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RESEARCH ARTICLE

# *APOE* and genetic risk variants influence Alzheimer's disease onset in carriers of an extra copy of *APP*, with and without Down syndrome

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## Abstract

**INTRODUCTION:** An extra copy of the amyloid precursor protein (*APP*) gene causes autosomal dominant Alzheimer's disease (AD) and AD in Down syndrome (DS), but the factors underlying variability in age at onset (AAO) remain unclear. We investigated whether sporadic AD risk variants modify AAO.

**METHODS:** We analyzed clinical and genetic data from 100 *APP* duplication (*APP*dup) carriers and 957 individuals with DS. Cox models assessed associations of apolipopro-

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tein E (*APOE*) ε2 and ε4 and the AD genetic risk score (AD-GRS; excluding *APOE* and chromosome 21 variants) with AAO.

**RESULTS:** Mean AAO was earlier in *APP*dup than DS (51 ± 7 vs. 53 ± 6 years; $P = 0.0005$). *APOE* ε2 delayed onset (hazard ratio [HR] = 0.47, $P < 0.0001$), whereas *APOE* ε4 (HR = 1.5, $P = 0.0003$) and higher AD-GRS (HR = 1.3 per standard deviation, $P < 0.0001$) accelerated onset. Predicted median AAO differed by 10 years between lowest and highest genetic risk.

**DISCUSSION:** Sporadic AD genetic risk factors are important modifiers of AAO in *APP*dup and DS, explaining part of the marked variability in onset.

KEYWORDS
Alzheimer's disease, amyloid precursor protein duplication, apolipoprotein E, autosomal dominant Alzheimer's disease, disease onset, Down syndrome, Down syndrome-associated Alzheimer's disease, polygenic risk score

## Highlights

- Sporadic Alzheimer's disease (AD) genetic variants modify AD onset in amyloid precursor protein duplications and Down syndrome.
- Apolipoprotein E (*APOE*) ε2 delays AD onset, while *APOE* ε4 and higher AD genetic risk score accelerate onset.
- Lowest versus highest genetic risk predicts an ≈ 10-year difference in AD onset.
- Amyloid beta, angiogenesis, and endocytosis pathways influence timing of AD onset.
- Trials in presymptomatic individuals should consider sporadic AD genetic risk.

## 1 | INTRODUCTION

An extra copy of the amyloid precursor protein *(APP)* gene on chromosome 21 leads to overproduction of abnormal amyloid beta (A$\beta$), causing early-onset Alzheimer's disease (AD) and/or cerebral amyloid angiopathy (CAA).[1] The most common cause is de novo trisomy 21, responsible for Down syndrome (DS), a condition that includes intellectual disability and cardiac malformations.[2–4] In rare cases, a small segment of chromosome 21 is duplicated without the DS critical region (small distal region on 21q22.13), leading to autosomal dominant AD (ADAD). Carriers typically present with cognitive decline, hemorrhages, or seizures.[5,6] In DS, early recognition of AD and/or CAA is complicated by intellectual disability and other co-morbidities.[7] In both ADAD *APP* duplications (*APP*dup) and DS-AD, the age at onset (AAO) varies widely (40–65 years), making it difficult to predict AAO.[8–14] This heterogeneity in AAO likely reflects a combination of environmental and genetic factors. Identifying modifiers of AAO in *APP*dup and DS is crucial for care planning and optimizing the timing of treatment initiation for emerging disease-modifying therapies.

Among established genetic risk factors for AD, the apolipoprotein E (*APOE*) genotype is most prominent.[15] Studies investigating *APOE* across different causes of ADAD reported that the *APOE* ε4 allele accelerated onset and the *APOE* ε2 allele delayed onset, with inconsistent significance.[12,16–19] In *APP*dup carriers, no significant effect of *APOE* was found, nor an association of duplication length or nearby duplicated genes with AAO or specific symptoms, possibly due to small sample size.[14] In DS, *APOE* ε4 has been linked to earlier AD onset and corresponding cerebrospinal fluid (CSF) changes, although associations with clinical onset measures have not been consistent.[20–22] These findings suggest that the *APOE* genotype may influence the disease trajectory in individuals carrying an additional copy of *APP*.

Genome-wide association studies (GWASs) have identified > 80 other AD risk variants beyond *APOE*.[23] Aggregating the effects of these variants into an AD genetic risk score (AD-GRS) provides a measure of cumulative genetic susceptibility to AD, which has been consistently associated with AAO. In ADAD and DS studies, the AD-GRS has been associated with CSF biomarkers and cognitive decline,[22,24,25] implying potential influence on AAO. These genetic variants are implicated in different biological pathways.[26] Constructing pathway-specific GRSs (pGRSs) allows us to determine which biological mechanisms most strongly modify AAO, thereby highlighting the pathways most relevant in individuals with an extra *APP* copy.

Although *APOE* and AD-GRS have been examined in DS-AD and ADAD, including *APP*dup, their contribution to variability in AAO remains unclear. Here, we hypothesized that genetic risk modifiers of AD, including *APOE* and AD-GRS, contribute to the observed

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**RESEARCH IN CONTEXT**

1. **Systematic review**: Literature on Alzheimer's disease (AD) in amyloid precursor protein (*APP*) duplications (*APP*dup) and Down syndrome (DS) shows that the age at onset (AAO) varies between 40 and 65 years. Several studies suggest an earlier onset in apolipoprotein E (*APOE*) ε4 carriers, with no other major contributors to this variability. Genome-wide studies in sporadic AD identified > 80 risk loci, and AD genetic risk scores (AD-GRS) influence both disease risk and AAO. However, the role of the AD-GRS as an AAO modifier in individuals with an extra *APP* copy has not been examined.
2. **Interpretation**: AAO was earlier in *APP*dup than DS with similar distributions. *APOE* ε2 delayed onset, while *APOE* ε4 and a higher AD-GRS accelerated onset. Lowest versus highest genetic risk predicted an ≈10-year AAO difference. Amyloid beta, angiogenesis, and endocytosis pathways showed the strongest AAO effects.
3. **Future directions**: *APOE* and polygenic risk may improve AAO prediction and trial design in individuals with an extra *APP* copy.

variation in AAO among individuals with an extra *APP* copy. Our aim was to investigate how these factors influence AAO in *APP*dup and DS individuals, to determine whether these effects are comparable across the two groups, and to identify specific biological pathways underlying this variability.

