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Pre-pandemic Alzheimer Disease Biomarkers and Anxious-Depressive Symptoms During the
COVID-19 Confinement in Cognitively Unimpaired Adults

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Abstract

Background and Objectives Increased anxious-depressive symptomatology is observed in the preclinical stage of Alzheimer's disease (AD), which may accelerate disease progression. We investigated whether amyloid- β , **cortical thickness in medial temporal lobe structures**, neuroinflammation and sociodemographic factors were associated with **greater** anxious-depressive symptoms during the COVID-19 confinement.

Methods This retrospective observational study included cognitively unimpaired older adults from the ALFA (Alzheimer and Families) cohort, the majority with a family history of sporadic AD. Participants performed the Hospital Anxiety and Depression Scale (HADS) during the COVID-19 confinement. A subset had available retrospective (on average: 2.4 years before) HADS assessment, amyloid [^{18}F] flutemetamol PET and structural MRI scans and CSF markers of neuroinflammation (interleukin-6 [IL-6], triggering receptor expressed on myeloid cells 2 and glial fibrillary acidic protein levels). We performed multivariable **linear** regression models to investigate the associations of **pre-pandemic AD-related** biomarkers and sociodemographic factors with HADS scores during the confinement. **We further performed an analysis of covariance in order to adjust by participants' pre-pandemic anxiety-depression levels.** Finally, we explored the role of stress and lifestyle changes (sleep patterns, eating, drinking, smoking habits, and medication use) on the tested associations and performed sex-stratified analyses.

Results **We included 921 (254 with AD biomarkers) participants.** Amyloid- β positivity (B=3.73; 95%CI=1.1 to 6.36; $p=.006$), caregiving (B=1.37; 95%CI=0.24 to 2.5; $p=.018$), sex (women: B=1.95; 95%CI=1.1 to 2.79; $p<.001$), younger age (B=-0.12; 95%CI=-0.18 to -0.052; $p<.001$) and lower education (B=-0.16; 95%CI=-0.28 to -0.042; $p=.008$) were associated with greater anxious-depressive symptoms during the confinement. Considering pre-pandemic anxiety-depression levels, we further observed an association

between **lower levels of CSF IL-6** ($B=-5.11$; $95\%CI=-10.1$ to -0.13 ; $p=.044$) and **greater** HADS scores. The results were independent of stress-related variables and lifestyle changes. Stratified analysis revealed that the associations were mainly driven by women.

Discussion Our results link AD-related pathophysiology and neuroinflammation with **greater** anxious-depressive symptomatology during the COVID-19-related confinement, notably in women. AD pathophysiology may increase neuropsychiatric symptomatology in response to stressors. This association may imply a worse clinical prognosis in people at risk for AD after the pandemic, and thus deserves to be considered by clinicians.

Trial Registration Information ClinicalTrials.gov Identifier NCT02485730

Introduction

There has been a global increase in anxious-depressive symptomatology with the COVID-19 pandemic and home confinement.^{1,2} This will bring long-term implications for mental health and cognitive decline in vulnerable populations.³⁻⁵

In this context, both anxiety³ and depression⁴⁻⁶ are associated with an increased risk for developing cognitive impairment⁷⁻⁹ and Alzheimer's disease (AD). The prevalence of AD is higher in women¹⁰, and both women and caregivers report higher anxiety and depression,^{11,12} particularly during the COVID-19 pandemic.¹³

Recent studies suggested an early link between amyloid-beta (A β) and worsening anxious-depressive symptoms in cognitively unimpaired (CU) adults.^{14,15} Moreover, AD pathology may alter brain structures that regulate the brain's response to stress and increase the proneness to develop anxious-depressive symptoms.¹⁶ Another mechanism linking AD with anxiety-depression might be neuroinflammation, which has an early involvement in the pathogenesis of the disease.¹⁷ Notably, the cerebrospinal fluid (CSF) interleukin-6 (IL-6) has been consistently reported to be elevated in both depressed and AD patients.^{16,18,19}

Altogether, it becomes relevant to investigate the COVID-19 confinement-related anxious-depressive symptomatology in adults at risk for cognitive decline and AD, addressing sex/gender differences and caregivers' mental health.

Therefore, here we focused on CU older adults, the majority with a family history (FH) of clinically diagnosed sporadic AD. Older adults with FH of sporadic AD are at higher risk for cognitive impairment and dementia,²⁰ and start showing AD-related pathological changes early during midlife.^{21,22} We investigated the associations of A β burden, neuroinflammation

and brain structure data acquired approximately 2.4 years before the pandemic with anxious-depressive symptomatology during the COVID-19 confinement. We hypothesized that (i) adults with A β burden, higher CSF IL-6 values and/or lower structural integrity in AD-related regions (**medial temporal lobe structures**) will show **greater** anxiety-depression during the confinement and (ii) these associations will be independent of the pre-confinement anxiety-depression levels. We also hypothesized that women and caregivers will present higher anxious-depressive symptoms during the confinement.

