Original article

Factors affecting climacteric women with SARS-CoV-2 infection: A multinational Latin America study (REDLINC XI)

María S. Vallejo [a], Juan E. Blümel [b, *], Ascanio Bencosme [c], Andrés Calle [d], Maribel Dextre [e], Karen Díaz [f], Marcela López [g], Carlos Miranda [h], Mónica Ñañez [i], Eliana Ojeda [j], Claudia Rey [k], Marcio A. Rodrigues [l], Carlos Salinas [m], Konstantinos Tserotas [n], Faustino R. Pérez-López [o]

[a] *Clínica Quilín, Facultad de Medicina, Universidad de Chile, Santiago de Chile, Chile*
[b] *Departamento de Medicina Interna Sur, Facultad de Medicina, Universidad de Chile, Santiago de Chile, Chile*
[c] *Ginecología Obstetricia, Hospital Metropolitano de Santiago, Santiago de los Caballeros, Dominican Republic*
[d] *Centro Integral de Salud Obstétrica y Femenina-CISOF, Quito, Ecuador*
[e] *Ginecología Obstetricia, Clínica Internacional-Clínica Javier Prado, Lima, Peru*
[f] *Centro Ciudad Mujer, Ministerio de Salud, Asunción, Paraguay*
[g] *Clínica Alemana y Hospital Militar, Santiago de Chile, Chile*
[h] *Hospital Central FAP-Instituto Médico Miraflores, Lima, Peru*
[i] *II Cátedra de Ginecología, Universidad Nacional de Córdoba, Córdoba, Argentina*
[j] *Departamento Académico de Medicina Humana, Universidad Andina del Cusco, Cusco, Peru*
[k] *Medicina Ginecológica Consultorios Médicos, Buenos Aires, Argentina*
[l] *Department Gynecology and Obstetrics, Federal University of Minas Gerais, Belo Horizonte, Brazil*
[m] *Hospital Los Ángeles, Puebla, Mexico*
[n] *Clínica Tserotas, Ciudad de Panamá, Panama*
[o] *Instituto Aragonés de Ciencias de la Salud, Facultad de Medicina, Universidad de Zaragoza, Zaragoza, Spain*

ARTICLE INFO

ABSTRACT

Objective: To evaluate the association between factors, especially those linked to the climacteric, and a history of COVID-19 infection.

Methods: This was an observational, cross-sectional, and analytical study in which women from ten Latin American countries, aged 40–64, who attended a routine health check-up were invited to participate. A positive history for COVID-19 was based on reverse transcription-polymerase chain reaction reports. We evaluated sociodemographic, clinical, lifestyle, anthropometric variables, and menopausal symptoms using the Menopause Rating Scale (MRS).

Results: A total of 1238 women were included for analysis, of whom 304 (24.6 %) had a positive history for COVID-19. The median [interquartile range: IQR] age of participants was 53 [IQR 12] years, duration of formal education was 16 [6] years, body mass index 25.6 [5.1] kg/m^2, and total MRS score 10 [13]. In a logistic regression model, factors positively associated with COVID-19 included postmenopausal status and having a family history of dementia (OR: 1.53; 95 % CI: 1.13–2.07, and 2.40; 1.65–3.48, respectively), whereas negatively associated were use of menopausal hormone therapy (current or past), being a housewife, and being nulliparous (OR: 0.47; 95 % CI: 0.30–0.73, 0.72; 0.53–0.97 and 0.56; 0.34–0.92, respectively). Smoking, being sexually active, and use of hypnotics were also factors positively associated with COVID-19.

Conclusion: Postmenopausal status and a family history of dementia were more frequent among women who had had COVID-19, and the infection was less frequent among current or past menopause hormone therapy users and in those with less physical contact.

* Corresponding author at: Departamento Medicina Sur, Facultad de Medicina, Universidad de Chile, Orquídeas 1068, Departamento 302, P.O. Box 7510258, Providencia, Santiago de Chile, Chile.

E-mail address: jeblumelm@gmail.com (J.E. Blümel).

