

The Dementia Genetic and Demographic Landscape of UK Biobank

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Introduction

Understanding Dementia Through Big Data

UK Biobank (UKB) is a large population-based cohort comprising over 500,000 individuals, offering extensive phenotypic, genetic, imaging, and longitudinal health record data, making it a valuable resource for dementia research.

As the cohort ages and dementia diagnoses accumulate through linked health records, UKB has become an increasingly important resource for studying dementia and Alzheimer's disease (AD). Key genetic variants associated with AD, including *APOE* and rare variants such as *TREM2*, are known to influence Alzheimer's disease and dementia risk, but their distribution and longitudinal impact within UKB have not been comprehensively summarised.

Hence, this study aims to characterise the genetic and demographic landscape of dementia in UKB, focusing on longitudinal ascertainment, incident dementia by genotype, and the intersection between AD, non-AD dementias, and potential protective factors.

Methods

Analyses were conducted using R within the UK Biobank Research Analysis Platform (UKB-RAP) powered by DNAnexus.

Dementia and AD diagnoses were identified from linked health records. Genetic analyses focused on established AD risk variants, including *APOE* ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$) genotypes and selected *TREM2* rare variants

Descriptive statistics (counts, frequencies, and proportions) were used to summarise cohort characteristics and genetic variant distributions.

UK Biobank (UKB)
Population-based cohort of 500,000 participants

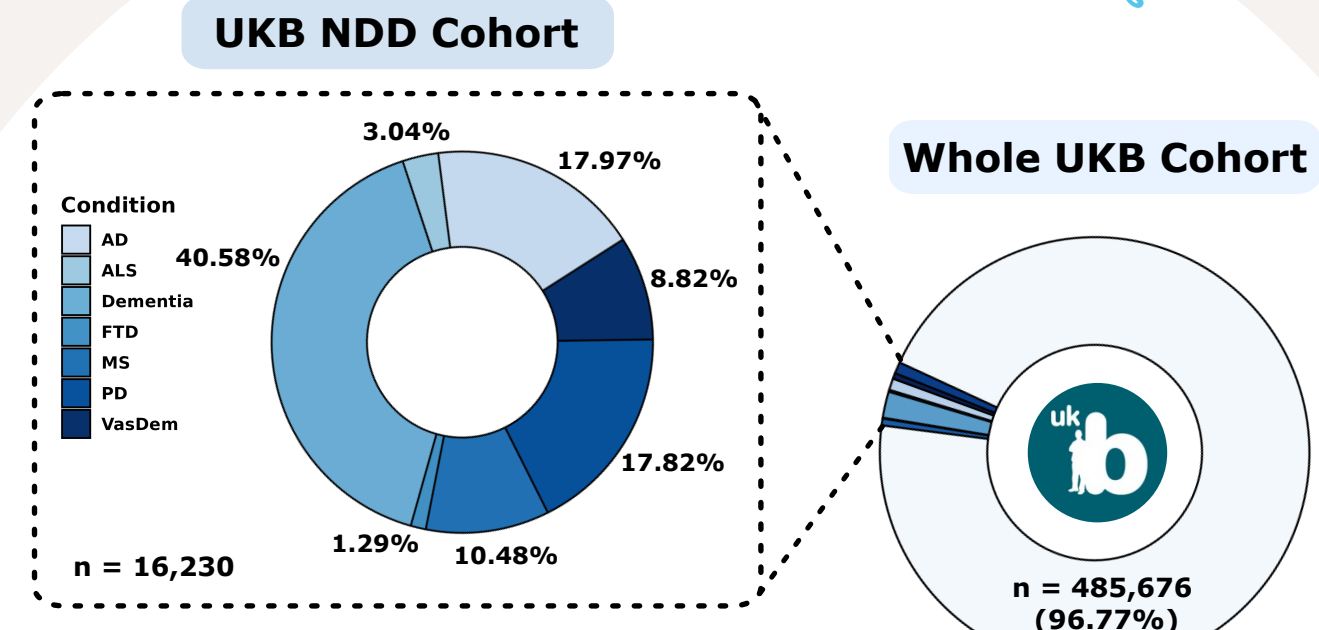


Figure 1 Doughnut plots showing the proportion of participants diagnosed with neurodegenerative disorders (NDDs) including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), dementia, frontotemporal dementia (FTD), multiple sclerosis (MS), Parkinson's disease (PD), and vascular dementia (VasDem) compared with the full UKB cohort.

