

# World Journal of *Psychiatry*

*World J Psychiatry* 2023 October 19; 13(10): 714-815



**ORIGINAL ARTICLE****Case Control Study**

- 714 Serum neuronal pentraxin 2 is related to cognitive dysfunction and electroencephalogram slow wave/fast wave frequency ratio in epilepsy

*Huang XF, Xu MX, Chen YF, Lin YQ, Lin YX, Wang F*

**Retrospective Study**

- 724 Correlation between cognitive impairment and metabolic imbalance of gut microbiota in patients with schizophrenia

*Ma J, Song XQ*

- 732 Sleep disturbances are associated with anxiety, depression, and decreased quality of life in patients with coronary heart disease

*Zheng D, Tan RJ, Liu W, Song PC, Li FD*

- 743 Clinical value of ankle flexion and extension exercises combined with a psychological intervention in knee osteoarthritis

*Liu Y, Chen R, Zhang Y, Wang Q, Ren JL, Wang CX, Xu YK*

- 753 Effects of different intervention methods on psychological flexibility, negative emotions and sleep quality in chronic hepatitis B

*Zheng Y, Wang XW, Xia CX*

- 763 Construction and validation of a personalized prediction model for postpartum anxiety in pregnant women with preeclampsia

*Lin LJ, Zhou HX, Ye ZY, Zhang Q, Chen S*

**Observational Study**

- 772 Depression among medical students in Tunisia: Prevalence and associated factors

*Amamou B, Alouani S, Ben Haouala A, Alouani S, Tlili MA, Mhalla A, Zaafrane F, Gaha L*

- 784 Correlation and pathways of behavioral activation systems mediating physical activity level and depressive symptoms among college students

*Zhu JH, Li SF, Wang P, Xin X, Zhao Q, Chen SC, Wang X*

- 793 Analysis of mental health status and related factors in patients with acute cerebral infarction

*Chen QQ, Lin FM, Chen DH, Ye YM, Gong GM, Chen FF, Huang SF, Peng SL*

- 803 International study of the Complex Stress Reaction Syndrome: Implications for transdiagnostic clinical practice

*Goldstein Ferber S, Weller A, Hayes AM, Vannorsdall TD, Ajlouni Y, Qudah M, Zalsman G, Shoval G, Jannini TB, Fiedler R, Chen LX, Shayani DR, Kachuki Dory E, Stolorowicz-Melman D, Evans C, Trow M, Di Lorenzo G, Rossi R*

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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Rui-Rui Wu, Production Department Director: Xu Guo, Editorial Office Director: Jia-Ping Yan.

**NAME OF JOURNAL**

*World Journal of Psychiatry*

**ISSN**

ISSN 2220-3206 (online)

**LAUNCH DATE**

December 31, 2011

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Rajesh R Tampi, Ting-Shao Zhu, Panteleimon Giannakopoulos

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2220-3206/editorialboard.htm>

**PUBLICATION DATE**

October 19, 2023

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**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

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**ONLINE SUBMISSION**

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## Observational Study

# International study of the Complex Stress Reaction Syndrome: Implications for transdiagnostic clinical practice

Sari Goldstein Ferber, Aron Weller, Adele M Hayes, Tracy D Vannorsdall, Yaroup Ajlouni, Mo'nes Qudah, Gil Zalsman, Gal Shoval, Tommaso Benedetto Jannini, Racquel Fiedler, Lily X Chen, Danielle R Shayani, Elin Kachuki Dory, Dana Stolowicz-Melman, Connor Evans, Megan Trow, Giorgio Di Lorenzo, Rodolfo Rossi

**Specialty type:** Psychiatry

**Provenance and peer review:**

Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A  
Grade B (Very good): B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Eseadi C, Nigeria;  
Stoyanov D, Bulgaria

**Received:** July 11, 2023

**Peer-review started:** July 11, 2023

**First decision:** August 16, 2023

**Revised:** August 25, 2023

**Accepted:** September 11, 2023

**Article in press:** September 11, 2023

**Published online:** October 19, 2023



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## Abstract

### BACKGROUND

The debate regarding diagnostic classification systems in psychiatry (categorical *vs* dimensional systems) has essential implications for the diagnosis, prevention and treatment of stress reactions. We previously found a unique pattern of stress reaction in a study executed during the coronavirus disease 2019 pandemic using large representative samples in two countries, and termed it the Complex Stress Reaction Syndrome (CSRS).

### AIM

To investigate CSRS, Type A (psychiatric symptoms, spanning anxiety, depression, stress symptoms, and post-traumatic stress disorder (PTSD)), with or without long-coronavirus disease (COVID) residuals (CSRS, Type B, neuropsychiatric symptoms spanning cognitive deficits and fatigue, excluding systemic symptoms). Our two-tailed hypothesis was that CSRS is a condition related to an unrecognized type of stress reaction in daily life in the general population (Type A) or that it is related to the severe acute respiratory syndrome coronavirus 2 infection and its long-COVID residuals (Type B).

### METHODS

977 individuals in four continents (North America, Europe, Australia and the Middle East) completed the online study questionnaire in six languages using the Qualtrics platform. The study was managed by six teams in six countries that promoted the study on social media. The questionnaire assessed anxiety, depression, stress symptoms and PTSD (CSRS, Type A), cognitive deficits and fatigue (CSRS, Type B). The data were analyzed using Proportion Analyses, Multivariate Analysis of Co-Variance (MANCOVA), linear regression analyses and validated clinical cutoff points.

### RESULTS

The results of the Proportion Analyses showed that the prevalence of 4 symptoms spanning anxiety, depression, stress symptoms, and PTSD was significantly higher than the most prevalent combinations of fewer symptoms across 4 continents, age groups, and gender. This supports the transdiagnostic argument embedded in the CSRS (Type A). The same pattern of results was found in infected/recovered individuals. The prevalence of the 4 psychiatric symptoms combination was significantly greater than that of 5 and 6 symptoms, when adding cognitive deficits and fatigue, respectively. MANCOVA showed a significant three-way interaction (age  $\times$  gender  $\times$  continent). Further analyses showed that the sources of this three-way interaction were threefold relating to two sub-populations at-risk: (1) Individuals that self-identified as non-binary gender scored significantly higher on all 4 psychiatric symptoms of the CSRS, Type A at young age groups ( $< 50$  years old) in North America compared to (self-identified) women and men located in the 4 continents studied, and to other ages across the adult life span; and (2) This pattern of results (CSRS, Type A) was found also in women at young ages ( $< 40$  years old) in North America who scored higher compared to men and women in other continents and other ages. Linear regression analyses confirmed the MANCOVA results.