## 2 | METHODS

### 2.1 | Study design

In this multicenter retrospective cohort study, individuals with an additional copy of *APP* were selected from the European Alzheimer & Dementia Biobank (EADB),[23] the Amsterdam Dementia Cohort (ADC),[27] the Netherlands Brain Bank, the French National Reference Centre for Patients with Early-Onset Alzheimer's Disease (CNRMAJ; Rouen University Hospital), the Dominantly Inherited Alzheimer Network Observational Study (DIAN Obs),[28] the Ace Alzheimer Center Barcelona (ACE), Down Alzheimer's Barcelona Neuroimaging Initiative (DABNI),[29] and the Hospital Universitario de la Princesa (HUP) in Madrid through diverse methods. All studies were approved by their local medical ethical committee.

### 2.2 | Population

All individuals carrying an *APP*dup were included if clinical and genetic data were available and when the duplication did not extend across the entire DS critical region (distal 21q22.13).[30] Previously reported *APP*dup carriers with available AAO and *APOE* genotype were additionally included after a PubMed literature search (search strategy described in the Supplementary Methods in supporting information). Individuals with DS were included if they had partial or full trisomy 21 including the triplication of *APP*, known AD status, and available genetic data.

### 2.3 | Procedures

Clinical characteristics were obtained from medical records or research databases and included self-reported sex, AD status, clinical symptoms, symptomatic AAO, age at AD diagnosis, or age at last visit. For *APP*dup carriers, AAO was defined as age at first symptom onset as indicated by the patient or patient's family. These symptoms include cognitive decline, hemorrhages, or seizures. For DS individuals, AAO corresponded to the age at (prodromal) AD diagnosis based on consensus between neurologists and neuropsychologists after independent visits. Progression to prodromal AD was defined as relevant cognitive or behavioral changes without interference in daily functioning (details in DABNI protocol).[29] For DS individuals with established AD at first study visit, age at that visit was used as AAO.

DNA was isolated from whole blood samples or brain tissue. High-density single nucleotide polymorphism (SNP) arrays were used for all cohorts, except for the DIAN samples, which underwent short-read whole genome sequencing (WGS). Genotyping, imputation, sequencing, and detection of *APP*dup or trisomy 21 are described in the Supplementary Methods. When available, *APP*dup size and additional duplicated genes were recorded.

The *APOE* alleles (ε2, ε3, and ε4) and common genotypes (ε2/ε2, ε2/ε3, ε3/ε3, ε3/ε4, ε2/ε4, and ε4/ε4) were defined using two SNPs (rs429358, rs7412). The ε1 allele was not observed. For analyses, *APOE* ε2 carriers (ε2/ε2, ε2/ε3) and *APOE* ε4 carriers (ε3/ε4, ε2/ε4, ε4/ε4) were compared to the reference genotype ε3/ε3. Individuals with *APOE* ε2/ε4 were assigned to the ε4 group, consistent with previous evidence of increased AD risk compared to ε3/ε3.[31]

The AD-GRS was calculated using genome-wide significant variants from the most recent AD-GWAS.[23] Of 83 SNPs (excluding the *APOE* locus), 6 were removed from all samples, as 2 were located on chromosome 21 and 4 had low imputation quality ($R^2 < 0.3$; Supplementary Methods). The AD-GRS was calculated with the remaining 77 SNPs as the sum of the variant dosages weighted by the effect estimates from the AD-GWAS. This was performed for *APP*dup carriers with available genetic data and for all DS individuals. The AD-GRS was standardized (mean = 0, standard deviation [SD] = 1) within each population subgroup. In seven DIAN samples, one missing SNP (rs62374257) was imputed to the minor-allele frequency from GnomAD to allow complete AD-GRS calculation.[32]

pGRSs were constructed for the five major AD-related pathways: Aβ metabolism, immune response, endocytosis, cholesterol/lipid metabolism, and angiogenesis.[26] Each pGRS incorporated

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pathway-specific variant weights to the original AD-GRS calculation (Table S1 in supporting information).[26]

### 2.4 | Outcomes

The primary outcome was symptomatic AAO of AD. Because AAO is more difficult to determine in individuals with DS than in those without intellectual disability,[7] we attempted to match the definition of AAO between cohorts as follows: (1) for *APP*dup carriers, AAO corresponded to the age at first symptom onset; (2) for DABNI, AAO reflected the age at prodromal AD diagnosis or, for individuals with dementia at first visit, age at that visit; and (3) for ACE/HUP, AAO corresponded to the age at clinical AD dementia diagnosis. In the following sections, these measures are collectively referred to as AAO.

### 2.5 | Statistical analysis

All analyses were performed in R version 4.4.1. Individuals unaffected at last follow-up were censored at that age. Descriptive statistics were used to compare *APP*dup carriers and DS individuals. We used *t* tests for age and Pearson chi-squared tests for dichotomous data. Differences in AAO were assessed using Kaplan–Meier curves and log-rank tests, and AAO variance differences were evaluated with the Levene test.

Cox proportional hazard models assessed associations of *APOE* ε2, *APOE* ε4, and AD-GRS with AAO. Because AD-GRS was not available for all individuals, Model 1 included *APOE* ε2 and ε4 only, whereas Model 2 additionally included AD-GRS. To account for different AAO definitions, cohort was included as a categorical covariate (0 = *APP*dup, 1 = DABNI, 2 = ACE/HUP). Sex and genetic principal components were not included. Hazard ratios (HRs) with 95% confidence intervals (CIs) and *p* values were reported. Potential interactions between *APOE* and AD-GRS were tested in separate models.

Analyses were conducted in the total cohort and stratified by *APP*dup and DS groups. The DS cohorts were further stratified by DABNI and ACE/HUP to assess differences in *APOE* and AD-GRS effects on AAO. Single-variant analyses were performed for all AD-GRS variants within the *APP*dup, DABNI, and ACE/HUP cohorts separately, with effects aligned to the GWAS effect allele. Cohort-specific estimates were pooled using an inverse variance weighted fixed-effect meta-analysis. Genomic inflation was assessed using the genomic inflation factor calculated from the meta-analysis *p* values, and calibration was visualized with a QQ plot. Effect-size concordance was assessed using beta–beta plots.

Predicted median AAO with 95% CIs were calculated, and cumulative incidence curves were constructed using the riskRegression package.[33] These curves were generated for *APP*dup and DS separately and were based on: (1) *APOE* genotypes (ε2, ε3/ε3, and ε4), (2) AD-GRS values at five levels (lowest: −2 SD from the mean, low: −1 SD, average: 0 SD, high: +1 SD, and highest: +2 SD), and (3) two extreme risk scenarios combining *APOE* and AD-GRS (lowest risk: *APOE* ε2 and lowest AD-GRS; highest risk: *APOE* ε4 and highest AD-GRS). Additionally, AD-GRS effects within each *APOE* genotype were illustrated by computing similar cumulative incidence curves.

