Genetic Predictors of Cognitive Decline and Labor Market Exit

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July 21, 2025

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Introduction

Research Question

How does genetic predisposition for Alzheimer's Disease (AD) affect health and labor market outcomes close to retirement?

- We highlight the importance of capturing the earliest stages of AD on economic outcomes
- We use Danish administrative data matched with genetic data from the iPSYCH project (genetic data on 140,000 individuals)
- Proxy-phenotype design: Genetic risk of AD

Alzheimer's Disease and Its Impact

- Alzheimer's Disease (AD) is a neurodegenerative disease and the most common form of dementia
- **Prevalence**
  - 7 million Americans are living with AD (Alzheimer's Association 2024)
  - Projected to double by 2050
- **Impact**
  - 5^{th} leading cause of death in the U.S.
  - Symptoms include: memory loss, cognitive difficulties, and personality changes
- **Economic Cost**
  - In 2024, AD is estimated to cost $360 billion USD in health and long-term care
  - Projected to rise to $1 trillion USD by 2050 (Alzheimer's Association, 2024)

Mechanisms

1. Cognitive decline before retirement reduces work capacity (Chandra et al., 2023)

2. AD family history leads to higher caregiving responsibilities, reducing labor supply (Maestas et al., 2024)

3. Individuals may retire early due to private knowledge of genetic risk

Previous Research

Jeong et al. (2024): Higher genetic risk of ADRD is associated with a lower probability of working for pay

- Sample with a mean age of 68

Shin et al. (2020): Genetic risk of AD is associated with changes in saving behavior and the composition of wealth holdings

Our contributions:

1. Younger sample (average age in our sample is 52-53)
2. Gender differences
3. Focus on labor supply

Preview of Findings

Genetic Risk of AD: Health and Labor Market Outcomes

Health

- Women and men with a child carrying the APOE-e4 allele have a 91% and 44% increased risk of dementia diagnosis

Labor Supply

- Increased genetic risk of AD in women is associated with lower employment and higher disability pension take-up

Cognitive Reserve Theory

- For women, a higher EA PGS buffers the impact of AD genetic risk on employment and disability pension receipt

Background

Genetic Determinants of Alzheimer's Disease

- Two primary ways to assess genetic risk for AD:
    1. Identify specific genes associated with AD
    2. Use polygenic scores (PGS) based on multiple small genetic variants that predict AD
- Focus on the **APOE-e4 allele**, one of three common alleles of the APOE gene (APOE-e2, APOE-e3, APOE-e4)
- APOE-e4 increases AD risk
- Associated with lower efficiency in lipid clearance and brain repair

APOE-e4

- Carriers of APOE-e4 are more likely to accumulate amyloid plaques in the brain
- Individuals can be:
    - **Homogeneous carriers**: Both alleles are APOE-e4
    - **Heterogeneous carriers**: One allele is APOE-e4
    - **Non-carriers**
- Homogeneous carriers have a 12-fold increased risk of AD, while heterogeneous carriers have a 4-fold increased risk

Data

Data Sources

- Data: Danish administrative data on labor market outcomes matched with genetic information from the 2015 iPSYCH
- **iPSYCH Study:**
  - One of the largest genetic studies on mental disorders, containing data on over 140,000 Danes
  - We match this genetic data to Danish registers on labor market outcomes, education, and key demographic variables
  - Attrition: Minimal, as individuals exit the sample only if they die or move out of the country

Sample Characteristics

- Labor market information is drawn from a sample of older individuals (aged 45-65), while genetic data is obtained from their children
- The decision to use children's genetic data was due to data constraints:
    - iPSYCH data includes individuals born no earlier than 1981
- Older individuals were chosen to study labor market outcomes near retirement age
- We use genetic information from the first-born child when multiple children exist in the iPSYCH sample

Health Outcomes

- **Hospital Contact (ICD10 codes)**:
  - Dementia in Alzheimer's Disease (F00)
  - Vascular Dementia (F01)
  - Other Dementias (F02), Unspecified Dementia (F03), and Alzheimer's Disease (G30)
- Data sourced from the National Patient Register (LPR) for the years 2005-2020

- **GP Visits**:
  - Based on the Health Insurance Registry (SSSY) for the years 2005-2020
  - Includes only in-person GP visits as defined by Nielsen (2019)
  - Excludes email and telephone consultations

