SUPPLEMENTAL MATERIAL

APOE-ε4 **genotype and dementia before and after TIA and stroke: Population-based Cohort Study**

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Supplemental Methods

OXVASC methodology

Study population

The Oxford Vascular Study (OXVASC) is a prospective, population-based cohort study of all incident acute vascular events in all territories (transient ischaemic attack, stroke, acute coronary and peripheral vascular events).[1-3]

During the period of the current substudy, the OXVASC study population consisted of all 92,728 individuals, irrespective of age, registered with 100 general practitioners (GPs) in nine general practices in Oxfordshire, UK. In the UK, general practices provide primary health care for registered individuals and hold a lifelong record of all medical consultations (from the National Health Service [NHS] and private health care), and details of treatments, blood pressure, and investigations. In Oxfordshire, an estimated 97% of the true residential population is registered with a general practice, with most non-registered individuals being young students. All participating practices held accurate age-sex patient registers, and allowed regular searches of their computerised diagnostic coding systems. The practices had all collaborated on a previous population-based study, for which they were originally selected to be representative of the urban and rural mix and the deprivation range of Oxfordshire as a whole.[4] Based on the index of multiple deprivation (IMD), the population was less deprived than the rest of England, but had a broad range of deprivation.
The OXVASC population is 94% white people, 3% Asian, 2% Chinese, and 1% Afro-Caribbean.[4] The proportion of whites is similar to that of the UK as a whole (88% white) and to many other western countries (Australia - 90%; France - 91%; Germany - 93.9%).

Case ascertainment

After a 3-month pilot study, the study started on April 1, 2002, and is ongoing. Patients with TIA/minor stroke were referred directly by their primary care physician or the emergency department to dedicated daily OxVASC emergency clinics for acute management. Patients with major stroke were admitted to the regional acute hospital covering the study population and were recruited by daily hot pursuit. Ascertainment also combined prospective daily searches for acute events (hot pursuit) and retrospective searches of hospital-care and primary-care administrative and diagnostic coding data (cold pursuit).

Hot pursuit was based on:

1. A daily (weekdays only), urgent open-access “TIA clinic” to which participating general practitioners (GPs) and the local accident and emergency department (A&E) send all individuals with suspected TIA or stroke whom they would not normally admit to hospital, with alternative on-call review provision at weekends. Patients too frail to attend are assessed at their residence by a study nurse or doctor.
2. Daily searches and case note review of admissions to the Emergency Assessment Unit, Medical Short Stay Unit, Coronary Care Unit and Cardiothoracic Critical Care Unit, Cardiology, Cardiothoracic, and Vascular Surgery wards, Acute Stroke Unit, Neurology ward and all other general wards when indicated.
3. Daily searches of the local A&E and eye hospital attendance registers.
4. Daily identification via the Bereavement Office of patients dead on arrival at hospital or who died soon after.
5. Daily searches of lists of all patients from the study population in whom a troponin-I level had been requested.
6. Daily assessment of all patients undergoing diagnostic coronary, carotid and peripheral angiography, angioplasty, stenting or vascular surgical procedures in any territory to identify both total burden of vascular invention and any potential missed prior acute events.

Cold pursuit procedures were:

1. Frequent visits to the study practices and monthly searches of practice diagnostic codes.
2. Monthly practice-specific list of all patients admitted to all acute and community NHS hospitals.
3. Monthly listings of all referrals for brain or carotid imaging studies performed in local hospitals.
4. Monthly reviews of all death certificates and coroners reports to review out-of-hospital deaths.
5. Practice-specific listings of all ICD-10 death codes from the local Department of Public Health.

Patients found on GP practice searches who have an event whilst temporarily out of Oxfordshire are included, but visitors who were not registered with one of the study practices are excluded. A study clinician assessed patients as soon as possible after the event in the hospital or at home. Informed consent was sought, if possible, or assent was obtained from a relative.