### CONCLUSION

These results show a combined mental health risk factor related to stress reactivity, suggesting that the CSRS is sensitive to populations at risk and may be applied to future identification of other vulnerable sub-populations. It also supports the transdiagnostic approach for more accurate prevention and treatment. Time will tell if such transdiagnostic syndromes will be part of the discussions on the next revisions of the traditional classification systems or whether the crisis in psychiatry further evolves.

**Key Words:** Transdiagnostic; Complex Stress Reaction Syndrome; Stress reactivity; Affective disorders; Debate in psychiatry

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**Core Tip:** The debate regarding diagnostic classification systems in psychiatry (categorical vs dimensional systems) has essential implications for the diagnosis, prevention and treatment of stress reactions and affective disorders. The results of this international study show a combined mental health risk factor related to stress reactivity and reduced positive affectivity, suggesting that the Complex Stress Reaction Syndrome (Type A) is sensitive to populations at risk and may be applied to future identification of other vulnerable sub-populations. It also supports the transdiagnostic approach for more accurate prevention and treatment. Time will tell if such transdiagnostic syndromes will be part of the discussions on the next revisions of the traditional classification systems or whether the crisis in psychiatry further evolves.

**Citation:** Goldstein Ferber S, Weller A, Hayes AM, Vannorsdall TD, Ajlouni Y, Qudah M, Zalsman G, Shoval G, Jannini TB, Fiedler R, Chen LX, Shayani DR, Kachuki Dory E, Stolorowicz-Melman D, Evans C, Trow M, Di Lorenzo G, Rossi R. International study of the Complex Stress Reaction Syndrome: Implications for transdiagnostic clinical practice. *World J Psychiatry* 2023; 13(10): 803-815

**URL:** <https://www.wjgnet.com/2220-3206/full/v13/i10/803.htm>

**DOI:** <https://dx.doi.org/10.5498/wjp.v13.i10.803>

## INTRODUCTION

The debate on diagnostic classification systems and the resulting crisis in psychiatry is evolving[1]. Many professionals doubt the validity of the categorical model, Diagnostic and Statistical Manual of mental disorders (DSM) and International Classification of Diseases (ICD), as clinical practice, supported by scientific evidence, shows that mixed symptomatology is often presented by many patients without meeting the full criteria of any traditional diagnostic category[2]. Updated search in *Reference Citation Analysis* (<https://www.referencecitationanalysis.com/>), Google Scholar and PubMed, shows that the transdiagnostic approach is evolving and that cutting edge studies are published in very high-ranked journals[3-7].

There are at least four transdiagnostic new classification systems: Hierarchical Taxonomy to Psychopathology[8], Research Domain Criteria[9], Bipolar-Schizophrenia Network on intermediate phenotypes[10], and Neuroscience-Based Nomenclature[11]. These dimensional transdiagnostic approaches showed biological evidence of specific underlying mechanisms for several mental disorders[12-15]. However, others claim that the findings on underlying biological mechanisms relate to a too wide range of disorders, ruling out the option of differential diagnosis and more accurate derived prevention and treatment[15,16]. The option of including dimensional categories in the traditional classifications has yet to be discussed.

The debate in psychiatry has crucial implications for the diagnosis of stress reactions. Optimal stress reactions are prerequisites of adaptive coping from evolutionary perspectives[17-19]. However, stress reactions are patient-specific, environment-specific, and timing-specific. Therefore, they include a wide range of behaviors and emotional conditions, which cross traditional classification categories and are addressed only partially by these systems[12-14,20,21]. Of special interest is the condition of exposure to multiple stressors, investigated mostly in disaster situations such as flooding, pandemics, hurricanes, earthquakes, and wars[22-25]. In the etiological explanations of the traditional nosology, the interactions of individual differences in coping capacities with the number and extent of environmental stressors have not been evidence-based to date.

Specifically, we previously found a unique transdiagnostic pattern of stress reaction in a binational study using large representative samples in two countries, Italy and Israel, executed during the coronavirus disease 2019 (COVID-19) pandemic[26]. The results showed a transdiagnostic combination of four stress-related symptoms [anxiety, depression, stress symptoms, and post-traumatic stress disorder (PTSD)] that was significantly more prevalent than combinations of fewer symptoms. We termed this combination of four symptoms the Complex Stress Reaction Syndrome (CSRS). We found this pattern of results in the two countries despite cultural and language differences between the two countries and between the methodologies used, suggesting convergent validity of the CSRS.

The pattern of multiple associated symptoms has been widely reported by others regarding the COVID-19 pandemic's impacts on mental health[27-29]. According to WHO reports, 22% of the population develops mental health problems in a dimensional pattern, reactive to emergencies[30]. Accordingly, we related the CSRS to the COVID-19 situation and included CSRS, Type A (psychiatric symptoms) and Type B (psychiatric and neuropsychiatric symptoms in COVID-infected and recovered individuals, excluding systemic symptoms of long-COVID)[26,31]. However, the possibility that CSRS is relevant in the post-COVID era, to capture the mixed clinical picture resulting from concomitant daily stressors in the general population, has only recently been proposed[16].

In a recent paper, we outlined the detailed description of the conceptual development of the CSRS, including its origins in clinical practice and its uniqueness as one transdiagnostic category[16], rather than a total transdiagnostic denial of the traditional psychiatric classifications as suggested by others. The framework underpinning the current study presents an elaboration of the first validation of the CSRS in our published binational study[26], by the inclusion of participants located in four continents in this current study, beyond the validation of the CSRS in only two countries.

