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The Role of Genomic-Informed Risk Assessments in Predicting Dementia Outcomes

Shea J. Andrews, PhD[1†], Caroline Jonson, PhD[2,3,4], Brian Fulton-Howard, PhD[5], Alan E Renton, PhD[5], Jennifer S Yokoyama, PhD[2], Kristine Yaffe, MD[1,2,6] for the Alzheimer's Disease Neuroimaging Initiative*

[1] Department of Psychiatry and Behavioral Sciences, University of California San Francisco, San Francisco, USA
[2] Department of Neurology, University of California San Francisco, San Francisco, USA
[3] Center for Alzheimer's and Related Dementias, National Institutes of Health, Bethesda, MD USA 20892
[4] DataTecnica LLC, Washington, DC USA 20037
[5] Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, USA
[6] Department of Epidemiology and Biostatistics, University of California

† Corresponding author
Shea Andrews, PhD
Assistant Professor
Department of Psychiatry and Behavioral Sciences
University of California San Francisco
Nancy Friend Pritzker Psychiatry Building
675 18th St
shea.andrews@ucsf.edu

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Abstract

Importance: By integrating genetic and clinical risk factors into genomic-informed dementia risk reports, healthcare providers can offer patients detailed risk profiles to facilitate understanding of individual risk and support the implementation of personalized strategies for promoting brain health.

Objective: To develop a genomic-informed risk assessment composed of family history, genetic, and clinical risk factors and, in turn, evaluate how the risk assessment predicted incident dementia.

Design: This longitudinal study included data from two clinical case-control cohorts with an average of 6.6 visits. Secondary analyses were conducted from July 2023 - March 2024.

Setting: Data were previously collected across multiple US locations from 1994 to 2023.

Participants: Older adults aged 55+ with whole-genome sequencing and dementia-free at baseline.

Exposures: An additive score comprising the modified Cardiovascular Risk Factors, Aging, and Incidence of Dementia Risk Score (mCAIDE), family history of dementia, *APOE* genotype, and an AD polygenic risk score.

Main Outcome(s) and Measure(s): The risk of progression to all-cause dementia was evaluated using Cox-proportional hazard models (hazard ratios with 95% confidence intervals [OR 9%CI]).

Results: A total of 3,429 older adults were included (aged 75 ± 7 years; 59% female; 75% non-Latino White, 15% Black, 5.2% Latino, 3.6% other, and 0.4% Asian; 27% MCI), with 751 participants progressing to dementia. The most common high-risk indicator was a family history of dementia (56%), followed by *APOE**ε4 genotype (36%), high mCAIDE score (34%), and high AD-PRS (11%). Most participants had at least one high-risk indicator, with 39% having one, 32% two, 9.8% three, and 1% four. The presence of 1, 2, 3, or 4 risk indicators was associated with a doubling (HR = 1.72, CI: 1.34-2.22, p = 2.5e-05), tripling (HR = 3.09, CI: 2.41-3.95, p = 4.4e-19), quadrupling (HR = 4.46, CI: 3.34-5.94, p = 2.2e-24), and a twelvefold increase (HR = 12.15, CI: 7.33-20.14, p = 3.2e-22) in dementia risk.

Conclusion & Relevance: We found that most participants in memory and aging clinics had at least one high-risk indicator for dementia. Furthermore, we observed a dose-response relationship where a greater number of risk indicators was associated with an increased risk of incident dementia.

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting nearly 7 million Americans [1]. This number is projected to more than double by 2060, posing an estimated economic burden exceeding one trillion dollars [1]. To date, there is no cure to stop or reverse disease progression; moreover, the recent anti-amyloid immunotherapies, which moderately delay progression, face significant barriers such as high costs and require extensive medical infrastructure for the administration and monitoring of adverse events [2]. In the absence of widely accessible and highly effective disease-modifying therapies, strategies targeting modifiable risk factors to promote brain health represent the primary approach to mitigating dementia risk [3]. Applying these strategies in a primary care setting will require risk assessment of genetic and clinical risk factors for risk stratification and communication of risk profiles for personalized risk reduction strategies [3].

