- Copyright - Il Pensiero Scientifico Editore downloaded by IP 3.133.159.224 Wed, 24 Apr 2024, 10:54:58

Supplementary material for

Sex and gender differences in the neurological and neuropsychiatric symptoms of long COVID: a narrative review

Adelaide Jensen, Alex W Castro, Maria Teresa Ferretti, Julie Martinkova, Anna Vasilevskaya, Antonella Santuccione Chadha, Maria Carmela Tartaglia

Corresponding author: Adelaide Jensen, email: ajens098@uottawa.ca

Table 1S. Summary of research articles reporting sex-disaggregated data

Reference	Sex-specific findings	Outcome(s)	Sample size (% females)	Age	Acute COVID-19 severity and/or hospitalization status	Interval between acute and long COVID (i.e., time at assessment)	Proportion of sample with long COVID symptoms	Criteria for COVID-19 diagnosis	Study design	Pre-COVID-19 medical comorbidities
Huang et al. 2021[8]	Males had worse COVID-19 disease severity 81% of females reported long COVID symptoms (vs 73% of males) Females were more likely to experience fatigue, anxiety and depression at 6 months post-covid	Self-report symptoms (new and persistent), shortness of breath, and health-related quality of life assessed in person at outpatient clinic	N=1733; 48% female	Median=57; range=47-65	Moderate to critical; hospitalized	6 months post symptoms onset	76%	Laboratory-confirmed (test not specified)	Ambidirectional cohort study	The most common comorbidities in the overall sample were hypertension (29%), diabetes (12%), and cardiovascular disease (7%) Presence of comorbidity was included as a confound in statistical analyses
Stavem et al. 2021[9]	Fewer females (53%) reported zero COVID-19 symptoms at follow-up (vs 67% of males). Symptoms included fever, headache, myalgia, cough, etc.	Long COVID comorbidities and acute symptoms assessed through postal or online survey	N=451; 56% female	Mean=49.8; SD=15.2	Non-hospitalized	1.5-6 months post positive COVID-19 diagnosis	47% of women and 33% of men	PCR	Prospective cross-sectional survey	28% of participants had 1 comorbidity, 21% had 2 or more Number of comorbidities was associated with presence of persistent symptoms
LaVergne et al. 2021[22]	In comparing those with and without post-acute COVID-19 sequelae in mild disease, NO difference in sex/gender Male sex was a risk factor for severe acute COVID-19 illness	Assessment of physiological samples and post-acute sequelae of COVID-19	N=119; 71% female	Mild: mean=39.2; SD=15.9 Moderate: mean=62.1; SD=14 Severe: mean=59.7; SD=13.3	Mild/asymptomatic, moderate, and severe	Up to 8 months post infection	49%	PCR	Cross-sectional	Most commonly reported comorbidities were hypertension, diabetes mellitus, and COPD Hypertension and diabetes were more commonly reported in the severe group, and COPD was more frequent in patients with moderate COVID-19 Presence of underlying health conditions not associated with long COVID
Bierle et al. 2021[31]	Headache, anorexia, and joint pain were more common in females Paresthesis and chest pain more common in males Female-to-male ratio was 2:1 in this sample	COVID-19 symptom characterization, review of medical records	N=42; 66.6% female	Median=46.5 (male) and 46.2 (female); range=21-74	Not specified	Mean=11 weeks (range=4-22) post COVID-19 symptoms onset	100%	Positive PCR test or rapid antigen test with viral prodrome or positive serology with viral prodrome	Retrospective	N/A
Carvalho-Schneider et al. 2021[32]	Female sex was not a significant predictor of persistent physical or neurological symptoms at 30 or 60 days after symptom onset	Structured phone interview assessing persistent symptoms	N=150; 56% female	Mean=49; SD=15	Noncritical covid outpatients and inpatients (no ICU)	Assessment at 7, 30, and 60 days post COVID-19 symptom onset	68% at 30 days, 60% at 60 days	PCR	Prospective follow-up	46% had no comorbidities, 34.7% had 1 comorbidity, and 18.7% had 2 or more comorbidities Relevant comorbidities included: obesity, chronic respiratory disease, dialysis, heart failure/previous cardiovascular event, liver cirrhosis, diabetes, immunossuppression, and pregnancy Persisting symptoms at day 30 post COVID-19 symptom onset were not associated with comorbidities

- Copyright - Il Pensiero Scientifico Editore downloaded by IP 3.133.159.224 Wed, 24 Apr 2024, 10:54:58

Table 1S.

