Prevalence of the apolipoprotein E ε4 allele in amyloid β-positive subjects across the spectrum of Alzheimer's disease

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ABSTRACT:

BACKGROUND: The prevalence of the apolipoprotein E (*APOE*) ε4 allele is ~50-60% in Alzheimer's disease (AD) dementia, compared to ~15-20% in the general population. However, since earlier studies included subjects without biomarker confirmation of amyloid β (Aβ) pathology, the true prevalence of *APOE* ε4 in AD is unclear.

OBJECTIVE: To determine *APOE* ε4 carrier prevalence in Aβ-positive (Aβ+) subjects (defined by PET and/or CSF biomarkers) across the spectrum of AD.

DESIGN: Cross-sectional, multicenter study.

SETTING: Combined sample from 42 cohorts worldwide.

PARTICIPANTS: 3,451 Aβ+ subjects, including 853 with a clinical diagnosis of AD-type dementia, 1,810 with mild cognitive impairment (MCI) and 788 cognitively normal subjects (CN). For comparison, we included 3,968 Aβ-negative (Aβ-) subjects (117 with clinically AD-type dementia, 1,525 MCI and 2,326 CN).

MAIN OUTCOME AND MEASURES: *APOE* ε4 carriership (either 1 or 2 alleles) was the main outcome measure. Generalized estimating equation models were used to assess effects of age, sex, education and geographical location.

RESULTS: Overall, the prevalence of *APOE* ε4 was 61% in AD-type dementia, 47% in MCI and 31% in CN. In Aβ+ subjects the prevalence was 66% in AD-type dementia, 64% in MCI and 51% in CN, roughly twice as high as in Aβ- subjects (24.8% in AD-type dementia, 27.9% in MCI and 24.5% in CN). The prevalence of *APOE* ε4 decreased with advancing age in Aβ+ CN (β for annual change in prevalence±standard error: -0.02±0.01, $p<0.05$) and Aβ+ MCI (β:-0.03±0.01, $p<0.01$), but not in Aβ+ AD dementia ($p=0.66$). A similar decrease was seen in Aβ- CN and MCI. The *APOE* ε4 prevalence was higher in Northern Europe than all other investigated regions except Australia ($p<0.05$), but did not vary by sex or education.

CONCLUSIONS AND RELEVANCE: Previous studies that diagnosed AD-type dementia according to clinical criteria have underestimated the contribution of *APOE* ε4 to AD-type dementia**.** The decreasing prevalence with age in early stages of AD corroborates the idea that *APOE* ε4 is associated with earlier age at onset of AD-type dementia and/or with an increased mortality rate in *APOE* ε4 carriers. Our results highlight disease heterogeneity related to age and geographical location.

Introduction

Alzheimer's disease (AD) is the most common type of dementia, and a major cause of morbidity and mortality worldwide.[1] Pathological metabolism and accumulation of β-amyloid (Aβ) peptides is thought to be an initiating event in AD, leading to downstream spread of tau pathology, synaptic loss, atrophy and cognitive decline.[2-4] Several risk factors may affect or accelerate the development of AD, including age, life-style, and genetic factors.[5-7] The strongest genetic risk factor associated with sporadic AD is the apolipoprotein E (*APOE*) gene.[8,9] *APOE* encodes for apolipoprotein E, which is a major lipid transporting protein in the brain. In humans, the gene exists in three allele variants called ε2, ε3, and ε4. Compared to *APOE* ε3/ε3 (the most common genotype), *APOE* ε4 heterozygosity increases the risk for developing clinical AD by about 3-4 times, and *APOE* ε4 homozygosity by about 10-15 times.[8,10] The overall prevalence of *APOE* ε4 positivity has been reported to be approximately 15-20% in the normal population[10,11] and 50-60% in patients with AD dementia [8,9,12]. These numbers, however, vary widely and may depend on different characteristics of the study population, including geographical location.[12] Additionally, most previous studies included clinically defined AD patients, without neuropathological confirmation and/or supportive pathophysiological AD biomarkers. Studies applying cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers have revealed that a substantial number of patients with a clinical diagnosis of AD dementia have no evidence of Aβ-pathology[13-16], which makes underlying AD pathology highly unlikely. Furthermore, this mismatch between the clinical diagnosis and Aβ biomarkers seems especially prevalent in *APOE* ε4 non-carriers, as illustrated by a clinical trial in which 36% of *APOE* ε4-negative patients with a diagnosis of "AD dementia" in fact lacked Aβ pathology as determined by PET.[17]

Another critical point of previous studies on the prevalence of *APOE* ε4 is the focus on the dementia stage of AD. AD is believed to follow a long trajectory in which Aβ pathology is present and clinical symptoms gradually develop before the threshold for dementia is reached.[18-20] Few studies have investigated *APOE* ε4 positivity in prodromal AD[21], *i.e.*, mild cognitive impairment (MCI) due to AD, but prevalence rates around 25-55% have been reported. Similarly, not many studies included the proportion of *APOE* ε4 carriers among people with preclinical AD, i.e. presence of Aβ pathology without clinical symptoms.[22-24] Earlier studies emphasize the importance of the matter; among 1345 study participants (including patients with AD-type dementia, MCI, other dementias, as well as cognitively normal individuals), *APOE* ε4 was found to be more strongly associated with biomarker evidence of Aβ pathology (irrespective of clinical status) than a clinical diagnosis of AD (Andreasson U et al., Mol Psychiatry. 2014 Feb;19(2):148-9). Similarly, the effect size of *APOE* ε4 increased if presence or absence of Aβ pathology was neuropathologically confirmed (Corneveaux JJ et al. Hum Mol Genet 2010; 19: 3295–3301).

We aimed to investigate the prevalence of *APOE* ε4 positivity across the clinical spectrum of AD in a large sample of Aβ biomarker-positive individuals, including cognitively normal controls (CN), MCI, and AD dementia. We also tested whether the prevalence of *APOE* ε4 positivity varied by age, sex and geographical location. For comparison, we included a group of Aβ-negative participants.

METHODS

Participants

For this study, we used data from the Amyloid Study Group, which is a worldwide collaborative project on Aβ PET and CSF biomarkers in conjunction with several demographic, clinical and genetic variables.[5,25] From all contributing sites, we received individual participant-level data on 9,480 individuals (3,611 CN, 3,972 MCI, 1,359 probable AD dementia and 538 non-AD dementia). In addition, we supplemented these data with the Swedish BIOFINDER study[26] (including 292 CN and 217 MCI). Since we aimed to investigate the prevalence of *APOE* ε4 across the clinical spectrum of AD, we applied the following selection procedure for this study: i) we excluded patients with a non-AD dementia, ii) among CN, MCI or AD dementia participants, we selected Aβ-positive (Aβ+) individuals as determined by PET and/or CSF and their Aβ-negative (Aβ-) counterparts for comparison, and iii) we excluded individuals who lacked information on *APOE* ε4 status.

Normal cognition was defined as normal scores on cognitive tests, the absence of cognitive complaints for which medical help was sought, or both.[5] Some of the CN participants had subjective cognitive impairment (SCD, n=533 [102 Aβ+, 431 Aβ-]), defined as presence of a cognitive complaint with presentation at a health care facility but normal

cognition on neuropsychological tests[27]. In this paper, SCD subjects were combined with the other CN.[20] MCI and probable AD dementia were defined according to established diagnostic criteria.[18,19,28] Aβ- "AD dementia" cases most likely do not have AD as the underlying cause of their cognitive impairment, although it should be noted that Aβ biomarkers are not perfect and could misclassify subjects, especially when biomarker signals are close to the cut-offs.[29,30].Characteristics of participants from each contributing site can be found in Supplemental Table 1.

PET/CSF procedures

Individual PET scans were dichotomized (Aβ+ or Aβ-) using quantitative thresholds or visual reads according to the method used at the study site.[5,25] CSF biomarkers were dichotomized as negative (normal) or positive (abnormal) using study-specific cutoffs.[5]
Detailed PET/CSF procedures for each site are presented in Supplemental Table 1.

APOE genotyping

By design, all participants in this study had data on *APOE* ε4 status. For 2,955/3,114 (95.5%) CN and 3,054/3,335 (91.6%) MCI subjects we had the specific genotypes (e.g. ε3/ε4, in addition to *APOE* ε4 status), which allowed breakdown into *APOE* ε4 non-carriers, heterozygotes and homozygotes. Specific genotypes were not available for AD dementia patients.

Age, sex, education and geographical location

Information on age was available for all participants. There were missing data for sex (130/7,419, 1.8%) and years of education (1,137/7,419, 15.3%). We used a previously

published classification system for geographical location[12] to divide the participants into Southern Europe (n=653[215 Aβ+, 438 Aβ-]), Central Europe (n=832[343 Aβ+, 489 Aβ-]), Northern Europe (n=1,667[792 Aβ+, 875 Aβ-), Australia (n=395[190 Aβ+, 205 Aβ-]), Northern America (n=3.359[1292 Aβ+, 2067 Aβ-]) or Asia (n=315[114 Aβ+, 201 Aβ-]). Some participants (n=637[303 Aβ+, 334 Aβ-], 8.1%) could not be classified, as they were included in a multicenter study that covered multiple geographical locations.

Statistical analyses

Baseline differences between diagnostic groups were assessed using analysis of variance (with post hoc Bonferroni correction) and X^2 tests, where appropriate. The prevalence of *APOE* ε4 positivity was obtained by calculating the percentage of *APOE* ε4-positive individuals of the total number of participants in each diagnostic group. Generalized estimating equations (GEE) were used to estimate the effects of age, sex, education and geographical location on the prevalence of *APOE* ε4 positivity. GEE was the method of choice for the study as it allows analysis of binary-correlated data, such that participant-level data from all cohorts can be modeled while simultaneously accounting for participants within studies. A logit link function for binary outcome with an exchangeable correlation structure was assumed to account for within-study correlation. Analyses were conducted using the total study population, unless specified otherwise. Age was entered as a continuous measure centered at the mean. We tested 2-way and 3-way interactions between variables, and these terms were retained in the model if they appeared significant by the Wald statistical test. The GEE derived unstandardized β-coefficients and standard errors (SE) of the main effect were reported. Significance level was set at a 2-sided P value less than .05. SPSS software (IBM, version 23.0) was used for statistics.

RESULTS

Participants

Demographic and clinical information for each diagnostic group is provided in Table 1. We included a total of 7,419 subjects, including 970 with a clinical diagnosis of AD dementia (853 Aβ+, 117 Aβ-), 3,335 with MCI (1,180 Aβ+, 1,525 Aβ-) and 3,114 CN subjects (788 Aβ+, 2,326 Aβ-). Demographic differences between the diagnostic groups included less males in the CN group compared to the other groups ($p<0.05$) and shorter education in the MCI group compared to the other groups ($p<0.001$). Furthermore, in the dementia group Aβ status was only determined using PET, and in the MCI group the proportion of subjects with CSF data (78%) was greater than that in the CN group (64.9%). In Aβ+ individuals only, comparisons within diagnostic groups between *APOE* ε4-positive and -negative groups showed that the mean age was lower in *APOE* ε4-positive than in *APOE* ε4-negative CN and MCI patients ($p<0.01$) (Supplemental Table 2).

