The effect of *APOE* and other common genetic variants on the onset of Alzheimer's disease and dementia: a community-based cohort study

Sven J van der Lee, Frank J Wolters, M Kamran Ikram, Albert Hofman, M Arfan Ikram, Najaf Amin, Cornelia M van Duijn

Summary

Background Alzheimer's disease is one of the most heritable diseases in elderly people and the most common type of dementia. In addition to the major genetic determinant of Alzheimer's disease, the *APOE* gene, 23 genetic variants have been associated with the disease. We assessed the effects of these variants and *APOE* on cumulative risk and age at onset of Alzheimer's disease and all-cause dementia.

Methods We studied incident dementia in cognitively healthy participants (aged >45 years) from the community-based Rotterdam Study, an ongoing prospective cohort study based in Rotterdam, the Netherlands, focusing on neurological, cardiovascular, endocrine, and ophthalmological disorders, and other diseases in elderly people. The Rotterdam Study comprises participants in three baseline cohorts (initiated in 1990, 2000, and 2006), who are re-invited to the research centre every 3–4 years, and continuously monitored by records from general practitioners and medical specialists. Cumulative incidence curves up to age 100 years were calculated for Alzheimer's disease and dementia, taking into account mortality as a competing event. These risk curves were stratified by *APOE* genotypes, tertiles of a weighted genetic risk score (GRS) of 23 Alzheimer's disease-associated genetic variants, and parental history of dementia.

Findings 12 255 of 14 926 participants (58·5% women) from the Rotterdam Study were included in this study. During a median follow-up of 11·0 years (IQR 4·9–15·9; 133 123 person years), 1609 participants developed dementia, of whom 1262 (78%) were classified as having Alzheimer's disease; 3310 people died of causes other than dementia. Both *APOE* and the GRS significantly modified the risks of Alzheimer's disease and dementia. There was evidence for a significant interaction between *APOE* genotypes and the GRS for the association with Alzheimer's disease (p=0·03) and dementia (p=0·04); the risk for carriers homozygous for *APOE* ε4 was modified most by the GRS. In carriers homozygous for *APOE* ε4, the difference between the high-risk tertile and the low-risk tertile by age 85 years was 27·0% for Alzheimer's disease ($p=8·5\times10^{-3}$) and 37·2% for dementia ($p=2·2\times10^{-4}$), which translates to a 7–10 year difference in age at onset. Comparing the risk extremes, which were carriers homozygous for *APOE* ε2 or heterozygous with one copy each of the ε2 and ε3 alleles in the low-risk tertile of the GRS versus carriers homozygous for *APOE* ε4 in the high-risk tertile of the GRS, the difference in risk by age 85 years was 58·6% (4·1% *vs* 62·7%; $p=6·2\times10^{-13}$) for Alzheimer's disease, and 70·3% (7·2% *vs* 77·5%; $p=3·0\times10^{-23}$) for dementia. These risk differences translate into an 18–29 years difference in age at onset for Alzheimer's disease and an 18–23 year difference in age at onset dementia. This difference becomes more pronounced when parental history of dementia is considered (difference in risk 83·8%; $p=1·1\times10^{-20}$).

Interpretation Common variants with small individual effects jointly modify the risk and age at onset of Alzheimer's disease and dementia, particularly in *APOE* ε4 carriers. These findings highlight the potential of common variants in determining Alzheimer's disease risk.

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Introduction

Alzheimer's disease is the most common form of dementia. It is a multi-factorial disease with a substantial genetic component (60–80%)[1] and the *APOE* gene is the strongest common genetic risk factor for Alzheimer's disease.[2] The gene has three common alleles: the protective allele *APOE* ε2, the neutral or reference allele *APOE* ε3, and the risk allele *APOE* ε4.[3] The effect of *APOE* ε4 is best described by the high absolute risk carriers have of developing Alzheimer's disease and dementia. According to findings from case-control studies,[4,5] carriers homozygous for *APOE* ε4 have an estimated risk of Alzheimer's disease of over 50% by age 85 years, compared with less than 10% for non-carriers by this age. Because of this high risk, there is increasing interest in including carriers homozygous for *APOE* ε4 in presymptomatic Alzheimer's disease treatment or prevention trials to reduce the necessary duration of these costly studies.[6,7] However, the clinical onset of Alzheimer's disease and dementia varies widely,[8] ranging from midlife to the ninth decade even within carriers homozygous for *APOE* ε4.[4]

In addition to *APOE*, 23 other genetic variants have been identified in the past decade that significantly modify

Research in context

Evidence before this study

We searched PubMed for articles published in English between Jan 1, 1990, and June 1, 2017, with combinations of the search terms "Alzheimer's disease", "dementia", "cumulative incidence", "age at onset", "genetic risk score", "*APOE*", "risk", and "lifetime risk". We found that in case-control studies, genetic risk scores of common genetic variants were significantly associated with Alzheimer's disease and age at onset beyond *APOE* genotypes. In these studies, genetic risk scores improve classification of cases and controls and might facilitate the identification of individuals at high risk and their inclusion in presymptomatic Alzheimer's disease treatment or prevention trials. However, to translate findings into practice, the combined effect of these variants needs to be validated in large community-based cohort studies that assess incident Alzheimer's disease and all-cause dementia, while controlling for competing risk of death by other causes than dementia.

Added value of this study

Our study shows that the small effect of common genetic variants together significantly modify the risk of Alzheimer's disease and all-cause dementia, and partly account for the variability in the age at onset, above and beyond the *APOE* genotype. Shifts in age at onset translated into a higher risk of Alzheimer's disease and dementia at all ages. The joint effect of common genetic variants on cumulative risk of Alzheimer's disease is most profound in *APOE* ε4 carriers. On the basis of all variants, we were able to stratify individuals into risk groups from very low (4·1% by 85 years) to extremely high (62·7%) cumulative risk of Alzheimer's disease.

Implications of all the available evidence

To our knowledge, this is the first time that the the potential of genetic variants beyond *APOE* in determining cumulative risk of Alzheimer's disease has been shown in a large community-based cohort. Including genetic variants beyond *APOE* could contribute towards better risk stratification in the community, facilitating planning of feasible and efficient preventive and curative clinical trials.

the risk of Alzheimer's disease.[9–19] Combining the effects of these 23 variants results in a polygenic risk score that is not only associated with risk of Alzheimer's disease,[20–22] but also with neuropathological hallmarks of Alzheimer's disease,[23] conversion of mild cognitive impairment to Alzheimer's disease,[24–26] and the age at onset of disease in both *APOE* ε4 carriers and non-carriers.[23] Since estimates of absolute risks of Alzheimer's disease can be overestimated as a result of selection bias and not taking into account competing risks (particularly of death by other causes in this case),[27] these findings await validation in large community-based cohort studies.[4,23]

In this study of a large community-based cohort followed up for up to 25 years for incident dementia, we measured the aggregated effect of common variants separately and in conjunction with *APOE* on the risk and age at onset of Alzheimer's disease and all-cause dementia. Since our knowledge of Alzheimer's disease genetics is far from complete and parental history of dementia adds to the prediction of Alzheimer's disease on top of *APOE* and the genetic risk score (GRS),[28] age at onset curves were constructed stratified by family history.

