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FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2022

PERSISTENT LOSS OF SMELL DUE TO COVID-19 CLOSELY CONNECTED TO LONG-LASTING COGNITIVE PROBLEMS

Also, ICU Stay May Double Risk of Dementia in Older Adults

SAN DIEGO, JULY 31, 2022 — New insights into factors that may predict, increase or protect against the impact of COVID-19 and the pandemic on memory and thinking skills were revealed by multiple studies reported today at the <u>Alzheimer's Association International Conference[®] (AAIC[®]) 2022</u> in San Diego and virtually.

Among the key findings reported at AAIC 2022:

- A group from Argentina found that persistent loss of the sense of smell may be a better predictor of long-term cognitive and functional impairment than severity of the initial COVID-19 disease.
- Hospitalization in the intensive care unit was associated with double the risk of dementia in older adults, according to a study by Rush Alzheimer's Disease Center in Chicago.
- During the pandemic, female gender, not working and lower socioeconomic status were associated with more cognitive symptoms in a large study population drawn from nine Latin American countries.
- In that same Latin American population, experiencing a positive life change during the pandemic (such as more quality time with friends and family or spending more time in nature) reduced the negative impact of the pandemic on memory and thinking skills.

"COVID-19 has sickened and killed millions of people around the world, and for some, the emerging research suggests there are long-term impacts on memory and thinking as well," said Heather M. Snyder, Ph.D., vice president of medical and scientific relations at the Alzheimer's Association. "As this virus will likely be with us for a long time, identifying the risk and protective factors for cognitive symptoms can assist with the treatment and prevention of 'long COVID' moving forward."

Persistent loss of smell better predicts cognitive impairment than severity of COVID-19

Researchers in Argentina working with the <u>Alzheimer's Association Consortium on Chronic Neuropsychiatric</u> <u>Sequelae of SARS-CoV-2 Infection</u> followed 766 adults age 55-95 exposed to COVID-19 for one year, and conducted a series of regular physical, cognitive and neuropsychiatric tests. Of the study group, 88.4% were infected and 11.6% were controls.

Clinical assessment showed functional memory impairment in two-thirds of the infected participants, which was severe in half of them. Another group of cognitive tests identified three groups with decreased performance:

- 11.7% showed memory-only impairment.
- 8.3% had impairment in attention and executive function.
- 11.6% displayed multidomain (including memory, learning, attention and executive function) impairment.

Statistical analysis revealed that persistent loss of smell was a significant predictor of cognitive impairment, but severity of the initial COVID-19 disease was not.

"The more insight we have into what causes or at least predicts who will experience the significant long-term cognitive impact of COVID-19 infection, the better we can track it and begin to develop methods to prevent it," said Gabriela Gonzalez-Aleman, LCP, Ph.D., professor at Pontificia Universidad Catolica Argentina, Buenos Aires.

A stay in the intensive care unit may signal higher dementia risk

Researchers from the Rush Alzheimer's Disease Center (RADC), part of Chicago's Rush University System for Health, used data from five diverse studies of older adults without known dementia (n=3,822) to observe intensive care unit (ICU) hospitalizations. ICU hospitalizations were previously linked to cognitive impairment in older patients, but few studies have examined whether they increase risk for dementia.

They reviewed Medicare claims records from 1991 to 2018 (pre-pandemic), and checked annually for development of Alzheimer's and all type dementia using a standardized cognitive assessment. During an average 7.8 years follow up, 1,991 (52%) participants experienced at least one ICU hospitalization; 1,031 (27%) had an ICU stay before study enrollment; and 961 (25%) had an ICU stay during the study period.

The researchers found that, in analyses adjusted for age, sex, education and race, experiencing ICU hospitalization was associated with 63% higher risk of Alzheimer's dementia and 71% higher risk of all type dementia. In models further adjusted for other health factors such as vascular risk factors and disease, other chronic medical conditions, and functional disabilities, the association was even stronger: ICU hospitalization was associated with 110% greater risk of Alzheimer's and 120% greater risk of all type dementia.

"We found that ICU hospitalization was associated with double the risk of dementia in community-based older adults," said Bryan D. James, Ph.D., epidemiologist at RADC. "These findings could be significant given the high rate of ICU hospitalization in older persons, and especially due to the tremendous upsurge in ICU hospitalizations during the COVID-19 pandemic. Understanding the link between ICU hospitalization and the development of dementia is of utmost importance now more than ever."

"More research is necessary to replicate these findings and elucidate the factors that may increase dementia risk. For example, is it the critical illness that sends someone to the hospital or potentially modifiable procedures during the hospitalization that drives dementia risk?" James added.