In the current multi-lingual international study, conducted across four continents, we aimed to investigate our two-tailed hypothesis that the CSRS is a condition related to the unrecognized type of stress reaction in daily life in the general population (Type A) or related to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection and its long-COVID neuropsychiatric residuals (Type B).

## MATERIALS AND METHODS

### ***Institutional review board***

Institutional review board approvals for this international study were provided by The Johns Hopkins University, Baltimore, Maryland, United States, and by Bar Ilan University, Ramat-Gan, Israel. The study survey used the Qualtrics platform (Qualtrics, Provo, Utah, United States) for data collection.

### ***Sample***

From a sample of 2024 individuals who approached the study questionnaire and partially completed it, 977 completed the entire study questionnaire, and this sample was used for the statistical analyses.

**Inclusion criteria:** Age > 18 years old.

**Recruitment regions:** Middle East, North America, Australia, Europe.

**Activating recruitment teams:** A team of research assistants executed the study on media platforms in each of the six active countries located in four continents. These teams were located in Israel, Jordan, Italy, Sweden, United States and Australia. Each team was led by at least one psychiatrist or psychologist.

**Languages:** The survey (*i.e.* the clinical research tools) was translated from English to 5 languages (Arabic, Hebrew, Italian, Swedish and German) using back translations to English for validation. All posts on the social media platforms were published in all 6 languages of the study to enhance recruitment.

**Qualtrics:** We uploaded the study survey in 6 languages on the Qualtrics platform. The data were saved on this platform and analyzed periodically for the recruitment rate. The final statistical analyses were executed using the data saved on this platform.

**Study period:** February 1, 2022-March 1, 2023.

**Clinical research tools:** We used the following clinical screening tools to identify mental health status (CSRS, Type A): Generalized anxiety disorder-7 (anxiety measure[32]; Cronbach's alpha = 0.931), patient health questionnaire-8[33] (depression measure; Cronbach's alpha = 0.903), perceived stress scale[34] (stress measure; Cronbach's alpha = 0.901), international trauma questionnaire[35] (a PTSD measure; Cronbach's alpha = 0.921). We also used neuropsychiatric measures for infected or recovered individuals (CSRS, Type B): (1) The Perceived Deficits Questionnaire-5, (a cognitive impairment measure[36]; Cronbach's alpha = 0.88); and (2) Fatigue[37], (Cronbach's alpha = 0.654). Participants were asked whether they were SARS-CoV-2 infected/recovered or not. These data were analyzed using validated clinical cutoff points to identify symptomatic conditions above the normative scores on each tool. Anonymity of participants was maintained throughout the study.

**Participation time:** Surveys took approximately 15 min to complete as measured in a pilot study before the onset of this research.

### ***Recruitment***

**Instagram:** We opened an account with promoting videos and photos related to the study and periodically added more related materials. The materials were translated and posted in all six languages of the study. The account displayed a link to the survey's international Qualtrics platform. Each post was user friendly.

**Facebook:** We used Facebook online groups to post a link to the survey. In the case of private Facebook groups, the research assistants in each active participating country contacted the group managers for permission.

**Reddit:** We promoted the study using this social media platform which is friendly and popular in the United States and Australia.

**Online meetings:** The international study teams in the six active countries conducted periodical, online meetings with the leading author and professional leads across each recruitment site to track the recruitment process and rate. To manage recruitment goals in each region, the leading author shared figures of the participants' rate per region, extracted from the data already gathered at those points.

### ***Statistical analyses***

The statistical approach included three steps: (1) We analyzed the frequency of all combinations of symptoms, to determine the most frequent combinations of two, three, four (CSRS, Type A), five and six (CSRS, Type B) symptoms. We then compared between the most prevalent combinations of each number of symptoms using Proportion Analyses; (2) Multivariate Analysis of Co-Variance (MANCOVA) to identify subpopulations at risk; and (3) We confirmed the identification of the subpopulations at risk by linear regression analyses.

## RESULTS

This sample included 655 women, 296 men, and 26 individuals who self-identified as non-binary gender. Of those, 253 aged 18-29, 294 aged 30-39, 204 aged 40-49, 151 aged 50-59, and 75 aged above 60 years old.

All symptoms were significantly correlated (Table 1). Proportion Analyses showed that in the general population, the prevalence of the four-symptom combination (CSRS, Type A) Anxiety, Depression, Stress and PTSD (30.98%, 95%CI: 28-33.8) was greater than that of the most prevalent combination of three symptoms (Anxiety, Stress, and PTSD; 12.78%, 95%CI: 10.7-14.9,  $P < 0.001$ ) and the most prevalent combination of two symptoms (Anxiety and Stress; 6.24%, 95%CI: 4.8-7.8,  $P < 0.001$ ), as well as more prevalent than the one most prevalent symptom (Stress; 18.81%, 95%CI: 16.6-21.6,  $P < 0.001$ ) (Table 2).

In the infected population we found the same pattern of results. As shown for the general population, in infected individuals the prevalence of the combination of four symptoms, Anxiety, Depression, Stress and PTSD (27%, 95%CI: 24.1-31.8) was greater than that of the most prevalent combination of three symptoms (Anxiety, Stress, and PTSD; 12.2%, 95%CI: 9.7-15.3,  $P < 0.001$ ), greater than that of the most prevalent combination of two symptoms (Anxiety and Stress; 5.9%, 95%CI: 4.2-8.3,  $P < 0.001$ ), and that of the one most prevalent symptom (Stress; 21%, 95%CI: 18-25,  $P < 0.01$ ).

However, when we added long-COVID neuropsychiatric symptoms (Cognitive deficits and Fatigue, CSRS, Type B) to the four psychiatric symptoms (CSRS, Type A), the prevalence of four psychiatric symptoms (CSRS, Type A) was still significantly greater than the most prevalent combinations of five symptoms (when adding Cognitive deficits, 8%, 95%CI: 6.3-11.1) or six symptoms (when adding Cognitive Deficits and Fatigue, 4%, 95%CI: 2.8-6.3) at  $P = 0.003$ ,  $P < 0.001$ , respectively), showing that the prevalence of CSRS, Type A is significantly greater than all combinations of symptoms studied. Thus, these results endorse our two-tailed hypothesis, confirming that one tail of the two (CSRS, Type A) is significant. These findings suggest that the CSRS, Type A is applicable for the general population without direct association with the neuropsychiatric part of long-Covid (CSRS, Type B), and that it is not necessarily related to the viral infection and its suspected residuals. Bonferroni correction for multiple comparisons was conducted and the results were significant at  $P < 0.01$ .