Labor Market Outcomes

- We define collectively exhaustive and mutually exclusive labor market attachment groups:
  1. Employment
  2. Unemployment benefits
  3. Disability pension
  4. Transfers (cash benefits, student grants, etc.)
  5. Pension (VERP, OAP, self-support)

Descriptive Statistics: Women Descriptive Statistics: Men

Methods

Estimation Strategy

We estimate a linear regression model relating genetic risk for AD to labor and health outcomes:

$$Y_{iat} = G_i^C \delta + X_{ia}\theta + \pi_a + \rho_t + \epsilon_{iat}$$

where:

- Y_{iat} is the health or labor market outcome for individual i, at age a, and year t
- G_i^C is the genetic risk measure for AD (APOE-e4 or polygenic risk score) of individual i's child
- X_{ia} is a vector of observable exogenous characteristics
- π_a is an age fixed effect
- ρ_t is a year fixed effect
- ϵ_{iat} is the residual error term

Spurious Associations with Other Genes

Genetic predisposition for AD may correlate with genetic predisposition to other phenotypes

Key Points:

- Principal components are included in the model to avoid spurious associations with other genes (control for population stratification)
- The polygenic score (PGS) for EA is known to correlate with labor earnings, raising concerns about confounding between AD risk and EA

Results:

- No clear relationship between AD PGS and EA PGS
- Distribution of AD PGS is similar between iPSYCH control and non-control groups

Bias in APOE Estimations

Child's genotype used as a proxy for parent's genotype introduces measurement error

Bias Magnitude:

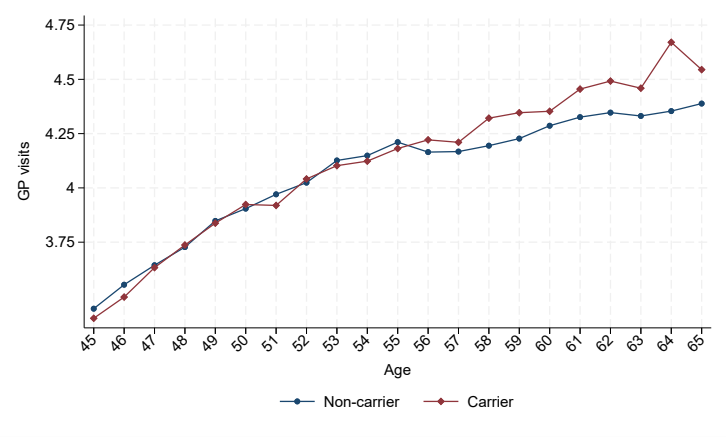
$$\begin{aligned}\text{True Effect} &\approx \text{Estimated Effect} \times \frac{1 - P(D = 1)}{P(D = 1|D^* = 1) - P(D = 1)} \\ &= \text{Estimated Effect} \times 2.19\end{aligned}$$

- $P(D = 1)$ is the probability of being a carrier (homogeneous or heterogeneous)
- $P(D = 1|D^* = 1)$ is the probability of a child being a carrier given that the parent is a carrier

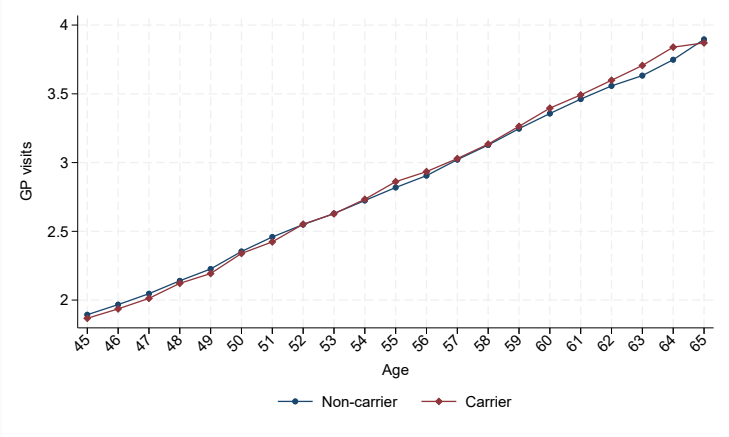
Can roughly double the estimated effects to account for the measurement error