1. Introduction

The initial publications from China related to the infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), reported a higher prevalence in men than in women [1]. A subsequent meta-analysis of 57 studies, including only two reports from Western countries, confirmed the higher prevalence of the disease in males [2]. In May 2020, a European meta-analysis that included 23 countries with more than one million patients showed that not only was the disease more frequent in men, but also that they were 60 % more likely to die than women if they acquired the disease [3]. When specifically comparing the morbidity and mortality caused by COVID-19 in men as compared with post-menopausal women, there are no significant differences. However, when analyzing premenopausal women, it is observed that they have lower morbidity and mortality from COVID-19 than men [4].

Experimental medicine studies show that ovariectomy or treating female mice with an estrogen receptor antagonist increased mortality in mice infected with the first reported severe acute respiratory syndrome coronavirus (SARS-CoV-1) [5]. However, women appear to be less prone to severe forms of the SARS-CoV-2 infection, probably due to the ovarian hormone modulation of the inflammation and the prevention of the cytokine storm [6]. Together, these data suggest that there are sex differences in the susceptibility of infection to SARS-CoV-2. Different mechanisms have been postulated to explain this effect. For example, estrogen could reduce virus receptors on cell surfaces (angiotensin-converting enzyme 2) and can also modulate the immune response, both innate and adaptive, to viral aggression [5]. Furthermore, women would carry genes on the X chromosome involved in the inflammatory response [7]. Therefore, the use of estrogen-only or estrogen/progestogen therapy has even been postulated, both in men and women, to treat and improve the clinical evolution of COVID-19 cases [8,9].

With this background, we evaluated the association between factors, especially those linked to the climacteric and the presence of COVID-19 in women from Latin America.

2. Methods

2.1. Study design, participants, and studied variables

This was a cross-sectional, observational, and analytic multinational study. Data collection was carried out between May and November 2021 in general gynecology consultations in ten Latin American countries: Argentina, Brazil, Chile, Dominican Republic, Ecuador, Mexico, Panamá, Paraguay, Perú, and Venezuela. Participants were women aged 40–64 years who attended a routine health check-up (convenience sampling). The majority of studied women had medium or high incomes and attended private clinical centers. The COVID-19 diagnosis was based on reverse transcription-polymerase chain reaction (RT-PCR) results. Included participants were otherwise healthy women (pre-COVID-19) who could read, understand and write in Spanish. Women with a diagnosis of dementia that did not allow them to understand the questionnaires or who suffered from deafness or blindness were excluded.

2.2. Studied variables

The following data were collected: age (years), years of education (years), body mass index (BMI), parity or number of children, having a current partner (yes/no), sexual activity (at least one sexual intercourse in the last year, yes/no), housewife (yes/no), smoker (yes/no), inactive lifestyle (<30 min physical activity three times a week, yes/no), menopausal stage (defined according to the STRAW +10 criteria), hysterectomy (yes/no), bilateral oophorectomy (yes/no), menopausal hormone therapy use (MHT; yes/no), former MHT users (yes/no), arterial

hypertension (yes/no), diabetes mellitus (yes/no), cardiovascular diseases (yes/no), cancer (yes/no), use of antidepressants (yes/no), use of hypnotics (yes/no), and a family history of dementia, as risk marker [10] (yes/no). Menopausal symptoms as assessed with the validated version of the Menopause Rating Scale (MRS). The MRS is composed of 11 items assessing menopausal symptoms divided into three subscales: Somatic domain (hot flushes, heart discomfort, sleeping problems, and muscle and joint problems); Psychological domain (depressive mood, irritability, anxiety, and physical and mental exhaustion); and Urogenital domain (sexual problems, bladder symptoms, and dryness of the vagina). Each item can be graded by the subject from 0 (not present) to 4 [11].

2.3. Statistical analyses

Statistical analysis was performed using the IBM SPSS Statistics version 21.0. Results are reported as mean ± standard deviations or median and interquartile range (IQR), frequencies, percentages, and odds ratios (OR) with a 95 % confidence interval (95 % CI). The Kolmogorov–Smirnov test was used to evaluate the normality of the data distribution and the Levene test to evaluate variance homogeneity. The U Mann–Whitney test was used to compare non-parametric data.

