Association of Global Cognitive Function with Psychological Distress and Adherence to Public Health Recommendations during the COVID-19 Pandemic: The Women's Health Initiative

Aladdin H. Shadyab, PhD,[1] Joseph C. Larson, MS,[2] Stephen R. Rapp, PhD,[3] Sally A. Shumaker, PhD,[4] Candyce H. Kroenke, ScD, MPH,[5] Jaymie Meliker, PhD,[6] Nazmus Saquib, PhD,[7] Farha Ikramuddin, MD, MHA,[8] Yvonne L. Michael, ScD, SM,[9] Joseph S. Goveas, MD,[10] Lorena Garcia, PhD,[11] Jean Wactawski-Wende, PhD,[12] Juhua Luo, PhD,[13] Kathleen M. Hayden, PhD,[4] Jiu-Chiuan Chen, MD, ScD,[14] Julie Weitlauf, PhD,[15] and Laura D. Baker, PhD[16]

[1]Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA, USA

[2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[3]Department of Psychiatry and Behavioral Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA

[4]Department of Social Sciences and Health Policy, Wake Forest School of Medicine, Winston-Salem, NC, USA

[5]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA

[6]Program in Public Health, Department of Family, Population and Preventive Medicine, Stony Brook University, Stony Brook, NY, USA

[7]College of Medicine, Sulaiman AlRajhi University, Al Buakyriyah, Saudia Arabia

[8]Division of Physical Medicine and Rehabilitation, Department of Rehabilitation Medicine, University of Minnesota School of Medicine, Minneapolis, MN, USA

[9]Department of Epidemiology and Biostatistics, Dornsife School of Public Health, Drexel University, Philadelphia, PA, USA

[10]Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

[11]Department of Public Health Sciences, School of Medicine, University of California, Davis, CA, USA

[12]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, State University of New York (SUNY) at Buffalo, Buffalo, NY, USA

[13]Department of Epidemiology and Biostatistics, School of Public Health, Indiana University, Bloomington, IN, USA

[14]Departments of Population and Public Health Sciences and Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

[15]Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, and Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA

[16]Department of Internal Medicine-Geriatrics, Wake Forest School of Medicine, Winston-Salem, NC, USA

Corresponding Author: Aladdin H. Shadyab, PhD, 9500 Gilman Drive #0725,University of California, San Diego, La Jolla, CA; email: ahshadya@health.ucsd.edu

ABSTRACT

Background: The association of cognitive function with symptoms of psychological distress during the coronavirus 2019 (COVID-19) pandemic or adherence to COVID-19 protective health behaviors is not well understood.

Methods: We examined 2,890 older women from the Women's Health Initiative cohort. Pre-pandemic (i.e., within 12 months prior to pandemic onset) and peri-pandemic global cognitive function scores were assessed with the modified Telephone Interview for Cognitive Status (TICS-m). Anxiety, stress, and depressive symptom severity during the pandemic were assessed using validated questionnaires. We examined adherence to protective behaviors that included safe hygiene, social distancing, mask wearing, and staying home. Multivariable models were adjusted for age, race, ethnicity, education, region of residence, alcohol intake, and comorbidities.

Results: Every five-point lower pre-pandemic TICS-m score was associated with 0.33-point mean higher (95% CI, 0.20,0.45) perceived stress, and 0.20-point mean higher (95% CI, 0.07,0.32) depressive symptom severity during the pandemic. Higher depressive symptom severity, but not anxiety or perceived stress, was associated with a 0.69-point (95% CI, -1.13, -0.25) mean decline in TICS-m from the pre- to peri-pandemic period. Every five-point lower peri-pandemic TICS-m score was associated with 12% lower odds (OR, 0.88; 95% CI, 0.80,0.97) of practicing safe hygiene.

Conclusions: Among older women, we observed that: 1) lower pre-pandemic global cognitive function was associated with higher stress and depressive symptom severity during the pandemic; 2) higher depressive symptom severity during the pandemic was associated with cognitive decline; and 3) lower global cognitive function during the pandemic was associated with lower odds of practicing safe hygiene.

Key words: depression, anxiety, stress, SARS-CoV-2, mental health

INTRODUCTION

Throughout the course of the coronavirus disease 2019 (COVID-19) pandemic, lockdowns, mask mandates, and social distancing measures brought unprecedented disruptions to our daily lives. Emerging evidence shows potentially negative psychosocial consequences from the response to the COVID-19 pandemic.[1-4] COVID-19 pandemic-related stressors that may be associated with psychological distress include persistent fear of infection, social isolation, negative economic consequences, and uncertainty about the future.[1]

In a nationally representative sample of 1,337 U.S. adults, 13.0% reported serious psychological distress due to the COVID-19 pandemic in April 2020.[2] The most common pandemic-related stressors included concerns about contracting COVID-19 (65.9%) and the pandemic's adverse effects on employment (65.1%) and personal finances (60.6%). Because psychosocial distress is associated with risk of future cognitive decline, psychological distress during the COVID-19 pandemic represents an important public health issue.[5-12] For example, depression and anxiety, two common symptoms of psychological distress, are associated with increased risk of cognitive decline, cognitive impairment, and dementia among older adults.[5-9] In the Health and Retirement Study, participants who had higher levels of psychological distress (including anxiety, negative emotions, hostility, pessimism, and hopelessness) had 20%-30% higher risk of dementia.[10]

Few studies have examined the association of cognitive function with psychological distress during the pandemic. The relationship between cognitive function and adherence to COVID-19 protective health behaviors (e.g., wearing masks and practicing safe hygiene) is also not well understood and may represent added risk among older adults with low cognitive function. In this analysis, we aimed to determine whether: 1) lower pre-pandemic cognitive function was associated with higher likelihood of experiencing symptoms of psychological distress during the pandemic; 2) symptoms of psychological distress during the pandemic were associated with cognitive decline from the pre- to peri-pandemic period; and 3) lower peri-pandemic cognitive function was associated with lower likelihood of adhering to key COVID-19 protective health behaviors. To address these

questions, we leveraged data from two ongoing observational ancillary studies and one intervention ancillary study from the Women's Health Initiative (WHI) cohort of older women. Relative to men, women have reported greater stress and poorer mental health during the COVID-19 pandemic.[13] Thus, from a public health perspective, continued monitoring and reporting of women's mental health outcomes during the pandemic is important.