To assess pathway-specific effects, Cox models were fitted for the five pGRSs in the total cohort, and in the stratified *APP*dup and DS groups. We added the three different cohorts as covariates. In a subset of *APP*dup carriers, duplication length and individual genes located on chromosome 21 (duplicated in ≥ 5 carriers) were associated with AAO in separate Cox models. HRs and 95% CIs were reported. We controlled for the false discovery rate (FDR) to correct for multiple testing; *q* values < 0.05 were considered statistically significant.

## 3 | RESULTS

### 3.1 | Population and clinical characteristics

In total, 100 *APP*dup carriers were included from the Netherlands ($n = 14$), France ($n = 46$), Spain ($n = 2$), EADB ($n = 6$), DIAN ($n = 8$), and from literature ($n = 24$, Supplementary Results in supporting information). We included 957 individuals with DS from the DABNI cohort ($n = 374$), ACE ($n = 12$), and HUP ($n = 571$). Clinical characteristics are summarized in Table 1. The mean age at last visit among asymptomatic individuals was 42.4 years (SD ± 9.7), which did not differ between *APP*dup and DS ($P = 0.43$). A higher proportion of *APP*dup carriers was symptomatic for AD compared to individuals with DS (91% vs. 34%; $P < 0.0001$). The total cohort had a mean AAO of 52.8 ± 5.8 years, with AAO distribution shown in Figure 1. Mean AAO was earlier in *APP*dup carriers (mean AAO 50.7 ± 6.6 years) than individuals with DS (53.3 ± 5.5 years; $P = 0.0005$). However, AAO variability was similar between groups (Levene test: $F = 1.12$, $P = 0.29$), and AAO did not differ between *APP*dup carriers and DS individuals with an available age at prodromal AD diagnosis ($P = 0.10$; Figure 2). *APOE* genotype distributions were similar across groups ($P_{APOE2} = 0.80$; $P_{APOE4} = 0.50$), with most individuals homozygous for *APOE* ε3 (70%). There were no homozygous ε2 carriers and only ten homozygous ε4 carriers in DS (four asymptomatic and six symptomatic). Among *APP*dup carriers, duplication size ranged from 0.14 Mb to 18.50 Mb, encompassing between 1 and 65 genes.

### 3.2 | Associations of *APOE* and AD-GRS with AAO

Figure 3 summarizes the Cox proportional hazard models. In the total cohort, *APOE* genotype was significantly associated with AAO. In Model 1, *APOE* ε2 delayed onset of AD (HR = 0.47 [0.32–0.67], $P < 0.0001$), whereas *APOE* ε4 accelerated onset (HR = 1.5 [1.2–1.9], $P = 0.0003$). In Model 2, the AD-GRS was significantly associated with AAO (HR = 1.3 [1.1–1.4], $P < 0.0001$), indicating earlier onset with a higher AD-GRS. No interaction between *APOE* ε2 or ε4 and the AD-GRS was observed ($P_{APOE2} = 0.62$; $P_{APOE4} = 0.36$; Table S2 in supporting information).

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**TABLE 1** Demographic and clinical characteristics.

| | Total cohort | | Stratified groups | | |
|---|---|---|---|---|---|
| | N | Total N = 1057[a] | *APP* duplications N = 100[a] | Down syndrome N = 957[a] | *p* value |
| **Age at last visit (asymptomatic)**[b] | 638 | 42.4 (9.7) | 46.0 (13.1) | 42.4 (9.6) | 0.43[c] |
| **Age at onset (symptomatic)** | 419 | 52.8 (5.8) | 50.7 (6.6) | 53.3 (5.5) | 0.0005[c] |
| **Sex** | 1051 | | | | 0.17[d] |
| Male | | 549 (52%) | 56 (60%) | 493 (52%) | |
| Female | | 502 (48%) | 38 (40%) | 464 (48%) | |
| **Alzheimer's disease** | 1057 | | | | <0.0001[d] |
| Symptomatic | | 419 (40%) | 91 (91%) | 328 (34%) | |
| Asymptomatic | | 638 (60%) | 9 (9.0%) | 629 (66%) | |
| ***APOE*** | 1057 | | | | |
| *APOE* ε2 carrier | | 108 (10%) | 9 (9.0%) | 99 (10%) | 0.80[d] |
| *APOE* ε4 carrier | | 212 (20%) | 17 (17%) | 195 (20%) | 0.50[d] |

[a]Mean (SD), no. (%)
[b]The age at last visit refers to the age at last visit of asymptomatic individuals only.
[c]Welch two-sample *t* test.
[d]Pearson chi-squared test. In the *APP* duplication group the asymptomatic individuals are from the Dutch ($n = 2$), French ($n = 2$), DIAN ($n = 4$) sites and from literature ($n = 1$). In the Down syndrome group, the asymptomatic individuals are from both the DABNI cohort ($n = 205$) and ACE/HUP ($n = 424$). Of the symptomatic individuals with DS in the DABNI cohort, 77 had established dementia before their first study visit.
Abbreviations: ACE/HUP, Ace Alzheimer Center Barcelona/Hospital Universitario de la Princesa; *APOE*, apolipoprotein E; *APP*, amyloid precursor protein; DABNI, Down Alzheimer's Barcelona Neuroimaging Initiative; DIAN, Dominantly Inherited Alzheimer Network; DS, Down syndrome; SD, standard deviation.