Logistic regression analysis was used to determine factors associated to SARS-CoV-2 infection. Continuous variables were categorized (yes = 1; no = 0) for logistic regression as follows: age (median): 0: ≤53 year, 1: >53 years, years of education (median): 0: ≤16 years, 1 >16 years; BMI (median): 0: ≤25.6 kg/m², 1: >25.6 kg/m²; and, severe menopausal symptoms: MRS score >14 [12]. The inclusion of different variables in the model was performed through a stepwise procedure, considering a 10 % level as significant. We also considered the different interactions between the variables found statistically significant in the univariate analysis. The Omnibus test and the Hosmer–Lemeshow tests were used to determine the regression model adequacy.

2.4. Ethical considerations

The study was approved by the ethics committee (Southern Metropolitan Health Service, Santiago de Chile, Chile; Memorandum 27/2021; March 22, 2021) and complies with the Declaration of Helsinki. All participants provided written informed consent.

3. Results

A total of 1374 women aged 40–64 years were invited to participate, of which 1306 (95.1 %) agreed and gave consent. Sixty-eight women (4.9 %) were not included due to incomplete or erroneous data. Thus, data of 1238 women (90.1 %) were analyzed. The median age of participants was 53 years [IQR: 12], years of education 16 [6], BMI 25.6 kg/m² [5.1], and a total MRS score of 10 [13]. Of 1238 women, 304 (24.6 %) had a clinical history of SARS-CoV-2 infection confirmed by RT-PCR testing. The remaining women had no clinical symptoms suggestive of COVID-19, and/or the RT-PCR testing was either negative or not performed.

Positive RT-PCR women developed COVID-19 at a median of eight months (IQR: 6 months) before to participating in the current study (May–November 2021). Of these, 55 (18.1 %) were hospitalized for a median of 10 days (IQR: 8 days). Table 1 displays women's characteristics grouped according to the history of having been diagnosed with COVID-19 or not. Among positive RT-PCR women, there were significantly ($p < 0.05$) fewer housewives (25.3 vs 31.7 %), nulliparous (6.9 vs 12.1 %), and current MHT users (9.9 vs 15.1). Women using MHT with estrogen and progestagen had half the prevalence of COVID-19 as non-users 13.9 % versus 25.7 %, $p < 0.004$; on the other hand, the users of estrogen-only did not have a significant change, 26.5 % versus

Table 1

Clinical characteristics of women who tested positive for SARS-CoV-2 with RT-PCR as compared to those without evidence of the disease.

Characteristic	Total $n = 1238$	No evidence of COVID-19 $n = 934$	Positive RT-PCR $n = 304$	OR (95 % CI)
Age >53 years[aa]	598 (48.3)	450 (48.0)	148 (48.7)	1.02 (0.79–1.32)
Years of education <16 years[a]	614 (49.6)	466 (49.9)	148 (48.7)	0.95 (0.74–1.23)
Body mass index > 25.6 kg/m^2[a]	614 (49.6)	468 (50.1)	146 (48.0)	0.92 (0.71–1.19)
Nulliparous	134 (10.8)	113 (12.1)	21 (6.9)	0.54 (0.33–0.88)[‡]
Has a partner	923 (74.6)	699 (74.8)	224 (73.7)	0.94 (0.70–1.26)
Sexually active	908 (73.3)	667 (71.4)	241 (79.3)	1.53 (1.12–2.09)[‡]
Housewife	373 (30.1)	296 (31.7)	77 (25.3)	0.73 (0.55–0.98)[‡]
Smoker	332 (26.8)	230 (24.6)	102 (33.6)	1.55 (1.17–2.05)[‡]
Inactive lifestyle	834 (67.4)	628 (67.2)	206 (67.8)	1.02 (0.78–1.35)
Postmenopausal status	797 (64.4)	588 (63.0)	209 (68.8)	1.30 (0.98–1.71)
Hysterectomy	164 (13.2)	122 (13.1)	42 (13.8)	1.07 (0.73–1.56)
Bilateral oophorectomy	62 (5.0)	46 (4.9)	16 (5.3)	1.07 (0.60–1.92)
MHT users	171 (13.8)	141 (15.1)	39 (9.9)	0.62 (0.41–0.94)[‡]
Former MHT users	134 (10.8)	110 (11.8)	24 (7.9)	0.64 (0.41–1.02)
Severe menopausal symptoms[bb]	399 (32.2)	286 (30.6)	113 (37.2)	1.34 (1.02–1.76)[‡]
Hypertension	271 (21.9)	199 (21.3)	72 (23.7)	1.15 (0.84–1.56)
Diabetes mellitus	124 (10.0)	91 (9.7)	33 (10.9)	1.13 (0.74–1.72)
History of cardiovascular diseases	69 (5.6)	46 (4.9)	23 (7.6)	1.58 (0.94–2.65)
History of cancer	54 (4.4)	39 (4.2)	15 (4.9)	1.19 (0.65–2.19)
Use of antidepressants	156 (12.6)	112 (12.0)	44 (14.5)	1.24 (0.85–1.81)
Use of hypnotics	194 (15.7)	127 (13.6)	67 (22.0)	1.80 (1.29–2.50)[‡]
Family history of dementia	148 (12.0)	87 (9.3)	61 (20.1)	2.44 (1.71–3.49)[‡]

