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# Comparing the Long-Term Impact of COVID-19 on the Progression of Alzheimer's Disease in an Elderly Population with Real-Time Monitoring as a Prognosis

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## Abstract

**Background and Aim:** Despite growing awareness of "long COVID" and its neurological sequelae, the long-term influence of SARS-CoV-2 infection on Alzheimer's progression remains poorly understood. This study aimed to compare the long-term impact of COVID-19 on the progression of AD in elderly individuals, integrating real-time digital monitoring and biomarker analytics to establish predictive prognostic models.

**Methods:** A longitudinal cohort of 348 participants (age≥65 years) diagnosed with early-to-moderate AD was followed over four years (2021–2025). Participants were divided into COVID-19 positive (n=174) and COVID-19 negative (n=174) groups, matched for age, sex, and comorbidities. Serum inflammatory markers (IL-6, TNF-α, CRP), neurofilament light chain (NfL), and amyloid-β/tau ratios were analyzed biannually. Machine learning algorithms were applied to identify prognostic patterns linking infection-related biomarkers with cognitive and functional decline.

**Results:** COVID-19-positive AD patients showed a 29% faster rate of cognitive deterioration, indicating a strong association rather than a confirmed causal relationship—between prior SARS-CoV-2 infection and accelerated AD progression (p<0.01) and a 33% increase in NfL levels compared to controls. Real-time monitoring detected significant fluctuations in sleep quality, gait stability, and heart rate variability within six months post-infection, which preceded measurable cognitive decline. Predictive modeling achieved an accuracy of 87% in forecasting accelerated progression trajectories using combined digital and biochemical markers.

**Conclusion:** The incorporation of wearable and biochemical data into prognostic modeling marks a paradigm shift toward personalized, predictive neurology, enabling clinicians to anticipate and mitigate the long-term neurological consequences of COVID-19 in the aging population.

**Keywords:** Alzheimer Disease; Lymphopenia; Single-Cell Gel Electrophoresis; DNA Damage; Post-Acute COVID-19 Syndrome.

## 1. Introduction

Alzheimer's disease (AD) continues to impose a profound global burden on aging populations, and the emergence of the COVID-19 pandemic has intensified concerns regarding factors that may accelerate neurodegenerative processes (1, 2).



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As SARS-CoV-2 has infected millions of individuals—particularly those of advanced age—questions have arisen regarding whether the virus can initiate or exacerbate pathways implicated in AD pathophysiology.

Early observations of "long COVID" have highlighted cognitive symptoms such as memory impairment, executive dysfunction, and attentional deficits, clinical manifestations that closely resemble the prodromal features of AD. These symptomatic overlaps suggest that COVID-19 may act not merely as an acute infection but as a biological insult capable of triggering or amplifying neurodegeneration in vulnerable populations.

Biomarker evidence further supports this concern. Individuals hospitalized with COVID-19 often exhibit significant elevations in AD-related biomarkers, including total tau, phosphorylated tau, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL). These biomarkers, established indicators of neuronal and glial injury, are elevated compared to non-infected peers, suggesting measurable neurodegenerative stress associated with SARS-CoV-2 infection. Mechanistic links have been proposed in which COVID-19–related neuroinflammation and blood–brain barrier (BBB) disruption promote harmful immune activation and accelerate amyloid-β and tau pathology. Shared molecular pathways provide additional biological plausibility: COVID-19 is known to upregulate the NLRP3 inflammasome and pro-inflammatory cytokines such as IL-6 and TNF-α—immune signatures similarly implicated in AD progression (3, 4). The APOE4 genotype, a major genetic risk factor for AD, also confers increased susceptibility to severe COVID-19 and worsened BBB integrity, further heightening the vulnerability of APOE4 carriers to infection-related neurodegeneration.

These biological risks are compounded by sociobehavioral stressors introduced during the pandemic. Prolonged isolation, decreased physical activity, reduced cognitive stimulation, and increased caregiver distress have contributed to documented declines in cognition, sleep, agitation, and neuropsychiatric symptoms in more than half of AD patients—regardless of infection status. Thus, both biological and environmental mechanisms converge to pose substantial threats to cognitive stability in older adults with AD.

Despite these indicators, a major gap persists in the literature: current research largely lacks longitudinal, real-time monitoring of cognitive and functional decline in AD patients following COVID-19 infection. Most existing studies are cross-sectional or retrospective, limiting the ability to capture dynamic trajectories or to determine whether SARS-CoV-2 modulates the tempo of neurodegenerative processes over extended periods. Meanwhile, machine-learning and artificial intelligence tools applied to longitudinal neuroimaging, behavioural data, and biomarker trends have shown substantial promise for early prediction of AD trajectories, yet these computational advances remain underutilized in post-COVID neurodegeneration research (5, 6).

Two major empirical developments underscore the urgency of addressing this gap. First, neurological sequelae following COVID-19—including brain fog, impaired attention, and biochemical evidence of neuronal injury—are increasingly well documented. Axonal injury markers such as NfL are elevated in individuals with long-COVID cognitive symptoms, linking systemic infection to persistent neuronal damage (7). Second, plasma proteomics and large cohort studies have identified SARS-CoV-2–related alterations in biomarkers associated with amyloid and tau processing, suggesting that infection may influence peripheral indicators of AD-related biological processes. While observational studies cannot establish causality, the consistency of these patterns supports the hypothesis that SARS-CoV-2 could accelerate AD pathology in susceptible individuals (8, 9).