Methods

Study population

This study included participants without dementia from the Rotterdam Study, a prospective community-based cohort study.[29] In 1990, residents aged 55 years and older residing in Ommoord, a district of Rotterdam, the Netherlands, were invited to participate in the study. Of 10 215 invited inhabitants, 7983 agreed to participate in the baseline examinations. In 2000, 3011 participants (of 4472 invitees) who had reached 55 years of age or moved into the study district since the start of the study were added to the cohort. In 2006, a further extension of the cohort was started in which 3932 participants, of 6057 invited, aged at least 45 years living in Ommoord were included.[29] Follow-up examinations take place every 3–4 years.[29] We excluded participants who did not contribute follow-up time beyond age 60 years.

The Rotterdam Study has been approved by the medical ethics committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, licence number 1071272-159521-PG). When visiting the study centre, all participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Procedures

Participants were screened for dementia at baseline and subsequent centre visits with the Mini-Mental State Examination and the Geriatric Mental Schedule organic level.[30] Those with a Mini-Mental State Examination score less than 26 or Geriatric Mental Schedule score greater than 0 underwent further investigation and informant interview, including the Cambridge Examination for Mental Disorders of the Elderly, details of which have been published previously.[30,31] Additionally, the entire cohort was under continuous surveillance for dementia through electronic linkage of the study database with medical records from general practitioners and the regional institute for outpatient mental health care.[30] With this linkage, the entire cohort is continuously monitored

for detection of interval cases of dementia between centre visits and there is therefore no interval censoring. Available information on cognitive testing and clinical neuroimaging was used when required for diagnosis of dementia subtype. A consensus panel led by a consultant neurologist established the final diagnosis according to standard criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders III-revised) and Alzheimer's disease (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association).[31] Follow-up for dementia was done until Jan 1, 2014, for the first cohort in the Rotterdam Study, until Jan 1, 2015, for the first extension, and until Jan 1, 2013, for the second extension of the cohorts (follow-up incomplete at time of data cutoff for this report).

DNA was extracted from blood samples drawn by venepuncture at the baseline visit using standard methods. The Rotterdam Study cohorts were genotyped using commercial genotyping arrays and genotyping quality control was done per cohort.[32] Preparation for imputation was done using scripts provided online (Haplotype Reference Consortium [HRC] or 1000 Genomes [1000G] imputation preparation and checking, version 4.2.1).[33] Imputation to the HRC[34] was facilitated by the Michigan Imputation Server. The server used SHAPEIT2 (version 2, .r790) to phase the data, and imputation to the HRC reference panel (version 1.0) was done with Minimac 3. Imputed genotypes were returned by the service. *APOE* genotype was identified by PCR on coded DNA samples in the baseline cohort[31] and with a bi-allelic TaqMan assay (rs7412 and rs429358; Applied Biosystems, Foster City, CA, USA) in the two extensions of the Rotterdam Study. Using data from genotyped individuals, we calculated the percentage of concordant alleles after imputation of the *APOE* ε2 and *APOE* ε4 allele (compared with direct genotyping), by dividing the number of concordant alleles by the total number of alleles.

Statistical analysis

All analyses were done in R (version 3.2.3). We compared baseline characteristics across *APOE* genotypes with the homozygous *APOE* ε3 genotype as the reference genotype and in the tertiles of the GRS with the low-risk genotype as the reference group using *t* tests for continuous measures and χ^2 tests for categorical measures.

We included 23 genetic variants that showed genome-wide significant evidence of association with Alzheimer's disease[9–19] to calculate a weighted GRS using reported effect estimates as weights. If several studies reported the effects of a variant, the effect estimate from the study with the largest sample size was used. The studies in which the associations were discovered and that report the weights we used are provided in the appendix. Because the number of participants who were diagnosed with other types of dementia for which genetic evidence is available was small (14 with dementia with Lewy bodies, 51 with dementia and Parkinson's disease, and six with frontotemporal dementia), genetic variants associated with other causes of dementia were not assessed. The GRS was calculated as the sum of the products of SNP dosages of the 23 genetic variants (excluding *APOE*) and their respective weights. All 23 variants selected for the calculation of the GRS were well imputed (median imputation score $R^2>0\cdot993$; appendix). The formula to calculate the GRS along with two examples is provided in the appendix. We split the population into high-risk, middle-risk, and low-risk categories on the basis of the tertiles of the GRS; for example, the low-risk group comprised individuals who had a GRS less than $-0\cdot325671$, the middle-risk group had a GRS between $-0\cdot325670$ and $-0\cdot050231$, and the high-risk group had a GRS greater than $0\cdot050230$ (appendix). The boundaries of the tertiles were calculated using data from participants entering the study before age 60 years, because survival bias is anticipated at old age. To assess the effect of parental history of dementia on cumulative incidence, we stratified the cohorts by those without parental history of dementia and those with at least one parent with dementia.

Cumulative incidence, or risk, of Alzheimer's disease and all-cause dementia was calculated up to 100 years based on all incident cases occurring during follow-up of the individuals without dementia for whom genotype data were available. Participants were censored at the date of dementia diagnosis, death, or loss to follow-up, or the administrative censoring date, whichever came first. We calculated cumulative incidence of both Alzheimer's disease and all-cause dementia (Alzheimer's disease plus non-Alzheimer's disease dementia) using the cumulative incidence function from package etm (etmCIF).[35,36] When estimating risk of Alzheimer's disease, we accounted for non-Alzheimer's disease dementia and mortality as competing events. When estimating risk of dementia, we accounted for mortality as a competing event. Briefly, the function estimates overall survival irrespective of the causes by a modification of the Kaplan-Meier estimate,[37] adapted for left truncation,[38] and calculates age and cause-specific risk estimates and corresponding 95% CIs. Risks curves for Alzheimer's disease and dementia in carriers heterozygous for *APOE* with one copy each of the ε2 and ε3 alleles and carriers homozygous for *APOE* ε2 showed similar patterns (appendix), as did the risks of carriers heterozygous for *APOE* with one copy each of ε2 and ε4 and carriers heterozygous for *APOE* with one copy each of ε3 and ε4 (appendix). These genotypes were therefore pooled in analyses as homozygous *APOE* ε2 or heterozygous with one copy each of ε2 and ε3, and heterozygous for *APOE* with one copy each of ε2 and ε4 or one copy each of ε3 and ε4. Analyses were stratified by *APOE* genotypes, tertiles of the GRS, and both *APOE* genotypes and tertiles of the GRS. We calculated the