Methods

Participants

Participants were recruited from the ALFA (ALzheimer's and FAMilies) and ALFA+ cohorts established at the Barcelona β Brain Research Center in Barcelona, Spain **as a research platform to characterize preclinical AD.**²⁰

The ALFA cohort includes 2743 CU (Clinical Dementia Rating Score [CDR]=0) older adults aged between 45-74 years, enriched for family history of AD (86% had at least one parent diagnosed with dementia) and APOE- ϵ 4 genotypes. At the baseline visit (2013-2014), sociodemographic, clinical, epidemiological, genetic and cognitive data were collected. Participants from the ALFA cohort were invited to participate in the ALFA+ study following a genetic risk enrichment strategy (APOE- ϵ 4 carriership, family history of sporadic AD). Four hundred and fifty participants from the ALFA cohort were enrolled in the nested ALFA+ study. These participants underwent advanced magnetic resonance imaging (MRI) and positron emission tomography (PET), lumbar puncture, clinical interviews, cognitive testing, lifestyle and risk factors evaluations. The inclusion criteria of ALFA+ participants were as follows: (i)

participation in ALFA study; (ii) aged 45 to 75 years at inclusion in ALFA study; (iii) long-term commitment to follow-up visits, assessments and study procedures. ALFA+ exclusion criteria were: (i) cognitive impairment (CDR>0, Mini Mental State Examination<27, semantic fluency<12); (ii) any unstable medical condition or significant systemic illness that could interfere with protocol compliance; (iii) any contraindication to the tests or study procedures; (iv) family history of monogenic AD.²⁰

In the current study, sociodemographic, genetic, clinical, and neuroimaging data collected between 2016 and 2019 from the ALFA and/or ALFA+ participants were used and are referred to as “pre-confinement” measurements. On May 8, **during the de-escalation phases of the confinement**, the invitation to participate in the current study was sent via e-mail to 2582 ALFA participants. **On March 14, 2020, during the first wave of the COVID-19 pandemic in Spain, the Spanish government declared a state of emergency and started a national lockdown to control increasing number of COVID-19 cases in the country. From March 15, all residents were confined to their homes except to make necessary purchases, work, and emergencies.**²³ **On May 2, the government started to implement “de-escalation phases” to ease the confinement restrictions.** Between May 8 and August 31, the period referred to as “confinement” hereafter, **967 ALFA participants agreed to take part in the current study and completed an online assessment** battery that included the Hospital Anxiety and Depression Scale (HADS), the Perceived Stress Scale (PSS), the Brief Resilience Scale (BRS) and an *ad-hoc* evaluation on caregiving and changes in lifestyle patterns (sleep, eating, drinking, smoking habits and medication use). **Of these, 265 were from the ALFA+ study and referred to as “biomarkers sample” in this article. The average time from pre-confinement to confinement assessments were 2.4 (±0.8) years.**

Study protocol approvals, registrations, and patient consents

The ALFA and ALFA+ study protocols have been approved by the Independent Ethics Committee “Parc de Salut Mar,” Barcelona and registered at ClinicalTrials.gov (ALFA Identifier: NCT01835717; ALFA+ Identifier: NCT02485730). The COVID-19 protocol (CovidImpact_BBRC2020) has been approved by the Independent Ethics Committee “Parc de la Salud” on March 16, 2020 (Identifier: 2020/9255). All participants signed an informed consent that had also been approved by the Independent Ethics Committee “Parc de la Salud”.

Clinical measurements

Anxiety and depression. Anxiety and depression were measured with the HADS consisting of 7-item anxiety and 7-item depression subscales. Each subscale has a possible total score ranging from 0 to 21 (≤ 7 normal, 8–10 borderline, ≥ 11 probable anxiety or depression).²⁴

Stress-related measurements. We measured self-perceived stress using the 10-item PSS²⁵ with higher scores indicating greater stress perception. We also assessed the ability to resist or recover from stress with the 6-item BRS.²⁶ Higher scores reflect greater stress resilience.

Caregiver status and changes in lifestyle patterns. Caregiver status was defined with the following question in the *ad-hoc* evaluation: “Are you a caregiver for a dependent person?” Furthermore, we investigated the changes in lifestyle patterns during the confinement reflecting neuropsychiatric-like behaviors (sleep patterns, eating, drinking and smoking habits, and medication use). **Participants answered a questionnaire aimed at**

evaluating change in sleep (hours), caloric food, alcohol and tobacco consumption, use of anxiolytics/antidepressants, sleeping pills and analgesics during the confinement as compared to pre-confinement (see Supplemental Figure e1 for the details). The sleep variables were coded to reflect less or more than 7 hours of sleep before and during the confinement. Then, we classified participants under the categories of “No change”, “Decreased” or “Increased” sleep hours. We categorized the responses to the questions of the rest of the variables as follows: “Decreased” (I have stopped consuming or I have decreased the consumption), “No change” (I have not changed the consumption) and “Increased” (I have increased the consumption moderately or I have increased the consumption significantly).

APOE genotyping. The *APOE* genotype was obtained from the allelic combination of the rs429358 and rs7412 polymorphisms. *APOE* status was determined based on the *APOE*- ϵ 4 allele and the participants were classified as *APOE*- ϵ 4 carriers or *APOE*- ϵ 4 non-carriers.

