ARC CENTRE OF EXCELLENCE IN POPULATION AGEING RESEARCH

Social environment, lifestyle, and genetics with risk of probable incident dementia:

A longitudinal analysis among older adults

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Outline

- Introduction
- Methods
- Key findings
- Discussion
- Q & A

Introduction

Background: Dementia

Dementia is a general term for decline in mental ability

- Short-term memory.
- Keeping track of a purse or wallet.
- Paying bills.
- Planning and preparing meals.
- Remembering appointments.
- Traveling out of the neighborhood.

Dementia is not a normal part of aging.

Dementia v.s. Alzheimer's

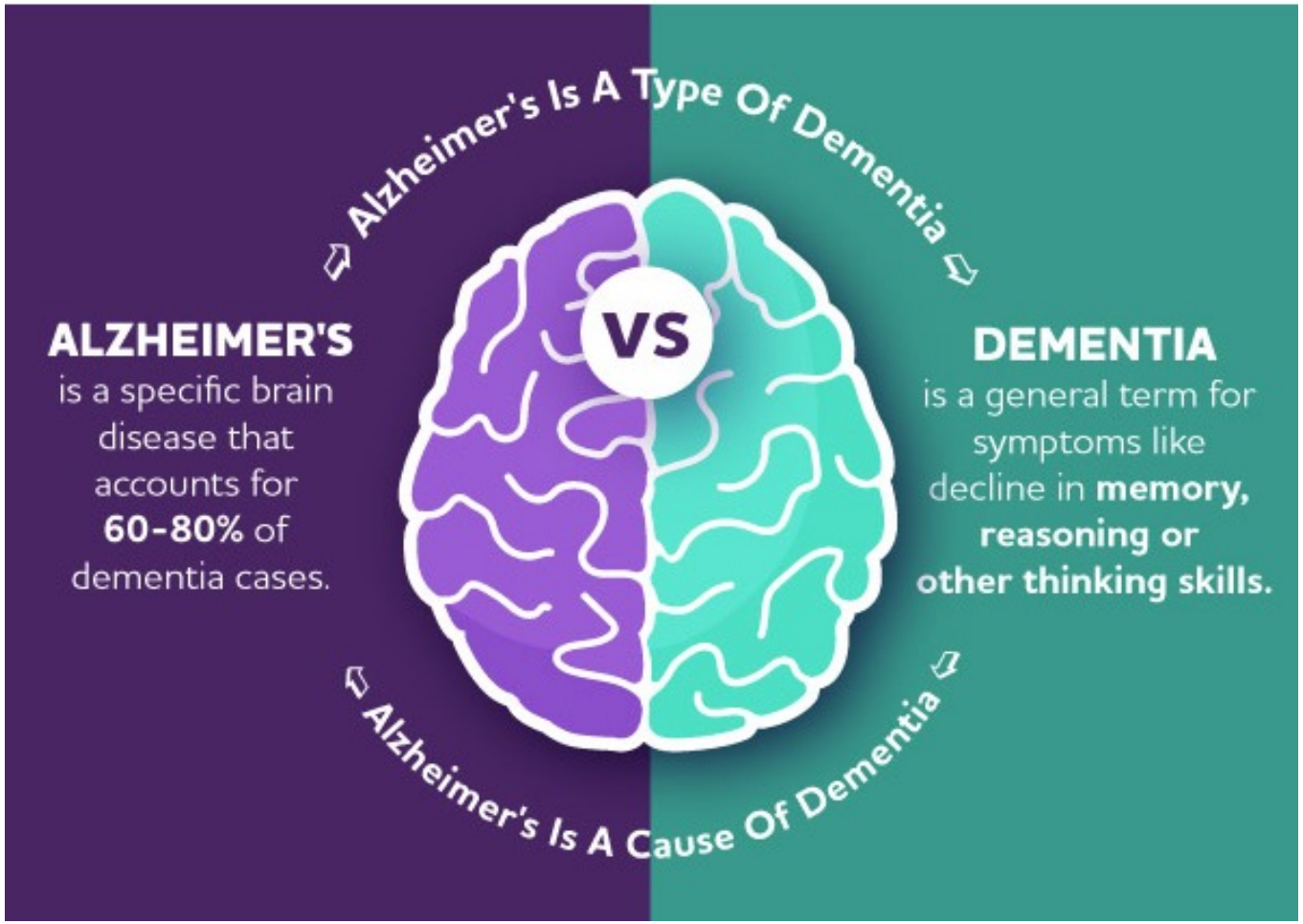


Figure cited from: https://www.alz.org/alzheimers-dementia/difference-between-dementia-and-alzheimer-s