See Online for appendix

	All (n=12 255)	Low-risk tertile (n=3402)	Middle-risk tertile (n=3292)*	High-risk tertile (n=3317)*	*APOE* ε3/ε3 (n=6662)	*APOE* ε4/ε4 (n=261)	*APOE* ε3/ε4 (n=2608)	*APOE* ε2/ε4 (n=312)	*APOE* ε2/ε3 (n=1453)	*APOE* ε2/ε2 (n=79)
Incident Alzheimer's disease cases	1262 (10·3%)	287 (8%)	341 (10%)	429 (13%)	585 (9%)	72 (28%)	385 (15%)	40 (13%)	97 (7%)	6 (8%)
Dementia cases other than Alzheimer's disease	347 (2·8%)	88 (3%)	90 (3%)	116 (3%)	162 (2%)	11 (4%)	95 (4%)	13 (4%)	38 (3%)	3 (4%)
Sex										
Women	7164 (58·5%)	1979 (58%)	1922 (58%)	1900 (57%)	3820 (57%)	139 (53%)	1518 (58%)	171 (55%)	875 (60%)†	46 (58%)
Men	5091 (41·5%)	1423 (42%)	1370 (42%)	1417 (43%)	2842 (43%)	122 (47%)	1090 (42%)	141 (45%)	578 (40%)	33 (42%)
Age at entry (years)	67·5 (8·4)	67·2 (8·1)	67·0 (7·9)	67·0 (7·9)	67·3 (8·2)	64·8 (6·0)‡	66·6 (7·6)‡	67·3 (8·0)	67·2 (8·2)	69·2 (8·4)†
Follow-up time (years)	10·9 (6·6)	11·2 (6·6)	11·2 (6·6)	11·2 (6·5)	11·2 (6·6)	10·0 (6·2)†	10·8 (6·5)†	10·6 (6·5)	11·8 (6·6)†	11·7 (6·2)
Smoking										
Never	4150 (33·9%)	1157 (34%)	1094 (33%)	1121 (34%)	2286 (34%)	70 (27%)†	830 (32%)†	96 (31%)	530 (36%)	28 (35%)
Former	5250 (42·8%)	1470 (43%)	1453 (44%)	1423 (43%)	2850 (43%)	126 (48%)	1199 (46%)	138 (44%)	592 (41%)	32 (41%)
Smoker at baseline	2479 (20·2%)	684 (20%)	665 (20%)	696 (21%)	1362 (20%)	60 (23%)	512 (20%)	69 (22%)	291 (20%)	14 (18%)
Data missing	376 (3·1%)	91 (3%)	80 (2%)	77 (2%)	164 (2%)	5 (2%)	67 (3%)	9 (3%)	40 (3%)	5 (6%)
Smoking pack-years	16·5 (22·5)	16·7 (23·1)	16·6 (22·3)	16·3 (22·2)	16·3 (22·3)	17·1 (22·9)	16·9 (22·4)	17·4 (22·9)	15·8 (23·1)	13·7 (21·3)
Educational level										
Primary	2210 (18·0%)	606 (18%)	589 (18%)	566 (17%)	1173 (18%)	37 (14%)	471 (18%)	44 (14%)	271 (19%)	15 (19%)
Further§	8242 (67·3%)	2319 (68%)	2244 (68%)	2291 (69%)	4562 (68%)	179 (69%)	1738 (67%)	212 (68%)	991 (68%)	54 (68%)
Higher¶	1582 (12·9%)	437 (13%)	418 (13%)	420 (13%)	845 (13%)	43 (16%)	362 (14%)	51 (16%)	177 (12%)	10 (13%)
Data missing	221 (1·8%)	40 (1%)	41 (1%)	40 (1%)	82 (1%)	2 (1%)	37 (1%)	5 (2%)	14 (1%)	0
Diabetes	1196 (9·8%)	336 (10%)	304 (9%)	334 (10%)	669 (10%)	25 (10%)	248 (10%)	31 (10%)	134 (9%)	9 (11%)
Hypertension	6711 (54·8%)	1886 (55%)	1838 (56%)	1872 (56%)	3737 (56%)	150 (57%)	1425 (55%)	178 (57%)	843 (58%)	54 (68%)†
Systolic blood pressure (mm Hg)	139·5 (21·8)	139·4 (22·0)	139·1 (21·3)	139·1 (21·8)	139·8 (21·8)	138·8 (22·5)	138 (21·2)‡	140·1 (22·5)	140 (21·8)	145·2 (24·9)†
Diastolic blood pressure (mm Hg)	76·8 (11·9)	76·7 (12·0)	76·6 (11·8)	76·7 (11·8)	76·9 (11·9)	77·5 (13·1)	76·1 (11·5)†	76·6 (12·1)	76·8 (12·0)	77·8 (12·4)
Body-mass index (kg/m²)	26·8 (4·0)	26·9 (4·0)	26·7 (3·9)	26·9 (4·1)	26·8 (4·0)	26·6 (3·5)	26·6 (3·9)†	26·8 (3·9)	27·1 (4·1)†	27 (4·4)
Serum cholesterol (mmol/L)	6·2 (1·2)	6·3 (1·2)	6·2 (1·2)	6·2 (1·2)	6·2 (1·2)	6·4 (1·2)†	6·4 (1·2)‡	6·1 (1·1)	5·9 (1·3)	6·1 (1·8)
Serum HDL cholesterol (mmol/L)	1·4 (0·4)	1·4 (0·4)	1·4 (0·4)	1·4 (0·4)	1·4 (0·4)	1·3 (0·4)†	1·3 (0·4)‡	1·4 (0·4)	1·4 (0·4)‡	1·4 (0·4)

Data are number (%) or mean (SD). Some percentages do not add up to 100 because of rounding. Measurement details of all non-genetic measures are described in detail elsewhere.[30] *APOE* ε3/ε3=carriers with two copies of the ε3 allele. *APOE* ε4/ε4=carriers with two copies of the ε4 allele. *APOE* ε3/ε4=carriers with one copy each of the ε3 and ε4 alleles. ε2/ε4=carriers with one copy each of the ε2 and ε4 alleles. ε2/ε3=carriers with one copy each of the ε2 and ε3 alleles. ε2/ε2=carriers with two copies of the ε2 allele. *No significant differences compared with the low-risk tertile. †p<0·05 for the comparison with *APOE* ε3/ε3. ‡p<0·001 for the comparison with *APOE* ε3/ε3. §Lower or intermediate general education, lower or intermediate vocational education, or higher general education. ¶Higher vocational education or university.

Table 1: **Demographics and baseline characteristics**

differences between the risk estimates by age 85 years, as previously described.[36] Multiplicative interaction between *APOE* genotypes (homozygous *APOE* ε2 or heterozygous ε2 and ε3, homozygous *APOE* ε3, heterozygous *APOE* ε2 and ε4 or ε3 and ε4, and homozygous *APOE* ε4) and the GRS as well as the single variants were tested with Cox proportional hazards and a Fine and Gray competing risk regression model, adjusting for main genetic effects, sex, age at inclusion, and squared age at inclusion. In a supplementary analysis, we further stratified the analysis by the presence or absence of parental history of dementia.

This study is registered with the Netherlands National Trial Register and WHO International Clinical Trials Registry Platform under the shared catalogue number NTR6831.

Data sharing

Because of ethical restrictions, data are available upon request. Interested researchers may contact our data management team (secretariat.epi@erasmusmc.nl) or the corresponding author (c.vanduijn@erasmusmc.nl).

Role of the funding source

There was no direct funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

12 255 of 14 926 participants from the Rotterdam Study were included in this study; 2671 participants were excluded, 743 due to insufficent screening at baseline,

527 due to prevalent dementia at study entry, and 1401 because they did not contribute follow-up time beyond age 60 years. Median follow-up was 11·0 years (IQR 4·9–15·9; 133 123 person-years). Follow-up for dementia was complete for 92% of 144 738 potential person-years. Table 1 shows the characteristics at study entry of the 12 255 individuals without dementia who were included in this study. During follow-up (mean 10·9 years [SD 6·6], IQR 4·9–15·9), 1609 participants developed dementia (all causes), of whom 1262 (78%) were classified as Alzheimer's disease; 3310 people died of causes other than dementia. By age 100 years, overall cumulative incidence, or the lifetime risk, of Alzheimer's disease was 25·0% (95% CI 23·8–26·3) and of dementia was 31·4% (30·1–32·8; table 2; appendix).