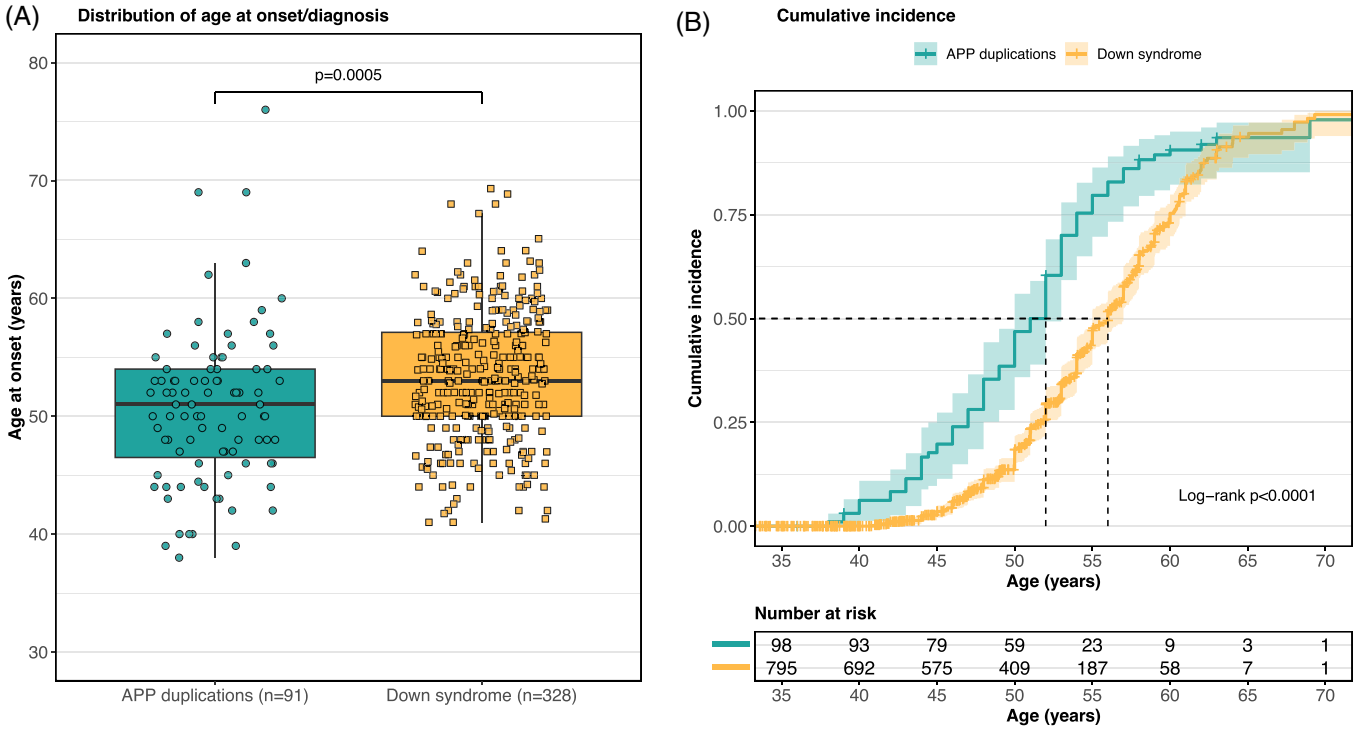


**FIGURE 1** Distribution of AAO and cumulative incidence of AD stratified by *APP* duplications and Down syndrome. A, AAO distribution stratified by *APP* duplications and Down syndrome. The definition of AAO differs per cohort and includes the age at symptom onset, age at (prodromal) AD diagnosis, or age at first visit in case of established AD. B, Cumulative incidence of symptoms stratified by *APP* duplications (median AAO [95% confidence interval] = 52 years [50–53]) and Down syndrome (median AAO = 56 years [55–57]). AAO, age at onset; AD, Alzheimer's disease; *APP*, amyloid precursor protein.

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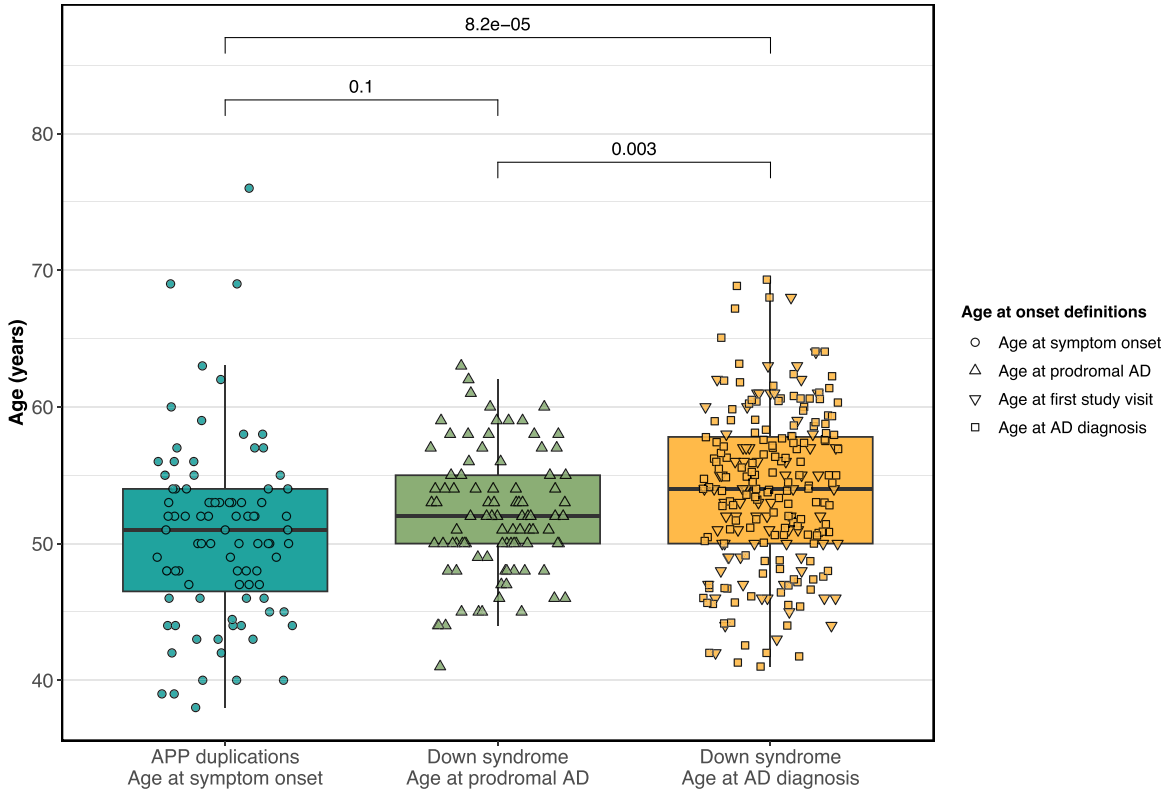


**FIGURE 2** Distribution of age at symptom onset, prodromal AD, and dementia diagnosis. Boxes represent IQR, with the median shown as the horizontal line. The left boxplot shows the age at symptom onset distribution of *APP* duplication carriers (median 51 years [IQR 47–54]), the middle boxplot shows the age at prodromal AD diagnosis in Down syndrome (52 years [50–55]), and the right boxplot shows the age at dementia diagnosis in Down syndrome (54 years [50–58]). In this last group, we included both individuals with age at first study visit with dementia and individuals with clinical age at dementia diagnosis. AD, Alzheimer's disease; *APP*, amyloid precursor protein; IQR, interquartile range.