Prevalence of APOE ε4 positivity

In Aβ+ subjects, the prevalence of *APOE* ε4 positivity was 50.9% in CN, 63.5% in MCI and 66.1% in AD dementia (Table 1). The prevalence of *APOE* ε4 positivity was higher in Aβ+ MCI and Aβ+ AD dementia than in Aβ+ CN ($p<0.001$), but there was no difference between Aβ+ MCI and Aβ+ AD dementia ($p=0.19$). For comparison, the *APOE* ε4 prevalence in Aβ- subjects was 24.5% in CN, 27.9% in MCI and 24.8% in AD dementia, which was significantly lower than in Aβ+ subjects (all $p<0.001$).

Prevalence of APOE ε4 positivity by age, sex and education

The prevalence of *APOE* ε4 positivity was lower at older age in Aβ+ CN (β for change in prevalence per year ± standard error: -0.02±0.01, $p<0.05$, Figure 1) and Aβ+ MCI (β=-0.03±0.01, $p<0.01$). For example, at age 50, the prevalence of *APOE* ε4 positivity was 61% in Aβ+ CN and 75% in Aβ+ MCI, compared to 42% and 47% at age 90, respectively (Supplemental Figure 1). There was no age effect in AD dementia (β=0.01±0.01, p=0.66). There was also no effect of age in AD dementia when excluding patients (n=91) with a known atypical presentation (e.g. posterior cortical atrophy or logopenic variant primary progressive aphasia), which are typically associated with lower prevalence of *APOE* ε4 (β=0.00±0.01, p=0.99, Supplemental Figure 2). In Aβ- subjects, the prevalence of *APOE* ε4 also decreased with age in CN (β=-0.03±0.01, $p<0.001$; difference with Aβ+: p=0.62) and MCI (β=-0.03±0.01, $p<0.001$; difference with Aβ-: p=0.82), but not in AD dementia (β=-0.01±0.02, p=0.55; difference with Aβ+: p=0.19)). All effects described above were similar when adjusting for sex and education.

In Aβ+ subjects, sex and education had no direct effects on *APOE* ε4 positivity, either across or within diagnostic groups (all $p>0.05$). Furthermore, in Aβ+ subjects there was an interaction between age and sex ($p<0.05$), whereby prevalence decreased with age for women but not for men. Examining the three-way interaction with diagnosis revealed that the interaction between age and sex was present in MCI ($p<0.01$), and at trend level in AD dementia (p=0.053), but not in CN subjects (p=0.26). In Aβ- MCI subjects, there was a trend towards greater *APOE* ε4 positivity in women (β: 0.19±0.10, p=0.06). There were no effects within or across diagnostic groups for education and no interaction effects (all $p>0.05$). See Supplemental Table 3 for an overview of all main and interaction effects.

Prevalence of specific APOE genotypes in CN and MCI

Next, we stratified CN (n=2,955 [751 Aβ+, 2,204 Aβ-]) and MCI (n=3,054 [1,638 Aβ+, 1,416 Aβ-]) subjects with *APOE* genotype information available into groups of *APOE* ε4 non-carriers, *APOE* ε4 heterozygotes and *APOE* ε4 homozygotes, and divided them into quartiles according to age. Both in CN and MCI the proportion of *APOE* ε4 heterozygotes and *APOE* ε4 homozygotes decreased with advancing age (Figure 2).

Prevalence of APOE ε4 positivity by geographical location

Finally, we assessed the effect of geographical location on prevalence of *APOE* ε4 positivity. Within Aβ+ subjects, we found that the prevalence of *APOE* ε4 positivity across diagnostic groups was higher in Northern Europe compared with all other geographical locations except Australia (all $p<0.001$, Bonferroni-corrected; Figure 3A). In addition, the prevalence of *APOE* ε4 positivity was lower in Southern Europe compared to North America, Central Europe ($p<0.05$, uncorrected) and Australia ($p<0.001$, Bonferroni-corrected), and higher in Australia than in Asia ($p<0.05$, uncorrected). Within Aβ- subjects, the prevalence of *APOE* ε4 positivity was higher in Northern Europe ($p<0.001$, Bonferroni-corrected) and Central Europe ($p<0.05$, uncorrected) compared to all other geographical locations (Figure 3B). These findings were similar when assessing each diagnostic group separately (Supplemental Figure 3 and Supplemental Table 4).

Discussion

We found that the prevalence of *APOE* ε4 positivity was 51% in preclinical AD (Aβ+ CN) 64% in prodromal AD (Aβ+ MCI) and 66 % in Aβ+ AD dementia. Among Aβ- subjects the prevalence of *APOE* ε4 positivity was 25% in CN, 28% in MCI and 25% in AD dementia.

Our estimates of *APOE* ε4 prevalence in Aβ biomarker-verified AD-type dementia are higher than reported in previous studies that defined AD-type dementia based on clinical criteria only. This resonates well with studies examining the effect size of *APOE* ε4 in pathology- or biomarker-confirmed cases (Andreasson U et al., Mol Psychiatry. 2014 Feb;19(2):148-9; Corneveaux JJ et al. Hum Mol Genet 2010; 19: 3295–3301) and suggests that the true prevalence of *APOE* ε4 in AD-type dementia may have been underestimated in previous studies.

A main finding of this study was that the prevalence of *APOE* ε4 decreased with age in preclinical and prodromal AD. There are several possible explanations. First, as *APOE* ε4 accelerates the onset of amyloid aggregation by approximately 15 years[5,22], the prevalence of ε4 carriers in Aβ+ subjects will be higher at younger age ranges. Second, supposedly due to the increased risk for cardiovascular diseases in ε4 carriers, *APOE* ε4 has been linked to increased mortality rates.[31-33] This fits our finding that *APOE* ε4 carriership also decreased with age in Aβ- CN and MCI subjects, although the reduction of *APOE* ε4 in Aβ- subjects can also be caused by individuals transitioning from Aβ- to Aβ+ with advancing age. Finally, the additive effects of *APOE* ε4 and Aβ may have resulted in a greater conversion from the CN and MCI groups to AD dementia.[34] Remarkably, the prevalence of *APOE* ε4 did not change with age in AD-type dementia. We tested whether this lack of an age effect was caused by the inclusion of atypical variants of AD dementia[35], but also after excluding these patients there were no age-effects on the prevalence of *APOE* ε4 carriership. The pathogenesis of early-onset AD is complex, since this group includes a mix of *APOE* ε4 carriers who develop the disease at younger age and of *APOE* ε4 non-carriers with rapidly progressive AD.[36,37] This may confound relationships between *APOE* ε4 and age especially in young patients with AD-type dementia. Furthermore, it has been shown that the mortality

effect of *APOE* ε4 is less pronounced at older age, which may explain the lack of an age effect even in late-onset AD patients.[38]

Another main finding was the lower prevalence of *APOE* ε4 in both Aβ+ and Aβ- CN subjects compared to the MCI and dementia stages. This may be explained by a selection bias, as the majority of the MCI and AD dementia subjects visited at a memory clinic, while most CN subjects were recruited as research volunteers. Also, *APOE* ε4+ MCI patients may be more likely to seek medical help as a consequence of a positive family history for dementia. Another possible reason is that *APOE* ε4 may accelerate the transition from preclinical to clinical AD. For example, *APOE* ε4 may have Aβ-independent effects on brain structure and function[39-43], which may act synergistically with Aβ pathology to shorten the time between start of Aβ deposition and cognitive decline. Another possibility is that *APOE* ε4 may cause a more rapid accumulation of Aβ, and thereby shorten the time until Aβ pathology reaches a critical threshold that may be required to trigger downstream effects, including spread of tau, atrophy, and cognitive decline.

We also found geographical differences in *APOE* ε4 prevalence, with higher prevalence in AD patients from Northern Europe, Central Europe, and Australia, and lower prevalence in patients from Southern Europe and Asia. This is consistent with previous epidemiological studies in clinically diagnosed AD dementia patients and MCI.[12,44] The novelty of this study is that we confirm these geographical differences in Aβ biomarker-defined AD, and throughout the continuum from preclinical to prodromal and dementia stages. Overall, the geographical trends are consistent with lower prevalence of *APOE* ε4 in general populations in Southern Europe and Asia compared to Northern Europe.[44-46] The different geographical prevalence of *APOE* ε4 may be important both for recruitment of participants in clinical trials, and for the use of *APOE* ε4 in algorithms to predict Aβ positivity.[47]

Strengths of this study include the large number of Aβ-positive subjects across the spectrum from preclinical to prodromal and dementia stages of AD. Limitations include that relatively few participants came from Central Europe, Southern Europe, Asia and Australia, and there were no participants from Africa and South America. There were no data on race of the participants, which may confound the results since race has been related to both *APOE* ε4 and AD.[46,48] Finally, Aβ positivity was determined using different modalities (i.e. PET or CSF) and methods (e.g. visual read versus quantitative threshold for PET and different assays for CSF). In previous studies, however, we found only little evidence for heterogeneity related to modality and methodology in the Amyloid Study Group data.[5,25]

With about 2/3 of prodromal AD and AD dementia patients being *APOE* ε4 carriers, our results emphasize the importance of *APOE* ε4 for the development of AD. This may be useful both for development of disease-modifying treatments, which may be focused on attenuating the detrimental effects of *APOE* ε4, and for understanding the molecular pathogenesis of AD. However, *APOE* ε4 does not explain all cases of AD, since ~1/3 of Aβ-biomarker-positive AD patients were *APOE* ε4-negative. This is important, since there may be molecular differences between *APOE* ε4-negative and -positive individuals with Aβ pathology, including differences in metabolism of Aβ and amyloid precursor protein (APP).[49] Furthermore, the finding that the prevalence of *APOE* ε4 decreases in CN and MCI subjects has potential implications for clinical trials in pre-dementia populations, as screening based on *APOE* status to enrich for Aβ positivity may be less effective with advancing age.

CONCLUSIONS

We have quantified the prevalence of *APOE* ε4 in Aβ biomarker-defined preclinical AD, prodromal AD and AD dementia. The results emphasize the prominent role of *APOE* ε4 in AD, but also points to disease heterogeneity, since *APOE* ε4 positivity is markedly less common in elderly subjects in pre-dementia stages of AD and in people from specific geographical locations, including Southern Europe and Asia. Further studies on phenotypic differences between *APOE* ε4-negative and *APOE* ε4-positive AD patients may be important to understanding different pathways that may lead to AD, and ultimately to tailor disease-modifying treatments to specific patient subgroups.