APOE genotype was imputed for 3% (208 of 7037) of individuals in the baseline cohort, 0·5% (15 of 2973) in the first extension of the cohort, and 5% (114 of 2245) in the second extension of the cohort with the best guess imputed genotypes (ie, rounded number of allele copies) of rs7412 (*APOE* ε2 determining variant) and rs429358 (*APOE* ε4 determining variant) as the *APOE* genotype. Using data from genotyped individuals, imputation of the *APOE* ε2 and *APOE* ε4 alleles was 98·9% (19 152 of 19 350) and 98·2% (19 016 of 19 350) concordant, respectively, with direct genotyping. Combining genotyped and imputed data, the *APOE* genotypes were available for 11 375 of all 12 255 participants. *APOE* genotypes had a strong effect on risk of Alzheimer's disease (figure 1). By 85 years, the risk for Alzheimer's disease was 48·3% (95% CI 40·1–57·3) for people homozygous for *APOE* ε4 and 18·4% (16·5–20·4) for those heterozygous for *APOE* ε4. Compared with carriers of the *APOE* ε4 genotype, non-carriers had a lower risk: 8·6% (95% CI 7·7–9·6) for carriers homozygous for *APOE* ε3 and 5·5% (4·1–7·4) for carriers homozygous for *APOE* ε2 or heterozygous with one copy each of the ε2 and ε3 alleles. Estimates of the risk curves for all-cause dementia by *APOE* genotypes were higher than for Alzheimer's disease (figure 1), but patterns were similar. Stratified by tertiles of the GRS, the risk of Alzheimer's disease by age 85 years was 15·8% (14·1–17·6) for the high-risk tertile, 11·8% (10·3–13·5) for the middle-risk tertile, and 7·7% (6·5–9·1) for the low-risk tertile (figure 2; appendix). The 8·1% risk difference by age 85 years between the high-risk and low-risk tertiles was statistically significant ($p=7·9\times10^{-14}$). Observed differences were similar for all-cause dementia (figure 2; appendix).

Figure 3 shows the risk curves of Alzheimer's disease and dementia stratified by both *APOE* and GRS risk groups. The corresponding risk estimates and 95% CIs by 5-year increments in age are summarised in the appendix. Carriers homozygous for *APOE* ε2 or heterozygous with one copy each of the ε2 and ε3 alleles in the low-risk tertile had the lowest risk by age 85 years: 4·1% (95% CI 2·1–7·7) for Alzheimer's disease and

	Alzheimer's disease	Dementia	Death by other causes	Number of participants	Alive without dementia (%)
60 years	0·0% (0·0–0·0)	0·0% (0·0–0·0)	0·0% (0·0–0·0)	3428	100
65 years	0·1% (0·0–0·2)	0·2% (0·1–0·4)	2·5% (2·1–3·0)	5220	97·3
70 years	0·5% (0·4–0·8)	1·0% (0·8–1·3)	6·8% (6·1–7·5)	5670	92·2
75 years	2·1% (1·7–2·4)	3·1% (2·6–3·5)	13·4% (12·5–14·3)	5423	83·5
80 years	5·7% (5·1–6·3)	8·1% (7·5–8·8)	22·7% (21·6–23·7)	4254	69·2
85 years	11·6% (10·8–12·4)	15·6% (14·7–16·5)	35·2% (34·0–36·4)	2630	49·2
90 years	19·0% (18·0–20·0)	24·4% (23·3–25·6)	48·6% (47·3–50·0)	1161	27·0
95 years	23·4% (22·2–24·6)	29·6% (28·3–30·9)	59·3% (57·9–60·7)	316	11·1
100 years	25·0% (23·8–26·3)	31·4% (30·1–32·8)	65·5% (64·0–66·9)	48	3·1

Data are risk (95% CI), unless otherwise specified. Cumulative incidence of Alzheimer's disease takes into account competing non-Alzheimer's disease dementia and mortality. Cumulative incidence of dementia takes into account competing mortality. The percentage of the population alive without dementia is shown as 100% minus dementia risk and risk of death by other causes than dementia.

Table 2: **Cumulative incidence of Alzheimer's disease, dementia, and death by other causes by age**

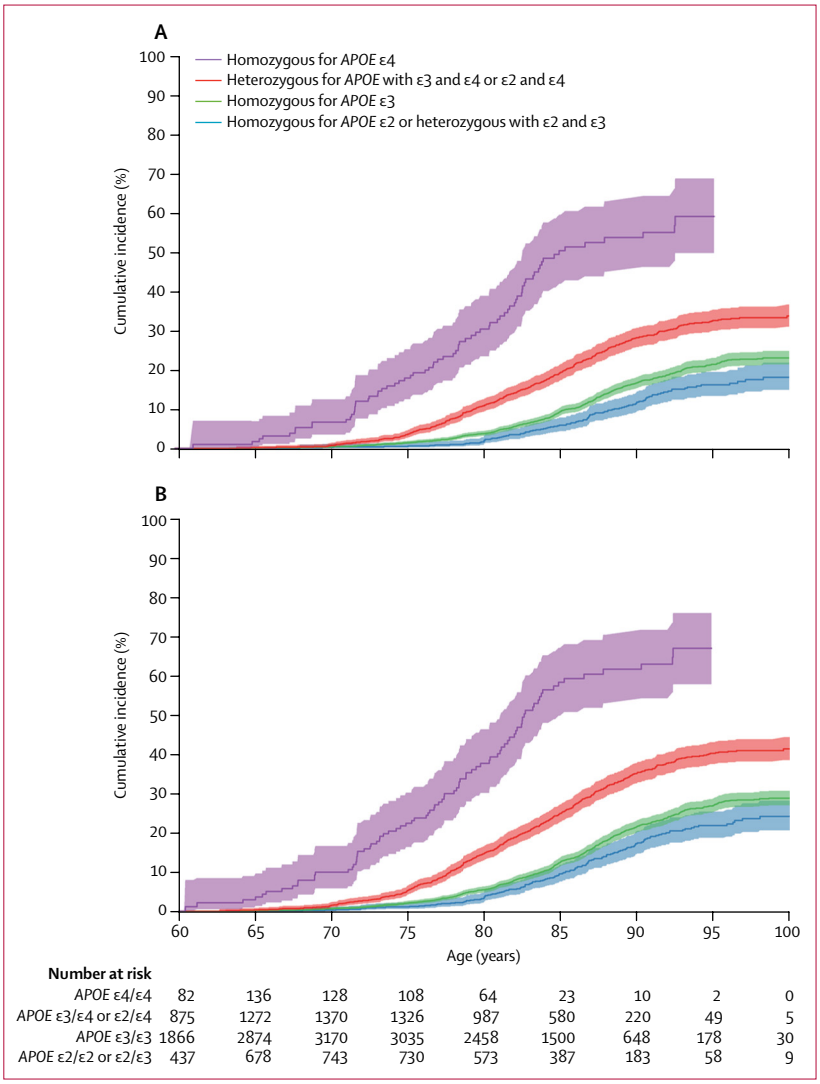

Figure 1: **Risk curves of Alzheimer's disease (A) and dementia (B) by *APOE* genotypes**
Shaded areas are 95% CIs.