Neuroimaging and CSF biomarker measurements

MRI acquisitions and MRI-based AD signature. Anatomical 3D T1-weighted Fast Field Echo sequence MRI images were obtained with a 3T scanner (Ingenia CX, Philips, the Netherlands) at the Barcelonaβeta Brain Imaging Center **with the following parameters: voxel size = 0.75 mm³ isotropic, field of view = 240 x 240 x 180 mm³, flip angle = 8°, repetition time = 9.9 ms; echo time = 4.6. ms and inversion time = 900 ms in sagittal acquisition.** FreeSurfer version 6.0 was used to determine the cortical thickness of regions vulnerable to AD. The so-called “AD signature” was calculated as the surface-area weighted average of the individual thickness values of the following regions:

entorhinal, inferior temporal, middle temporal, and fusiform cortices in both hemispheres.^{17,27}

PET imaging acquisitions and pre-processing. [¹⁸F] Flutemetamol PET scans were acquired in a Siemens Biograph Mct (Munich, Germany) after performing a cranial CT scan for attenuation correction. 185 MBq (range 166.5 – 203.5 MBq) of [¹⁸F] flutemetamol was injected to the participants and 4 frames of 5 minutes each were acquired following the waiting period of 90 minutes. An OSEM3D algorithm with 8 iterations and 21 subsets were used to reconstruct the images with point spread function and time-of-flight corrections into a 1.02 x 1.02 x 2.03 mm matrix. The acquired images were preprocessed using SPM12. Averaged PET images were coregistered to corresponding MRI scans. Following the segmentation of MRIs, the images were normalized to Montreal Neurological Institute (MNI) space together with the PET images. The standardized value uptake ratio (SUVR) was calculated in MNI space from the standard regions (bilateral frontal and parietotemporal areas) and the whole cerebellum as reference region. We then transformed the SUVR values to the centiloid (CL) scale. Amyloid positivity was ascertained using CL values.²⁸

We defined the cut-off value for CL with a threshold of 12 to classify the participants as A β -negative (<12 CL) or A β -positive (\geq 12 CL).

CSF measurements. IL-6 was measured with the Roche NeuroToolKit, a panel of automated Elecsys® and prototype immunoassays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) on a cobas e 411 or e 601 instrument at the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden. Glial fibrillary acidic protein (GFAP) and soluble fragment of triggering receptor expressed on myeloid cells 2 (sTREM2), measured with the Roche NeuroToolKit, and also reflecting neuroinflammatory processes,²⁹ were used to test the specificity of the associations

between IL-6 and anxiety-depression. We used the log₁₀-transformed versions of the IL-6 and GFAP measurements for the analyses as they were not normally distributed.²⁹

All participants were blinded to the results of their CSF and amyloid PET assessments.

Statistical Analysis

The characteristics of the samples were defined with means and standard deviations or medians and ranges for continuous variables and frequencies and percentages for categorical variables.

With descriptive purposes, we investigated the differences by sex, caregiver status, A β positivity in pre-confinement HADS scores and stress-related measurements (PSS and BRS) with t-tests. We also reported raw HADS change scores by group and explored the differences between these groups in lifestyle changes during the confinement with Chi-square analyses.

In our main analyses, we performed two sets of multivariable **linear** regression models with HADS total scores during the confinement **as the outcome variable**. First, we investigated whether AD-related biomarkers showed cross-sectional associations with HADS total scores in the biomarkers sample. To this end, **we included A β positivity, CSF IL-6 and cortical thickness in AD signature regions as independent variables** and demographics, *APOE- ϵ 4* status and caregiver status as covariates in the model. We also investigated the factors associated with HADS total scores in the whole sample considering **the demographics, APOE- ϵ 4 status and caregiver status as independent variables**. **In a second step, we performed the models adjusting by pre-confinement anxiety-depression levels in the subgroup of participants with available pre-**

confinement HADS scores (see the Results section). In these models, we also controlled for the inter-individual variability in the time lag between pre-confinement and confinement HADS assessments.

As sensitivity analysis, we explored whether anxiety or depression (HADS-Anxiety and HADS-Depression as dependent variables) drove the results of the main analyses. In addition, **considering the higher prevalence of anxiety and depression in women,**¹¹ we performed sex-stratified analyses **to investigate whether the tested associations were driven by women.**

All analyses were performed using RStudio v1.4.1103-4 and SPSS 27 (IBM, Armonk, NY) statistical software. Statistical significance was considered when the results yielded a two-tailed p -value lower than 0.05.

Data Availability

The data supporting the findings of the current study may be available on a reasonable request from the ALFA study management team.

Results

From the ALFA participants that accepted to participate in the study, those with complete HADS evaluation during the confinement were included in the present study (N=921/2582, 35.67%). Of these, 254 participants had available AD biomarkers data (biomarker sample, see Figure 1). The majority of participants were residing in the northeast region of Spain, Catalonia (Supplemental Figure e2). Participants that accepted to participate in the current study (as compared to those that declined

[N=1661] had significantly higher years of education ($t_{2580}= 3.87; p<.001$) and lower pre-confinement HADS scores ($t_{1754}=-2.68; p=.007$).

Table 1 shows the demographic, biological, imaging, and clinical data of the biomarkers sample and whole sample included in the study. A total of 253 (99.35%) in the biomarkers sample and 767 (83.28%) in the whole sample had pre-confinement HADS scores. In brief, there were 61.7% of women (N=568), 14.5% of caregivers (N=134), 99.1% of white Caucasian (0.9% Latinos), 10.2% (N=26) of A β -positive participants (biomarkers sample only) and 10.7% (N=99) with a self-reported clinical diagnosis of anxiety or depression during the confinement (**Table 1**).

Fifty-one percent of all participants (N=473) completed the HADS in May, 46.5% (N=428) in June, 1.4% (N=13) in July and 0.8% (N=7) in August. **Thirty-six percent (N=330) of all participants completed the HADS during the de-escalation phase 0, 13.1% (N=121) during phase 1, 35.9% (N=332) during phase 2, 11% (N=102) during phase 3, and 3.9% (N=36) during phase 4.** The month or phase of the confinement when the HADS was completed did not show any effect on the total anxiety-depression scores (**Supplemental Figure e3**).