As shown in Table 2, more people reported the combination of all 4 psychiatric symptoms (CSRS, Type A) than the combinations of fewer symptoms.

In further analyses to detect subpopulations at risk, a MANCOVA was conducted with four continents, five age groups and three types of gender as independent variables, while keeping the 4 psychiatric components of the CSRS, Type A as dependent variables, controlling for COVID-infected/recovered *vs* non infected/recovered individuals as a covariate. A three-way interaction was found: Continent  $\times$  age  $\times$  gender [ $F(14,925) = 1.747$ ,  $P < 0.05$  with observed power of 0.903] (Figures 1 and 2). The covariate did not significantly add to the explained variance. Follow up analyses showed that the sources of the three-way interaction were threefold, consistently over the 4 dependent variables (Anxiety, Depression, Stress and PTSD, CSRS, Type A): (1) In North America, participants aged  $< 50$  years old, self-identifying as non-binary, reported significantly higher scores than both women and men ( $P < 0.05$ ); (2) Women at young ages ( $< 40$  years old) in North America scored higher compared to men and women in other continents and other ages; and (3) In North America, women at young ages ( $< 40$  years old) and participants self-identifying as non-binary gender, aged  $< 50$ , scored above the clinical cutoff points, although women's scores were significantly lower ( $P < 0.05$ ) than the scores of the non-binary gender at these young ages.

The sources of the three-way interaction, which in turn correspond to identified populations at risk, were confirmed by linear regression analyses, which do not require an assumption of variables' normal distributions.

Specifically, Anxiety score was negatively associated with being a man [ $b = -1.42$  (-2.22, -0.62)] and positively associated with non-binary gender [ $b = 3.81$  (1.53, 6.10)], negatively associated with age groups 50-60 [ $b = -1.36$  (-2.56, -0.15)] and  $> 60$  [ $b = -3.06$  (-4.59, -1.53)] and living in Australia [ $b = -2.96$  (-3.85, -2.07)] or the Middle-East [ $b = -2.06$  (-3.84, -1.36)] compared to North America.

Depression score was negatively associated with being a man [ $b = -1.57$  (-2.42, -0.72)] and positively associated with non-binary gender [ $b = 5.08$  (2.65, 7.51)] while negatively associated with age group  $> 60$  [ $b = -2.89$  (4.52, 1.26)] and living in Australia [ $b = -2.01$  (-2.96, -1.06)] or the Middle-East [ $b = -2.97$  (-4.28, -1.64)] compared to North America.

Stress symptoms score was negatively associated with being a man [ $b = -2.02$  (-3.15, -0.88)] and positively associated with non-binary gender [ $b = 4.65$  (1.40, 7.90)], negatively associated with age groups 50-60 [ $b = -2.12$  (-3.84, -0.40)] and  $> 60$  [ $b = -5.33$  (-7.51, -3.16)] and living in Australia [ $b = -3.24$  (-4.51, -3.98)] or the Middle East [ $b = -4.49$  (-6.25, -2.72)] compared to North America.

PTSD score was negatively associated with being a man [ $b = -2.89$  (-4.09, -1.70)] and positively associated with non-binary gender [ $b = 6.34$  (2.92, 9.75)], negatively associated with older age group  $> 60$  [ $b = -4.86$  (-7.15, -2.57)] and living in Australia [ $b = -3.53$  (-4.86, -2.20)], Europe [ $b = -3.43$  (-6.02, -0.85)] or the Middle East [ $b = -4.44$  (-6.29, -2.59)] compared to North America.

## DISCUSSION

The results of this study show that the prevalence of 4 symptoms, combining anxiety, depression, stress symptoms and PTSD, was significantly higher than the most prevalent combinations of fewer symptoms across 4 continents, age groups ( $> 18$  years old), and gender. This supports the transdiagnostic hypothesis embedded in the CSRS (Type A) and shows its clinical value as a future potential diagnosis spanning 4 conventional diagnostic categories.



**Table 1 Correlation coefficients between all six dependent variables**

Correlation table	PHQ	PSS	ITQ	GAD	Cognitive	Fatigue
PHQ	1	0.79 <sup>a</sup>	0.74 <sup>a</sup>	0.80 <sup>a</sup>	0.4 <sup>a</sup>	0.24 <sup>a</sup>
PSS	0.79 <sup>a</sup>	1	0.74 <sup>a</sup>	0.79 <sup>a</sup>	0.3 <sup>a</sup>	0.25 <sup>a</sup>
ITQ	0.74 <sup>a</sup>	0.74	1	0.71 <sup>a</sup>	0.34 <sup>a</sup>	0.31 <sup>a</sup>
GAD	0.80 <sup>a</sup>	0.79 <sup>a</sup>	0.71	1	0.311	0.25 <sup>a</sup>
Cognitive	0.4 <sup>a</sup>	0.3 <sup>a</sup>	0.34 <sup>a</sup>	0.311 <sup>a</sup>	1	0.30 <sup>a</sup>
Fatigue	0.24 <sup>a</sup>	0.25 <sup>a</sup>	0.31 <sup>a</sup>	0.25 <sup>a</sup>	0.30 <sup>a</sup>	1

<sup>a</sup>*P* < 0.001.

As shown in Table 1, all components of the CSRS type A and type B are significantly correlated. PHQ: Patient Health Questionnaire; PSS: Perceived Stress Scale; ITQ: International Trauma Questionnaire; GAD: Generalized Anxiety Disorder.

