Alzheimer's disease research progress in the Mediterranean region

Sexton, Claire; Solis, Michele; Aharon-peretz, Judith; Alexopoulos, Panagiotis; Apostolova, Liana G.; Bayen, Eléonore; Birkenhager, Betty; Cappa, Stefano; Constantinidou, Fofi; Fortea, Juan; Gerritsen, Debby L.; Hassanin, Hany I.; Ibanez, Agustin; Ioannidis, Panagiotis; Karageorgiou, Elissaios; Korczyn, Amos; Leroi, Iracema; Lichtwarck, Bjorn; Logroscino, Giancarlo; Lynch, Chris

DOI:
10.1002/alz.12588

Received: 30 August 2021 | Revised: 14 December 2021 | Accepted: 16 December 2021

DOI: 10.1002/alz.12588

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

Alzheimer's disease research progress in the Mediterranean region: The Alzheimer's Association International Conference Satellite Symposium

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Abstract

As research and services in the Mediterranean region continue to increase, so do opportunities for global collaboration. To support such collaborations, the Alzheimer's Association was due to hold its seventh Alzheimer's Association International Conference Satellite Symposium in Athens, Greece in 2021. Due to the COVID-19 pandemic, the meeting was held virtually, which enabled attendees from around the world to hear about research efforts in Greece and the surrounding Mediterranean countries. Research updates spanned understanding the biology of, treatments for, and care of people with Alzheimer's disease (AD_ and other dementias. Researchers in the Mediterranean region have outlined the local epidemiology of AD and dementia, and have identified regional populations that may expedite genetic studies. Development of biomarkers is expected to aid early and accurate diagnosis. Numerous efforts have been made to develop culturally specific interventions to both reduce risk of dementia, and to improve quality of life for people living with dementia.

KEYWORDS
Alzheimer's disease, biomarkers, care, dementia, genetics, prevention

1 | INTRODUCTION

To find effective treatments for Alzheimer's disease (AD) and other dementias, research must be conducted globally. Different populations experience diverse social determinants of health, and environmental and genetic risk factors, which makes it essential to understand the local epidemiology in different parts of the world, and to promote regional research efforts. Since 2015, the Alzheimer's Association International Conference (AAIC) has hosted Satellite Symposia in different regions around the globe to foster international collaborations

geared toward prevention and treatment of AD and all dementias. For 2021, the AAIC Satellite Symposium was hosted by, but not in, Athens, Greece: the COVID-19 pandemic meant that this meeting was held virtually over 2 days in May, and consisted of speakers from all over the world, with a special focus on the Mediterranean region. The online format allowed many more people to attend the meeting than an in-person version, with >1500 registered attendees from 87 countries.

AD and dementia are relatively common in the Mediterranean region. One estimate finds a prevalence of AD of 6.9% in southern Europe, which includes Spain, Italy, and Greece.[1] In Greece, the prevalence rate for dementia is 5%,[2] and 75% of those cases are AD. Incidence is high, at 19 cases per 1000 person-years.[3] The age- and sex-standardized prevalence of mild cognitive impairment (MCI) in people aged 65 years and older in Greece is 13% according to the HELIAD study (Hellenic Longitudinal Investigation of Aging and Diet).[4] In response to this high prevalence, services for people with dementia and their caregivers are taking root in Greece.

At the Athens symposium, scientists from several Mediterranean countries came together with other leaders in the field to focus on regional research efforts that could benefit all people with AD and dementia within the region and around the world. Presentations included epidemiological studies that suggest lifestyle factors contribute to risk, genetic clues from regional studies and specialized populations, biomarker development, approaches to tailoring interventions to be appropriate for a particular region, and the latest research on how best to care for people living with dementia.

RESEARCH IN CONTEXT

1. **Systematic review**: With increases in Alzheimer's disease (AD) and related dementias projected to rise precipitously in low- and middle-income countries, it is essential to have region-specific research in these countries. With its mix of diverse populations and cultures, the Mediterranean region warrants special attention.
2. **Interpretation**: AD research in the Mediterranean region has a foothold in some countries, and is just getting underway in others. Strengthening and sharing research within the region will help identify new risk factors, as well as develop interventions and care approaches that are tailored to the needs and habits of the different populations there.
3. **Future directions**: Established research programs in Mediterranean countries can foster new research communities in neighboring countries, as well as participation in global collaborations. This network approach to AD research will help reduce health disparities and risk for everyone.

2 | EPIDEMIOLOGY

Robust prevalence and incidence studies have not been carried out for all countries in the Mediterranean; however, extrapolating from known estimates some important benchmarks have been established. AD prevalence is highest in countries along the southern edge of the Mediterranean Sea and in the Middle East, with Turkey as one of the world's hotspots.[5] Within Europe, dementia prevalence is higher in southern Europe than in northern Europe, yet the incidence rate is lower in the south.[1] This suggests better survivorship in the Mediterranean, and a north–south gradient of incidence.[6]

Regional differences in AD prevalence and incidence highlight potential risk factors. Lifestyle might help explain the variability: a Mediterranean diet has been found to protect against AD,[7] and the habit of taking a midday nap might also be a factor.[8] The HELIAD study in Greece also finds that a low level of education increases risk, as does the Great Age study in southern Italy and the Neurocognitive Study for the Aging (NEUROAGE) in Cyprus.[9,10] Several population-based studies from the Mediterranean areas show that there are risk factors for dementia that are linked to the Mediterranean lifestyle, including diet and metabolic risk factors. Such evidence stems from both the United States and the Mediterranean areas.[7,11]