METHODS

Study Population

The WHI is a large, prospective study investigating major determinants of chronic diseases among postmenopausal women. The WHI recruited 161,808 postmenopausal women ages 50-79 years during 1993-1998 to participate in an Observational Study (N=93,676) or one or more of three Clinical Trials (N=68,133). The clinical trials included two Hormone Therapy (HT) trials (which ended in 2002 and 2004), a Dietary Modification (DM) trial (which ended in 2005), and a Calcium and Vitamin D supplementation trial (which ended in 2005). In 2005, 76.9% of 150,075 eligible WHI women consented for an additional five years of follow-up in the first Extension Study. In 2010, 86.8% of 107,706 women consented to further follow-up through 2015 in the second Extension Study. The third Extension Study is currently ongoing. The WHI study design and methods are described in detail elsewhere. [14]

The present study included WHI participants from three ancillary studies with measures of global cognitive function: Women's Health Initiative Memory Study Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO), WHI Sleep Hypoxia Effects on Resilience (WHISPER), and Cocoa Supplement and Multivitamin Outcomes Study for the Mind (COSMOS-Mind). Participants for these ancillary studies were drawn from the WHI cohort, and there is no overlap in participation. All participants provided written informed consent, and these studies obtained Institutional Review Board approval at the Fred Hutchinson Cancer Research Center.

WHIMS-ECHO (N=2,893) is an ancillary, observational follow-up study to the larger WHIMS, a randomized clinical trial that aimed to determine the effects of hormone therapy on global

cognitive function and incidence of dementia among a subset of women ages 65-79 years recruited into the WHI HT trials, which ended in 2002 and 2004 but continued to follow women through 2007.[15] Follow-up in the observational WHIMS-ECHO study for cognitive outcomes started in 2008 and continued through November 2021. WHISPER (N=5,000) examines the relationship between sleep-disordered breathing and other sleep exposures, and cardiovascular disease, cancer, and cognitive trajectory. WHI women ages 65 and older were enrolled into WHISPER between 2017 and 2018 and followed for up to 3 years. COSMOS-Mind (N=2,262), an ancillary study to the larger COSMOS randomized clinical trial, assessed the effects of cocoa extract and a multivitamin on cognitive function in adults ages 65 years and older; the trial ended on December 31, 2020.[16] COSMOS-Mind recruited a group of women from the WHI who were not participants of WHIMS-ECHO. Women in COSMOS-Mind were followed for 3 years.

Global Cognitive Function Measure

The modified Telephone Interview for Cognitive Status (TICS-m) is designed to assess global cognitive function and was administered annually by trained and certified interviewers as part of the WHIMS-ECHO, WHISPER, and COSMOS-Mind protocols. TICS-m is a 16-item instrument that assesses orientation, attention and concentration, short- and long-delay free recall, mental calculation, naming, repetition, social knowledge, and praxis.[17] TICS-m has good reliability (i.e., Cochran's alpha=0.78) and validity (i.e., sensitivity of 94% and specificity of 100% for discriminating cognitively normal from demented individuals).[18,19]

For the present study, we designated January 30, 2020, the day when the Director-General of the World Health Organization declared COVID-19 a public health emergency of international concern, as the start of the pandemic. The participant sample included women who completed the TICS-m within 12 months prior to the onset of the COVID-19 pandemic (i.e., January 30, 2019 through January 29, 2020), and the WHI COVID-19 questionnaire that was administered to all WHI participants between June 2020 and October 2020. The most recent TICS-m score was used. For analyses in the subset of women with cognitive assessments completed during the pandemic, peri-

pandemic TICS-m scores were collected between January 30, 2020 and February 23, 2021 (i.e., the last date through which TICS-m scores were available at the time of these analyses).

Psychological Distress Measures

Anxiety. Anxiety was assessed using the PROMIS Anxiety Short Form 4a questionnaire, which was included as part of the WHI COVID-19 questionnaire.[20] This questionnaire has excellent reliability (i.e., Cronbach's alpha=0.89) and good construct validity, with higher PROMIS anxiety scores associated with greater number of anxiety disorders in a prior study.[21] The questionnaire contains the following four items rated on a 5-point Likert-type scale (where response choices vary from 1= "never" to 5= "always") that assess anxiety levels in the past seven days: 1) "I felt fearful;" 2) "I found it hard to focus on anything other than my anxiety;" 3) "My worries overwhelmed me;" and 4) "I felt uneasy." Raw scores were summed and then converted to standardized T-scores according to the PROMIS Anxiety Short Form 4a Conversion Table, resulting in a mean score of 50 and a standard deviation of 10. Higher scores indicate greater levels of perceived anxiety. Scores of ≥60 are 1 standard deviation (SD) above the population mean and are indicative of clinically significant anxiety symptoms.[22-24]

Stress. Stress was assessed with the Perceived Stress Scale (PSS-4), which was included on the WHI COVID-19 questionnaire.[25] PSS-4 has demonstrated good reliability (Cronbach's alpha=0.74) and validity, showing positive correlations with the Symptom Checklist-90-Revised anxiety and depression scales (r=0.51 and r=0.69, respectively).[26] PSS-4 asks: "In the past 4 weeks, how often have you felt: 1) that you were unable to control the important things in your life; 2) confident about your ability to handle your personal problems; 3) that things were going your way; and 4) that difficulties were piling up so high that you could not overcome them?" Each item was rated on a 5-point Likert type scale (with response choices varying from 1= "never" to 5= "very often"). Total scores were obtained by summing across the four items, with higher scores representing greater levels of perceived stress.