Baseline data collection form

Data are collected using event-specific forms, for TIA and stroke, acute coronary syndrome or acute peripheral vascular events. Standardised clinical history and cardiovascular examination are recorded. Information recorded from the patient, their hospital records and their general practice records includes details of the clinical event, medication, past medical history, education and occupational history, marital status, living arrangements, family history, functional status, abbreviated mental test score (AMTS), all investigations relevant to their admission (including blood results, electrocardiography, brain imaging and vascular imaging-duplex ultrasonography, CT-angiography, MR-angiography or DSA) and all interventions occurring subsequent to the event.

If a patient died before assessment, we obtained an eyewitness account of the clinical event and reviewed any relevant records. If death occurred outside the hospital or before investigation, the autopsy result was reviewed. Clinical details are sought from primary care physicians or other clinicians on all deaths of possible vascular aetiology. In a previous study, only 3/823 interviewed patients reported previous vascular events that had not been ascertained using these multiple methods, thus the ascertainment rate is >99% of events presenting to medical attention.[3]

All surviving TIA and stroke patients are followed-up face-to-face at 1, 6, 12, 60 and 120 months after the initial event by a research nurse or physician and all recurrent vascular events were recorded together with the relevant clinical details and investigations. If face-to-face follow up is not possible, telephone follow-up is performed or enabled via the general practitioner. Cognitive function is tested using MMSE and MoCA at face-to-face interview and T-MoCA and TICSm on telephone follow-up.[5,6] All recurrent vascular events that presented to medical attention would also be identified acutely by ongoing daily case ascertainment within OXVASC. If a recurrent vascular event was suspected at a follow-up visit or referred by the GPs to clinic or admitted, the patient was re-assessed and investigated by a study physician.

Brain imaging and white matter disease severity grading

In the early years of the OxVASC study, CT was the default baseline brain imaging modality. In later periods, MRI was used. Therefore, methodology was developed to define the severity of leukoaraiosis in a reproducible manner whether the patient had received CT or MR brain imaging.[7] Leukoaraiosis was prospectively and independently coded by a neuroradiologist and by an experienced neurologist. Assessments were made blind to clinical data.

Leukoaraiosis was graded according a qualitative scale ("Oxford scale") based on the severity score (absent, mild, moderate, or severe) of the Blennow scale for CT scans, and a modified version of the Fazekas scale, considering periventricular and deep white matter lesions altogether, for MRI scans. Within the OXVASC cohort, the inter-rater agreement on presence and severity of leukoaraiosis on CT was assessed by κ statistics in a subset of 996 consecutive cases and for MRI on 100 cases. We also performed an agreement study between CT and MRI in the 416 patients who had had both modalities of imaging, using the SAS software to calculate both simple and weighted κ.
Within the OXVASC cohort, the inter-rater agreement on presence and severity of leukoaraiosis on CT was assessed by κ statistics in a subset of 996 consecutive cases and for MRI on 100 cases. We also performed an agreement study between CT and MRI in the 416 patients who had had both modalities of imaging, using the SAS software to calculate both simple and weighted κ.

The inter-rater agreement on presence of leukoaraiosis in 996 consecutive cases imaged by CT and rated by the Oxford scale was moderate to good (κ = 0.64, 0.59–0.69, for presence of any leukoaraiosis, and 0.58, 0.55–0.62 for severity). The inter-rater agreement on presence of leukoaraiosis in 100 consecutive cases imaged by MRI and rated by the Oxford scale was also good (κ = 0.78, 0.65–0.90 for presence and 0.66, 0.56–0.76 for severity of leukoaraiosis). In the 416 patients who had both CT and MRI, agreement between independent assessments made on the different modalities was not significantly less than the interobserver reproducibilities of either modality alone. Therefore, intra- and inter-rater reproducibility for both CT and MRI evaluations of leukoaraiosis was good as well as the concordance between the MRI and CT data.

