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Evaluation of a Genetic Risk Score to Improve Risk Prediction for Alzheimer's Disease

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Abstract

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SUPPLEMENTARY MATERIAL

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Effective prevention of Alzheimer's disease (AD) requires the development of risk prediction tools permitting preclinical intervention. We constructed a genetic risk score (GRS) comprising common genetic variants associated with AD, evaluated its association with incident AD and assessed its capacity to improve risk prediction over traditional models based on age, sex, education, and *APOE* $\epsilon 4$. In eight prospective cohorts included in the International Genomics of Alzheimer's Project (IGAP), we derived weighted sum of risk alleles from the 19 top SNPs reported by the IGAP GWAS in participants aged 65 and older without prevalent dementia. Hazard ratios (HR) of incident AD were estimated in Cox models. Improvement in risk prediction was measured by the difference in C-index ($-C$), the integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI>0). Overall, 19,687 participants at risk were included, of whom 2,782 developed AD. The GRS was associated with a 17% increase in AD risk (pooled HR = 1.17; 95%CI = [1.13–1.21] per standard deviation increase in GRS; p -value = 2.86×10^{-16}). This association was stronger among persons with at least one *APOE* $\epsilon 4$ allele (HR_{GRS} = 1.24; 95%CI = [1.15–1.34]) than in others (HR_{GRS} = 1.13; 95%CI = [1.08–1.18]; $p_{\text{interaction}} = 3.45 \times 10^{-2}$). Risk prediction after seven years of follow-up showed a small improvement when adding the GRS to age, sex, *APOE* $\epsilon 4$, and education ($-C_{\text{index}} = 0.0043$ [0.0019–0.0067]). Similar patterns were observed for IDI and NRI>0. In conclusion, a risk score incorporating common genetic variation outside the *APOE* $\epsilon 4$ locus improved AD risk prediction and may facilitate risk stratification for prevention trials.

Keywords

Alzheimer's disease; clinical utility; cohort studies; genetic risk score; IGAP; meta-analysis; risk prediction

INTRODUCTION

With increasing prevalence and no effective treatment, Alzheimer's disease (AD) has become a global public health priority and a threat to healthcare systems [1]. Failure of recent clinical trials to improve cognitive functions in AD patients [2, 3] and studies suggesting a long preclinical phase of the disease [4] underline the need for earlier interventions, moving from early clinical dementia with mild cognitive complaints to a stage of preclinical AD with pathological changes of AD but no discernible clinical signs.

In this context, building accessible, easy to use prediction tools is of key importance to predict who, or which groups of persons, will develop the pathology of AD. Tools based on several genetic or imaging markers are already being used to improve enrollment in clinical trials by including asymptomatic, at-risk participants [5]. In the Dominantly Inherited Alzheimer Network Trial Units (DIAN-TU) [6] and Alzheimer Prevention Initiative (API) trials [7], risk of developing AD is assessed based on carriage of known autosomal dominant AD mutations, which represents a perfect predictor of early-onset AD, or *APOE* $\epsilon 4$ status, an important but imperfect predictor of late-onset AD [8–10]. In the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) trials, risk is assessed using positron emission tomography (PET) imaging of brain amyloid load but such imaging is expensive and exposes the screened population to radiation [11]. Other biomarkers can be measured in

the cerebrospinal fluid (CSF) but lumbar puncture has relatively low acceptance rates in asymptomatic adults.

Recent genome-wide association studies (GWAS) and follow-up genotyping studies have broadened the spectrum of genetic variation known to underlie late-onset AD and provided a promising ground on which to build a prediction tool [8, 12–16]. Since the effect sizes associated with individual genetic variants are small, ranging from a 23% reduction to a 22% increase in risk, an aggregated genetic risk score (GRS) could perform better than any individual variant. Such an approach has been successfully used to replicate association of genetic variants with AD, [17–23] but also to show associations of AD-related genetic variants with mild cognitive impairment [21, 22] and endophenotypes such as brain volumes measured by MRI, [24–27] cognitive tests, [18, 20, 22, 28] age at onset [23, 29], or CSF biomarkers of AD [23, 30]. These results hinted at potential benefits of using genetic information to improve the selection of asymptomatic, at-risk participants in preclinical biomarker or drug trials.

So far, the genetic variations associated with AD outside the APOE locus have shown little improvement in risk prediction over known predictors [8, 18, 19, 21–24, 26]. Moreover, only two of them have used the most recent set of single nucleotide polymorphisms (SNPs) available [21, 23] and only one used a prospective design [21] which might be better suited in a preclinical context.

Our objectives were to extend those results by constructing a GRS based on the most up-to-date results and assess its association with risk of developing incident AD and its utility for risk prediction of AD over age, sex, education, and *APOE* $\epsilon 4$ in eight prospective cohorts.

MATERIALS AND METHODS

Study samples

We used the prospective cohorts from IGAP: the Framingham Heart Study (FHS), the Three City study (3C), the Rotterdam study, the Cardiovascular Health Study (CHS), the Age, Gene/Environment Susceptibility (AGES) study, the Religious Order Study/Memory and Aging Project (ROSMAP), the Adult Changes in Thought (ACT) study, and the Washington Heights-Inwood Community Aging Project (WHICAP). In most samples, baseline was defined as the time of inclusion in the study. In the FHS, we defined baseline as the time of blood draw for DNA extraction (~1990) although participants have been under dementia surveillance since 1974, to avoid survival biases. Participants aged less than 65 years at baseline were excluded as well as persons with prevalent dementia. Local ethics committees at each site approved the study and all participants provided written informed consent at enrollment (Supplementary Methods 1).

Alzheimer's disease assessment

Screening procedures for dementia and AD were broadly congruent across studies although they differed in some specifics (Supplementary Methods 1). Most of the studies used standard screening procedures based on history, medical review, screening questions, and cognitive assessments that flagged participants with potential cognitive impairment. These

participants underwent complete neurological and neuropsychological evaluation. An initial decision was made regarding the presence or absence of dementia, using the DSM-IV criteria; [31] a diagnosis of possible, probable, or definite AD was made as a second step using NINCDS-ADRDA (National Institute of Neurological Disorders and Stroke Alzheimer's Disease and Related Disorders Association) criteria [32].

Genetic data

Each study had genome-wide data acquired on various genotyping platforms that have been described elsewhere [16]. Genetic data were imputed using various versions of the 1000 Genomes reference panel, varying preimputation criteria and imputation software. In each study, genetic data was used as the expected allele count, i.e., allele dosage.