Acknowledgements (to-do)

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Translational Alzheimer Neurobiology, Karolinska Institutet, and Geriatric Medicine, Karolinska University Hospital, Stockholm, Sweden (Nordberg); Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Mölndal, Sweden (Nordlund, A Wallin); Department of Psychiatry and Psychotherapy, Charité Berlin, German Center for Neurodegenrative Diseases (DZNE), Berlin, Germany (Peters); Department of Psychiatry, Service of Old Age Psychiatry, University Hospital of Lausanne, Lausanne, Switzerland (Popp); Department of Neurology, Memory and Aging Center, University of California,San Francisco (Rabinovici); Turku PET Centre and Division of Clinical Neurosciences Turku, University of Turku and Turku University Hospital, Turku, Finland (Rinne); Neurology Service, Universitary Hospital Marqués de Valdecilla, IDIVAL, Santander, Spain (Rodríguez- Rodríguez, Sanchez-Juan); Department of Nuclear Medicine and Centre for PET, Austin Health, Melbourne, Australia (Rowe, Villemagne); Department of Psychiatry and Psychotherapy, University Medical Center, Georg-August University, Göttingen, Germany (Wiltfang); Neurologie de la Mémoire et du Langage, Centre Hospitalier Sainte-Anne, Université Paris 5, Paris, France (Sarazin); Sektion Gerontopsychiatrie, Universität Heidelberg, Heidelberg, Germany (Schröder); Department of Geriatrics-Gerontology-Gerontopsychiatry, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania (Spiru); Neurochemistry Laboratory and Biobank, Department of Clinical Chemistry, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, the Netherlands (Teunissen); Laboratory for Cognitive Neurology and Alzheimer Research Centre KU Leuven, Catholic University Leuven, Leuven, Belgium (Vandenberghe); Department of Imaging and Pathology, Catholic University Leuven, Leuven, Belgium (Van Laere); Departments of Neurology and Laboratory Medicine, Donders Institute for Brain, Cognition and Behaviour, Radboud Alzheimer Center, Radboud University Medical Center, Nijmegen, the Netherlands (Verbeek, van Waalwijk van Doorn); Danish Dementia Research

Center, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark (Frederiksen, Waldemar); UCL Institute of Neurology, Queen Square, London, United Kingdom (Zetterberg). Center for Vital Longevity, School of Behavioral and Brain Sciences, The University of Texas at Dallas, Dallas, Texas 75235 (Rodrigue). Postgraduate Institute of Medical Education and Research (PGIMER), Department of Biochemistry, Research Block-A, Chandigarh, India (Gill, Prabhakar). Janssen Research and Development, Titusville, New Jersey (Novak). Department of Psychiatry and Psychotherapy, University Medical Center, Georg-August University, Göttingen, Germany (Rüther, Wiltfang).

Disclosures

Dr Aarsland reported having received research support or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals, and GE Health. Dr Anders Wallin reported having received speakers' bureau fees from Esai and Triolab and serving on the advisory board for Nutrica and Esai. Dr Blennow reported having received personal fees (advisory boards or consulting) from Roche Diagnostics, IBL International, Novartis, Fujirebio Europe, and Eli Lilly and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg. Dr Chen reported having received grants from the National Institutes of Health (NIH). Dr Drzezga reported having received speaker honoraria and consulting fees from GE Healthcare, AVID/Lilly, and Piramal. Dr Fagan reported having received grants from NIH, DiamiR, Fred Simmons and Olga Mohan, and Charles and Joanne Knight Alzheimer's Research Initiative of the Washington University Knight Alzheimer's Disease Research Center; having received personal fees from IBL International, Roche, and AbbVie. Dr Fladby reported having a patent "Methods and compositions for monitoring phagocytic activity," PCT/US2011/062233, pending. Dr Fleisher

reported having been a full-time employee of the Banner Alzheimer's Institute; being a full-time employee of Eli Lilly; maintaining a voluntary faculty appointment at the University of California, San Diego; having been a member of data and safety monitoring boards for Merck, Pfizer, and the National Institute of Aging (NIA); having received grant funding from NIA and Avid Radiopharmaceutical; and having been a consultant for Eli Lilly, Grifols, Avid Radiopharmaceuticals, and Siemens Imaging. Dr Förster reported having received personal fees (consultancy) from Piramal, Bayer, and GE. Dr Frisoni reported having received grants and/or personal fees from Lilly, Bristol-Myers Squibb, Bayer, Lundbeck, Elan, AstraZeneca, Pfizer, Taurx, Wyeth, GE, Baxter, Avid, Roche, Piramal, and the Alzheimer's Association. Dr Gill reported having received grants from the Indian Council of Medical Research, New Delhi, India. Dr. Grimmer reported having received personal fees from Eli Lilly. Dr Hampel is supported by the AXA Research Fund, the Fondation Université Pierre et Marie Curie and the Fondation pour la Recherche sur Alzheimer, Paris, France, reported having received grants, personal fees, and/or nonfinancial support from Boehringer-Ingelheim, Bristol-Myers Squibb, Elan, Novartis, Eisai, Pfizer, sanofi-aventis, Roche Pharmaceuticals and Diagnostics, GE Healthcare, Avid, Eli Lilly, GlaxoSmithKline Biologicals, Jung-Diagnostics, and Cytox and having a patent, "Method for predicting whether subjects with mild cognitive impairment (MCI) will develop Alzheimer's disease," pending; a patent, "3-Hydroxykynurenin im Serum als diagnotischer Marker für die Demenz vom Alzheimer-Typ," pending; a patent, "Neurodegenerative markers for psychiatric conditions," pending; a patent, "Ratio Aß42/40 im Plasma in der Früh- und Differentialdiagnose der Alzheimer Krankheit," pending; a patent "Liquordiagnostisches in vitro Verfahren zur Diagnose von Demenz Erkrankungen und neuroinflammatorischen Erkrankungen," pending; and a patent, "In vitro Verfahren zur Diagnose von neurodegenerativen Erkrankungen," pending. Dr Hansson has received research support from GE Healthcare, AVID radiopharmaceuticals and Hoffmann-

La Roche. Dr Jagust reported having received personal fees from Banner Alzheimer Institute/Genentech, Synarc/Bioclinica, and Novartis. Dr Jansen reported having received research support from Biogen. Dr Klunk reported being a co-inventor of the amyloid imaging tracer PiB and, as such, having a financial interest in the license agreement. (PiB intellectual property is owned by the University of Pittsburgh, and GE Healthcare holds a license agreement with the University of Pittsburgh based on the PiB technology described in this article and receives "inventors share" payments from the University of Pittsburgh based on income from that license.) . Dr Kornhuber reported having received grants from German Federal Ministry of Education and Research (BMBF): Kompetenznetz Demenzen (01GI0420) and German Federal Ministry of Education and Research (BMBF): The Frontotemporo-Lobar Degeneration Consortium (FTDL-C), 01GI1007A and having a patent, PCT/ EP2004/003963, "Diagnosis of Alzheimer's disease," issued; a patent, EP 1811304 A1, "Large Aß-peptide binding particles (LAPS) in diagnosis and therapy of Alzheimer's dementia," issued; a patent, WO2007/082750 A1, "Immunoglobulin- bound Ab-peptides and immunoglobulins-binding Ab-peptides in diagnosis and therapy of Alzheimer's dementia," issued; a patent, EP 2437067A2, "Methods of differentially diagnosing dementias," issued; and a patent, "New formulations for diagnosis of Alzheimer's disease," pending. Dr Landau reported having received grants from NIH and personal fees from Biogen Idec, Genentech, and Synarc. Dr Lleo reported having received grants from Instituto de Salud Carlos III (Fondo de Investigación Sanitario, PI10/ 01878; PI13/01532; PI11/2425; PI11/3035 and the CIBERNED program). Dr Mintun reported being an employee of Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly. Dr Morris reported having received grants from NIH (P50AG005681, P01AG003991, P01AG026276, U19AG032438). Dr Mroczko reported having received grants and personal fees from the Leading National Research Centre (KNOW), Medical University of Bialystok, Poland; and consultation and/or lecture honoraria

from Roche, Cormay and Biameditek. Dr Peters reported having received grants and/or personal fees from Lilly, Roche, Genentech, Lundbeck, Affiris, Piramal, Novartis, and Trx-Pharmaceuticals. Dr Popp reported having received grants from the Swiss National Science Foundation (SNF 320030L_141179) and from the Nestlé Institute of Health Sciences. Dr Rabinovici reported having received grants from Avid Radiopharmaceuticals and personal fees from GE Healthcare and Piramal. Dr Rinne reported having received grants from Sigrid juselius Foundation and Turku University Hospital clinical grants. Dr Rowe reported having received grants from Avid Radiopharmaceuticals, Piramal Imaging, AstraZeneca, GE Healthcare, Avid/Lilly, Navidea, CSIRO, NHMRC, Alzheimer's Association, and an anonymous foundation and having had a patent licensed for PET image processing. Dr Sarazin reported having received personal fees from Novartis (lecture) and Allianz (lecture). Dr Scheltens reported having received grants from GE Healthcare, Piramal, and Merck, paid to his institution. Dr Soininen reported having received grants from the Academy of Finland, European Union 7ThFP 601055 VPH-DARE, Kuopio University Hospital VTR, and University of Eastern Finland. Dr Teunissen reported being a member of the international advisory board at Innogenetics and Roche; and having research contracts at Probiodrug, Boehringer, Roche, EIP Pharma and IBL. Dr van der Flier reported having received grants from Boehringer Ingelheim, Piramal Imaging, and Roche. Dr Van Laere reported having received grants through KU Leuven from Merck, Janssen Pharmaceuticals, UCB, Novartis, Pfizer, and GE Healthcare. Dr Vandenberghe reported having received clinical trial agreements with GEHC, Merck, Forum, and Roche; grants from Research Foundation–Flanders (FWO) and KU Leuven; and nonfinancial support from GEHC. Dr Verbeek reported having served on an advisory board for Roche. Dr Verhey reported having received compensation as a speaker and consultant for Nutricia Advanced Medical Food. Dr Visser reported having received research support from Biogen, grants from EU/EFPIA Innovative

Medicines Initiative Joint Undertaking, EU Joint Programme–Neurodegenerative Disease Research (JPND), ZonMw, and Bristol-Myers Squibb; having served as member of the advisory board of Roche Diagnostics; and having received nonfinancial support from GE Healthcare. Dr Vos receives research support from ZonMW and from the Innovative Medicines Initiative Joint Undertaking under EMIF grant agreement n° 115372, resources that are composed of financial contributions from EU FP7 (FP7/2007-2013) and in-kind contributions from EFPIA. Dr Waldemar reported being a board member of the Lundbeck Foundation.Dr Wolk reported having received personal fees from GE Healthcare and Piramal Pharma and grants from Avid Radiopharmaceuticals. Dr Zetterberg is co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg. The authors received compensation (ie, salary) as employees of their respective organizations. No other disclosures were reported.