Background: Dementia burden globally

The number of individuals with dementia is increasing

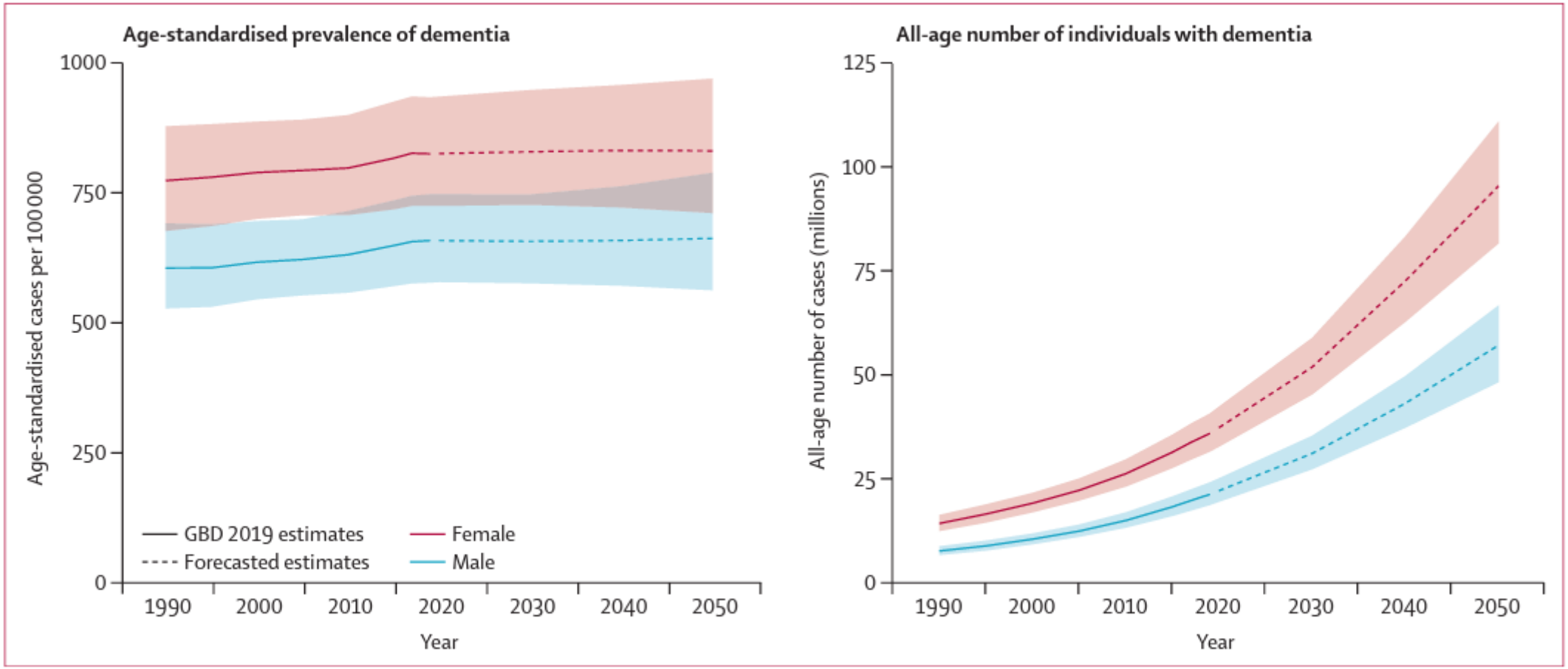


Figure 2: **Estimated trends in the global age-standardised dementia prevalence (A) and all-age number of cases (B), with 95% uncertainty intervals, 2019–50**
GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

Figure cited from: Nichols E, Steinmetz JD, Vollset SE, *et al.* Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *The Lancet Public Health* 2022; **7**: e105–25.