Results

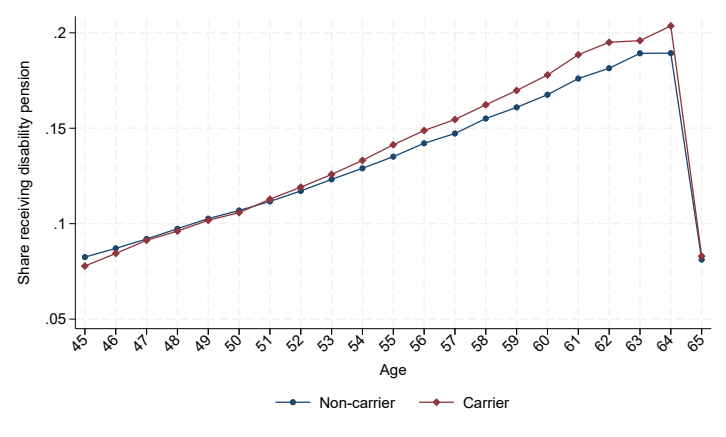
Carrier Status, GP Visits, and Disability



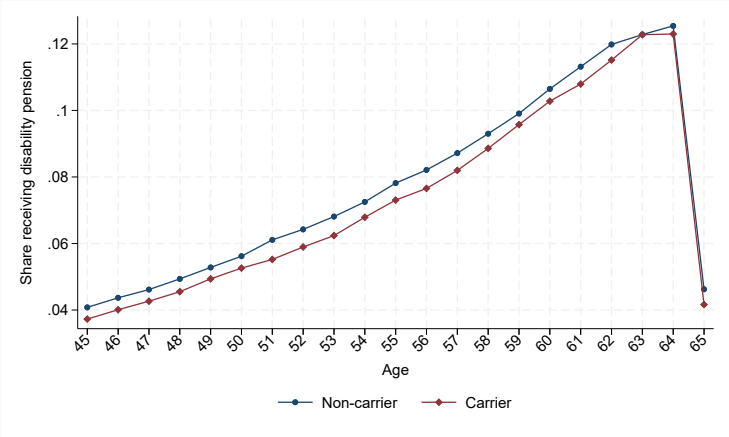
(a) Women: GP visits



(b) Men: GP visits



(c) Women: Disability Status



(d) Men: Disability Status

APOE-e4 Carrier Status and Health Outcomes

	Dementia		GP visits	
	Age 45-65	Age 55-65	Age 45-65	Age 55-65
	(1)	(2)	(3)	(4)
Panel A: Women				
APOE-e4 Carrier	0.00016***	0.00035***	0.03496	0.09410***
	(0.00004)	(0.00010)	(0.02265)	(0.03399)
N	106,374	61,992	106,374	61,992
Pct. Change	91.40	93.91	0.81	2.16
Panel B: Men				
APOE-e4 Carrier	0.00008**	0.00018**	0.01978	0.05163*
	(0.00004)	(0.00008)	(0.02046)	(0.02981)
N	99,993	66,369	99,993	66,369
Pct. Change	44.44	52.93	0.65	1.51

Key Take-Aways: Health Outcomes

Dementia Risk: APOE-e4 carrier status significantly increases the risk of dementia

- Women (age 45-65): 91% increase in risk
- Men (age 45-65): 44% increase in risk
- Robust to using AD PGS AD PGS

GP Visits: Genetic risk of AD associated with GP visits

- Consistent with an incapacitation story
- But could also reflect health costs of care-taking

APOE-e4 Status and Labor Market Attachment: Women

	Employment	Unemployment	DP	Transfers	Pension
	(1)	(2)	(3)	(4)	(5)
Panel A: Age 45-65					
APOE-e4 Carrier	-0.00342*	-0.00031	0.00390**	0.00036	-0.00052
	(0.00183)	(0.00050)	(0.00176)	(0.00105)	(0.00087)
$N \times$ *Years*	1,005,275	1,005,275	1,005,275	1,005,275	1,005,275
N	105,896	105,896	105,896	105,896	105,896
R^2	0.364	0.007	0.308	0.061	0.212
Mean	0.75	0.02	0.12	0.06	0.05
Pct. Change	-0.46	-1.31	3.15	0.58	-1.14
Panel B: Age 55-65					
APOE-e4 Carrier	-0.00716**	0.00037	0.00769***	0.00013	-0.00103
	(0.00290)	(0.00074)	(0.00272)	(0.00126)	(0.00179)
$N \times$ *Years*	360,716	360,716	360,716	360,716	360,716
N	61,814	61,814	61,814	61,814	61,814
R^2	0.346	0.007	0.335	0.037	0.253
Mean	0.68	0.02	0.16	0.04	0.10
Pct. Change	-1.05	1.70	4.88	0.30	-1.06