Participants in the whole sample had significantly higher pre-confinement HADS scores ($t_{766}= 40.8; p<.001$, $t_{920}= 43.4; p<.001$, respectively), were younger ($t_{920}= 255.7; p<.001$), and had higher years of education ($t_{920}= 122.4; p<.001$) than participants in the biomarkers sample. Biomarkers sample included a higher number of APOE- $\epsilon 4$ carriers ($X^2= 32.7; p<.001$).

Association of confinement HADS total scores with confinement-related variables

In the absence of a control condition, we used proxies of length and intensity of the confinement to assess its association with HADS measurements. Participants that started the confinement at an earlier date or that were confined in smaller-size dwellings did not show higher HADS scores. **However, anxiety-depression scores were higher in participants that went outdoors less frequently ($F=21.4$, $p<.001$), and in those that did not have any open-air space (e.g. garden, terrace, balcony) at their dwellings ($F=4.24$, $p=.04$).**

Pre-confinement and confinement HADS measurements

In the pre-confinement evaluation, the majority of participants scored within the normal ranges of HADS-Anxiety (76.7%) and HADS-Depression (96%).²⁴ During the confinement, 16.6% of the participants showed a significant increase ($p<.001$) in anxious symptomatology (10.8% changed from normal to borderline, 2.5% from borderline to probable, 3.3% from normal to probable) and 9.9% showed a significant increase ($p<.001$) in depressive symptomatology (6.1% changed from normal to borderline, 0.9% from borderline to probable, 2.9% from normal to probable). The change in clinical HADS categories from pre-confinement to confinement are provided by sex and caregiver status in **Supplemental Table e1**.

In the pre-confinement evaluations, women had significantly higher total anxiety-depression scores than men (biomarkers sample: $t_{245.4}= 3.87$; $p<.001$, whole sample: $t_{765}= 4.65$; $p<.001$). Caregivers also showed higher HADS scores at the pre-confinement as compared non-caregivers (biomarkers sample: $t_{235}= 2.67$; $p=.008$, whole sample: $t_{832}= 3.21$; $p<.001$). A β -positive or A β -negative participants did not show any difference in pre-confinement HADS total scores ($t_{203}= 1.84$; $p=.067$).

Raw mean change in HADS scores (biomarkers sample: 1.5, whole sample: 1.32) were higher in women (1.55±6) vs men (0.72±4.6), younger (1.68±5.7) vs older (0.76±5.3) adults, non-caregivers (1.4±5.5) vs caregivers (0.29±5), Aβ-positive (1.81±7.7) vs Aβ-negative (1.6±5.9) participants, APOE-ε4 non-carriers (1.35±5.1) vs APOE-ε4 carriers (1.04±6.1), participants with lower CSF IL-6 levels (1.85±5.9) vs higher IL-6 levels (1.09±5.6), those with lower years of education (1.4±5.3) vs higher years of education (1.04±5.6).

The mean HADS total, HADS-Anxiety and HADS-Depression scores by sex, caregiver and Aβ status during pre-confinement and confinement are shown on **Supplemental Figure e4**.

Differences in stress-related measurements and lifestyle changes by sex, caregiver status and amyloid status

During the confinement, women had higher PSS scores than men (biomarkers sample: $t_{240} = 1.97$; $p = .05$, whole sample: $t_{863} = 3.47$; $p < .001$). The two groups did not show any difference in BRS scores (biomarkers sample: $t_{250} = -0.58$; $p = .562$; whole sample: $t_{858.3} = 0.69$; $p = .493$). Compared to non-caregivers, caregivers had higher PSS scores (biomarkers sample: $t_{228} = 2.07$; $p = .04$, whole sample: $t_{181.5} = 4.56$; $p < .001$). Nevertheless, caregivers had significantly higher BRS scores than non-caregivers (whole sample only: $t_{826} = 2.23$; $p = .05$). There were no significant differences between Aβ-positive or Aβ-negative participants in PSS ($t_{193} = 1.24$; $p = .216$), or BRS ($t_{202} = 1.56$; $p = .12$) scores.

Regarding the analyses investigating the changes in lifestyle patterns, we observed sex differences in hours of sleep and food consumption (women, $X^2 = 7.52$; $p = .023$; $X^2 = 37.5$; $p < .001$, respectively). Additionally, we observed a significant difference between

caregivers and non-caregivers in food consumption (caregivers, $X^2= 6.41$; $p=.041$). There were no significant differences between A β -positive or A β -negative participants in any of the investigated lifestyle domain (**Supplemental Table e2**).

Factors associated with total anxiety-depression during the confinement

In the biomarkers sample, A β positivity (B=3.73; 95%CI=1.1 to 6.36; $p=.006$), but not thickness in AD signature (B=-5.31; 95%CI=-14.5 to 3.87; $p=.255$) or CSF IL-6 (B=-5.13; 95%CI=-10.4 to 0.11; $p=.055$), showed a cross-sectional association with **greater** total anxiety-depression scores independent of age, sex and years of education. When the model was adjusted by pre-confinement HADS scores, higher pre-confinement anxiety-depression scores were associated with greater confinement HADS scores and the association between A β positivity and HADS total scores remained significant. Additionally, lower levels of CSF IL-6 were associated with greater HADS total scores irrespective of the pre-confinement anxiety-depression level (**Table 2 & Figure 2/A**).