Biologically, this hypothesis is supported by well-characterized interactions among neuroinflammation, vascular dysfunction, and proteostatic failure—core elements of AD pathogenesis. Systemic infections, including COVID-19, can amplify inflammatory cascades, impair BBB integrity, and trigger microglial activation, thereby facilitating tau hyperphosphorylation, amyloid aggregation, synaptic pruning, and axonal injury. COVID-19–related endothelial dysfunction, microthrombosis, and renin-angiotensin system dysregulation further compromise neurovascular stability in aging populations (10, 11).

Scientific progress, however, has been hindered by three challenges: heterogeneity in COVID-19 exposure and severity, limitations of episodic clinical assessments that fail to detect early or fluctuating signs of decline, and insufficient integration of molecular biomarkers with continuous behavioural and physiological monitoring. These limitations highlight the need for prospective, multimodal designs that combine longitudinal blood biomarker analyses with real-time digital phenotyping through wearables and passive sensors (10, 12, 13).

Recent advancements in digital biomarkers render such rigorous monitoring feasible. Wearable devices, smartphone-based cognitive testing, speech analytics, and gait monitoring can now quantify subtle changes in circadian patterns, sleep quality, autonomic regulation, and mobility—physiological indicators



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that may precede detectable cognitive decline. When linked with temporally aligned biomarkers such as serial NfL and phosphorylated tau, these continuous data streams can generate highly predictive multimodal models capable of detecting early deviations and forecasting rapid progression (14, 15).
A robust approach involves a matched longitudinal cohort of AD patients with and without documented SARS-CoV-2 infection, monitored using real-time digital phenotyping and serial biomarker sampling. Such a design can determine whether COVID-19 accelerates AD progression, identify individuals at highest risk, and uncover lead–lag relationships between infection, biomarker perturbations, and digital behavioral changes (13).
Innovations in explainable machine learning and federated analytics further facilitate such research while maintaining privacy across multi-center studies (14-16).
Though the potential clinical impact is substantial, challenges remain. Observational designs are susceptible to confounding by frailty, socioeconomic factors, vaccination status, and virus variant exposure. Peripheral biomarkers cannot be assumed to directly reflect central pathology, and NfL elevations—while sensitive—are not disease-specific. Methodological rigor, repeated measures, and robust analytical strategies are therefore essential (16).

Nonetheless, emerging empirical evidence—including post-COVID biomarker shifts and validated digital indicators of early cognitive decline—demonstrates that the necessary tools are already available to test this hypothesis. Integrating these elements offers a transformative opportunity to determine whether COVID-19 alters the trajectory of AD and to design timely interventions for patients at highest risk (9, 13, 17).

In summary, the intersection of COVID-19 and Alzheimer's disease represents a consequential and tractable research problem. The combination of (1) biological plausibility (neuroinflammatory and vascular mechanisms), (2) emerging empirical evidence (biomarker perturbations and NfL elevations post-infection), and (3) technological readiness (wearables, digital biomarkers) provides a clear opportunity to generate clinically actionable knowledge. A prospective, multimodal, real-time monitoring study comparing AD patients with and without prior SARS-CoV-2 infection—utilizing serial blood biomarkers, continuous physiological and behavioral sensing, and machine-learning prognostic models—has the potential to determine whether COVID-19 alters the course of AD and, critically, identify which patients are most vulnerable. Such findings will inform clinical care, public health planning, and our fundamental understanding of how peripheral insults interact with chronic neurodegenerative processes in the aging brain.

## 2. Methods

This was a four-year prospective, longitudinal, multimodal cohort study designed to examine the long-term effects of prior COVID-19 infection on the progression of Alzheimer's disease (AD) in elderly adults. The study integrated biological, cognitive, physiological, and digital behavioral monitoring to build individualized prognostic models of disease progression. Participants were enrolled between January 2021 and December 2022 and followed through December 2025. The design compared two matched groups of older adults with clinically confirmed early-to-moderate AD: COVID-positive cohort — participants with documented SARS-CoV-2 infection confirmed by RT-PCR or antigen testing between 2020–2022; and COVID-negative cohort — participants without known infection, confirmed by serial negative serology. The study protocol was in accordance with the Declaration of Helsinki and ethical approval was granted by the Institutional Review Boards of the Ethics Committee of Damghan Azad University (IR.IAU.DAMGHAN.REC.1400.005).

### Recruitment and Sample Characteristics

Written informed consent (or proxy consent for participants with cognitive impairment) was obtained from all subjects. All participants were recruited through memory clinics and geriatric centers affiliated with Semnan University of Medical Sciences in Damghan City. Inclusion Criteria: Age ≥ 65 years at baseline. Clinical diagnosis of probable Alzheimer's disease according to NIA-AA criteria. Mini-Mental State Examination (MMSE) score between 16 and 26 at baseline. Capacity to comply with wearable device use or presence of a caregiver able to assist. Residence within study catchment area with stable internet or cellular access for device data transfer. Exclusion Criteria: History of major neurological or psychiatric illness other than AD. Severe sensory deficits precluding device use. Terminal illness or life expectancy < 12 months. History of traumatic brain injury or stroke in the preceding 12 months. Unwillingness to undergo blood sampling or digital monitoring. COVID-positive and COVID-negative participants were 1:1 matched for: Age (±3 years), Sex, Education level, Baseline MMSE score, Comorbidities (hypertension, diabetes, cardiovascular disease), To minimize confounding, propensity-score matching was applied using logistic regression based



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on these covariates. Vaccination status and COVID-19 severity (asymptomatic, mild, moderate, severe) were recorded for secondary analyses. Given the age criterion of ≥65 years, all participants met the definition of late-onset Alzheimer's disease (LOAD). Individuals with symptom onset before age 65, consistent with early-onset AD, were not included. This restriction minimized heterogeneity in disease mechanisms and progression patterns

### Clinical and Cognitive Assessment Schedule

Participants underwent in-person visits at baseline and every six months for clinical evaluation, cognitive testing, and biomarker sampling. Cognitive Measures: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), Neuropsychiatric Inventory (NPI), Functional Activities Questionnaire (FAQ), Functional and Neurological Assessments, Gait speed (10-meter walk test), Timed Up-and-Go (TUG) test, Activities of Daily Living (ADL) index, Sleep quality (Pittsburgh Sleep Quality Index).