Depressive symptom severity. Depressive symptom severity was assessed with the 15-item Geriatric Depression Scale (GDS), which was collected from January 30, 2020 through February 23, 2021 as part of the WHIMS-ECHO, WHISPER, and COSMOS-Mind annual cognitive assessments.[27] The GDS is a self-report screening instrument assessing various symptoms of depression, including satisfaction with life, boredom, level of happiness, and feeling helpless, with responses rated as 'yes' or 'no.' The GDS has excellent reliability (with an average reliability across studies of 0.85) and validity (with sensitivity and specificity rates of 92.7% and 65.2%, respectively, and positive and negative predictive values of 82.6% and 83.3%, respectively, when measured against ICD-10 diagnostic criteria for major depressive episode).[28,29] Total scores are summed, with higher scores indicating greater depressive symptom severity. A score of ≥5 is indicative of mild to severe depressive symptom severity.[27]

Adherence to COVID-19 Protective Health Behaviors

The WHI COVID-19 questionnaire assessed adherence to COVID-19 protective health behaviors using the following question: "Since March 2020, what steps have you taken to reduce your risk of being infected by COVID-19?" Response options included protective health behaviors recommended by the Centers for Disease Control and Prevention at the time of the questionnaire (June 2020 to October 2020), which were analyzed as four separate binary variables (fully adherent or inconsistently/not adherent) for analysis, similar to a recent study:[30] 1) practices safe hygiene (women were considered to have practiced safe hygiene if they responded 'yes' to all of the following options: washes hands frequently, tries not to touch face, and disinfects surfaces frequently); 2) maintains social distancing (women were considered to maintain social distancing if they responded 'yes' to all of the following options: maintains physical distance from people outside household, avoids in-person social or religious activities, avoids or limit in-person shopping, and avoids shaking hands); 3) wears a face mask in public; and 4) stays home.

Covariates

Covariates included: age; education; region of residence; history of cardiovascular disease (defined as myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or stroke), diabetes, hypertension, and cancer; and alcohol use, which were collected as part of ongoing WHI follow-up. These covariates were selected as they may impact pre-pandemic cognitive or mental health status, or impact adherence to health behaviors in older adults, according to prior literature.[5-7,30-32] We included covariates for race and ethnicity due to differences in the levels of exposure and outcomes to the COVID-19 pandemic across racial and ethnic groups.[33] We also examined number of people living in household and concerns about the pandemic, which were captured on the WHI COVID-19 questionnaire.

Statistical Analysis

Descriptive statistics of study characteristics in the overall sample are presented by pre-pandemic TICS-m score categorized using an established cutpoint, with >31 indicating normal cognition and ≤31 indicating impaired cognition.[34] Continuous variables are presented as means (standard deviations), and categorical variables are presented as frequencies and proportions. Differences in participant characteristics by TICS-m- grouping were evaluated using two-sample t-tests for continuous variables and chi-square tests for categorical variables.

Multiple linear regression models were used to determine associations of pre-pandemic global cognitive function with anxiety, stress, or depressive symptoms during the pandemic, which were examined separately as the dependent variables. The independent variable in each model was pre-pandemic TICS-m score, which was examined both as a dichotomous variable using cutpoints (≤31 vs. >31) and a continuous variable to evaluate linear associations. Models were adjusted for: age; study source (WHIMS-ECHO, WHISPER, and COSMOS-Mind); race; ethnicity; education; history of cardiovascular disease, diabetes, hypertension, and cancer; alcohol intake; region of residence; number of people living in household; total number of prior TICS-m screens to control for practice effects; and number of months from pandemic start (January 30, 2020) to date of psychological

distress symptom collection (i.e., on the COVID-19 questionnaire) during the pandemic. Analyses are presented as a 5-point change in TICS-m score, which represents an approximate one standard deviation change in our data.

Associations of stress, anxiety, or depressive symptoms during the pandemic with change in pre- to peri-pandemic global cognitive function measured using the TICS-m were examined using multiple linear regression models. Separate models were fit with anxiety, perceived stress, and depressive symptom severity as the independent variables of interest. The dependent variable in the models was calculated as the difference between the pre- and peri-pandemic TICS-m scores. Models were adjusted for similar confounders as described above, with the addition of number of months between pre- and peri-pandemic TICS-m measurements.

Associations of peri-pandemic global cognitive function with adherence to COVID-19 protective health behaviors were evaluated using logistic regression models. The following outcomes were examined in separate logistic regression models: 'practices safe hygiene,' 'maintains social distancing (yes/no),' 'wears a face mask in public (yes/no)' 'stays home (yes/no),' or 'adherence to all measures (yes/no),' as defined above. Models were adjusted for

age; study source; race; ethnicity; education; history of cardiovascular disease, diabetes, hypertension, and cancer; alcohol intake; region of residence; number of people living in household; total number of prior TICS-m tests; and number of months from pandemic start to date of psychological distress symptom collection.

Sensitivity analyses were conducted restricting peri-pandemic TICS-m screens to those occurring after March 13, 2020, the day when COVID-19 was declared a national emergency in the United States and after which most social and other changes were implemented throughout the country. Sensitivity analyses were performed using cutpoints for depressive symptom severity (i.e., mild to severe depressive symptoms [GDS score ≥5] relative to not depressed (GDS score 0-4])[27] and clinically significant anxiety symptoms (i.e., PROMIS anxiety ≥60 vs. <60)[22-24] to examine: 1) the association of pre-pandemic cognitive function with any depressive symptoms or clinically significant

anxiety symptoms during the pandemic using logistic regression models, adjusted for similar confounders as above and 2) the association of any depressive symptoms or clinically significant anxiety symptoms during the pandemic with changes in pre- to peri-pandemic cognitive function, using similar analyses as above.[27] To determine whether cognitive impairment impacted participant response to questions on adherence to COVID-19 protective health behaviors, sensitivity analyses were performed excluding women with TICS-m ≤31 from the analyses.

In all analyses, we explored interactions with age (categorized according to 80 years, as the majority [57.9%] of the sample was above this age), number of people living in household, history of cardiovascular disease, and history of diabetes. *P*-values were considered statistically significant at $P<0.017$ (i.e., 0.05/3 using Bonferroni correction) for analyses examining stress, anxiety, and depressive symptoms, and $P<0.01$ (i.e., 0.05/5) for analyses examining the five outcomes for COVID-19 protective behaviors. Statistical analyses were conducted using Statistical Analyses Software (SAS), Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Analytic Sample

In total, 3,283 women completed TICS-m within the 12 months prior to the start of the COVID-19 pandemic and completed the WHI COVID-19 questionnaire administered between June 2020 and October 2020. After excluding first those who self-reported having previously tested positive for COVID-19 (n=22) and then those missing data on stress or anxiety symptoms during the pandemic (n=371), there remained 2,890 women with pre-pandemic global cognitive function data (n=2,211 from WHISPER; n=434 from WHIMS-ECHO; and n=245 from COSMOS-Mind). A subset (n=1,690) of these women had peri-pandemic depressive symptom data.