Reference	Sex-specific findings	Outcome(s)	Sample size (% females)	Age	Acute COVID-19 severity and/or hospitalization status	Interval between acute and long COVID (i.e., time at assessment)	Proportion of sample with long COVID symptoms	Criteria for COVID-19 diagnosis	Study design	Pre-COVID-19 medical comorbidities
Gebhard et al. 2021[37]	Females more often reported at least 1 persistent neuropsychiatric symptom (43% vs 31.5% in men) Being responsible for household work (in men), taking care of family (women) or being pregnant at the time of acute illness was associated with lower odds of developing long covid	COVID-19 symptom and risk factor characterization through phone, email, or paper form interview	N=1285; 45.9% female	Mean=43.59; SD=16.54	Outpatients (16.5%) and inpatients (83.5%)	Mean=197 days post COVID-19 symptom onset	36.8%	PCR	Prospective observational	Comorbidities in overall sample: mental disorder (5%), autoimmune/rheumatoid disease (7.3%), neurological disease (4.6%), cardiovascular disease (10.9%), pulmonary disease (7.1%), and cancer (5.1%) Pre-existing mental illness and cardiovascular problems increased the odds of developing long COVID in females but not in males Obesity increased the odds of developing long COVID in males but not in females
Menges et al. 2021[38]	Higher percentage of females and initially hospitalized individuals reported not having fully recovered Females were less likely to have recovered than males A higher percentage of females (vs males) reported new or ongoing symptoms Younger individuals and females more frequently reported symptoms of fatigue, but there was no significant associations between sex and fatigue There was a higher percentage of grade >1 dyspnea among older participants, females, and initially hospitalized patients There was an association between grade >1 dyspnea with female sex, initial hospitalization, higher BMI, and presence of comorbidities A higher percentage of older and female participants reported depressive symptoms Younger patients and females more often reported symptoms of stress There was no association between sex and these symptoms (in multivariate analyses) There was an association between healthcare use and female sex	Prevalence of impaired health status and physical and mental health symptoms, assessed by electronic baseline questionnaire	N=431; 50% female	Median=47; Range=33-58	Mild-moderate (51%), severe-very severe (38%); hospitalized (19%)	6-8 months post initial COVID-19 diagnosis	38.5%	PCR	Population-based prospective cohort study	34% of sample had one or more chronic medical comorbidities Presence of comorbidity was associated with grade >1 dyspnea at follow-up
Halpin et al. 2020[39]	Females had a higher prevalence of symptoms of PTSD, fatigue, breathlessness, worse quality of life (i.e., more problems with mobility, self-care, daily activities) compared to males	COVID-19 rehabilitation screening and health-related quality of life assessed by telephone interview	N=100; 46% female	ICU patients: Median=58.5; Range=34-84 Ward patients: Median=70.5; Range=20-93	Hospitalized (ICU and ward)	4-8 weeks post hospital discharge	Not reported	PCR	Prospective follow-up	70.6% of ward patients and 56.3% of ICU patients had 3 or more comorbidities The most common comorbidities were overweight/obesity, hypertension, and type 2 diabetes
Boscolo-Rizzo et al. 2021[45]	72% of those reporting persistent symptoms were female (vs 28.9% male), but sex was not associated with persistence of chemosensory dysfunction	Self-reported questionnaire on long-term smell and taste dysfunction, assessed by telephone interview	N=268; 61.9% female	Median=48	Mild to moderate; home isolated	Baseline=3 weeks from first positive PCR test; follow up 12 months later	21.3%	PCR	Prospective follow-up	34% of sample had one or more comorbidities

- Copyright - Il Pensiero Scientifico Editore downloaded by IP 3.133.159.224 Wed, 24 Apr 2024, 10:54:58

Table 1S.