Key Takeaways for Labor Market Outcomes: Women

Employment and Disability Pension:

- Women aged 45-65:
  - Significant but small employment effects
  - Effects of DP (equal and opposite) $\approx$ 3%
  - Suggests a 1-1 shift from work to DP
- Women aged 55-65 - larger effects:
  - Larger employment effects
  - Similar but larger DP effects $\approx$ 5%
- Robust to using PGS

APOE-e4 Status and Labor Market Attachment: Men

	Employment	Unemployment	DP	Transfers	Pension
	(1)	(2)	(3)	(4)	(5)
Panel A: Age 45-65					
APOE-e4 Carrier	0.00063	0.00050	-0.00122	-0.00028	0.00036
	(0.00183)	(0.00059)	(0.00150)	(0.00087)	(0.00090)
$N \times$ *Years*	940,718	940,718	940,718	940,718	940,718
N	98,560	98,560	98,560	98,560	98,560
R^2	0.251	0.013	0.187	0.051	0.166
Mean	0.81	0.03	0.07	0.04	0.05
Pct. Change	0.08	1.78	-1.69	-0.72	0.71
Panel B: Age 55-65					
APOE-e4 Carrier	-0.00124	0.00076	-0.00054	0.00014	0.00088
	(0.00276)	(0.00081)	(0.00223)	(0.00105)	(0.00167)
$N \times$ *Years*	407,980	407,980	407,980	407,980	407,980
N	65,436	65,436	65,436	65,436	65,436
R^2	0.240	0.011	0.196	0.038	0.189
Mean	0.75	0.03	0.09	0.03	0.09
Pct. Change	-0.16	2.76	-0.57	0.43	0.97

Cognitive Reserve Theory

Cognitive reserve: the brain's ability to withstand greater levels of damage without showing symptoms of cognitive decline

- Higher educational attainment is associated with cognitive reserve

Grossman's Health Capital Model (1972): higher education increases the productivity of health investment

$\Rightarrow$ cognitive decline will happen from a higher level

- To test the theory, we use the EA-PGS and interact it with *APOE-e4* carrier status

Cognitive Reserve Theory: Women (Age 55–65)

	Employment	Disability Pension	Earnings	Wealth
	(1)	(2)	(3)	(4)
APOE-e4 Carrier	-0.00742**	0.00800***	-879.31	-13,490.20
	(0.00290)	(0.00274)	(1,372.18)	(8,573.90)
EA PGS	0.01457***	-0.01099***	6,033.66***	93,725.60***
	(0.00169)	(0.00154)	(805.94)	(5,169.71)
APOE-e4 $\times$ EA PGS	0.00351	-0.00480*	323.59	-8,303.47
	(0.00290)	(0.00274)	(1,405.29)	(8,918.78)
$N \times$ *Years*	360,716	360,716	382,779	382,779
N	61,814	61,814	62,063	62,063
R^2	0.347	0.336	0.500	0.098
Mean	0.68	0.16	284,489.22	432,197.07
Pct. Change (Carrier)	-1.09	5.08	-0.31	-3.12
Pct. Change (EA PGS)	2.14	-6.97	2.12	21.69
Pct. Change (Interaction)	0.51	-3.05	0.11	-1.92

Conclusions

Summing Up

- **Health Outcomes**
  - Women (aged 55-65): dementia $\approx$ 94% and GP visits $\approx$ 2.16%
  - Men (aged 55-65): dementia $\approx$ 53% and GP visits $\approx$ 1.5%
- **Labor Market Outcomes**
  - Women with higher genetic risk of AD:
    - Less likely to be employed
    - More likely to receive disability pensions
  - For men, no employment effects

Summing Up

- **Cognitive Reserve Theory**
  - Weak evidence for women (DP)
- **So What?**
  - We highlight additional productivity costs from AD that are felt well before retirement
  - Most studies on the effects of “health shocks” on economic outcomes use very large acute shocks e.g. hospital admissions (Dobkin, et al. 2018)
  - We estimate labor effects from a very slow degenerative disease around the peak of the life-cycle

