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Prospective Evaluation of Cognitive Health and Related Factors in Elderly at Risk for Developing Alzheimer's Dementia: A Longitudinal Cohort Study

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Abstract

BACKGROUND: The CHARIOT PRO Main study is a prospective, non-interventional study evaluating cognitive trajectories in participants at the preclinical stage of Alzheimer's disease (AD) classified by risk levels for developing mild cognitive impairment due to AD (MCI-AD).

OBJECTIVES: The study aimed to characterize factors and markers influencing cognitive and functional progression among individuals at-risk for developing MCI-AD, and examine data for more precise predictors of cognitive change, particularly in relation to APOE ε4 subgroup.

DESIGN: This single-site study was conducted at the Imperial College London (ICL) in the United Kingdom. Participants 60 to 85 years of age were classified as high, medium (amnestic or non-amnestic) or low risk for developing MCI-AD based on RBANS z-scores. A series of clinical outcome assessments (COAs) on factors influencing baseline cognitive changes were collected in each of the instrument categories of cognition, lifestyle exposure, mood, and sleep. Data collection was planned to occur every 6 months for 48 months, however the median follow-up time was 18.1 months due to early termination of study by the sponsor.

RESULTS: 987 participants were screened, among them 690 participants were actively followed-up post baseline, of whom 165 (23.9%) were APOE ε4 carriers; with at least one copy of the allele. The mean age was 68.73 years, 94.6% were white, 57.4% were female, and 34.8% had a Family History of Dementia with a somewhat larger percentage in the APOE ε4 carrier group (42.4%) compared to the non-carrier group (32.4%). Over half of the participants were married and 53% had a Bachelor's or higher degree. Most frequently, safety events typical for this population consisted of upper respiratory tract infection (10.4%), falls (5.2%), hypertension (3.5%) and back pain (3.0%).

CONCLUSION (clinical relevance): AD-related measures collected during the CHARIOT PRO Main study will allow identification and evaluation of AD risk factors and markers associated with cognitive performance from the pre-clinical stage. Evaluating the psycho-biological characteristics of these pre-symptomatic individuals in relation to their natural neurocognitive trajectories will enhance current understanding on determinants of the initial signs of cognitive changes linked to AD.

Key words: CHARIOT, aging registry, cognitive health, pre-clinical, Alzheimer Disease.

Introduction

An increasing body of scientific evidence suggests that, in the field of Alzheimer's disease (AD), the optimal time to intervene with disease-modifying therapies is prior to the emergence of clinical symptoms of mild cognitive impairment (MCI) or AD dementia (1). The term "asymptomatic at-risk state for AD" (ARAD) (2) has been proposed as a descriptor for asymptomatic individuals with evidence of cerebral amyloid-β (Aβ) burden. Such individuals are at increased risk of progression to clinically symptomatic AD (3) and hence, potentially, good candidates for trials of preventative interventions.

Amongst cognitively normal (CN) individuals, subtle deficits or decreases in cognitive performance over time (even within the range of "normal" values) have been found to be associated with higher Aβ burden and/or carriage of the apolipoprotein (APOE) epsilon 4 allele with subsequent cognitive decline (3) and progression to MCI or dementia due to AD (4, reviewed in 5). This suggests that evolution of certain cognitive profiles may be sufficient in themselves (even in the absence of supporting biomarker information) to constitute an ARAD.

However, a putative ARAD cognitive profile has not

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yet been clearly identified or specified. Whereas many publications have focused on what may be termed 'late' MCI defined as individuals most likely to transition to dementia within a year or two, information is limited on cognitive characterization of memory and other cognitive domains and how these manifest and change, in cognitively healthy individuals in the "pre-clinical" stages. Such information may indeed improve our understanding of the natural evolution of AD over time both cognitively and functionally, and help to identify opportunities for intervention.

The goals of this non-interventional cohort study were (a) to prospectively collect information on cognitively healthy individuals to determine the value of biomedical, lifestyle and neuropsychological markers in predicting clinical progression or cognitive decline consistent with AD; and (b) to develop a well-characterized longitudinally followed, prospective readiness cohort, asymptomatic yet at risk for AD for future clinical trials. Here, we report on the methods employed for the extensive phenotyping of the study participants, as well as the population characteristics of the sample at baseline.

Methods

Study design

The CHARIOT (Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in dementia Research) PRO (Prospective Readiness cOhort) Main Study was a prospective, single center, non-interventional study conducted at the Imperial College London (ICL) in the United Kingdom. The Main Study recruited participants between the ages of 60-85 years from the CHARIOT Register at ICL, or self-referred. The CHARIOT Register is a community-based research register of older individuals without a diagnosis of dementia in the United Kingdom, who have provided informed consent to be invited to interventional and non-interventional studies for the prevention of AD and other age-related neurodegenerative diseases. The Register is managed by physicians, investigators, and staff of the School of Public Health (SPH) at ICL. Established in 2011, the Register is based on a collaboration between SPH and General Practitioner surgeries in central and west London, and now consists of ~ 30,000 consented volunteers (6).