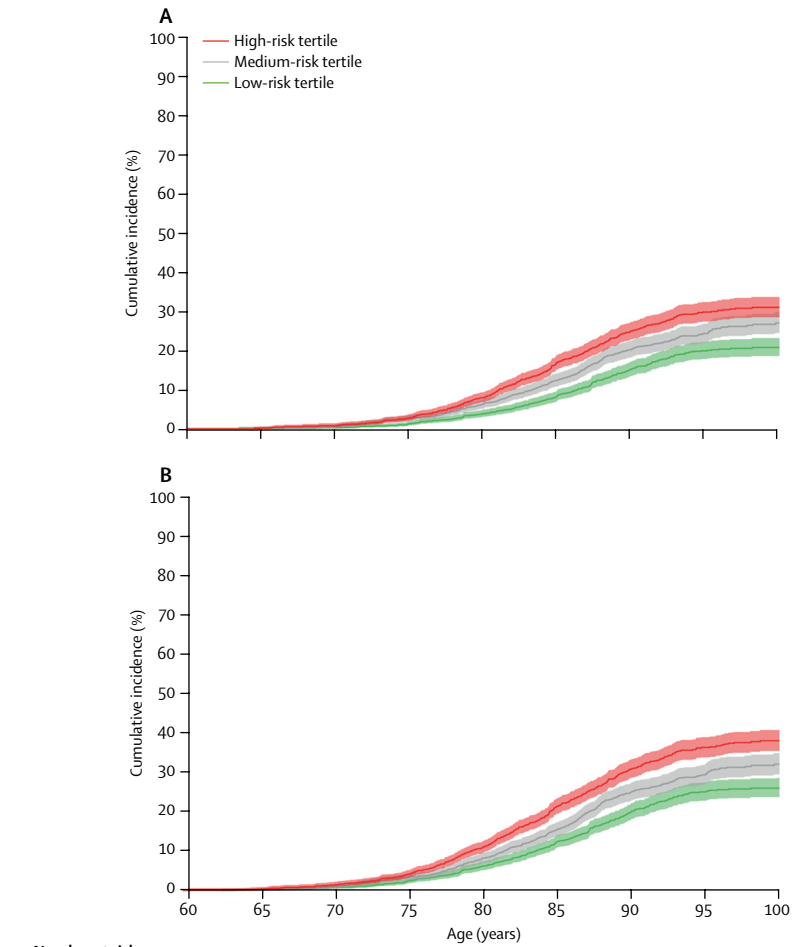

***Figure 2*: Risk curves of Alzheimer's disease (A) and dementia (B) by tertiles of the genetic risk score**
Shaded areas are 95% CIs.

7·2% (4·5–11·5) for dementia. Carriers homozygous for *APOE* ε4 in the high-risk tertile had the highest risk by age 85 years: 62·7% (95% CI 47·2–78·2) for Alzheimer's disease and 77·5% (63·1–89·3) for dementia. Thus, by age 85 years, there was 58·6% risk difference ($p=6·2\times10^{-13}$) for Alzheimer's disease and a 70·3% risk difference ($p=3·0\times10^{-23}$) for dementia between these genetic risk extremes. Within the *APOE* genotype categories, the risks of both Alzheimer's disease and all-cause dementia were higher in the high-risk tertile of the GRS than in the low-risk tertile (figure 3; appendix). Furthermore, the effect of the joint risk score was largest in *APOE* ε4 carriers (figure 3). When tested, there was significant evidence for interaction between *APOE* genotypes and the GRS for Alzheimer's disease (p=0·03) and dementia (p=0·04; appendix), which was not driven by a particular single variant (appendix). By age 85 years, the risk of Alzheimer's disease for carriers homozygous for *APOE* ε4 in the GRS high-risk tertile was 62·7% (95% CI 47·2–78·2) compared with 35·7% (22·6–53·2) in the low-risk tertile, equating to a risk difference of 27·0% ($p=8·5\times10^{-3}$). The risk difference for Alzheimer's disease by this age for carriers heterozygous for *APOE* with one copy each of the ε3 and ε4 alleles or one copy each of ε2 and ε4 was 13·8% ($p=4·2\times10^{-8}$), for carriers homozygous for *APOE* ε3 was 6·1% ($p=4·9\times10^{-7}$), and for carriers homozygous for *APOE* ε2 or heterozygous with one copy each of ε2 and ε3 was 0·7% (p=0·35). A similar pattern was noted for dementia: by age 85 years, the risk difference between the high-risk tertile and the low-risk tertile was 37·2% ($p=2·2\times10^{-4}$) for carriers homozygous for *APOE* ε4, 15·6% ($p=2·1\times10^{-8}$) for carriers heterozygous for *APOE* with one copy each of ε3 and ε4 or one copy each of ε2 and ε4, 6·1% ($p=1·7\times10^{-5}$) for carriers homozygous for *APOE* ε3, and 2·0% (p=0·22) for carriers homozygous for *APOE* ε2 or heterozygous with one copy each of ε2 and ε3.

Figure 4 shows the risk by age for *APOE* and GRS categories for Alzheimer's disease and all-cause dementia, respectively. These figures show that carriers homozygous for *APOE* ε4 in the high-risk tertile attained 5% risk of Alzheimer's disease by age 67 years (64 years for dementia) and 12·5% by age 71 years (67 years for dementia). By comparison, carriers homozygous for *APOE* ε2 or heterozygous with one copy each of the ε2 and ε3 alleles in the low-risk tertile attained 5% risk of Alzheimer's disease by age 85 years (82 years for dementia) and 12·5% by age 100 years (90 years for dementia). The difference in age at onset in individuals with the highest compared with the lowest genetic risk was 18–29 years for Alzheimer's disease and 18–23 years for dementia. Also, differences in age at onset within *APOE* genotypes can be observed from figure 4. In carriers homozygous for *APOE* ε4, a 40% risk of Alzheimer's disease was attained 10 years earlier by those in the high-risk tertile (79 years) compared with those in the low-risk tertile (89 years). Also, for all-cause dementia, the difference in age at which 40% risk was attained is 9 years comparing carriers homozygous for *APOE* ε4 in the high-risk (75 years) and low-risk tertile (84 years).

Parental history of dementia was assessed at baseline and was available for 8793 (71·8%) of the 12 255 participants based on a family history questionnaire. When stratifying by parental history of dementia, the risk for dementia by age 85 years increased to 91·0% (95% CI 66·9–99·4) in the highest risk group (homozygous for *APOE* ε4, high-risk tertile and positive parental history of dementia), making the difference between the highest and the lowest risk group (homozygous for *APOE* ε2 or heterozygous with ε2 and ε3, low-risk tertile and no parental history of dementia) even more pronounced (83·8%; $p=1·1\times10^{-20}$). The risk graphs for all-cause dementia stratified by absence and presence of parental history of dementia are shown in the appendix.