**Table 2 All combinations of symptoms reported**

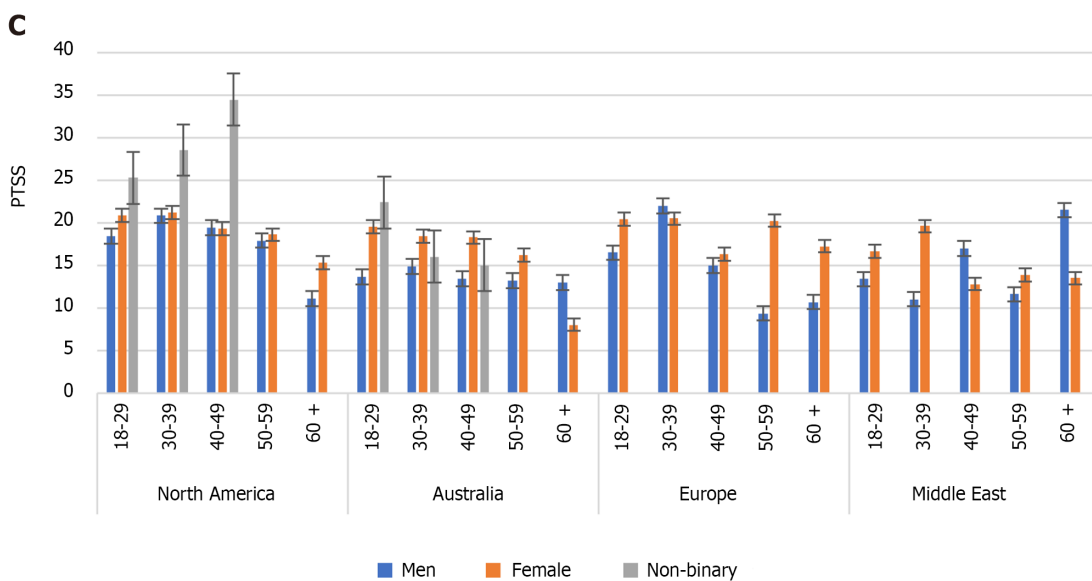
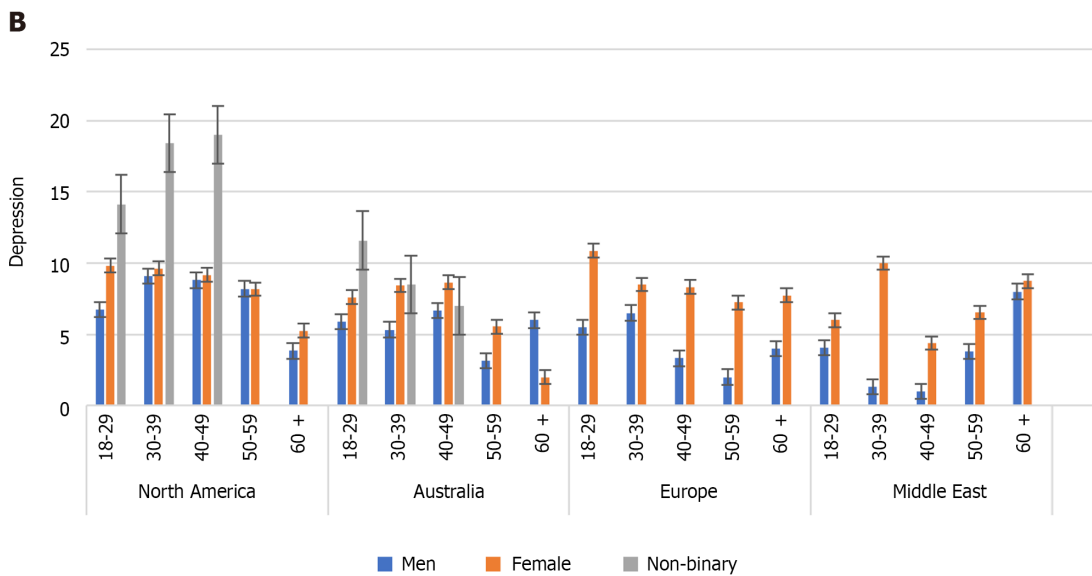
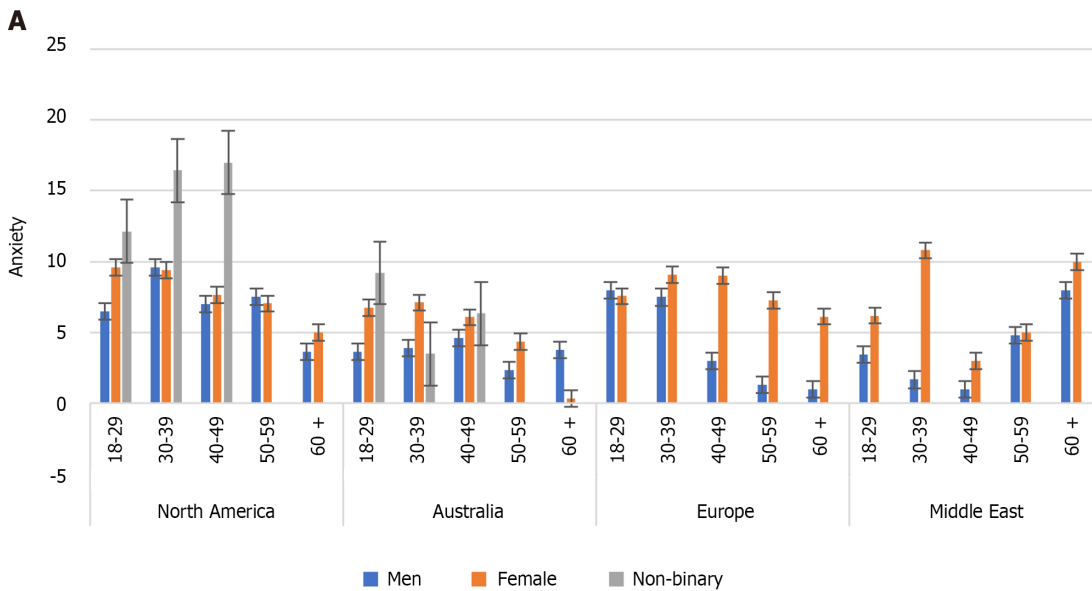
General population	Percentage
Combination	
None	10
Stress	20
Depression	0
Anxiety	3
PTSD	2
Stress + depression	0
Anxiety + depression	0
PTSD + depression	0
Stress + anxiety	6
Stress + PTSD	4
Anxiety + PTSD	1
Stress + depression + anxiety	3
Stress+ depression + PTSD	1
Stress + anxiety + PTSD	13
Depression+ anxiety + PTSD	0
All	31