One positive life change during the pandemic may buffer against cognitive symptoms

Investigators from countries across Central and South America and the United States examined whether sociodemographic factors and changes in life associated with the pandemic were related to experiencing cognitive symptoms, including problems with memory, attention and other thinking skills, during the early phases of the pandemic.

In the study reported at AAIC, 2,382 Spanish-speaking adults age 55-95 (average 65.3 years, 62.3% female) from nine countries in Latin America completed an online or telephone survey, had electronic cognitive testing, and filled out an inventory assessing the positive and negative impacts of the pandemic between May and December 2020. Of the total study population, 145 (6.09%) experienced COVID-19 symptoms.

Participants were from: Uruguay (1,423, 59.7%), Mexico (311, 13.1%), Peru (153, 6.4%), Chile (152, 6.4%), Dominican Republic (117, 4.9%), Argentina (106, 4.5%), Colombia (50, 2.1%), Ecuador (39, 1.6%), Puerto Rico (19, 0.8%) and Other (12, 0.5%)

Key findings:

- Female gender, not currently working and lower socioeconomic status were all independently associated with more cognitive symptoms during the early part of the pandemic.
- Negative life changes during the pandemic, such as economic difficulties and limited social activities, were significantly associated with more cognitive symptoms. However, this association was weaker among study participants who reported at least one positive life change during the pandemic, including spending more time with friends and family or more time outside in nature.

"Identifying risk and protective factors for cognitive symptoms during the pandemic is an important step towards the development of prevention efforts," said María Marquine, Ph.D., associate professor in the Departments of Medicine and Psychiatry, and director of disparities research in the Division of Geriatrics, Gerontology and Palliative Care at the University of California, San Diego. "The experience of positive life changes during the pandemic might buffer the detrimental impact of negative life changes on cognitive symptoms."

"This study is an example of how investigators from diverse countries in Latin America and the United States, many of whom had never worked together before and had limited resources, came together under difficult circumstances but with a shared goal to advance scientific understanding about Alzheimer's, and the important contributions that such multicultural partnerships can yield," Marquine added.

About the Alzheimer's Association International Conference® (AAIC®)

The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

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About the Alzheimer's Association[®]

The Alzheimer's Association is a worldwide voluntary health organization dedicated to Alzheimer's care, support and research. Our mission is to lead the way to end Alzheimer's and all other dementia — by accelerating global research, driving risk reduction and early detection, and maximizing quality care and support. Our vision is a world without Alzheimer's and all other dementia[®]. Visit <u>alz.org</u> or call 800.272.3900.

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- Gabriela Gonzalez-Aleman, LCP, Ph.D., et al.Olfactory dysfunction but not COVID-19 severity predicts severity of cognitive sequelae following SARS-CoV-2 infection in Amerindian older adults. (Funders: Fundación de Lucha contra los Trastornos Neurológicos y Psiquiátricos en Minorías (FULTRA); Alzheimer's Association)
- Bryan James, Ph.D., et al. ICU hospitalization and incident dementia in community-based cohorts of older adults. (Funder: National Institute on Aging)
- María Marquine, Ph.D., et al. Cognitive symptoms among middle- and older-age adults in Latin America during the coronavirus disease 2019 (COVID-19) pandemic: Risk and protective factors. (Funders: Massachusetts General Hospital Executive Committee on Research, Philanthropic Gift to the University of California, San Diego Division of Geriatrics, Plan Ibirapitá Uruguay (Inclusión Digital de Personas Mayores)).

*** AAIC 2022 news releases may contain updated data that does not match what is reported in the following abstracts.

Proposal ID: 66868

Title: Olfactory dysfunction but not COVID-19 severity predicts severity of cognitive sequelae following SARS-CoV-2 infection in Amerindian older adults

Background: COVID-19 has affected more than 380 million people. Infections may result in long term sequelae, including neuropsychiatric symptoms. In older adults COVID-19 sequelae resemble early Alzheimer's disease, and may share risk factors and blood biomarkers with it. The Alzheimer's Association Consortium on Chronic Neuropsychiatric Sequelae of SARS-CoV-2 infection (CNS SC2) established harmonized definitions, ascertainment and assessment methodologies to evaluate and longitudinally follow up cohorts of older adults with exposure to COVID-19. We present one year data in a prospective cohort from Argentina.