In the whole sample, younger age (B=-0.12; 95%CI=-0.18 to -0.052; $p<.001$), being a woman (B=1.95; 95%CI=1.1 to 2.79; $p<.001$), lower years of education (B=-0.16; 95%CI=-0.28 to -0.042; $p=.008$) and being a caregiver (B=1.37; 95%CI=0.24 to 2.5; $p=.018$) showed cross-sectional associations with **greater** HADS total scores during the confinement. Pre-confinement HADS scores were associated with greater confinement HADS scores. The associations of age and sex with total anxiety-depression scores were still significant after controlling for the pre-confinement HADS scores (**Table 2 & Figure 2/B**).

Models with HADS subscales (anxiety and depression) as dependent variables showed similar associations in both samples. Among the AD-related biomarkers, only amyloid- β

positivity showed a specific association with greater HADS-Anxiety scores irrespective of the pre-confinement anxiety level (**Supplemental Table e3**).

Sensitivity analyses

Amyloid results. Given the relatively small percentage of A β -positive subjects in our cohort, we confirmed the robustness of the results with continuous CL levels that showed an association with HADS total scores irrespective of pre-confinement HADS scores (B=0.055; 95%CI=0.005 to 0.1; $p=.031$).

Models excluding the participants that are currently diagnosed with or under the treatment of anxiety-depression. We performed our main analyses without the participants with self-reported clinical diagnosis and/or under the treatment of anxiety-depression. Our main results in the biomarkers sample or the whole sample remained significant in these analyses. Additionally, IL-6 showed a cross-sectional association with greater HADS total scores during the confinement (B=-5.13; 95%CI=-9.98 to -0.27; $p=.039$).

Associations with neuroinflammation markers. We investigated whether the observed association between neuroinflammation and HADS total scores was specific to IL-6 as hypothesized. **To this end, we performed our main model in the biomarkers sample including the sTREM2 and GFAP while taking into account of the pre-confinement HADS scores.** Results showed that the association between neuroinflammation and anxious-depressive symptoms was restricted to IL-6 since STREM2 and GFAP did not show any association with HADS (sTREM2, B=-0.31, $p=.13$; GFAP, B=1.63, $p=.618$).

Adjustments by measurements of stress. The models considering the pre-confinement anxiety-depression levels were adjusted by PSS and BRS scores **to evaluate whether**

stress-related variables had any confounding effect on the reported results. The main results remained significant after this adjustment (**Supplemental Table e4**).

Stratified analyses by sex. The results of the sex-stratified analyses adjusted by pre-confinement HADS levels are reported in **Table 3**. These analyses revealed that women are driving the associations reported above (**Table 3**).

Adjustments by changes in lifestyle patterns. **We observed differences in hours of sleep and/or food consumption by sex and caregiver status during the confinement.**

Therefore, we adjusted our main analyses by hours of sleep and food consumption to control for a potential confounding effect of these variables on the associations tested. Following these adjustments, the previously observed associations did not change. Changes in sleep hours, however, showed an association with HADS total scores ($F=6.23$; $p=.002$).

Discussion

The main results of the present study in CU adults at increased risk for developing AD were as follows: (i) A β positivity and lower CSF IL-6 levels measured 2.4 years before the pandemic were associated with **greater** anxious-depressive symptomatology during the COVID-19 confinement, (ii) women and caregivers presented higher anxious-depressive symptoms during the confinement, (iii) the results were mainly seen in women and were independent of demographics, stress-related measurements and changes in lifestyle patterns during the confinement.

Our sample consisted of adults with low burden of anxiety-depression before the COVID-19 pandemic. Even so, and in line with previous reports,¹ 16.6 % and 9.9% of the

participants showed clinically significant increases in anxious-depressive symptoms, respectively. The change in HADS total scores in the biomarkers sample (1.5) is considered a significant difference in clinical settings.³⁰ **Further, we did not find any effect of specific confinement phase or month on the anxious-depressive symptoms. However, we observed that participants going outdoors less frequently (once a week or less during the confinement and de-escalation phases), and those spending the confinement in a dwelling without any open-air space showed higher anxiety-depression.** Overall, these results support that our sample showed modest but clinically meaningful changes associated with the COVID-19 confinement.

Amyloid- β positivity was associated with **greater** anxious-depressive symptoms during the confinement irrespective of the pre-confinement anxiety-depression level. This association was driven by anxiety symptoms. These results are consistent with cross-sectional^{31,32} and longitudinal^{33,34} data showing that A β burden is associated with neuropsychiatric symptoms in CU adults. The results were independent of self-reported perceived stress and stress resilience. However, these associations might be mediated by the physiological stress response.³⁵ The dysregulation of the hypothalamic-pituitary-adrenal axis may result in a chronic stress response and in elevated adrenal glucocorticoids which may first, increase the deposition of A β plaques, the accumulation of tau and, ultimately, cause damage of brain structure and function.^{16,36,37} Contrary to our expectations, but in line with this temporality of events, brain integrity in AD-related regions was not associated with anxiety-depression. This may indicate that the increase in neuropsychiatric symptomatology in preclinical AD might occur before affecting the brain structure.³⁸ However, these associations may exist with other brain regions not included in our AD signature such as the insula.³⁹

Previous findings suggest neuroinflammation as a mechanism by which anxiety and depression are linked to AD pathophysiology.^{16,40} Our results showed that the associations between neuroinflammation and anxiety-depression are specific to IL-6 but not to other neuroinflammation markers such as GFAP and sTREM2. Elevated IL-6 levels have been reported previously in depressed subjects¹⁹ and in AD patients.^{16,18} Moreover, long-lasting stressful events, such as the pandemic, may induce the expression of IL-6.⁴¹ Unexpectedly, however, we observed that participants with lower CSF IL-6 levels showed higher anxiety-depression during the confinement irrespective of their anxiety-depression level at the pre-confinement. A possible explanation is that, the levels of IL-6 might be lower at early stages of the disease⁴² and therefore the associations with anxiety-depression might be different in preclinical AD. Future studies with longitudinal data are required to replicate our results and investigate whether the association of IL-6 with neuropsychiatric symptomatology is different throughout the AD continuum.