Selection of SNPs and construction of the GRS

To construct the genetic risk score, we selected the top SNP in each locus reaching genome-wide significance in the combined discovery-replication stages of the IGAP meta-analysis, [16] with the exception of APOE. Thus, 19 SNPs were selected: rs6656401 (CR1), rs6733839 (BIN1), rs35349669 (INPP5D), rs190982 (MEF2C), rs9271192 (HLA-DRB5/HLA-DRB1), rs10948363 (CD2AP), rs2718 058 (NME8), rs1476679 (ZCWPW1), rs11771145 (EPHA1), rs28834970 (PTK2B), rs9331896 (CLU), rs10838725 (CELF1), rs983392 (MS4A6A), rs10792 832 (PICALM), rs11218343 (SORL1), rs17125944 (FERMT2), rs10498633 (SLC24A4/RIN3), rs4147 929 (ABCA7), and rs7274581 (CASS4). We then recoded the odds ratios (OR) from the IGAP meta-analysis so they would all indicate an increased risk of AD and used the log(OR) and corresponding alleles to compute a weighted sum of risk allele dosages (Supplementary Methods 2). For descriptive purposes, we applied an additional transformation so that one unit of the GRS would be interpreted as one additional risk allele. Finally as one SNP (rs9271192) was missing in FHS, WHICAP, and Rotterdam because of poor imputation quality, an 18 SNP-based GRS was computed in these cohorts.

Statistical analyses

We used Cox regression models to estimate associations between individual SNPs, GRS, and risk of incident AD. Follow-up time was defined as time from inclusion to (1) first diagnosis of AD in incident cases, (2) last follow-up evaluation for persons who remained alive and did not develop AD, and (3) last time without known dementia for participants who developed dementia due to etiologies other than AD and those who died during follow-up.

We adjusted all models for age at baseline, sex, education levels, and presence or absence of at least one *APOE* $\epsilon 4$ allele (referred below as *APOE* $\epsilon 4$ status). Additional adjustment for study center and familial relationships was performed in multicentric studies and studies with related participants, respectively. We considered the GRS as a continuous variable and as tertiles. To meta-analyze results of studies utilizing the 18- and 19-SNP GRSs, we scaled all GRS so that their mean would be zero and their standard deviation one. Finally, we studied an additional model including an interaction term between *APOE* $\epsilon 4$ status and

GRS. For all models, we verified that proportional hazards assumption was met by examining Schoenfeld residuals graphically.

We assessed improvement in risk prediction in each study by comparing a “base” Cox regression model containing age, sex, education, and *APOE* $\epsilon 4$ status to a “new” model containing the base model and the GRS as a continuous variable. Improvement in risk prediction was evaluated at fixed follow-up times of 5, 6, 7, and 8 years to allow comparison across studies. Three complementary measures of improvement in discrimination adapted to censored data were estimated: the difference in C-index (ΔC), the integrated discrimination improvement (IDI), and the continuous net reclassification improvement (NRI >0) (Supplementary Methods 3). To help interpret those results, we used published simulated data to illustrate ranges of values for C-index, IDI, and NRI >0 that correspond to small, medium, and large effects (Supplementary Methods 3).

We used random-effects inverse variance meta-analyses to compute pooled estimations of hazard ratio (HR) and ΔC . Heterogeneity across studies was quantified using I^2 .

All analyses were performed using R and various R packages (Supplementary Methods 4). The R scripts used to generate the results presented in this study are freely available on request.

RESULTS

Overall, 19,687 participants at risk were included in this project, of whom 2,782 developed AD after times of follow-up ranging from a mean of 5.9 years in AGES to 10.9 years in Rotterdam. Other demographic characteristics of participants in the individual studies are presented in Table 1. After a fixed period of 7 years of follow-up, observed risk of AD ranged from 0.068 [0.047–0.097] in WHICAP to 0.214 [0.190–0.240] in ROSMAP (Supplementary Table 1). These varying risks reflect the varying ages and baseline cognitive status of the cohorts. As expected, observed risk of AD increased with time in all cohorts.

We first considered associations between individual SNPs and risk of incident AD. Most of the associations were not statistically significant (Table 2). Effect sizes were globally small, ranging from 0.92 [0.85–1.01] for *CR1* to 1.07 [0.93–1.22] for *CASS4* and were different from the estimations drawn from the IGAP meta-analysis (Table 2). As expected, having at least one copy of *APOE* $\epsilon 4$ was strongly associated with risk of incident AD (HR = 2.08; 95% CI = [1.92–2.26]; p -value = 2.09×10^{-72} ; $I^2 = 0\%$). As the samples used in this project were partially overlapping with the ones used in the original IGAP study, we ran an additional IGAP meta-analysis after excluding those and did not find significant changes in the estimations of HRs for the SNPs considered (Supplementary Table 2).

Distributions of the GRS across studies are provided in Supplementary Figure 1. In nearly all studies, association of the GRS reached or was close to statistical significance, using a p -value threshold of 0.05 (Fig. 1). Effect sizes were remarkably consistent across studies, with HRs ranging from 1.12 in CHS to 1.24 in ROSMAP. When meta-analyzed, those results yielded a pooled HR of 1.17 (95% CI = [1.13–1.21] per standard deviation (SD) increase in GRS; p -value = 2.86×10^{-16}) with no evidence of important heterogeneity ($I^2 = 0\%$). When

considering tertiles of the GRS, being in the third tertile was associated with a HR of 1.42 (95% CI = [1.29–1.55]; p -value = 1.09×10^{-13}) when compared to the first tertile (Supplementary Figure 2).

We observed a significant interaction between *APOE* $\epsilon 4$ status and the GRS (p -value = 3.45×10^{-2}), with a higher effect size in *APOE* $\epsilon 4$ carriers (HR = 1.24; 95% CI = [1.15–1.34] per SD increase in GRS; p -value = 7.63×10^{-8} ; $\hat{P}^2 = 31\%$) than in non-carriers (HR = 1.13; 95% CI = [1.08–1.18] per SD increase in GRS; p -value = 2.40×10^{-7} ; $\hat{P}^2 = 0\%$) (Fig. 1). *APOE* $\epsilon 4$ carriers that were in the third tertile of GRS had an increased risk of incident AD of 62% (HR = 1.62; 95% CI = [1.26–2.07]; p -value = 1.33×10^{-4} ; $\hat{P}^2 = 55\%$) compared to *APOE* $\epsilon 4$ carriers in the first tertile of GRS. In *APOE* $\epsilon 4$ non-carriers, this risk was increased by 33% (HR = 1.33; 95% CI = [1.19–1.49]; p -value = 8.18×10^{-7} ; $\hat{P}^2 = 0\%$) in the third tertile of GRS compared to the first tertile (Supplementary Figure 2).