Reference	Sex-specific findings	Outcome(s)	Sample size (% females)	Age	Acute COVID-19 severity and/or hospitalization status	Interval between acute and long COVID (i.e., time at assessment)	Proportion of sample with long COVID symptoms	Criteria for COVID-19 diagnosis	Study design	Pre-COVID-19 medical comorbidities
Ekstrom et al. 2021[46]	Higher percentage in females (vs males) of symptoms of tiredness/fatigue, headache, sore throat, joint/muscle pain, abdominal symptoms, and more bed-bound disease severity Higher percentage of males (vs females) reported cough as a symptom Females reported a higher overall number of symptoms than males (63.7% vs 53.6%) There was a trend toward female sex being associated with long-term COVID-19 symptoms (however not statistically significant)	Self-reported symptoms assessed by online questionnaire	N=1644; 60.6% female	Mean=25.3	50% bed bound, 0.4% hospitalized	4+ weeks from symptom onset	10.8%	31% of sample self-reported antibody testing or active infection	Prospective follow-up	3.7% of sample were daily smokers and 11% were occasional smokers, but smoking was not significantly associated with long-term COVID-19 symptoms
Islam et al. 2021[47]	More females reported self-medicating, persistent symptoms, and moderate to severe depression (vs males)	Online survey assessing health status, COVID-19 symptoms, treatment and medications, depression and anxiety (PHQ-9), and fear of re-infection	N=1002; 42.1% female	Mean=34.7; Range=18-81	21% hospitalized	Post recovery from COVID-19, interval time not specified	20%	Positive test (not specified)	Cross-sectional survey	Underlying health conditions reported by participants were diabetes (21.1%), hypertension (24.9%), heart disease (8.2%), cancer (2.4%), kidney problems (5.9%), and asthma/respiratory problems (25.4%) Underlying asthma/respiratory problems were significantly associated with moderate to severe depression Other pre-existing comorbidities were not significantly associated with self-medicating behaviour or persistent long COVID symptoms
Khademi et al. 2021[48]	Females reported experiencing anxiety and depression symptoms significantly more often than males	Depression and anxiety symptoms (PHQ-4) and post-traumatic stress symptoms assessed over telephone interview	N=602; 36% female	Mean=53.2	Mild (non-hospitalized) and severe (hospitalized)	1.5 months post COVID-19 diagnosis	Not reported	Not specified	Prospective cross-sectional	N/A
Romero-Duarte et al. 2021[49]	Headache, depressive symptoms, anxiety symptoms, and fatigue were more common in females (vs males)	General/systemic, respiratory, neurological, and mental health symptoms assessed through patient primary care records	N=797; 46.3% female	Mean=63	Hospitalized or admitted to ICU	6 months post hospital discharge	63.9%	PCR	Retrospective observational	67.5% of overall sample had one or more comorbidities. Some common comorbidities included hypertension (51.3%), diabetes mellitus (20.8%), cardiovascular disease (20.6%), and pneumopathy (13.4%) Associations between comorbidity and persistent symptoms were not reported
Beck et al. 2021[50]	Female sex was associated with increased likelihood of psychological distress (66.7% vs 33.3% males) Females had significantly more PTSD symptoms 30 days post-discharge (90% vs 10% males)	Psychological distress and PTSD symptoms assessed by telephone interview	N=126; 39.7% female	Mean 58.2; SD=16.10	Severe, ICU patients	30 days post hospital discharge	Not reported	PCR	Prospective observational cohort study	14.8% of participants had pre-existing psychological comorbidities
Zhou et al. 2021[51]	Females reported significantly higher PTSD scores (vs males) The authors found NO differences in other COVID-19 symptoms between the sexes	Assessment of persistent COVID-19 symptoms and PTSD through semi-structured questionnaires	N=89; 48.3% female	Median=43; Range=31-52	Hospitalized	3+ weeks post hospital discharge	57.3% (not fully recovered from acute COVID-19)	Positive RNA detection (not specified)	Longitudinal	N/A
Mazza et al. 2021[52]	Significantly worse persistence of depressive symptomatology, psychopathological symptoms, and working memory, and lower systemic immune-inflammatory (SII) scores in females (vs males)	Assessment of systemic inflammation, psychiatric clinical interview, self-report questionnaires, neuropsychological testing	N=226; 34% female	Mean=58; SD=12.79	Severe, admitted to ER	3 months post hospital discharge	Not reported	PCR	Prospective	Individuals with previous psychiatric diagnosis had worse psychopathological symptoms at follow-up

