

Genetic Predisposition, Modifiable Risk Factors And Age Of Dementia Onset

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Background

- Genome-wide association studies have identified numerous genetic variants associated with dementia.
- We investigated whether genetic predisposition to dementia is associated with earlier dementia onset and whether a favorable health risk profile can offset genetic risk and delay dementia onset.

Methods

Population: UK Biobank, a prospective, community-based cohort (N=484,693; age 40-69; 54% female).

Exposures:

- Applied a polygenic risk score comprising over 1M variants associated with dementia, previously developed and validated in the FinnGen cohort.
- Created a dementia modifiable risk score based on 12 risk factors, score range 0-12: diabetes, hypercholesterolemia, hypertension, smoking, physical inactivity, depression, obesity, alcohol consumption, low educational attainment, hearing loss, traumatic brain injury, and social isolation.

Outcome: Age at all-cause dementia onset determined from ICD-9/10 codes through linkage to national health registry.

Analysis:

- To account for population structure, PRS was residualized using the first 10 genetic ancestry principal components and then standardized (mean = 0, standard deviation [SD] = 1).
- Estimated hazard ratios for dementia before age 65 (early-onset) and after age 65 (late-onset), adjusted for age, sex, and race.
- Estimated restricted mean survival time up to age 85 for dementia-free survival, unadjusted.