The planned sample size of enrolled participants for the CHARIOT PRO Main study was 700. In order to yield sufficient likelihood of detecting a rare event (e.g., progression to MCI-AD), 630 participants should be enrolled with consideration of 10% overall dropout rate.

Table 1S of Supplementary Material presents the precision estimates with a sample size of 630 for varying rates (proportions) of rare event of interest. For example, with a sample size of 630 participants, the probability of detecting at least one event with a true event rate of 0.001 is 46.8%, and for all others it is greater than this. In total, 987 participants were screened, and 712 were eligible for follow-up, with 690 actively followed-up post baseline.

The Main Study was conducted in accordance with Good Clinical Practice (GCP) Guidelines, Guidelines for Good Pharmacovigilance Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), applicable national guidelines, and to the Declaration of Helsinki. An independent ethics committee approved participant written informed consent forms before enrollment collected during the baseline clinic visit.

Objectives

The investigations were aimed at better understanding the natural history of cognitive changes in asymptomatic participants that may precede the occurrence of clinically overt MCI or dementia due to AD. In addition, the study aimed to evaluate the sensitivity of baseline neuropsychological, biological and lifestyle measures for predicting longitudinal AD-related cognitive decline, in order to improve screening of individuals at risk for developing AD for future clinical trials.

Study population and selection criteria

Individuals aged 60 to 85 years without dementia were recruited and screened from the CHARIOT Register or self-referred. Concomitant therapies for treatment of stable medical conditions known in older population were permitted.

Participants were not eligible for enrollment if they met any of the following exclusion criteria: a previous diagnosis of dementia, MCI or other neurological disease or condition (such as Parkinson's disease); met criteria for AD dementia (per National Institute on Aging-Alzheimer's Association) at baseline; a history of traumatic brain injury, stroke or evidence of transient ischemic attack (TIA); epileptic seizures – excluding febrile seizures in childhood; significant psychiatric illness; hydrocephalus at any time; uncontrolled hypothyroidism or hyperthyroidism; any clinically significant unstable illness, metabolic problems or nutritional deficiencies; a clinically significant infection within 30 days of study entry; HIV positivity; history of alcohol or drug dependence or abuse; used memantine or cholinesterase inhibitors; chronically used medications known to impair cognition such as sedatives, anticonvulsants, or pain medications; had significant sensory or motor dysfunction; any physical disability that would prevent completion of study procedures or assessments; concurrent participation in an interventional or non-interventional trial (with exceptions, also based on PI judgement). Following baseline assessment, participants were excluded from

follow-up if their age- and education-adjusted cognitive performance (z-score) on any Index of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) fell more than 1.5 standard deviations below normal (unless adjudicated for inclusion by the sponsor's medical monitor).

Sample size, schedule of events

The study aimed to enroll 700 participants. Over a two-year period, 987 participants were screened and 712 were enrolled. All enrolled participants were genotyped for apolipoprotein ε4 (APOE ε4) allele carrier or non-carrier status, and both participants and study investigators were blinded to APOE genotype status. Screening and baseline assessments were performed by study investigators, including trained psychometricians across one or two visits within 30 days. Enrolled participants were evaluated across the large number of study instruments every six months from baseline, for four years. The trial, however, was terminated early by the sponsor such that median follow-up time reached 18.1 months.

Outreach to participants who failed to attend their regularly scheduled bi-annual visit followed a 2-step approach. First, three attempts were made to contact the participant (via email or telephone within 1 week), and if needed a second step involved contact by a regular mail letter with delivery confirmation sent to participant's home. If the participant failed to respond to all outreach attempts, they were considered lost to follow-up.

Evaluations and Outcome Measures

Data collected at each time point per schedule of assessments is shown in Table 2S of Supplementary Materials. These included evaluations of medical status, vital signs, anthropometrics, cognitive function, mood, sleep, diet, physical and leisure activity, functional activity and biological sample collection (urine, saliva and blood). Use of medications known to impair cognition was prohibited within 48 hours or 4 times the half-life (whichever longer) before baseline cognitive assessments. All outcome measures were administered by or under the supervision of a qualified health professional or psychologist as appropriate.

At the time of initial enrollment, participants were classified as hypothetically at high (67, 9.4%), medium (91, 12.8%) or low (554, 77.8%) risk for developing MCI-AD, based on the participant's age and education-adjusted baseline cognitive performance on the RBANS Indices, as shown in Table 1.

