Supplementary Material

# Table 1 – Gender Disparities of CI across NADs\_Summary of Findings

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| **Condition/ NAD** | **Title & DOI** | **Author(s), Year** | **Study Design** | **Population** | **Main Findings** | **Quality/ Risk of Bias (Tool Used)** |
| **Hashimoto's Thyroiditis (HT)** | No studies found. | N/A | N/A | N/A | N/A | N/A |
| **Graves' Disease (GD)** | Long-Term Outcome of Graves' Disease: A Gender Perspective. DOI: 10.1089/whr.2023.0073 | Calissendorff et al. 2023 | Prospective cohort study (Longitudinal Follow-Up; 6–10 years). | N: 1186 GD patientsGender: 973 women (82%), 213 men (18%)Age: Mean 47 (±14) years (women), 49 (±14) years (men)Ethnicity/Country: Sweden | - Short-Form Health Status (SF-36): Women have worse bodily pain scores.- Thyroid-Related Patient-Reported Outcome (ThyPRO): Women have higher depression (p<0.05), impaired sex life (p<0.05), and cosmetic complaints (p<0.05).- Hypothyroidism: 2× higher prevalence in women (29.5% vs. 14.9% in men, p<0.05) | accordingly Levothyroxine use: Women twice as likely to require it post-antithyroid drugs (ATD) (p<0.05).- Feeling of recovery: No gender difference, but levothyroxine users (33.2%) felt less recovered vs. non-users (13.9%). | Tool: Newcastle-Ottawa Scale (NOS) for cohort studies. Strengths: large cohort, long follow-up (6–10 years), validated assessment tools, adjustment for age/comorbidity. Limitations: observational design; possible confounding (menopausal status, biochemical thresholds for levothyroxine, thyroid antibody levels), selection bias (60% response rate), self-report bias. Risk of Bias: Moderate. |
| **Fibromyalgia (FMS)** | Sex-Related Differences in Symptoms and Psychosocial Outcomes in Patients With Fibromyalgia: A Prospective Questionnaire Study. DOI:10.1016/j.mayocpiqo.2020.06.009 | Jiang et al. 2020 | Prospective cohort questionnaire study. | N: 668 patients Gender: 606 women (90.7%), 62 men (9.3%)Age: Mean 47.2±13.0 yearsEthnicity/Country: 93.5% White men, 88.6% White women; USA (the Fibromyalgia and Chronic Fatigue Clinic). | - Higher tender point count (TPC) in women (p<0.001).- No sex differences in depression, anxiety, sleep problems, FMS symptom severity, cognitive dysfunction, or quality of life (QoL), after Benjamini-Hochberg adjustment.- Lower symptom severity in women (p=0.03) pre-adjustment; (Revised Fibromyalgia Impact Questionnaire). | Tool: ROBINS-I (Risk Of Bias In Non-randomized Studies).- Strengths: relatively large cohort, validated questionnaires, adjusted for confounders (age, BMI, education).- Limitations: selection bias (single-center; limited generalizability), self-report bias (subjective symptom reporting), non-balanced gender representation.Risk of Bias: Moderate. |
| Gender Differences in Symptoms, Health-Related Quality of Life, Sleep Quality, Mental Health, Cognitive Performance, Pain-Cognition, and Positive Health in Spanish Fibromyalgia Individuals: The Al-Ándalus Project. DOI:10.1155/2016/5135176  | Segura-Jiménez et al. 2016 | Cross-sectional study | N: 652 participants (405 FMS patients, 247 healthy controls) Gender: FMS patients (384 women, 21 men), healthy controls (195 women, 52 men)Age: Mean ~49 years (FMS women), ~47 years (FMS men)Ethnicity/Country: Spain (Andalusia). | FMS Group:- Men had better working memory (PASAT; p<0.01).- Women had shorter sleep latency (47.9 vs. 72.7 mins, p=0.013).Healthy controls non-FMS Group:- Men had higher pain thresholds (all tender points except epicondyles, p<0.01), and better working memory than women (p<0,01).- Women had better verbal memory (RAVLT, P ≤ 0.01). | Tool: ROBINS-I.- Strengths: relatively large sample, comprehensive assessments using validated tools, adjusted for confounders.- Limitations: cross-sectional design (no causality), small male subgroup, self-report bias.Risk of Bias: Moderate. |