Table 1. Participant characteristics

	CN			MCI			AD dementia		
	Total	**Aβ-**	**Aβ+**	**Total**	**Aβ-**	**Aβ+**	**Total**	**Aβ-**	**Aβ+**
N	3,552	2,764	788	3,335	1,525	1,810	970	117	853
Age[a]	67.3±11.8	65.8±12.0	72.6±9.4	70.2±8.6	68.4±8.9	71.8±8.0	69.4±9.4	71.6±9.6	69.1±9.3
Sex (% male)[b]	43.9	42.9	47.2	53.6	54.8	52.7	56.4	64.1	55.3
MMSE[c]	29.0±1.2	29.0±1.2	28.8±1.3	26.9±2.5	26.7±2.6	26.5±2.6	21.8±4.8	22.9±4.0	21.6±4.9
Education, yrs[d]	14.3±3.7	14.3±3.7	14.3±3.8	12.4±4.4	11.9±4.3	12.9±4.4	13.8±3.6	13.6±3.6	13.9±3.6
Modality for Aβ positivity[e] (% PET vs % CSF)	41.6/58.4	42.9/57.1	36.1/63.9	22.9/78.0	21.0/79.0	22.8/77.2	100/0	100/0	100/0
APOE ε4 positivity[f]	30.5	24.6	50.9	47.2	27.9	63.5	61.1	24.8	66.1
Region:									
North America	1,469	1,044	425	1,077	412	665	375	50	325
Australia	200	140	60	76	26	50	118	4	114
Northern Europe	712	568	144	714	365	349	241	38	203
Central Europe	195	154	41	536	304	232	101	12	89
Southern Europe	269	221	48	343	163	180	41	1	40
Asia	80	71	9	141	76	65	94	12	82

Data are presented as mean±SD unless indicated otherwise. Differences between diagnostics groups (assessed separately for Aβ-positive and Aβ-negative groups) were assessed using ANOVA (age, education, MMSE) and X^2 tests (sex, modality and APOE ε4 status) with post hoc Bonferroni tests.

[a] Aβ- CN < MCI/AD, $p<0.001$, MCI < AD, $p<0.01$; Aβ+ CN/MCI > AD dementia, $p<0.001$

[b] Aβ- CN < MCI/AD, p<0.05; Aβ+ CN > MCI/AD dementia, p<0.05
[c] Aβ- CN < MCI/AD, p<0.001, MCI < AD, p<0.05; Aβ+ AD dementia < CN/MCI, p<0.001, MCI < CN, p<0.001
[d] Aβ- MCI < CN/AD, p<0.001; Aβ+ MCI < CN/AD dementia, p<0.001
[e] Aβ- AD > MCI/CN, CN > MCI, , p<0.001; Aβ+ AD dementia > CN/MCI, p<0.001; CN > MCI, p<0.001
[f] Aβ+ AD dementia/MCI > CN, p<0.001

Aβ = amyloid-β, CN = cognitively normal, MCI = mild cognitive impairment, AD = Alzheimer's disease; MMSE = Mini-mental state examination; PET = Positron emission tomography; CSF = Cerebrospinal fluid; APOE = Apolipoprotein E.

FIGURE LEGENDS:

Figure 1. Prevalence of APOE ε4 positivity by age, diagnosis and Aβ status

Curves were plotted using the point estimates generated by generalized estimating equations and are within the age limits of the diagnostic groups. The models were adjusted for study (site) effect. The 95% confidence intervals are presented in eFigure 1in the Supplement.

AD = Alzheimer's disease; APOE = Apolipoprotein E

Figure 2. Distribution of APOE ε4 negative, APOE ε4 heterozygous and APOE ε4 homozygous subjects across different age quartiles (Fig-2A; Q1= <67 years, Q2= 67-73.2, Q3= 73.21-78.76, Q4= >78.77 years: Fig-2B; Q1= <66.67 years, Q2= 66.68-72.28, Q3= 72.29-77.19, Q4= >77.2: Fig-2C; Q1= <59.5 years, Q2= 59.5-67.1, Q3= 67.11-75.65, Q4= >73.66 years; Fig-2D; Q1=<62 years, Q2= 62.01-68.41, Q3= 68.42-75.0, Q4= >75.01 years).

Aβ = Amyloid-beta; APOE = Apolipoprotein E; Q = Quartile.

Figure 3. Distribution of APOE ε4 negative and APOE ε4 positive subjects by geographical location for all Aβ+ (A) and Aβ- (B) participants across diagnostic groups. A further breakdown into diagnostic groups is provided in eFigure 2 in the Supplement.

Aβ = Amyloid-beta; APOE = Apolipoprotein E

FIGURE 1.

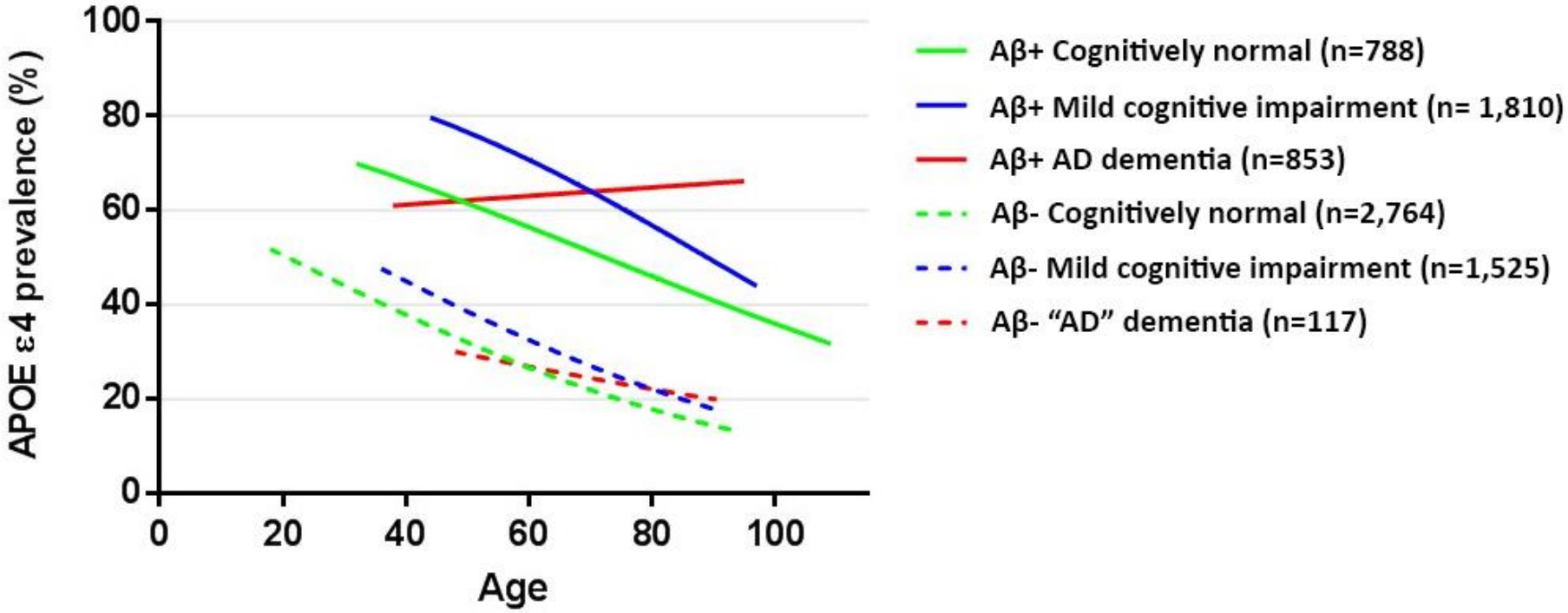

APOE ε4 prevalence (%)
100
80
60
40
20
0
0
20
40
60
80
100
Age
Aβ+ Cognitively normal (n=788)
Aβ+ Mild cognitive impairment (n= 1,810)
Aβ+ AD dementia (n=853)
Aβ- Cognitively normal (n=2,764)
Aβ- Mild cognitive impairment (n=1,525)
Aβ- "AD" dementia (n=117)

FIGURE 2.