Table 1. Participant Risk Group Classification

Risk Group Classification	RBANS Immediate and or Delayed Memory Index Score	Other RBANS Non-memory Domain(s)
High Risk	-0.6 to ≥-1.5 SD below normal	One or more -0.6 to ≥-1.5 SD below normal
*Medium Risk (amnestic)	-0.6 to ≥-1.5 SD below normal	All > -0.6 SD below normal
*Medium Risk (nonamnestic)	> -0.6 SD below normal	One or more -0.6 to ≥-1.5 SD below normal
Low Risk	> -0.6 SD below normal	All > -0.6 SD below normal

RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, SD = standard deviation

Cognition

All participants completed the RBANS, Mini Mental State Examination (MMSE), the Memory and Executive Function modules of the Neuropsychological Assessment Battery (NAB), and the National Adult Reading Test (NART). In addition, three supplemental cognitive assessments were administered: the CogState Brief Battery (CBB), the Cognitive Drug Research Assessment System (CDR-AS), or the Trail-Making and Verbal Fluency subtests of the Delis Kaplan Executive Function System (DKEFS). To minimise participant burden and fatigue, each participant was randomly allocated to undertake only one of these three assessments. Randomization was stratified by RBANS risk classification. Once randomized at baseline, the participant retained the same allocation at all follow-up visits.

Mini-Mental State Examination (MMSE)

The MMSE is a brief 11-item face-to-face examination used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. The examination includes stimuli for comprehension, reading, writing, and drawing tasks. It is widely translated and has shown validity and reliability in psychiatric, neurologic, geriatric and other medical populations (7).

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS (8) includes 12 subtests yielding five indices: the Attention Index is comprised of Digit Span and Coding, the Language Index consists of Picture Naming and Semantic Fluency subtests, the Visuospatial/Construction Index is made up of Figure Copy and Line Orientation subtests, the Immediate Memory Index is comprised of List Learning and Story

Memory subtests, and the Delayed Memory Index consists of List Recall, List Recognition, Story Recall and Figure Recall subtests. This face-to-face assessment takes approximately 25 minutes to complete.

Neuropsychological Assessment Battery (NAB)

NAB is a comprehensive, modular neuropsychological test battery designed to assess a range of cognitive skills and functions of adults from 18 to 97 years old. The specific cognitive domains of attention/concentration, language, memory, visuospatial and executive functioning are measured by specific co-developed and normed modules within the NAB. For the purposes of this investigation, the Memory and Executive Function modules were administered as these functions are considered to be most impacted early in the AD disease course (9). The NAB is administered face-to-face, and assessment time depends upon disease severity, with more impaired participants completing it faster. Specifically, the NAB Memory module takes approximately 45 minutes, whereas the Executive Function module is approximately 30 minutes in duration.

National Adult Reading Test (NART)

NART is a widely used measure of word reading that assesses pronunciation of 50 English words with irregular grapheme-phoneme and stress rules. Reading tests, such as the NART, have been shown to provide a good estimate of premorbid intellectual functioning, including in patients with neurodegenerative disorders (10). The NART is administered face-to-face and takes approximately 10 minutes to complete.

CogState Brief Battery (CBB)

The CogState Brief Battery is an approximately 15 minute computerized battery with demonstrated reliability, validity, and short term stability (11), developed expressly for maximal sensitivity to detect change. Employing playing cards as stimuli to assure cross-cultural acceptability, CogState consists of four tasks that respectively measure the functions of attention, processing speed, visual learning, and working memory. CogState employs standard psychometric paradigms (i.e., simple and choice reaction time, n-back and pattern separation learning), and has been validated for detection of dementia in both clinical and community based screening samples. Change over time (6-18 months) on the pattern separation learning task has been seen in healthy older adults testing positive for amyloid compared with those negative for amyloid (12). CogState can be administered via the internet or on a stand-alone computer and is available in over 50 languages.

Cognitive Drug Research Assessment System (CDR-AS)

The Cognitive Drug Research Assessment System (13) is an approximately 20 minute computerized battery designed to reliably measure changes in cognitive function in clinical trial situations. The fully automated system includes tests of episodic memory, working memory, attention and reaction time.

Delis Kaplan Executive Function System (DKEFS)

The DKEFS is a paper and pencil measure of verbal and nonverbal executive functions and has been normed and validated for children and adults from 8 to 89 years of age. The measure consists of nine subtests. For the purposes of this study, the Trail Making Test (TMT) and Verbal Fluency subtests were used. These two paradigms have a long history of frequent use in AD research (14). Total time to complete these two subtests of the DKEFS is approximately 20 minutes.