Overall, 3,040 women completed TICS-m on or after January 30, 2020 and completed the WHI COVID-19 questionnaire. After excluding first those who tested positive for

COVID-19 (n=16) and then those missing data on stress or anxiety (n=324), there remained 2,700 women with peri-pandemic global cognitive function data (n=2,240 from WHISPER; n=374 from WHIMS-ECHO; and n=86 from COSMOS-Mind). A subset of these women (n=1,690) also had global cognitive function data collected within 12 months prior to pandemic onset.

Descriptive Characteristics of Sample

Among the 2,890 women with pre-pandemic global cognitive function data, mean age was 82.8 (SD 5.8) years; 78.8% were White; 16.8% were African American; 1.0% were Asian; 1.1% were more than one race; 0.2% were American Indian/Alaskan Native; 2.1% were of unknown race; and 6.7% were of Hispanic ethnicity. Overall, 52.1% were college graduates; 9.2% had history of cardiovascular disease; 22.1% had history of diabetes; and 71.5% had history of hypertension. Approximately half (50.4%) reported living with at least one person in the same household; 6.6% had a family member or close friend die from COVID-19; and 92.7% were somewhat or very concerned about the pandemic. The most common pandemic-related concerns included the health, safety, and infection of family and friends (79.8%); the ability to be with family and friends (63.4%); and perceived risk of COVID-19 infection (61.9%). Regarding adherence to COVID-19 protective health behaviors, 96.7% wore a face mask; 81.5% stayed home; 60.3% maintained social distancing; and 43.9% practiced safe hygiene. The mean (SD) most recent pre-pandemic TICS-m score was 35.2 (4.6). The mean (SD) most recent peri-pandemic TICS-m score was 35.3 (SD 4.7). There was a mean of 16.0 (SD 2.4) months between pre- and peri-pandemic TICS-m screens.

Relative to women with pre-pandemic TICS-m scores >31, women with scores ≤31 were older, less likely to be college graduates, less likely to report >1 alcoholic drink per week, and more likely to have history of diabetes or hypertension (Table 1). Women with TICS-m scores ≤31 were less likely to be: concerned about the risk of COVID-19 infection, the health and safety of family and friends, the ability to be with family or friends, and the nation and economy (Supplementary Table

S1). They were more likely to be concerned about having enough money, personal safety, and financial security (Supplementary Table S1).

Pre-pandemic Global Cognitive Function and Symptoms of Psychological Distress During the Pandemic

Multivariable associations of pre-pandemic global cognitive function with stress, anxiety, and depressive symptom severity during the pandemic are shown in Table 2. Pre-pandemic cognitive function was not significantly associated with peri-pandemic anxiety. Every five-point lower pre-pandemic TICS-m score was associated with 0.33-point mean higher perceived stress during the pandemic (95% CI, 0.20, 0.45; *P*<0.001). Women with TICS-m scores ≤31 compared with >31 had 0.62-point mean higher perceived stress (95% CI, 0.35, 0.90; *P*<0.001). Every five-point lower pre-pandemic TICS-m score was associated with 0.20-point mean higher depressive symptom severity score during the pandemic (95% CI, 0.07, 0.32; P=0.003). Findings for anxiety, perceived stress, or depressive symptom severity did not vary by age, number living in household, history of CVD, or history of diabetes (Supplementary Table S2). In sensitivity analyses using cut-points for depressive symptom severity, 223/1690 women (13.2%) had any depressive symptoms during the pandemic, whereas 1467/1690 (86.8%) were not depressed. Every five-point lower pre-pandemic TICS-m score was associated with 21% higher odds of any depressive symptoms during the pandemic (OR 1.21; 95% CI, 1.02-1.45; Supplementary Table S3). Overall, 268/2890 (9.3%) women had clinically significant anxiety symptoms (i.e., a PROMIS anxiety score ≥60) during the pandemic. Pre-pandemic TICS-m was not significantly associated with peri-pandemic anxiety defined using this cut-point (Supplementary Table S3).

Psychological Distress and Pre- to Peri-pandemic Change in Global Cognitive Function

Multivariable associations of stress, anxiety, and depressive symptom severity during the pandemic with pre- to peri-pandemic change in global cognitive function are presented in Table 3. Anxiety or perceived stress scores during the pandemic were not significantly associated with pre- to peri-pandemic change in global cognitive function (Table 3). Every five-point higher depressive

symptom severity during the pandemic was associated with 0.69-point mean decline in TICS-m score from the pre- to peri-pandemic period (95% CI, -1.13, -0.25; *P*=0.002; Table 3). Findings for anxiety, perceived stress, or depressive symptom severity did not vary by age, number living in household, history of CVD, or history of diabetes (Supplementary Table S4). In sensitivity analyses limited to participants with peri-pandemic TICS-m scores collected after March 13, 2020, findings were similar (Supplementary Table S5). Having any depressive symptoms during the pandemic was associated with a non-significant 0.41-point mean decline in global cognitive function (95% CI, -0.99, 0.16) from the pre- to peri-pandemic period (Supplementary Table S6). Having clinically significant anxiety symptoms during the pandemic was not significantly associated with change in global cognitive function (Supplementary Table S6).

Peri-pandemic Global Cognitive Function and Adherence to COVID-19 Protective Health Behaviors

Multivariable associations of peri-pandemic global cognitive function with adherence to COVID-19 protective health behaviors are presented in Table 4. Every five-point lower peri-pandemic TICS-m score was associated with 12% lower odds (OR, 0.88; 95% CI, 0.80-0.97; *P*=0.007) of practicing safe hygiene. There were no significant associations of pre-pandemic global cognitive function with other COVID-19 protective behaviors. The odds of maintaining social distancing were 17% lower for every five-point lower TICS-m score among women older than 80 years (OR, 0.83; 95% CI, 0.74-0.94) but not among those 80 years or younger in age-stratified analyses. Other findings did not vary by age, number living in household, history of CVD, or history of diabetes (Supplementary Table S7). Findings were similar when excluding women with TICS-m ≤31 from the analyses (Supplementary Table S8).

DISCUSSION

In a sample of older WHI women, we observed that lower pre-pandemic global cognitive function was associated with higher perceived stress and depressive symptom severity during the COVID-19 pandemic, independent of age, race, ethnicity, education, region of residence, alcohol intake, and comorbidities. We also observed that greater depressive symptom severity during the pandemic was associated with a decline in pre- to peri-pandemic global cognitive function. Women with lower peri-pandemic global cognitive function were less likely to report practicing safe hygiene during the pandemic.