Our findings showed that the associations between anxiety-depression and A β were driven by women. We also observed greater changes in sleep patterns in women than men, which is a factor associated with increasing amyloid levels.⁴³ While sleep patterns showed an association with greater anxiety-depression, the association with A β remained significant after adjustments by sleep. Women also showed greater changes in eating patterns than men. **These results are in line with previous research reporting higher prevalence of neuropsychiatric symptomatology¹¹ and higher cognitive vulnerability to AD-related pathophysiology in women.**⁴⁴ Altogether, these findings point at the necessity to address whether the associations of neuropsychiatric symptomatology with AD pathologies in preclinical AD are driven by women. They may also suggest that sex-specific mechanisms linking anxiety-depression and AD exist. **Future studies are required to evaluate the biological and sociocultural factors that may explain**

differences in pathophysiological and neuropsychiatric profiles between women and men.

In the whole sample, being a woman and being a caregiver were independently associated with greater anxious-depressive symptoms during the confinement. These results are consistent with previous findings,^{45–47} showing higher perceived stress, anxiety and depression during the pandemic in women and caregivers. **One explanation for higher anxiety-depression observed in caregivers could be related to taking care of patients with chronic illnesses (e.g. dementia).**¹³ **Further studies accounting for the condition of the care recipient and the caregiver burden can elucidate whether confinement had an additive effect on the mental health burden of the caregivers.**

Further, the observed associations in women, but not in caregivers, were independent of the anxiety-depression levels measured before the pandemic. The pandemic may have exacerbated system-level deficits and disparities which could have increased anxiety-depression in women.⁴⁶ Regarding the caregivers, they showed higher stress resilience than non-caregivers during the confinement, suggesting that they may have more cognitive resources to cope. This may explain the results that did not indicate an increase in anxious-depressive symptoms in caregivers when their pre-confinement anxiety-depression levels were taken into account.⁴⁸

Lastly, we observed associations of younger age and lower education level with **greater** anxious-depressive symptoms during the confinement. These results are consistent with the literature and could be explained by unique stressors (e.g. job loss or unemployment)⁴⁹ or false beliefs and insufficient information about the pandemic in younger or lower-educated adults.⁵⁰

This study is not free of limitations. First, **our study focuses on participants at increased risk for developing AD since the majority of our sample have a family history of sporadic AD. The lack of a control group limits the generalizability of our results to the general population and does not allow disentangling the contribution of the natural history of the disease to the observed increases in anxious-depressive symptoms. In the same vein, whether the observed results are attributable to the effect of the confinement itself or to the general effect of the pandemic remains unclear, as they are temporally overlapping and interrelated events. Nevertheless, individual differences in confinement intensity (going outdoors less than once a week and spending the confinement in a dwelling without an open-air space) showed associations with greater anxiety-depression, which supports our interpretation.** Further, the study design does not allow studying the causal effects between amyloid- β and anxiety-depression. Future studies are required to investigate whether anxiety and depression precede amyloid or are a consequence of it. **Additionally, our approach for the missing data was to exclude the participants with missing data and this may have led to less power to detect some effects.** Lastly, the percentage of amyloid positivity was low (10%). However, our results were robust across continuous amyloid measurements.

Overall, our findings showed a negative impact of COVID-19 confinement on mental health in people at increased risk for AD and support the link between neuropsychiatric symptomatology and brain A β burden in preclinical AD, notably in women. Future studies are warranted to investigate the consequences of the pandemic **and related confinement** on mental health and on the clinical prognosis of individuals at the preclinical stage of AD.

Glossary

A β : Amyloid-beta

AD: Alzheimer's disease

ALFA: ALzheimer and FAMILies

FH: Family history

CL: Centiloid

IL-6: Interleukin-6

GFAP: Glial fibrillary acidic protein

sTREM2: Soluble fragment of triggering receptor expressed on myeloid cells 2

HADS: Hospital anxiety and depression scale

MRI: Magnetic resonance imaging

PET: Positron emission tomography

PSS: Perceived stress scale

BRS: Brief resilience scale

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Table 1

Variable	Biomarkers Sample (N=254)	Whole Sample (N=921)
Age, mean (SD), y	63.5 (4.78)	62.7 (6.36)
Caucasian, No. (%)	252 (99.2)	912 (99.1)
Female, No. (%)	154 (60.6)	568 (61.7)
Education, mean (SD), y	13.4 (3.49)	13.8 (3.41)
APOE-ε4 Carrier, No. (%) ^a	146 (57.5)	342 (37.1)
Caregiver, No. (%) ^b	39 (15.4)	134 (14.5)
Amyloid Positivity (>12CL), No. (%) ^c	26 (10.2)	-
AD Signature (<i>Cth</i> , <i>mm</i>), mean (SD) ^d	2.42 (0.096)	-
IL-6 (pg/mL), median (range) ^e	3.6 (12.1)	-
GFAP (ng/mL), median (range) ^f	7.2 (23.8)	-
sTREM2 (ng/mL), mean (SD) ^g	7.92 (2.25)	-
Pre-Confinement HADS Total Scores, mean (SD) ^h	6.57 (4.81)	7.59 (5.14)
HADS-Anxiety Scores, mean (SD) ^h	4.73 (3.22)	5.39 (3.38)
HADS-Depression Scores, median (range) ^h	1 (9)	1 (13)
Confinement HADS Total Scores, mean (SD)	8.07 (5.98)	8.91 (6.23)
HADS-Anxiety Scores, mean (SD)	5.19 (3.48)	5.56 (3.55)
HADS-Depression Scores, median (range)	2 (14)	2 (17)
PSS Scores, mean (SD) ⁱ	16 (8.68)	16.9 (8.65)
BRS Scores, mean (SD) ^j	3.16 (0.39)	3.15 (0.37)
Time from Pre-Confinement to Confinement Evaluations, mean (SD), y	2.37 (0.77)	2.41 (0.76)
Currently Diagnosed/Under Treatment for Anxiety-Depression, No. (%) ^k	26 (10.2)	99 (10.7)