With the advent of biologically based definitions of AD using biomarkers, epidemiology may soon be able to shift from trying to delay onset of clinical disease to finding ways to delay the onset of AD pathology in a population. Early studies in other countries show the feasibility of using low-cost, blood-based biomarkers for AD in a community setting.[12]

3 | GENETICS

3.1 | Regional studies

Studies of regional populations can clarify the roles of suspected genetic contributors to AD risk.[13] For example, work from the Dementia Genetics Spanish Consortium (DEGESCO) has helped establish the tau-encoding *MAPT* gene as a true risk factor for dementia. Studies in this Spanish population further confirmed an association between a rare variant called A152T in the *MAPT* gene and the risk of neurodegenerative diseases,[14] and explored its effect on the phenotype in a family with frontotemporal dementia (FTD) from the Basque Country that cosegregated A152T with a rare *GRN* mutation.[15] In addition, two studies with the same cohort found that the H1 haplotype of *MAPT* confers risk for AD.[14,16] This link was especially strong in people who do not carry the apolipoprotein E (*APOE*) ε4 risk allele. The clear signals from these studies may have been aided by the genetic homogeneity of the Spanish population, plus the high prevalence of the protective H2 haplotype found there.

Genetic studies of FTD emerging from Turkey and Greece add evidence for involvement of some known risk genes, and some new. A screen of 95 people with dementia in Turkey found that 5.4% carried a pathogenic mutation in known FTD risk genes (*MAPT*, *GRN*,

and *C9ORF72*),[17] whereas whole exome sequencing has pointed to *TREM* mutation involvement in an FTD-like syndrome.[18] In Greek cohorts, C9ORF72 expansions are high among those with FTD,[19] and pathogenic mutations in the usual suspects, such as *C9ORF72*, *GRN*, *MAPT*, and *PSEN1*, are also found.[20] In the latter screen, a novel mutation was found in VCP (valosin-containing protein), which has since been replicated in a recent study.[21] VCP can act to disaggregate tau, and the mutation impairs this ability. Also, the finding that the TARDBP p.I383V mutation was found in 3.5% of the Greek FTD population suggests that it is likely pathogenic.[22] An interesting international study comparing cohorts to FTD patients with known mutations, including the Mediterranean area, has also been published recently.[23]

Within a region, studies of ethnic differences in dementia may hold clues because any differences found against a backdrop of shared environment may be ascribed to a narrower range of factors that distinguish ethnicities, such as genetic background, lifestyle, or socioeconomic status. For example, the prevalence of AD among Arabs in Israel is four times higher than for persons from Jewish heritage,[24] and once Arabs seek care at a dementia clinic, their cognitive impairment already affects their functional abilities, more so than for Jews.[25] This finding may reflect ethnic differences in awareness about dementia, attitudes toward dementia, accessibility to clinics, or risk factors at play. Regardless of the uncertainty as to why, the finding provides an important benchmark around which health-care services and interventions may be planned to reduce disparities.

A recent study of an extended Arab family in Israel has revealed a genetic signal related to early-onset AD related to a structural rearrangement involving duplication of the gene encoding amyloid precursor protein (APP). People carrying these duplications develop signs of dementia or intracerebral hemorrhages in their 40s; asymptomatic carriers have microbleeds, and lower scores on some cognitive evaluations.

The above studies suggest that more research on underrepresented populations is required for a better understanding of genetic contribution to AD. Differing frequency of variants, co-gene expression, polygenic risk scores, and gene–environment interactions are part of a research agenda that will benefit from more global and diverse studies. In addition, identification of causative genetic variants in Mediterranean FTD cohorts, including the ones found in the *C9orf72*, *TARDBP*, *GRN*, and *VCP* genes, provides valuable insights in the genetic epidemiology of dementia in the region. Beyond that, each of these genetic variants offers the opportunity to a better understanding of the pathophysiology of FTD and amyotrophic lateral sclerosis, which form part of the same spectrum. These advances could pave the way for targeted treatment approaches soon.

3.2 | Sporadic and genetically determined early-onset AD

Early-onset AD offers an opportunity to find risk factors that may differ from those that operate in later development of AD. Defined as occurring between the ages of 40 and 65, early-onset AD has both genetic forms and sporadic forms.

People with Down syndrome (DS) offer a unique opportunity to study genetically determined cases of early-onset AD. DS = is caused by an extra copy of chromosome 21, which results in overexpression of its genes, including the *APP* gene. An extra *APP* gene is both sufficient (in the general population) and necessary (in DS) to develop early-onset AD dementia. As life expectancy increases for people with DS, this has revealed that >90% of individuals with DS will develop dementia in the seventh decade.[26] The Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) studies this growing population. Neuropsychological tests can isolate cognitive changes associated with early and later stages of AD from the intellectual disability associated with DS.[27] Brain pathology in people with DS also resembles that described in AD,[28] as do changes in diverse biomarkers.[29] A recent study found that plasma levels of the neurofilament light chain (NfL) biomarker in DS had both diagnostic[30] and prognostic use in DS.[31] The prolonged and well-characterized preclinical phase of AD found in people with DS provides an opportunity for prevention and treatment trials, and several consortia have assembled to study this population, and any insights from these studies may well translate to the broader AD population.