| Gender influence on clinical manifestations, depressive symptoms and brain-derived neurotrophic factor (BDNF) serum levels in patients affected by fibromyalgia. DOI:10.1007/s10067-022-06133-y  | Iannuccelli et al. 2022 | Cross-sectional study | N: 241 participants (201 FMS patients, 40 healthy controls) Gender: Patients (172 women, 29 men) matched by age/sex with the healthy controlsAge: Mean 49 years (FMS group)Ethnicity/Country: Italy (Sapienza University of Rome). | - FMS Women: Higher pain, fatigue, memory issues, tenderness, balance problems and sensitivity to environmental stimuli compared to males.- FMS Men: Higher depressive symptoms (72.4% vs. 51.9%, p=0.038).- BDNF: Lower in FMS patients compared to healthy controls (p<0.0001); FMS men had lower BDNF than FMS women and than healthy control men, FMS women had lower BDNF than healthy control women. | Tool: ROBINS-I.- Strengths: validated tools employed, BDNF measured via ELISA with sensitivity controls, adjusted for confounders (age, BMI).- Limitations: small male subgroup, single-center recruitment (selection bias), cross-sectional design (no causality).Risk of Bias: Moderate. |
| **Guillain-Barré Syndrome (GBS)** | Factors associated with long-term functional outcomes and psychological sequelae in Guillain–Barre syndrome. DOI: 10.1007/s00415-010-5653-x  | Khan et al. 2010 | Prospective observational cohort study with structured interviews and medical record review. | N: 76 (from 157 initially identified; 62% recruitment rate)Gender: 60% males, 40% femalesAge: Mean 56 years Ethnicity/Country: Australia (Royal Melbourne Hospital)  | - Demographic: Females and older adults (57+ years) had worse functional (↓FIM scores) and psychological outcomes (↑DASS scores).- Clinical severity indicators: ICU admission, prolonged acute hospital length of stay (LOS) >11 days, and discharge destination (to a rehabilitation facility) linked to lower function and higher participation restrictions.- Time since diagnosis showed no association with outcomes of functional independence or psychological wellbeing.- Overall, a high percentage of participants reported moderate, severe or extreme levels of depression, anxiety and stress. | Tool: Newcastle-Ottawa Scale (NOS).- Strengths: validated tools used, comprehensive assessments.- Limitations: small sample, regional bias, self-reporting bias, no adjustment for confounders.Risk of Bias: Moderate. |
| **Myasthenia Gravis (MG)** | Gender differences in quality of life among patients with myasthenia gravis in China. DOI: 10.1186/s12955-020-01549-z | Dong et al. 2020 | Cross-sectional study (using online questionnaires). | N: 1815 patients (from 2000 initially recruited)Gender: 1194 females (66%), 621 males (34%)Age: Mean 43.4 years (males), 39.8 years (females)Ethnicity/Country: China  | - Gender Disparity: Females reported lower HRQoL across all domains (physical, social, and emotional; p < 0.05).- Comorbidities: Interaction between gender and comorbidities worsened HRQoL more in females (p < 0.05).- Key Factors: Unemployment (p < 0.001), MG exacerbations (p < 0.001), and active lifestyle (p < 0.001) strongly influenced HRQoL.- Clinical: Females had worse MG activities of daily living scale (MG-ADL) scores and higher rates of autoimmune thyroid disease. | Tool: JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies.- Strengths: validated tools used, comprehensive assessments, adjustment for confounders.- Limitations: convenience sampling, self-reporting bias, no objective clinical severity measures, lack of causality due to study design.Risk of Bias: Moderate. |
| Female sex and overweight are associated with a lower quality of life in patients with myasthenia gravis: a single center cohort study. DOI: 10.1186/s12883-023-03406-0  | Wilcke et al. 2023 | Mixed retrospective-prospective cohort study (monocentric). | N: 165 patients.Gender: 85 males (51.5%) , 80 females (48.5%).Age: Mean 59.8 years at study entry; females younger at symptom onset (50.1 vs. 58.4 years).Ethnicity/Country: Germany. | - Gender: Females had lower HRQoL (MG-QoL15) and worse functional status (MG-ADL).- BMI: Higher BMI correlated with poorer HRQoL (β = +1.29 per BMI unit, p = 0.005) and MG-ADL (p = 0.017).- Clinical: Disease severity (QMG) strongly impacted HRQoL (β = +17.6, p < 0.001). Females experienced longer diagnosis delays (2.15 vs. 0.87 years, p = 0.034).- Comorbidities: Females had higher rates of depression (28.7% vs. 15.3%, p = 0.04) and autoimmune diseases (27.5% vs. 9.4%, p = 0.004). | Tool: JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies.- Strengths: validated tools used, comprehensive assessments, adjustment for confounders (age, disease severity).- Limitations: small sample for BMI analysis, retrospective design, convenience sampling.Risk of Bias: Moderate. |