- Copyright - Il Pensiero Scientifico Editore downloaded by IP 3.133.159.224 Wed, 24 Apr 2024, 10:54:58

Table 1S.

Reference	Sex-specific findings	Outcome(s)	Sample size (% females)	Age	Acute COVID-19 severity and/or hospitalization status	Interval between acute and long COVID (i.e., time at assessment)	Proportion of sample with long COVID symptoms	Criteria for COVID-19 diagnosis	Study design	Pre-COVID-19 medical comorbidities
Sykes et al. 2021[53]	Females reported more anxiety, low mood, myalgia, fatigue, sleep disturbance, and memory impairment compare to males	Quality of life, dyspnea, and COVID-19 symptom burden assessed through in-person clinical assessment, questionnaires, and chest x-ray	N=134; 34.3% female	Mean=59.6; SD=14	Severe; hospitalized for COVID-19 pneumonia	Median=113 days post hospital discharge	86%	PCR	Prospective follow-up	14.2% had three or more pre-existing comorbidities, the most common being smoking history (44%), alcohol use (42.5%) and hypertension (41%) Associations between comorbidities and study outcomes were not reported
Xiong et al. 2021[55]	Physical decline/fatigue, post-activity polypnoea, and alopecia were more common in females (vs males)	Self-reported persistent COVID-19 symptoms assessed by telephone interview	N=293; 54.5% female	Median=52; Range=41-62	Moderate to severe; hospitalized	3 months post hospital discharge	49.6%	Positive diagnosis (not specified)	Longitudinal follow-up	Comorbidities were reported by 32.9% of COVID-19 survivors, including hypertension (15.2%), diabetes (7.4%), COPD (4.1%), coronary heart disease (3.3%), chronic kidney disease (2.2%), and carcinoma (0.9%) Associations between comorbidity and study outcomes were not reported
Blomberg et al. 2021[56]	In home-isolated patients aged 16+ years, female sex was associated with fatigue at 6 months	COVID-19 symptom characterization, in-person interviews	N=247; 51% female	Median=46; Range=30-58	Mild; home-isolated	6 months following initial COVID-19	55%	PCR	Prospective; long-term follow-up	44% of patients with COVID-19 had a comorbidity, including 69% of hospitalized patients and 37% of home-isolated patients Comorbidities included: asthma or COPD, hypertension, chronic heart disease, rheumatic disease, diabetes mellitus, immunosuppression, and current or prior smoker
Gaber et al. 2021[59]	Females were more likely to suffer from long-term healthcare problems post-covid (91%) 45% of females reported persistent symptoms (vs 27% of males) The most common symptoms reported were fatigue, sleep disturbance, and mood disturbance	Questionnaires assessing COVID-19 incidence and symptoms in hospital employees (e.g., sleep disturbances, fatigue, shortness of breath, mood disorders)	N=138; 92% female	Not specified	Not specified	3-4 months from peak of first wave	45%	Antibody test	Retrospective	N/A
Walsh-Messinger et al. 2021[60]	There were 21 females and only 1 male in the post-COVID syndrome group, suggesting that females may be more prone to a prolonged course of illness and/or post-COVID complications. Long COVID was assessed by duration of symptoms	Duration and characterization of COVID-19 symptoms; perceived stress (PSS), depression symptoms (CESD-R), and anxiety symptoms (GAD-7) assessed through online survey	N=148	Mean ~19 (university students)	Mild to moderate; none hospitalized	28+ days post onset of COVID-19 symptoms	51%	Positive diagnosis (not specified)	Retrospective cohort study	Some participants were smokers or used vaping devices, however there were no statistically significant differences in cigarette or vape usage between COVID negative, recovered, and long COVID groups
Taboada et al. 2021[61]	Female sex was associated with limitations in functional status measured by the Post-COVID-19 Functional Status scale	Post-COVID-19 Functional Status Scale assessed through structured interviews	N=183; 40.5% female	Mean 65.9; SD=14.1	Hospitalized (ICU and non-ICU)	6 months post hospitalization	47.5%	PCR	Cross-sectional observational	Most common comorbidities were hypertension (44.2%), hyperlipidemia (37.2%), and obesity (28.9%) Comorbidity was not significantly associated with study outcomes
Garcia-Abellan et al. 2021[62]	Female sex predicted long-term symptoms including fatigue, myalgia, dyspnea, cough, and nasal congestion	Long-term clinical, virological and serological outcomes	N=146; 40% female	Median=64; Range=54-76	All hospitalized	2 months and 6 months post hospital discharge	At 2 months: 9.6% (general), 7.4% (gastrointestinal), 2.9% (respiratory) At 6 months: 7.8% (general), 4.3% (gastrointestinal), 1% (respiratory)	PCR	Prospective longitudinal	72.6% of participants had one or more comorbid diseases, including cardiovascular disease (21.2%), hypertension (21.9%), diabetes (22.6%), and chronic obstructive lung disease (5.5%)
Sudre et al. 2021[63]	Disease lasting 28-56 days disproportionately affected females (14.9% vs 9.5% of males), but not in individuals aged 70 years and older Long COVID was characterized by symptoms of fatigue, headache, dyspnea, and anosmia	Prevalence and risk factors of long COVID assessed through COVID symptom study app	N=4182; 71.5% female	Median=42; Range=32-53	Varying severity	2 subgroups: symptoms lasting 28-56 days (LC28) vs symptoms lasting 56+ days (LC56)	13.3% (includes LC28 and LC56)	PCR (assumed)	COVID study app questionnaires	Obesity (26.3%), asthma (10%), lung disease (13.6%), diabetes (2.9%), heart disease (1.6%), and kidney disease (0.4%)