Similar to those with DS, people with dominantly inherited genetic forms of AD offer a prolonged look at the years preceding disease onset. Though making up less than 1% of AD cases, these are important leads to AD pathology, as they are caused by single point mutations in genes involved in APP processing, usually to the *PSEN1* gene. Fifteen years ago, the Dominantly Inherited Alzheimer Network (DIAN) was established to create an international network of sites, some in the Mediterranean, to find and systematically study these rare cases. Longitudinal evaluations of enrollees in the DIAN Observational Study have elucidated a stereotyped progression of change that begins with amyloid deposition as early as two decades before disease onset, followed by brain hypometabolism, atrophy, then tau deposition that coincides with disease onset.[32] This study can also incorporate new biomarkers, such as plasma levels of NfL, which they found tracks with symptom onset.[33]

With a clear picture of these biomarker and brain changes afforded by its observational study, DIAN has developed a trial platform (DIAN-TU) to test multiple drugs that can be delivered closer to the time a particular pathology is underway. A recent Phase 2/3 trial of an amyloid beta (Aβ) immunotherapy had a profound effect on disease biomarkers, but not cognition (https://clinicaltrials.gov/ct2/show/NCT01760005).[34]

Of early-onset cases of AD, only 6% are due to autosomal dominant genetic mutations. The remainder, which consists of familial and sporadic cases, has not been systematically studied. To rectify this, the Longitudinal Early-Onset AD Study (LEAD) was launched to characterize early-onset AD, and to establish a network of centers in the United States to provide a cohort ready for intervention studies.[35] Study participants are extensively evaluated for 4 years, and initial results suggest that early-onset AD has a similar frequency of *APOE* ε4 alleles as late-onset ones. Yet, early-onset AD displays more severe brain atrophy and tau deposition than other forms of early-onset dementia.

4 | BIOMARKERS: PROGRESS AND POTENTIAL

Biomarkers can provide a window to changes in the brain prior to the development of cognitive symptoms; they can also assess disease progression. Biomarkers can be obtained from cerebrospinal fluid (CSF) or blood, and include AD-related markers such as Aβ and tau, markers of axonal injury like NfL, and indices of synaptic (neurogranin) or glial (YK140) health.

These diverse biomarkers are biologically interconnected, according to results from the Spanish ALFA+ (Alzheimer's and Families) longitudinal cohort. ALFA has assessed and tracked nearly 3000 middle-aged people who are offspring of people with AD, and so at higher risk of developing AD.[36] A recent multimodal biomarker study performed in a nested group from this cohort finds that multiple CSF biomarkers change very early on, prior to any cognitive impairment and already in participants with low burden of Aβ pathology.[37] Their levels are low compared to levels found in AD, but they are sufficient to discern patterns of change.[37] Changes in Aβ presaged other biomarker changes: once an individual became Aβ positive, as determined in CSF, multiple biomarkers abruptly began to rise, including phosphorylated tau (p-tau), total tau (t-tau), and neurogranin. Some age-dependent changes were sensitive to Aβ status, too: p-tau increased with age only in people who were Aβ positive. These early changes, even before a person has an appreciable Aβ burden, suggest that interventions will need to be very early.

Understanding how biomarkers vary in people with MCI could help discern who will progress to dementia and who will not. It is harder to know which biomarkers give the most information. A recent study built a biomarker-based prognostic model based on data from multiple European and North American cohorts of people with MCI. The study found that CSF biomarkers that indexed amyloid, tau, and neurodegeneration had the best performance in predicting risk.[38]

Electroencephalography (EEG) provides a useful, if overlooked, measure of brain activity that could provide AD biomarkers. Non-invasive and economical, EEG approaches have been explored for a variety of uses, including early diagnosis, differential diagnosis, to predict conversion to AD, and to track disease progression. One method is resting state EEG, which can pick up signals associated with neurodegeneration in MCI and AD.[39] Applying machine learning algorithms to EEG data may help discriminate AD and MCI from cognitively unimpaired individuals.[40] Event-related potentials (ERPs), which measure a brain's response to a stimulus or task, can measure the functioning of the relevant brain networks. Finally, event-related oscillations can be parsed for cognition-specific insights. For example, amnestic MCI is marked by changes to visual cognitive networks, but not visual sensory networks.[41] Multi-feature computational approaches of multimodal EEG signals (ERP, oscillations, source analysis, functional connectivity, spatiotemporal decoding) can be combined with progressive feature elimination to obtain the best multilevel combined predictors of EEG for dementia characterization.

5 | ADDRESSING CHALLENGING BEHAVIORS IN COGNITIVE IMPAIRMENT AND DEMENTIA

As the COVID-19 pandemic disrupted life worldwide, nursing homes faced not only illness, but changed behaviors from their residents. Surveys of nursing home practitioners in the Netherlands noted both increases and decreases in challenging behaviors in their residents,[42] and a second (unpublished) survey suggested that this depended on the resident: those without dementia showed an increase in challenging behaviors, whereas those with psychotic and agitated behavior had decreases. These might be related to the decrease in stimulation during pandemic lockdowns, as Dutch nursing homes went 2 months without visitors. Finding ways to increase tranquility in the nursing home environment—by limiting the presence of suppliers, providing care to residents in their own room, and possibly limiting visits in the living rooms—might have benefits for all residents.