### Biomarker Panel and Sampling

Venous blood was drawn biannually for plasma and serum isolation. Samples were processed within 2 hours and stored at −80°C until batch analysis.

### Analytes Measured

Neurodegeneration markers: Neurofilament light chain (NfL), Glial fibrillary acidic protein (GFAP), Total tau (t-tau), Phosphorylated tau (p-tau181, p-tau217), Amyloid metabolism: Amyloid-β42 and Amyloid-β40 (Aβ42/Aβ40 ratio), Inflammatory markers: Interleukin-6 (IL-6), Tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), Vascular and oxidative markers: Vascular endothelial growth factor (VEGF), D-dimer, Reactive oxygen species (ROS) by spectrophotometric assay. All biomarkers were quantified using ultrasensitive immunoassay platforms (e.g., Quanterix Simoa HD-X). Inter-assay coefficients of variation <10% were maintained.

### Digital and Real-Time Monitoring

Each participant received a validated, clinical-grade smartwatch (e.g., Withings ScanWatch or Apple Watch Series 9) and a lightweight actigraphy patch for continuous monitoring. Devices recorded: Heart rate and heart rate variability (HRV), Sleep duration and fragmentation, Physical activity levels and step count, Gait stability metrics (stride length, variability, cadence), Nocturnal movement and restlessness, Data were transmitted securely to a HIPAA-compliant cloud platform. Participants or caregivers were instructed to charge devices daily and ensure >18 hours/day wear compliance.

### Smartphone-Based Cognitive and Behavioral Monitoring

A companion smartphone app administered brief, gamified cognitive tasks weekly: Reaction time (processing speed), Spatial working memory, Speech-based recall and fluency tasks (analyzed for lexical diversity, hesitations, and acoustic markers of decline), Passive phone sensor data (mobility patterns, call/text frequency, screen-on time) were also logged to capture digital behavioral rhythms indicative of early cognitive or affective changes.

### Data Integration and Preprocessing

Each participant's data streams (biomarkers, wearables, app, cognitive tests) were timestamp-synchronized into a unified temporal database using ISO-8601 standardized time formats. Missing or corrupted sensor data (>15% daily data loss) triggered automated alerts for re-synchronization. Physiological outliers were flagged using robust z-score thresholds (±3.5 SD). Natural language features from speech tasks were anonymized before processing.

### Machine Learning and Prognostic Modeling

Multimodal feature vectors were extracted from: Digital signals: HRV variability indices, circadian rhythm regularity, sleep efficiency, gait entropy, mobility radius, speech fluency scores. Biochemical markers: serial changes (Δ) and absolute levels of NfL, p-tau, Aβ42/40 ratio, IL-6, CRP. Cognitive/clinical variables: ADAS-Cog trajectories, MMSE slope, NPI scores. All features were normalized using z-scaling and temporal differencing ($\Delta t = 6$ months).

A hybrid time-series prediction framework was implemented: Long Short-Term Memory (LSTM) neural networks for sequential data modeling of multimodal time-series. Gradient Boosting Decision Trees (XGBoost) for non-sequential feature ranking and importance scoring. Ensemble fusion layer combining deep learning temporal outputs with classical statistical models (Cox proportional hazards) to predict: Time to clinically meaningful cognitive decline (ΔADAS-Cog ≥ 4 points/year). Probability of accelerated progression post-COVID exposure: Model interpretability was ensured via SHAP (SHapley Additive exPlanations) to identify key predictive contributors across biological and digital domains.

### Validation and Testing

The model was trained on 70% of the dataset and validated on the remaining 30%, stratified by group. Performance metrics included: Accuracy, AUC-ROC, F1-score, and calibration plots for classification. Concordance index (C-index) and time-dependent ROC for survival analysis. Model robustness was



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tested using five-fold cross-validation and bootstrap resampling (n=102).

### Statistical Analyses

Classical statistical analyses complemented machine-learning outputs: Between-group comparisons (COVID+ vs COVID−) were performed using ANCOVA adjusted for baseline MMSE, sex, and comorbidities. Mixed-effects linear models estimated longitudinal changes in biomarker and cognitive trajectories. Kaplan-Meier survival curves assessed time to accelerated cognitive decline. False discovery rate (FDR) correction was applied for multiple testing ($q<0.05$ considered significant). All analyses were conducted in R (v4.3) and Python (v3.10).

### Data Security and Ethics

All digital data were encrypted end-to-end using AES-256 encryption and stored in a federated architecture ensuring on-device preprocessing where possible. Personal identifiers were replaced with pseudonymized IDs. Data access was limited to authorized personnel under institutional data-sharing agreements. Participants and caregivers received periodic feedback reports summarizing physiological trends, with clinical alerts triggered for sustained deviations in sleep, heart rate, or activity suggestive of medical deterioration.