Measures of improvement in risk prediction after 7 years of follow-up are presented in Fig. 2 and Supplementary Table 3. The “base” model, comprised of age, sex, education, and *APOE* $\epsilon 4$ status had good discrimination abilities, as illustrated by C-index ranging from 0.688 [0.641–0.735] in AGES to 0.803 [0.776–0.830] in FHS (Supplementary Table 3). Calibration of the models at 7 years of follow-up was good across studies (Supplementary Figure 3).

When adding the GRS in this model, the difference in C-index was small, ranging from 0.002 in FHS to 0.009 in WHICAP, and was not statistically different from zero, except in the Rotterdam study (Fig. 2). Meta-analysis of the difference in C-index yielded a pooled estimation of 0.0043 [0.0019–0.0067], homogeneous across studies ($\hat{P}^2 = 0\%$) and statistically different from zero (p -value = 4.92×10^{-4}). As for hazard ratio, difference in C-index was higher in *APOE* $\epsilon 4$ carriers ($-C = 0.0112$ [0.0015–0.0208]; p -value = 2.32×10^{-2} ; $\hat{P}^2 = 42\%$) than in non-carriers ($-C = 0.0018$ [–0.0003–0.0039]; p -value = 9.83×10^{-2} ; $\hat{P}^2 = 0\%$) (Fig. 2). Similar patterns were observed for IDI and NRI>0 across studies (Supplementary Table 3). Using fixed follow-up periods of 5, 6, and 8 years did not modify those figures, except in *APOE* $\epsilon 4$ carriers where a slight improvement was observed with increasing follow-up time (Supplementary Table 3 and Supplementary Figure 4).

DISCUSSION

In this large set of prospective cohorts from IGAP, we studied the association of an aggregate measure of the genetic variants identified in a previous work [16] with incident AD. We observed that, compared to SNPs considered separately, the aggregate measure showed a significant association with incident AD, even without inclusion of *APOE* $\epsilon 4$. Persons in the top tertile of this genetic risk score had a 42% higher risk of AD compared to persons in the bottom tertile, with higher risk among *APOE* $\epsilon 4$ carriers (62%) than in non-carriers (33%). When assessing the utility of this measure for individual risk prediction at 7 years, we observed small improvement over age, sex, education, and *APOE* $\epsilon 4$ status, with stronger effect in *APOE* $\epsilon 4$ carriers.

In this study, an increase in one standard deviation of the GRS, corresponding approximately to 2.5 risk alleles, was associated with a 17% increase in risk of developing AD. GRSs have been previously used to increase statistical power when studying associations with either AD status or AD-related endophenotypes. Results have often shown significant associations, depending greatly on whether *APOE* $\epsilon 4$ was included or not in the GRS [17–30]. Previous work from the Rotterdam Study, which was included in this study, reported similar increases of 14% ($p = 0.010$) [18] and 15% ($p = 0.058$) [21] in AD risk for an increase of one standard deviation of the GRS. These results confirm the small increase in risk carried on average by common genetic variants identified by GWAS and legitimate the use of GRSs to increase statistical power to identify such associations.

Persons in the top tertile of our GRS had a 42% higher risk of incident AD compared to persons in the bottom tertile. A recent study by Slegers et al. reported an odds ratio of AD of 5.69 [4.17–7.75] when comparing the fifth quintile of a GRS to the third quintile [23]. Although their GRS included *APOE* $\epsilon 4$ and had different units which makes the comparison to our GRS difficult, these results highlight the benefit of using a sufficient number of variants outside *APOE* $\epsilon 4$ to improve stratification of participants at higher risk of AD in the context of preclinical biomarkers or drug trials.

C-indexes for the base model were relatively high in all the studies indicating good predictive value. Our decision to include or exclude variables in this model was based on literature, expected availability and expected heterogeneity in the measure across studies. In terms of clinical utility for individual risk prediction, the estimations of differences in C-index, $NRI > 0$ and IDI were small across all of the studies, indicating limited clinical utility over age, sex, education, and *APOE* $\epsilon 4$ status. Those results are in agreement with previous studies that reported little clinical utility of genetic data outside *APOE* $\epsilon 4$ in improving risk prediction of AD over other predictors such as age and education level [8, 18, 19, 21–23]. Given our results, the GRS seems currently more useful for risk stratification in a population than for individual risk prediction.

The significant interaction of the GRS with *APOE* $\epsilon 4$ status hinted at potentially useful strategies. Such results could be the basis for a genetic risk prediction decision tree. One could assess the *APOE* genotype, and according to it, follow-up with more complex genetic analysis. The GRS could help refine risk and age-at-onset predictions in the *APOE* $\epsilon 4$ positive subgroup that is currently the focus of several prevention efforts. Further, this measure could be a useful adjunct for risk stratification in clinical trials among the 75% of the population who are *APOE* $\epsilon 4$ negative, as 50% of the population burden of AD will manifest in this subgroup.

All the samples we used came from population studies and it would be interesting to see if the predictive performances of this GRS are improved in selected population, either persons consulting for memory complaints, mild cognitive impairment, or persons with other risk factors such as diabetes or hypertension. The timing is also of importance in assessing the utility of such a genetic risk prediction tool. We restricted our samples to persons over 65 years of age but the GRS could work best in young to middle-aged populations where gene-

environment interactions leading to AD have not had the chance to express themselves. Such questions will require an even larger sample size to answer reliably.

The main limitation of this study is the use of study populations that were already part of the initial IGAP study where the variants used in the GRS were discovered [16]. As such, it is currently not feasible to obtain a large sample outside IGAP for independent validation. Nevertheless, the eight cohorts studied here were a small fraction of the larger sample used in the discovery of the SNPs constituting the GRS. We could have used the ORs derived from the independent replication stage of IGAP but as these were very close to the ones we used to construct our GRS, this should not have dramatically affected our results. The encouraging results we obtained should therefore be replicated in an independent cohort study.

There are other decisions we made in the construction of the GRS that could be argued but in this initial attempt to construct and validate a GRS, we chose a conservative approach. Thus our selection of the SNPs used in the GRS was based purely on statistical grounds. By selecting SNPs based on GWAS p -value threshold, we limited the number of false positive signals in our GRS, but we also excluded signals that could be replicated in future studies. For example, a follow-up study has already reported replication of the TRIP4 locus that was suggestive in the IGAP meta-analysis [33]. We also excluded some signals that failed to reach genome-wide association threshold in IGAP but have persuasive biological evidence in favor of a real implication in the pathophysiology of AD, such as *CD33* [34]. Future work on alternative versions of a GRS could expand the list of SNPs included using a less stringent threshold of p -values and other criteria, e.g. predicted functionality or biological evidence.