A lack of guidance for managing challenging behavior complicates the care of people with dementia. One intervention called the Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms (TIME) approaches problem behavior with a three-stage plan that involves a full assessment of the person, case conferences in which interdisciplinary staff create a shared understanding of the behavior, and formulation of a treatment plan that is enacted and systematically evaluated. Following this intervention can reduce agitation and aggression, as well as symptoms of depression, delusions, and disinhibition.[43] Important aspects of this intervention include its interdisciplinary nature, flexibility, ease of implementation, and its reliance on staff to problem-solve.[44]

Psychotropic drug use is high in nursing homes, despite frequent side effects and limited usefulness. A review of 11 studies showed that psychosocial interventions could reduce psychotropic drug use in nursing homes. Interventions targeting care staff and aiming to change the culture surrounding medication use were the most successful, but involving the prescribing physician in the intervention was also important.[45] Ultimately, the goal is to achieve drug prescriptions only when truly indicated.

6 | REDUCING RISK: TAILORING INTERVENTIONS FOR REGIONAL POPULATIONS

To maximize the impact of interventions aimed at mitigating risk factors for AD and dementia, it is important to offer practical approaches that fit with the needs and habits of a particular population. There is no shortage of ideas for potential interventions, and researchers in the Mediterranean region are pursuing some that address sensory loss, diet, sleep, physical activity, and education about brain health. For maximum effect, however, each one will have to be tailored to a population, whether in the Mediterranean or beyond. Each risk factor may be independent, and so may have additive benefits. They are also interrelated, in that targeting one can tip off a cascade of benefits in other domains.

For interventions that encourage healthy lifestyles, it is important to identify trusted community leaders who can model behavior, and promote perceptions of what older people can do.

Hearing and vision impairments are highly prevalent in dementia, and together these worsen quality of life, often resulting in less social activity and increased isolation. In Cyprus, the longitudinal NEUROAGE study finds that though about 40% of older participants report hearing problems, only 23% of those have sought hearing correction.[46] Five years later, those who had reported subjective hearing loss performed significantly lower than those without hearing loss. This is in contrast to the longitudinal cohort analyses of NEUROAGE which demonstrated cognitive stability in a 5-year period for the cognitively healthy cohort.[10] To see if sensory interventions might help with quality of life, a multi-national study SENSE-Cog (www.sense-cog.eu), has been recruiting people in Cyprus, Greece, Ireland, France, and the United Kingdom for a definitive pragmatic trial of hearing and vision rehabilitation for people living with dementia at home. A key element of the intervention is the involvement of a sensory support therapist working with the participant and their care partner to foster uptake and adherence of hearing aids and glasses. Preliminary analyses show that this approach is feasible for these populations, and has a positive impact on quality of life.[47]

Many studies have looked for a link between nutrition and dementia, but results have been inconsistent.[48] This may be because many have looked at isolated food groups or nutrients, whereas a whole dietary pattern may be what matters. A hint of this has come from studies of the Mediterranean diet, which is marked by consumption of olive oil, legumes, fruits and vegetables, fish, some dairy, and low amounts of meat. The Mediterranean diet has since been associated with better survival and has been studied in cancer and cardiovascular disease. More recently, it has been associated with protection from dementia. Recent randomized controlled trials and observational epidemiological studies have found beneficial associations between this diet and cognition in the Mediterranean region itself, with one in Spain (PREDIMED),[49] and another in Greece (HELIAD).[7,50]

Sleep disturbances are prevalent in dementia, and include REM sleep behavior disorder, altered sleep–wake rhythms, periodic limb movements, and insomnia. These have been associated with cognitive decline, and in the case of REM sleep behavior disorder, in which a person acts out their dreams, precedes cognitive decline by several years. Associations with cognition, as well as with markers of AD pathology, suggest a bi-directional relationship between sleep and dementia, and that improving sleep might reduce risk of dementia. Studies of continuous positive airway pressure (CPAP) machines to treat sleep apnea show some benefit, including a delay in MCI onset,[51] and a slow wave sleep enhancer called trazodone slowed cognitive decline.[52] An ongoing study in Greece finds that cognitive behavioral therapy approaches to treat insomnia in people with MCI can improve sleep, and cognitive outcomes will be examined in the future.

Epidemiological studies stress the protective role of a physically active lifestyle in preventing dementia[53] and interventional studies indicate a positive effect on neuropsychiatric symptoms.[54] Maintenance of mobility facilitates opportunities for more social interaction and community engagement for older adults contributing to their mental health too.[55] The Retirement in Action (REACT) trial aimed to establish whether a community-based active aging intervention could prevent decline in physical functioning in UK older adults already at increased risk of mobility limitations.[56] The intervention consisted of a multimodal exercise program delivered in 64 group sessions over 12 months, including aerobic exercise, strength training, balance and flexibility exercises, and a health behavioral maintenance program aiming to support the maintenance of lifestyle changes in the long term. Seven hundred seventy-seven people over the age of 65 with mobility limitations (classified as frail or pre-frail) participated in the study.[56,57] The REACT intervention was both effective and cost-effective. The difference in mobility between intervention and control participants was statistically significant and clinically meaningful at 6, 12, and 24 months (that is, 12 months after the completion of the intervention).[57] For older adults at risk of mobility limitations, the REACT intervention prevented decline in physical function over a 24-month period. The results indicate that the well-established trajectory of declining physical functioning in older age is modifiable.