Genomic-informed risk assessments are innovative and recently developed integrated profiles that compile information from clinical risk factors, family history, polygenic risk scores (PRS), and monogenic mutations [4,5]. Currently, the eMERGE consortium is evaluating the clinical utility of genomic-informed risk assessments for eleven health conditions, including asthma, diabetes, hypocholesterolemia, and obesity, within the US healthcare system [4,5]. The selection of these traits was based on PRS analytic viability, feasibility, translatability, and, critically, potential clinical actionability—a consideration previously not applicable to AD until recently. Given the demonstrated benefits of personalized multi-domain lifestyle interventions, which include improved cognitive performance and risk factor profiles among high-risk older adults recruited from a primary care setting [6], it is now timely to consider such genomic-informed dementia risk reports to promote brain health.

As AD is a complex multifactorial disease influenced by genetic and environmental factors, genomic-informed dementia risk reports should ideally integrate three components of genetic risk – family history, monogenic, and polygenic – along with clinical risk factors. Highly penetrant mutations in *APP, PSEN1,* and *PSEN2* are linked to monogenic forms of AD, while the *APOE**ε4 allele increases the risk of sporadic AD [7]. PRS further quantify the genetic risk originating from a further 80+ AD-associated loci with small effect sizes [7]. In the absence of these specific genetic tests, a family history of AD may indicate a heightened genetic predisposition, especially for first-degree relatives of AD patients [8]. Finally, up to 12 modifiable risk factors contribute substantially – approximately 40% – to AD risk, with dementia risk scores quantifying individual risk arising from environmental factors related to clinical, lifestyle, and behavioral risk factors [9–11].

Our goal was to develop a genomic-informed risk assessment for non-demented patients evaluated at memory and aging clinics based on their family history, genetic, and clinical risk factors and, in turn, evaluate how the risk assessment predicted incident dementia.

Methods

Cohort

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We used the genetic and phenotypic data from participants who contributed to the National Alzheimer's Coordinating Center (NACC) database and Alzheimer's Disease Neuroimaging Initiative (ADNI). The NACC consists of over 45,000 participants from 30+ past and present US-based Alzheimer Disease Core Centers and Alzheimer Disease Research Centers funded by the National Institute on Aging [12]. ADNI was launched in 2003 as a public-private partnership with the primary goal of testing whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of mild cognitive impairment (MCI) and early AD [13]. Participants provided informed consent, and institutional review board approval was locally obtained.

We analyzed longitudinal data for participants with 2+ visits, who were cognitively unimpaired (CU) or had a primary diagnosis of MCI at baseline, who were at least age 55 at their initial visit or whose estimated age-of-onset of cognitive impairment was at least 55, and who had been whole genome-sequenced. Diagnostic criteria for NACC and ADNI have been previously described [12,13].

Demographic and Clinical Risk Factors

Race/ethnicity

Race and ethnicity were self-reported by study participants, with categories defined by the National Institutes of Health, including American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. Ethnicity categories included Hispanic or Latino or not Hispanic or Latino. If individuals did not identify with these racial and ethnic categories, they could report "other."

Modified Cardiovascular Risk Factors, Aging, and Incidence of Dementia Risk Score

The Cardiovascular Risk Factors, Aging, and Incidence of Dementia Risk Score (CAIDE) was developed in a Finnish population-based cohort to estimate 20-year dementia risk based on an individual's midlife risk factor profile, including age, gender, education, systolic blood pressure, body mass index, total cholesterol, and physical activity [14]. The Modified Cardiovascular Risk Factors, Aging, and Incidence of Dementia Risk Score (mCAIDE) recalibrated the CAIDE risk score to predict late-life dementia in a diverse US population using the same risk factors [15]. The mCAIDE risk scores for each participant were calculated using the published equations for mCAIDE using the following variables: age, sex, education, hypertension, obesity, and hypercholesteremia. We utilized self-reported data for age, sex, and educational attainment. Obesity was defined as a Body mass index (BMI) >30, and hypertension as a sitting systolic blood pressure >140 mmHg. For NACC, hypercholesteremia was identified through self-reported medical history or clinician assessment. In ADNI, it was determined by a fasting total cholesterol level exceeding 6.21 mmol/L. Physical activity assessments were unavailable; however, CAIDE remains predictive of dementia when physical activity is not included [16]. Missing data was imputed using a Random Forrest algorithm via the `MissForest` R package [17]. A mCAIDE score of ≥ 6 was determined to be "high-risk".