Table 2

Biomarkers Sample	HADS Total	
	B Value (95% CI)	p Value
<i>Adj. R² = 0.242</i>		
Age	-0.37 (-0.55 to -0.18)	<.001
Sex (women)	1.99 (0.27 to 3.71)	.024
Years of Education	-0.27 (-0.5 to -0.03)	.028
APOE-ε4 Carriers	-0.21 (-1.9 to 1.47)	.803
Caregivers	-1.37 (-3.62 to 0.87)	.228
Amyloid Positivity	2.6 (0.074 to 5.12)	.044
AD Signature	-3.67 (-12.5 to 5.17)	.413
IL-6	-5.11 (-10.1 to -0.13)	.044
Time Difference	0.21 (-0.7 to 1.12)	.645
Pre-Confinement HADS	0.41 (0.23 to 0.58)	<.001
Whole Sample		
<i>Adj. R² = 0.307</i>		
Age	-0.09 (-0.15 to -0.033)	.002
Sex (women)	1.34 (0.55 to 2.13)	.001
Years of Education	-0.1 (-0.22 to 0.011)	.075
APOE-ε4 Carriers	-0.26 (-1.3 to 0.51)	.511
Caregivers	-0.54 (-1.6 to 0.51)	.315
Time Difference	-0.064 (-0.44 to 0.32)	.742
Pre-Confinement HADS	0.63 (0.55 to 0.71)	<.001

Table 3

Women	HADS Total			
	Biomarkers Sample		Whole Sample	
	B (95% CI)	<i>p</i> value	B (95% CI)	<i>p</i> value
Age	-0.49 (-0.77 to -0.22)	<.001	-0.15 (-0.24 to -0.072)	<.001
Years of Education	-0.28 (-0.61 to 0.056)	.102	-0.15 (-0.31 to 0.006)	.059
APOE-ε4 Carriers	-0.2 (-2.67 to 2.26)	.871	-0.35 (-1.45 to 0.75)	.53
Caregivers	-1.73 (-4.77 to 1.29)	.259	-0.51 (-1.95 to 0.93)	.484
Amyloid Positivity	5.17 (1.28 to 9.06)	.01	-	-
AD Signature	-1.15 (-13.7 to 11.4)	.855	-	-
IL-6	-5.1 (-11.7 to 1.67)	.14	-	-
Time Difference	-0.62 (-0.8 to 2.05)	.391	-0.074 (-0.62 to 0.47)	.788
Pre-Confinement HADS	0.32 (0.1 to 0.55)	<.001	0.62 (0.51 to 0.73)	<.001
Men	HADS Total			
	Biomarkers Sample		Whole Sample	
	B (95% CI)	<i>p</i> value	B (95% CI)	<i>p</i> value
Age	-0.23 (-0.46 to 0.009)	.059	-0.001 (-0.076 to 0.074)	.976
Years of Education	-0.22 (-0.54 to 0.11)	.188	-0.055 (-0.21 to 0.1)	.486
APOE-ε4 Carriers	0.063 (-2.13 to 2.26)	.955	-0.2 (-1.23 to 0.83)	.707
Caregivers	-1.61 (-4.97 to 1.75)	.342	-1.07 (-2.61 to 0.46)	.170
Amyloid Positivity	-0.39 (-3.43 to 2.65)	.797	-	-
AD Signature	-3.59 (-15.9 to 8.77)	.563	-	-
IL-6	-4.14 (-11.4 to 3.15)	.26	-	-
Time Difference	-0.003 (-1.08 to 1.08)	.995	-0.065 (-0.56 to 0.43)	.798
Pre-Confinement HADS	0.61 (0.31 to 0.91)	<.001	0.66 (0.55 to 0.77)	<.001

Table 1: Demographic, biological, imaging and clinical characteristics of the study participants

Abbreviations: CL= Centiloid, AD= Alzheimer 's Disease, Cth= Cortical Thickness, IL-6= Interleukin-6, GFAP= Glial Fibrillary Acidic Protein, sTREM2= Soluble Fragment of Triggering Receptor Expressed on Myeloid Cells 2, HADS= Hospital Anxiety Depression Scale, PSS= Perceived Stress Scale, BRS= Brief Resilience Scale.

a: Whole Sample N=913; b: Biomarkers Sample N=238, Whole Sample N=834; c: Biomarkers Sample N=206; d: Biomarkers Sample N=246; e: Biomarkers Sample N=234; f: Biomarkers Sample N=236; g: Biomarkers Sample N=236, h: Biomarkers Sample N=253, Whole Sample N=767; i: Biomarkers Sample N=242, Whole Sample N=865; j: Biomarkers Sample N=252, Whole Sample N=904; k: Biomarkers Sample N=252, Whole Sample N=907.