Next steps involve adapting and tailoring the program for implementation in Greece and other European countries, which would build upon the positive effects of a combined cognitive and physical training program that has been tested in Greece.[58]

Many people are not aware there are steps they can take to safeguard their brain health. In France, an educational series called "My Brain Robbie" (https://mybrainrobbie.org/) has been developed to teach school children about neuroprotective factors such as education, physical activity, preventing traumatic brain injury, a healthy diet, and the danger of tobacco, drug, and alcohol use. The program is delivered by medical students, who themselves learned that they could modify their own dementia risk.

7 | CHALLENGES IN DEMENTIA CARE: REGIONAL POLICIES AND INITIATIVES

While treatments are under development, many things can be done now to support people with dementia. There is no one-size-fits-all solution, however; support programs should be tailored to a particular population's needs, habits, infrastructure, and culture. When deployed effectively, they can make a difference for quality of life. Sharing insights about dementia care in different parts of the world can illuminate some of the important ingredients for effective care practice.

Without medications to treat cognitive impairment, non-pharmaceutical interventions have been developed to improve quality of life for those with dementia. In Greece, cognitive stimulation, rehabilitation, and training programs are delivered in day centers.[59] One study found that 3 years of following a cognitive and physical training intervention seemed to reduce the number of people with MCI who progressed to dementia.[60]

New technologies are emerging quickly, and can take on multiple roles; for example, a cognitive training application based on a virtual shopping task not only strengthens memory, planning, and other

cognitive skills, but can also be used to screen for MCI.[61,62] The Virtual Supermarket (VSM) test is multilingual and fully self-administered in its latest iteration.[63] Performance oin the VSM has been shown to correlate with brain activation as measured by a portable EEG device.[64] Studies have validated the diagnostic utility of the Turkish version of the VSM for detecting amnestic MCI[65] and MCI due to small vessel disease.[66] The Arabic version of the VSM is currently being tested in Egypt. At the same time, the first assessment of attitudes of Greek nurses toward computerized dementia screening indicates that nurses are willing to use these tools in their everyday practice and to facilitate their integration in the public health-care system.[67,68] A systematic cognitive rehabilitation program, the Categorization Program (CP), has been found effective in helping older adults without dementia improve cognitive abilities. The program targets thought organization, working memory, and executive functioning and it is based on cognitive theory and neurorehabilitation principles. Preliminary findings with participants with MCI indicate that the program is feasible and results in cognitive improvement. Currently, clinical trials are underway with the CP in Cyprus. A new neuropsychological battery called R4Alz developed in Greece can measure cognition for people of all education levels, and differentiate between subjective cognitive impairment, MCI, dementia, and healthy aging.[69]

In Greece, it is estimated that 5% of people 65 years and older have dementia.[2] This amounts to 200,000 people, and 89% of these are cared for at home. The annual cost of dementia amounts to about 3 billion euros. Until recently there were few dementia services in Greece, but in 2018 Greece began to implement a national action plan for dementia. Today, there are 21 day-care facilities and 31 memory clinics around the country, but a national dementia registry is still lacking, and more coordination between care and services is needed. Funding is the main challenge.

AD advocacy organizations in Greece have also geared their activities toward caregivers, providing training programs, legal and financial advice, counseling, in-home care activities, and a dementia helpline. Furthermore, in Greece, initiatives have been performed to promote "Dementia Friendly Communities" (https://www.actondementia.eu). During the pandemic, the Athens Alzheimer's Association fielded thousands of phone calls, online consultations, and interventions for people with dementia.

Dementia-related design of the built environment commanded attention in last year's World Alzheimer Report (https://www.alzint.org/resource/world-alzheimer-report-2020/).[70] The 2020 Report reviews dementia-related design looking to take research into policy and practice and includes case studies from around the world, and makes several key recommendations, including placing dementia-related design into national dementia plans, recognizing dementia as a disability and the impact that this can have on design and planning, and better educating dementia associations about design and its relevance. Design deserves special attention now, because pandemic-related lockdowns have relegated some dementia care back to institutionalized environments.

As cognition declines, risk of driving accidents increases. Yet, 50% of people continue to drive for at least 3 years after diagnosis. Experiments with a driving simulator (www.nrso.ntua.gr/driverbrain)[71] in Greece found that among older people who still had a driver's license and who drove regularly, those with MCI or AD slowed their driving and left a larger space between themselves and the car ahead. Despite these compensations, these drivers still had slower reaction times and increased accident probability. Nevertheless, self-awareness of driving ability was found to be compromised even in patients with MCI.[72] Distraction is also a factor, with accident probability increasing sharply for people with MCI when a mobile phone is in the simulation.[73] In addition, a greater negative impact of depressive symptoms in driving was found in drivers with MCI than in cognitively healthy older drivers.[74]

With a growing older adult population, Egypt began to develop geriatric medicine services more than 40 years ago,[75] including a new geriatric hospital that opened in 2018, and a new cognitive training lab at Ain Shams University Specialized Hospital, which aims to provide cognitive training interventions.[76] The cognitive training lab protocols were designed in conjunction with a Greek consortium, but adapted for the Arabic population. So far, Arabic versions of standardized cognitive training tools have been developed and validated, and >20 Egyptian professionals have been educated to set up cognitive training services with successful completion of the first feasibility study of cognitive training exercises for Egyptian adults in 2020.[77]

8 | CONCLUSION

Research on the biology, epidemiology, diagnosis, treatment, and care for people with AD and other dementias in the Mediterranean region is growing. The region serves as a nexus of collaboration, with established centers in the Mediterranean working with AD leaders elsewhere in the world and fostering the nascent programs in the region. These collaborations will be essential for understanding the complex etiology of AD in the region, for meeting the increased need for dementia care there, and for tailoring interventions to the region's diverse and culturally rich populations within the Mediterranean. Insights about AD made in this unique place may well translate worldwide.