Definitions of TIA/stroke events
Although new definitions for stroke and TIA have been suggested recently,[8,9] in order to enable comparison with previous studies, the classic definitions of TIA and stroke are used throughout.[9] A stroke is defined as rapidly developing clinical symptoms and/or signs of focal, and at time global (applied to patients in deep coma and to those with subarachnoid haemorrhage), loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[10] A TIA is an acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and which is thought to be caused by inadequate cerebral or ocular blood supply as a result of arterial thrombosis, low flow or embolism associated with arterial, cardiac or haematological disease.[4] All cases were reviewed as soon as possible after presentation by the same senior neurologist (PMR) throughout the study. For the current analyses, we included patients who had definite or probable TIA as adjudicated by PMR and excluded patients with possible TIA. Brain imaging was not used to define TIA. With the high rate (97%) of imaging or autopsy in OXVASC, strokes of unknown type were coded as ischaemic.

Dementia diagnosis
We examined issues around measured dementia diagnosis with reference to the OxVASC methodology in three previous publications in Stroke, specifically the impact of selection[11] and attrition[12] biases and problems interfering with cognitive testing.[13]

In OxVASC, we used multiple methods of follow-up which have been shown to substantially reduce attritional biases in identification of dementia in OxVASC.[12] Dementia was defined as pre- or post-event according to whether the diagnosis was made before or after the index event.[11] Pre-event dementia diagnosis was made using the following information: i) baseline clinical assessment by study physician and discussion with relatives or other informant; ii) any dementia diagnosis, and related consultations and investigations, where available, in the primary care record, with hand-searching of the entire record including individual consultations, clinic letters, and hospitalisation documentation. In many cases, diagnosis was recorded in hospital notes or clinic letters but not in the primary care diagnosis list. In

other cases, the diagnosis was made by STP on the basis of cognitive and functional impairment apparent from hand-searching of the medical record including individual primary care consultations or clinical hospital physician, nursing and allied health care professional records.

In patients without pre-event dementia, post-event dementia was diagnosed by STP using the same methodology (i.e. using the baseline and follow-up clinical and cognitive assessment data, supplemented by hand-searching of primary care records to death or 5-year follow-up). MMSE was done at each follow-up interview, and dementia was diagnosed if MMSE was <24 and remained <24 for all subsequent follow-ups in patients in whom cognitive testing was not affected by problems such as poor vision, hemiparesis or depression. A small number of subjects had a MoCA but no MMSE in whom none had dementia. In patients with telephone testing, incomplete testing or inability to perform a cognitive test at study interview (e.g. severe deafness) or with missing study follow-up assessment, dementia was diagnosed by STP on the basis of all available study assessment data and hand-searching of primary care, hospital and death records, based on DSM-IV criteria as described for pre-event dementia.[11,12]

Regarding date of dementia diagnosis, although study interview did not routinely occur between 1 and 5 years after the index event, some patients had data from a study interview during this period because of a recurrent event. In other patients, details of a dementia diagnosis made between 1 and 5-year follow-up were obtained at the 5-year study follow-up and the date of diagnosis was obtained from medical records. For patients who did not have 5-year follow-up (eg because of death or drop-out between 1 and 5 years, untestability, telephone/email follow-up without a cognitive test), all available medical records were reviewed by STP. Where available, the exact date of diagnosis was recorded. If there was no clear date given in records, an approximate date of diagnosis was assigned based on review of study and medical records and information from informants where available.

We did not assess for functional impairment in patients diagnosed with dementia using the MMSE scores partly because it can be difficult attributing functional impairment to cognition versus physical disability in patients with cerebrovascular events. However, we performed sensitivity analyses to check whether this may have affected our results. Thirty-seven patients had low MMSE with a modified Rankin score of <2. In sensitivity analyses, removal of these patients had no significant effect on our findings and specifically, no impact on the relationship between event severity and dementia (HR=1.12 (1.10-1.13) per point increase in NIHSS vs 1.12 (1.10-1.13) adjusted for age, sex and education). Similarly, use of a lower cut-point (MMSE<20) in tested patients, did not change the relationship between event severity and post-event dementia (HR= 1.12 per point increase in NIHSS, $p<0.0001$).