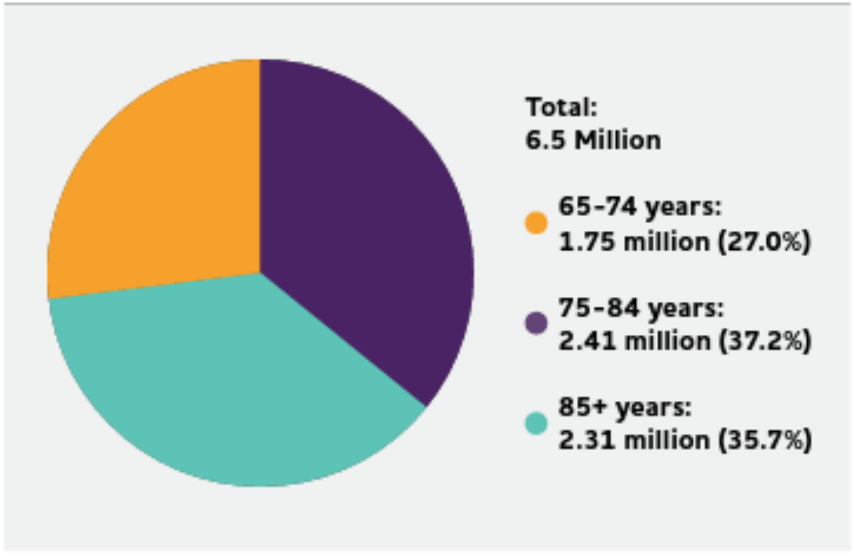
Background: dementia burden in the US

1 in 9 people (10.7%) aged 65+ has Alzheimer's dementia in 2022

By 2060: ~13.8 million aged 65+ with Alzheimer's dementia

Racial disparities

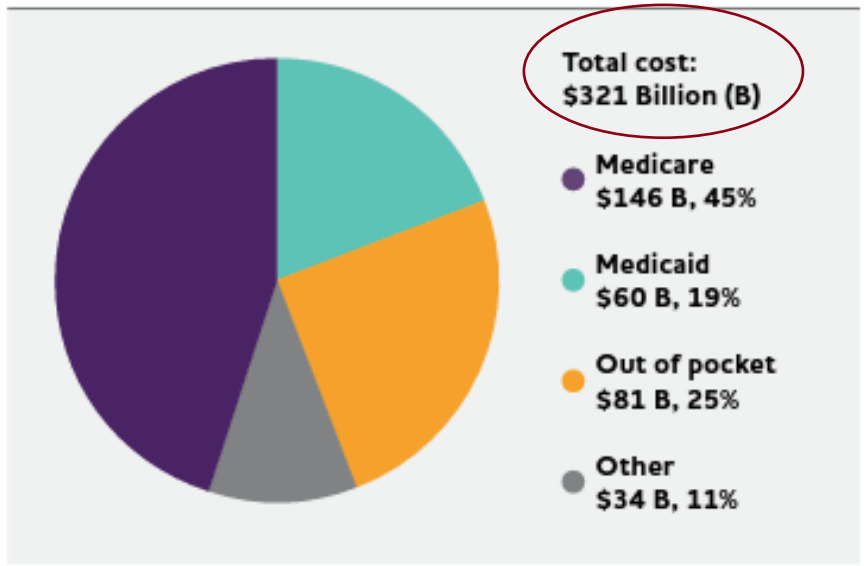
Number and Ages of People 65 or Older with Alzheimer's Dementia, 2022*



*Percentages do not total 100 due to rounding.

Created from data from Rajan et al.[A2,224]

Distribution of Aggregate Costs of Care by Payment Source for Americans Age 65 and Older with Alzheimer's or Other Dementias, 2022*



*Data are in 2022 dollars.

Created from data from the Lewin Model.[A12] "Other" payment sources include private insurance, health maintenance organizations, other managed care organizations and uncompensated care.

Figure cited from: Alzheimer's Association. 2022 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2022;18.

Background: Dementia prevention

Dementia can be prevented, but not cured

THE LANCET COMMISSIONS | VOLUME 396, ISSUE 10248, P413-446, AUGUST 08, 2020

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

Prof Gill Livingston, MD • Jonathan Huntley, PhD • Andrew Sommerlad, PhD • Prof David Ames, MD • Prof Clive Ballard, MD • Prof Sube Banerjee, MD • et al. Show all authors

Published: July 30, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)30367-6 • Check for updates

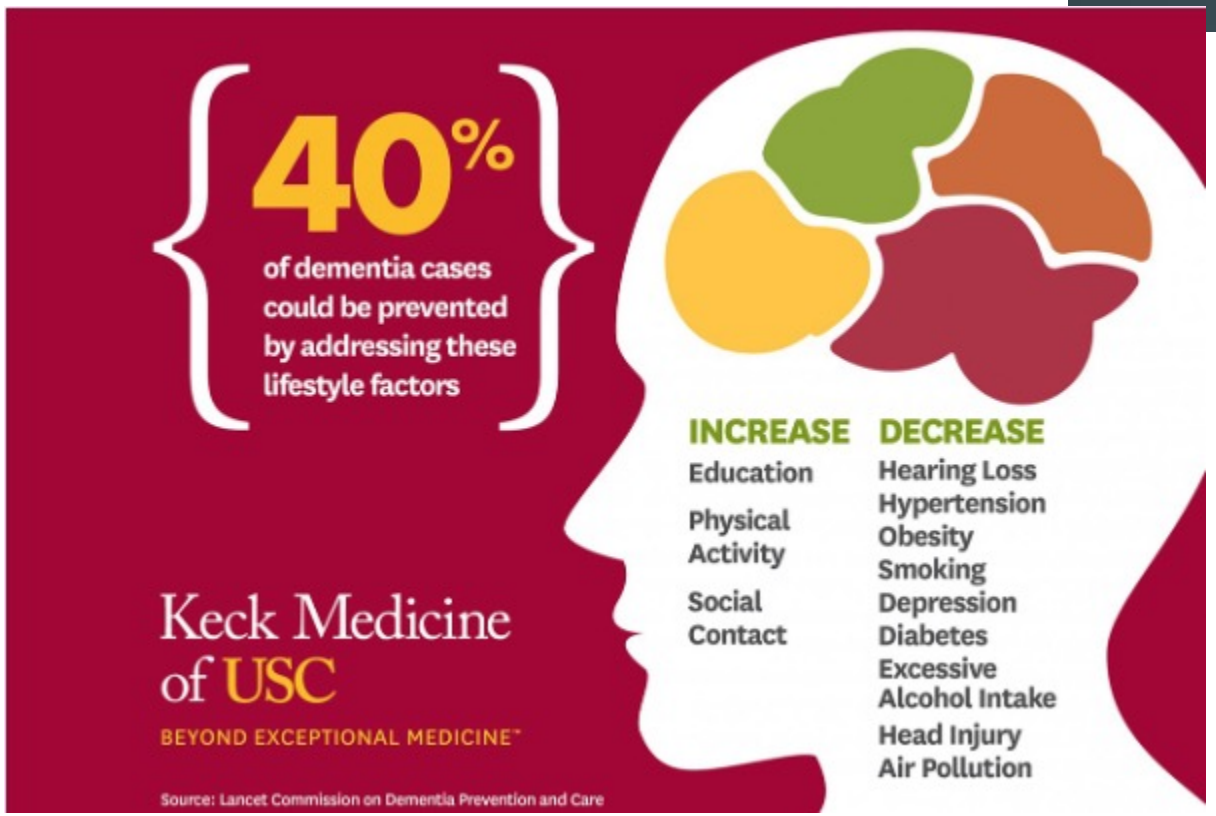
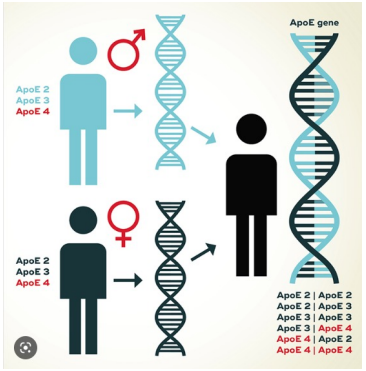