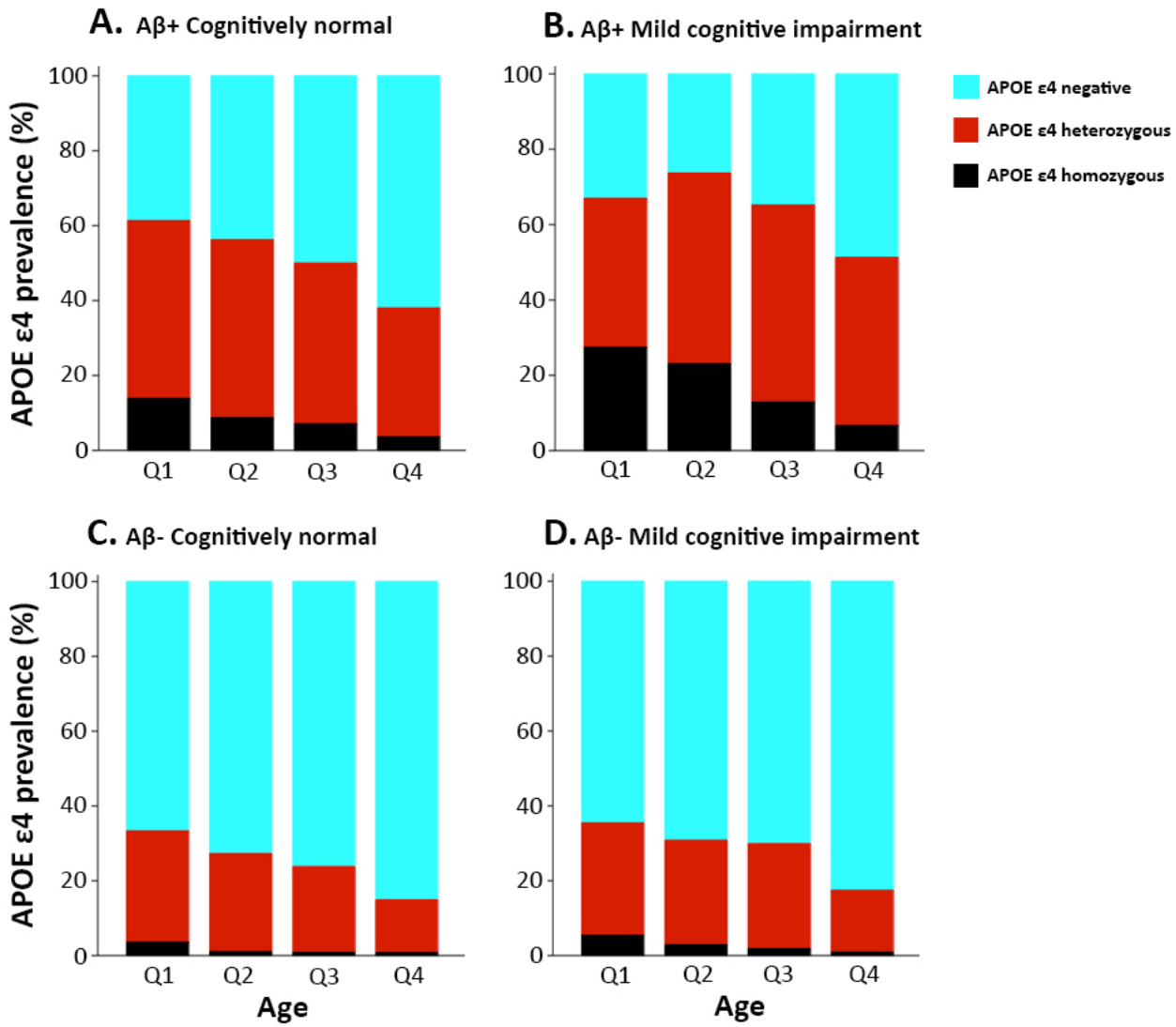
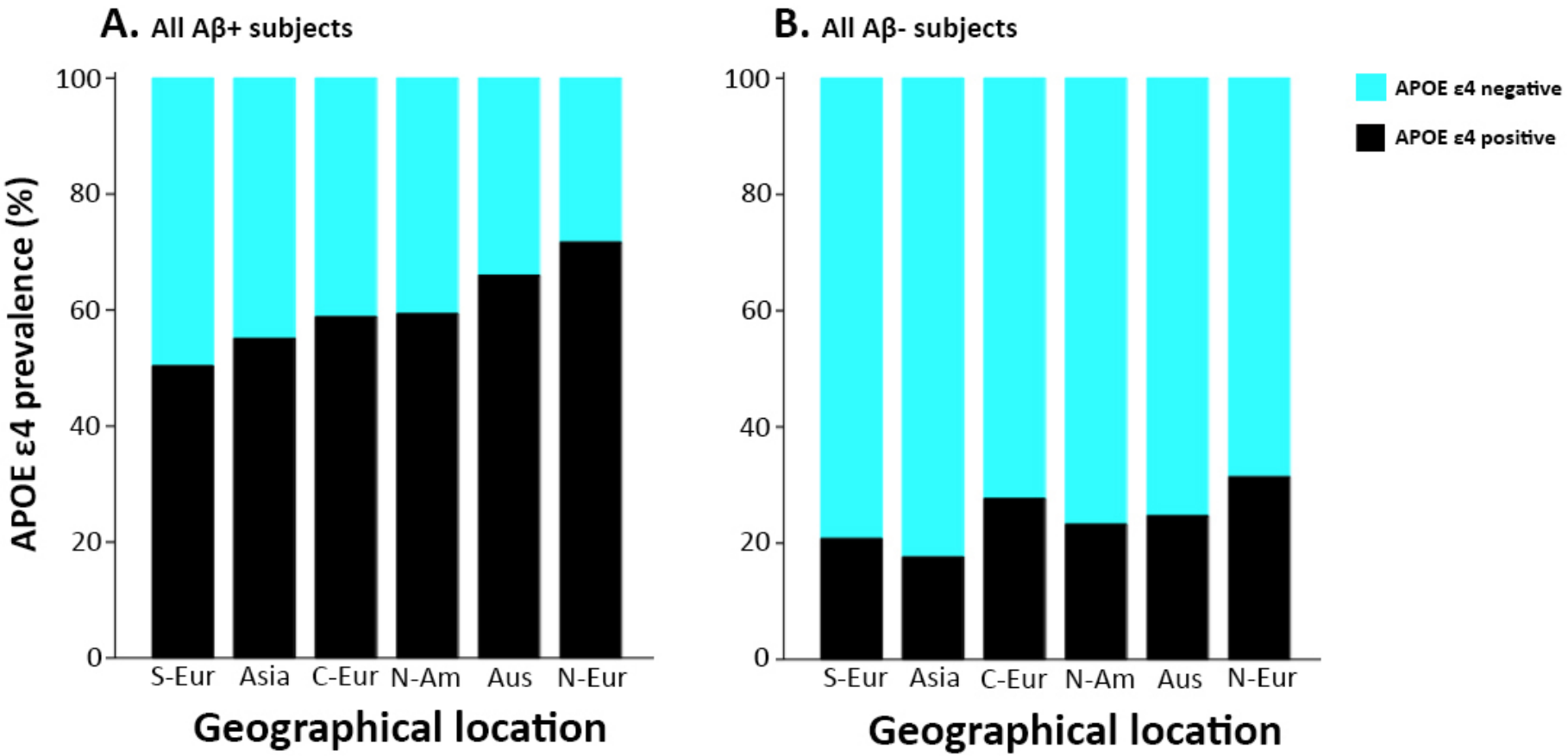

A. Aβ+ Cognitively normal
B. Aβ+ Mild cognitive impairment
C. Aβ- Cognitively normal
D. Aβ- Mild cognitive impairment
APOE ε4 prevalence (%)
100
80
60
40
20
0
Q1
Q2
Q3
Q4
Age
APOE ε4 negative
APOE ε4 heterozygous
APOE ε4 homozygous

FIGURE 3.


A. All Aβ+ subjects
B. All Aβ- subjects
APOE ε4 prevalence (%)
100
80
60
40
20
0
S-Eur
Asia
C-Eur
N-Am
Aus
N-Eur
Geographical location
APOE ε4 negative
APOE ε4 positive

SUPPLEMENTAL TABLE 1A. Characteristics for all contributing centers (Aβ+ and Aβ- combined)													
	CN			MCI			AD dementia						
Center	**N**	**APOE ε4 (% positive)**	**Age**	**N**	**APOE ε4 (% positive)**	**Age**	**N**	**APOE ε4 (% positive)**	**Age**	**Region**	**Modality**	**Method**	**Cut-off**
ADNI	480	25	74.9	695	49	72.8	158	68	75.7	North-America	PET CSF	Florbetapir, SUVr PiB, SUVr Luminex	1.11 1.114 192
AIBL	178	40	72.1	56	54	75.7	52	71	72.4	Australia	PET	PiB, SUVr	1.5
Antwerp	40	33	57.9	87	39	75.4				Central-Europe	CSF	Innotest	639
AVID				26	23	74.1	6	50	78.0	North-America	PET	Florbetapir, SUVr	Visual read
Barcelona	93	25	64.2	64	38	70.1				Southern-Europe	CSF	Innotest	500
Barcelona-SantPau	92	24	61.3	83	39	67.6	22	41	70.8	Southern-Europe	CSF	Innotest	550
Berkeley	75	28	75.6							North-America	PET	PiB, DVR	1.08
Brescia	81	20	53.0	104	40	70.7				Southern-Europe	CSF	Innotest	500
Brussels										Central-Europe	CSF	Innotest	430
Caen	74	24	60.8	17	41	71.9	15	73	70.5	Central-Europe	PET	Florbetapir, SUVr	1.1
Chandigargh	45	0	60.6							Asia	CSF	Innotest	662.65
Coimbra				60	47	69.4				Southern-Europe	CSF	Innotest	542
Dallas	106	24	71.3							North-America	PET	Florbetapir, SUVr	1.22
DCN				362	42	66.2				Central-Europe	CSF	Innotest	600
DESCRIPA	51	57	66.0	75	51	69.3				Multiple regions	CSF	Innotest	550

EDAR	20	40	66.7	54	54	68.7				Multiple regions	CSF	Luminex®	389
Gothenburg	113	36	63.9	89	49	61.5				Northern-Europe	CSF	Innotest	450
Krakow	5	20	69.4	12	8	74.1				Central-Europe	CSF	Innotest	380
Lausanne	15	40	68.5	18	44	73.4				Central-Europe	CSF	Innotest	550
LeARN	16	44	63.8	38	61	64.7				Multiple regions	PET CSF	PiB, BPnd; SUVr Innotest	Visual read 550
Leuven	16	19	70.9				15	60	73.2	Central-Europe	PET	Flutemetamol, SUVr; DVR PiB, SUVr; DVR	Visual read Visual read
London/Turku				17	41	71.7				Multiple regions	PET	PiB, SUVr	> 2 SD controls
Lorenskog	32	69	58.6	79	46	61.1				Northern-Europe	CSF	Innotest	550
Lund	292	29	73.0	217	49	71.2				Northern-Europe	CSF	Innotest	530
Mattsson	118	31	64.1	302	52	68.9				Multiple regions	CSF	Innotest	482
Melbourne	22	18	70.7	20	60	70.8	66	53	69.1	Australia	PET	Florbetaben, SUVr PiB, DVR	1.4/1.45 Visual read
Munich	15	53	64.2	14	50	68.9	41	61	66.7	Central-Europe	PET	PiB, SUVr	Visual read
Nijmegen	4	50	71.5	13	62	72.7				Northern-Europe	CSF	Innotest	500
Paris	8	25	66.4	10	40	70.9	20	40	62.6	Central-Europe	PET	PiB, SUVr	1.4
Pennsylvania	13	31	70.7							North-America	PET	PiB, SUVr	1.15
Phoenix	136	29	46.0	53	40	71.1	45	51	74.7	North-America	PET	Florbetapir, SUVr	1.08

Pittsburgh	148	21	77.8	93	40	75.6	51	75	70.7	North-America	PET	PiB, SUVr	1.67 (atrophy corrected)
Samsung				113	29	72.2	67	51	70.4	Asia	PET	PiB, SUVr	1.5
San Francisco	5	20	64.0	14	57	64.9	90	46	67.8	North-America	PET	PiB, DVR	Visual read
Santander	3	0	65.0	28	32	68.3	19	53	68.4	Southern-Europe	PET	PiB, SUVr	Visual read
Seoul	35	51	71.4	28	50	70.8	27	56	69.0	Asia	PET	PiB, SUVr	1.5
St. Louis	944	32	66.3	196	57	73.9	25	56	77.3	North-America	PET CSF	PiB, MCBP Innotest	0.18 459
Stockholm				19	68	62.1	26	81	68.0	Northern-Europe	PET CSF	PiB, SUVr Innotest	1.5 550
Thessaloniki				4	0	73.5				Southern-Europe	CSF	Innotest	450
Tours	20	45	68.6	10	50	76.4	10	70	67.5	Central-Europe	PET	Florbetapir, SUVr	Visual read
Turku				29	55	71.0	4	50	71.9	Northern-Europe	PET	PiB, SUVr	1.5
VUMC Amsterdam	255	37	64.2	230	56	68.8	211	68	62.8	Northern-Europe	PET CSF	PiB, BPnd & SUVr Innotest	Visual read 550