Characteristics

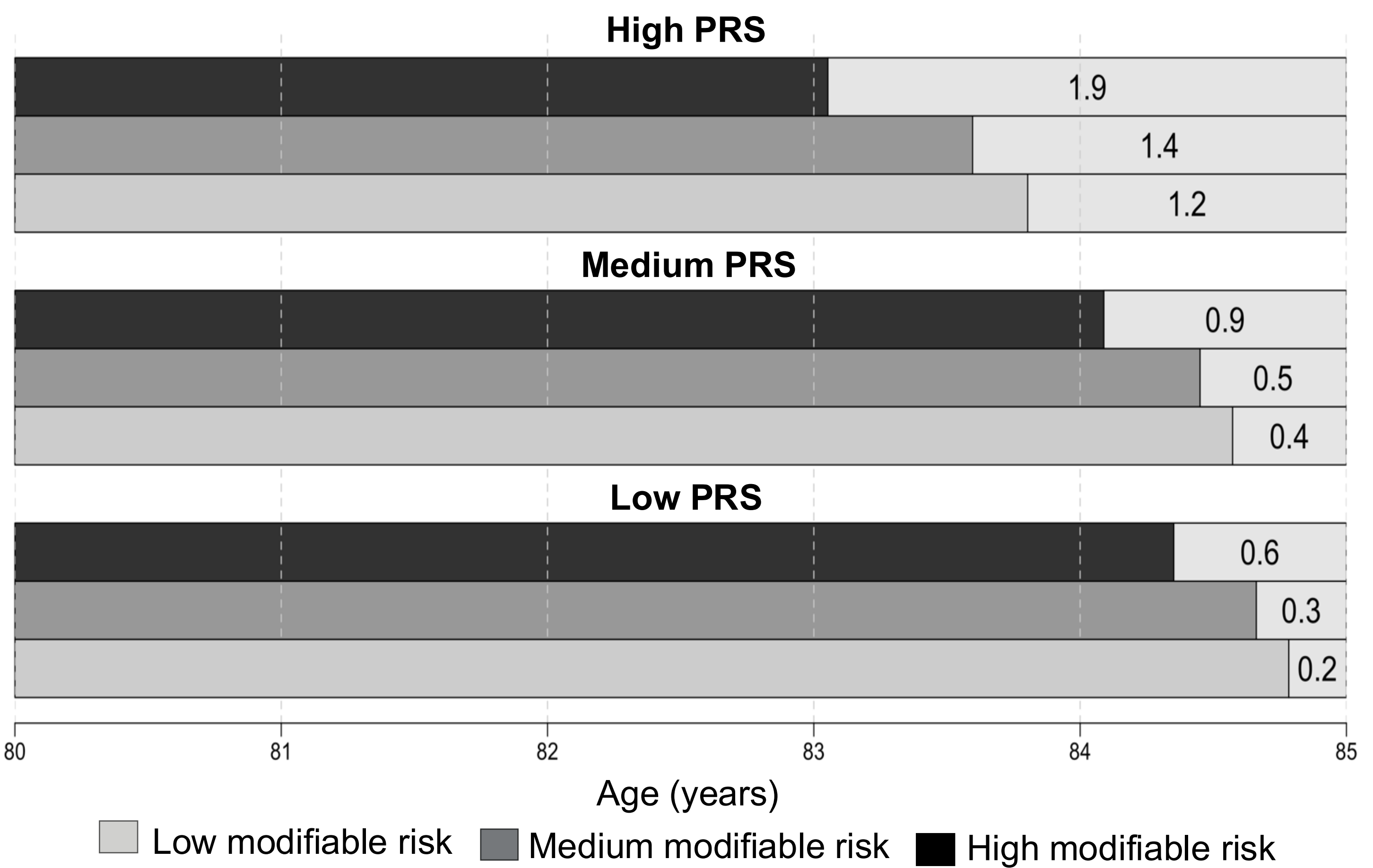
N: 484,693

Age, years (mean (SD))	56.5 (8.1)
Female, %	221,850 (55%)
Non-Hispanic White , %	456,809 (94.2%)
Education, %	
Less than high school	195,430 (40%)
Greater than high school	288,755 (60%)
Abnormal Blood Glucose, N (%)	24,568 (5.1%)
Abnormal Total Cholesterol, N (%)	218,618 (47.4%)
Abnormal Blood Pressure, N (%)	365,450 (75.6%)
Smoking, N (%)	50,926 (10.6%)
Physical Inactivity, N (%)	49,103 (13.1%)
Depression, N (%)	52,089 (11.5%)
Obesity, N (%)	117,631 (24.4%)
Alcohol Consumption, N (%)	70,299 (14.8%)
Hearing Loss, N (%)	20,495 (12.9%)
Traumatic Brain Injury, N (%)	5,217 (1.1%)
Social Isolation, N (%)	69,219 (14.8%)
Modifiable Risk Score, N (%)	
Low (0-1)	27,594 (25.4%)
Medium (2-3)	54,284 (50.0%)
High (>3)	26,673 (24.6%)
Polygenic risk score, N	
Low (0-20%)	96,939
Medium (20-80%)	290,816
High (80-100%)	96,938

Results

- 9,338 incident dementia cases over a median follow-up time of 13.6 years (IQR 12.9 – 14.3).
- For each SD-increase in PRS, the hazard of dementia was 1.38 (95% CI: 1.28-1.48) times higher for early onset dementia and 1.79 (95% CI: 1.76 – 1.82) times higher for late onset dementia.
- The average dementia-free survival was nearly one year longer for those with the high genetic risk but a favorable modifiable risk compared to high genetic risk an unfavorable risk profile, as measured by the restricted mean survival up to age 85 (**Figure**).
- Adjusting for *APOE* did not change findings.

Restricted mean survival time for dementia up to age 85, by genetic and modifiable risk categories.



Polygenic risk score (PRS) was classified into 3 percentile-based categories: low ($\leq 20\%$), medium (20-80%), and high ($\geq 80\%$). Dementia modifiable risk score was categorized low (0-1), medium (2-3), and high (>3). Modifiable risk scores were categorized into tertiles: low modifiable risk (0-1), medium modifiable risk (2-3), and high modifiable risk (>3).

Conclusions

- Dementia PRS is associated with an increased risk of both early and late onset dementia and with an earlier age at dementia onset.
- A favorable modifiable risk factor profile is associated with delayed dementia onset and may partially offset genetic predisposition.
- These results emphasize the importance of early-life and midlife lifestyle risk factor management for the prevention and delay of dementia.

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