Data are presented as frequencies *n* (%). MHT, menopausal hormone therapy; CI, confidence interval.

[a] Median was used as cut-off value.

[b] Total MRS score of >14 used as cut-off.

[‡] $p < 0.05$.

25.2 %, $p = 0.86$. Positive COVID-19 RT-PCR tested women presented a higher frequency of being sexually active (79.3 vs 71.4 %), being smokers (33.6 vs 24.6 %), having severe menopausal symptoms (37.2 vs 30.6 %), being hypnotic users (22.0 vs 12.6), and having a family history of dementia (20.1 vs 9.3 %). There were no significant differences for age, years of education, BMI, having a partner, inactive lifestyle, being postmenopausal, hysterectomy, bilateral oophorectomy, arterial hypertension, diabetes mellitus, use of antidepressants, or a history of cancer or cardiovascular diseases.

Table 2 displays the logistic regression model that analyzes the association between a positive RT-PCR result and factors presented in Table 1 that achieved a $p < 0.10$. The model did not include women with oophorectomy. Factors positively associated with COVID-19 included postmenopausal status and having a familial history of dementia (OR: 1.53; 95 % CI: 1.13–2.07 and 2.40; 1.65–3.48, respectively);

Table 2

Factors associated with positive SARS-CoV-2 testing: logistic regression.

Characteristic	OR	95 % CI
Current MHT users	0.47	0.30–0.73
Former MHT users	0.51	0.31–0.83
Nulliparous	0.56	0.34–0.92
Housewife	0.72	0.53–0.97
Smoker	1.35	1.01–1.81
Postmenopausal status	1.53	1.13–2.07
Use of hypnotics	1.72	1.21–2.43
Sexually active	1.72	1.23–2.39
Family history of dementia	2.40	1.65–3.48

whereas negatively associated were MHT use (current or past), being a housewife and being nulliparous (OR: 0.47; 95 % CI: 0.30–0.73; 0.72; 0.53–0.97 and 0.56; 0.34–0.92, respectively). Smoking habits, being sexually active, or being a hypnotic user were also significant factors positively associated with having had COVID-19.

4. Discussion

The prevalence of COVID-19 in the mid-aged women studied between May and November 2021 was high, highlighting the magnitude of the pandemic. Logistic regression showed that being postmenopausal was positively associated with COVID-19; whereas use of MHT (current or past) was negatively associated with COVID-19. Certain conditions, such as sexual relationships, that increase physical closeness were positively associated with COVID-1, whereas being housewives or not having children were negatively associated with the disease. Smoking, hypnotic use, and/or having a family history of dementia were positively associated with COVID-19.

The SARS-CoV-2 pandemic has had many unique clinical characteristics and socio-economic implications in climacteric women [13]. Iberoamerican and Caribbean women are central in the family structure and contribute to the informal economy, suffering high-risk conditions that contribute to coronavirus dissemination [14,15]. As of February 9, 2022, the disease had affected 61.2 million individuals in Latin America [16]. However, this last figure probably corresponds to only 10 % of the continent population, which reflects a selection bias corresponding to wealthy women who have relatively easy access to medical care. However, likely, the percentage of affected women with COVID-19 in our study (24.6 %) is closer to reality than the official figures (10 %) [16] since access to RT-PCR testing was limited in many regions of the continent.