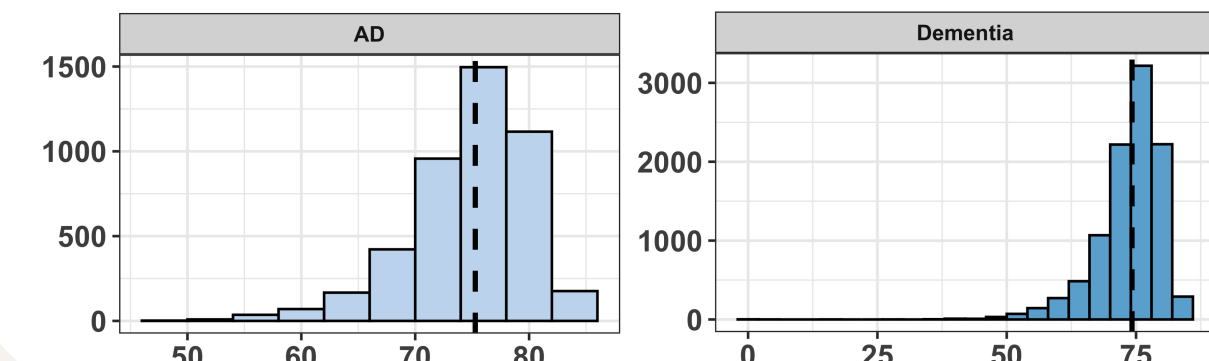


Figure 2 Histogram plots illustrating the age at onset with dotted lines indicating the mean age.

Table 1 Baseline characteristics and *TREM2* variant frequencies in AD cases and controls from UKB

	Overall (N=375,666)	AD cases (N=3522)	AD Controls (N=372,144)	P
Age ¹	56.70 (8.03)	64.64 (4.20)	56.62 (8.019)	<0.001
Sex (M) ²	173402 (46.16%)	1694 (48.10%)	171708 (46.14)	0.605
rs75932628/ <i>TREM2</i> ²	2380 (0.63%)	64 (1.82%)	2316 (0.62%)	<0.001
rs143332484/ <i>TREM2</i> ²	7119 (1.90%)	101 (2.87%)	7018 (1.89%)	<0.001

Notes:
¹ Mean (SD)
² N (%)
P-values from logistic regression adjusted for age, sex, and the first 10 ancestry principal components