SUPPLEMENTAL TABLE 1B. Characteristics for all contributing centers (Aβ- groups only)												
	Aβ- CN			Aβ- MCI			Aβ- dementia					
Center	**N**	**APOE ε4 (% positive)**	**Age**	**N**	**APOE ε4 (% positive)**	**Age**	**N**	**APOE ε4 (% positive)**	**Age**	**Modality**	**Method**	**Cut-off**
ADNI	347	18	74.4	247	20	71.3	23	9	79.7	PET CSF	Florbetapir, SUVr PiB, SUVr Luminex	1.11 1.114 192
AIBL	123	29	70.4	20	15	73.5	1	0	80.3	PET	PiB, SUVr	1.5
Antwerp	28	25	52.7	32	22	75.5				CSF	Innotest	639
AVID				18	6	74.3	2	0	82	PET	Florbetapir, SUVr	Visual read
Barcelona	71	21	62.4	24	13	68.5				CSF	Innotest	500
Barcelona-SantPau	81	20	61	43	21	66.2				CSF	Innotest	550
Berkeley	39	23	75.7							PET	PiB, DVR	1.08
Brescia	66	18	51.2	49	20	70.8				CSF	Innotest	500
Brussels	2	0	66	1	0	68				CSF	Innotest	430
Caen	65	20	59.3	9	22	70.8	2	50	81.5	PET	Florbetapir, SUVr	1.1
Chandigargh	42	0	60							CSF	Innotest	662.65
Coimbra				32	41	69.2				CSF	Innotest	542
Dallas	89	21	70.8							PET	Florbetapir, SUVr	1.22
DCN				217	31	64.8				CSF	Innotest	600
DESCRIPA	29	41	64.3	20	50	67.1				CSF	Innotest	550
EDAR	16	50	66.1	26	35	67.2				CSF	Luminex®	389
Gothenburg	95	33	63.9	62	42	60.5				CSF	Innotest	450
Krakow	4	0	70.8	11	0	73.7				CSF	Innotest	380
Lausanne	15	40	68.5	18	44	73.4						
LeARN	12	33	62.2	16	56	65.1				PET CSF	PiB, BPnd; SUVr Innotest	Visual read 550
Leuven	13	8	72.6				3	0	78.7	PET	Flutemetamol, SUVr; DVR PiB, SUVr; DVR	Visual read Visual read
London/Turku				7	14	70.9				PET	PiB, SUVr	> 2 SD controls

Lorenskog	23	70	56.8	61	36	59.9				CSF	Innotest	550
Lund	215	19	72.9	89	18	70.4				CSF	Innotest	530
Mattsson	83	20	63.1	126	33	66.5				CSF	Innotest	482
Melbourne	17	12	71	6	17	64.8	3	0	66	PET	Florbetaben, SUVr PiB, DVR	1.4/1.45 Visual read
Munich	12	50	63.4	10	50	70.2	4	25	61.3	PET	PiB, SUVr	Visual read
Nijmegen	2	50	73.5	7	29	73.3				CSF	Innotest	500
Paris	8	25	66.4	2	0	81.9	1	0	64.9	PET	PiB, SUVr	1.4
Pennsylvania	10	20	72.6							PET	PiB, SUVr	1.15
Phoenix	119	27	42.2	29	17	69.3	7	0	76.3	PET	Florbetapir, SUVr	1.08
Pittsburgh	81	12	74.3	33	27	69.5	2	100	79	PET	PiB, SUVr	1.67 (atrophy corrected)
Samsung				63	8	71.6	7	43	76.7	PET	PiB, SUVr	1.5
San Francisco	4	25	61.8	7	43	61.1	10	20	70.2	PET	PiB, DVR	Visual read
Santander	3	0	65	11	18	66.5	1	0	64	PET	PiB, SUVr	Visual read
Seoul	29	48	71.6	13	38	69.5	5	20	76.8	PET	PiB, SUVr	1.5
St. Louis	793	27	65.3	78	37	71.9	6	17	73.3	PET CSF	PiB, MCBP Innotest	0.18 459
Stockholm				6	50	62.1	3	100	66	PET CSF	PiB, SUVr Innotest	1.5 550
Thessaloniki				4	0	73.5			70			
Tours	7	14	68.7	4	25	79.3	2	0	64	PET	Florbetapir, SUVr	Visual read
Turku				10	30	70.4				PET	PiB, SUVr	1.5
VUMC Amsterdam	221	33	63.6	114	39	67.8	35	37	71.9	PET CSF	PiB, SUVr; BPnd Innotest	Visual read 550

SUPPLEMENTAL TABLE 1C. Characteristics for all contributing centers (Aβ+ group only)												
	Aβ+ CN			Aβ+ MCI			Aβ+ AD dementia					
Center	**N**	**APOE ε4 (% positive)**	**Age**	**N**	**APOE ε4 (% positive)**	**Age**	**N**	**APOE ε4 (% positive)**	**Age**	**Modality**	**Method**	**Cut-off**
ADNI	133	42	76.2	448	65	73.6	135	79	75.1	PET CSF	Florbetapir, SUVr PiB, SUVr Luminex	1.11 1.114 192
AIBL	55	65	75.9	36	75	76.9	51	73	72.2	PET	PiB, SUVr	1.5
Antwerp	12	50	69.8	55	49	75.4				CSF	Innotest	639
AVID				8	63	73.6	4	75	76.0	PET	Florbetapir, SUVr	Visual read
Barcelona	22	36	70.0	40	53	71.0				CSF	Innotest	500
Barcelona-SantPau	11	55	64.2	40	58	69.0	22	41	70.8	CSF	Innotest	550
Berkeley	36	33	75.6							PET	PiB, DVR	1.08
Brescia	15	27	60.5	55	58	70.6				CSF	Innotest	500
Brussels				5	60	69.0				CSF	Innotest	430
Caen	9	56	71.9	8	63	73.3	13	77	68.8	PET	Florbetapir, SUVr	1.1
Chandigargh	3	0	69.0							CSF	Innotest	662.65
Coimbra				28	54	69.5				CSF	Innotest	542
Dallas	17	35	73.9							PET	Florbetapir, SUVr	1.22
DCN				145	59	68.3				CSF	Innotest	600
DESCRIPA	22	77	68.2	55	51	70.1				CSF	Innotest	550
EDAR	4	0	68.8	28	71	70.1				CSF	Luminex®	389
Gothenburg	18	56	64.3	27	67	63.8				CSF	Innotest	450
Krakow	1	100	64.0	1	100	78.0				CSF	Innotest	380
LeARN	4	75	68.5	22	64	64.4				PET CSF	PiB, BPnd; SUVr Innotest	Visual read 550
Leuven	3	67	63.3				12	75	71.8	PET	Flutemetamol, SUVr; DVR PiB, SUVr; DVR	Visual read Visual read
London/Turku				10	60	72.3				PET	PiB, SUVr	> 2 SD controls
Lorenskog	9	67	63.1	18	78	65.3				CSF	Innotest	550
Lund	77	58	73.3	128	70	71.8				CSF	Innotest	530

Mattsson	35	54	66.5	176	65	70.6				CSF	Innotest	482
Melbourne	5	40	69.7	14	79	73.4	63	56	69.2	PET	Florbetaben, SUVr PiB, DVR	1.4/1.45 Visual read
Munchen	3	67	67.3	4	50	65.5	37	65	67.3	PET	PiB, SUVr	Visual read
Nijmegen	2	50	69.5	6	100	72.0				CSF	Innotest	500
Paris				8	50	68.1	19	42	62.5	PET	PiB, SUVr	1.4
Pennsylvania	3	67	64.3							PET	PiB, SUVr	1.15
Phoenix	17	41	72.5	24	67	73.3	38	61	74.4	PET	Florbetapir, SUVr	1.08
Pittsburgh	67	31	81.9	60	47	78.9	49	74	70.3	PET	PiB, SUVr	1.67 (atrophy corrected)
Samsung				50	56	72.8	60	52	69.7	PET	PiB, SUVr	1.5
San Francisco	1	0	73.0	7	71	68.7	80	49	67.5	PET	PiB, DVR	Visual read
Santander				17	41	69.5	18	56	68.6	PET	PiB, SUVr	Visual read
Seoul	6	67	70.8	15	60	71.9	22	64	67.2	PET	PiB, SUVr	1.5
St. Louis	151	60	71.7	118	69	75.2	19	68	78.5	PET CSF	PiB, MCBP Innotest	0.18 459
Stockholm				13	77	62.0	23	78	68.3	PET CSF	PiB, SUVr Innotest	1.5 550
Tours	13	62	68.5	6	67	74.5	8	88	66.9	PET	Florbetapir, SUVr	Visual read
Turku				19	68	71.3	4	50	71.9	PET	PiB, SUVr	1.5
VUMC Amsterdam	34	65	67.8	116	73	69.7	176	74	62.6	PET CSF	PiB, SUVr; BPnd Innotest	Visual read 550

Supplementary Table 2. Characteristics for APOE ε4 +/- in Aβ+ controls, MCI and AD dementia subjects

	Aβ+ CN		**Aβ+ MCI**		**Aβ+ AD dementia**	
	APOE ε4 - (n=387)	**APOE ε4 + (n=401)**	**APOE ε4 - (n=661)**	**APOE ε4 + (n=1149)**	**APOE ε4 - (n=289)**	**APOE ε4 + (n=564)**
Age[a]	73.8±10.0	71.5±8.7	73.0±8.7	71.0±7.5	68.8±10.4	69.3±8.7
Sex % (male)	47.9	46.6	53.0	52.5	55.8	55.1
MMSE	28.9±1.2	28.7±1.3	26.5±2.6	26.5±2.5	21.3±5.2	21.8±4.7
Education, yrs	14.5±3.6	14.1±4.0	12.6±4.7	13.0±4.2	13.8±3.7	13.9±3.6
Modality for Aβ positivity (% PET vs % CSF)	37.5/62.5	36.4/63.6	75.8/24.2	78.0/22.0	100/0	100/0

Data are presented as mean±SD unless indicated otherwise. Differences between APOE ε4 positive and negative groups were assessed using independent sample t-tests [age, education, MMSE] and X^2 tests (sex, modality and APOE ε4 status).

[a] APOE ε4 negative preclinical AD/prodromal AD > APOE ε4 positive preclinical AD/prodromal AD, $p<0.01$

AD = Alzheimer's disease; MMSE = Mini-mental state examination; PET = Positron emission tomography; CSF = Cerebrospinal fluid; APOE = Apolipoprotein E.

Supplementary Table 3. Main and interaction effects of age, diagnosis, sex, education and geographical location on APOE status

	Aβ positive								Aβ negative							
	Total		**CN**		**MCI**		**AD**		**Total**		**CN**		**MCI**		**AD**	
	β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p
Age	-0.020	0.021	-0.021	0.031	-0.03	0.004	0.005	0.656	-0.023	0.000	-0.025	0.000	-0.026	0.000	-0.013	0.549
Dx	0.365	0.001							0.104	0.171						
Age*Dx		0.017														
Sex	-0.005	0.93	-0.038	0.694	-0.02	0.739	-0.046	0.757	-0.114	0.130	-0.088	0.36	-0.188	0.062	-0.297	0.313
Age*Sex		0.018				0.010										
Age*Sex*Dx		0.001														
Edu	-0.117	0.130	-0.210	0.177	0.032	0.753	-0.143	0.372	-0.091	0.327	-0.142	0.256	-0.062	0.645	-0.128	0.801
Age*Edu								0.019								
Age*Edu*Dx																
Geo. Location	-0.009	0.812	-0.049	0.207	-0.070	0.313	0.061	0.095	0.049	0.49	-0.022	0.578	-0.037	0.533	-0.313	0.023
Age*Geo. Location		0.006		0.000		0.028										
Age*Geo. Location*Dx		0.033														

β coefficients and p values of significant main and interactions are displayed, as derived from generalized estimating equation models.