For cases in which there was uncertainty (mainly in deciding whether cognitive impairment was sufficiently severe pre-event to be classed as pre-event dementia rather than progressing post-event to dementia), all study and medical records information was reviewed and resolved by discussion between STP and PMR.

For this study, we did not identify Mild Cognitive Impairment (MCI) and such patients were not therefore included in the dementia diagnosis group.

Supplemental Table I. Comparison of demographic and clinical characteristics and vascular risk profile for patients tested for APOE genotype and for those not tested but eligible, and not tested and not eligible.

	APOE Tested	**APOE not tested, eligible**	**p**	**APOE not tested, not eligible**	**P***
	N=1767	N=114		N=424	
Mean/SD age	73.0/13.0	78.5/11.2	<0.0001	79.2/12.0	<0.0001
Age ≥ 75	889 (50)	81 (71.1)	<0.0001	311 (73.3)	<0.0001
Male sex	901 (51.0)	52 (45.6)	0.27	18.0 (42.5)	0.002
Education<12 yrs	1195 (67.6)	69 (60.5)	0.12	279 (65.8)	0.55
Premorbid Rankin ≥3	266 (15.1)	168 (39.6)	<0.0001	168 (39.6)	<0.0001
Premorbid Barthel <20	345 (19.5)	98 (23.1)	0.002	98 (23.1)	<0.0001
Prior stroke	192 (10.9)	68 (16.0	0.64	68 (16.0)	0.003
Mod/severe WMD	506/1721 (29)	150/315 (47.6)	0.005	150/315 (47.6)	<0.0001
NIHSS mean	2.7/4.9	2.9/4.4	0.64	8.9/8.9	<0.0001
Dysphasia	235 (13.3)	12 (10.5)	0.39	155/416 (37.3)	<0.0001
Low baseline cognitive score	278/1556 (17.9)	36/101 (35.6)	<0.0001	40/52 (76.9)	<0.0001
Pre-stroke dementia	110 (6.2)	15 (13.2)	0.004	100 (23.6)	<0.0001
Post-stroke dementia	345 (19.5)	32/99 (32.3)	0.007	55 (17)	0.12
Time to death, years	3.8/2.0	3.0/2.1	<0.0001	1.6/2.2	<0.0001
Death <31 days	55 (3.1)	11 (9.6)	<0.0001	189 (44.6)	<0.0001

Numbers are n (%) unless otherwise specified. p adj=adjusted for age and sex. * not tested, not eligible group versus tested group

Supplemental Table II. Subdistribution Hazard ratios (HR)[14,15] accounting for the competing risk of death for 5-year incidence of post-event dementia according to APOE status, unadjusted and adjusted for age, sex, education (model 1), and for age, sex, education, stroke severity, prior stroke, white matter disease (WMD), diabetes, dysphasia (model 2), and model 2 adjusted for baseline cognitive score (model 3).

	Subdistribution Hazard ratio (95% CI)							
	Unadjusted	p	Model 1	p	Model 2	p	Model 3	p
All patients N=1657								
ε4/ε3	0.92 (0.70-1.20)	0.53	0.96 (0.73-1.26)	0.79	1.00 (0.75-1.32)	0.99	1.15 (0.85-1.55)	0.38
ε4/ε4	2.11 (1.09-4.09)	0.03	3.44 (1.82-6.47)	<0.001	3.55 (1.95-6.45)	<0.001	2.95 (1.35-6.44)	0.007
TIA and minor stroke only, N=1199								
ε4/ε3	1.11 (0.77-1.61)	0.577	1.14 (0.78-1.66)	0.503	1.15 (0.79-1.67)	0.459	1.21 (0.82-1.78)	0.349
ε4/ε4	2.20 (0.91-5.32)	0.080	4.12 (1.70-9.96)	0.002	3.95 (1.63-9.57)	0.002	2.38 (0.66-8.57)	0.183
Major stroke (NIHSS≥3) only, N=458								
ε4/ε3	1.15 (0.85-1.55)	0.38	0.83 (0.56-1.22)	0.34	0.84 (0.56-1.27)	0.41	1.10 (0.70-1.73)	0.67
ε4/ε4	2.95 (1.35-6.44)	0.007	4.62 (1.76-12.1)	0.002	4.92 (1.95-12.4)	0.001	5.28 (1.93-14.4)	0.001

ε3/ε3 is the reference group for all analyses.