Figure cited from: https://hscnews.usc.edu/experts-find-dementia-risk-can-be-reduced-by-targeting-12-risk-factors-throughout-life

Background

Determinants of dementia



Polygenetic risk score:

- An aggregation of genetic risk derived from genome-wide association studies (multiple risk alleles e.g. APOE, mutations in APP, PSEN1, PSEN2 etc.)

Modifiable lifestyle risk factors:

- Smoking, heavy drinking, physical inactivity, and an unbalanced diet

Genetic * Lifestyles
Social environment * Lifestyles?

Social determinants of health (SDOH):

- Dementia disproportionately affects individuals with lower socioeconomic status
- The measurement of aggregate social environmental risk remains a topic of debate
- Polysocial risk score

Background: Study objectives

Using longitudinal cohort data from the Health and Retirement Study (HRS) in the US, the current study aims to:

- ✓ Develop a polysocial risk score for dementia in the US population;
- ✓ Assess the association between social environment, measured by the polysocial risk score, and the risk of probable incident dementia;
- ✓ Explore the interaction between social environment and lifestyle with probable incident dementia, despite genetic predisposition

Methods

Methods: Study design and participants

- ✓ **Data source**: HRS, a longitudinal panel study of a representative sample of people in the US aged 50 years and older (data collection started in 1992)

- ✓ **Study design**: A retrospective cohort study from 2006 to 2018 of HRS

- ✓ **Inclusion criteria**:
  - Aged 60 years and older
  - Not demented at baseline
  - Participated in the enhanced face-to-face interview since 2006 and had records of polygenetic risk scores

- ✓ **Study sample**: The final sample consisted of 5,199 study participants:
  - 603 African Americans
  - 4,596 European Americans

HRS | HEALTH AND RETIREMENT STUDY

Methods: Development of the polysocial risk score for dementia

Development of the polysocial risk score for dementia

- ✓ Key factors of SDOH (21): five important aspects identified by the **Healthy People 2030** issued by the *US Department of Health and Human Services*:

  1) **Economic stability**: annual personal income, annual total household income, total household wealth, out-of-pocket health expenditures, poverty status, and employment status;
  2) **Education Access and Quality**: highest education obtained
  3) **Health Care Access and Quality**: health insurance coverage, long-term care insurance coverage, life insurance coverage;
  4) **Neighborhood and built environment**: home type, rural/urban residence, and neighborhood safety
  5) **Social and community context**: region of living, marital status, religious activity involvement, living arrangement, social support, social cohesion, lifetime stressful events, and discrimination

- ✓ Missing data imputation: multiple imputations by chained equations with 20 sets of imputations

- ✓ Performed forward stepwise Cox models to identify key determinants and calculated and categorized the polysocial risk score

Methods: Measurement

- **Dementia**
  - ✓ We measured dementia using a composite score calculated based on the cognitive assessment results:
    - The immediate (0-10) and delayed (0-10) word recall test
    - The serial 7s test (0-5)
    - The backward counting test (0-2)

  - ✓ The composite score ranged from 0-27:
    - Participants that scored 0-6 were categorized as having probable incident dementia
    - Those that scored 7-27 were considered as not having probable incident dementia

- **Genetic predisposition**
  - ✓ Used the polygenetic risk scores for Alzheimer's disease developed based on a genome-wide association study (GWAS) meta-analysis conducted by the International Genomics of Alzheimer's Project (IGAP) in 2019

  - ✓ We used the polygenetic risk scores that included only variants with a significant association (p-value < 0.01) with Alzheimer's Disease in the GWAS, as well as two imputed SNPs comprising APOE-ε4 status (rs7412 and rs429358).