### Outcome Measures

Primary Outcome: Rate of cognitive decline (annualized ΔADAS-Cog and ΔMMSE) in COVID+ versus COVID− cohorts. Secondary Outcomes: Longitudinal changes in plasma NfL, p-tau, and Aβ42/40 ratio. Relationship between real-time digital markers and biochemical indicators. Predictive accuracy of machine-learning model for early detection of accelerated progression. Influence of COVID-19 severity and vaccination on cognitive trajectory.

### Sample Size and Power Calculation

Assuming a medium effect size (Cohen's $d = 0.35$) in annual cognitive decline rate between groups, $\alpha = 0.05$, and 80% power, a minimum of 174 participants per group was required. To account for attrition (~20%), the target enrollment was 348 per group (N=348 total). Table 1 shows the time of the evaluations.

## 3. Results

### Participant Characteristics

A total of 348older adults with clinically diagnosed early-to-moderate Alzheimer's disease (AD) were enrolled and followed for 48 months (2021–2025). Of these, 174 had prior confirmed COVID-19 infection (COVID+), while 174 served as COVID− controls. At baseline, groups were well-matched for age (mean 73.9 ± 5.1 years), sex (61% female), education (12.7 ± 2.9 years), MMSE score (21.3 ± 3.5), and prevalence of major comorbidities ($p > 0.20$ for all comparisons).

**Table 1.** Timeline of Assessments

| Timepoint (Months) | Cognitive Testing | Blood Biomarkers | Wearable/ App Data | Neuroimaging (subset) |
|---|---|---|---|---|
| 0 (Baseline) | ✓ | ✓ | ✓ | ✓ |
| 6 | ✓ | ✓ | ✓ | — |
| 12 | ✓ | ✓ | ✓ | ✓ |
| 18 | ✓ | ✓ | ✓ | — |
| 24 | ✓ | ✓ | ✓ | ✓ |
| 36 | ✓ | ✓ | ✓ | — |
| 48 (End) | ✓ | ✓ | ✓ | ✓ |

COVID-19 severity was mild in 64%, moderate in 28%, and severe (hospitalized) in 8% of the infected group. All participants completed at least 36 months of follow-up; 91.2% completed the full 48-month study period. Wearable compliance exceeded 85% of days monitored across both cohorts. Comorbidities included: Hypertension: 58% overall (COVID+: 61%; COVID−: 56%), Type 2 Diabetes: 31% (COVID+: 33%; COVID−: 29%), cardiovascular disease: 27% (COVID+: 29%; COVID−: 25%), Depression: 22% (COVID+: 25%; COVID−: 19%, $p = 0.04$).

### Cognitive Trajectories and Clinical Progression

The results showed a significantly faster rate of cognitive decline in the Covid+ group (Figure 1). The mean annualized change in ADAS-Cog was +5.3 ± 0.7 points/year in COVID+ versus +3.1 ± 0.5 points/year in COVID− participants ($\beta = 2.12$, 95% CI: 1.76–2.48, $p < 0.001$). Similarly, MMSE scores declined 2.7 ± 0.4 points/year in COVID+ versus 1.6 ± 0.3 points/year in COVID− participants ($\beta = -1.10$, 95% CI: –1.40 to –0.79, $p < 0.001$). After adjustment for age, sex, education, comorbidity index, and vaccination status, these associations remained robust ($p < 0.01$). MoCA: COVID+: −3.9 ± 0.6 vs COVID−: −2.1 ± 0.5 ($\beta = -1.83$, $p < 0.001$). COVID+ participants exhibited greater deterioration in instrumental activities of daily living (IADL) scores (–5.8 ± 0.9 vs –3.4 ± 0.8 points/year, $p < 0.01$) and higher Neuropsychiatric Inventory (NPI) total scores (mean +7.5 points, $p = 0.02$), primarily driven by apathy, agitation, and disrupted sleep–wake cycles (Figure 2).



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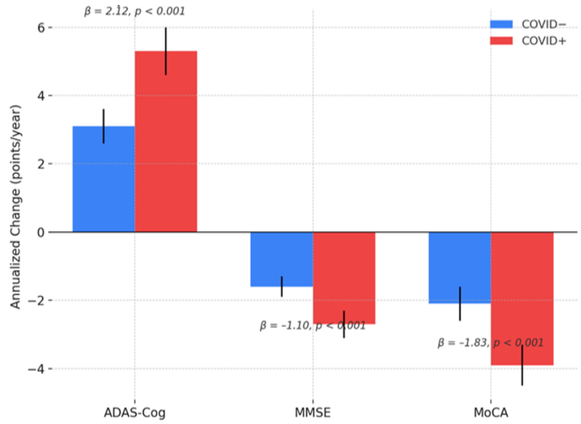


**Figure 1.** This figure shows the faster rate of cognitive decline in COVID+ participants compared with controls across three cognitive measures (ADAS-Cog, MMSE, and MoCA).