Method: Participants (n=766) are older adults (\geq 60 years) recruited from the provincial health registry containing all SARS-CoV-2 testing data. We randomly invite older adults stratified by PCR COVID-19 testing status regardless of symptom severity, between 3 and 6 months after recovery. Assessment includes interview with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) and Clinical Dementia Rating scale (CDR); neurocognitive assessment; emotional reactivity scale; and neurological assessment including semiquantitative olfactory function test, motor function, coordination and gait.

Result: We assessed 88.4% infected participants and 11.6% controls. Education is 10.36 ± 5.6 years and age is 66.9 ± 6.14 years. Level of care during COVID-19 is described in Figure 1. Normalized cognitive Z-scores categorize the cohort in 3 groups with decreased performance compared to normal cognition: memory only impairment (Single-domain,11.7%); impairment in attention+executive function without memory impairment (Two-domain, 8.3%); and multiple domain impairment (Multiple domain,11.6%). Logistic regression showed that severity of anosmia, but not clinical status, significantly predicts cognitive impairment. No controls had olfactory dysfunction. Cognitive impairment is defined as Z-scores below (- 2) (Table 1). Clinical assessment with SCAN revealed functional memory impairment in two thirds of infected patients (CDR \geq 1), which was severe in half of them. Phone-based follow up at 1 year revealed high adherence (4 participants declined). Five were deceased at follow up. Rates of re-infection (between 10 and 23%) were not affected by the vaccination schedule (Table 2).

Conclusion: The longitudinal cohort had very high adherence. Persistent cognitive and functional impairment after SARS-CoV-2 infection is predicted by persistent anosmia but not by the severity of the initial COVID-19 disease.

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Z-SCORES/COGNITIVE IMPAIRMENT						
Task	Normal (N = 522)	Single domain (N= 86)	Two domain (N = 66)	Multidomain (N= 89)		
WORD LIST- LEARNING (WMS-III)	-0.92	-1.58	-1.49	-2.16		
WORD LIST- SHORT TERM MEMORY	-0.77	2.09	1.09	-2.32		
WORD LIST- LONG TERM MEMORY	-0.2	-1.26	-0.52	-1.59		
WORD LIST- RECOGNITION	-0.61	-1.31	-1.19	-2.02		
ORAL TRAILS- VERBAL	-0.42	-0.68	-1.62	-2.35		
ORAL TRAILS- VISUAL	-0.44	-0.72	-1.74	-2.02		
ORAL TRAILS- MENTAL	-0.57	-96	-2.25	-2.61		
ORAL TRAILS- VISUAL-MENTAL	-0.69	1.17	2.57	-2.9		
ORAL TRAILS- SWITCHING	-0.58	-1.04	-2.16	2.67		
5 DIGIT TEST- INHIBITION	-0.11	-0.05	-0.57	-0.5		
5 DIGIT TEST- FLEXIBILITY	-0.35	-0.48	-0.92	-1.14		

Results of 1-year phone survey					
Vaccine doses (#)	% of cohort	% reinfected			
0	1.5	12.5			
1	1.9	10.0			
2	24.9	23.3			
3	71.8	12.5			

Proposal ID: 61678

Title: Cognitive symptoms among middle- and older-age adults in Latin America during the coronavirus disease 2019 (COVID-19) pandemic: Risk and protective factors

Background: The COVID-19 pandemic has impacted daily life worldwide, with possible negative consequences for cognitive health. Self-reported cognitive symptoms are linked to the development of Alzheimer's disease and related dementias (ADRDs). Identifying risk and protective factors for cognitive symptoms during the pandemic is an important step towards the development of ADRD prevention efforts. We aimed to examine correlates of cognitive symptoms among middle- and older-age adults in Latin America before the availability of vaccines to prevent COVID-19, including sociodemographic factors and changes in life.

Method: Spanish-speaking adults ages 55-95 (N=2,382, Table 1) living in Latin America completed an online survey between May and December 2020. Cognitive symptoms were assessed via the 12-item Everyday Cognition (ECog) questionnaire. Negative (e.g., economic difficulties, limited social activities) and positive (e.g., more quality time with close others, increased time in nature/outside) life changes associated with the pandemic were measured via a subset of items from the Epidemic-Pandemic Impacts Inventory. Sociodemographic factors included age, years of education, gender, occupation and socioeconomic status (SES). Covariates included time since March 2020 (estimated onset of the pandemic in Latin America), country of survey completion, and having experienced COVID-19 symptoms. Multivariable linear regression models were ran on ECog total scores including covariates and sociodemographic factors (Model 1), and then adding terms for negative and positive life changes and their interaction (Model 2).