ACKNOWLEDGMENTS

We thank Danny Frenkel, Eric McDade, Paraskevi Sakka, and Bruce Miller for their contributions to the AAIC Satellite Symposium and the manuscript and acknowledge all the presenters at the conference. We also thank Joanna Graca for her assistance with the preparation of the manuscript.

CONFLICTS OF INTEREST

Claire Sexton is a full-time employee of the Alzheimer's Association and, in the past 36 months, reports consultation fees from Jazz Pharmaceuticals and support for attending meetings and/or travel to the AAIC Satellite Symposium Sydney (2019) and Society for the Study of Ingestive Behavior (SSIB) Annual Meeting (2019). CES also reports an unpaid role as a trustee of Dementia Adventure (2018–2020). Michelle Solis is a freelance science writer and, in the past 36 months, reports contracts from Lieber Institute for Brain Development, Simons

Foundation Autism Research Initiative, Scientific American, American Chemical Society, Pharmaceutical Journal, Allen Institute for Brain Science; payment or honoraria for articles or reports written for Lieber Institute for Brain Development, Simons Foundation Autism Research Initiative, Scientific American, American Chemical Society, Pharmaceutical Journal, Allen Institute for Brain Science. Judith Aharon-Peretz, in the past 36 months, reports consultation fees from Medison. Panagiotis Alexopoulos, in the past 36 months, reports payment or honoraria and support for attending meetings and/or travel from Vianex Pharmaceutical company. Liana G Apostolova, in the past 36 months, reports grants or contracts from NIH, Alzheimer Association, AVID Pharmaceuticals, Life Molecular Imaging, Roche Diagnostics; received consulting fees from Biogen, Two Labs, IQVIA, NIH, Florida Dept. Health, NIH Biobank, Eli Lilly; received payment or honoraria from AAN, MillerMed, ASiM, Health and Hospitality Corporation, Mayo Clinic; received support for attending meetings and/or travel from Alzheimer's Association; participated on a DSMB or Advisory Board for IQVIA, NIA R01 AG061111, UAB Nathan Schock Center; held stock or stock options in Semiring Inc., Cassava Inc; received equipment, materials, drugs, medical writing, gifts, or other services from AVID Pharmaceuticals, Life Molecular Imaging, Roche Diagnostics. Eléonore Bayen, in the past 36 months, reports grants or contracts from Covid Solidarity Grant, Atlantic Institute; reports participation on the Advisory Board of SafelyYou company (https://www.safely-you.com/). Betty Birkenhager has nothing to disclose. Stefanno Cappa, in the past 36 months, reports grants or contracts from the Italian Ministry of Health (Ricerca Corrente, Neuroscience and Neurorehabilitation Network); and received speaker fees from Biogen, Roche, Nutricia. Fofi Constantinidou is a salaried employee, University of Cyprus and, in the past 36 months, reports grants or contracts from Cyprus Research Innovation Foundation (Excellence/1218/0117, Excellence/1216/0411, Excellence/1216/0404, Post-Doc/0916/0257); EU, H2020-PHC-2015 (#668648). FC also reports payment or honoraria from Iberoamerican Congress, Invited Presentation (2021); Korean Rehabilitation Research Symposium (2021); participated on a DSMB or Advisory Board for the Sense-Cog project; and held a leadership or fiduciary role for ACRM, ESLA, Cyprus Association of Registered SLPs. Juan Fortea, in the past 36 months, reports grants or contracts from Fondo de Investigaciones Sanitario (FIS), Instituto de Salud Carlos III (PI14/01126, PI17/01019); National Institutes of Health (NIA grants 1R01AG056850 - 01A1; R21AG056974 and R01AG061566); Fundació La Marató de TV3 (grant 20141210); Generalitat de Catalunya (grant SLT006/17/00119); Fundació Catalana Síndrome de Down and Fundació Víctor Grífols i Lucas partially supported this work, all paid to his institution. JF served as a consultant for Novartis and Lundbeck; received honoraria for lectures from Roche, NovoNordisk, Esteve, and Biogen, payments made