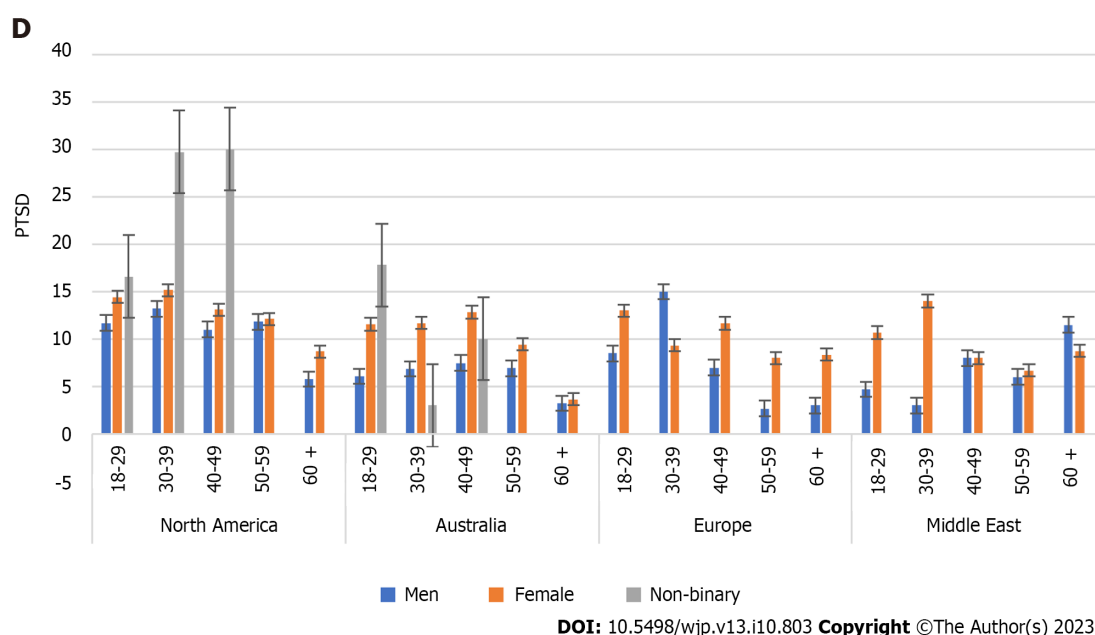
PTSD: Post-traumatic stress disorder.

The results show that the CSRS is sensitive to demographic variability and especially to the differences between cultures, locations and gender types. The overall analyses confirm the transdiagnostic hypothesis by showing that over 4 continents and gender types more symptoms were significantly more prevalent than fewer symptoms.

One identified source for the significant three-way interaction found in this study (age × gender × continent), and confirmed by regression analyses showed, that the group that self-identified as non-binary gender scored significantly higher on all four psychiatric symptoms of the CSRS at young ages (< 40 years old) in North America compared to (self-identified) women and (self-identified) men located in the 4 continents studied, and to other ages across the adult life span. These results show a combined mental health risk factor, suggesting that the CSRS, Type A is sensitive to populations at risk and may be applied to future identification of other vulnerable sub-populations.

In the scientific literature, identifying as non-binary at a young age has been recognized as a risk factor for increased mental health problems compared to other age groups and to other gender identities including other types on the gender identity spectrum such as the transgender identity[38,39]. The reduced affective wellbeing of those who identify as non-binary gender have been documented in research and theoretical conceptualizations[38,40,41]. To describe the unique type of distress that non-binary gender individuals might experience the term “gender minorities stress” was suggested





**Figure 1** The measures assessing the four psychiatric features of the Complex Stress Reaction Syndrome (CSRS, Type A, mean  $\pm$  SD). A: The Generalized Anxiety Disorder (anxiety measure); B: The Patient Health Questionnaire-8 (depression measure); C: The Perceived Stress Scale (perceived stress measure); D: The International Trauma Questionnaire (post-traumatic stress disorder measure).

[42]. We note that more conservative social views in continents other than North America may have inhibited people from identifying as non-binary and prevented an even larger magnitude of the non-binary gender stress reactivity in our findings. The emotional burden of this minority and its dramatic impact on this study's results attests to the extreme distress experienced by this sub-population.