We found a clear positive association between COVID-19 and estrogen-deficient clinical conditions. Therefore, it seems that the chronic hypoestrogenism status of postmenopausal women could be associated with an increased risk of the disease. In contrast, there was a decreased COVID-19 risk associated with MHT use. The Ding et al. [17] study showed in Chinese women that menopause is an independent risk factor for COVID-19; and that estradiol and anti-müllerian hormone levels were negatively correlated with COVID-19 severity, attributing this effect to the hormonal regulation of cytokines related to immunity and inflammation. In contrast, the Mishra et al. [18] study found no association between menopause and COVID-19 outcome in an Indian population [18]. Both studies did not incorporate healthy controls. The large British COVID-19 Symptom matched study reported that estrogen exposure in women using MHT had a lower risk of COVID-19, with a reduction in the risk of hospital attendance [19]. We also found a decrease in COVID-19 in MHT users, but this effect was seen only in women using estrogen and progestin, and not in those using estrogen alone. It has been suggested that the combination of estradiol and progesterone may improve the immune dysregulation that leads to the COVID-19 cytokine storm [20]. However, the low number of COVID-19 patients with MHT, associated with the multiple variables that can influence the clinical re-

sponse to this infection, makes it impossible for us to delve into this finding.

In our current study, housewife and nulliparous women were less likely to have COVID-19. Children have oligosymptomatic COVID-19 and may be potential vectors to the adult population [21]; that is why women without children could be less exposed to acquiring the disease. Similarly, women who remain at home have less chance of being in contact with infected people. Having sexual activity also appeared as a factor associated with COVID-19, possibly due to the close physical contact that occurs during intercourse.

In our logistic regression model, the smoking habit was a positive factor associated with COVID-19. This association is not only present with COVID-19 [22,23]; smokers are also five times more likely to get the flu than non-smokers [24]. Smokers repeatedly touch their face, increasing the hand-to-mouth contact that facilitates the chance of viral body invasion; also, their lung flow significantly increases thus aiding viral penetration into the respiratory alveoli. Smokers are also more susceptible to bacterial and viral infections [25]. Smoking affects the macrophage and cytokine response and thus the ability to contain the infection. Similarly, the risk of pneumonia due to infection with pneumococci, legionella, and mycoplasma is 3 to 5 times higher among smokers [26]. On the other hand, cigarette smoking produces a dose-dependent upregulation of the respiratory tract angiotensin-converting enzyme 2 which can be upregulated by viral infections. In addition, SARS-CoV-2 infection creates positive feedback loops that increase ACE2 levels and facilitate viral dissemination [27]. In addition, smoking-induced hypoestrogenism is another factor that could explain the association we have observed between smoking and COVID-19 [28]. A meta-analysis of 186 studies that analyzed 210,447 deaths among 1,304,587 patients with COVID-19 calculated a relative risk of dying of 1.28 (95 % CI: 1.17–1.40) among ever smokers, 1.29 (95 % CI: 1.03–1.62) for current smokers and 1.25 (95 % CI: 1.11–1.42) for former smokers compared with never smokers [29].

Sleep disorders are very common among hospitalized COVID-19 patients [30]. The use of hypnotics appears in our study as a factor associated with COVID-19. However, in severe disease forms, hypnotic treatment was associated with a significantly favorable outcome [31]. The deterioration of sleep quality is linked to the climacteric and some studies have shown improvement with MHT [32,33]. For this reason, the use of hypnotics could be considered a surrogate marker of the hypoestrogenism typical of menopause, a factor associated with a higher risk of presenting COVID-19. However, during the pandemic, studies have shown an increase in insomnia, anxiety disorders, and depressive symptoms related to the incertitude of life [34,35].

The existence of basal diseases or poor health can increase the risk of general complications and mortality due to COVID-19. In our cohort, we searched for cardiovascular diseases, diabetes, hypertension, and cancer [36]. However, there was no significant association because, perhaps, the studied population included just young postmenopausal women. A meta-analysis places dementia as the main risk factor for morbidity and mortality from COVID-19 in the population aged above 65 [37]. Due to the age range of our studied women, we could not consider this antecedent within the comorbidities. Therefore, we analyzed a family history of dementia as a surrogate marker of dementia among our studied women. Our model found a family history of dementia as the strongest factor associated to COVID-19. Since it has been postulated that conditions associated with hypoestrogenism, such as primary onset menopause and dementia, have a genetic basis [38], we could theorize that hypoestrogenism could be one of the factors that explain our findings. There is a need for more research in this regard.