to him. JF has a patent WO2019175379 A1 Markers of synaptopathy in neurodegenerative disease issued; JF also served on advisory boards for AC Immune, Zambon, and Lundbeck; held a leadership or fiduciary role for Spanish Neurological Society, T21 Research Society, Lumind foundation, Jérôme-Lejeune Foundation, Alzheimer's Association with no payments, and from National Institutes of Health, with payments for the participation in Study Sections. JF reports his institution received support from AC Immune to acquire Quanterix NfL Kits. Debby L. Gerritsen, in the past 36 months, reports grants or contracts from The Netherlands Organization for Health Research and Development and the Dutch Alzheimer Society; received payment or honoraria for training a group of geropsychologists about depression in long term care; received support for attending meetings and/or travel for presenting at the Krems Dementia Conference in 2019 and the Alzheimer Europe Conference in 2019; held a leadership or fiduciary role for Dutch committee on acknowledging quality of interventions in long term care. Hany I. Hassanin, in the past 36 months, reports travel support from the Atlantic Institute to attend the Atlantic senior Fellow ceremony in Oxford, UK, July 2019. Agustin Ibanez, in the past 36 months, reports partial support by grants from CONICET; ANID/FONDECYT Regular (1210176, 1210195); FONCYT-PICT 2017-1820; ANID/FONDAP/15150012; Takeda CW2680521; Sistema General de Regalías (BPIN2018000100059), Universidad del Valle (CI 5316); Alzheimer's Association GBHI ALZ UK-20-639295; and the MULTI-PARTNER CONSORTIUM TO EXPAND DEMENTIA RESEARCH IN LATIN AMERICA (ReDLat, supported by National Institutes of Health, National Institutes of Aging [R01 AG057234], Alzheimer's Association [SG-20-725707], Rainwater Charitable foundation - Tau Consortium, and Global Brain Health Institute). The contents of this publication are solely the responsibility of the authors and do not represent the official views of these Institutions. AI received travel support; Alzheimer's Association GBHI ALZ UK-20-639295. AI held the role as President for the Latin American Chapter of the Society for Social Neuroscience. Panagiotis Ioannidis has nothing to disclose. Elissaios Karageorgiou, in the past 36 months, reports EU Horizon2020 grant; received consulting fees for unrelated clinical trials safety board; received payment or honoraria for lectures; received support for attending meetings and/or travel via active grants; held stock in the Neurological Institute of Athens. Amos Korczyn, in the past 36 months, held a volunteer role as Chairperson of the MSAP of the Israeli Alzheimer Association, EMDA. Iracema Leroi, in the past 36 months, reports grants or contracts from European Union, Horizon 2020 grant Health Research Board, Ireland x2, Trinity College Dublin Covid Response Grant, Irish Research Board and ESTHER Ireland; received consulting fees for advisory board from Biogen x 1; participated on DSMB for NIHR funded trial in the UK; held a role as Director, Lewy Body Ireland. Bjorn Lichtwarck has nothing to disclose. Giancarlo Logroscino, in the past 36 months, received payment or honoraria from Roche, GE-General Electric, Amplifon. Chris Lynch has nothing to disclose. Patrizia Mecocci, in the past 36 months, received payment or honoraria from Roche, Neopharmed-Gentili, Neuraxpharm. Jose Luis Molinuevo, in the past 36 months, reports the project leading to these results has received funding from "la Caixa" Foundation (ID 100010434), under agreement LCF/PR/GN17/50300004 and the Alzheimer's Association and an international anonymous charity foundation through the TriBEKa Imaging Platform project (TriBEKa-17-519007). Additional support has been received from the Universities and Research Secretariat, Ministry of Business and Knowledge of the Catalan Government under the grant no. 2017-SGR-892; consulting fees as consultant or at advisory boards for the following for-profit