Moreover, inclusion of rare variants could also improve the GRS. It is unlikely that a unique rare variant could dramatically improve risk stratification due to its low prevalence in any population, but they could improve risk prediction in selected individuals and inclusion of genetic information in genes known to harbor multiple rare variants that alter risk for the disease could represent an interesting addition.

The SNPs used to create the GRS were based on studies using a case-control design. Thus, it is possible that the genetic risk factors identified so far only act very late in the pathophysiology of AD. Nevertheless, designing a GWAS of incident AD with a number of incident cases similar to IGAP would require prospective follow-up of hundreds of thousands of participants, which is currently not feasible.

Finally our GRS did not consider any gene-gene or gene-environment interactions which could be of importance [19].

Our study has several strengths. First it presents data from the largest set of prospective studies of AD to date. The large sample sizes ensure sufficient statistical power and fairly precise estimations of risk while the prospective design ensure more accurate assessment of AD onset date. Second, we accounted for the differences in follow-up time by choosing a fixed time for estimating measures of improvement in risk prediction, ensuring comparability across studies. Finally, all studies used homogeneous definitions for the

variables used as confounders and the statistical analyses were performed using the same statistical script.

In conclusion, we have shown that evaluation of the clinical utility of a GRS requires more than study of its association with incidence of a disease. In the context of AD, a risk prediction tool build using newly identified genetic information outside *APOE ε4* showed a statistically significant, small improvement in individual AD risk prediction after 7 years of follow-up over age, sex, education, and *APOE ε4* status. Nevertheless, this GRS may be a useful tool for improving risk stratification in clinical trials aimed at preventing the onset of clinical AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- [1]. Thies W, Bleiler L, Alzheimer's Association. 2013 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2013; 9:208–245. [PubMed: 23507120]
- [2]. Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, Raman R, Sun X, Aisen PS, Siemers E, Liu-Seifert H, Mohs R, Alzheimer's Disease Cooperative Study Steering Committee, Solanezumab Study Group. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014; 370:311–321. [PubMed: 24450890]
- [3]. Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, Sabbagh M, Honig LS, Porsteinsson AP, Ferris S, Reichert M, Ketter N, Nejadnik B, Guenzler V, Miloslavsky M, Wang D, Lu Y, Lull J, Tudor IC, Liu E, Grundman M, Yuen E, Black R, Brashear HR, Bap-ineuzumab 301 and 302 Clinical Trial Investigators. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014; 370:322–333. [PubMed: 24450891]
- [4]. Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurol*. 2013; 12:207–216. [PubMed: 23332364]
- [5]. Solomon A, Mangialasche F, Richard E, Andrieu S, Bennett DA, Breteler M, Fratiglioni L, Hooshmand B, Khachaturian AS, Schneider LS, Skoog I, Kivipelto M. Advances in the prevention of Alzheimer's disease and dementia. *J Intern Med*. 2014; 275:229–250. [PubMed: 24605807]
- [6]. Moulder KL, Snider BJ, Mills SL, Buckles VD, Santacruz AM, Bateman RJ, Morris JC. Dominantly inherited Alzheimer network: Facilitating research and clinical trials. *Alzheimers Res Ther*. 2013; 5:48. [PubMed: 24131566]
- [7]. Reiman EM, Langbaum JBS, Fleisher AS, Caselli RJ, Chen K, Ayutyanont N, Quiroz YT, Kosik KS, Lopera F, Tariot PN. Alzheimer's Prevention Initiative: A plan to accelerate the evaluation of presymptomatic treatments. *J Alzheimers Dis*. 2011; 26(Suppl 3):321–329. [PubMed: 21971471]
- [8]. Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M, Bis JC, Smith AV, Carassquillo MM, Lambert JC, Harold D, Schrijvers EMC, Ramirez-Lorca R, Debette S, Longstreth WT, Janssens ACJW, Pankratz VS, Dartigues JF, Hollingworth P, Aspelund T, Hernandez I, Beiser A, Kuller LH, Koudstaal PJ, Dickson DW, Tzourio C, Abraham R, Antunez C, Du Y, Rotter JI, Aulchenko YS, Harris TB, Petersen RC, Berr C, Owen MJ, Lopez-Arrieta J, Varadarajan BN, Becker JT, Rivadeneira F, Nalls MA, Graff-Radford NR, Champion D, Auerbach S, Rice K, Hofman A, Jonsson PV, Schmidt H, Lathrop M, Mosley TH, Au R, Psaty BM, Uitterlinden AG, Farrer LA, Lumley T, Ruiz A, Williams J, Amouyel P, Younkin SG, Wolf PA, Launer LJ, Lopez OL, Duijn CM, Breteler MMB, CHARGE Consortium; GERAD1 Consortium; EADI1 Consortium. Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA*. 2010; 303:1832–1840. [PubMed: 20460622]
- [9]. Genin E, Hannequin D, Wallon D, Slegers K, Hiltunen M, Combarros O, Bullido MJ, Engelborghs S, De Deyn P, Berr C, Pasquier F, Dubois B, Tognoni G, Fiévet N, Brouwers N, Bettens K, Arosio B, Coto E, Del Zompo M, Mateo I, Epelbaum J, Frank-Garcia A, Helisalmi S, Porcellini E, Pilotto A, Forti P, Ferri R, Scarpini E, Siciliano G, Solfrizzi V, Sorbi S, Spalletta G, Valdivieso F, Vepsäläinen S, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossú P, Hanon O, Piccardi P, Annoni G, Seripa D, Galimberti D, Licastro F, Soininen H, Dartigues J-F, Kamboh MI, Van Broeckhoven C, Lambert JC, Amouyel P, Champion D. APOE and Alzheimer disease: A major gene with semi-dominant inheritance. *Mol Psychiatry*. 2011; 16:903–907. [PubMed: 21556001]
- [10]. Ohara T, Ninomiya T, Kubo M, Hirakawa Y, Doi Y, Hata J, Iwaki T, Kanba S, Kiyohara Y. Apolipoprotein genotype for prediction of Alzheimer's disease in older Japanese: The Hisayama Study. *J Am Geriatr Soc*. 2011; 59:1074–1079. [PubMed: 21649613]
- [11]. Sperling RA, Rentz DM, Johnson KA, Karlawish J, Donohue M, Salmon DP, Aisen P. The A4 Study: Stopping AD before symptoms begin? *Sci Transl Med*. 2014; 6:228fs13.
- [12]. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown

- KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Love S, Kehoe PG, Hardy J, Mead S, Fox N, Rossor M, Collinge J, Maier W, Jessen F, Schürmann B, Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frölich L, Hampel H, Hüll M, Rujescu D, Goate AM, Kauwe JSK, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, Deyn PPD, Broeckhoven CV, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Mühleisen TW, Nöthen MM, Moebus S, Jöckel K-H, Klopp N, Wichmann H-E, Carrasquillo MM, Pankratz VS, Younkin SG, Holmans PA, O'Donovan M, Owen MJ, Williams J. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet.* 2009; 41:1088–1093. [PubMed: 19734902]
- [13]. Lambert J-C, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fiévet N, Barberger-Gateau P, Engelborghs S, Deyn PD, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O, European Alzheimer's Disease Initiative Investigators, Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossú P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Ritchie K, Blanché H, Dartigues J-F, Tzourio C, Gut I, Broeckhoven CV, Alperovitch A, Lathrop M, Amouyel P. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet.* 2009; 41:1094–1099. [PubMed: 19734903]
- [14]. Hollingworth P, Harold D, Sims R, Gerrish A, Lambert J-C, Carrasquillo MM, Abraham R, Hamshe ML, Pahwa JS, Moskva V, Dowzell K, Jones N, Stretton A, Thomas C, Richards A, Ivanov D, Widdowson C, Chapman J, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Beaumont H, Warden D, Wilcock G, Love S, Kehoe PG, Hooper NM, Vardy ERLC, Hardy J, Mead S, Fox NC, Rossor M, Collinge J, Maier W, Jessen F, Rütther E, Schürmann B, Heun R, Kölsch H, Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frölich L, Hampel H, Gallacher J, Hüll M, Rujescu D, Giegling I, Goate AM, Kauwe JSK, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, Deyn PPD, Broeckhoven CV, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Mühleisen TW, Nöthen MM, Moebus S, Jöckel K-H, Klopp N, Wichmann H-E, Pankratz VS, Sando SB, Aasly JO, Barcikowska M, Wszolek ZK, Dickson DW, Graff-Radford NR, Petersen RC, Alzheimer's Disease Neuroimaging Initiative; Duijn CM, Breteler MMB, Ikram MA, Destefano AL, Fitzpatrick AL, Lopez O, Launer LJ, Seshadri S, CHARGE consortium; Berr C, Campion D, Epelbaum J, Dartigues J-F, Tzourio C, Alperovitch A, Lathrop M, EADI1 consortium, Feulner TM, Friedrich P, Riehle C, Krawczak M, Schreiber S, Mayhaus M, Nicolhaus S, Wagenpfeil S, Steinberg S, Stefansson H, Stefansson K, Snædal J, Björnsson S, Jonsson PV, Chouraki V, Genier-Boley B, Hiltunen M, Soininen H, Combarros O, Zelenika D, Delepine M, Bullido MJ, Pasquier F, Mateo I, Frank-Garcia A, Porcellini E, Hanon O, Coto E, Alvarez V, Bosco P, Siciliano G, Mancuso M, Panza F, Solfrizzi V, Nacmias B, Sorbi S, Bossú P, Piccardi P, Arosio B, Annoni G, Seripa D, Pilotto A, Scarpini E, Galimberti D, Brice A, Hannequin D, Licastro F, Jones L, Holmans PA, Jonsson T, Riemenschneider M, Morgan K, Younkin SG, Owen MJ, O'Donovan M, Amouyel P, Williams J. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nat Genet.* 2011; 43:429–435. [PubMed: 21460840]
- [15]. Naj AC, Jun G, Beecham GW, Wang L-S, Vardarajan BN, Buross J, Gallins PJ, Buxbaum JD, Jarvik GP, Crane PK, Larson EB, Bird TD, Boeve BF, Graff-Radford NR, Jager PLD, Evans D, Schneider JA, Carrasquillo MM, Ertekin-Taner N, Younkin SG, Cruchaga C, Kauwe JSK, Nowotny P, Kramer P, Hardy J, Huentelman MJ, Myers AJ, Barmada MM, Demirci FY, Baldwin CT, Green RC, Rogaeva E, George-Hyslop PS, Arnold SE, Barber R, Beach T, Bigio EH, Bowen JD, Boxer A, Burke JR, Cairns NJ, Carlson CS, Carney RM, Carroll SL, Chui HC, Clark DG, Corneveaux J, Cotman CW, Cummings JL, Decarli C, Dekosky ST, Diaz-Arrastia R, Dick M, Dickson DW, Ellis WG, Faber KM, Fallon KB, Farlow MR, Ferris S, Frosch MP, Galasko DR, Ganguli M, Gearing M, Geschwind DH, Ghetti B, Gilbert JR, Gilman S, Giordani B, Glass JD, Growdon JH, Hamilton RL, Harrell LE, Head E, Honig LS, Hulette CM, Hyman BT, Jicha GA, Jin L-W, Johnson N, Karlawish J, Karydas A, Kaye JA, Kim R, Koo EH, Kowall NW, Lah JJ, Levey AI, Lieberman AP, Lopez OL, Mack WJ, Marson DC, Martiniuk F, Mash DC, Masliah E,

McCormick WC, McCurry SM, McDavid AN, McKee AC, Mesulam M, Miller BL, Miller CA, Miller JW, Parisi JE, Perl DP, Peskind E, Petersen RC, Poon WW, Quinn JF, Rajbhandary RA, Raskind M, Reisberg B, Ringman JM, Roberson ED, Rosenberg RN, Sano M, Schneider LS, Seeley W, Shelanski ML, Slifer MA, Smith CD, Sonnen JA, Spina S, Stern RA, Tanzi RE, Trojanowski JQ, Troncoso JC, Deerlin VMV, Vinters HV, Vonsattel JP, Weintraub S, Welsh-Bohmer KA, Williamson J, Woltjer RL, Cantwell LB, Dombroski BA, Beekly D, Lunetta KL, Martin ER, Kamboh MI, Saykin AJ, Reiman EM, Bennett DA, Morris JC, Montine TJ, Goate AM, Blacker D, Tsuang DW, Hakonarson H, Kukull WA, Foroud TM, Haines JL, Mayeux R, Pericak-Vance MA, Farrer LA, Schellenberg GD. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nat Genet.* 2011; 43:436–441. [PubMed: 21460841]