4.1. Limitations and strength

The main limitation of the study is the convenience sample related to access to medical care. Therefore, it is not representative of the main continental population and general medical care during the COVID-19 pandemic. Another limitation worth mentioning is the fact of considering for analysis factors among those who had a positive COVID-19 test before the survey as compared to those with a negative test or never performed. Indeed, there could have been asymptomatic cases among the latter. Despite these limitations, the study has several strengths: first, it was carried out in multiple locations in Latin America, which reduces local biases; second, the wide range of analyzed factors; moreover, the infection diagnosis was made by RT-PCR. Finally, the surveys were carried out by physicians with extensive clinical experience, using the same protocol.

5. Conclusion

In conclusion, postmenopausal status and a family history of dementia were positively associated with COVID-19, whereas current or past MHT use and living in situations with less physical contact were negatively associated with COVID-19.

Contributors

María S. Vallejo contributed to conception and design of the study, data collection, drafting the initial version of the paper, and text revision.

Juan E. Blümel contributed to conception and design of the study, statistical analysis, and text revision.

Ascanio Bencosme contributed to data collection and text revision.
Andrés Calle contributed to data collection and text revision.
Maribel Dextre contributed to data collection and text revision.
Karen Díaz contributed to data collection and text revision.
Marcela López contributed to data collection and text revision.
Carlos Miranda contributed to data collection and text revision.
Mónica Ñañez contributed to data collection and text revision.
Eliana Ojeda contributed to data collection and text revision.
Claudia Rey contributed to data collection and text revision.
Marcio A. Rodrigues contributed to data collection and text revision.
Carlos Salinas contributed to data collection and text revision.
Konstantinos Tserotas contributed to data collection and text revision.
Faustino R. Pérez-López contributed to conception and design of the study, text revision, and translation.

All authors read the final version.

Ethical approval

The study was approved by the local ethics committee (Southern Metropolitan Health Service, Santiago de Chile, Chile. Memorandum No. 4:102/2921. April 20, 2021) and was in complete agreement with the Declaration of Helsinki. All women provided written informed consent.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of competing interest

The authors declare that they have no competing interest.

References

[1] W.J. Guan, Z.Y. Ni, Y. Hu, et al., Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 382 (18) (2020) 1708–1720, https://doi.org/10.1056/NEJMoa2002032.

[2] B.B. Abate, A.M. Kassie, M.W. Kassaw, Sex difference in coronavirus disease (COVID-19): a systematic review and meta-analysis, BMJ Open 10 (2020) e040129.

[3] F.R. Pérez-López, M. Tajada, R. Savirón-Cornudella, et al., Coronavirus disease 2019 and gender-related mortality in european countries: a meta-analysis, Maturitas 141 (2020) 59–62, https://doi.org/10.1016/j.maturitas.2020.06.017.

[4] X.W. Wang, H. Hu, Z.Y. Xu, et al., Association of menopausal status with COVID-19 outcomes: a propensity score matching analysis, Biol. Sex Differ. 12 (1) (2021) 16, https://doi.org/10.1186/s13293-021-00363-6.

[5] R. Channappanavar, C. Fett, M. Mack, Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection, J. Immunol. 198 (10) (2017) 4046–4053.

[6] K. Hamzaoglu, C.T. Erel, Should estrogen be used in the co-treatment of COVID-19 patients? What is the rationale? Maturitas 140 (2020) 80, https://doi.org/10.1016/j.maturitas.2020.06.015.

[7] A. Ramírez-de-Arellano, J. Gutiérrez-Franco, E. Sierra-Diaz, A.L. Pereira-Suárez, The role of estradiol in the immune response against COVID-19, Hormones (Athens) 20 (4) (2021) 657–667, https://doi.org/10.1007/s42000-021-00300-7.

[8] Z. Suba, Prevention and therapy of COVID-19 via exogenous estrogen treatment for both male and female patients, J. Pharm. Pharm. Sci. 23 (1) (2020) 75–85, https://doi.org/10.18433/jpps31069.