Mood

Geriatric Depression Scale (GDS)

GDS is a basic self-reported screening test used to identify depression in older adults (15). The 15-question version asks participants how they felt over the past week, and uses a Yes/No response format to enable the questionnaire to be used with moderately cognitively impaired individuals.

State-Trait Anxiety Scale

The Spielberger State-Trait Anxiety Inventory (STAI, forms Y-1 and Y-2) is a 40-item self-report instrument to assess current state anxiety and general anxiety levels (16). The STAI includes twenty items to assess the presence or absence of current (state) anxiety and twenty to assess general (trait) predisposition to anxiety, with each item scored from 1 to 4 according to intensity or frequency.

Patient Reported Outcome Measures

Revised Perceived Deficits Questionnaire (PDQ)

The PDQ was originally designed to capture decline in cognitive function most often caused by multiple sclerosis. In recent years, the PDQ has been used in at least one study of MCI (17). The PDQ is a 20-item questionnaire that covers four domains of cognitive function from the participant's perspective: attention/

concentration, retrospective memory, prospective memory, and planning/organization. The response options are answered on a five-point Likert scale, with 0 = never, 1 = rarely, 2 = sometimes, 3 = often, and 4 = almost always. Subscales can be calculated by summing raw scores for the relevant five items (subscale range is 0 to 20), and the total score is calculated by summing raw scores for all of the PDQ items (scale range is 0 to 80). A higher score indicates greater perceived cognitive impairment.

Work Productivity and Activity Impairment (WPAI)

The WPAI Questionnaire is an instrument to measure impairments in both paid work and unpaid work, yet un-validated within an older population, some of whom remain in employment including volunteer work. The scale consists of 6 questions regarding work and activity impairment due to health problems. The WPAI elicits data on hours worked, hours missed due to the target condition, hours missed due to other health problems and hours missed for any other reasons. Hours missed for «other reasons» is not used in the scoring, but only as a prompt to the respondent to exclude those hours from the count of actual hours worked. The WPAI yields four types of scores: (1) absenteeism (work time missed), (2) presenteeism (impairment at work / reduced on-the-job effectiveness), (3) work productivity loss (overall work impairment/absenteeism plus presenteeism), and (4) activity impairment. The sum of specific health problem impairment and impairment due to other health reasons is equal to impairment due to all health reasons. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, that is, worse outcomes (18).

Health Utilities Index Mark 3 (HUI3)

The HUI3 is a generic, preference-weighted, health status assessment completed by the participant that measures health status and health-related quality of life and allows the computation of utility scores. The 15-item questionnaire (15Q) is designed for self-completion, includes 15 multiple-choice HUI3 questions plus one global health question (Q16) common in many health surveys (19).

Lifestyle Measures

Imperial Lifestyle Questionnaire (ILQ)

Participants were asked to complete a self-reported questionnaire to address a wide range of health and lifestyle characteristics: demographics (age, marital status, ethnicity); socioeconomic status (education, income, employment status, type of occupation); activities of daily living (assessed by the Lawton scale (20)); occupational and leisure time physical activity (the Physical Activity for the Elderly Scale, PASE(21)) and the short form of the International Physical Activity Questionnaire, IPAQ(22)); leisure activities (frequency of social visits, reading, musical and artistic pastimes, speaking a second language, solo recreational mental activities e.g. puzzles); midlife experiences (occupation, physical and leisure activities, travel, training); smoking (type, quantity, duration; details of smoking at age 40, time since cessation; second-hand smoke exposure); health history (diagnosed conditions, related treatments, Rose angina questionnaire, surgical procedures, multivitamin use, weight and dietary change over time, use of medical services, family history); and female reproductive history (menstruation, childbearing, breastfeeding, hormone replacement therapy use).

A follow-up version of the above-listed content was administered every six months after baseline. The follow-up questionnaire was as above, except for factors that would not have changed since baseline: subsets of the questions on demographics (ethnicity, early education), the series on mid-life experiences, history of surgical procedures, previously diagnosed medical conditions, history of weight and dietary changes, history of use of medical services, family health history, childbearing and HRT use).

Scottish Collaborative Group Food Frequency Questionnaire

The semi-quantitative Scottish Collaborative Group food frequency questionnaire (SCG-FFQ) is a 150-item instrument designed to assess the habitual diet of United Kingdom residents over the previous 3 months. The SCG-FFQ is derived from the dietary questionnaires used in the Scottish Heart Health/ MONICA Study. The SCG-FFQ provides quantitative estimates of the intake of food and nutrients and is appropriate for ranking individuals into broad categories of intake (e.g., high, medium, and low) as opposed to absolute levels of intake. The SCG-FFQ has been validated among older adults in the United Kingdom (23).