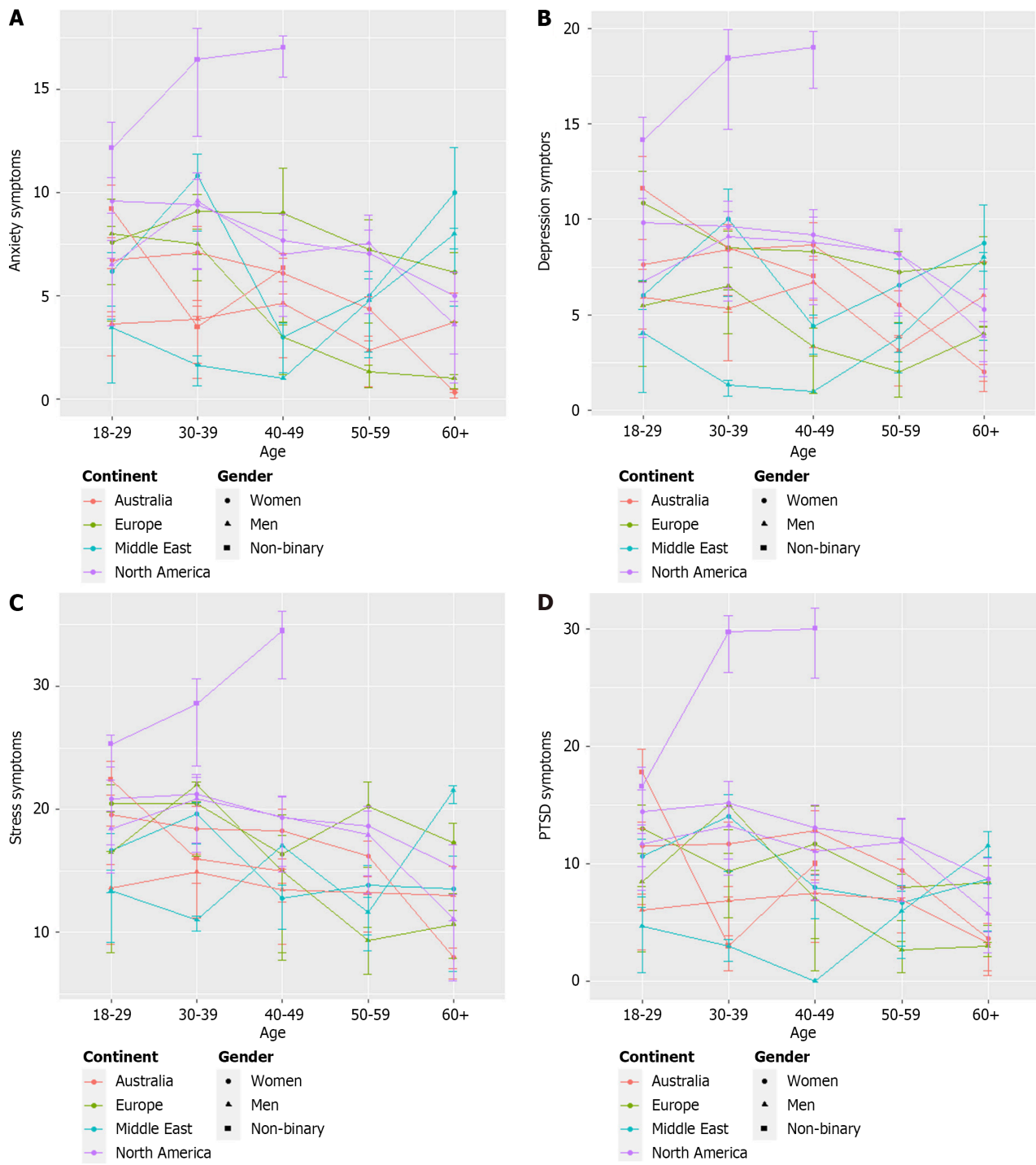
An additional source for the three-way interaction is related to another sub-population at risk which scored above the clinical cutoffs of all the four types of symptomatology included in the CSRS, Type A, young age groups identifying as a woman in North America. Being a woman at young age has been reported as a risk factor long before the COVID-19 outbreak[43,44], during the COVID-19 pandemic[45] and in the post-COVID era[46] in very large, epidemiological studies. Thus, our results show the sensitivity of the CSRS, Type A in measuring a specific stress reactivity spanning several conventional categories in both minoritized and majority subpopulations.

In this study, the psychiatric pattern of symptoms (CSRS, Type A) was similar in infected/recovered SARS-CoV-2 patients and in the non-infected population, suggesting that the CSRS, Type A is sensitive to a clinical picture in daily life, beyond its relevance to catastrophes, including the COVID-19 pandemic[16]. The neuropsychiatric part of the CSRS relating to neuropsychiatric components of the long-COVID syndrome (CSRS, Type B), did not add to the explained variance and the same pattern of results was found in infected/recovered individuals. These results show that the psychiatric part of the CSRS (Type A), when controlling for infected-non infected conditions, is the type of CSRS which is sensitive to at-risk sub-populations. In accordance with a current debate, this study also suggests that the long-COVID syndrome is a too broad diagnostic category in neuropsychiatry, resulting in recent contradictory results[47,48]. Thus, the CSRS shows relevance for daily life stressors, beyond the pandemic situation and not as a mandatory result of the viral infection.

Thus, the CSRS, Type A represents a unique transdiagnostic clinical picture combining symptomatology of affective disorders with stress reactivity[16,26,31]. The prevalence of affective disorders spans a wide range of symptomatology, with dramatic cross-cultural differences[49]. Reports on prevalence of stress reactions are also present across a wide range mental disorders[50]. Furthermore, earlier studies reported that at-risk populations do not necessarily meet the full criteria of affective disorders and stress reactivity categories[40,44]. As it arises from the current findings, and according to our previous arguments[26], the CSRS, Type A identifies, and is sensitive to individual differences in stress reactivity and reduced positive affectivity, within a transdiagnostic spectrum.

The correlative design of this study is the most appropriate for the current stage of CSRS development as only after assuring the face validity of the hypothesized syndrome by empirical data, including its highly associated symptoms, a follow up design on etiological questions related to more causal assumptions may be investigated. In fact, to show that any transdiagnostic hypothesis is related to associations between symptoms spanning several traditional categories, a correlative design should be employed.

As the aim of this research is primarily transdiagnostic, its correlative design affords testing the relationship and extent of association between a given number of variables (symptoms) spanning traditional classifications without meeting them in full. This type of design also allows testing whether a correlative combination of more symptoms is more prevalent than a combination of fewer symptoms from a given number of hypothesized variables, in a given hypothesized combination.



DOI: 10.5498/wjp.v13.i10.803 Copyright ©The Author(s) 2023.

**Figure 2** Three-way interactions between continents, age groups and gender identifying the sub-populations at risk by the four psychiatric features of the Complex Stress Reaction Syndrome (CSRS, Type A). A: Three-way-interaction for the Generalized Anxiety Disorder (anxiety measure); B: Three-way-interaction for the Patient Health Questionnaire-8 (depression measure); C: Three-way-interaction for the Perceived Stress Scale (perceived stress measure); D: Three-way-interaction for the International Trauma Questionnaire (post-traumatic stress disorder measure).