[9] J.M. Masterson, C. Bui, Y. Zhang, et al., Feminising hormone therapy reduces testicular ACE-2 receptor expression: implications for treatment or prevention of COVID-19 infection in men, Andrologia 53 (11) (2021) e14186, https://doi.org/10.1111/and.14186.

[10] P.A. Wolf, Contributions of the Framingham heart study to stroke and dementia epidemiologic research at 60 years, Arch. Neurol. 69 (5) (2012) 567–571, https://doi.org/10.1001/archneurol.2011.977.

[11] S. Aedo, J. Porcile, C. Irribarra, Calidad de Vida relacionada con el climaterio en una población chilena de mujeres saludables, Rev. Chil. Obstet. Ginecol. 71 (2006) 402–409.

[12] J.E. Blümel, E. Arteaga, J. Parra, et al., Decision-making for the treatment of climacteric symptoms using the menopause rating scale, Maturitas 111 (2018) 15–19, https://doi.org/10.1016/j.maturitas.2018.02.010.

[13] P. Chedraui, F.R. Pérez-López, The severe acute respiratory syndrome due to coronavirus 2 (SARS-CoV-2) infection and the climacteric woman, Climacteric 23 (6) (2020) 525–527, https://doi.org/10.1080/13697137.2020.1837547.

[14] The World Bank, Reversing the disproportionate impact of the pandemic on female workers in Latin America and the Caribbean. https://www.worldbank.org/en/news/press-release/2021/03/04/impacto-desproporcionado-de-la-pandemia-sobre-las-mujeres-trabajadoras-en-alc (Visited February 26, 2022).

[15] United Nations in focus: gender equality matters in COVID-19 response. https://www.unwomen.org/en/news/in-focus/in-focus-gender-equality-in-covid-19-response?gclid=CjwKCAiAvOeQBhBkEiwAxutUVBEzl9-TTeWZkPKEtdIuD4HCHMqkPnldffPRjTCVsqIPXwBTdAbiaxoCKZ0QAvD_BwE (Visited February 26, 2022.

[16] Statista, Número de casos confirmados de coronavirus (COVID-19) en América Latina y el Caribe al 17 de febrero de 2022. https://es.statista.com/estadisticas/1105121/numero-casos-covid-19-america-latina-caribe-pais/ (Visited February 26, 2022).

[17] T. Ding, J. Zhang, T. Wang, et al., Potential Influence of menstrual status and sex hormones on female severe acute respiratory syndrome coronavirus 2 infection: a cross-sectional multicenter study in Wuhan, China, Clin. Infect. Dis. 72 (9) (2021) e240–e248, https://doi.org/10.1093/cid/ciaa1022.

[18] N. Mishra, R. Sharma, P. Mishra, et al., COVID-19 and menstrual status: ¿Is menopause an independent risk factor for SARS Cov-2? J. Midlife Health 11 (4) (2020) 240–249, https://doi.org/10.4103/jmh.JMH_288_20.

[19] R. Costeira, K.A. Lee, B. Murray, et al., Estrogen and COVID-19 symptoms: associations in women from the COVID Symptom Study, PLoS One 16 (9) (2021) e0257051, https://doi.org/10.1371/journal.pone.0257051.

[20] F. Mauvais-Jarvis, S.L. Klein, E.R. Levin, Estradiol, progesterone, immunomodulation, and COVID-19 outcomes, Endocrinology 161 (9) (2020) bqaa127, https://doi.org/10.1210/endocr/bqaa127.

[21] C. García-Vera, S. Castejón-Ramírez, E. Laín Miranda, et al., COVID-19 in children: clinical and epidemiological spectrum in the community, Eur. J. Pediatr. (2021) 1–8, https://doi.org/10.1007/s00431-021-04235-4.

[22] C.A. Jiménez-Ruiz, D. López-Padilla, A. Alonso-Arroyo, et al., COVID-19 and smoking: a systematic review and meta-analysis of the evidence, Arch. Bronconeumol. 57 (Suppl. 1) (2021) 21–34, https://doi.org/10.1016/j.arbres.2020.06.024.