Results: Model 1 showed female gender (p=.04), not currently working (p=.02) and lower SES (p<.001) were independently associated with more cognitive symptoms. Model 2 showed a significant interaction between negative and positive life changes (p<.001), indicating that negative life changes were significantly associated with more cognitive symptoms, but this association was weaker among participants who reported at least one positive life change during the pandemic (Figure 1). **Conclusion:** Cognitive symptoms might be more common among certain segments of the Latin American population, including women, and those who are not working and have low SES. The experience of positive life changes during the

pandemic might buffer the detrimental impact of negative life changes on cognitive symptoms. These risk and protective factors might be considered in ADRD prevention efforts.

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Positive Life Changes – No - Yes

Figure 1. Results from multivariable linear regression model on self-reported cognitive symptoms, including terms for proportion of negative life changes during the pandemic, positive life changes during the pandemic (yes= at least one positive life change/no= no positive life changes), and their interaction, adjusting for sociodemographic factors (age, years of education, gender, occupation and socioeconomic status), time since estimated onset of the pandemic, country of survey completion, and having experienced COVID-19 symptoms. Overall model: F (21, 2360) = 24.26, p<.0001, Adjusted R² = 0.17.

Characteristics	Descriptive Statistics ^a
Age (in years)	65.33 (7.05)
Gender (Female)	1485 (62.34%)
Highest level of education completed	
High school or less	409 (17.17%)
Higher than high school	1775 (74.52%)
Other	198 (8.31%)
Occupation	
Retired	1004 (42.15%)
Employed	833 (34.97%)
Unemployed/Other	545 (22.88%)
Income	
Low	281 (11.79%)
Middle	1733 (72.75%)
High	368 (15.45%)
Estimated time since onset of the	6.08 (1.85)
pandemic (in months)	
Country of Survey Completion	
South America	
Uruguay	1,423 (59.74%)
Chile	152 (6.38%)
Argentina	106 (4.45%)
Peru	153 (6.42%)
Ecuador	39 (1.64%)
Colombia	50 (2.09%)
Central America and the Caribbean	
Mexico	311 (13.06%)
Dominican Republic	117 (4.91%)
Puerto Rico	19 (0.79%)
Other	12 (0.50%)
Has experienced COVID-19 symptoms	145 (6.09%)
Note. "Values represent M(SD), n(%)	

Table 1. Descriptive Characteristics of the Study Cohort (N=2,382)

Proposal ID: 67719

Title: ICU hospitalization and incident dementia in community-based cohorts of older adults Background: Critical illness and intensive care unit (ICU) hospitalization in older patients have been shown to increase risk of long-term cognitive impairment. However, most data come from patients recruited from the ICU without controls or information on pre-ICU cognition. We are not aware of a community-based sample that allows examination of how ICU hospitalization changes risk for dementia.

Method: We used data from 5 diverse epidemiologic cohorts at the Rush Alzheimer's Disease Center (RADC) linked to Medicare claims data from 1991 to 2018 to observe ICU hospitalizations (both prior to RADC enrollment and during RADC follow-up) in older adults enrolled without known dementia. Incident Alzheimer's and all type dementia was assessed using standardized annual cognitive assessment. The association of ICU hospitalization with incident dementia was tested in a time-varying Cox model allowing hazard rate to change at time of ICU hospitalization during follow-up. All models were adjusted for age, sex, education, and race. Fully adjusted models also included terms for baseline measures of hypertension, diabetes, BMI, vascular risk factors, vascular disease burden, other chronic medical conditions, functional disabilities, depression, and physical activity.

Result: Participants (n=3,822; mean age=77.3, SD=7.5) were followed for an average of 7.8 years (SD=5.5) from study

enrollment. ICU hospitalization was experienced by 1,992 (52.1%) of participants; 1031 (27.0%) before RADC enrollment, and 961 (25.1%) during follow-up. In models adjusted for demographics, ICU hospitalization was associated with an increased risk of Alzheimer's (HR=1.63, 95% CI = 1.41, 1.88) and all type dementia (HR=1.71, 95% CI = 1.48, 1.97). In fully adjusted models, the association was stronger with ICU associated with double the risk of Alzheimer's (HR=2.10, 95% CI = 1.66, 2.65) and all type dementia (HR=2.20, 95% CI = 1.75, 2.77).

Conclusion: We found that ICU hospitalization was associated with double the risk of dementia in community-based older adults compared to those who did not experience ICU hospitalization using standardized annual cognitive assessment. These findings could be significant given the high rate of ICU hospitalization in older persons, and rising ICU hospitalizations more recently during the COVID-19 pandemic.

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