Family History of Dementia

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A family history of dementia (FHx) was determined based on at least one self-reported first-degree blood relative living/lived with dementia. Participants with a family history of dementia were determined to be "high-risk".

Genetic Risk Factors

Whole-Genome Sequencing

Whole genome-sequencing data for NACC and ADNI participants was generated by the Alzheimer's Disease Sequencing Project (ADSP). ADSP is a collaborative research effort that seeks to identify novel genetic risk factors for AD [18]. The data collected and generated through the ADSP included whole exome sequencing and whole genome sequencing (WGS) from family, case-control, and cohort study designs [18]. The Release 4 WGS dataset contains 35,569 participants from 40 cohorts that have undergone standardized data management pipelines for variant calling and quality control [19,20]. Briefly, samples were sequenced by multiple centers with different platforms and libraries. The Genome Center for Alzheimer's Disease (GCAD) mapped short reads against the hg38 reference genome using BWA MEM, called variants using the GATK HaplotypeCaller for each sample, and subsequently jointly called genotypes across all samples using GATK. QC checks included those without a GATK pass, monomorphic across all samples, or low call rate across all studies (<80%), DP<10, GQ<20, mean average depth >500, and ABhet ratio outside of 0.25 to 0.75.

Variants flagged by GCAD for removal were excluded, with additional variant and sample QC conducted using GenoTools [21]. Variants were excluded if the call rate <0.95, not in Hardy–Weinberg equilibrium ($p < 1\times10\text{-}4$); samples were excluded if the call rate was <0.95, discordant sex was reported based on X chromosome heterozygosity, cryptic relatedness, and either insufficient or excessive heterozygosity. Genetic ancestry was determined using the PGS Catalog Calculator, which projects samples onto principal components from known ancestral populations in the jointly called 1000 Genomes Projects and Human Diversity Project (1KG+HGDP) and uses a Random Forests classifier to assign participants to a continental genetic ancestry group [22].

Autosomal Dominant AD mutations

Carriers of monogenic AD variants will be identified by examining 220 variants in *PSEN1* (n = 191), *PSEN2* (n = 8), and *APP* (n = 21) previously implicated with Autosomal Dominant AD mutations (ADAD) [23]. WGS was used to match variants based on chromosome, position, reference allele, and alternate allele (mutant allele in contrast to the reference allele). Individuals with at least one alternate allele in the ADAD-linked variants were classified as ADAD variant carriers.

APOE genotype

The SNPs defining the *APOE* genotype (rs7412 & rs429358) were extracted from the WGS data and combined to define *APOE* genotype: ε4 carriers had either the ε2/ε4, ε3/ε4, or ε4/ε4 genotype.

AD Polygenic Risk Score

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PRS-CSx was used to construct a cross-ancestry AD-PRS excluding the *APOE* region (variants located ± 250 kb from the *APOE* ε4 defining SNP rs429358) using ancestry-specific EUR [24], AFR [25], EAS [26], and AMR [27] summary statistics with ancestry-matched LD reference panels from 1000 Genomes using the 'auto' and 'meta' flags to automatically estimate the phi parameter of the inverse-variance weighted meta-analysis of the summary statistics in the Gibbs sampler [28]. Ancestry-normalized cross-ancestry AD-PRS were subsequently estimated in the whole of ADSP using the Polygenic Score Catalog Calculator using the score file generated by PRS-CSx [22]. The Ancestry normalization uses a two-step ancestry adjustment procedure that regresses out ancestry PCs from the raw PRS such that the mean and variance of the PRS distribution are consistent across all populations [29,30]. Principal components for the 1KG+HGDP reference were estimated using FRAPOSA, with ADSP projected into the reference PCA space and a Random Forest classifier used to determine the population to which each individual is genetically similar [22]. Risk stratification within ADSP, excluding participants from NACC and ADNI, was determined by establishing a percentile cutoff. This cutoff was defined as where the odds ratio for dementia risk in the high-risk group was significantly greater than 2 compared to the rest of the cohort (Supplementary Figure 1) [4]. The 85th percentile was the cutoff used to determine a "high-risk" AD-PRS in NACC and ADNI. Due to sample overlap between ADSP and participants contributing to the AFR AD GWAS, we used PLINK to estimate pairwise genetic relatedness between participants in ADSP and ADGC and excluded ~3,000 participants from PRS estimation and subsequent statistical analysis.