  - ✓ The polygenetic risk scores were standardized within the ethnicity to follow a standard normal distribution.

  - ✓ Participants were categorized into low, intermediate, and high genetic risk groups within the ethnicity.

Methods: Measurement

Lifestyle and other covariates

- ✓ Lifestyle risk: smoking, drinking and physical inactivity
  - ✓ Smoking: Being a current smoker or not
  - ✓ Drinking: Reference to previous studies and the 2020-2025 Dietary Guidelines for Americans
    - No or heavy drinking (0 drink or >14 drinks per week)
    - moderate drinking (1-14 drinks per week)
  - ✓ Physical activity:
    - Regular physical activity: having moderate physical activity at least 5 days a week or vigorous activity once a week, following the recommendation by the American Heart Association.

- ✓ Covariates: identified by previous studies as important risk factors for developing dementia, including sex, age, race, depression, hypertension, diabetes, and hearing impairment

Methods: Statistical analysis

- ✓ **Baseline characteristics**: presented by polygenetic and polysocial risk score categories and tested for differences

- ✓ **Survival analysis approach**:
  - At risk: Participants were all at risk when entering the cohort in 2006
  - Event: Onset of dementia
  - Censored: The date of onset of dementia, death, or loss to follow-up, whichever came first before the interview end date during the 2018 wave
  - Regression models: Ran four separate sets of Cox proportional hazard regression models to assess the association between polysocial risk score and probable dementia incidence
  - The proportionality of hazards assumption verification
  - Results report: hazard ratios (HR) , 95% CI, and p value
  - Explored racial disparities

- ✓ **Tested for interactions:**
  - Added interaction terms between the polysocial risk score and lifestyle risk (smoking, exercise and drinking separately)

Methods: Statistical analyses

✓ **Sensitivity analyses**:

- Genetic predisposition measurement: Used another set of polygenic risk scores for Alzheimer's disease, the same meta-analysis study conducted by the IGAP but without the two imputed SNPs comprising APOE-ε4 status (rs7412, rs429358).
- Smoking measurement: Changed to ever smoked or not
- Drinking measurement: Changed to three categories of no drinking, moderate drinking, and heavy drinking
- Used cumulative incidence function model to re-estimate the regression results