- Copyright - Il Pensiero Scientifico Editore downloaded by IP 3.133.159.224 Wed, 24 Apr 2024, 10:54:58

Table 1S.

Reference	Sex-specific findings	Outcome(s)	Sample size (% females)	Age	Acute COVID-19 severity and/or hospitalization status	Interval between acute and long COVID (i.e., time at assessment)	Proportion of sample with long COVID symptoms	Criteria for COVID-19 diagnosis	Study design	Pre-COVID-19 medical comorbidities
Jacobson et al. 2021[64]	Sex was not associated with presence of persistent long COVID symptoms	Survey assessing persistent functional impairment and work productivity and activity	N=118; 46.6% female	Mean=43.3; SD=14.4	Hospitalized and non-hospitalized	3-4 months post COVID-19 diagnosis	81.8% of hospitalized patients and 64.2% of non-hospitalized patients	PCR	Prospective follow-up	33.1% of overall sample had one or more pre-existing comorbidities, including 54.5% of hospitalized patients and 28.1% of non-hospitalized patients
Gonzalez-Hermosillo et al. 2021[65]	45% of patients with fatigue were female (vs 27.8% without) (not significant, p=.09) Risk trend toward female sex observed but did not reach significance (p=.07) No significant differences between the sexes on long covid symptoms	Demographics, clinical characteristics, pre-existing comorbidities, and lab findings retrieved from medical records	N=130; 34.6% female	Mean=51; Range=18-80	Moderate to severe; hospitalized	6 months post hospital discharge	91.5%	PCR	Prospective longitudinal observational	Comorbidities in overall sample: hypertension (40.7%), overweight (47.6%), obesity (29.2%), diabetes (31.5%), chronic heart disease (16.9%), COPD (3%), chronic kidney disease (10.7%), immunosuppressive condition (11.5%), and psychiatric disorder (1.5%) There was no significant difference in comorbidities between patients with and without fatigue
Moreno-Perez et al. 2021[66]	Sex was not an independent predictor of long COVID	Incidence of long COVID condition and identification of risk factors assessed during hospital visit	N=227; 47.3% female	Median=56; Range=42-67	Mild (34.3%) and severe (77.5%)	2-4 months post COVID-19 onset	50.9%	PCR	Prospective cohort study	Comorbidities in overall sample included: hypertension (36.5%), diabetes (11.6%), obesity (30.6%), cardiovascular disease (6.9%), chronic respiratory disease (18.1%), immunosuppression (4.7%) Presence of comorbidity not significantly associated with post-COVID-19 syndrome
Pilotto et al. 2021[67]	There were no differences in neurological features and complaints between COVID-19 severity subgroups in terms of sex	Neurological and cognitive manifestations of COVID-19 assessed through structured clinical interview	N=165; 30.3% female	Mean=64.8; SD=12.6	Mild to severe; hospitalized	6 months post hospital discharge	Not reported	Not specified	Longitudinal prospective	Pre-existing comorbidities were a significant predictor of total number of neurological symptoms