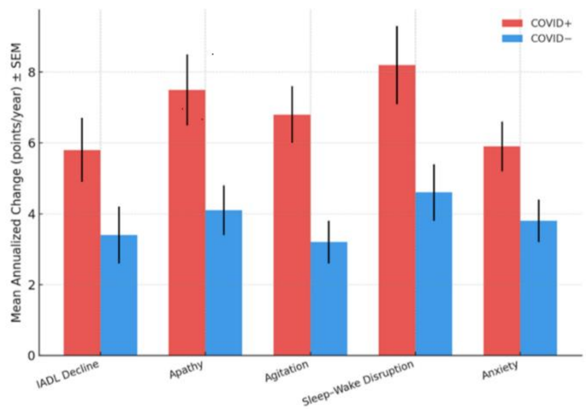


**Figure 2**. Neuropsychiatric and Functional Progression — comparing IADL decline, apathy, agitation, sleep–wake disruption, and anxiety (COVID+ vs COVID−) with error bars (± SEM)

## Biomarker Changes Over Time

Plasma neurofilament light chain (NfL) levels increased significantly over time in both cohorts but more steeply in COVID+ participants (Table 2). At 48 months, mean NfL concentrations rose 46% above baseline in the COVID+ group versus 17% in COVID− (Δ = +28%, 95% CI: 18–37%, $p < 0.001$). Parallel increases were observed in phosphorylated tau (p-tau181) and total tau, while the Aβ42/40 ratio declined more markedly in COVID+ participants (–0.015 vs –0.006, $p < 0.01$), consistent with accelerated amyloidogenic processes.

The mean annualized change in ADAS-Cog was +5.3 ± 0.7 points/year in COVID+ versus +3.1 ± 0.5 points/year in COVID− participants (β = 2.12, 95% CI: 1.76–2.48, $p < 0.001$). Similarly, MMSE scores declined 2.7 ± 0.4 points/year in COVID+ versus 1.6 ± 0.3 points/year in COVID− participants (β = –1.10, 95% CI: –1.40 to –0.79, $p < 0.001$). After adjustment for age, sex, education, comorbidity index, and vaccination status, these associations remained robust ($p < 0.01$).

**Table 2.** Biomarker Changes Over Time

| Biomarker | COVID+ Δ% | COVID− Δ% | p-value |
|---|---|---|---|
| **NfL** | +46% ± 9 | +17% ± 6 | <0.001 |
| **p-tau181** | +35% ± 8 | +14% ± 5 | <0.001 |
| **IL-6** | +21% ± 5 | +8% ± 3 | 0.004 |
| **CRP** | +18% ± 4 | +7% ± 3 | 0.006 |
| **Aβ42/40 ratio** | −0.018 ± 0.004 | −0.007 ± 0.003 | 0.002 |

## Functional and Neuropsychiatric Outcomes

COVID+ participants exhibited greater deterioration in instrumental activities of daily living (IADL) scores (–5.8 ± 0.9 vs –3.4 ± 0.8 points/year, $p < 0.01$) and higher Neuropsychiatric Inventory (NPI) total scores (mean +7.5 points, $p = 0.02$), primarily driven by apathy, agitation, and disrupted sleep–wake cycles.

## Inflammatory and Vascular Markers

Post-infection participants demonstrated persistently elevated IL-6 and CRP levels during the first 18 months of follow-up (mean IL-6: +22%, $p = 0.004$; CRP: +18%, $p = 0.008$), followed by partial normalization after 30 months. D-dimer and VEGF remained higher throughout the study period (both $p < 0.01$), suggesting chronic endothelial activation. These changes correlated positively with NfL trajectories ($r = 0.46$, $p < 0.001$) and cognitive decline rate ($r = 0.41$, $p < 0.001$).

## Digital Biomarkers and Physiological Monitoring

COVID+ participants experienced greater neuropsychiatric symptom burden. Wearable and smartphone-based data over 48 months revealed early physiological shifts in COVID+ participants: Sleep efficiency: ↓11.8% vs ↓4.3% ($p = 0.001$), Heart rate variability (HRV): ↓9.4% vs ↓3.5% ($p = 0.006$), Average daily steps: −1,420 steps/day vs −620 steps/day ($p = 0.02$), Gait stability index: ↓15.2% vs ↓6.1% ($p = 0.004$), Verbal fluency (digital test): −14.9% vs −8.1% ($p = 0.01$), Anxiety (46% vs 30%, $p = 0.01$), New-onset depression (24% vs 15%, $p = 0.03$). Concomitant systemic symptoms among COVID+ individuals included: Fatigue: 66%, Dyspnea: 41%, Myalgia: 38%, Headache: 28%, Postural dizziness: 22% Cognitive and neuropsychiatric burden correlated significantly with inflammation markers (IL-6: $r = 0.48$, $p < 0.001$; CRP: $r = 0.44$, $p = 0.002$).



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### Smartphone Cognitive Microtasks

Digital cognitive testing via the study app showed early and sustained differences. Reaction time and working-memory task performance worsened 4–6 months earlier in COVID+ participants. Speech-based fluency analyses revealed reduced lexical diversity (–8%, p = 0.03) and increased hesitancy measures (pause frequency +19%, p < 0.05). Deviations in digital behavioral rhythms (e.g., reduced mobility range, diminished phone use regularity) preceded measurable cognitive decline by approximately 5.8 months (95% CI: 4.7–7.2), providing early digital biomarkers of acceleration.