Key findings

Key findings: Study sample selection and baseline characteristics

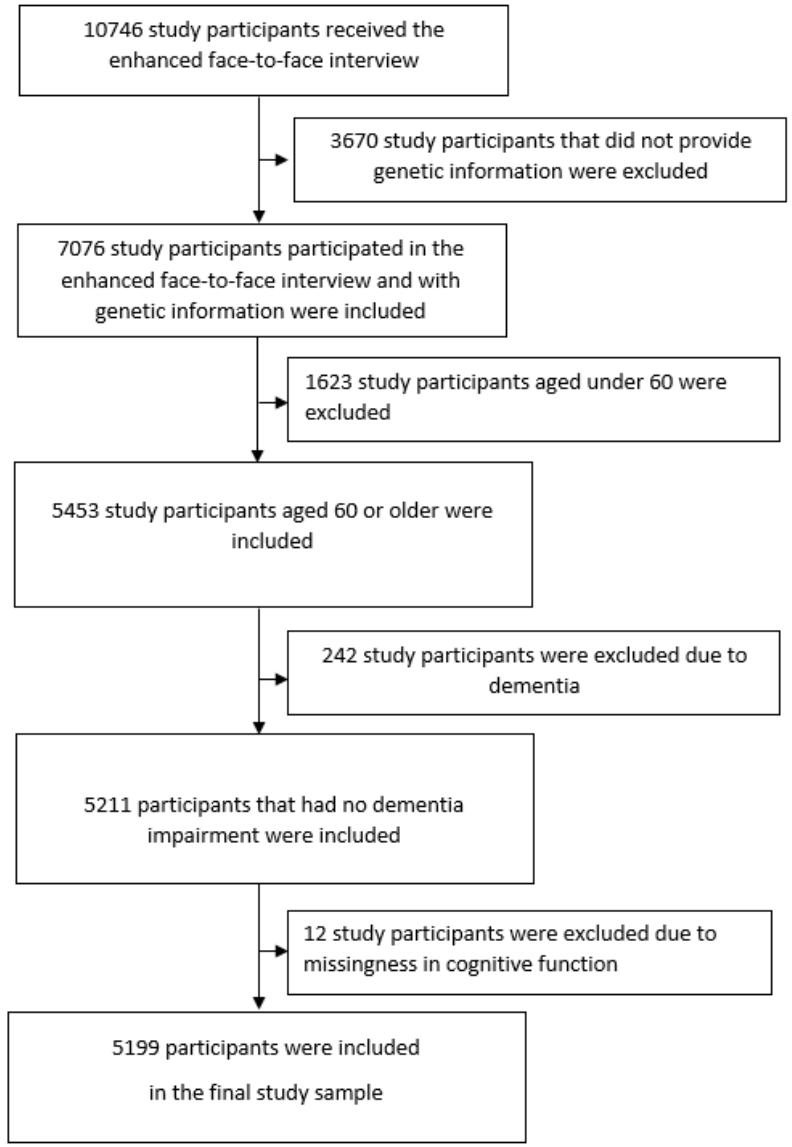


Figure 1. Sample selection flowchart

Key message

✓ **The sample consisted of 5199 study participants (2018):**

- Mean age: 73.4 (SD: 8.3)
- Female: 58.0%
- African American: 11.6%
- Mean years of follow-up: 6.2 years (median: 6.0 years [IQR: 3.8-8.5]
- Total number of participants who developed dementia during follow-up: 1045

✓ **Difference of baseline characteristics across polygenetic risk score and polysocial risk score:**

- Across polygenetic risk score group: No significant difference among the covariates at baseline for different groups

- Across polysocial risk score group:
  - The baseline characteristics overall differed significantly: e.g. the percentage of smoking, physical inactivity, hypertension, and diabetes

Key findings: Polysocial risk score results

Key message

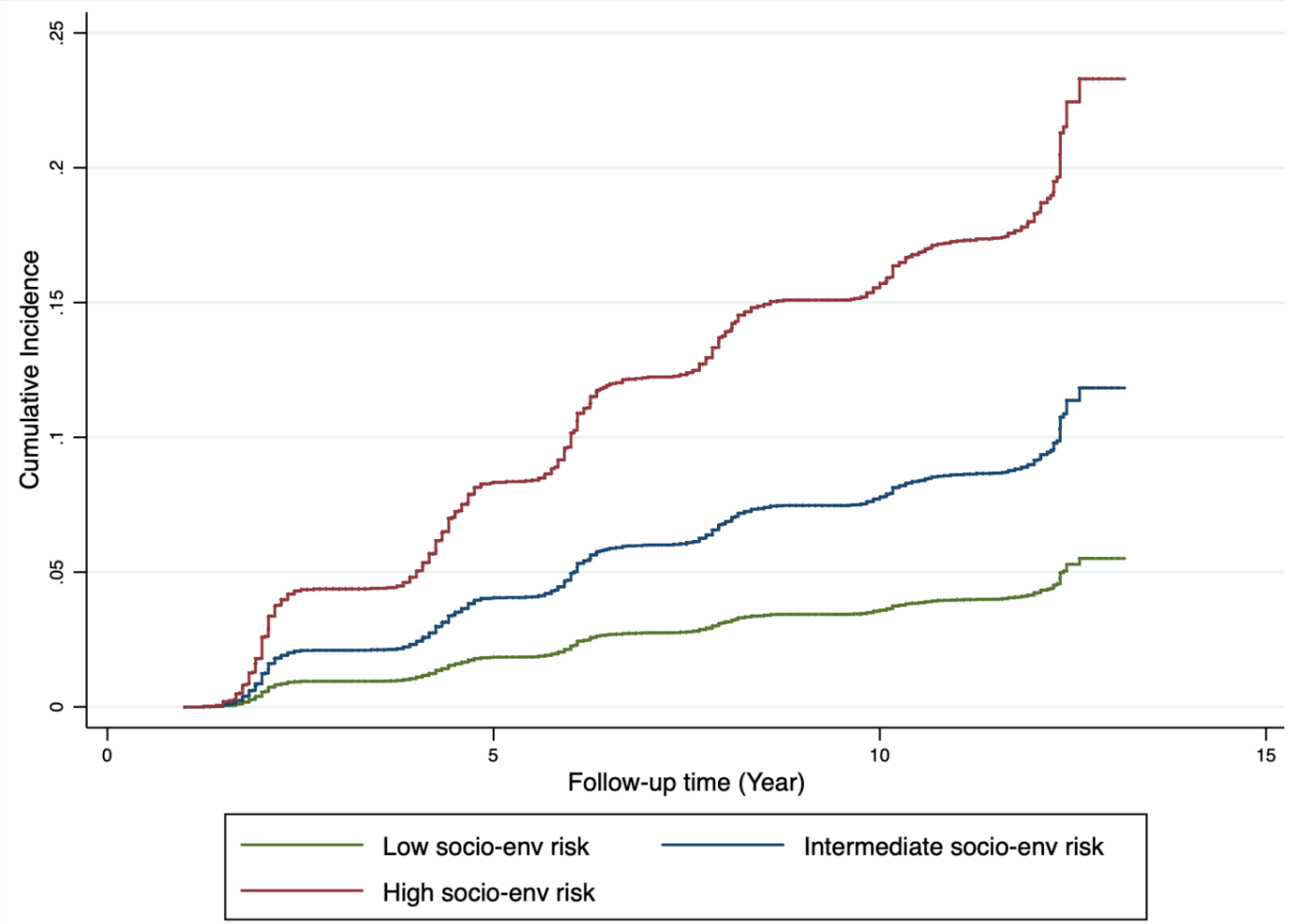
✓ **Eleven SDOH were retained in the model to construct the polysocial risk score for dementia:**