| | Cohort | N | HR [95% CI] | p–value |
|---|---|---|---|---|
| **APOE e2** | Total cohort | 1057 | 0.47 [0.32–0.67] | <0.0001 |
| | APP duplications | 100 | 0.34 [0.14–0.81] | 0.016 |
| | Down syndrome | 957 | 0.60 [0.41–0.89] | 0.010 |
| **APOE e4** | Total cohort | 1057 | 1.5 [1.2–1.9] | 0.0003 |
| | APP duplications | 100 | 1.5 [0.86–2.5] | 0.16 |
| | Down syndrome | 957 | 1.6 [1.2–2.1] | 0.0005 |
| **AD–GRS** | Total cohort | 1028 | 1.3 [1.1–1.4] | <0.0001 |
| | APP duplications | 71 | 1.3 [0.93–1.8] | 0.13 |
| | Down syndrome | 957 | 1.3 [1.1–1.4] | <0.0001 |

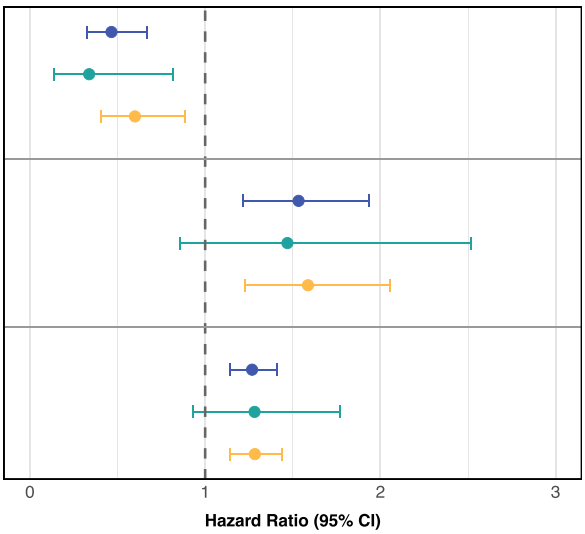


**FIGURE 3** Cox proportional hazard model of *APOE* and AD genetic risk score associated with age at onset. The HRs for the *APOE* ε2 and ε4 correspond to the results from Model 1 (*APOE* ε2 + *APOE* ε4). The HRs for the AD-GRS correspond to the results from Model 2 (*APOE* ε2 + *APOE* ε4 + AD-GRS). The AD-GRS included 77 single nucleotide polymorphisms associated with AD in which the *APOE* genotype was not included. AD, Alzheimer's disease; AD-GRS, Alzheimer's disease genetic risk score; *APOE*, apolipoprotein E; *APP*, amyloid precursor protein; CI, confidence interval; HR, hazard ratio; IQR, interquartile range.

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Stratified analyses by *APP*dup and DS yielded consistent results. *APOE* ε2 delayed onset ($HR_{APPdup}$ = 0.34 [0.14–0.81], $P$ = 0.016; $HR_{DS}$ = 0.60 [0.41–0.89], $P$ = 0.010), while *APOE* ε4 accelerated onset (HR*APP*dup = 1.5 [0.86–2.5], $P$ = 0.16; HRDS = 1.6 [1.2–2.1], $P$ = 0.0005). The effect of AD-GRS was similar in *APP*dup (HR = 1.3 [0.93–1.8], $P$ = 0.13) and DS (HR = 1.3 [1.1–1.4], $P$ < 0.0001). In stratified analyses of the DS cohorts, the effect of the *APOE* ε2 was weaker in the DABNI cohort (Figure S1 in supporting information). The meta-analysis of the single variant analyses underlying the AD-GRS showed that the association was not driven by a single variant (Table S3 in supporting information), but by small effects of all variants (genomic inflation factor = 1.45; Figure S2 in supporting information).

## 3.3 | Median AAO prediction

Given differences in AAO between *APP*dup and DS, we report stratified results that showed similar overall patterns in both groups (Figure 4 and Table S4 in supporting information). In *APP*dup, predicted median AAO was 51.1 years [49.8–52.3] in *APOE* ε4, 52.5 years [51.3–53.9] in *APOE* ε3/ε3, and 56.2 years [53.9–58.2] in *APOE* ε2. Corresponding AAOs in DS were 51.8 years [51.1–52.8], 53.5 years [52.6–54.3], and 57.3 years [55.1–59.4], respectively. For the AD-GRS, predicted median AAO in *APP*dup ranged from 50.6 years [49.3–52.0] at the highest AD-GRS (+2 SD) to 54.7 years [53.2–56.9] at the lowest AD-GRS (−2 SD). In DS, these AAOs ranged from 51.4 years [50.4–52.5] at the highest to 56.1 years [54.5–57.5] at the lowest AD-GRS. Combining *APOE* and AD-GRS, predicted median AAO differed by 9.4 years between the genetic extremes in *APP*dup (highest risk: 49.4 years [47.7–50.7]; lowest risk: 58.8 years [56.5–61.1]). In DS, the corresponding difference was 10 years (highest risk: 50.1 years [49.2–51.1]; lowest risk: 60.1 years [57.6–62.4]). Cumulative incidence curves stratified by *APOE* are presented in Figure S3 in supporting information and corresponding predicted AAOs in Table S5 in supporting information. Within each *APOE* genotype, higher AD-GRS values were consistently associated with earlier predicted median AAO.

## 3.4 | Pathway-specific GRS analyses

Pathway-specific GRS analyses are shown in Figure 5, and correlations between each pGRS are presented in Figure S4 in supporting information. In the total cohort, the Aβ pGRS (HR = 1.2 [1.1–1.3], $q$ = 0.013) and angiogenesis pGRS (HR = 1.1 [1.0–1.3], $q$ = 0.034) were associated with AAO. The pGRS for endocytosis (HR = 1.1 [1.0–1.2], $q$ = 0.11), immune response (HR = 1.1 [0.97–1.2], $q$ = 0.21), and cholesterol/lipids (HR = 1.1 [0.96–1.2], $q$ = 0.31) did not reach statistical significance. In DS, the endocytosis pGRS was associated with AAO (HR = 1.2 [1.0–1.3], $q$ = 0.034). The effects in *APP*dup and DS were comparable, albeit less significant in *APP*dup, consistent with smaller sample size.

## 3.5 | Duplication length and chromosome 21 gene content

Finally, in a selection of *APP*dup carriers ($n$ = 92), we did not find an association of duplication length with AAO (HR = 1.00 [0.96–1.05], $P$ = 0.95). We then assessed the association of 23 individual genes from chromosome 21 with AAO (located between chr21:13,609,777–29,536,93; GRCh38/hg38). Duplication of none of these genes were significantly associated with AAO (Table S6 in supporting information).