Descriptive Statistics: Women

	Women aged 45 to 65		Women aged 55 to 65	
	Mean	SD	Mean	SD
Homogeneous carrier	0.03	0.17	0.03	0.17
Heterogeneous carrier	0.28	0.45	0.28	0.45
Age	52.45	5.22	58.62	2.89
Married	0.61	0.49	0.62	0.49
Control group (iPSYCH)	0.34	0.47	0.33	0.47
Lower sec., primary, unknown	0.24	0.43	0.25	0.44
General upper secondary	0.04	0.20	0.04	0.18
Vocational education	0.37	0.48	0.33	0.47
Short cycle tertiary	0.04	0.19	0.04	0.19
Bachelor	0.25	0.43	0.27	0.45
Master, doctoral	0.06	0.25	0.07	0.25
Experience	20.03	9.53	22.74	10.68
Year	2013.75	4.32	2015.46	3.75
GP visits	4.33	4.70	4.35	4.74
Dementia	0.00	0.01	0.00	0.02
Employment	0.75	0.44	0.68	0.47
Unemployment	0.02	0.15	0.02	0.15
Disability Pension	0.12	0.33	0.16	0.36
Other Transfers	0.06	0.24	0.04	0.20
Pension	0.05	0.21	0.10	0.30
Earnings (DKK)	309,881.21	230,492.19	285,356.46	238,635.23
Income from Shares (DKK)	1,390.93	7,483.68	1,897.33	8,596.73
Disposable Income (DKK)	287,963.68	117,021.56	286,304.43	120,902.28
Net Wealth (DKK)	277,004.38	871,114.50	432,520.27	972,974.69
$N \times$ *Years*	1,123,485		375,336	
N	106,374		61,992	

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Descriptive Statistics: Men

	Men aged 45 to 65		Men aged 55 to 65	
	Mean	SD	Mean	SD
Homogeneous carrier	0.03	0.17	0.03	0.17
Heterogeneous carrier	0.28	0.45	0.28	0.45
Age	53.40	5.50	59.04	3.01
Married	0.66	0.47	0.68	0.47
Control group (iPSYCH)	0.35	0.48	0.34	0.47
Lower sec., primary, unknown	0.25	0.44	0.25	0.44
General upper secondary	0.04	0.20	0.04	0.20
Vocational education	0.44	0.50	0.42	0.49
Short cycle tertiary	0.05	0.22	0.04	0.20
Bachelor	0.13	0.34	0.14	0.35
Master, doctoral	0.09	0.29	0.10	0.30
Experience	23.24	9.65	25.05	10.78
Year	2013.23	4.42	2014.49	4.14
GP visits	3.03	4.23	3.43	4.51
Dementia	0.00	0.01	0.00	0.02
Employment	0.81	0.39	0.75	0.43
Unemployment	0.03	0.17	0.03	0.16
Disability Pension	0.07	0.26	0.09	0.29
Other Transfers	0.04	0.19	0.03	0.18
Pension	0.05	0.22	0.09	0.29
Earnings (DKK)	418,762.20	330,770.13	375,798.13	330,229.50
Income from Shares (DKK)	8,471.34	38,478.96	9,238.66	39,879.88
Disposable Income (DKK)	354,849.90	209,190.83	354,381.95	212,788.61
Net Wealth (DKK)	507,119.12	1,496,333.75	712,262.50	1,635,967.50
$N \times$ *Years*	1,084,496		440,274	
N	99,993		66,369	

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AD PGS and Health Outcomes

	Dementia		GP visits	
	Age 45-65	Age 55-65	Age 45-65	Age 55-65
	(1)	(2)	(3)	(4)
Panel A: Women				
AD PGS	0.00007***	0.00016***	0.01031	0.02040
	(0.00002)	(0.00005)	(0.01045)	(0.01583)
N	106,374	61,992	106,374	61,992
Pct. Change	43.31	43.54	0.24	0.47
Panel B: Men				
AD PGS	0.00004**	0.00009**	0.01164	0.03286**
	(0.00002)	(0.00004)	(0.00963)	(0.01385)
N	99,993	66,369	99,993	66,369
Pct. Change	23.87	27.08	0.38	0.96