Multiple studies have reported a negative impact of the COVID-19 pandemic on psychological health among younger and older adults.[1-4,35-40] A systematic review and meta-analysis of 55 studies found a 16.0% and 15.2% prevalence of depression and anxiety, respectively, during the COVID-19 pandemic.[36] In a representative sample of 1,441 U.S. adults age 18-39 years, depressive symptoms were more than 3-fold higher during COVID-19 compared with before the pandemic, increasing from 8.5% to 27.8%.[39] Further, women were more likely to report depressive symptoms than men.[39] Prior to COVID-19, studies had identified an 8.8% and 7.3% prevalence of depression and anxiety, respectively, in the general population.[41,42]

Because maintaining good mental health is critical to overall well-being and quality of life in older adults, identifying subgroups who may be particularly vulnerable to pandemic-related psychological distress is important in the public health response to the pandemic. Older adults may have unique risk factors rendering them more vulnerable to psychological distress. For example, a study among 2,785 older adults with a median age of 70 years observed that frailty and multimorbidity, two common geriatric syndromes among older adults, were associated with greater psychological distress during the COVID-19 pandemic.[35] Our findings extend this prior study by suggesting that low cognitive function, which is prevalent especially among the oldest of older adults, may be a risk factor for pandemic-related psychological distress. Our findings also suggest that depressive symptom severity during the pandemic may be associated with cognitive decline; however,

given the short period of observation and the fact that affective state can impact cognitive test performance, this finding should be interpreted with caution.

The mechanisms underlying the association between psychological distress and poor cognitive health have not been fully elucidated. Prior studies have shown that depression is associated with higher risk of cognitive decline and cognitive impairment in older adults.[7,43] It is possible that late-life depression is a symptom in the progression to future cognitive impairment, which may partly explain the association of lower pre-pandemic global cognitive function with depressive symptom severity during the pandemic in our study.[7,44] Our study was unique in that it examined symptoms of psychological distress during an unprecedented pandemic that severely disrupted people's daily lives. Future studies are needed to determine the long-term impact of COVID-19 pandemic-related psychological distress on cognitive outcomes among older women, including the extent to which psychological distress during the pandemic may accelerate cognitive decline and the development of mild cognitive impairment or dementia.

Key public health measures recommended by the Centers for Disease Control and Prevention to mitigate the spread of COVID-19 have included wearing masks, washing hands, maintaining six feet of distance with others who do not live in your household, avoiding crowds and indoor spaces, and cleaning and disinfecting frequently touched surfaces.[45] However, the efficacy of these recommendations depends in large part on the public's willingness to adhere to them. Prior studies identified male sex, younger age, high psychological distress, low perceived risk of COVID-19, and limited exposure to and perceived efficacy of public health recommendations, as predicting non-adherence to COVID-19 protective behaviors.[46,47] Female sex and having a chronic disease have been identified as predicting adherence to these behaviors among adults.[46,48] Our findings suggest that low cognitive function during the pandemic may be associated with lower adherence to practicing safe hygiene. This finding is supported by a recent analysis from the Health and Retirement Study, which showed that better memory performance was associated with greater adherence to COVID-19 protective behaviors (e.g., mask usage, hand washing, social distancing, and use of hand sanitizers).[30] Memory and executive function are essential to the initiation and maintenance of health behaviors and

the development of habits.[27] Thus, individuals with impaired cognition may have difficulty adhering to COVID-19-related protective behaviors, as such behaviors must be planned, decisions must be made about situations in which to engage in such behaviors (e.g., large crowds), and failure to protect oneself (e.g., through mask wearing) must be monitored and detected.[27] Thus, older adults with impaired cognition should be prioritized in public health messaging to promote COVID-19-related protective health behaviors.

Our study has several limitations. Our findings may generalize only to older women. Further, our study included women from three WHI ancillary studies, and we did not include men from COSMOS-Mind, given our focus on the women in WHI; selection bias may be possible. The period of follow-up to determine pre- to peri-pandemic change in cognitive function was relatively short, and we assessed psychological distress measures at a single time point. This may partly explain the modest associations of psychological distress measures with cognitive function observed in our study. Greater follow-up is needed to determine the extent of the impact of the COVID-19 pandemic on cognitive and mental health among older women, including assessment of social and lifestyle changes that occurred due to the pandemic and whether these are associated with cognitive decline in the long term. All measures of psychological distress were self-reported using screening instruments, and we lacked information on diagnosis of depression and anxiety. We also lacked information on psychiatric treatments that could have influenced cognitive function. Adherence to protective behaviors was assessed via self-report and thus may not fully reflect actual adherence for those with cognitive impairment. However, our findings were similar when we excluded women with TICS-m $\leq$31, suggesting this is an unlikely explanation of our findings. Strengths of this study include a large sample, information on a broad range of covariates, examination of several key psychological distress measures, and availability of well validated global cognitive function measures both preceding and during the pandemic.

In conclusion, in a sample of older WHI women, lower pre-pandemic global cognitive function was associated with higher perceived stress and depressive symptom severity during the COVID-19 pandemic. Further, depressive symptom severity during the pandemic was associated with a decline in global cognitive function from the pre- to peri-pandemic periods. We also observed that older women with lower global cognitive function during the pandemic were less likely to practice safe hygiene. The long-term impact of the COVID-19 pandemic on cognitive and mental health outcomes among older women requires further study.

FUNDING

The Women's Health Initiative was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services (75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, and 75N92021D00005). WHIMS-ECHO was funded by the National Institute on Aging, National Institutes of Health, U.S. Department of Health and Human Services (HHSN-271-2017-00002C). The Cocoa Supplement and Multivitamin Outcomes Study in the Mind (COSMOS-Mind) was supported by the National Institute on Aging, National Institutes of Health, U.S. Department of Health and Human Services (5R01AG050657-04). Women's Health Initiative Sleep Hypoxia Effects on Resilience (WHISPER) was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services (5R01HL133684-04). A.H.S. was supported by 1RF1AG074345-01 from the National Institute on Aging, National Institutes of Health, U.S. Department of Health and Human Services.