Accelerometry

Willing participants were requested to wear actigraph wristwatch-like device that monitored rest and activity cycles for a prescribed time period to assess job-related, transportation-related, and recreation, sport and leisure-time physical activities. The measure also captures and quantifies periods of inactivity (e.g., sitting).

Sleep

Berlin Questionnaire

The Berlin Questionnaire is a simple sleep apnea screening questionnaire (10 items) used to quickly identify the risk (low to high) of sleep disordered breathing. The questionnaire consists of 3 categories and risk is based on the responses to individual items and overall scores in the symptom categories (24).

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a self-rated questionnaire which assesses sleep quality and disturbance over a 1 month time period. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. The sum of scores for the 7 components gives 1 global score ranging from 0 (better) to 21 (worse). A total score of >5 is associated with poor sleep quality (25).

Safety Evaluation

Study events, whether serious or non-serious, were recorded throughout the study period from the time of informed consent until completion of the participant's last study-related procedure. A serious study event meets one or more of the following parameters: fatal; immediately life-threatening; requires hospitalization or prolongs existing hospitalization; permanently (or significantly) disabling; a congenital anomaly or birth defect (in an offspring); or medically significant. All serious study events were reported to the sponsor by study-site personnel within 30 days of their knowledge of the event. Each suspected adverse event included reporting of description (e.g. signs and symptoms or diagnosis), seriousness criteria, severity rating, duration (onset and resolution date), actions taken and outcome.

Results

Sample disposition and baseline characteristics

The study started in February 2014 and truncated in December of 2016 with a median follow-up time of 18.1 months. The early discontinuation was due to introduction of a follow-on ongoing substudy that enrolled participants from the Main study and the Register and was designed to enhance the scientific strength of the main study objectives, through the addition of more detailed AD-related assessments, including biomarker evaluation of participants' Aβ status (positron emission tomography and/or cerebrospinal fluid protein analysis), alongside brain structural and functional explorations via Magnetic Resonance Imaging (MRI).

For the main study, a total of 690 participants who met the primary analysis set criteria at baseline were analyzed.

Participant disposition is shown in Figure 1S of Supplementary Materials. The overall study attrition rates were 28% screen failure (275 out of 987), and 13% post baseline (91 out of 712).

No participant completed the study as it was terminated early. Discontinuations post baseline were primarily due to early study termination by sponsor (486, 83.1%), secondly due to withdrawal by the participant and lost to follow-up (80, 13.7%), and thirdly due to other reasons such as physician decision and protocol deviation (19, 3.2%). The participant overall estimated median time in study was 18.1 months, with 21.6 months for APOE ε4 carriers, and 17.8 months for non-carriers. The annual attrition due to participant dropout was within the expected range of approximately 10% per year. 72.5% of enrolled participants completed their 12 month visit, 51.4% completed their 18 month visit, 29.7% and 9.9 % completed their 24 month and 30 month visits respectively. Study participation rate by APOE ε4 status is shown in Figure 1S. The attrition rate was lower amongst APOE ε4 carriers than amongst non-carriers at all follow-up time-points, but due to incomplete follow-up and small sample sizes, the difference was not tested for statistical significance.

Demographic and baseline disease characteristics by participant APOE ε4 status are shown in Table 2. The mean (SD) age was 68.73 (3.757) years and was similar between APOE ε4 carriers and non-carriers. This age range is younger than might be expected in AD interventional trials as the initial inclusion criteria for age range was 60-75 years, but was increased to 85 years in a much later amendment to more closely reflect expected age of participants in interventional trials. The majority of study participants were white (94.6%) and 57.4% were female with very similar percentages in the two sub-groups. Of the 690 participants followed up post baseline, 165 (23.9%) were APOE ε4 carriers (the vast majority with 1 copy of the allele (97.0%)), and 525 (76.1%) were non-carriers. The percent of participants with family history of dementia of any type was 34.8%, with a somewhat larger percentage in the carrier group (42.4%) compared to the non-carrier group (32.4%). Over half of the participants (58.6%) were married, and 53% had a Bachelor's degree or higher- level education reflecting a high socioeconomic status. Summary statistics of baseline cognitive measures for participant by APOE ε4 status is shown in Table 3. The baseline values for the primary cognition outcome measures were numerically comparable between APOE ε4 carriers and noncarriers. There were no meaningful patterns of difference in performance for any of the assessment scale baseline values across the two subgroups.