companies: Roche Diagnostics, Genentech, Novartis, Lundbeck, Oryzon, Biogen, Lilly, Janssen, Green Valley, MSD, Eisai, Alector, BioCross, GE Healthcare, ProMIS Neurosciences, NovoNordisk, Zambón, Cytox and Nutricia; received payment or honoraria by the following for-profit companies: Roche Diagnostics, Lundbeck, Biogen, Eisai, Zambón, and Nutricia; reports as consultant or at advisory boards for the following for-profit companies, or has given lectures in symposia sponsored by the following for-profit companies: Roche Diagnostics, Genentech, Novartis, Lundbeck, Oryzon, Biogen, Lilly, Green Valley, MSD, Eisai, Alector, ProMIS Neurosciences, NovoNordisk, Cytox. John Papatriantafyllou, in the past 36 months, received honoraria for lecture from Lavipharm Hellas; held president role for Hellenic Dementia Society, unpaid. Sokratis Papegeorgiou has nothing to disclose. Antonis Politis has nothing to disclose. Rema Raman, in the past 36 months, received research funding from the National Institute on Aging (NIA), Alzheimer's Association, Eli Lilly, Janssen, and Eisai. RR serves as the Vice-Chair of the Board for the Alzheimer's Association's San Diego/Imperial Chapter. Karen Ritchie has nothing to disclose. Pascual Sanchez-Juan, in the past 36 months, reports support by grants from IDIVAL, Instituto de Salud Carlos III (Fondo de Investigación Sanitario, PI08/0139, PI12/02288, PI16/01652), JPND (DEMTEST PI11/03028), the CIBERNED program, Siemens Healthineers (Valdecilla Study of Memory and Brain Aging); reports consulting for Roche, Zambon, and Biocross; received payment from Roche and Nutricia for educational events; participated in advisory boards for Roche, Zambon and Biocross. Mary Sano, in the past 36 months, reports grants or contracts from NIA and consulting fees from Avenir, Biogen Idec, BioXcel, Eisai, Genentech, F. Hoffman LaRoche, Minerva Neuroscience, Novartis, NovoNordisk, Pfizer, vTv Therapeutics, Karuna. MS has also received support for attending meetings and/or travel for Alzheimer's Association activities as a member of the Medical and Scientific Advisory Group (MSAG); participated on a Data Safety Monitoring Board or Advisory Board for Syneos; and reports roles as President of the International Psychogeriatric Association and Board Member of the National Association of Veteran Research and Education Foundations. Nikolas Scarmeas, in the past 36 months, received grants or contracts from EISAI Elenbecestat clinical tiral - Recruiting site for multinational, multicenter industry sponsored phase III treatment trial for Alzheimer's disease; EPAD study - Recruiting site for multinational, multicenter IMI sponsored observational study of prodromal stages of dementia - both paid to his institution; received honorarium for delivering three scientific presentations in Korea - Aricept International Symposium; served as Chair of Data Safety Monitoring Board for Albert Einstein College of Medicine – NIH-funded clinical trial. Luiza Spiru, in the past 36 months, reports grants or contracts from European Commission, Pharma Industry, Private Sector, National Ministry of Research and Education; received payment as Independent Expert on Ethics, Innovation and Gerontechnology Aging- Noncommunicable Diseases, for the EU Commission; received support for attending meetings and/or travel from the EU Commission, private funds; has patent pending - original formula for Nutritional Supplements; participated on a Data Safety Monitoring Board or Advisory Board for EU Projects: 2019 – 2023: Principal Investigator and coordinator for in the european research project RADAR-AD (Remote Assessment of Disease and Relapse – Alzheimer's Disease) within IMI 2 (Innovative Medicine Initiative), Grant Nr. 806999, financed from H2020 R&D and EFPIAprograms; 2018- 2021: PETAL project: AAL-2016 [Ambient Assistive Living: intelligent lights to be used for the cognitive delay MCI patients, independent seniors, at home or in residential houses, out/in patients for Memory Clinics]; 2018–2022: IOANNA project: AAL-2017 [Integration Of All stores Network and Navigation Assistant]; 2018–2022: Ella4Life project: AAL-2017 [Virtual Assistant for Seniors]; 2019: VirtuAAL project: AAL-2018 SCP [Virtual And Augmented Reality For Combating Cognitive Impairment]; 2019–2022: FrAAgiLe project: AAL-2018 [Platform for detecting frailty and falls]; 2019–2021: POSITIVE project: AAL-2018 [Personalized Platform assisting seniors in healthy fulfilled and active life]; 2019–2023: SMART BEAR EC H2020 Project [Smart Big Data Platform to Offer Evidence-based Personalized Support for Healthy and Independent Living at Home] - coordinating the Romanian Pilot of 1,000 elderlies at home; 2020–2022: iCan project: AAL-2019 [ICT-based assistant for everyday life]; 2020–2023: ReMember-Me project: AAL-2019 [Smart assistant to prevent and detect cognitive decline, promote cognitive function and social inclusion among older adults]. LS held role: UNPAID, 2020-2024: COST Action CA 19121 (GoodBrother: Network on Privacy - Aware Audio- and Video-Based Applications for Active and assisted living) member of the Management Committee for Romania and leader of WG 3 - Audio-and video-based AAL applications; 2020–2024: COST Action CA 19136 (NET4AGE-FRIENDLY: International Interdisciplinary Network on Smart Healthy Age-friendly Environments) member of the Management Committee for Romania and leader of WG 4 - SHAFE impact and sustainability: policy development, funding forecast, and cost-benefit evaluations. Afroditi Stathi, in the past 36 months, reports grants or contracts from National Institute for Health Research - Public Health Research Programme (UK). A multicenter randomized controlled trial of a peer-volunteer led active aging program to prevent decline in physical function in older people at risk of mobility disability-The ACE (Active, Connected, Engaged) study; received travel funding to visit and collaborate with colleagues at the University of Sydney, Australia. Participated as Trial Steering Committee Member: NIHR-Health Technology Assessment Programme, Home Health Promotion Intervention for people with mild frailty, University College London. AS served as Chair of Scientific Advisory Committee for the study: "Understanding the experiences of physically inactive people in midlife" studyled by the University of Bristol and funded by the Centre for Ageing Better (2020–2021); and was an Invited Advisory Committee Member, European Research Council study: "Meaningful Mobility: A novel approach to movement within and between places in later life." University of Groningen, Netherlands, 2-3 September. Magda Tsolaki has nothing to disclose. Görsev Yener, in the past 36 months, reports a Project Grant from TÜBİTAK (National Funding Agency), The Scientific and Technological Research Council of Turkey. Ioannis Zaganas, in the past 36 months, received support for attending meetings and/or travel from Akcea, Biomarin, Sanofi Genzyme; and participated on a DSMB or Advisory Board for BioMarin, Genesis Pharma, Sanofi Genzyme. Stelios Zygouris, in the past 36 months, reports grants or contracts from

Global Brain Health Institute & Alzheimer's Association Pilot Awards for Global Brain Health Leaders (Grant funding for project GBHI_ALZ-18-541600); received support from Global Brain Health Institute funding for attending the Alzheimer's Association International Conference (AAIC) Satellite Symposium, Sao Paulo, Brazil. M. Carrillo is a full-time employee of the Alzheimer's Association and reports, in the past 36 months, participating on a Data Safety Monitoring Board or Advisory Board for US POINTER and holding a role for EASTERSEALS.

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How to cite this article: Sexton C, Solis M, Aharon-Peretz J, et al. Alzheimer's disease research progress in the Mediterranean region: The Alzheimer's Association International Conference Satellite Symposium. *Alzheimer's Dement*. 2022;1-12. https://doi.org/10.1002/alz.12588