[23] R.K. Reddy, W.N. Charles, A. Sklavounos, et al., The effect of smoking on COVID-19 severity: a systematic review and meta-analysis, J. Med. Virol. 93 (2021) 1045–1056, https://doi.org/10.1002/jmv.26389.

[24] H. Lawrence, A. Hunter, R. Murray, et al., Cigarette smoking and the occurrence of influenza - systematic review, J. Infect. 79 (5) (2019) 401–406, https://doi.org/10.1016/j.jinf.2019.08.014.

[25] M. Aghapour, P. Raee, S.J. Moghaddam, Airway epithelial barrier dysfunction in chronic obstructive pulmonary disease: role of cigarette smoke exposure, Am. J. Respir. Cell Mol. Biol. 58 (2) (2018) 157–169 2018.

[26] R.N. van Zyl-Smit, G. Richards, F.T. Leone, Tobacco smoking and COVID-19 infection, Lancet Respir. Med. 8 (7) (2020) 664–665, https://doi.org/10.1016/S2213-2600(20)30239-3.

[27] J.C. Smit, E.L. Sausville, V. Girish, et al., Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract, Dev. Cell 53 (5) (2020) 514–529 https://doi.org/10.1016/j.devcel.2020.05.012, e3.

[28] X. Ruan, A.O. Mueck, Impact of smoking on estrogenic efficacy, Climacteric 18 (1) (2015) 38–46, https://doi.org/10.3109/13697137.2014.929106.

[29] Y. Mahamat-Saleh, T. Fiolet, M.E. Rebeaud, et al., Diabetes, hypertension, body mass index, smoking and COVID-19-related mortality: a systematic review and meta-analysis of observational studies, BMJ Open 11 (10) (2021) e052777, https://doi.org/10.1136/bmjopen-2021-052777.

[30] Y. Xie, E. Xu, Z. Al-Aly, Risks of mental health outcomes in people with covid-19: cohort study, BMJ 376 (2022) e068993, https://doi.org/10.1136/bmj-2021-068993.

[31] L. Hu, S. Chen, Y. Fu, et al., Risk factors associated with clinical outcomes in 323 Coronavirus Disease 2019 (COVID-19) hospitalized patients in Wuhan, China, Clin. Infect. Dis. 71 (16) (2020) 2089–2098, https://doi.org/10.1093/cid/ciaa539.

[32] J.E. Blümel, A. Cano, E. Mezones-Holguín, et al., A multinational study of sleep disorders during female mid-life, Maturitas 72 (4) (2012) 359–366, https://doi.org/10.1016/j.maturitas.2012.05.011.

[33] Z. Pan, S. Wen, X. Qiao, et al., Different regimens of menopausal hormone therapy for improving sleep quality: a systematic review and meta-analysis, Menopause (2022), https://doi.org/10.1097/GME.0000000000001945.

[34] T. Caycho-Rodríguez, J.M. Tomás, L.W. Vilca, et al., Socio-demographic variables, fear of COVID-19, anxiety, and depression: prevalence, relationships and explanatory model in the general population of seven latin american countries, Front. Psychol. 12 (2021) 695989, https://doi.org/10.3389/fpsyg.2021.695989.

[35] J. Santabárbara, I. Lasheras, D.M. Lipnicki, et al., Prevalence of anxiety in the COVID-19 pandemic: an updated meta-analysis of community-based studies, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 109 (2021) 110207, https://doi.org/10.1016/j.pnpbp.2020.110207.

[36] P.P. Mattey-Mora, C.A. Begle, C.K. Owusu, et al., Hospitalised versus outpatient COVID-19 patients' background characteristics and comorbidities: a systematic review and meta-analysis, Rev. Med. Virol. (2021) e2306, https://doi.org/10.1002/rmv.2306.

[37] I.D. Saragih, I.S. Saragih, S.O. Batubara, C.J. Lin, Dementia as a mortality predictor among older adults with COVID-19: a systematic review and meta-analysis of observational study, Geriatr. Nurs. 42 (5) (2021) 1230–1239, https://doi.org/10.1016/j.gerinurse.2021.03.007.

[38] J.S.E. Laven, Early menopause results from instead of causes premature general ageing, Reprod. Biomed. Online (2022) https://doi.org/10.1016/j.rbmo.2022.02.027, S1472-6483(22)00220-6.