Results

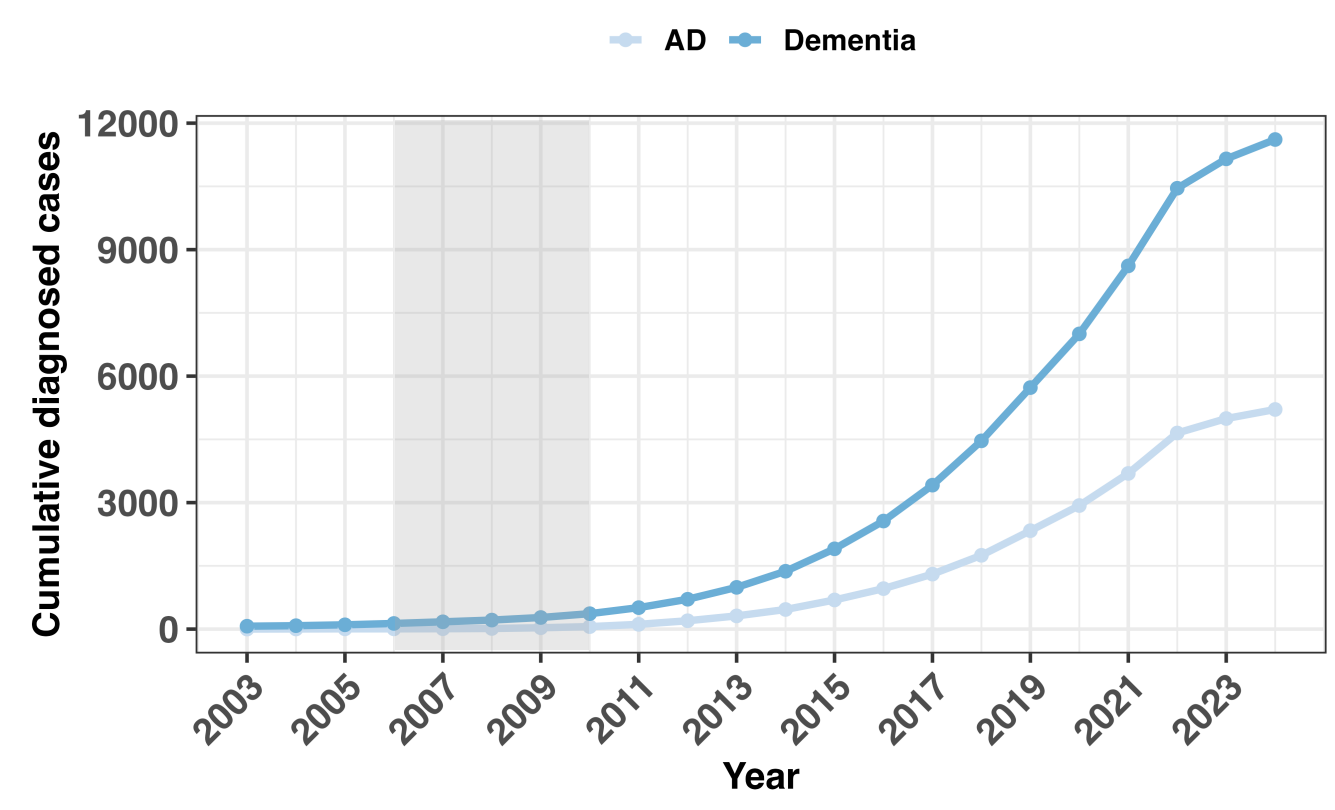


Figure 3 Cumulative numbers of diagnosed cases for AD (light blue) and all-cause dementia (dark blue) over time. The shaded grey region highlights the baseline recruitment period of the UKB (2006–2010).