Abbreviations: AD = Alzheimer's disease; CN = Cognitively normal; Dx = Diagnosis; Edu = Education; Geo. Location = Geographical location; MCI = Mild cognitive impairment

Supplementary table 4. Differences according to geographical location

		Amyloid-beta positive			Amyloid-beta negative		
		APOE ε4+ (%)	**Prevalence APOE ε4+ greater than**	**p**	**APOE ε4+ (%)**	**Prevalence APOE ε4+ greater than**	**p**
North-America	**Total**	59	Southern-Europe	0.007	23		
	CN	63			27		
	MCI	76	Central-Europe Southern-Europe	0.041 0.020	15	Asia	0.050
	AD	63	Southern-Europe Asia	0.014 0.038	-		
Australia	**Total**	66	Southern-Europe* Asia	0.000 0.033	25		
	CN	46	North-America Southern-Europe	0.013 0.011	23		
	MCI	64	Central-Europe Southern-Europe Asia	0.011 0.006 0.048	23		
	AD	68			14		
Northern-Europe	**Total**	70	North-America* Central-Europe* Southern-Europe* Asia*	0.000 0.000 0.000 0.000	31	North-America* Southern-Europe* Asia*	0.000 0.000 0.000
	CN	60	North-America* Southern-Europe	0.003 0.007	29	North-America Southern-Europe	0.008 0.007
	MCI	72	North-America Central-Europe* Southern-Europe* Asia	0.017 0.000 0.000 0.027	34	North-America* Southern-Europe Asia*	0.001 0.008 0.000
	AD	74	Southern-Europe* Asia*	0.002 0.003	47	North-America	0.004
Central-Europe	**Total**	59	Southern-Europe	0.036	28	North-America Southern-Europe Asia	0.030 0.021 0.011
	CN	59			23		
	MCI	57			30	North-America Asia*	0.039 0.002
	AD	65			17		
Southern-Europe		50			21		
	CN	38			20		
	MCI	54			23		
	AD	48			-		
Asia		55			18		
	CN	-			20		
	MCI	57			14		
	AD	55			33		

SUPPLEMENTAL FIGURE LEGENDS:

Figure S1. Prevalence of APOE ε4 positivity by age, diagnosis and Aβ status

95% confidence intervals of slopes included in Figure 1 for cognitively normal (A), mild cognitive impairment (B) and Alzheimer dementia (C). Curves were plotted using the point estimates generated by generalized estimating equations and are within the age limits of the diagnostic groups, adjusted for study (site) effect.

Figure S2. Prevalence of APOE ε4 in AD dementia without atypical variants

The slopes indicate that the prevalence of APOE ε4 was similar when including or excluding subjects with an atypical (non-amnestic) presentation of AD dementia.

Figure S3.

Distribution of APOE ε4 negative and APOE ε4 positive subjects by geographical location for all Aβ+ (A-C) and Aβ- (D, E) participants across diagnostic groups.

Aβ = Amyloid-beta; APOE = Apolipoprotein E

FIGURE S1.

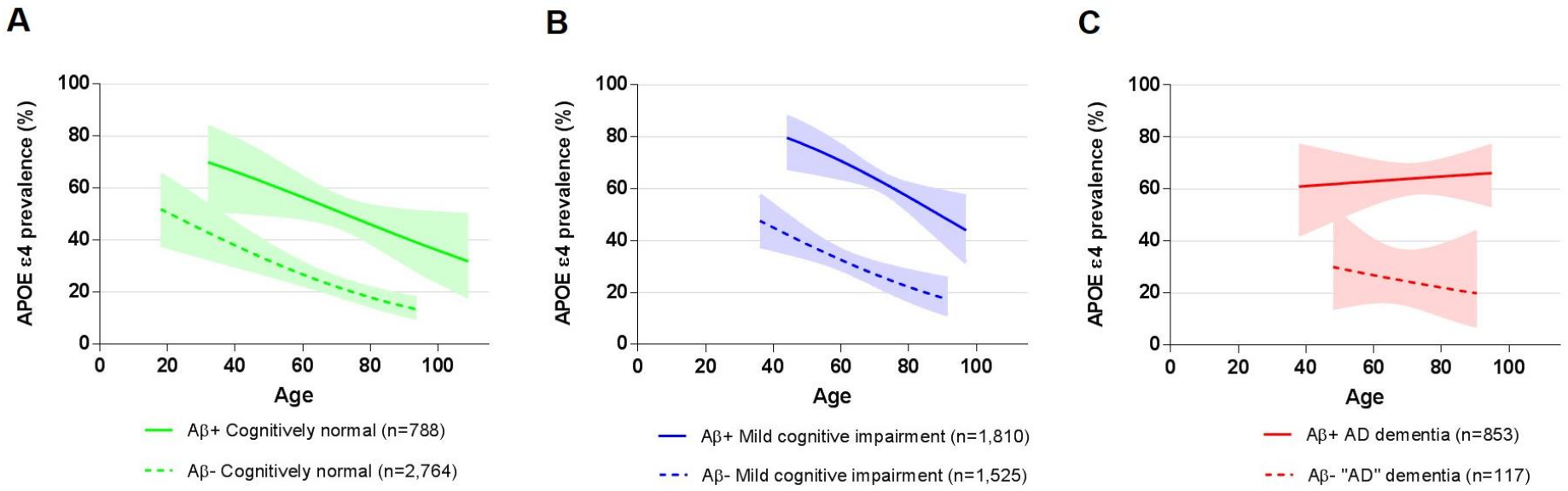

A
B
C
APOE ε4 prevalence (%)
Age
0
20
40
60
80
100
Aβ+ Cognitively normal (n=788)
Aβ- Cognitively normal (n=2,764)
Aβ+ Mild cognitive impairment (n=1,810)
Aβ- Mild cognitive impairment (n=1,525)
Aβ+ AD dementia (n=853)
Aβ- "AD" dementia (n=117)

FIGURE S2.

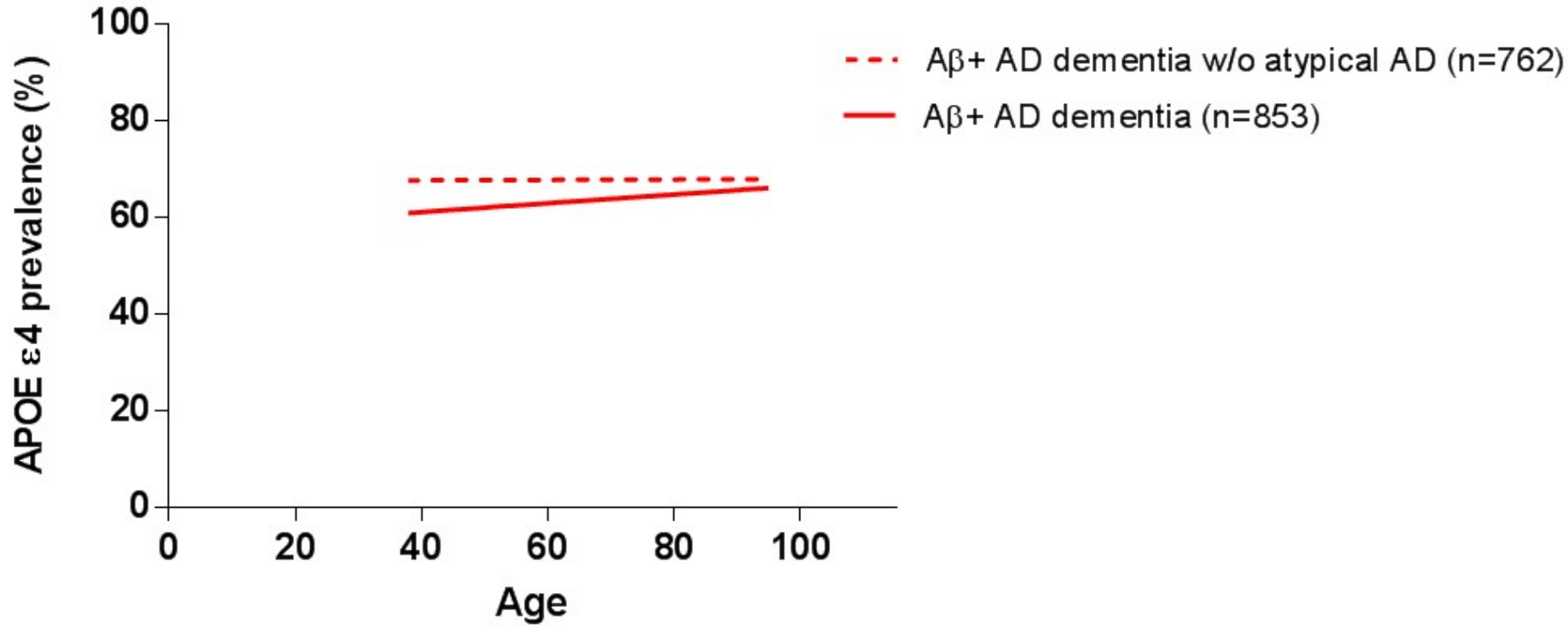
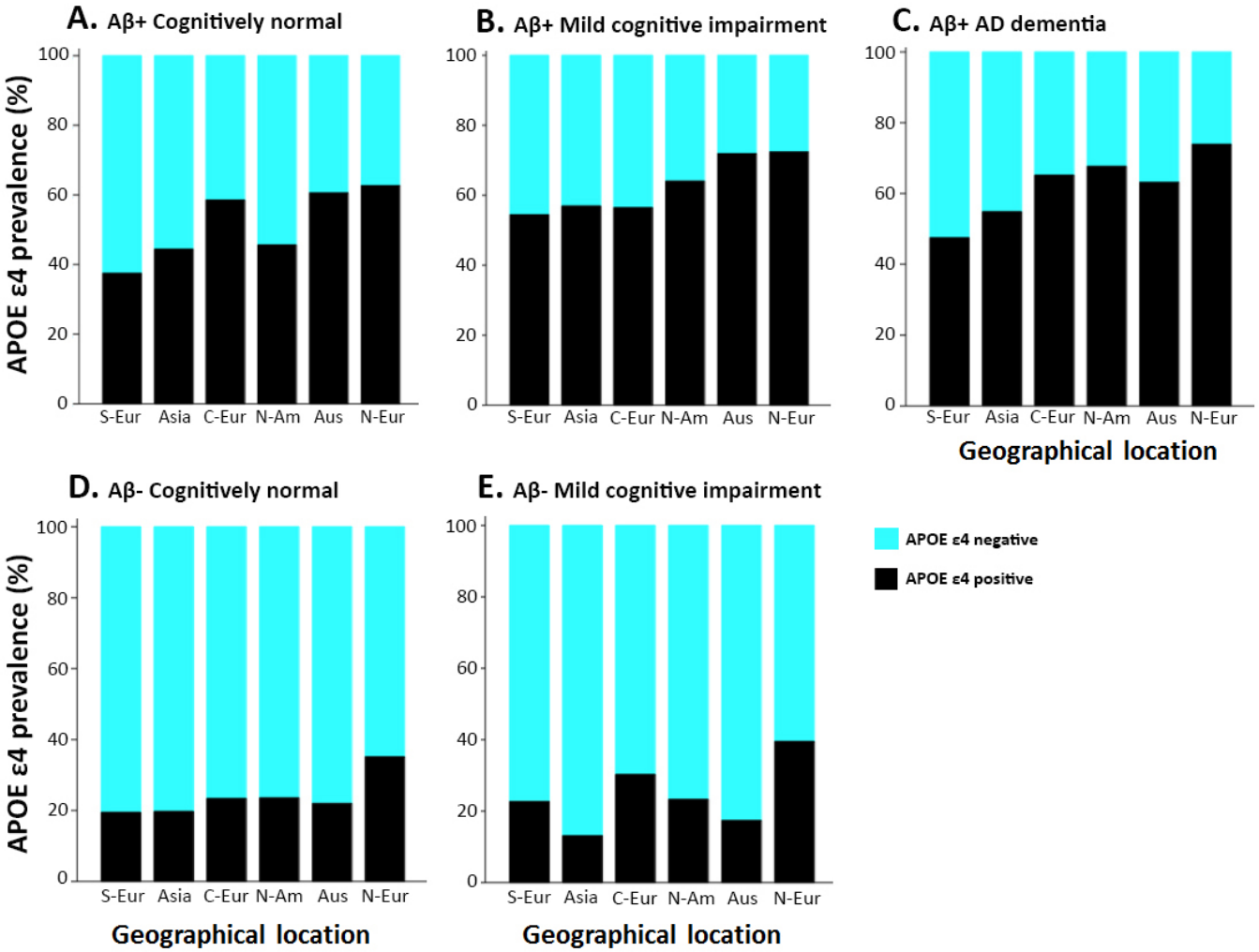