Statistical Analysis

Baseline characteristics of the joint NACC and ADNI cohorts were summarized across participants progressing from CU or MCI to all-cause dementia and non-progressors as percentages for categorical variables and mean (SD) for continuous variables, with differences between progressors/non-progressors determined using t-tests for continuous variables and Chi-square tests for categorical variables. To estimate the proportion of participants identified as high-risk for dementia in our genomic-informed risk assessment, we analyzed the prevalence of each risk indicator, including carriers of ADAD variants, *APOE**ε4 allele carriers, those with a family history of dementia, and individuals with high mCAIDE (≥6) and AD-PRS (≥85th percentile). We summed the presence of these risk indicators weighted equally to derive a cumulative risk score for each participant for a score ranging from 0-5. Cox-proportional hazard models were used to estimate the risk of dementia progression associated with increasing risk burden, adjusting for cohort and race/ethnicity. Age in years was used as the time-to-event scale, with AD age of onset used for incident dementia cases and age at last visit for participants who did not progress to dementia during the course of the study. Censoring was accounted for in the analysis to allow for valid inferences. Hazard Ratios (HR) with 95% confidence intervals (95% CI) were calculated for each group by comparing the hazard rates for individuals with one or more risk indicators to those with no risk indicators. P-values were 2-sided with statistical significance set at less than 0.05. All analyses were performed using R version 4.3.3.

Results

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The majority of individuals attending memory and aging clinics exhibit at least one high-risk indicator for dementia.

A total of 3,429 older adults, with an average age of 75 years (SE = 7), were included (Table 1). This cohort was comprised of 59% females and had a racial composition of 75% non-Latino White, 15% Black, 5.2% Latino, 3.6% other races, and 0.4% Asian; 27% of these individuals were diagnosed with MCI. Throughout the study, which was conducted over an average of 6.6 visits (SE = 3.4), 751 participants progressed from CU/MCI to all-cause dementia. The most common high-risk indicator identified was a family history of dementia, affecting 56% of the participants. This was followed by possession of at least one *APOE**ε4 allele (36%), a high mCAIDE score (34%), and high AD-PRS (11%). No participants carried an ADAD mutation. Most participants had at least one risk factor, with individuals who developed dementia having a significantly higher risk indicator burden (Table 1). Specifically, 18% of participants had no identified risk indicators, 39% had one, 32% had two, 9.8% had three, and 1% had four (Figure 1).

An Increasing burden of dementia risk indicators is associated with an increased risk of dementia, exhibiting a dose-response relationship.

We evaluated the association of risk indicator burden with incident dementia using Cox proportional hazard models. We observed that each additional risk indicator was linked to a 71% increase in the risk of dementia onset (HR = 1.71, 95% CI: 1.58-1.84, p = 2.6e-42; Supplementary Table 1). Specifically, the presence of 1, 2, 3, or 4 risk indicators was associated with a doubling (HR = 1.72, CI: 1.34-2.22, p = 2.5e-05), tripling (HR = 3.09, CI: 2.41-3.95, p = 4.4e-19), quadrupling (HR = 4.46, CI: 3.34-5.94, p = 2.2e-24), and a twelvefold increase (HR = 12.15, CI: 7.33-20.14, p = 3.2e-22) in dementia risk, respectively (Figure 2; Supplementary Table 2).

Discussion

Genomic-informed risk assessments provide a way for healthcare providers to convey integrated risk profiles to patients, encompassing clinical risk factors, family history, PRS, and monogenic mutations. In this study, we evaluated the prevalence high-risk indicators for dementia among participants, including family history, presence of ADAD mutations, *APOE* genotype, AD-PRS, and mCAIDE risk score. We found that the majority of participants in memory and aging clinics had at least one high-risk indicator for dementia. Furthermore, we observed a dose-response relationship where a greater number of risk indicators was associated with an increased risk of incident dementia.

The primary application for genomic-informed dementia risk scores and personalized reports would be to assist in the risk prediction of dementia, especially among patients experiencing subjective cognitive decline [3]. These reports can also be used in primary prevention efforts in a primary care setting by enabling effective risk stratification and clear communication of risk profiles to patients and highlighting modifiable risk factors that can improve an individual's risk profile [3]. Furthermore, to enhance their utility, genomic-informed dementia risk reports should be integrated with blood-based biomarkers and comprehensive neuropsychological assessments. This integration would assist in the early identification of patients with early or pre-clinical AD, who could then be referred to dementia specialists for further evaluation using

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cerebrospinal fluid (CSF) and PET biomarkers [31]. Ultimately, confirmation of amyloid pathology would facilitate the initiation of secondary prevention, including disease-modifying therapies such as anti-amyloid immunotherapies [32].