| **Multiple Sclerosis (MS)** | Can we predict cognitive decline after initial diagnosis of multiple sclerosis? Results from the German National early MS cohort (KKNMS). DOI: 10.1007/s00415-018-9142-y | Johnen et al. 2019 | Prospective multicenter cohort study (NationMS), longitudinal (baseline and 1-year follow-up). Bayesian multilevel regression models. | N: 1123 patients; newly diagnosed multiple sclerosis (MS) or clinically isolated syndrome (CIS).Gender: 2.2:1 female-to-male ratio.Age: Median of onset is 31,71 years.Ethnicity/Country: Germany. | - 22% of patients had CI at baseline (processing speed/executive function most affected). - Baseline CI predictors: Older age, male sex, lower education, higher physical disability (EDSS), and depression (BDI-II) linked to greater CI severity. - Demographic, clinical, and conventional MRI data insufficient for identifying short-term cognitive change risks in newly diagnosed MS or CIS patients. | Tool: Newcastle-Ottawa Scale (NOS).- Strengths: large multicenter cohort, standardized protocols, controlled for age/gender/education.- Limitations: short follow-up, unmeasured confounders (cognitive reserve), practice effects in cognitive testing.Risk of Bias: Moderate. |
| Sex Differences in Resting-State Functional Connectivity in Multiple Sclerosis. DOI: 10.3174/ajnr.A3630 | Koenig et al. 2013 | Cross-sectional case-control study. | N: 64 participants; 32 MS patients matched with 32 healthy controls. Gender: MS patients (16 males, 16 females), healthy controls (16 males, 16 females). Age: Mean age of 41.85 years. Ethnicity/Country: USA. | - MS patients showed stronger connectivity from posterior cingulate to medial frontal gyri, anterior cingulate, right putamen, and left middle temporal gyrus compared to healthy controls (P < .0005). - Male MS patients had weaker connectivity to the caudate compared to female MS patients (P = .004). While male controls have stronger connectivity between posterior cingulate and left prefrontal cortex than female controls.- Female MS patients had stronger connectivity between posterior cingulate and left prefrontal cortex compared to female controls. | Tool: Newcastle-Ottawa Scale (NOS).- Strengths: Age/sex matching of controls, standardized MRI protocols and motion correction, blinded neuropsychological assessments.- Limitations: small sample size,cingle-center design (potential selection bias), lack of longitudinal data to assess causality. Risk of Bias: Moderate. |
| What Can We Learn from Sex Differences in MS? DOI: 10.3390/jpm11101006  | Coyle et al. 2021 | Integrative Literature review. | N/A (discusses global MS demographics). | - MS is more common in females, with high variability.- Relapsing MS is the most common phenotype (RRMS).- PPMS has a later age of onset (decade later than RRMS).- MS disease activity decreases during pregnancy (3rd trimester), rebounds postpartum, and may worsen after menopause.- Males more likely to develop primary progressive MS (PPMS), with worse prognosis, cognitive impairment, and disability.- Males with RRMS show more motor issues and fewer optic neuritis cases.- MS males have lower LH, FSH, and testosterone levels.- Sex hormones (estriol, testosterone) have immunomodulatory effects on MS. - Progressive MS males show more severe HPT axis abnormalities than RRMS males.- Obesity and high BMI in adolescence increase MS risk in males.- Neuroimaging: Greater gray matter atrophy in males; hormonal influences on CNS structure.- Comorbidities: Higher vascular comorbidities in males; mental health issues in females.- Treatment: Safety considerations for disease-modifying therapies (DMTs) during pregnancy and breastfeeding. | Tool: SANRA (Scale for the Assessment of Narrative Review Articles).- Strengths: comprehensive scope and up-to-date coverage of data, clinically relevant insights (pregnancy, DMT use).- Limitations: methodological limitations (literature review).Risk of Bias: Moderate. |