Table 2. Participant demographic characteristic by APOE ε4 status

Characteristics	APOE ε4 Status		Total
	Non-carrier	Carrier	
Analysis set: all enrolled	525	165	690
Age (years)			
N	525	165	690
Mean (SD)	68.95 (3.867)	68.02 (3.294)	68.73 (3.757)
Median	68.00	68.00	68.00
<65	36 (6.9%)	20 (12.1%)	56 (8.1%)
>=65	489 (93.1%)	145 (87.9%)	634 (91.9%)
Sex			
N	525	165	690
Female	301 (57.3%)	95 (57.6%)	396 (57.4%)
Male	224 (42.7%)	70 (42.4%)	294 (42.6%)
Race			
N	525	165	690
White	502 (95.6%)	151 (91.5%)	653 (94.6%)
Black Or African American	2 (0.4%)	2 (1.2%)	4 (0.6%)
Asian	12 (2.3%)	5 (3.0%)	17 (2.5%)
Multiple	4 (0.8%)	6 (3.6%)	10 (1.4%)
Other	5 (1.0%)	1 (0.6%)	6 (0.9%)
Ethnicity			
N	525	165	690
Hispanic Or Latino	10 (1.9%)	3 (1.8%)	13 (1.9%)
Not Hispanic Or Latino	484 (92.2%)	142 (86.1%)	626 (90.7%)
Unknown	8 (1.5%)	3 (1.8%)	11 (1.6%)
Not Reported	23 (4.4%)	17 (10.3%)	40 (5.8%)
ApoE4 Status			
N	525	165	690
Non-carrier	525 (100.0%)	0	525 (76.1%)
Carrier	0	165 (100.0%)	165 (23.9%)
1 allele	0	160 (97.0%)	160 (23.2%)
2 alleles	0	5 (3.0%)	5 (0.7%)
Family history of AD or dementiaa			
N	525	165	690
No	355 (67.6%)	95 (57.6%)	450 (65.2%)
Yes	170 (32.4%)	70 (42.4%)	240 (34.8%)
Highest Level of Formal Education			
N	525	165	690
Did Not Complete Upper Secondary Education Or High School	85 (16.2%)	28 (17.0%)	113 (16.4%)
Completed Upper Secondary Education Or High School	93 (17.7%)	29 (17.6%)	122 (17.7%)
Some Post-Upper Secondary Education	64 (12.2%)	25 (15.2%)	89 (12.9%)
Completed Bachelor's Degree Or Equivalent	182 (34.7%)	48 (29.1%)	230 (33.3%)
Completed Master's Degree, Equivalent Or Higher	101 (19.2%)	35 (21.2%)	136 (19.7%)
Marital Status			
N	521	165	686
Single	82 (15.6%)	29 (17.6%)	111 (16.1%)
Separated	4 (0.8%)	5 (3.0%)	9 (1.3%)
Married	306 (58.3%)	98 (59.4%)	404 (58.6%)
Divorced	69 (13.1%)	23 (13.9%)	92 (13.3%)
Widowed	60 (11.4%)	10 (6.1%)	70 (10.1%)

Notes: ApoE4 = apolipoprotein E (E4 allele), a Family history of AD or dementia includes first-degree relative, parents, or siblings, percentages are calculated with the number of all enrolled subjects with a given demographic or disease characteristic in each column as the denominators.

Table 3. Summary of Baseline Cognition Outcome Measures by ApoE4 Status

	ApoE4 Status		
	Non-carrier	**Carrier**	**Total**
Analysis set: all enrolled	525	165	690
MMSE			
Total score (raw)a			
N	476	147	623
Mean (SD)	28.8 (1.3)	29.0 (1.3)	28.8 (1.3)
Median	29	29	29
CogState Brief Battery			
Composite Score 1 (DET-IDN) Speed of Performance (log 10 ms)b			
N	156	38	194
Mean (SD)	0.07 (0.883)	0.14 (0.835)	0.09 (0.872)
Median	0.13	0.30	0.20
Composite Score 2 (OCL-ONB) Accuracy of Performance (arcsine proportion correct)a			
N	155	38	193
Mean (SD)	0.02 (0.783)	0.05 (0.685)	0.03 (0.763)
Median	0.03	0.00	0.00
DKEFS - Trail-Making Test (scaled score)a			
Number-letter switching			
N	175	60	235
Mean (SD)	12.3 (2.2)	11.6 (2.8)	12.1 (2.3)
Median	13	12	13
DKEFS - Verbal Fluency (scaled score)a			
Letter fluency			
N	175	60	235
Mean (SD)	13.3 (3.4)	12.9 (3.5)	13.2 (3.4)
Median	13	13	13
Category fluency			
N	175	60	235
Mean (SD)	13.9 (3.3)	13.1 (3.3)	13.7 (3.3)
Median	14	12.5	14
Category switching			
N	175	60	235
Mean (SD)	13.2 (3.2)	12.9 (3.6)	13.2 (3.3)
Median	13	13	13
NAB (standard score)a			
Memory index score			
N	475	149	624
Mean (SD)	105.4 (14.3	103.5 (14.3)	104.9 (14.3)
Median	105	102	104
Executive functions index score			
N	475	149	624
Mean (SD)	114.2 (15.3)	114.8 (15.6)	114.4 (15.4)
Median	114	117	115
CDR-AS Composite Scores			
Power of attention (ms)b			
N	132	44	176
Mean (SD)	1271.4 (159.0)	1247.4 (133.9)	1265.4 (153.1)
Median	1249	1215	1245.5
Continuity of Attention (#)a			
N	132	44	176
Mean (SD)	90.5 (4.9)	90.4 (3.6)	90.5 (4.6)
Median	92.0	91.4	91.7