Supplemental Table III. Hazard ratios (HR) for early (≤1 year) and late (>1 year) post-event dementia according to APOE-ε4 status, unadjusted and adjusted for demographic factors (model 1), and for age, sex, education, stroke severity, prior stroke, white matter disease (WMD), diabetes, dysphasia (model 2), and model 2 adjusted for baseline cognitive score (model 3) for TIA and minor stroke and separately for major stroke.

	Hazard ratio (95% CI)							
	Unadjusted	p	Model 1	p	Model 2	p	Model 3	p
TIA and minor stroke only, N=1199								
ε4/ε3								
Early	1.44 (0.78-2.66)	0.24	1.47 (0.79-2.72)	0.22	1.67 (0.89-3.15)	0.11	1.85 (0.96-3.59)	0.15
Late	0.98 (0.62-1.56)	0.94	0.94 (0.59-1.49)	0.78	0.92 (0.58-1.48)	0.73	0.96 (0.70-1.55)	0.88
ε4/ε4								
Early	-	-	-	-	-	-	-	-
Late	3.40 1.47-7.84)	0.004	5.13 (2.20-12.00)	<0.0001	5.47 (2.32-12.91)	<0.0001	2.58 (0.94-7.10)	0.07
Major stroke (NIHSS≥3) only, N=58								
ε4/ε3								
Early	0.61 (0.36-1.02)	0.06	0.68 (0.40-1.14)	0.14	0.74 (0.44-1.25)	0.26	1.13 (0.62-2.03)	0.70
Late	0.86 (0.48-1.52)	0.60	0.94 (0.53-1.68)	0.84	0.94 (0.51-1.70)	0.83	1.01 (0.55-1.85)	0.98
ε4/ε4								
Early	3.19 (1.00-10.14)	0.05	6.82 (2.04-22.85)	0.002	9.76 (2.79-34.13)	<0.0001	11.90 (3.03-46.77)	<0.0001
Late	4. 36 (0.58-32.71)	0.15	3.77 (0.49-29.0)	0.20	1.92 (0.23-16.06)	0.55	1.41 (0.16-12.8)	0.76

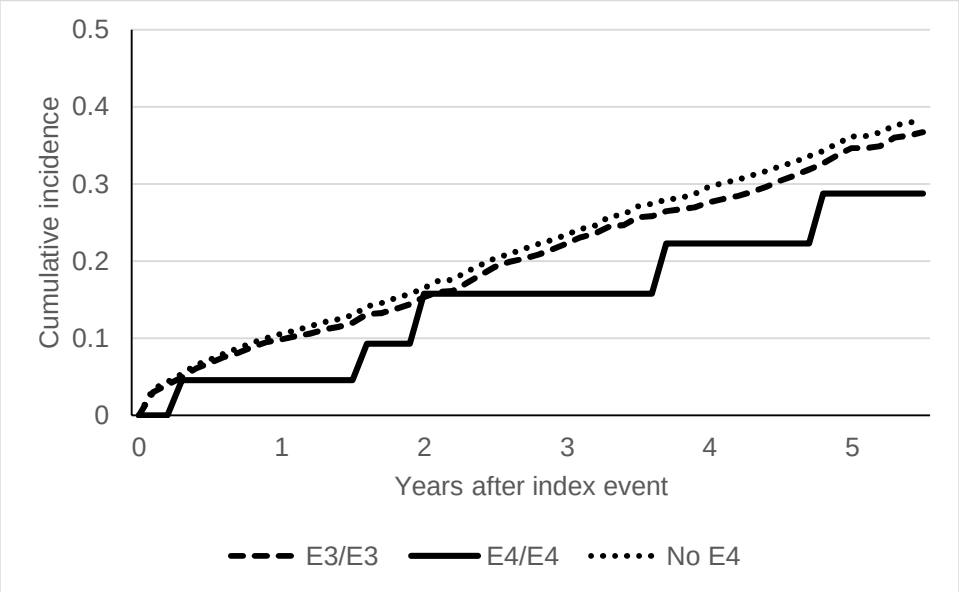
ε3/ε3 is the reference group for all analyses.
Note that numbers with APOE-ε4/ε4 were very small for early (n=3) and late (n=6) post-event dementia so these results should be interpreted with caution.