The clinical utility of genomic-informed risk assessments has been demonstrated for atherosclerotic cardiovascular disease (ASCVD). In a prospective cohort of middle-aged patients (n = 7,342), 42% of individuals identified as high risk for ASCVD undertook proactive measures to reduce their disease risk, subsequently improving blood lipid and blood pressure profiles [33]. This finding demonstrates that communication of personalized ASCVD risk motivates changes in health behavior and supports the integration of genomic information into clinical care for disease prevention. The ongoing GenoVA and eMERGE studies are now evaluating the clinical utility of genomic-informed risk assessments for 11 health conditions, including asthma, diabetes, hypocholesteremia, and obesity, in the U.S. healthcare system [4,5,29]. These initiatives could provide valuable insights into the development of genomic-informed dementia risk reports.

Before implementing genomic-informed risk assessments for dementia in clinical practice, several limitations need to be addressed. First, as different dementia risk scores are composed of different predictors and algorithms, the discriminative performance of different dementia risk scores needs to be validated across diverse populations. Our use of mCAIDE was determined by the lack of extensive lifestyle and social determinants of health data, precluding the use of more comprehensive dementia risk scores. Second, the predictive accuracy of PRS models is affected by the sample size ratio between the EUR and minor GWAS, between-ancestry genetic architecture differences (LD, MAF, genetic correlation, heritability, effect size), and LD reference panels [34,35]. As such, the choice of PRS model to use for portability across populations will differ between traits. We used PRS-CSx due to good overall performance when ancestry-specific GWAS from multiple populations are available; however, it is critical to assess the validity of different PRS models to determine the best approach to use [28]. Third, NACC participants — typically older, more educated, predominantly female, and with a lower prevalence of hypertension, diabetes, and depressive symptoms but a higher prevalence of subjective cognitive decline — do not represent the broader U.S. population [36]. This may lead to overestimates of genetic risk indicators and underestimations of environmental risk factors. Finally, we treated each risk indicator as contributing to dementia risk equally in line with the eMERGE genomic-informed risk assessment design, however, more predictive models may be developed that weight each risk indicator by its relative risk. As such, before genomic-informed risk assessments can be routinely applied in clinical settings, it is crucial to validate the performance of both clinical and polygenic risk scores across diverse populations. Moreover, strategies for effectively communicating these risk assessments to patients must be developed and tested to ensure they are understood and can inform patient care appropriately.

Conclusions

In conclusion, most participants in memory and aging clinics possess at least one high-risk indicator for dementia. Furthermore, a higher burden of risk indicators is significantly associated with a higher likelihood of developing dementia. By integrating genetic and clinical

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risk factors into genomic-informed dementia risk reports, healthcare providers can offer patients detailed risk profiles. This comprehensive approach not only facilitates a better understanding of individual risk but also supports the implementation of personalized strategies for promoting brain health.

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Author Contributions: Dr. Andrews had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. The code to support the analysis of this study is available at:
https://github.com/AndrewsLabUCSF/GIDRR

Concept and design: SJA
Acquisition, analysis, or interpretation of data: SJA, CJ, BFH, AER
Drafting of the Manuscript: SJA
Critical review of the manuscript for important intellectual content: KY, JSY, CJ, BFJ, AER
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Tables