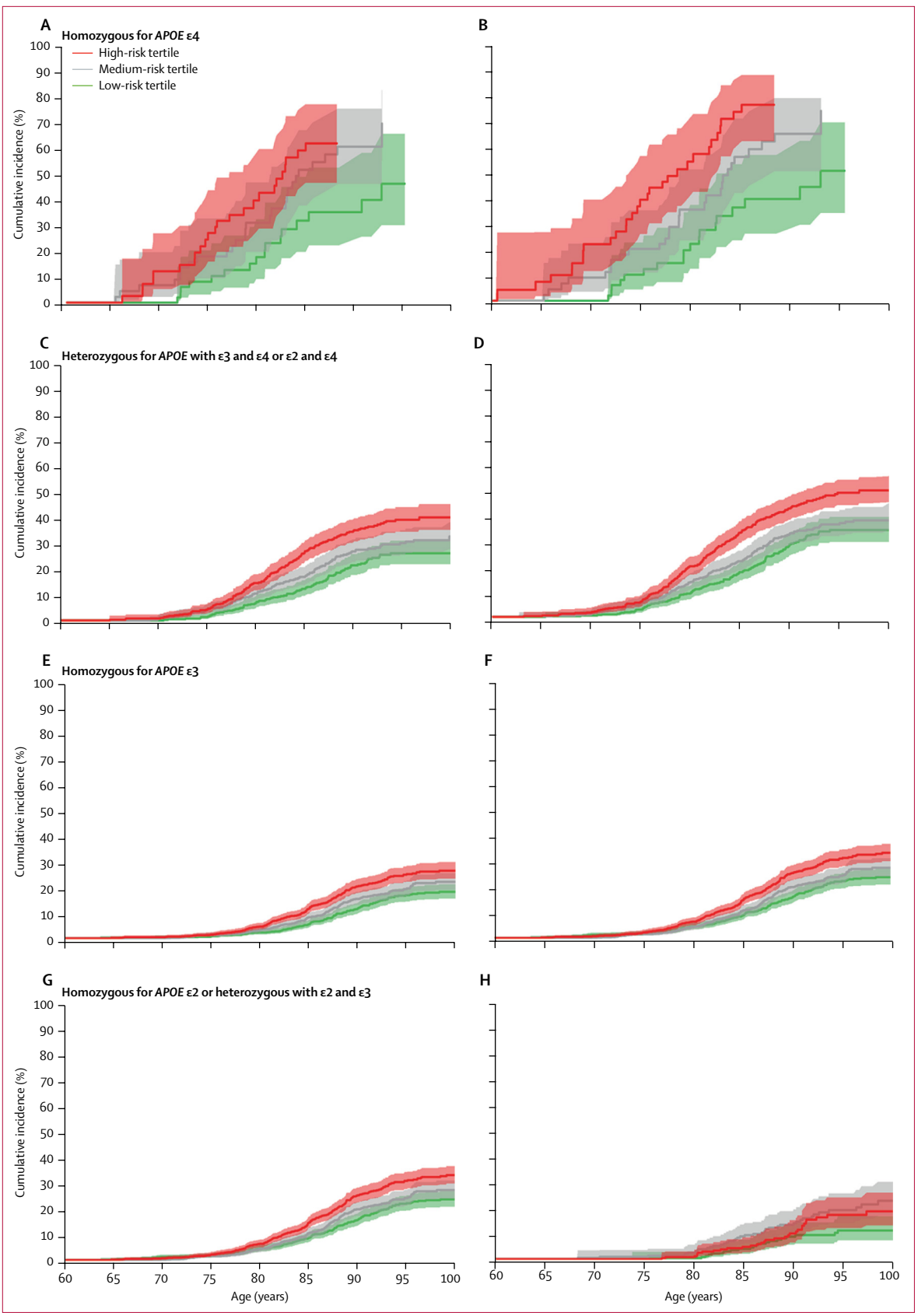

Figure 3: **Risk curves of Alzheimer's disease and dementia by *APOE* genotypes and tertiles of the genetic risk score**
The risk curves show the cumulative incidence of Alzheimer's disease (A, C, E, and G) and dementia (B, D, F, and H) for *APOE* carriers with two copies of the ε4 allele (A and B), *APOE* carriers with one copy each of the ε3 and ε4 alleles or one copy each of ε2 and ε4 (C and D), *APOE* carriers with two copies of the ε3 allele (E and F), and *APOE* carriers with two copies of the ε2 allele or one copy each of the ε2 and ε3 alleles (G and H). Shaded areas are 95% CIs.

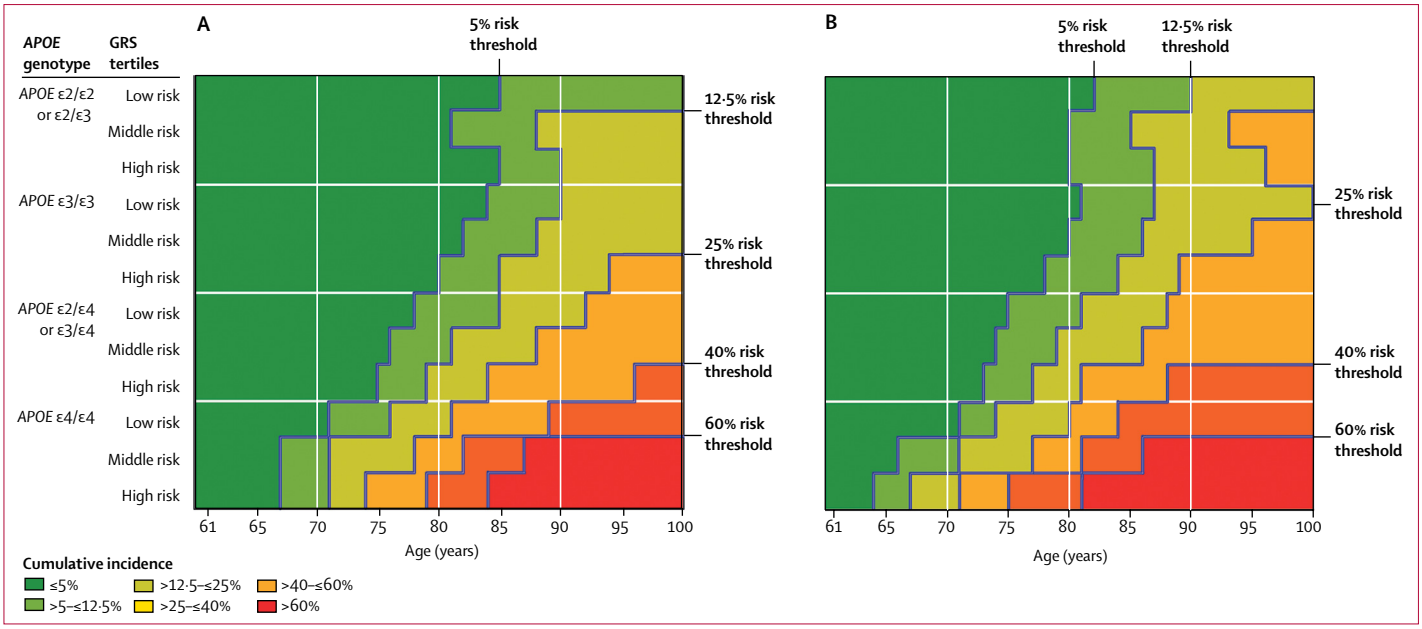

Figure 4: **Risk of Alzheimer's disease (A) and dementia (B) by age, *APOE* genotypes, and tertiles of the genetic risk score**
The age by which the risks of 5%, 12·5%, 25%, 40% and 60% is attained is marked. *APOE* ε2/ε2 or ε2/ε3=carriers with two copies of the ε2 allele or one copy each of the ε2 and ε3 alleles. *APOE* ε3/ε3=carriers with two copies of the ε3 allele. *APOE* ε2/ε4 or ε3/ε4=carriers with one copy each of the ε2 and ε4 alleles or one copy each of the ε3 and ε4 alleles. ε4/ε4=carriers with two copies of the ε4 allele. GRS=genetic risk score.

Discussion

In this large community-based study, a GRS of common genetic variants modified the risk and onset of Alzheimer's disease and dementia above and beyond the effect of *APOE*, when taking into account the competing risk of mortality. The risk modification by the joint effect of common variants was most pronounced in carriers homozygous for *APOE* ε4, in whom there was a difference of up to 10 years in onset age between those in the low-risk and those in the high-risk tertile of the GRS. This shift in age at onset translated into a higher risk of Alzheimer's disease and dementia at all ages and into significant differences in risk by age 85 years. The same set of genetic variants that identified the carriers homozygous for *APOE* ε4 at highest risk of Alzheimer's disease also identified a risk subgroup that has a very low risk of Alzheimer's disease and dementia (carriers homozygous for *APOE* ε2 or heterozygous with one copy each of the ε2 and ε3 alleles, with few common risk variants). Between these subgroups with the highest risk and with the lowest risk, there was a difference of almost two decades in age at onset. These differences became more pronounced when parental history of dementia was considered.

