase-4/Cluster of Differentiation 26; EFIRM - Electric Field-Induced Release and Measurement; ELISA - Enzyme-Linked Immunosorbent Assay; ESSDAI - EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI - EULAR Sjögren's Syndrome Patient Reported Index; EVs - Extracellular Vesicles; FGF2 - Basic Fibroblast Growth Factor; FCN1 - Ficolin-1; FLCs - Free Light Chains; FKBP1A - FK506 Binding Protein 1A; G-CSF - Granulocyte Colony-Stimulating Factor; GM-CSF - Granulocyte Macrophage Colony-Stimulating Factor; GNA13 - G Protein Subunit Alpha 13; GRN - Granulin; HC - Healthy Control; H2B - Histone H2B; HLA-DQA1 - HLA Class II Gene, DQA1 Allele; HLA-DQB1 - HLA Class II Gene, DQB1 Allele; HPLC - High-Performance Liquid Chromatography; ICOS - Inducible T-cell CO-Stimulator; IFN-γ - Interferon Gamma; IgA - Immunoglobulin A; IgG - Immunoglobulin G; IL-1B - Interleukin-1 beta; IL-1ra - IL-1 Receptor Antagonist; IL-5 - Interleukin-5; IL-6 - Interleukin-6; IL-8 - Interleukin-8; IP-10 - Interferon Gamma-Induced Protein 10; KLKs - Kallikreins; LC-HRMS - Liquid Chromatography-High Resolution Mass Spectrometry; LC-MS/MS - Liquid Chromatography-Tandem Mass Spectrometry; LCN2 - Neutrophil Gelatinase-Associated Lipocalin; LCP1 - Lymphocyte Cytosolic Protein 1; LSP1 - Lymphocyte-Specific Protein 1; MCP-1 - Monocyte Chemoattractant Protein 1; MCTD - Mixed Connective Tissue Disease; MIF - Macrophage Migration Inhibitory Factor; MIP-1α/CCL3 - Macrophage Inflammatory Protein 1 Alpha; miRNA - MicroRNA; MMP9 - Matrix Metalloproteinase 9; MPO - Myeloperoxidase; MSG - Minor Salivary Gland; MVP - Major Vault Protein; MUC5B - Mucin 5B; NGAL - Neutrophil Gelatinase-Associated Lipocalin; NMR - Nuclear Magnetic Resonance; NPC2 - Niemann-Pick Disease, Type C2; NWS - Non-Stimulated Whole Saliva; PAPPA - Pregnancy-Associated Plasma Protein A; PASS - Patient-Acceptable Symptom State; PCA - Principal Component Analysis; PCR - Polymerase Chain Reaction; PDGF-BB - Platelet-Derived Growth Factor BB; PIP - Prolactin-Inducible Protein; PLS-DA - Partial Least Squares Discriminant Analysis; PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRPs - Proline-Rich Proteins; PRTN3 - Myeloblastin; PSP - Parotid Secretory Protein; pSjS - Primary Sjögren's Syndrome; PSS - Primary Sjögren's Syndrome; RANTES - Regulated on Activation, Normal T Cell Expressed and Secreted; RD - Radiation Therapy for Head and Neck Cancers; RETN - Resistin; RZS - Rheumatoid Arthritis; S100A - S100 Calcium-Binding Protein A; S100A8, S100A11 - Proteins from the S100 family; SCC - Squamous Cell Carcinoma; SERPINB1 - Serpin Family B Member 1; SIRPA - Signal-Regulatory Protein Alpha; SLUR1 - Secreted Ly-6/uPAR-Related Protein 1; SP1 - Salivary Protein 1; SPP1 - Secreted Phosphoprotein 1; SSA/Ro - Autoantigen SSA/Ro; sSjS - Secondary Sjögren's Syndrome; SWATH-MS - Sequential Window Acquisition of All Theoretical Fragment Ion Spectra; SWS - Stimulated Whole Saliva; THBS1 - Thrombospondin 1; TNFa - Tumor Necrosis Factor alpha; TNF-α - Tumor Necrosis Factor Alpha; UPLC-MS - Ultra-Performance

Liquid Chromatography-Mass Spectrometry; UMOD - Uromodulin; VEGF - Vascular Endothelial Growth Factor; WDR1 - WD Repeat Domain 1.

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