Osikomaiya et al. 2021[68]	Sex was not associated with presence of persistent symptoms after hospital discharge	Identification of long COVID risk factors and description of persistent symptoms through assessment of patient medical files	N=274; 33.9% female	Mean=41.8; SD=11.8	Asymptomatic to severe. Most were mild (50.7%) or moderate (39%)	Median=15 days post hospital discharge	40.9%	PCR	Retrospective	21.5% of participants had one or more comorbid conditions, including hypertension (72.9%), diabetes mellitus (15.3%), other (8.5%), peptic ulcer disease (6.8%), rheumatoid arthritis (5.1%), and asthma (3.4%) Presence of multiple comorbidities was not associated with persistent COVID-19 symptoms
Woo et al. 2020[69]	Sex was not a predictor of cognitive deficits	Cognitive impairment assessed through telephone interview	N=18; 57.1% female	Mean=42.2; SD=14.3	Mild to moderate; non-ICU outpatients	20-105 days post recovery from mild-moderate disease	64%	PCR	Cross-sectional	Comorbidities reported by post-COVID sample were asthma (16.7%), hypothyrodism (16.7%), hypertonus (i.e., muscle stiffness) (11.1%), coagulation disorder (11.1%), diabetes mellitus (5.6%), multiple sclerosis (5.6%), autoimmune hepatitis (5.6%), and follicular lymphoma (5.6%) Associations between comorbidity and study outcomes were not reported
Peghin et al. 2021[95]	Female sex was an independent risk factor of long COVID	COVID-19 symptom characterization assessed by telephone interview	N=599; 40% female	Mean=53	Asymptomatic to critical; hospital outpatients and inpatients	6 months post symptom onset	40,20%	PCR	Bidirectional prospective interview	11.2% of participants were current smokers, and 22% were previous smokers
Philips et al. 2021[96]	Females had 2 days longer shedding durations at the 25th percentile and the median compared to males in same group	Viral shedding (i.e., duration of RT-PCR-tested SARS-CoV-2 detection) and variability due to health/social factors through search in province-wide database	N=6604; 64.5% female	Mean=57.9	Non-hospital/ICU (63.5%), hospitalized (20.9%), ICU (6.8%), ER visit (31.8%)	Median follow-up=26 days after first viral test	Not reported	PCR	Retrospective	Comorbidities in overall sample included: asthma (16.1%), congestive heart failure (10.2%), COPD (12.7%), hypertension (45.7%), and diabetes (25.8%)

Not all studies reported the same descriptive statistics for participant age. Some reported mean and SD, while other reported median.

BMI: body mass index; CES-D: Center for Epidemiologic Studies Depression Scale; COPD: chronic obstructive pulmonarydisease; ER: emergency room; GAD-7: Generalised anxiety disorder assessment; NEWS: National early warning score; PCR: polymerase chain reaction; PHQ-4: Patient health questionnaire-4; PSS: Perceived stress scale; PTSD: Posttraumatic stress disorder.