- [16]. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, DeStafano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thornton-Wells TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin CF, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau MT, Choi SH, Reitz C, Pasquier F, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Morón FJ, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fiévet N, Huentelman MW, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuinness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossú P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Deniz Naranjo MC, Bosco P, Clarke R, Brayne C, Galimberti D, Mancuso M, Matthews F, European Alzheimer's Disease Initiative (EADI); Genetic and Environmental Risk in Alzheimer's Disease; Alzheimer's Disease Genetic Consortium; Cohorts for Heart and Aging Research in Genomic Epidemiology. Moebs S, Mecocci P, Del Zompo M, Maier W, Hampel H, Pilotto A, Bullido M, Panza F, Caffarra P, Nacmias B, Gilbert JR, Mayhaus M, Lannefelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson PV, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley T, Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RF, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JS, Boerwinkle E, Riemenschneider M, Boada M, Hiltunen M, Martin ER, Schmidt R, Rujescu D, Wang LS, Dartigues JF, Mayeux R, Tzourio C, Hofman A, Nöthen MM, Graff C, Psaty BM, Jones L, Haines JL, Holmans PA, Lathrop M, Pericak-Vance MA, Launer LJ, Farrer LA, van Duijn CM, Van Broeckhoven C, Moskvina V, Seshadri S, Williams J, Schellenberg GD, Amouyel P. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet.* 2013; 45:1452–1458. [PubMed: 24162737]
- [17]. Rodriguez-Rodriguez E, Sánchez-Juan P, Vázquez-Higuera JL, Mateo I, Pozueta A, Berciano J, Cervantes S, Alcolea D, Martinez-Lage P, Clarimón J, Lleó A, Pastor P, Combarros O. Genetic risk score predicting accelerated progression from mild cognitive impairment to Alzheimer's disease. *J Neural Transm.* 2013; 120:807–812. [PubMed: 23180304]
- [18]. Verhaaren BFJ, Vernooij MW, Koudstaal PJ, Uitterlinden AG, van Duijn CM, Hofman A, Breteler MMB, Ikram MA. Alzheimer's disease genes and cognition in the non-demented general population. *Biol Psychiatry.* 2013; 73:429–434. [PubMed: 22592056]
- [19]. Ebbert MTW, Ridge PG, Wilson AR, Sharp AR, Bailey M, Norton MC, Tschanz JT, Munger RG, Corcoran CD, Kauwe JSK. Population-based analysis of Alzheimer's disease risk alleles implicates genetic interactions. *Biol Psychiatry.* 2014; 75:732–737. [PubMed: 23954108]
- [20]. Marden JR, Walter S, Tchetgen Tchetgen EJ, Kawachi I, Glymour MM. Validation of a polygenic risk score for dementia in black and white individuals. *Brain Behav.* 2014; 4:687–697. [PubMed: 25328845]
- [21]. Adams HHH, de Bruijn RFAG, Hofman A, Uitterlinden AG, van Duijn CM, Vernooij MW, Koudstaal PJ, Ikram MA. Genetic risk of neurodegenerative diseases is associated with mild cognitive impairment and conversion to dementia. *Alzheimers Dement.* 2015; 11:1277–1285. [PubMed: 25916564]

- [22]. Carrasquillo MM, Crook JE, Pedraza O, Thomas CS, Pankratz VS, Allen M, Nguyen T, Malphrus KG, Ma L, Bisceglia GD, Roberts RO, Lucas JA, Smith GE, Ivnik RJ, Machulda MM, Graff-Radford NR, Petersen RC, Younkin SG, Ertekin-Taner N. Late-onset Alzheimer's risk variants in memory decline, incident mild cognitive impairment, and Alzheimer's disease. *Neurobiol Aging*. 2015; 36:60–67. [PubMed: 25189118]
- [23]. Sleegers K, Bettens K, De Roeck A, Van Cauwenberghe C, Cuyvers E, Verheijen J, Struyfs H, Van Dongen J, Vermeulen S, Engelborghs S, Vandebulcke M, Vandenberghe R, De Deyn PP, Van Broeckhoven C, BELNEU consortium. A 22-single nucleotide polymorphism Alzheimer's disease risk score correlates with family history, onset age, and cerebrospinal fluid A β 42. *Alzheimers Dement*. 2015; 11:1452–1460. [PubMed: 26086184]
- [24]. Biffi A, Anderson CD, Desikan RS, Sabuncu M, Cortellini L, Schmansky N, Salat D, Rosand J, Alzheimer's Disease Neuroimaging Initiative (ADNI). Genetic variation and neuroimaging measures in Alzheimer disease. *Arch Neurol*. 2010; 67:677–685. [PubMed: 20558387]
- [25]. Sabuncu MR, Buckner RL, Smoller JW, Lee PH, Fischl B, Sperling RA, Alzheimer's Disease Neuroimaging Initiative. The association between a polygenic Alzheimer score and cortical thickness in clinically normal subjects. *Cereb Cortex*. 2012; 22:2653–2661. [PubMed: 22169231]
- [26]. Kohannim O, Hua X, Rajagopalan P, Hibar DP, Jahanshad N, Grill JD, Apostolova LG, Toga AW, Jack CR, Weiner MW, Thompson PM, Alzheimer's Disease Neuroimaging Initiative. genetic profiling to empower drug trials and predict brain atrophy. *Neuroimage Clin*. 2013; 2:827–835. [PubMed: 24179834]
- [27]. Chauhan G, Adams HHH, Bis JC, Weinstein G, Yu L, Töglhofer AM, Smith AV, van der Lee SJ, Gottesman RF, Thomson R, Wang J, Yang Q, Niessen WJ, Lopez OL, Becker JT, Phan TG, Beare RJ, Arfanakis K, Fleischman D, Vernooij MW, Mazoyer B, Schmidt H, Srikanth V, Knopman DS, Jack CR, Amouyel P, Hofman A, DeCarli C, Tzourio C, van Duijn CM, Bennett DA, Schmidt R, Longstreth WT, Mosley TH, Fornage M, Launer LJ, Seshadri S, Ikram MA, Debette S. Association of Alzheimer's disease GWAS loci with MRI markers of brain aging. *Neurobiol Aging*. 2015; 36:1765.e7–1765.16. [PubMed: 25670335]
- [28]. Gui H, Jiang CQ, Cherny SS, Sham PC, Xu L, Liu B, Jin YL, Zhu T, Zhang WS, Thomas GN, Cheng KK, Lam TH. Influence of Alzheimer's disease genes on cognitive decline: The Guangzhou Biobank Cohort Study. *Neurobiol Aging*. 2014; 35:2422.e3–2422.e8. [PubMed: 24863667]
- [29]. Naj AC, Jun G, Reitz C, Kunkle BW, Perry W, Park YS, Beecham GW, Rajbhandary RA, Hamilton-Nelson KL, Wang L-S, Kauwe JSK, Huentelman MJ, Myers AJ, Bird TD, Boeve BF, Baldwin CT, Jarvik GP, Crane PK, Rogaeva E, Barmada MM, Demirci FY, Cruchaga C, Kramer PL, Ertekin-Taner N, Hardy J, Graff-Radford NR, Green RC, Larson EB, St George-Hyslop PH, Buxbaum JD, Evans DA, Schneider JA, Lunetta KL, Kamboh MI, Saykin AJ, Reiman EM, De Jager PL, Bennett DA, Morris JC, Montine TJ, Goate AM, Blacker D, Tsuang DW, Hakonarson H, Kukull WA, Foroud TM, Martin ER, Haines JL, Mayeux RP, Farrer LA, Schellenberg GD, Pericak-Vance MA, Alzheimer Disease Genetics Consortium. Albert MS, Albin RL, Apostolova LG, Arnold SE, Barber R, Barnes LL, Beach TG, Becker JT, Beekly D, Bigio EH, Bowen JD, Boxer A, Burke JR, Cairns NJ, Cantwell LB, Cao C, Carlson CS, Carney RM, Carrasquillo MM, Carroll SL, Chui HC, Clark DG, Corneveaux J, Cribbs DH, Crocco EA, DeCarli C, DeKosky ST, Dick M, Dickson DW, Duara R, Faber KM, Fallon KB, Farlow MR, Ferris S, Frosch MP, Galasko DR, Ganguli M, Gearing M, Geschwind DH, Ghetti B, Gilbert JR, Glass JD, Growdon JH, Hamilton RL, Harrell LE, Head E, Honig LS, Hulette CM, Hyman BT, Jicha GA, Jin L-W, Karydas A, Kaye JA, Kim R, Koo EH, Kowall NW, Kramer JH, LaFerla FM, Lah JJ, Leverenz JB, Levey AI, Li G, Lieberman AP, Lin C-F, Lopez OL, Lyketsos CG, Mack WJ, Martiniuk F, Mash DC, Masliah E, McCormick WC, McCurry SM, McDavid AN, McKee AC, Mesulam M, Miller BL, Miller CA, Miller JW, Murrell JR, Olichney JM, Pankratz VS, Parisi JE, Paulson HL, Peskind E, Petersen RC, Pierce A, Poon WW, Potter H, Quinn JF, Raj A, Raskind M, Reisberg B, Ringman JM, Roberson ED, Rosen HJ, Rosenberg RN, Sano M, Schneider LS, Seeley WW, Smith AG, Sonnen JA, Spina S, Stern RA, Tanzi RE, Thornton-Wells TA, Trojanowski JQ, Troncoso JC, Valladares O, Van Deerlin VM, Van Eldik LJ, Vardarajan BN, Vinters HV, Vonsattel JP, Weintraub S, Welsh-Bohmer KA, Williamson J, Wishnek S, Wolter RL, Wright CB, Younkin SG, Yu C-E, Yu L. Effects of multiple genetic Loci on age at onset in late-onset