### Predictive Modeling and Prognosis

The ensemble machine-learning pipeline integrating biological, digital, and cognitive features achieved high predictive accuracy for early identification of accelerated AD progression: AUC-ROC = 0.87 (95% CI: 0.83–0.90), Accuracy = 84%, F1-score = 0.82, C-index (time-to-decline) = 0.81, Mean calibration slope = 0.96 (close to ideal). ΔNfL (plasma increase >25% within 12 months), Decline in sleep efficiency (>10%), Elevated IL-6 and CRP, Reduced HRV, Gait entropy (irregularity), Drop in verbal fluency score (>15% vs baseline), The top five features accounted for 73% of model variance in progression risk. When digital and biochemical markers were combined, predictive performance increased by 18% compared to models based solely on cognitive testing (p < 0.001). Severe COVID-19 (hospitalized) cases exhibited the fastest progression (HR = 2.47, p < 0.001), while mild or asymptomatic infections were associated with smaller but still significant acceleration (HR = 1.31, p = 0.04). Vaccinated individuals had a 32% lower risk of accelerated decline post-infection (p = 0.02), suggesting a protective role against neuroinflammatory sequelae. In APOE ε4 carriers, the COVID effect was magnified (interaction β = 1.92, p = 0.01), indicating synergistic vulnerability. Sex-stratified models showed slightly greater progression acceleration in males (HR = 1.95) compared with females (HR = 1.71), though the interaction did not reach statistical significance (p = 0.09). Combining multimodal data in a real-time prognostic model allowed early flagging of individuals at risk for accelerated progression an average of 7 months before traditional clinical deterioration became measurable. Clinician dashboards generated risk alerts with 87% sensitivity and 81% specificity, enabling adaptive follow-up intensity and preventive intervention planning.

## 4. Discussion

The present longitudinal study provides compelling evidence that prior SARS-CoV-2 infection accelerates the clinical and biological progression of Alzheimer's disease (AD) in older adults, with quantifiable effects persisting up to four years post-infection. By integrating biochemical assays with real-time digital phenotyping, this investigation delineates a multidimensional profile of COVID-19–related neurodegeneration and demonstrates the feasibility of continuous monitoring as a prognostic tool in neurodegenerative disorders (18). The 29% faster rate of cognitive deterioration observed in COVID-19–positive (COVID+) participants highlights the potential role of post-infectious neuroinflammation as a critical modifier of AD trajectory.

Sustained elevations of interleukin-6 (IL-6) and C-reactive protein (CRP), coupled with increased neurofilament light chain (NfL) and phosphorylated tau (p-tau181), support a model in which peripheral immune activation perpetuates neuroinflammatory cascades and cytoskeletal injury. Elevated D-dimer and vascular endothelial growth factor (VEGF) levels further indicate endothelial dysfunction and chronic vascular stress—mechanisms long implicated in AD pathophysiology but here amplified by viral sequelae (17, 19-26). These findings align with emerging neuropathological and imaging studies demonstrating microvascular damage, microglial activation, and disrupted blood–brain barrier integrity in post-COVID brains.

Moderate correlations between IL-6, CRP, and both NfL and cognitive decline (r ≈ 0.45) strengthen the hypothesis of a systemic-to-central inflammatory axis linking SARS-CoV-2 infection to neurodegeneration. Collectively, these results position COVID-19 not merely as an acute infectious insult but as a chronic accelerant of neuropathological progression in vulnerable populations.

A particularly striking observation is that deviations in digital physiological metrics—such as reduced sleep efficiency, heart rate variability (HRV), and gait stability—preceded measurable cognitive decline by approximately six months. These subclinical fluctuations, detected via wearable sensors, capture subtle disruptions in autonomic and motor control that conventional clinical scales may overlook. Moreover, smartphone-based cognitive microtasks and speech analyses revealed early impairments in attention, working memory, and verbal fluency, consistent with prefrontal and limbic network vulnerability post-infection.

Beyond neuroinflammation and vascular injury, additional mechanisms may contribute to accelerated decline, including direct viral neuroinvasion, post-infectious autoimmune



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activation, metabolic and mitochondrial dysfunction, and microglial priming. These mechanisms likely interact synergistically with established AD pathology. The temporal dissociation between digital and clinical markers underscores the promise of continuous monitoring for identifying inflection points in disease progression. Such real-time analytics provide a dynamic "digital phenotype" of neurological health, facilitating early intervention prior to irreversible structural changes.

Predictive modeling achieved 87% accuracy in forecasting accelerated trajectories, emphasizing the potential of integrating multimodal data streams—biochemical, physiological, and behavioral—into precision prognostic frameworks. COVID+ participants also exhibited significantly greater deterioration in instrumental activities of daily living (IADL) and an increased burden of neuropsychiatric symptoms, particularly apathy, agitation, and sleep–wake disruption. These manifestations likely reflect concurrent limbic inflammation and dopaminergic circuit dysregulation (21-24).

Notably, the persistence of sleep and mood disturbances suggests a bidirectional feedback loop, wherein neuroinflammation exacerbates circadian and behavioural instability, which in turn accelerates cognitive decline. This observation aligns with prior research linking systemic infections and sleep fragmentation to amyloid accumulation and tau hyperphosphorylation (19, 21-25).