# 4 | DISCUSSION

We investigated whether established genetic risk factors for sporadic AD modify AAO in individuals with an extra copy of *APP*, either in ADAD or as part of trisomy 21. To our knowledge, this is the first study to demonstrate robust effects of both *APOE* and AD-GRS on AAO in *APP*dup carriers and the largest study of genetic modifiers in individuals with an extra copy of *APP*. In both *APP*dup and DS, onset of AD was accelerated by *APOE* ε4 and a high AD-GRS, and delayed by *APOE* ε2 and a low AD-GRS. The effects of *APOE* and AD-GRS were independent and, at the extremes of genetic risk, amounted to a 9- to 10-year difference in AAO. These modifying effects were consistent across *APP*dup carriers and those with DS, and were not driven by any single variant. Pathway analyses instead pointed to variants related to the Aβ and angiogenesis pathways as having the strongest influence on AAO, suggesting that these pathways may be particularly important in shaping the effects of *APP* overexpression.

Our findings show that *APOE* ε4 accelerates and *APOE* ε2 delays AAO, consistent with sporadic AD and with several studies in ADAD and DS.[15–18,20,21,34,35] Across studies, effect directions are largely consistent, although effect sizes and significance vary and one report described an association in the opposite direction.[18] Studies focusing on specific pathogenic variants often report clearer effects, whereas analyses pooling multiple ADAD variants tend to show smaller or non-significant effects, suggesting variant-dependent modification.[17,19,21,25] In DS, *APOE* associations with clinical outcomes have not been consistently observed, including no association with age at memory change in a previous smaller study.[22] In our study, the *APOE* ε4 effect did not reach statistical significance in the smallest group (*APP*dup), although effect sizes were comparable to those in DS. Notably, *APOE* ε2 showed a larger delaying effect than *APOE* ε4's accelerating effect. We speculate that in individuals with an extra *APP* copy, *APOE* ε2 may confer relatively stronger protection by enhancing amyloid clearance, whereas the already elevated amyloid burden may constrain the additional acceleration attributable to *APOE* ε4. Overall, these findings support *APOE* as a modifier of AAO in the context of an extra *APP* copy.

The AD-GRS was also associated with AAO in individuals with an extra *APP* copy: higher scores accelerated AAO, and lower scores delayed AAO. Again, these findings are in line with literature on sporadic AD.[35] The AD-GRS has not previously been evaluated in *APP*dup,

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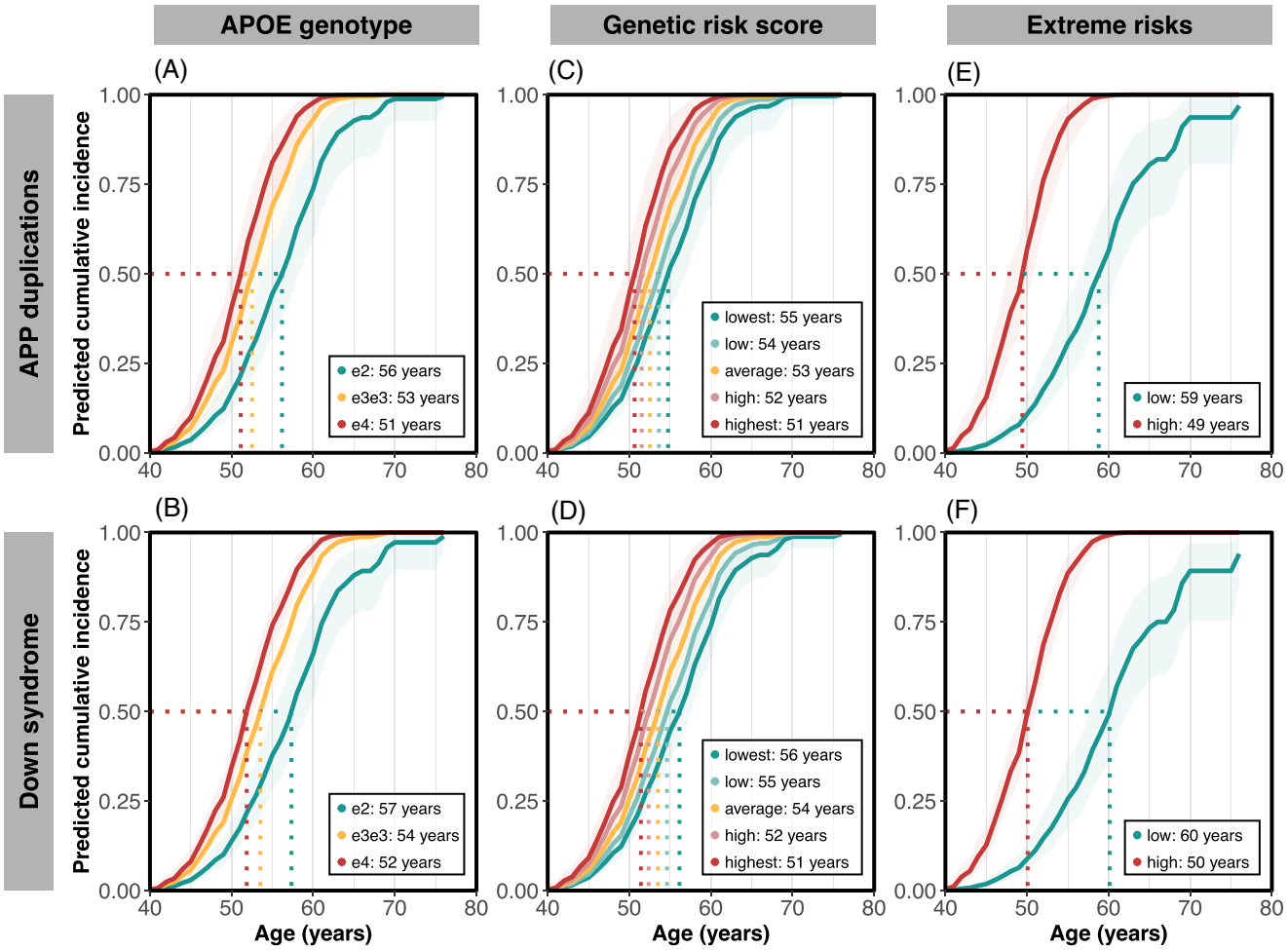


**FIGURE 4** Predicted cumulative incidence for *APOE* genotypes, genetic risk scores, and extremes stratified by *APP* duplications and Down syndrome. These figures show the predicted cumulative incidence curves stratified by *APP* duplications and Down syndrome. In (A) and (B), the predicted curves for the different *APOE* genotypes are shown. (C) and (D) show the predicted curves for the different scores for the AD-GRS, in which the lowest risk corresponds with −2 SDs below the mean AD-GRS, the low risk with −1 SD, average with the mean AD-GRS, high risk with +1 SD, and highest risk with +2 SD. The AD-GRS includes 77 single nucleotide polymorphisms (*APOE* is excluded). In (E) and (F), the predicted cumulative incidence curves of the two most extreme risk groups are shown. The lowest risk includes *APOE* ε2 and the lowest AD-GRS (−2 SD), the highest risk includes *APOE* ε4 and the highest AD-GRS (+2 SD). AD-GRS, Alzheimer's disease genetic risk score, *APOE*, apolipoprotein E; *APP*, amyloid precursor protein; SD, standard deviation.

but prior work linked the AD-GRS to AD biomarkers in ADAD,[24] and to memory performance and CSF profiles in DS.[22] In our *APP*dup sample, the direction and magnitude of the effect were consistent, but did not reach statistical significance due to the smaller sample size. Together, these studies and our results support the notion that polygenic AD susceptibility contributes to variation in AAO in individuals with an extra copy of *APP*.