- Alzheimer disease: A genome-wide association study. *JAMA Neurol.* 2014; 71:1394–1404. [PubMed: 25199842]
- [30]. Martiskainen H, Helisalmi S, Viswanathan J, Kurki M, Hall A, Herukka S-K, Sarajärvi T, Natunen T, Kurkinen KMA, Huovinen J, Mäkinen P, Laitinen M, Koivisto AM, Mattila KM, Lehtimäki T, Remes AM, Leinonen V, Haapasalo A, Soininen H, Hiltunen M. Effects of Alzheimer's disease-associated risk loci on cerebrospinal fluid biomarkers and disease progression: A polygenic risk score approach. *J Alzheimers Dis.* 2015; 43:565–573. [PubMed: 25096612]
- [31]. American Psychiatric Association and American Psychiatric Association. Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders: DSM-IV. 1994
- [32]. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984; 34:939–944. [PubMed: 6610841]
- [33]. Ruiz A, Heilmann S, Becker T, Hernández I, Wagner H, Thelen M, Mauleón A, Rosende-Roca M, Bellenguez C, Bis JC, Harold D, Gerrish A, Sims R, Sotolongo-Grau O, Espinosa A, Alegret M, Arrieta JL, Lacour A, Leber M, Becker J, Lafuente A, Ruiz S, Vargas L, Rodríguez O, Ortega G, Dominguez M-A, Mayeux R, Haines JL, Pericak-Vance MA, Farrer LA, Schellenberg GD, Chouraki V, Launer LJ, van Duijn C, Seshadri S, Antúnez C, Breteler MM, Serrano-Ríos M, Jessen F, Tárrega L, Noöthen MM, Maier W, Boada M, Ramirez A. Follow-up of loci from the International Genomics of Alzheimer's Disease Project identifies TRIP4 as a novel susceptibility gene. *Transl Psychiatry.* 2014; 4:e358. IGAP. [PubMed: 24495969]
- [34]. Bradshaw EM, Chibnik LB, Keenan BT, Ottoboni L, Raj T, Tang A, Rosenkrantz LL, Imboywa S, Lee M, Von Korff A, Alzheimer Disease Neuroimaging Initiative. Morris MC, Evans DA, Johnson K, Sperling RA, Schneider JA, Bennett DA, De Jager PL. CD33 Alzheimer's disease locus: Altered monocyte function and amyloid biology. *Nat Neurosci.* 2013; 16:848–850. [PubMed: 23708142]

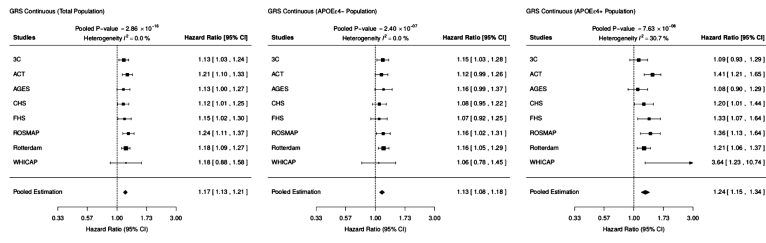


Fig. 1. Association of a genetic risk score based on IGAP with incident AD. The hazard ratios are estimated for an increase in one standard deviation of the genetic risk score.