The correlative design used in this study aimed also to show the sensitivity of CSRS to populations at risk who score beyond the clinical cutoff of the measures used. As such, the study also aimed to investigate the generalizability of the CSRS across continents, gender types and age-groups. This required comparisons between continents, gender types and age-groups. Thus, a correlative design and its aligned conclusion on associations between symptoms as related to demographic factors, may be derived even when employing statistical comparisons between independent (demographic, in this case) variables, and their assumed related “causal” impact on the dependent (CSRS, Type A) variables. The advantage of this approach and conclusions regarding association between independent (demographic) and dependent (CSRS, Type A) variables is threefold from both scientific and clinical perspectives: (1) It shows the generalizability of the CSRS; (2) It shows the CSRS, Type A as clinically essential for the identification of populations at risk, suggesting that the CSRS, Type A is sensitive to a unique transdiagnostic mental health condition; and (3) It includes a suspected indication

to treat. Furthermore, the results of the analysis of variance were confirmed by significant associations between the same demographic variables and the most prevalent combination of symptoms (CSRS, Type A) in linear regression analyses. Thus, the same populations at risk, as well as the sensitivity of the CSRS to these populations, are apparent in the results of this study.

The limitations of this study lie in the sampling methods utilized, which used convenience sampling[51]. This type of convenience online sampling became very popular and legitimate during the pandemic, although very large samples have been criticized before and after the pandemic[52,53]. Additional limitations include the use of self-report measures (symptoms) and not diagnostic interviews (signs), and the possible bias towards samples who are computer literate. However, in our binational research[26], we combined the methodology of representative sampling (Israel) with convenience sampling (Italy) and found similar results, although employing two different sampling methodologies, supporting the validity of the online convenience sampling. Yet to come, international studies with representative sampling, are warranted for further support of the CSRS, Type A validity and its clinical value.

This current international study emphasizes the importance of transdiagnostic approaches for clinical identification of individual differences and sub-populations at risk that do not meet the full criteria of any traditional category. This will afford the development of more accurate prevention and treatment for those with emotional needs who remain without a clear diagnosis and proper clinical care.

## CONCLUSION

This study shows a global new picture of the indication to treat derived from (1) The different populations included from around the globe; and (2) Allowing a transdiagnostic perspective. Although the categorical model of diseases remains largely used worldwide[26], the future will tell if transdiagnostic categories will be part of the next revisions of the DSM and ICD conventional systems to facilitate a resolution of the crisis in the field of psychiatry[1]. Indeed, a transdiagnostic approach recognizes the inherent complexity and heterogeneity of mental disorders by focusing on shared underlying dimensions rather than rigid diagnostic categories. This allows for a more nuanced understanding of psychopathology and better captures the overlapping symptomatology often observed across different disorders. Hence, future international transdiagnostic clinical research is warranted. To support psychiatrists in their clinical practice, future research may utilize transdiagnostic approaches to classify patients who show a mixed clinical picture when applied in face-to-face clinical meetings (signs) compared to remote self-scoring (symptoms) by the same patients.

## ARTICLE HIGHLIGHTS

### Research background

The debate regarding diagnostic classification systems in psychiatry (categorical *vs* dimensional systems) has essential implications for the diagnosis, prevention and treatment of stress reactions.

### Research motivation

We previously found a unique pattern of stress reaction in a study executed during the coronavirus disease 2019 pandemic using large representative samples in two countries, and termed it the Complex Stress Reaction Syndrome (CSRS). In the current international study, in four continents, using six languages we aimed to investigate the generalization of the CSRS and its sensitivity to populations at risk.

### Research objectives

We aimed to investigate CSRS, Type A [psychiatric symptoms, spanning anxiety, depression, stress symptoms, and post-traumatic stress disorder (PTSD)], with or without long-COVID residuals (CSRS, Type B, neuropsychiatric symptoms spanning cognitive deficits and fatigue, excluding systemic symptoms). Our two-tailed hypothesis was that CSRS is a condition related to an unrecognized type of stress reaction in daily life in the general population (Type A) or that it is related to the severe acute respiratory syndrome coronavirus 2 infection and its long-COVID residuals (Type B).

### Research methods

Media-supported study using the Qualtrics platform.

### Research results

The results of the Proportion Analyses showed that the prevalence of 4 symptoms spanning anxiety, depression, stress symptoms, and PTSD was significantly higher than the most prevalent combinations of fewer symptoms across 4 continents, age groups, and gender (CSRS, Type A). Further analyses identified two populations at risk: (1) Individuals that self-identified as non-binary gender; and (2) Women at young ages (< 40 years old) in North America.

### Research conclusions

These results show a combined mental health risk factor related to stress reactivity, suggesting that the CSRS is sensitive to populations at risk and may be applied to future identification of other vulnerable sub-populations. It also supports the



transdiagnostic approach for more accurate prevention and treatment. Time will tell if such transdiagnostic syndromes will be part of the discussions on the next revisions of the traditional classification systems or whether the crisis in psychiatry further evolves.

### Research perspectives

A follow-up international study to investigate whether the condition of multiplicity of stressors is the etiological source for developing the CSRS, Type A clinical status, is warranted.

## ACKNOWLEDGEMENTS

The authors thank Daniel Mandelbaum for his assistance in statistical analyses. We also thank Adi Ramot for graphical contributions to the media posts.

## FOOTNOTES

**Author contributions:** Goldstein Ferber S developed the CSRS conceptualization and was the leading author; Rossi R supervised the statistical analyses and data collection; All the other authors contributed to the study and the last version of this paper.

**Institutional review board statement:** IRB approvals for this international study were provided by The Johns Hopkins University, Baltimore, Maryland, USA, and by Bar Ilan University, Ramat-Gan, Israel. The study survey used the Qualtrics platform (Qualtrics, Provo, Utah, USA) for data collection.

**Informed consent statement:** All study participants provided online informed consent prior to study enrollment.

**Conflict-of-interest statement:** The authors declare no conflict of interest.

**Data sharing statement:** The study data are available upon request.

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**Corresponding Author's Membership in Professional Societies:** Sigma Xi Honor Society Nomination.

**S-Editor:** Fan JR

**L-Editor:** A

**P-Editor:** Zhang XD

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