ACKNOWLEDGEMENTS

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller

Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg

Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA)Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller;

(Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner

Women's Health Initiative Memory Study:(Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland

Sponsor's Role: The National Heart, Lung, and Blood Institute has representation on the Women's Health Initiative Steering Committee, which governed the design and conduct of the study, the interpretation of the data, and preparation and approval of manuscripts.

Author Contributions: Conception or design of the work: Shadyab, Rapp, Shumaker, and Baker; Acquisition and analysis of data: Rapp, Shumaker, Baker, and Larson; Preparation of manuscript: Shadyab; Interpretation of data: All authors; Critical revision of the work for important intellectual content: All authors; Final approval of the version to be published: All authors.

CONFLICT OF INTEREST:

The authors report no conflicts of interest.

REFERENCES

1. Petzold MB, Bendau A, Plag J, et al. Risk, resilience, psychological distress, and anxiety at the beginning of the COVID-19 pandemic in Germany. *Brain Behav*. 09 2020;10(9):e01745. doi:10.1002/brb3.1745

2. McGinty EE, Presskreischer R, Anderson KE, Han H, Barry CL. Psychological Distress and COVID-19-Related Stressors Reported in a Longitudinal Cohort of US Adults in April and July 2020. *JAMA*. 12 22 2020;324(24):2555-2557. doi:10.1001/jama.2020.21231

3. Ferrucci R, Averna A, Marino D, et al. Psychological Impact During the First Outbreak of COVID-19 in Italy. *Front Psychiatry*. 2020;11:559266. doi:10.3389/fpsyt.2020.559266

4. Bendau A, Plag J, Kunas S, Wyka S, Ströhle A, Petzold MB. Longitudinal changes in anxiety and psychological distress, and associated risk and protective factors during the first three months of the COVID-19 pandemic in Germany. *Brain Behav*. 02 2021;11(2):e01964. doi:10.1002/brb3.1964

5. Gulpers B, Ramakers I, Hamel R, Köhler S, Oude Voshaar R, Verhey F. Anxiety as a Predictor for Cognitive Decline and Dementia: A Systematic Review and Meta-Analysis. *Am J Geriatr Psychiatry*. 10 2016;24(10):823-42. doi:10.1016/j.jagp.2016.05.015

6. Gulpers BJA, Oude Voshaar RC, van Boxtel MPJ, Verhey FRJ, Köhler S. Anxiety as a Risk Factor for Cognitive Decline: A 12-Year Follow-Up Cohort Study. *Am J Geriatr Psychiatry*. 01 2019;27(1):42-52. doi:10.1016/j.jagp.2018.09.006

7. Potvin O, Forget H, Grenier S, Préville M, Hudon C. Anxiety, depression, and 1-year incident cognitive impairment in community-dwelling older adults. *J Am Geriatr Soc*. Aug 2011;59(8):1421-8. doi:10.1111/j.1532-5415.2011.03521.x

8. Wilson RS, Barnes LL, Mendes de Leon CF, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. *Neurology*. Aug 13 2002;59(3):364-70. doi:10.1212/wnl.59.3.364

9. Geerlings MI, Schoevers RA, Beekman AT, et al. Depression and risk of cognitive decline and Alzheimer's disease. Results of two prospective community-based studies in The Netherlands. *Br J Psychiatry*. Jun 2000;176:568-75. doi:10.1192/bjp.176.6.568

10. Sutin AR, Stephan Y, Terracciano A. Psychological Distress, Self-Beliefs, and Risk of Cognitive Impairment and Dementia. *J Alzheimers Dis*. 2018;65(3):1041-1050. doi:10.3233/JAD-180119

11. Goveas JS, Espeland MA, Woods NF, Wassertheil-Smoller S, Kotchen JM. Depressive symptoms and incidence of mild cognitive impairment and probable dementia in elderly women: the Women's Health Initiative Memory Study. *J Am Geriatr Soc*. Jan 2011;59(1):57-66. doi:10.1111/j.1532-5415.2010.03233.x

12. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry*. May 2006;63(5):530-8. doi:10.1001/archpsyc.63.5.530

13. Connor J, Madhavan S, Mokashi M, et al. Health risks and outcomes that disproportionately affect women during the Covid-19 pandemic: A review. *Soc Sci Med*. 12 2020;266:113364. doi:10.1016/j.socscimed.2020.113364

14. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin Trials*. Feb 1998;19(1):61-109. doi:10.1016/s0197-2456(97)00078-0

15. Espeland MA, Rapp SR, Manson JE, et al. Long-term Effects on Cognitive Trajectories of Postmenopausal Hormone Therapy in Two Age Groups. *J Gerontol A Biol Sci Med Sci*. Jun 01 2017;72(6):838-845. doi:10.1093/gerona/glw156

16. Baker LD, Rapp SR, Shumaker SA, et al. Design and baseline characteristics of the cocoa supplement and multivitamin outcomes study for the Mind: COSMOS-Mind. *Contemp Clin Trials*. 08 2019;83:57-63. doi:10.1016/j.cct.2019.06.019

17. Welsh K, Breitner J, Magruder-Habib K. Detection of dementia in the elderly using telephone screening of cognitive status. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology*. 1993;6:103-110.

18. Cook SE, Marsiske M, McCoy KJ. The use of the Modified Telephone Interview for Cognitive Status (TICS-M) in the detection of amnestic mild cognitive impairment. *J Geriatr Psychiatry Neurol*. Jun 2009;22(2):103-9. doi:10.1177/0891988708328214

19. Lacruz M, Emeny R, Bickel H, Linkohr B, Ladwig K. Feasibility, internal consistency and covariates of TICS-m (telephone interview for cognitive status-modified) in a population-based sample: findings from the KORA-Age study. *Int J Geriatr Psychiatry*. Sep 2013;28(9):971-8. doi:10.1002/gps.3916

20. Pilkonis PA, Choi SW, Reise SP, et al. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS®): depression, anxiety, and anger. *Assessment*. Sep 2011;18(3):263-83. doi:10.1177/1073191111411667

21. Kroenke K, Yu Z, Wu J, Kean J, Monahan PO. Operating characteristics of PROMIS four-item depression and anxiety scales in primary care patients with chronic pain. *Pain Med*. Nov 2014;15(11):1892-901. doi:10.1111/pme.12537

22. Goveas JS, Ray RM, Woods NF, et al. Associations between changes in loneliness and social connections, and mental health during the COVID-19 Pandemic: The Women's Health Initiative. *J Gerontol A Biol Sci Med Sci*. Dec 16 2021;doi:10.1093/gerona/glab371

23. Marrie RA, Zhang L, Lix LM, et al. The validity and reliability of screening measures for depression and anxiety disorders in multiple sclerosis. *Mult Scler Relat Disord*. Feb 2018;20:9-15. doi:10.1016/j.msard.2017.12.007

24. Schalet BD, Cook KF, Choi SW, Cella D. Establishing a common metric for self-reported anxiety: linking the MASQ, PANAS, and GAD-7 to PROMIS Anxiety. *J Anxiety Disord*. Jan 2014;28(1):88-96. doi:10.1016/j.janxdis.2013.11.006

25. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. Dec 1983;24(4):385-96.