Supplemental Table IV. Subdistribution Hazard ratios (HR)[14,15] accounting for the competing risk of death for early (≤1 year) and late (>1 year) post-event dementia according to APOE-ε4 status, unadjusted and adjusted for demographic factors (model 1), and for age, sex, education, stroke severity, prior stroke, white matter disease (WMD), diabetes, dysphasia (model 2), and model 2 adjusted for baseline cognitive score (model 3) for TIA and minor stroke and separately for major stroke.

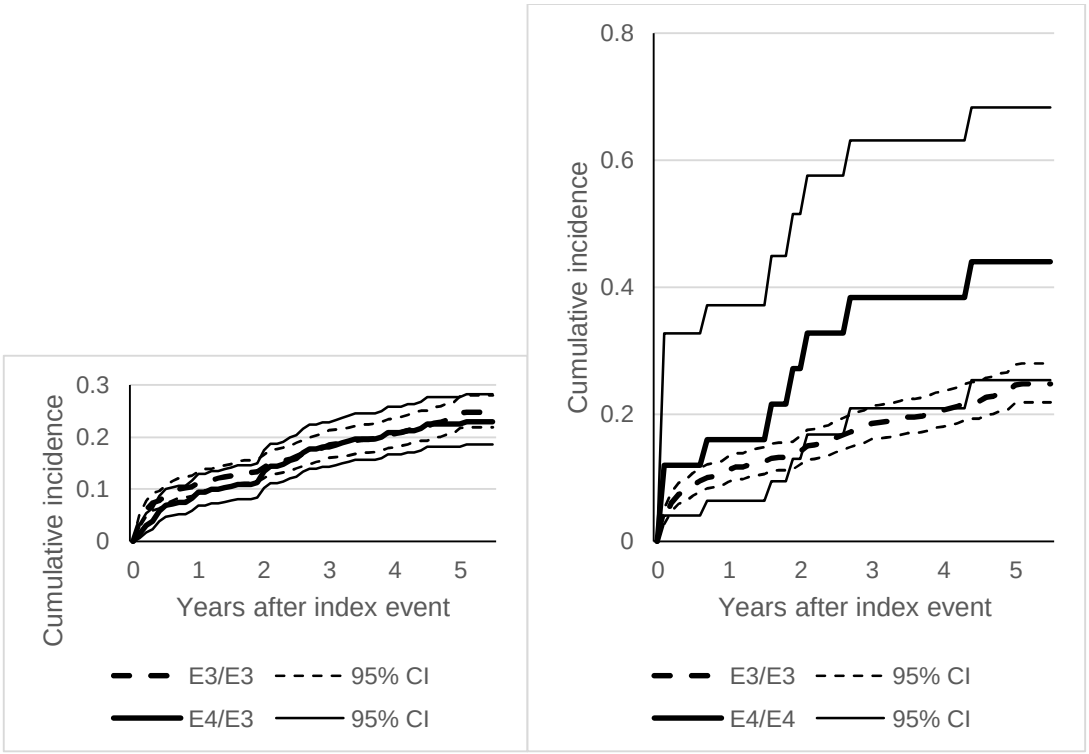
	Subdistribution Hazard ratio (95% CI)							
	Unadjusted	p	Model 1	p	Model 2	p	Model 3	p
All								
ε4/ε3								
Early	0.82 (0.56-1.20)	0.303	0.87 (0.59-1.27)	0.466	0.95 (0.64-1.42)	0.809	1.24 (0.80-1.91)	0.334
Late	1.03 (0.71-1.51)	0.865	1.01 (0.61-1.67)	0.958	1.06 (0.72-1.56)	0.760	1.06 (0.71-1.59)	0.766
ε4/ε4								
Early	1.80 (0.65-5.03)	0.260	3.10 (0.99-9.68)	0.051	3.37 (1.24-9.13)	0.017	2.29 (0.63-8.27)	0.207
Late	2.93 (1.16-7.42)	0.023	1.09 (0.74-1.61)	0.666	5.76 (2.61-12.7)	<0.001	4.21 (1.55-11.5)	0.005
TIA and minor stroke only								
ε4/ε3								
Early	1.31 (0.75-2.32)	0.345	1.35 (0.77-2.37)	0.297	1.59 (0.90-2.81)	0.113	1.69 (0.92-3.12)	0.092
Late	0.99 (0.60-1.61)	0.954	1.01 (0.61-1.67)	0.958	1.03 (0.63-1.68)	0.907	1.08 (0.66-1.77)	0.770
ε4/ε4								
Early	1.23 (0.18-8.68)	0.833	2.02 (0.22-18.3)	0.531	1.87 (0.20-17.5)	0.582	1.00 (0.07-15.3)	1.000
Late	3.00 (1.06-8.51)	0.039	6.25 (2.30-17.0)	<0.001	7.39 (2.78-19.7)	<0.001	4.20 (0.98-18.0)	0.053
Major stroke (NIHSS≥3) only								
ε4/ε3								
Early	0.61 (0.36-1.04)	0.069	0.67 (0.40-1.14)	0.143	0.67 (0.39-1.17)	0.163	1.11 (0.61-2.03)	0.730
Late	1.10 (0.60-2.01)	0.754	1.23 (0.66-2.28)	0.518	1.08 (0.59-1.99)	0.804	1.13 (0.60-2.16)	0.700
ε4/ε4								
Early	3.41 (0.80-14.5)	0.096	6.19 (1.92-20.0)	0.002	6.41 (2.17-18.9)	0.001	9.64 (3.56-26.1)	<0.001
Late	8.19 (3.59-18.7)	<0.001	8.12 (4.00-16.5)	<0.001	3.59 (1.54-8.34)	0.003	2.99 (1.00-8.98)	0.051