Strengths of this study include the community-based setting, the prospective ascertainment of dementia, the completeness (92%) and length of follow-up (up to 25 years), and adjustment for competing risk of mortality. We estimated cumulative incidences up to age 100 years, with a large number of participants in the higher age groups; for example, at age 90 years, 1161 participants were included. However, despite the large sample, because of stratification by *APOE* subgroups and high-risk, middle-risk, and low-risk tertiles, some subgroups became small by age 100 years, rendering risk estimates unstable. This issue limits our ability to interpret our findings in this growing group of people at risk for clinical dementia.[39] Additionally, since the Rotterdam Study includes participants of native Dutch descent, there might be cohort-specific effects, and although our overall risk estimates are comparable with those reported previously,[40] differences need to be explored in other cohorts, including those with a non-European background. As our knowledge of the genes involved in Alzheimer's disease expands with new discoveries of common and rare genetic variants, intermittent re-estimations of the risks will be necessary. Also, taking into account mortality as a competing risk, we might have been conservative in our estimations. An inherent assumption of correcting for competing risk of mortality is that the genetic variants studied do not affect mortality other than through Alzheimer's disease and all-cause dementia. A study of the genetics of longevity[41] showed a small decrease (of about 5 months) in lifespan in *APOE* ε4 allele carriers and no evidence of an effect for the other Alzheimer's disease-associated variants.[41] A general limitation of epidemiological studies is non-participation,[42] which could lead to non-response bias if those in a preclinical phase of dementia and a high genetic risk have a lower participation rate. Compared with other biobanks such as the UK Biobanks (response rate <20%), the initial response rate of the Rotterdam Study is high (72%). The near-complete follow-up for dementia (92% of potential person-years) lowers possible non-response bias

related to dementia occurring at every follow-up visit to the study centre. Although we used left-truncation to further mitigate the problem, we cannot exclude an underestimation of the risk of dementia as a result of non-response bias.

The identification of subgroups at high genetic risk of Alzheimer's disease with an earlier disease onset in the general population has important implications for precision medicine. Pathological changes related to Alzheimer's disease begin to develop up to decades before the earliest clinical symptoms.[8] Therefore, preventive interventions are increasingly started in the subgroup of individuals with a high genetic risk at a younger age (NCT02565511).[6,7] An important additional benefit for these costly trials is that selection of only the highest risk subgroups will decrease the duration of the trials,[6] and individuals at highest risk should have a chance to access the most promising treatments. At the other end of the risk spectrum are individuals with a very low risk of Alzheimer's disease and a late onset age. These people are of interest for inclusion in epidemiological studies aiming to discover protective factors, and if these low-risk individuals, against expectation, develop Alzheimer's disease at an early age, they are of interest for inclusion in genetic studies because they possibly carry high-risk rare genetic variants.

An interesting finding in this study is the interaction between *APOE* genotypes and other genetic risk factors. Differential effect estimates of common genetic variants by *APOE* ε4 genotypes have been reported previously.[20,21,43] We add to these findings that these differential effects of common variants also affect absolute risk and age at onset. The interaction between *APOE* genotypes and the other common genetic variants associated with Alzheimer's disease might be driven by biological pathways that have been identified for Alzheimer's disease on the basis of the effects of common genetic variants.[44] These include endocytosis, haemostasis, cholesterol transport, haemopoietic cell lineage, protein folding, clathrin complex, immune response, and protein ubiquitination.[44] *APOE* is a part of at least four of these pathways,[44,45] which might explain the observed interaction. The interaction of GRSs with *APOE* might also be explained by a higher percentages of misdiagnosis of Alzheimer's disease in non-*APOE* ε4 carriers. In the absence of information on biomarkers in CSF, on imaging, or at autopsy in our community-based study, these suggestions cannot be proven.

Cumulative incidence of Alzheimer's disease and all-cause dementia has been estimated previously, with and without adjustment for competing risks.[4,5,27,40,46–49] The overall estimates in the current study of risks[27,40] and the risks by 85 years of age stratified by *APOE* genotypes are comparable with previous reports adjusting for competing risks.[40] We found similar patterns of the risk curves of Alzheimer's disease and dementia, which is expected because most all-cause dementia is of the Alzheimer's disease type, but might also be due in part to the effects of the studied genetic variants (*APOE* and 23 other risk loci of Alzheimer's disease) on other types of dementia and stroke.[45,50–52] Previous estimates showed significant effects of common genetic variants on age at onset;[20,23,53] we now show that these variants modify the absolute risk of Alzheimer's disease by shifting risk curves, especially within *APOE* ε4 genotype carriers. The added value of GRSs of common variants with small effects in terms of improved discrimination between Alzheimer's disease cases and controls was reported previously as marginal.[20–22,24] However, our study and that by Desikan and colleagues[23] showed that effects are substantial for risk and age at onset. In this study, we chose to include only 23 genome-wide significant variants in our GRS. Although the discrimination of the GRS is likely to improve by including more variants that are not replicated, the improvement in the area under the curve[22] is marginal (0·715 *vs* 0·717). The small gain of adding these non-validated variants does not outweigh the costs.

In summary, we show that the small effect of common genetic variants together significantly modify the risk of Alzheimer's disease and all-cause dementia and might even partly determine the variability in the age at onset within and across *APOE* genotypes. Our findings contribute towards improvement in efficacy of clinical trials and better risk prediction for Alzheimer's disease and dementia.

Contributors

SJvdL did the analysis and wrote the first draft of the manuscript. FJW collected dementia data and co-wrote the manuscript. MKI supervised data collection. AH supervised the Rotterdam Study and secured funding. MAI supervised the Rotterdam Study, secured funding, and co-wrote the manuscript. NA co-wrote the manuscript and supervised the analysis. CMvD conceived the study, secured funding, and co-wrote the manuscript.

Declaration of interests

We declare no competing interests.