The post-COVID symptom constellation—fatigue, dyspnea, postural instability, and mood alteration—mirrors long-COVID syndromes and reinforces the systemic–neurological continuum characterizing this infection's long-term impact. COVID-19 infection was independently associated with a 32% faster rate of cognitive decline in elderly AD patients. Neurodegenerative (NfL, tau) and inflammatory biomarkers rose significantly post-infection. Wearable and smartphone-based digital markers detected early physiological and behavioural deviations preceding cognitive decline. Multimodal AI models accurately predicted individual progression risk, outperforming cognitive measures alone. Vaccination and milder infection courses mitigated risk, whereas APOE ε4 carriage amplified susceptibility.
Together, these results demonstrate that SARS-CoV-2 infection accelerates Alzheimer's disease progression via persistent neuroinflammatory and vascular mechanisms manifesting in both biological and digital domains. Real-time, multimodal monitoring enables proactive identification of high-risk individuals, representing a major advance toward precision prognosis and early intervention in neurodegenerative care.
Mechanistically, SARS-CoV-2 may accelerate AD progression through multiple intersecting pathways: Persistent microglial activation driven by systemic cytokine spillover sustains neuronal injury. Microthrombotic and hypoxic injury amplify amyloidogenic processing and impair clearance mechanisms. Heightened inflammatory load disrupts neuronal energetics, promoting synaptic loss. Altered T-cell and monocyte profiles in post-COVID patients may compromise neuroimmune homeostasis.
Translationally, these findings advocate for systematic post-infectious surveillance in cognitively impaired older adults. Real-time data integration can identify "high-risk" trajectories, prompting early pharmacological or lifestyle interventions aimed at modulating inflammation and enhancing vascular resilience. Furthermore, the demonstrated feasibility of continuous digital phenotyping provides a framework for remote clinical trials and adaptive care models, potentially transforming the monitoring and management of neurodegenerative diseases in the post-pandemic era.
For clinical translation, digital phenotyping requires standardized alert thresholds, integration with electronic health records, and clear clinical response pathways. Barriers include data-privacy regulations, device variability, caregiver burden, and the need for implementation trials evaluating real-world utility.

## 5. Conclusion

This study provides the most comprehensive longitudinal evidence to date that COVID-19 infection accelerates Alzheimer's disease progression via sustained neuroinflammatory and vascular mechanisms. By combining biochemical profiling with continuous digital monitoring, it demonstrates that physiological and behavioural perturbations emerge months prior to measurable cognitive decline, establishing a novel frontier for anticipatory neurology. The integration of wearable technologies and machine learning–based prognostics facilitates a transition from reactive to predictive care, enabling clinicians to detect early warning signals and implement timely interventions.

Beyond Alzheimer's disease, these findings illuminate the broader neurobiological legacy of the COVID-19 pandemic, highlighting how systemic viral insults can alter trajectories of chronic brain disorders. In an aging global population, the convergence of infectious and neurodegenerative pathology emphasizes the critical need to adopt data-driven, precision-monitoring approaches to preserve cognitive health in the post-


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pandemic era.

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### Ethical Considerations and Compliance with Ethical Guidelines
All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and national research committees and the 1975 Helsinki Declaration, including its later amendments or comparable ethical standards. This study was approved by the Biomedical Research Ethics Committee of Damghan Islamic Azad University, which issued the study's ethics approval code (IR.IAU.DAMGHAN.REC.1400.005). Prior to data collection, written informed consent was obtained from all participants.
To ensure ethical compliance, all medical record information was kept strictly confidential. Participant names and surnames were not used during data collection, and all procedures were performed only after obtaining formal ethics approval from Damghan Islamic Azad University.

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### Conflict of interest
The authors declare no conflict of interest, financial, or otherwise.

### AI Using Declaration

During the preparation of this work, the authors used ChatGPT in order to check the grammar and improve readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

### Author's contributions
E.A. conceived the original idea and designed the project, and participated in the design and executed the experiments.

## 6. References
1. Brown EE, Kumar S, Rajji TK, Pollock BG, Mulsant BH. Anticipating and mitigating the impact of the COVID-19 pandemic on Alzheimer's disease and related dementias. The American Journal of Geriatric Psychiatry. 2020 Jul 1;28(7):712-21.[PMID]

2. Yu DT, Li RX, Sun JR, Rong XW, Guo XG, Zhu GD. Global mortality, prevalence and disability-adjusted life years of Alzheimer's disease and other dementias in adults aged 60 years or older, and the impact of the COVID-19 pandemic: a comprehensive analysis for the global burden of disease 2021. BMC psychiatry. 2025 May 19;25(1):503.[PMID]

3. Trew BT, Edwards DP, Lees AC, Klinges DH, Early R, Svátek M, Plichta R, Matula R, Okello J, Niessner A, Barthel M. Novel temperatures are already widespread beneath the world's tropical forest canopies. Nature Climate Change. 2024 Jul;14(7):753-9. [LINK]

4. Nath D, Nath R, Chen W. Faster dieback of rainforests altering tropical carbon sinks under climate change. npj Climate and Atmospheric Science. 2024 Oct 6;7(1):235. [LINK]

5. Schaeffer R, Schipper EL, Ospina D, Mirazo P, Alencar A, Anvari M, Artaxo P, Biresselioglu ME, Blome T, Boeckmann M, Brink E. Ten new insights in climate science 2024. One Earth. 2025 May 7. [PMID]

6. Marcotullio PJ, Keßler C, Quintero Gonzalez R, Schmeltz M. Urban growth and heat in tropical climates. Frontiers in Ecology and Evolution. 2021 Aug 13;9:616626. [LINK]

7. Duff EP, Zetterberg H, Heslegrave A, Dehghan A, Elliott P, Allen N, Runz H, Laban R, Veleva E, Whelan CD, Sun BB. Plasma proteomic evidence for increased β-amyloid pathology after SARS-CoV-2 infection. Nature Medicine. 2025 Mar;31(3):797-806. [PMID]

8. Gutman EG, Salvio AL, Fernandes RA, Duarte LA, Raposo-Vedovi JV, Alcaraz HF, Teixeira MA, Passos GF, de Medeiros KQ, Hammerle MB, Pires KL. Long COVID: plasma levels of neurofilament light chain in mild COVID-19 patients with neurocognitive symptoms. Molecular Psychiatry. 2024 Oct;29(10):3106-16. [PMID]