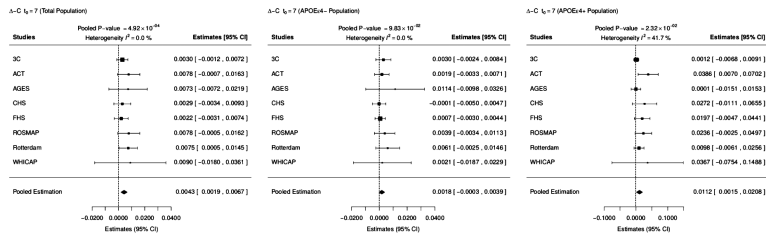


Fig. 2. Improvement in risk prediction of a genetic risk score based on IGAP after a fixed follow-up period of 7 years. In each study, Δ -C represents the difference in C-indexes between a model adjusted for age, sex, education and APOE ϵ 4 status (base) and a model with additional adjustment for the genetic risk score (base+GRS)

Table 1

Baseline characteristics of the participants across studies

	3C	ACT	AGES	CHS	FHS	ROSMAP	Rotterdam	WHICAP
N at risk	6079	2110	2553	1998	1757	1262	3334	594
Incident AD % (N)	7.7% (468)	19.8% (418)	11.0% (280)	18.4% (367)	13.1% (231)	28.4% (359)	18.2% (607)	8.8% (52)
Follow-up time (years)	6.31 (3.13)	8.04 (4.99)	5.85 (2.16)	6.52 (3.49)	7.61 (4.49)	7.93 (4.72)	10.85 (5.77)	6.20 (4.56)
GRS	19.64 (2.58)	19.81 (2.61)	19.95 (2.53)	19.61 (2.48)	19.15 (2.28)	19.68 (2.52)	19.20 (2.48)	18.52 (2.49)
Age (years)	74.23 (5.46)	75.63 (6.53)	75.52 (5.12)	74.81 (4.72)	76.05 (7.35)	78.37 (7.05)	73.99 (6.52)	76.71 (6.75)
Male % (N)	39.2% (2384)	43.7% (922)	40.4% (1031)	37.8% (755)	42.7% (751)	30.5% (385)	39.7% (1325)	38.4% (228)
APOE e4% (N)	20.6% (1250)	25.2% (531)	27.6% (704)	22.7% (454)	20.5% (360)	24.2% (305)	27.7% (922)	20.9% (124)
Education % (N)								
- High school	63.8% (3881)	10.1% (214)	20.5% (523)	21.5% (430)	17.0% (298)	4.2% (53)	43.7% (1456)	22.1% (131)
- GED degree	12.6% (765)	24.7% (522)	50.5% (1290)	30.0% (600)	37.8% (664)	14.5% (183)	25.8% (860)	28.3% (168)
- College	23.6% (1433)	25.5% (538)	16.1% (412)	24.4% (488)	23.7% (416)	16.1% (203)	24.9% (831)	35.5% (211)
- College degree		39.6% (836)	12.8% (328)	24.0% (480)	21.6% (379)	65.2% (823)	5.6% (187)	14.1% (84)

Results are presented as mean (standard deviation) unless stated otherwise.

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Table 2
Association of individual SNPs with risk of incident Alzheimer’s disease and comparison with IGAP

Locus	SNP	Chr.	Position	EAF	Alleles	Studies	HR	Current Study			IGAP	
								p-value	I2	OR	95% CI	OR
CRI	rs6656401	1	207692049	0.20	A/G	8	0.92	(0.85–1.01)	7.58 × 10 ⁻⁰²	29.4	1.18	(1.14–1.22)
BIN1	rs6733839	2	127892810	0.41	T/C	8	0.96	(0.86–1.07)	4.96 × 10 ⁻⁰¹	68.0	1.22	(1.18–1.25)
INP5D	rs35349669	2	234068476	0.49	T/C	8	0.97	(0.90–1.04)	4.05 × 10 ⁻⁰¹	42.2	1.08	(1.05–1.11)
MEF2C	rs190982	5	88223420	0.59	A/G	8	1.02	(0.95–1.09)	6.22 × 10 ⁻⁰¹	27.2	1.08	(1.05–1.11)
HLA-DRB5/HLA-DRB1	rs9271192	6	32578530	0.28	C/A	5	0.99	(0.92–1.06)	7.01 × 10 ⁻⁰¹	0.0	1.11	(1.08–1.15)
CD2AP	rs10948363	6	47487762	0.27	G/A	8	0.97	(0.88–1.06)	4.80 × 10 ⁻⁰¹	60.0	1.10	(1.07–1.13)
NME8	rs2718058	7	37841534	0.63	A/G	8	0.98	(0.91–1.05)	5.08 × 10 ⁻⁰¹	29.9	1.08	(1.05–1.11)
ZCWPW1	rs1476679	7	10004446	0.71	T/C	8	1.01	(0.95–1.07)	7.55 × 10 ⁻⁰¹	0.0	1.10	(1.06–1.12)
EPHA1	rs11771145	7	143110762	0.66	G/A	8	1.02	(0.97–1.09)	4.16 × 10 ⁻⁰¹	0.0	1.11	(1.08–1.14)
PTK2B	rs28834970	8	27195121	0.37	C/T	8	1.04	(0.98–1.09)	2.22 × 10 ⁻⁰¹	0.0	1.10	(1.08–1.13)
CLU	rs9331896	8	27467686	0.62	T/C	8	1.03	(0.97–1.09)	3.16 × 10 ⁻⁰¹	0.0	1.16	(1.12–1.19)
CELF1	rs10838725	11	47557871	0.32	C/T	8	1.01	(0.95–1.08)	6.64 × 10 ⁻⁰¹	5.3	1.08	(1.05–1.11)
MS4A6A	rs983392	11	59233508	0.60	A/G	8	1.00	(0.91–1.09)	9.69 × 10 ⁻⁰¹	56.1	1.11	(1.09–1.15)
PICALM	rs10792832	11	85867875	0.64	G/A	8	1.03	(0.98–1.10)	2.61 × 10 ⁻⁰¹	9.5	1.15	(1.12–1.18)
SORL1	rs11218343	11	121435587	0.96	T/C	8	1.00	(0.86–1.15)	9.86 × 10 ⁻⁰¹	7.8	1.30	(1.22–1.39)
FERMT2	rs17125944	14	53400629	0.09	C/T	8	1.01	(0.91–1.12)	9.16 × 10 ⁻⁰¹	17.8	1.14	(1.09–1.19)
SLC24A4/RIN3	rs10498633	14	92926952	0.78	G/T	8	1.03	(0.95–1.12)	4.90 × 10 ⁻⁰¹	37.2	1.10	(1.06–1.14)
ABCA7	rs4147929	19	1063443	0.19	A/G	8	0.94	(0.83–1.07)	3.50 × 10 ⁻⁰¹	61.4	1.15	(1.11–1.19)
CASS4	rs7274581	20	55018260	0.92	T/C	8	1.07	(0.93–1.22)	3.33 × 10 ⁻⁰¹	43.2	1.14	(1.09–1.19)

Positions on the genome are from hg19; Alleles are displayed as effect / other alleles; IGAP columns: results from the stage I+2 meta-analysis published by Lambert et al., 2013 [16]. SNP, single nucleotide polymorphism; Chr, chromosome number; EAF, effect allele frequency; HR, hazard ratio; 95% CI, 95% confidence interval; OR, odds ratio.