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References

1 Gatz M, Reynolds CA, Fratiglioni L, et al. Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry* 2006; **63:** 168–74.
2 Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993; **43:** 1467–72.
3 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:** 1349–56.
4 Genin E, Hannequin D, Wallon D, et al. *APOE* and Alzheimer disease: a major gene with semi-dominant inheritance. *Mol Psychiatry* 2011; **16:** 903–07.
5 Seshadri S, Drachman DA, Lippa CF. Apolipoprotein E epsilon 4 allele and the lifetime risk of Alzheimer's disease. What physicians know, and what they should know. *Arch Neurol* 1995; **52:** 1074–79.
6 Moulder KL, Snider BJ, Mills SL, et al. Dominantly Inherited Alzheimer Network: facilitating research and clinical trials. *Alzheimers Res Ther* 2013; **5:** 48.
7 Reiman EM, Langbaum JB, Fleisher AS, et al. Alzheimer's Prevention Initiative: a plan to accelerate the evaluation of presymptomatic treatments. *J Alzheimers Dis* 2011; **26** (suppl 3)**:** 321–29.
8 Jack CR Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol* 2013; **12:** 207–16.
9 Lambert JC, Heath S, Even G, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* 2009; **41:** 1094–99.
10 Hollingworth P, Harold D, Sims R, et al. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nat Genet* 2011; **43:** 429–35.
11 Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet* 2013; **45:** 1452–58.
12 Guerreiro R, Wojtas A, Bras J, et al. TREM2 variants in Alzheimer's disease. *N Engl J Med* 2013; **368:** 117–27.
13 Naj AC, Jun G, Beecham GW, et al. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nat Genet* 2011; **43:** 436–41.
14 Desikan RS, Schork AJ, Wang Y, et al. Polygenic overlap between C-reactive protein, plasma lipids, and Alzheimer disease. *Circulation* 2015; **131:** 2061–69.
15 Jun G, Ibrahim-Verbaas CA, Vronskaya M, et al. A novel Alzheimer disease locus located near the gene encoding tau protein. *Mol Psychiatry* 2016; **21:** 108–17.
16 Seshadri S, Fitzpatrick AL, Ikram MA, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA* 2010; **303:** 1832–40.
17 Jonsson T, Stefansson H, Steinberg S, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *N Engl J Med* 2013; **368:** 107–16.
18 Ruiz A, Dols-Icardo O, Bullido MJ, et al. Assessing the role of the TREM2 p.R47H variant as a risk factor for Alzheimer's disease and frontotemporal dementia. *Neurobiol Aging* 2014; **35:** 444.e1–4.
19 Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet* 2009; **41:** 1088–93.
20 Sleegers K, Bettens K, De Roeck A, et al. A 22-single nucleotide polymorphism Alzheimer's disease risk score correlates with family history, onset age, and cerebrospinal fluid Abeta42. *Alzheimers Dement* 2015; **11:** 1452–60.
21 Chouraki V, Reitz C, Maury F, et al. Evaluation of a genetic risk score to improve risk prediction for Alzheimer's disease. *J Alzheimers Dis* 2016; **53:** 921–32.
22 Escott-Price V, Sims R, Bannister C, et al. Common polygenic variation enhances risk prediction for Alzheimer's disease. *Brain* 2015; **138:** 3673–84.
23 Desikan RS, Fan CC, Wang Y, et al. Genetic assessment of age-associated Alzheimer disease risk: development and validation of a polygenic hazard score. *PLoS Med* 2017; **14:** e1002258.
24 Rodriguez-Rodriguez E, Sanchez-Juan P, Vazquez-Higuera JL, et al. Genetic risk score predicting accelerated progression from mild cognitive impairment to Alzheimer's disease. *J Neural Transm (Vienna)* 2013; **120:** 807–12.
25 Adams HH, de Bruijn RF, Hofman A, et al. Genetic risk of neurodegenerative diseases is associated with mild cognitive impairment and conversion to dementia. *Alzheimers Dement* 2015; **11:** 1277–85.
26 Lacour A, Espinosa A, Louwersheimer E, et al. Genome-wide significant risk factors for Alzheimer's disease: role in progression to dementia due to Alzheimer's disease among subjects with mild cognitive impairment. *Mol Psychiatry* 2017; **22:** 153–60.
27 Seshadri S, Wolf PA, Beiser A, et al. Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study. *Neurology* 1997; **49:** 1498–504.
28 Wolters FJ, van der Lee SJ, Koudstaal PJ, et al. Parental family history of dementia in relation to subclinical brain disease and dementia risk. *Neurology* 2017; **88:** 1642–49.
29 Ikram MA, Brusselle GGO, Murad SD, et al. The Rotterdam Study: 2018 update on objectives, design and main results. *Eur J Epidemiol* 2017; **32:** 807–50.
30 de Bruijn RFAG, Bos MJ, Portegies MLP, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. *BMC Med* 2015; **13:** 132.
31 Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM. Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. *Neurology* 2012; **78:** 1456–63.
32 van Leeuwen EM, Kanterakis A, Deelen P, et al. Population-specific genotype imputations using minimac or IMPUTE2. *Nat Protoc* 2015; **10:** 1285–96.
33 McCarthy Group Tools. HRC or 1000G Imputation preparation and checking. http://www.well.ox.ac.uk/~wrayner/tools/#Checking (accessed Jan 10, 2016).
34 McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet* 2016; **48:** 1279–83.
35 Allignol A, Schumacher M, Beyersmann J. Empirical transition matrix of multi-state models: the etm package. *J Stat Softw* 2011; **38:** 1–15.
36 Meister R, Schaefer C. Statistical methods for estimating the probability of spontaneous abortion in observational studies—analyzing pregnancies exposed to coumarin derivatives. *Reprod Toxicol* 2008; **26:** 31–35.
37 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53: 457–81.
38 Tsai WY, Jewell NP, Wang MC. A Note on the product-limit estimator under right censoring and left truncation. *Biometrika* 1987; **74:** 883–86.
39 Alzheimer's Association. 2016 Alzheimer's disease facts and figures. *Alzheimers Dement* 2016; **12:** 459–509.
40 Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. *Lancet Neurol* 2007; **6:** 1106–14.
41 McDaid AF, Joshi PK, Porcu E, et al. Bayesian association scan reveals loci associated with human lifespan and linked biomarkers. *Nat Commun* 2017; **8:** 15842.

42 Galea S, Tracy M. Participation rates in epidemiologic studies. *Ann Epidemiol* 2007; **17:** 643–53.

43 Marden JR, Mayeda ER, Walter S, et al. Using an Alzheimer disease polygenic risk score to predict memory decline in black and white Americans over 14 years of follow-up. *Alzheimer Dis Assoc Disord* 2016; **30:** 195–202.

44 International Genomics of Alzheimer's Disease Consortium (IGAP). Convergent genetic and expression data implicate immunity in Alzheimer's disease. *Alzheimers Dement* 2015; **11:** 658–71.

45 Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol* 2013; **9:** 106–18.

46 Myers RH, Schaefer EJ, Wilson PW, et al. Apolipoprotein E epsilon4 association with dementia in a population-based study: the Framingham study. *Neurology* 1996; **46:** 673–77.

47 Bickeboller H, Campion D, Brice A, et al. Apolipoprotein E and Alzheimer disease: genotype-specific risks by age and sex. *Am J Hum Genet* 1997; **60:** 439–46.

48 Cupples LA, Farrer LA, Sadovnick AD, Relkin N, Whitehouse P, Green RC. Estimating risk curves for first-degree relatives of patients with Alzheimer's disease: the REVEAL study. *Genet Med* 2004; **6:** 192–96.

49 Seshadri S, Beiser A, Kelly-Hayes M, et al. The lifetime risk of stroke: estimates from the Framingham Study. *Stroke* 2006; **37:** 345–50.

50 Bras J, Guerreiro R, Darwent L, et al. Genetic analysis implicates *APOE*, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. *Hum Mol Genet* 2014; **23:** 6139–46.

51 Khan TA, Shah T, Prieto D, et al. Apolipoprotein E genotype, cardiovascular biomarkers and risk of stroke: systematic review and meta-analysis of 14,015 stroke cases and pooled analysis of primary biomarker data from up to 60,883 individuals. *Int J Epidemiol* 2013; **42:** 475–92.

52 Guerreiro R, Escott-Price V, Darwent L, et al. Genome-wide analysis of genetic correlation in dementia with Lewy bodies, Parkinson's and Alzheimer's diseases. *Neurobiol Aging* 2016; **38:** 214.e7–10.

53 Naj AC, Jun G, Reitz C, et al. Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease: a genome-wide association study. *JAMA Neurol* 2014; **71:** 1394–404.