Table 1: Cohort Description

	Non-progressors N = 2,678	Progressors N = 751	P
Cohort			
NACC	1,986 (74%)	479 (64%)	
ADNI	692 (26%)	272 (36%)	
Visits[1]	6.9 (3.4)	5.5 (3.1)	<0.001[2]
Age[1]	74 (7)	77 (6)	<0.001[2]
Female	1,654 (62%)	364 (48%)	<0.001[3]
Baseline Diagnosis			<0.001[3]
Cognitively Unimpaired	2,303 (86%)	214 (28%)	
Mild Cognitive Impairment	375 (14%)	537 (72%)	
Race/Ethnicity			<0.001[3]
NLW	1,955 (73%)	630 (84%)	
Asian	12 (0.4%)	2 (0.3%)	
Black	464 (17%)	64 (8.5%)	
Latinx	141 (5.3%)	38 (5.1%)	
Other	106 (4.0%)	17 (2.3%)	
Education[1]	15.74 (3.07)	15.69 (3.17)	0.7[2]
BMI[1]	27.7 (5.1)	26.2 (4.3)	<0.001[2]
Systolic Blood Pressure[1]	134 (18)	137 (18)	<0.001[2]
Hypercholesterolemia	1,123 (42%)	295 (39%)	0.2[3]
mCAIDE[1]	4.64 (2.03)	4.89 (1.81)	<0.001[2]
AD-PRS[1]	-0.13 (1.10)	0.26 (1.05)	<0.001[2]
Risk Indicators			
Family History of Dementia	1,454 (54%)	450 (60%)	0.006[3]
APOE ε4+	834 (31%)	414 (55%)	<0.001[3]
AD-PRS $\geq$ 85%	258 (9.6%)	122 (16%)	<0.001[3]
mCAIDE $\geq$ 6	886 (33%)	266 (35%)	0.2[3]
Risk Indicator Burden			<0.001[3]
0	546 (20%)	81 (11%)	
1	1,084 (40%)	240 (32%)	
2	811 (30%)	297 (40%)	
3	222 (8.3%)	114 (15%)	
4	15 (0.6%)	19 (2.5%)	

[1]Mean (SD); [2] t-test, [3] chi-square test

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Figures

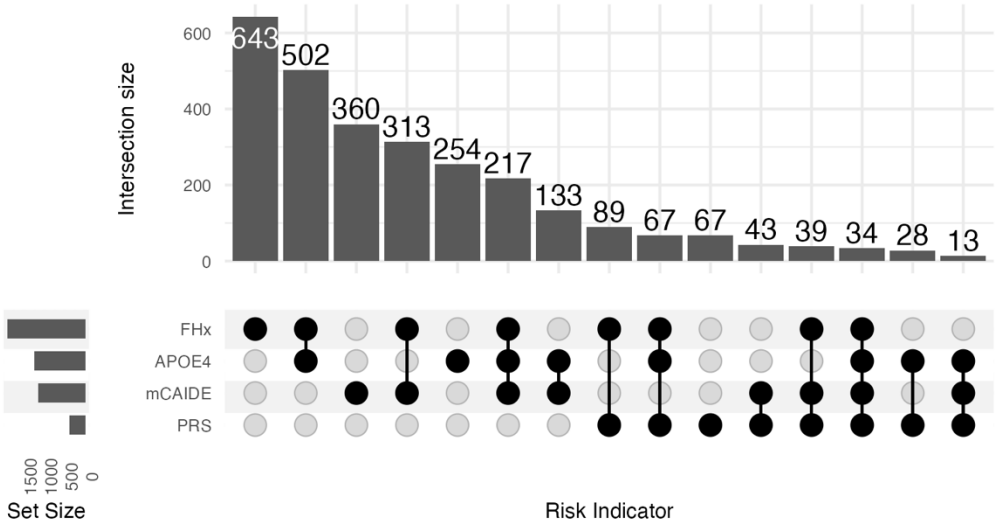

Figure 1: Upset plot showing the total number of participants with a given risk indicator (horizontal bars) and the number of participants in which risk indicators co-occurred (vertical bars).

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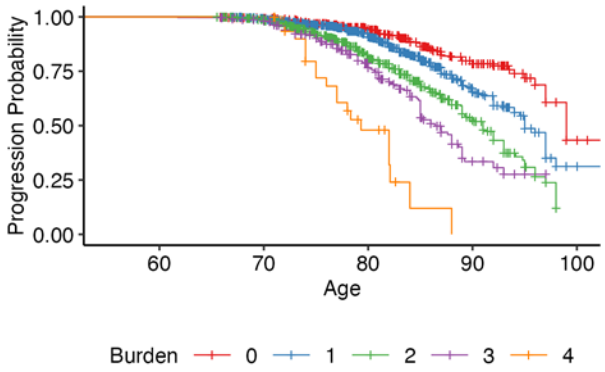

Figure 2: Kaplan-Meier Estimates of Dementia Progression by Number of Risk Indicators