When considered jointly, *APOE* and the AD-GRS corresponded to an estimated 9- to 10-year difference in AAO between individuals at the lowest and highest genetic risk. In sporadic AD, the AAO difference between these extreme risks was larger (≈ 20 years).[35] However, AD onset in individuals with an extra *APP* copy occurs within a narrower and earlier range (≈ 40–60 years) than in sporadic AD (≈ 60–100 years), making a 9- to 10-year shift substantial and relatively comparable to sporadic AD. Several non-genetic risk factors have been proposed in DS, including sensory impairment, sleep disturbances, and mental health problems, but evidence is mixed and inconsistent across studies.[20,36] By contrast, no non-genetic modifiers of AAO are known for *APP*dup.[14] Thus, *APOE* and the AD-GRS remain the only reproducible predictors of AAO in individuals with an extra copy of *APP*.

Pathway-specific analyses implicated the A$\beta$ and angiogenesis pathways as modifiers of AAO. Although not significant in *APP*dup (both $q = 0.16$), effect sizes were similar in DS, suggesting a consistent pattern across groups. This supports a prominent role for amyloid processing and vascular biology in *APP*-driven AD, whereas the immune response pathway showed only a small effect despite its major contribution in sporadic AD.[26] In the context of *APP* overexpression, common variants affecting *APP* processing, amyloid clearance, and amyloid-related vascular pathology may have amplified effects on AAO

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| Pathway | Cohort | N | HR [95% CI] | p–value | q–value |
|---|---|---|---|---|---|
| Beta–amyloid | Total cohort | 1028 | 1.2 [1.1–1.3] | 0.0008 | 0.013 |
| | APP duplications | 71 | 1.4 [1.0–1.8] | 0.031 | 0.078 |
| | Down syndrome | 957 | 1.2 [1.0–1.3] | 0.0091 | 0.034 |
| Angiogenesis | Total cohort | 1028 | 1.1 [1.0–1.3] | 0.0083 | 0.034 |
| | APP duplications | 71 | 1.3 [0.98–1.6] | 0.066 | 0.12 |
| | Down syndrome | 957 | 1.1 [1.0–1.3] | 0.013 | 0.039 |
| Endocytosis | Total cohort | 1028 | 1.1 [1.00–1.2] | 0.053 | 0.11 |
| | APP duplications | 71 | 0.92 [0.69–1.2] | 0.55 | 0.55 |
| | Down syndrome | 957 | 1.2 [1.0–1.3] | 0.0051 | 0.034 |
| Immune response | Total cohort | 1028 | 1.1 [0.97–1.2] | 0.16 | 0.21 |
| | APP duplications | 71 | 1.3 [0.95–1.7] | 0.10 | 0.15 |
| | Down syndrome | 957 | 1.0 [0.92–1.2] | 0.54 | 0.55 |
| Cholesterol/lipid | Total cohort | 1028 | 1.1 [0.96–1.2] | 0.25 | 0.31 |
| | APP duplications | 71 | 1.4 [0.95–1.9] | 0.093 | 0.15 |
| | Down syndrome | 957 | 1.0 [0.94–1.2] | 0.46 | 0.53 |

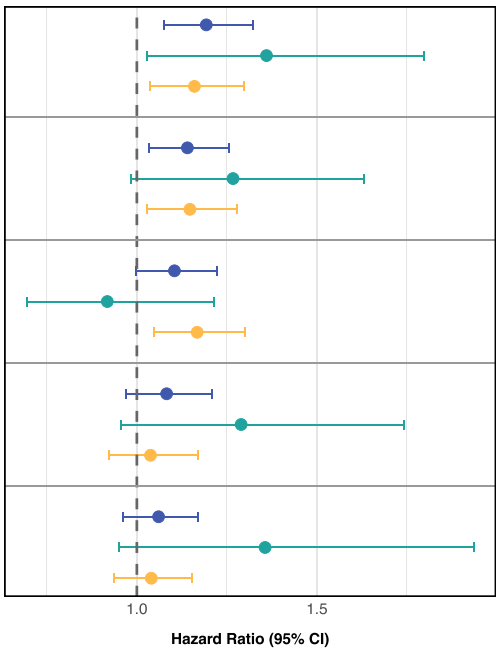


**FIGURE 5** Cox proportional hazard models of pathway-specific genetic risk scores with age at onset. The amyloid beta pGRS included 60 SNPs, the angiogenesis pGRS 41 SNPs, the endocytosis pGRS 34 SNPs, the immune response pGRS 42 SNPs, and the cholesterol/lipid pGRS 39 SNPs. The *APOE* genotype was not included in these pGRSs. *APOE*, apolipoprotein E; *APP*, amyloid precursor protein; CI, confidence interval; HR, hazard ratio; pGRS, pathway genetic risk score; SNP, single nucleotide polymorphisms.

even when baseline amyloid production is high.[1] We also observed an association of the endocytosis pathway with AAO in DS but not in *APP*dup, possibly because endosomal function is already disrupted in DS and therefore more sensitive to modification by common genetic variation.[37] We urge consideration of these observations when developing interventions aimed at postponing AAO of AD in individuals with an extra copy of *APP*.