26. Vallejo MA, Vallejo-Slocker L, Fernández-Abascal EG, Mañanes G. Determining Factors for Stress Perception Assessed with the Perceived Stress Scale (PSS-4) in Spanish and Other European Samples. *Front Psychol*. 2018;9:37. doi:10.3389/fpsyg.2018.00037

27. Burke WJ, Roccaforte WH, Wengel SP. The short form of the Geriatric Depression Scale: a comparison with the 30-item form. *J Geriatr Psychiatry Neurol*. 1991 Jul-Sep 1991;4(3):173-8. doi:10.1177/089198879100400310

28. Kieffer KM, Reese RJ. A Reliability Generalization Study of the Geriatric Depression Scale. *Educational and Psychological Measurement*. 2002;62(6):969-994. doi:https://doi.org/10.1177/0013164402238085

29. Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. *Int J Geriatr Psychiatry*. Oct 1999;14(10):858-65. doi:10.1002/(sici)1099-1166(199910)14:10<858::aid-gps35>3.0.co;2-8

30. O'Shea DM, Davis JD, Tremont G. Verbal memory is associated with adherence to COVID-19 protective behaviors in community dwelling older adults. *Aging Clin Exp Res*. Jul 2021;33(7):2043-2051. doi:10.1007/s40520-021-01905-z

31. DiMatteo MR. Social support and patient adherence to medical treatment: a meta-analysis. *Health Psychol*. Mar 2004;23(2):207-18. doi:10.1037/0278-6133.23.2.207

32. Allan JL, McMinn D, Daly M. A Bidirectional Relationship between Executive Function and Health Behavior: Evidence, Implications, and Future Directions. *Front Neurosci*. 2016;10:386. doi:10.3389/fnins.2016.00386

33. Karaca-Mandic P, Georgiou A, Sen S. Assessment of COVID-19 Hospitalizations by Race/Ethnicity in 12 States. *JAMA Intern Med*. 01 01 2021;181(1):131-134. doi:10.1001/jamainternmed.2020.3857

34. Knopman DS, Roberts RO, Geda YE, et al. Validation of the telephone interview for cognitive status-modified in subjects with normal cognition, mild cognitive impairment, or dementia. *Neuroepidemiology*. 2010;34(1):34-42. doi:10.1159/000255464

35. Wang Y, Fu P, Li J, et al. Changes in psychological distress before and during the COVID-19 pandemic among older adults: the contribution of frailty transitions and multimorbidity. *Age Ageing*. 06 28 2021;50(4):1011-1018. doi:10.1093/ageing/afab061

36. Cénat JM, Blais-Rochette C, Kokou-Kpolou CK, et al. Prevalence of symptoms of depression, anxiety, insomnia, posttraumatic stress disorder, and psychological distress among populations affected by the COVID-19 pandemic: A systematic review and meta-analysis. *Psychiatry Res*. 01 2021;295:113599. doi:10.1016/j.psychres.2020.113599

37. Losada-Baltar A, Jiménez-Gonzalo L, Gallego-Alberto L, Pedroso-Chaparro MDS, Fernandes-Pires J, Márquez-González M. "We Are Staying at Home." Association of Self-perceptions of Aging, Personal and Family Resources, and Loneliness With Psychological Distress During the Lock-Down Period of COVID-19. *J Gerontol B Psychol Sci Soc Sci*. 01 18 2021;76(2):e10-e16. doi:10.1093/geronb/gbaa048

38. Salari N, Hosseinian-Far A, Jalali R, et al. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. *Global Health*. 07 06 2020;16(1):57. doi:10.1186/s12992-020-00589-w

39. Ettman CK, Abdalla SM, Cohen GH, Sampson L, Vivier PM, Galea S. Prevalence of Depression Symptoms in US Adults Before and During the COVID-19 Pandemic. *JAMA Netw Open*. 09 01 2020;3(9):e2019686. doi:10.1001/jamanetworkopen.2020.19686

40. Lorant V, Smith P, Van den Broeck K, Nicaise P. Psychological distress associated with the COVID-19 pandemic and suppression measures during the first wave in Belgium. *BMC Psychiatry*. 02 18 2021;21(1):112. doi:10.1186/s12888-021-03109-1

41. Vilagut G, Forero CG, Barbaglia G, Alonso J. Screening for Depression in the General Population with the Center for Epidemiologic Studies Depression (CES-D): A Systematic Review with Meta-Analysis. *PLoS One*. 2016;11(5):e0155431. doi:10.1371/journal.pone.0155431

42. Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. *Psychol Med*. May 2013;43(5):897-910. doi:10.1017/S003329171200147X

43. Yaffe K, Blackwell T, Gore R, Sands L, Reus V, Browner WS. Depressive symptoms and cognitive decline in nondemented elderly women: a prospective study. *Arch Gen Psychiatry*. May 1999;56(5):425-30. doi:10.1001/archpsyc.56.5.425

44. Richard E, Reitz C, Honig LH, et al. Late-life depression, mild cognitive impairment, and dementia. *JAMA Neurol*. Mar 01 2013;70(3):374-82. doi:10.1001/jamaneurol.2013.603

45. Centers for Disease Control and Prevention. How to protect yourself & others. Retrieved from https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html. Accessed January 30, 2022.