APOE ε4 prevalence (%)
100
80
60
40
20
0
0
20
40
60
80
100
Age
Aβ+ AD dementia w/o atypical AD (n=762)
Aβ+ AD dementia (n=853)

FIGURE S3.


A. Aβ+ Cognitively normal
B. Aβ+ Mild cognitive impairment
C. Aβ+ AD dementia
D. Aβ- Cognitively normal
E. Aβ- Mild cognitive impairment
APOE ε4 prevalence (%)
0
20
40
60
80
100
S-Eur
Asia
C-Eur
N-Am
Aus
N-Eur
Geographical location
APOE ε4 negative
APOE ε4 positive

REFERENCES:

Lopez OL, Jagust WJ, DeKosky ST, et al. 2003. Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1. Arch Neurol 60: 1385–1389

1. Scheltens P, Blennow K, Breteler MM, et al. Alzheimer's disease. *Lancet.* 2016.
2. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science.* 1992;256(5054):184-185.
3. Jack CR, Jr., Holtzman DM. Biomarker modeling of Alzheimer's disease. *Neuron.* 2013;80(6):1347-1358.
4. Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med.* 2012;367(9):795-804.
5. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA.* 2015;313(19):1924-1938.
6. Jack CR, Jr., Therneau TM, Wiste HJ, et al. Transition rates between amyloid and neurodegeneration biomarker states and to dementia: a population-based, longitudinal cohort study. *Lancet Neurol.* 2016;15(1):56-64.
7. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet.* 2017.
8. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science.* 1993;261(5123):921-923.
9. Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet.* 1993;342(8873):697-699.
10. Raichlen DA, Alexander GE. Exercise, APOE genotype, and the evolution of the human lifespan. *Trends Neurosci.* 2014;37(5):247-255.
11. Ringman JM, Coppola G. New genes and new insights from old genes: update on Alzheimer disease. *Continuum (Minneap Minn).* 2013;19(2 Dementia):358-371.
12. Ward A, Crean S, Mercaldi CJ, et al. Prevalence of apolipoprotein E4 genotype and homozygotes (APOE e4/4) among patients diagnosed with Alzheimer's disease: a systematic review and meta-analysis. *Neuroepidemiology.* 2012;38(1):1-17.
13. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. *J Neuropathol Exp Neurol.* 2012;71(4):266-273.
14. Ossenkoppele R, Prins ND, Pijnenburg YA, et al. Impact of molecular imaging on the diagnostic process in a memory clinic. *Alzheimers Dement.* 2013;9(4):414-421.
15. Palmqvist S, Zetterberg H, Mattsson N, et al. Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer disease. *Neurology.* 2015;85(14):1240-1249.
16. Chetelat G, Ossenkoppele R, Villemagne VL, et al. Atrophy, hypometabolism and clinical trajectories in patients with amyloid-negative Alzheimer's disease. *Brain.* 2016;139(Pt 9):2528-2539.
17. Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med.* 2014;370(4):322-333.
18. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol.* 2014;13(6):614-629.
19. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):270-279.

20. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):280-292.
21. Louwersheimer E, Wolfsgruber S, Espinosa A, et al. Alzheimer's disease risk variants modulate endophenotypes in mild cognitive impairment. *Alzheimers Dement.* 2016;12(8):872-881.
22. Jack CR, Jr., Wiste HJ, Weigand SD, et al. Age-specific population frequencies of cerebral beta-amyloidosis and neurodegeneration among people with normal cognitive function aged 50-89 years: a cross-sectional study. *Lancet Neurol.* 2014;13(10):997-1005.
23. Morris JC, Roe CM, Xiong C, et al. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol.* 2010;67(1):122-131.
24. Papp KV, Rentz DM, Mormino EC, et al. Cued memory decline in biomarker-defined preclinical Alzheimer disease. *Neurology.* 2017;88(15):1431-1438.
25. Ossenkoppele R, Jansen WJ, Rabinovici GD, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *JAMA.* 2015;313(19):1939-1949.
26. Palmqvist S, Zetterberg H, Blennow K, et al. Accuracy of brain amyloid detection in clinical practice using cerebrospinal fluid beta-amyloid 42: a cross-validation study against amyloid positron emission tomography. *JAMA Neurol.* 2014;71(10):1282-1289.
27. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement.* 2014;10(6):844-852.
28. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):263-269.
29. Zwan M, van Harten A, Ossenkoppele R, et al. Concordance between cerebrospinal fluid biomarkers and [11C]PIB PET in a memory clinic cohort. *J Alzheimers Dis.* 2014;41(3):801-807.
30. Landau SM, Lu M, Joshi AD, et al. Comparing positron emission tomography imaging and cerebrospinal fluid measurements of beta-amyloid. *Ann Neurol.* 2013;74(6):826-836.
31. Tilvis RS, Strandberg TE, Juva K. Apolipoprotein E phenotypes, dementia and mortality in a prospective population sample. *J Am Geriatr Soc.* 1998;46(6):712-715.
32. Wang X, Lopez O, Sweet RA, et al. Genetic Determinants of Survival in Patientswith Alzheimer's Disease. *J Alzheimers Dis.* 2015;45(2):651-658.
33. Beydoun MA, Beydoun HA, Kaufman JS, et al. Apolipoprotein E epsilon4 allele interacts with sex and cognitive status to influence all-cause and cause-specific mortality in U.S. older adults. *J Am Geriatr Soc.* 2013;61(4):525-534.
34. Donohue MC, Sperling RA, Petersen R, et al. Association Between Elevated Brain Amyloid and Subsequent Cognitive Decline Among Cognitively Normal Persons. *JAMA.* 2017;317(22):2305-2316.
35. Ossenkoppele R, Mattsson N, Teunissen CE, et al. Cerebrospinal fluid biomarkers and cerebral atrophy in distinct clinical variants of probable Alzheimer's disease. *Neurobiol Aging.* 2015;36(8):2340-2347.
36. Cohen ML, Kim C, Haldiman T, et al. Rapidly progressive Alzheimer's disease features distinct structures of amyloid-beta. *Brain.* 2015;138(Pt 4):1009-1022.
37. Ossenkoppele R, van der Flier WM, Zwan MD, et al. Differential effect of APOE genotype on amyloid load and glucose metabolism in AD dementia. *Neurology.* 2013;80(4):359-365.
38. Corrada MM, Paganini-Hill A, Berlau DJ, Kawas CH. Apolipoprotein E genotype, dementia, and mortality in the oldest old: the 90+ Study. *Alzheimers Dement.* 2013;9(1):12-18.
39. Dumanis SB, Tesoriero JA, Babus LW, et al. ApoE4 decreases spine density and dendritic complexity in cortical neurons in vivo. *J Neurosci.* 2009;29(48):15317-15322.

40. Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. *Neuron.* 2009;63(3):287-303.
41. Liu Y, Yu JT, Wang HF, et al. APOE genotype and neuroimaging markers of Alzheimer's disease: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry.* 2015;86(2):127-134.
42. Jagust WJ, Landau SM, Alzheimer's Disease Neuroimaging I. Apolipoprotein E, not fibrillar beta-amyloid, reduces cerebral glucose metabolism in normal aging. *J Neurosci.* 2012;32(50):18227-18233.
43. Reiman EM, Chen K, Alexander GE, et al. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proc Natl Acad Sci U S A.* 2004;101(1):284-289.
44. Norberg J, Graff C, Almkvist O, et al. Regional differences in effects of APOE epsilon4 on cognitive impairment in non-demented subjects. *Dement Geriatr Cogn Disord.* 2011;32(2):135-142.
45. Arboleda GH, Yunis JJ, Pardo R, et al. Apolipoprotein E genotyping in a sample of Colombian patients with Alzheimer's disease. *Neurosci Lett.* 2001;305(2):135-138.
46. Corbo RM, Scacchi R. Apolipoprotein E (APOE) allele distribution in the world. Is APOE*4 a 'thrifty' allele? *Ann Hum Genet.* 1999;63(Pt 4):301-310.
47. Insel PS, Palmqvist S, Mackin RS, et al. Assessing risk for preclinical beta-amyloid pathology with APOE, cognitive, and demographic information. *Alzheimers Dement (Amst).* 2016;4:76-84.
48. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA.* 1997;278(16):1349-1356.
49. Mattsson N, Insel PS, Palmqvist S, et al. Increased amyloidogenic APP processing in APOE varepsilon4-negative individuals with cerebral beta-amyloidosis. *Nat Commun.* 2016;7:10918.