Table 2: Results from the multivariable linear regression analyses with HADS total scores during the confinement

Abbreviations: HADS= Hospital Anxiety and Depression Scale, CI= Confidence Interval, AD= Alzheimer 's Disease, IL-6= Interleukin-6.

The unstandardized B represents the variation in HADS total confinement scores with 1-unit variation in a given predictor.

Biomarkers Sample N= 179, Whole Sample N= 693.

Table 3: Results from the stratified multivariable linear analyses by sex in the biomarkers sample and whole sample

Abbreviations: HADS= Hospital Anxiety and Depression Scale, CI= Confidence Interval, AD= Alzheimer's Disease, IL-6= Interleukin-6.

The unstandardized B represents the variation in HADS total scores with 1-unit variation a given predictor.

Figure 1: Flow diagram illustrating the recruitment and number of participants included in cross-sectional and longitudinal analyses

Abbreviations: HADS= Hospital Anxiety Depression Scale.

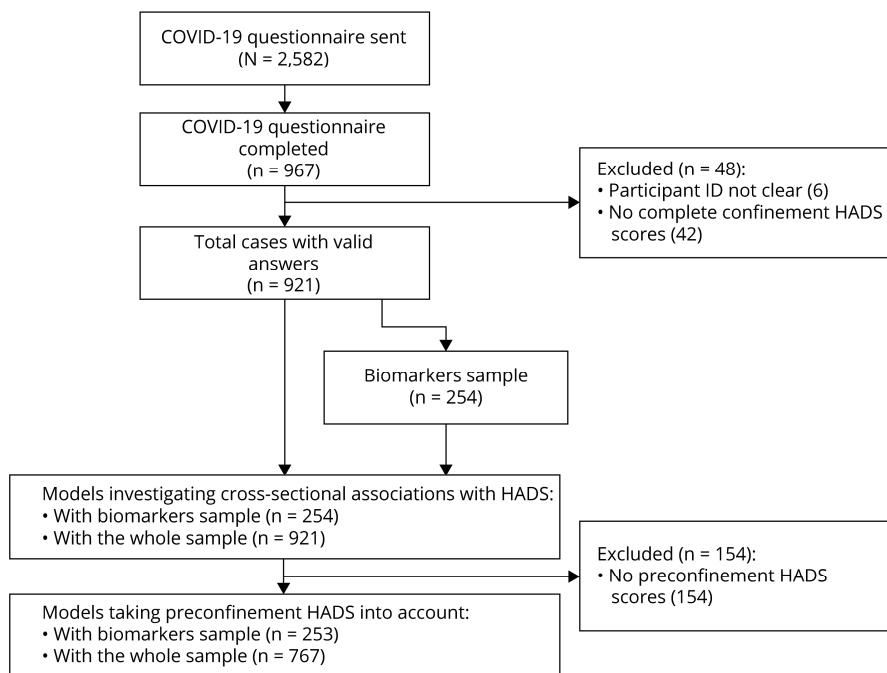
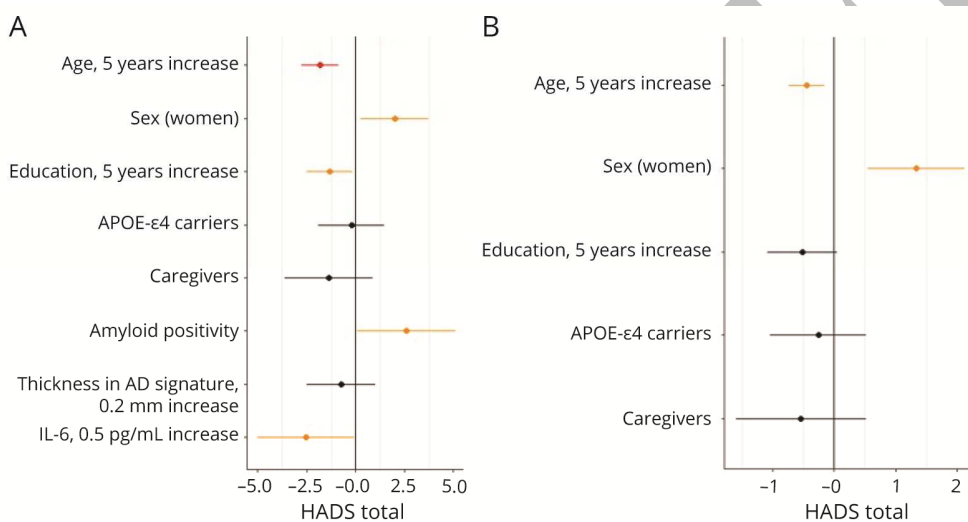


Figure 2: Forest plots showing the multivariable linear associations with HADS total scores during the confinement

The estimated amount of changes (95% CI) in confinement HADS total scores from the multivariable linear regression model fits within the biomarkers sample (Panel A) and the whole sample (Panel B) are shown for a given difference in each factor. Both models are adjusted by pre-confinement HADS scores and the individual variability between pre-confinement and confinement HADS assessments.

The colors on the figure represent: black= non-significant p value, brown= $p < .05$, orange= $< .01$, red= $< .001$.

Abbreviations: CI= Confidence Interval, HADS= Hospital Anxiety and Depression Scale, AD= Alzheimer's Disease, IL-6= Interleukin-6.



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