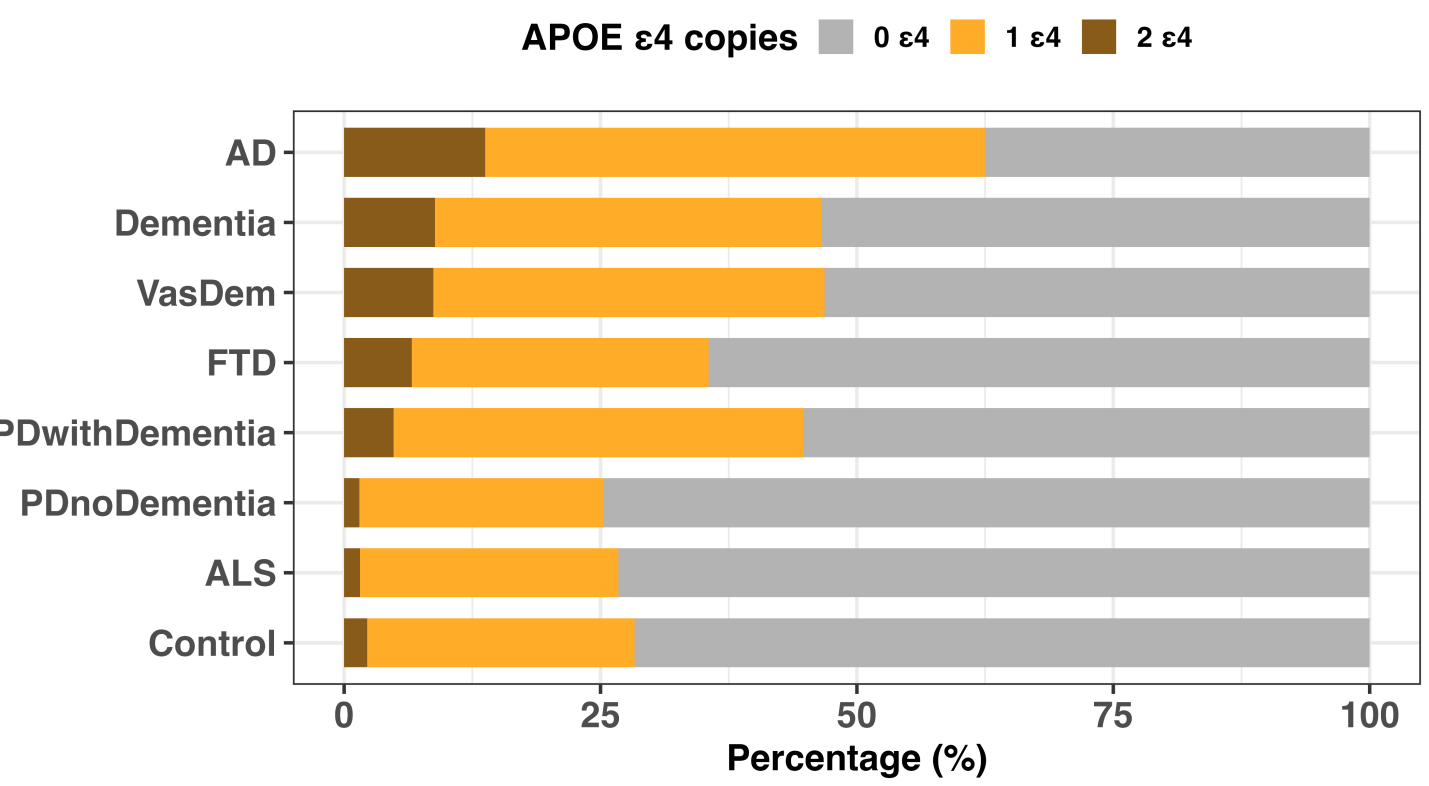
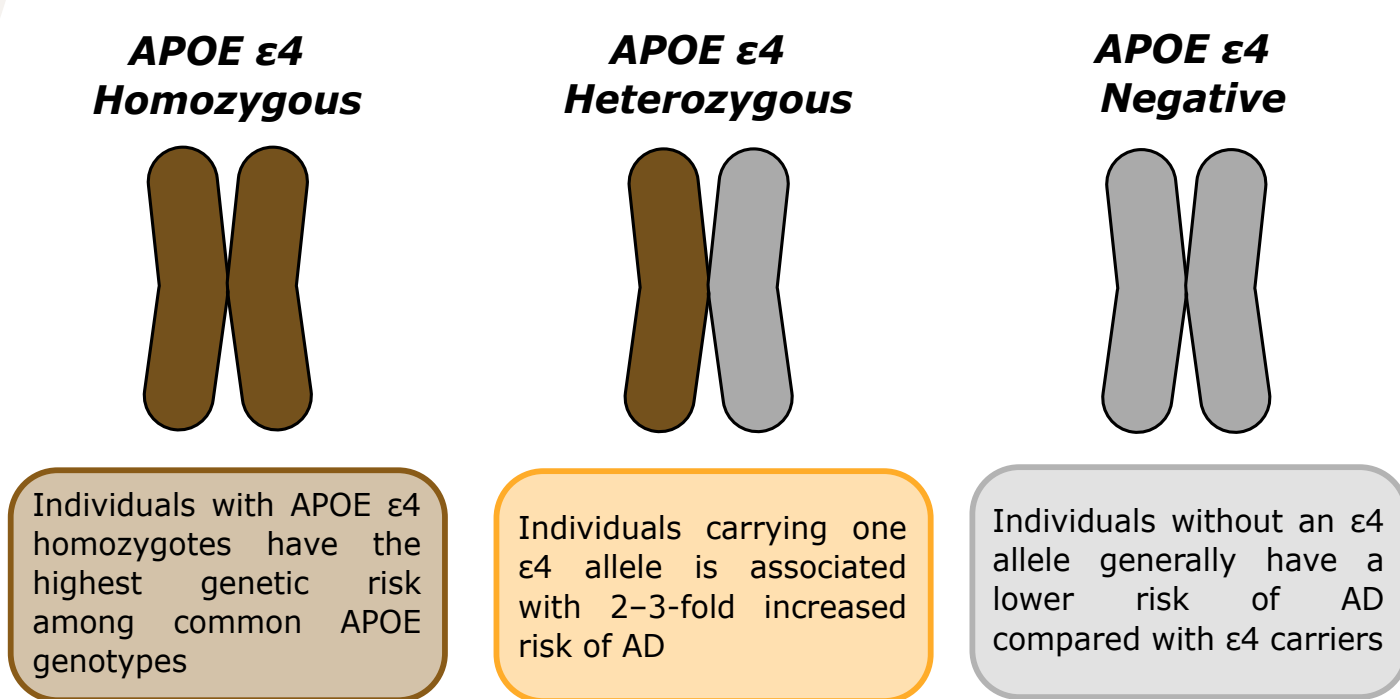


Figure 4 Distribution of *APOE* $\epsilon 4$ genotypes in UKB controls and neurodegenerative disorders, including ALS, PD without dementia, PD with dementia, FTD, VasDem, dementia, and AD. Bars show the percentage of individuals carrying 0, 1, or 2 *APOE* $\epsilon 4$ alleles within each diagnostic category.

Conclusions

- Dementia diagnoses in UKB have increased substantially during longitudinal follow-up, highlighting the value of UKB as a resource for ageing and dementia research.
- APOE* $\epsilon 4$ was enriched among AD, dementia, and VasDem cases, with dementia and VasDem showing comparable $\epsilon 4$ frequencies and AD exhibiting the highest frequency overall, consistent with its established role as a major genetic risk factor.
- In rare variant analyses, *TREM2* risk variants showed significantly higher frequencies in AD cases compared with controls within the filtered European-ancestry subset.

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