| Potential biological contributers to the sex difference in multiple sclerosis progression. DOI: 10.3389/fimmu.2023.1175874  | Alvarez-Sanchez et al. 2023 | Integrative Literature review. | N/A (synthesizing human and animal studies, with diverse demographics) | - Males exhibit faster progression, more cortical lesions, and cognitive decline (verbal and non-verbal memory, information processing speed, attention, and executive functioning deficits) than females. - Males exhibit lower functional connectivity and network efficiency. - Females show better remyelination, robust anti-viral responses, and hormonal neuroprotection. - These gender-related disparities related to numerous factors (including immune, hormonal, structural, environmental, metabolic, and gastrointestinal). | Tool: SANRA.- Strengths: comprehensive coverage of existing studies; highlights understudied mechanisms.- Limitations: methodological limitations (literature review).Risk of Bias: Moderate. |
| Quantitative effect of sex on disease activity and disability accumulation in multiple sclerosis. DOI: 10.1136/jnnp-2022-328994  | Magyari et al. 2022 | Observational cohort study (Nationwide population-based). | N: 9647 patients; RRMS treated with DMTs (since 1996).Gender: 3028 males, 6619 females.Age: Mean age at onset is 34.3 (male), 33.5 (females).Ethnicity/Country: Danish population (Denmark). | - Women had 16% higher relapse rates than men, but this difference disappeared after age 50.- Men showed faster disability accumulation (annual EDSS increase: 0.07 vs. 0.05 in women, p = 0.017).- Men had higher hazards of reaching EDSS 4 (HR: 1.34) and EDSS 6 (HR: 1.43) (p < 0.001).- Gender-related differences in neurodegenerative symptoms became pronounced after age 45. | Tool: ROBINS-I.- Strengths: nationwide registry data minimizing selection bias, adjustment for confounders, large sample size.- Limitations: exclusion of untreated/progressive MS patients, lack of MRI data, potential unmeasured confounders (lifestyle factors).Risk of Bias: Moderate. |
| Estriol-mediated neuroprotection in multiple sclerosis localized by voxel-based morphometry. DOI: 10.1002/brb3.1086 | MacKenzie-Graham et al. 2018 | Randomized Controlled Trial (Phase 2) “A Combination Trial of Copaxone plus Estriol in RRMS” | N: 111 RRMS patients (62 estriol-treated, 49 placebo-treated). - Gender: Female. - Age: 18–50 years (mean 37.3 ± 7.5). - Ethnicity/Country: 81.1% Caucasian, 9.9% Black, 8.1% Hispanic; USA-based. | - Estriol preserved gray matter (GM) in frontal and parietal cortices, correlating with improved PASAT scores. - Estriol group had less whole GM atrophy (0.5% vs. 1.5% annualized loss). - Early intervention with a neuroprotective agents is better to prevent GM loss and cognitive impairment (CI). - No significant effects on motor outcomes. | Tool: Cochrane Risk of Bias 2.0 (RoB 2) .- Strengths: randomized, blinded outcome assessment, controlled for multiple comparisons.- Limitations: small sample size, multi-site MRI variability, potential practice effects on PASAT.Risk of Bias: Moderate. |
| **Narcolepsy Type 1 (NT1)** | Gender medicine and sleep disorders: from basic science to clinical research. DOI: 10.3389/fneur.2024.1392489 | Perger et al. 2024 | Integrative literature review. | N/A (depends on each study included; some studies are not accessible). | Females exhibit an earlier onset of EDS and cataplexy, more severe EDS, and longer diagnostic delay compared to males.Males experienced fewer nocturnal awakenings compared to females.Neurobiological differences suggest sex-specific variations in narcolepsy symptoms and sleep patterns. Findings underscore the need for more systematic studies to confirm sex-related disparities and their mechanisms. | Tool: SANRA.- Strengths: comprehensive Scope, multidisciplinary analysis, balanced synthesis (acknowledges conflicting data and methodological heterogeneity), clinical relevance.- Limitations: narrative design limitations, geographic bias (European cohorts), confounding variables.Risk of Bias: Moderate.  |

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