ε3/ε3 is the reference group for all analyses.
Note that numbers with APOE-ε4/ε4 were very small for early (n=3) and late (n=6) post-event dementia so these results should be interpreted with caution.

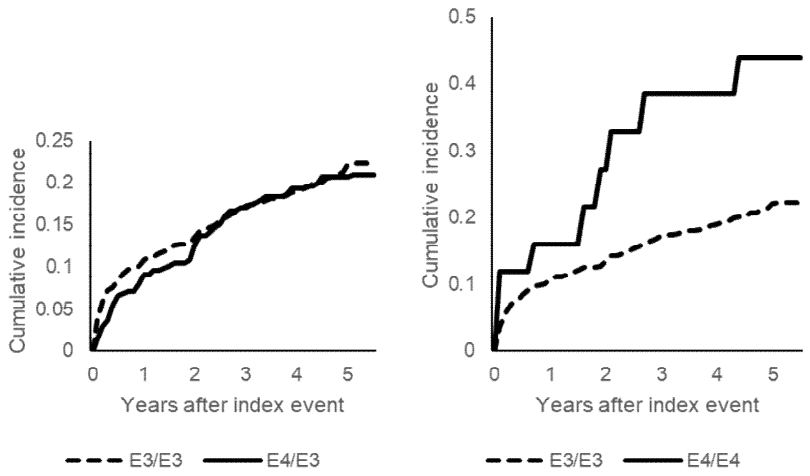
Supplemental Figure I.



Kaplan-Meier curves for death by time after index event by APOE status.



Kaplan-Meier curves for cumulative incidence of dementia by APOE-E4 status



Cumulative Incidence Function curves for dementia by APOE-ε4 status accounting for the competing risk of death

Supplemental Figure II.

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