Table 3. Summary of Baseline Cognition Outcome Measures by ApoE4 Status (continued)

	ApoE4 Status		
	Non-carrier	**Carrier**	**Total**
Mean (SD)	196.2 (68.3)	189.0 (64.9)	194.4 (67.3)
Median	188	200	188.5
Response Variability (#)b			
N	132	44	176
Mean (SD)	51.9 (9.9)	55.0 (10.8)	52.7 (10.2)
Median	50.5	53.4	51.3
Quality of Working Memory (#)a			
N	132	44	176
Mean (SD)	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)
Median	1.94	1.89	1.94
Quality of Episodic Secondary Memory (#)a			
N	132	44	176
Mean (SD)	183.4 (48.5)	177.3 (41.5)	181.9 (46.8)
Median	185.8	175.0	183.3
Speed of Memory (ms)b			
N	132	44	176
Mean (SD)	4367.5 (883.1)	4476.8 (1226.7)	4394.8 (977.6)
Median	4225	4243	4225
RBANS			
Total scale score			
N	522	165	687
Mean (SD)	106.7 (12.1)	106.3 (12.4)	106.6 (12.2)
Median	106	106	106
Delayed memory index score			
N	522	165	687
Mean (SD)	103.4 (9.3)	103.3 (10.1)	103.3 (9.5)
Median	102	102	102
Immediate memory index score			
N	522	165	687
Mean (SD)	106.8 (12.6)	105.8 (12.5)	106.6 (12.6)
Median	109	106	106
Attention index score			
N	522	165	687
Mean (SD)	107.6 (15.3)	106.1 (14.9)	107.3 (15.2)
Median	106	103	106
Visuospatial/constructional index score			
N	522	165	687
Mean (SD)	100.4 (13.8)	101.4 (16.4)	100.6 (14.5)
Median	100	100	100
Language index score			
N	522	165	687
Mean (SD)	106.5 (11.7)	106.5 (12.2	106.5 (11.8)
Median	105	104	105

Key: ApoE4 = apolipoprotein E (E4 allele), CDR = Cognitive Drug Research, Assessment System, DKEFS = Delis Kaplan Executive Function System; MMSE = Mini-Mental State Examination, NAB = Neuropsychological Assessment Battery; a. Higher scores indicate better performance; b. Lower scores indicate better performance; Score ranges: MMSE (raw): 0 to 30, DKEFS scaled scores: 0 to 19, NAB standard scores: mean=100, SD = 15; Percentages are calculated with the number of all enrolled subjects with a given cognition outcome measurement in each column as the denominators; The RBANS Index scores and Total Scale were calculated using Age based norms

Safety

As this was a non-interventional study, safety analyses focused on safety events that referred to occurrence of any untoward medical event such as any unfavorable and unintended sign, symptom, syndrome, or disease. The incidence of any safety event was 64.8% for APOE ε4 non-carriers and 71.5% for carriers. The most frequently occurring safety events with incidence of 3% or more were upper respiratory tract infection (10.4% overall) and fall (5.2%). The incidence of serious safety events

was 4.1% overall, which was numerically slightly higher among non-carriers (4.6%) than carriers (3.4%). The most frequently occurring serious safety events were prostate cancer, renal cell carcinoma, and Parkinson's disease, occurring in two participants each (0.3%), and all others occurred in 1 participant each.

Discussion

We report on baseline characteristics of 690 cognitively healthy participants, who were prospectively evaluated every 6 months for a period of 30 months (or early termination) for changes in performance on neuropsychological test measures from baseline. Data from this study, though short in duration, will allow for examination of biological, genetic, health, and lifestyle factors and markers that influence cognitive progression among individuals at-risk for developing MCI-AD.