46. Park CL, Russell BS, Fendrich M, Finkelstein-Fox L, Hutchison M, Becker J. Americans' COVID-19 Stress, Coping, and Adherence to CDC Guidelines. *J Gen Intern Med*. 08 2020;35(8):2296-2303. doi:10.1007/s11606-020-05898-9

47. Pollak Y, Dayan H, Shoham R, Berger I. Predictors of non-adherence to public health instructions during the COVID-19 pandemic. *Psychiatry Clin Neurosci*. 11 2020;74(11):602-604. doi:10.1111/pcn.13122

48. Islam JY, Vidot DC, Camacho-Rivera M. Determinants of COVID-19 preventive behaviours among adults with chronic diseases in the USA: an analysis of the nationally representative COVID-19 impact survey. *BMJ Open*. 02 09 2021;11(2):e044600. doi:10.1136/bmjopen-2020-044600

Table 1. Descriptive characteristics of COSMOS-MIND, WHIMS-ECHO, and WHISPER cohorts by pre-pandemic global cognitive function score (n=2890)

	Pre-pandemic TICS-m score ≤ 31 (n=576)		*Pre-pandemic TICS-m score > 31 (n=2,314)*		
Characteristic	*n*	*%*	*n*	*%*	*p-value*[a]
Demographics					
Age, mean (SD)	84.8	(5.9)	82.3	(5.7)	<0.001
Race					<0.001
White	392	68.1	1885	81.5	
African American	147	25.5	338	14.6	
American Indian / Alaska Native	1	0.2	6	0.3	
Asian	9	1.6	21	0.9	
Native Hawaiian / Pacific Islander	1	0.1	1	0.0	
More than one race[b]	8	1.4	23	1.0	

Unknown / Not reported	19	3.3	41	1.8	
Ethnicity					<0.001
Hispanic / Latina	57	9.9	136	5.9	
Not Hispanic / Latina	517	89.8	2176	94.0	
Unknown / Not reported	2	0.3	2	0.1	
Education					<0.001
≤ High school diploma / GED	137	23.8	243	10.5	
School after high school	217	37.7	771	33.3	
≥ College graduate	219	38.0	1288	55.7	
Alcohol Intake, drinks/wk					<0.001
None	362	62.8	1055	45.6	
≤1	94	16.3	515	22.3	
>1	113	19.6	723	31.2	
Medical History					
CVD	65	11.3	200	8.6	0.05
Diabetes	156	27.1	482	20.8	0.001
Hypertension	448	77.8	1618	69.9	<0.001

Cancer	99	17.2	440	19.0	0.31

[a]p-values from t-tests for continuous and chi-square tests for categorical demographics

[b]Participants marking more than one race included the following combinations: white & African American, white/American Indian, white/Asian, white/Pacific Islander, African American/American Indian, white/African American/American Indian, white/American Indian/Asian.

Table 2. Association of pre-pandemic global cognitive function with anxiety, stress, and depressive symptom severity during the pandemic.

	Continuous pre-pandemic TICS-m, 5-point decrease		**Categorical pre-pandemic TICS-m, ≤31 vs. >31 (ref)**	
	Estimate[a,b] (95% CI)	**p-value**	**Estimate[a,b] (95% CI)**	**p-value**
Anxiety (n=2890)	0.22 (-0.12, 0.56)	0.21	0.54 (-0.22, 1.30)	0.16
Stress (n=2890)	0.33 (0.20, 0.45)	<0.001	0.62 (0.35, 0.90)	<0.001
Depressive symptom severity (n=1690)	0.20 (0.07, 0.32)	0.003	0.33 (0.06, 0.60)	0.02

[a]Estimates are from linear models with the pandemic symptom of psychological distress as a function of pre-pandemic cognitive function.

[b]Models are adjusted for age, study source (COSMOS-MIND,WHIMS-ECHO, WHISPER), race, ethnicity, education, history of CVD, history of treated diabetes, history of treated hypertension, history of cancer, alcohol, region, number in household, total TICS-m tests taken, and months from pandemic start (1/30/20) to pandemic symptom collection.

Table 3. Associations of anxiety, stress, and depressive symptom severity during the pandemic with pre- to peri-pandemic change in global cognitive function (n=1690)

	Estimate[a,b] (95% CI)	**p-value**
Anxiety	-0.07 (-0.20, 0.05)	0.25
Stress	-0.30 (-0.64, 0.04)	0.08
Depressive symptom severity	-0.69 (-1.13, -0.25)	0.002

[a]Estimates are for peri – pre TICS-m score change associated with a 5-point increase in pandemic symptom score variable of interest derived from linear models with the peri-pre change in TICS-m score as a function of the symptom of psychological distress.

[b]Models are adjusted for age, study source (COSMOS-MIND,WHIMS-ECHO, WHISPER), race, ethnicity, education, history of CVD, history of treated diabetes, history of treated hypertension, history of cancer, alcohol, region, number in household, total TICS-m tests taken, months from pandemic start (1/30/20) to pandemic symptom collection, and months between pre and peri TICS-m measurements.

Table 4. Association of peri-pandemic global cognitive function with adherence to COVID-19 protective health behaviors (N=2,700)

	Continuous peri-pandemic TICS-m, 5 point decrease		**Categorical peri-pandemic TICS-m, ≤31 vs. >31 (ref)**	
Outcome	**Odds Ratio[a,b] (95% CI)**	**p-value**	**Odds Ratio[a,b] (95% CI)**	**p-value**
Practices safe hygiene	0.88 (0.80, 0.97)	0.007	0.88 (0.71, 1.09)	0.24
Maintains social distancing	0.92 (0.84, 1.00)	0.06	0.96 (0.78, 1.18)	0.69
Wears a face mask	0.87 (0.67, 1.12)	0.27	0.96 (0.55, 1.69)	0.89
Stays home	1.07 (0.95, 1.20)	0.28	0.97 (0.75, 1.26)	0.82
Adherence to all protective behaviors	0.91 (0.83, 1.00)	0.06	0.97 (0.78, 1.21)	0.79

[a]Odds ratios and corresponding p-values are derived from logistic regression models with the protective health behaviors as a function of peri-pandemic cognitive function.

[b]Models are adjusted for age, study source (COSMOS-MIND,WHIMS-ECHO, WHISPER), race, ethnicity, education, history of CVD, history of treated diabetes, history of treated hypertension, history of cancer, alcohol, region, number in household, total TICS-m tests taken, and months from pandemic start (1/30/20) to completion of COVID-19 questionnaire.