- Economic stability: Individual income, total household income, total wealth, poverty, employment
- Education access and quality: education, marital status
- Health care access and quality: life insurance coverage
- Neighborhood and built environment: home type
- Social and community context: living arrangement (whether living alone), social support (from spouse, children, friends and other relatives)

✓ **Tertiles of the polysocial risk score**:

- Low risk: 0-17 (n=1939)
- Intermediate risk: 18-25 (n=1609)
- High risk: 26-49 (n=1651)

Key findings: Cumulative incidence of dementia by polysocial risk score



Number at risk Baseline	Follow-up at Year 4	Follow-up at Year 8	End of follow up
Low risk: 1939	1,521	1,302	513
Intermediate risk: 1609	1,463	1,029	450
High risk: 1651	1,372	992	419

Key findings: Cox model results

Key message

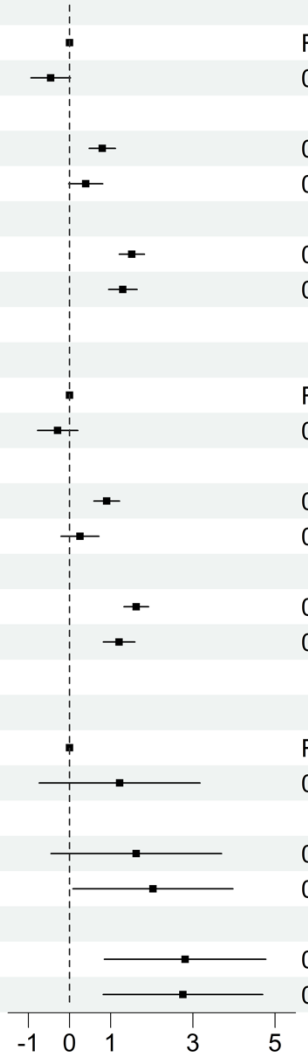
- ✓ Compared with the group with lowest social environmental risk, **intermediate and high-risk groups** were more likely to develop probable incident dementia during follow up:
    - 1.3 times (aHR=2.28, 95% CI=1.74-2.99) and 3.9 times (aHR=4.86, 95%CI=3.73-6.32) more likely

- ✓ **Regular exercise** (aHR=0.74, 95%=0.62-0.89) and **moderate drinking** (aHR=0.63, 95% CI=0.51-0.78) could help reduce the risk of probable incident dementia, despite genetic predisposition and social environmental risk.

- ✓ **Being an African American** was found to be associated with a 1.7 times higher risk of developing probable incident dementia (aHR=2.67, 95%CI=2.23-3.19). This association was consistent across all social environmental risk groups.

Key findings: Interaction results

Subgroup	No. of Events/ Total No.	Incidence/1000 person-yr (95% CI)	Cox Model Coefficients (95% CI)	P Value
Low social environmental risk				
Non-regular exercise	52/936	5.69 (4.34 - 7.47)	Ref.	Ref.
Regular exercise	24/820	3.25 (2.18 - 4.84)	-0.46 (-0.94 - 0.02)	0.061
Intermediate social environmental risk				
Non-regular exercise	142/1143	14.55 (12.34 - 17.15)	0.80 (0.48 - 1.11)	0.000
Regular exercise	39/673	8.45 (6.18 - 11.57)	0.39 (-0.02 - 0.81)	0.063
High social environmental risk				
Non-regular exercise	367/1238	37.44 (33.80 - 41.47)	1.51 (1.21 - 1.82)	0.000
Regular exercise	85/389	28.50 (23.04 - 35.24)	1.30 (0.95 - 1.64)	0.000
Low social environmental risk				
No or heavy drinking	54/1107	5.15 (3.94 - 6.72)	Ref.	Ref.
Moderate drinking	22/649	3.65 (2.40 - 5.54)	-0.29 (-0.78 - 0.20)	0.246
Intermediate social environmental risk				
No or heavy drinking	154/1371	14.58 (12.45 - 17.07)	0.90 (0.59 - 1.21)	0.000
Moderate drinking	27/445	7.08 (4.86 - 10.33)	0.25 (-0.21 - 0.71)	0.281
High social environmental risk				
No or heavy drinking	402/1373	37.65 (34.14 - 41.51)	1.62 (1.32 - 1.92)	0.000
Moderate drinking	50/254	23.72 (17.98 - 31.30)	1.21 (0.82 - 1.59)	0.000
Low social environmental risk				
Smoking	1/137	1.15 (0.16 - 8.17)	Ref.	Ref.
Non-smoking	75/1619	4.79 (3.82 - 6.01)	1.22 (-0.74 - 3.17)	0.222
Intermediate social environmental risk				
Smoking	7/190	7.40 (3.53 - 15.52)	1.62 (-0.45 - 3.70)	0.126
Non-smoking	174/1626	12.96 (11.17 - 15.03)	2.03 (0.08 - 3.98)	0.041
High social environmental risk				
Smoking	37/221	27.96 (20.26 - 38.59)	2.81 (0.85 - 4.77)	0.005
Non-smoking	415/1406	36.20 (32.88 - 39.86)	2.76 (0.82 - 4.70)	0.005