To explore whether additional genes on chromosome 21 contribute to delayed onset in DS, we examined duplication length and gene content in *APP*dup carriers. Consistent with previous findings,[14] no duplicated genes were associated with AAO, suggesting that variation within the smaller duplicated regions observed in *APP*dup carriers does not substantially modify disease onset. In contrast, the broader trisomy in DS may include additional chromosome 21 genes that could influence AAO. Experimental studies have shown that triplication of chromosome 21 regions beyond *APP* can modulate amyloid pathology and survival in *APP*-overexpressing mouse models, implicating genes such as *DYRK1A*, *BACE2*, and *SYNJ1* as potential modifiers.[38] These findings raise the possibility that genes outside the *APP*dup regions contribute to disease heterogeneity in DS, although their effects on AAO remain to be established and are difficult to disentangle from the effect of intellectual deficits on diagnosing AD in DS.[39]

A major strength of this study is the large, combined cohort of individuals with an extra copy of *APP*. The inclusion of asymptomatic DS individuals is important as excluding unaffected individuals may reduce the power to detect genetic modifiers that delay AAO. A limitation is the different AAO definition across cohorts, constraining direct comparisons of mean onset ages between *APP*dup and DS. In *APP*dup, AAO reflected retrospective age at first symptoms, whereas in DS, AAO was defined as age at (prodromal) AD diagnosis or age at first visit with already established dementia. By definition, symptom onset precedes clinical AD diagnosis, and in DS, clinical recognition is delayed due to pre-existing intellectual disability, frequent comorbidities, and atypical clinical presentations.[7] These factors likely contributed to an underestimation of true symptom onset in DS. Importantly, the absolute difference in mean AAO between *APP*dup and DS was small (≈ 2.5 years). We therefore interpret the younger mean AAO observed in *APP*dup primarily as a definitional rather than a true biological difference. This interpretation is supported by the observation that AAO in individuals with DS who had a recorded age at prodromal AD diagnosis was comparable to the AAO observed in *APP*dup carriers. Moreover, the variability in onset was similar between *APP*dup and DS, consistent with a previous meta-analysis showing comparable AAO variability in DS-AD and ADAD.[11] Future studies could also investigate whether *APOE* and AD-GRS influence the timing of amyloid positron emission tomography positivity and other AD-related biomarker changes. However, such analyses may be more feasible in DS than in *APP*dup, as individuals with DS are often followed longitudinally before symptom onset, whereas *APP*dup carriers are typically identified after symptom onset or through a known family history.

In conclusion, our findings suggest that incorporating the *APOE* genotype and AD-GRS could improve prediction of AAO in these individuals. Because these genetic factors likely act through specific biological pathways, they may also influence response to

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pathway-targeted interventions. Our pathway analyses highlight the roles of A$\beta$, angiogenesis, and endocytosis mechanisms in *APP*-driven AD, implying that the pathways implicated in sporadic and genetically determined AD overlap. Future (pharmacological) studies in pre-symptomatic individuals with an extra *APP* copy should consider underlying genetic risk for sporadic AD, as these variants may enhance or diminish treatment efficacy.

## AUTHOR CONTRIBUTIONS

Joan Groeneveld, Juan Fortea, Lisa Vermunt, Gael Nicolas, Oriol Dols-Icardo, Olivia Belbin, and Sven J. van der Lee conceptualized and designed the study. Joan Groeneveld, Danna Perlaza, Clàudia Olivé, Lou Grangeon, Niccolo Tesi, Chenyang Jiang, Itziar de Rojas, David Wallon, Stéphane Rousseau, Diego Real de Asúa, Fernando Moldenhauer, Ruihao Mu, Kévin Cassinari, Aline Zarea, Joaquim Aumatell Escabias, Marc Hulsman, Alan E. Renton, Alison M. Goate, and Gael Nicolas had a major role in the acquisition of data. Marta Rovira, Joaquim Aumatell Escabias, Marc Hulsman, and Clàudia Olivé had a major role in cleaning and computing the data. Joan Groeneveld, Danna Perlaza, and Clàudia Olivé were responsible for the statistical analysis. Joan Groeneveld, Danna Perlaza, Clàudia Olivé, Maria Victoria Fernandez, Olivia Belbin, Gael Nicolas, Oriol Dols-Icardo, and Sven J. van der Lee interpreted the data. Joan Groeneveld and Danna Perlaza drafted the manuscript. Clàudia Olivé, Niccolo Tesi, Chenyang Jiang, Itziar de Rojas, David Wallon, Stéphane Rousseau, Marta Rovira, Jean-Charles Lambert, Yolande A.L. Pijnenburg, Everard G. B. Vijverberg, Johannes Levin, Mathias Jucker, Eric McDade, Juan Fortea, Henne Holstege, Flora H. Duits, Lisa Vermunt, Maulikkumar Patel, Matthew Johnson, Alan E. Renton, Alison M. Goate, Carlos Cruchaga, Cyril Pottier, Maria Victoria Fernandez, Olivia Belbin, Gael Nicolas, Oriol Dols-Icardo, and Sven J. van der Lee carefully read the manuscript. Joan Groeneveld, Danna Perlaza, Clàudia Olivé, David Wallon, Alan E. Renton, Carlos Cruchaga, Olivia Belbin, Maria Victoria Fernandez, Olivia Belbin, Gael Nicolas, Oriol Dols-Icardo, and Sven J. van der Lee revised the manuscript.

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## CONFLICT OF INTEREST STATEMENT

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Pharma Consortium (Biogen, Eisai, Eli Lilly and Company/Avid Radiopharmaceuticals, F. Hoffman-La Roche/Genentech, and Janssen). He is a co-inventor of the "Methods of diagnosing AD with phosphorylation changes" technology licensed by Washington University to C2N Diagnostics, US Patent 11,085,935 B2, Aug 10, 2021 (Bateman, Barthelemy, McDade, Li). Washington University also holds 5% equity in C2N. Through these relationships, Washington University and Eric McDade are entitled to receive royalties from the license agreement with C2N. He is co-author of the Alzheimer Association's 2024 Alzheimer's disease updated diagnostic criteria. He has received travel support from the Alzheimer's Association for work related to the development of the document. He has served as a consultant, a member of advisory boards, or a DSMB member for Eli Lilly, Alector, Alzamend, Sanofi, AstraZeneca, Hoffman La-Roche, and Merck. Author disclosures are available in the Supporting Information.

## DATA SHARING

Individual de-identified participant and summary statistics of genetic data not published in this article will be made available upon reasonable request to any qualified investigator by contacting Dr. S.J. van der Lee (s.j.vanderlee@amsterdamumc.nl). Requests regarding data from the DABNI Cohort will be assessed by Dr. Juan Fortea and Dr. Oriol Dols-Icardo. The raw data from DIAN Obs are available under restricted access to maintain individual and family confidentiality. These samples contain rare disease-causing variants that could be used to identify the participating individuals and families. Access can be obtained by request through the online resource request system on the DIAN Website: https://dian.wustl.edu/.

## CONSENT STATEMENT

All participants or their legal representatives provided written informed consent, including consent for genetic analyses.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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## Appendix A: Collaborators list

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