This study assessed APOE genotype status for all enrolled participants. Though prevalence of APOE ε4 carriers in our cohort was as expected within a cognitively normal population (~25% of enrolled participants), we noted a paucity of APOE ε4 homozygotes (~1% of enrolled participants). Observed prevalence of APOE ε4 homozygosity markedly differs from frequency reported by other cohorts that include cognitively healthy older adults. For instance, prevalence of dual ε4 alleles in the cognitively normal participant group ranged from 3.6% in the Uniform Data Set of the Alzheimer's Disease Centres (UDS) program, to 6.1% in the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing (AIBL) project up to 9.2% in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study (26). Notably these studies used total MMSE scores (24-30) to define normal cognition, as opposed to a more stringent cognitive assessment tool for designation of 'cognitive normal' status .

Thus, a probable explanation for the reduced homozygosity (ε4+/+) observed in the CPRO main study cohort could be the more sensitive test of cognition (RBANS) used for defining cognitive normal status during study screening and subsequent enrolment. There was no marked APOE ε4 genotype-related difference in cognitive test performance at baseline. This was to be expected since all participants were to be cognitively healthy at baseline and performed within age-matched population norms. Modelling of the longitudinal data will inform on which of these assessments could potentially detect the very earliest cognitive changes.

Our study has important caveats and limitations that should be discussed. The study lacked a biomarker assessment of the participants' amyloid pathology, an important predictor of clinical progression. In addition, no participant progressed to MCI during the study. Despite these lacks, the study included proxy measures of Aβ pathology and information on established risk factors for AD-related cognitive deterioration such as the major genetic risk determinant - APOE genotype status, as well as ample collection of relevant demographic information including age, sex, family history of dementia and subjective cognitive complaints (3, 27, 28).

Due to the relatively young age-range of the participants and the early termination of the study, the cohort may have included a significant proportion of cognitively high-functioning individuals who were unlikely to demonstrate clinical progression over the relatively short duration of follow-up. Furthermore, the early termination of the study reduced availability of data points due to low participation rates at later time points. Nevertheless, we do not expect this attribute to limit the ability to perform longitudinal modeling and analysis, in view of related studies that have reported cognitive changes even within such limited time frames (29, 30).

The CHARIOT PRO Main Study data will be useful for assessing impact of available AD-related measures, including lifestyle exposures and biological factors, on cognitive trajectories from the pre-symptomatic stage. Such analyses may contribute towards better understanding of risk-resilience, and maintenance of cognitive function that may be evident at the preclinical AD stage, in high risk individuals.

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Conflict of interest/disclosures: Janssen Research & Development, LLC, funded the study. Michael T. Ropacki was formerly an employee of Janssen and is an industry consultant. Gerald. Novak, H. Michael Arrighi, and Nandini Raghavan are employees of Janssen Research & Development, LLC and own stock/stock options in the company. Nzeera Ketter is a former employee, and H. Robert Brashear is an employee of Janssen AI Research & Development, LLC and both own stock/stock options in the company. Jianing Di is an employee of Janssen China Research and Development Center and owns stock/stock options in the company. Lefkos Middleton served as principal study investigator at Imperial College of London (ICL), has a consultancy agreement with Eli Lilly, Astra Zeneca and Takeda and is National Coordinator for the TOMMORROW, Amaranth and Generation Clinical Studies; and does not hold any agreement with any of the funders in relation to patents, products in development relevant to this study or marketed products. Chinedu Udeh-Momoh, Josip Car, Robert Perneczky, Geraint Price, Tresa Andrews and Heather Ward served as co-principal study investigators at ICL for Janssen Research & Development, LLC and all declare no conflict of interest. Catherine Robb, Darina Bassil, Martin Cohn,

Parthenia Giannakopoulou, Dinithi Perera, Lisa Curry and Bowen Su were study investigators at ICL and declare no conflict of interest.

Ethical standards: To ensure the quality and integrity of the research, this study was conducted in accordance with Good Clinical Practice (GCP) Guidelines, Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for pharmaceutical Engineering (ISPE), applicable national guidelines, and to the Declaration of Helsinki 2013, as modified by the 52nd World Medical Assembly, Edinburgh, Scotland, 2000, and clarified by the World Medical Assembly (WMA) General Assembly, Washington 2002 and Tokyo 2004. The Chariot-Pro Main study has received National Research Ethics Services approval (15/L0/0711) and internal Imperial College London (ICL) Research Ethics, Joint Research Compliance Office approval (JRCO:15/1C/2791). Prior to consenting onto the Chariot-Pro Main study, participants were provided with a detailed study information sheet outlining study procedures, as well as risks and benefits associated with participation. Participants were provided with a minimum of 48-hours to consider the information provided, and fully understand the study requirements prior to discussing further with study staff, where necessary; after which signed informed consent was obtained prior to undertaking any study procedures at the screening visit.

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