Key message

- No significant interaction between social environment and lifestyle.
- The association between regular exercise and moderate drinking with the probable incident dementia was consistent across all social environmental risk groups.

Key findings: Sensitivity analysis

- Observed the same pattern of associations in the four sensitivity analyses.
- Adjusting the measurement of genetic risk, smoking, or drinking did not significantly alter the direction or magnitude of the coefficients.
- The results obtained from the cumulative incidence function-based proportional hazard model were also highly consistent with the main findings.

Discussion

Discussion: Results interpretation

- **Social environment in preventing dementia**
  - Consistently, those in unfavorable social environment have a higher chance of developing dementia; the conclusion holds after controlling the genetic, lifestyle, and other risk factors.
  - Many SDOH matter, covering from economic stability to social support; education has the highest weight among all selected SDOH; social support is also important
- **Healthy lifestyles in preventing dementia**
  - Reconfirmed that having a healthy lifestyle could help reduce the risk of developing dementia
  - Highlighted that a healthy lifestyle can help mitigate the negative impact of an unfavourable social environment on dementia risk
  - Underscored the significance of healthy lifestyle interventions in preventing dementia, especially among those with an unfavourable social environment

Discussion: Results interpretation

- **Racial disparities in the risk of developing dementia**
  - The long-standing and persistent health inequities: African Americans have a higher risk of developing unfavorable health outcomes, including dementia, than European Americans
  - Provided supporting evidence for the existence of structural racism in the US: no significant interactions between race and social environment
  - Reflected the accumulated risks that African Americans face from birth due to racism: eg. limiting their access to quality education, high-income jobs etc.

Structural racism

"The totality of ways in which societies foster racial discrimination, through mutually reinforcing inequitable systems of housing, education, employment, earnings, benefits, credit, media, health care and criminal justice."

Discussion: Strengthens and Limitation

Strengthens

- Adopted a novel tool, the polysocial risk score approach, to quantify the collective effect of multiple social factors;
- Contained all essential determinants of dementia, including genetic, lifestyle, and aggregated social factors;
- Included both African and European American participants;
- Long follow-up time and large sample size.

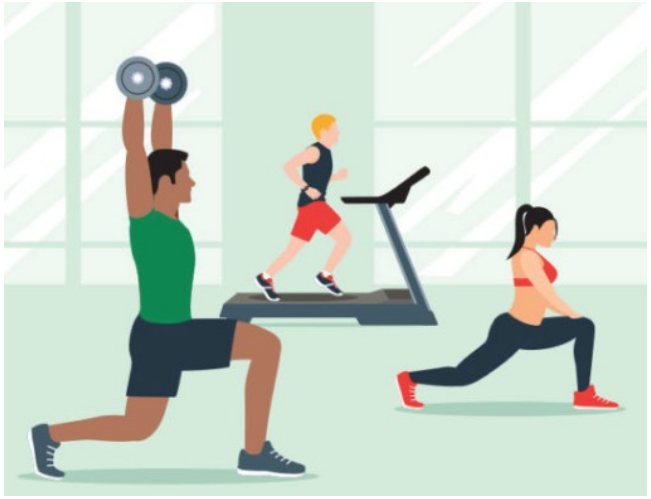
Limitations

- The measurement of dementia was based on cognition function assessment results;
- Self-reported data on diseases status;
- The list of social determinants of health included in constructing the polysocial risk score was not exhaustive;
- The polygenetic risk scores released by the HRS for African Americans were developed based on GWAS studies among European Ancestry groups;
- Did not include diet as one lifestyle risk factor due to data availability;
- Did not include people of other ethnic backgrounds as HRS only has polysocial risk score for European and African Americans.

Key take-home message for dementia prevention

An unfavourable social environment is not deterministic: a healthy lifestyle can help reduce your dementia risk

Try to stay mentally active, socially connected, and economically stable.



High genetic risk for dementia is not scary

Any questions?

Thanks!

Any further questions/comments are welcome

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