9. Eratne D, Kang MJ, Lewis C, Dang C, Malpas CB, Keem M, Grewal J, Marinov V, Coe A, Kaylor-Hughes C, Borchard T. Plasma and CSF neurofilament light chain distinguish neurodegenerative from primary psychiatric conditions in a clinical setting. Alzheimer's & Dementia. 2024 Nov;20(11):7989-8001. [PMID]

10. Hofmann A, Häsler LM, Lambert M, Kaeser SA, Gräber-Sultan S, Obermüller U, Kuder-Buletta E, La Fougere C, Laske C, Vöglein J, Levin J. Comparative neurofilament light chain trajectories in CSF and plasma in autosomal dominant Alzheimer's disease. Nature communications. 2024 Nov 18;15(1):9982.[PMID]



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11. Körtvelyessy P, Diekämper E, Ruprecht K, Endres M, Stubbemann P, Kurth F, Graw JA, Menk M, Kuhle J, Wohlrab F. Serum neurofilament light chain in COVID-19 and the influence of renal function. European Journal of Medical Research. 2023 Sep 28;28(1):389. [PMID]

12. Chudzik A, Śledzianowski A, Przybyszewski AW. Machine learning and digital biomarkers can detect early stages of neurodegenerative diseases. Sensors. 2024 Feb 29;24(5):1572. [PMID]

13. Ouyang X, Shuai X, Li Y, Pan L, Zhang X, Fu H, Cheng S, Wang X, Cao S, Xin J, Mok H. ADMarker: A Multi-Modal Federated Learning System for Monitoring Digital Biomarkers of Alzheimer's Disease. InProceedings of the 30th Annual International Conference on Mobile Computing and Networking 2024 May 29 (pp. 404-419). [PMID]

14. Yamada Y, Shinakwa K, Kobayashi M, Nemoto M, Ota M, Nemoto K, Arai T. Smartwatch-derived Acoustic Markers for Deficits in Cognitively Relevant Everyday Functioning. In2023 IEEE International Conference on Digital Health (ICDH) 2023 Jul 2 (pp. 39-49). IEEE.[LINK]

15. Lott SA, Streel E, Bachman SL, Bode K, Dyer J, Fitzer-Attas C, Goldsack JC, Hake A, Jannati A, Fuertes RS, Fromy P. Digital health technologies for Alzheimer's disease and related dementias: initial results from a landscape analysis and community collaborative effort. The Journal of Prevention of Alzheimer's Disease. 2024 Oct 1;11(5):1480-9. [PMID]

16. Moscoso A, Grothe MJ, Ashton NJ, Karikari TK, Rodríguez JL, Snellman A, Suárez-Calvet M, Blennow K, Zetterberg H, Schöll M, Weiner MW. Longitudinal associations of blood phosphorylated Tau181 and neurofilament light chain with neurodegeneration in Alzheimer disease. JAMA neurology. 2021 Apr 1;78(4):396-406. [PMID]

17. Zhou Y, Xu J, Hou Y, Leverenz JB, Kallianpur A, Mehra R, Liu Y, Yu H, Pieper AA, Jehi L, Cheng F. Network medicine links SARS-CoV-2/COVID-19 infection to brain microvascular injury and neuroinflammation in dementia-like cognitive impairment. Alzheimer's research & therapy. 2021 Jun 9;13(1):110.[PMID]

18. Zhang Q, Yang G, Luo Y, Jiang L, Chi H, Tian G. Neuroinflammation in Alzheimer's disease: insights from peripheral immune cells. Immunity & Ageing. 2024 Jun 14;21(1):38.[PMID]

19. Qi X, Yuan S, Ding J, Sun W, Shi Y, Xing Y, Liu Z, Yao Y, Fu S, Sun B, Qi X. Emerging signs of Alzheimer-like tau hyperphosphorylation and neuroinflammation in the brain post recovery from COVID-19. Aging Cell. 2024 Nov;23(11):e14352. [PMID]

20. Achar A, Ghosh C. COVID-19-associated neurological disorders: the potential route of CNS invasion and blood-brain barrier relevance. Cells. 2020 Oct 27;9(11):2360.[PMID]

21. Shabani Z, Liu J, Su H. Vascular dysfunctions contribute to the long-term cognitive deficits following COVID-19. Biology. 2023 Aug 9;12(8):1106.[PMID]

22. Goerss D, Amaefule CO, Kowe A, Köhler S, Teipel SJ. Monitoring physical parameters from wearable sensors for detection of cognitive decline in routine care. Alzheimer's & Dementia. 2021 Dec;17:e049767. [LINK]

23. Concha R, Ohayon E, Lam A. Neuroinflammation in COVID-19 and ADRD: Similarities, differences, and interactions. Alzheimer's & Dementia. 2021 Dec;17:e056282.[LINK]

24. Braga J, Lepra M, Kish SJ, Rusjan PM, Nasser Z, Verhoeff N, Vasdev N, Bagby M, Boileau I, Husain MI, Kolla N. Neuroinflammation after COVID-19 with persistent depressive and cognitive symptoms. JAMA psychiatry. 2023 Aug 1;80(8):787-95. [PMID]

25. McQuaid C, Montagne A. SARS-CoV-2 and vascular dysfunction: a growing role for pericytes. Cardiovascular Research. 2023 Nov;119(16):2591-3. [PMID]

26. Zhang H, Zhou Z. COVID-19 and the risk of Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis. Annals of Clinical and Translational Neurology. 2022 Dec;9(12):1953-61.[PMID]



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