

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1: Field IDs Used in Analyses

52	Month of birth
31	Sex
189	Townsend deprivation index at recruitment
34	Year of birth
54	UK Biobank assessment centre
6138	Qualifications
21000	Ethnic background
3659	Year immigrated to UK (United Kingdom)
738	Average total household income before tax
21001	Body mass index (BMI)
21003	Age when attended assessment centre
53	Date of attending assessment centre
20018	Prospective memory result
20016	Fluid intelligence score centre
2178	Overall health rating
22009	Genetic principal components
884	Number of days/week of moderate physical activity 10+ minutes
130836	Date F00 first reported (dementia in alzheimer's disease)
130837	Source of report of F00 (dementia in alzheimer's disease)
130838	Date F01 first reported (vascular dementia)
130839	Source of report of F01 (vascular dementia)
130840	Date F02 first reported (dementia in other diseases classified elsewhere)
130841	Source of report of F02 (dementia in other diseases classified elsewhere)
130842	Date F03 first reported (unspecified dementia)
130843	Source of report of F03 (unspecified dementia)
131036	Date G30 first reported (alzheimer's disease)
131037	Source of report of G30 (alzheimer's disease)
42018	Date of all cause dementia report
42019	Source of all cause dementia report
42020	Date of alzheimer's disease report
42021	Source of alzheimer's disease report
42022	Date of vascular dementia report
42023	Source of vascular dementia report
42024	Date of frontotemporal dementia report
42025	Source of frontotemporal dementia report
25010	Volume of brain, grey+white matter
25009	Volume of brain, grey+white matter (normalised for head size)

25019	Volume of hippocampus (left)
25020	Volume of hippocampus (right)
26521	Volume of EstimatedTotalIntraCranial (whole brain)
46	Hand grip strength (left)
47	Hand grip strength (right)
42040	GP clinical event records
42039	GP prescription records
42038	GP registration records
25781	Total volume of white matter hyperintensities (from T1 and T2_FLAIR images)
4079	Diastolic blood pressure, automated reading
94	Diastolic blood pressure, manual reading
4080	Systolic blood pressure, automated reading
93	Systolic blood pressure, manual reading

eTable 2: Read Codes for Dementia Diagnoses

'F110.', 'XaIKB', 'XaIKC', 'Eu00.', 'X002x', 'X002x', 'X002x', 'X002x', 'X002x', 'X002x', 'X002x', 'X002x', 'X0030', 'X0030', 'X0030', 'X0030', 'X0030', 'X0030', 'Eu00.', 'X0030', 'X0030', 'Eu002', 'Eu00z', 'Eu00z', 'Fyu30', 'XE1Xs', 'Xa0IH', 'E0040', 'E0041', 'E0042', 'E0043', 'E004z', 'XE1Xs', 'XE1Xs', 'XE1Xs', 'X003R', 'Xa0IH', 'Xa0IH', 'Xa0IH', 'X003T', 'X003V', 'Eu01y', 'Eu01z', 'F21y2', 'F21y2', 'XaIRJ', 'Eu020', 'F111.', 'A411.', 'F11x7', 'E011.', 'E011.', 'E011.', 'E011.', 'E0111', 'E0112', 'E011z', 'XE1Xu', 'X00Rk', 'E0120', 'Eu021', 'XabVp', 'XabVp', 'Eu022', 'Eu023', 'X003P', 'X003P', 'XaOfZ', 'Eu106', 'Eu106', 'Eu106', 'E000.', 'E001.', 'E0010', 'E0011', 'E0012', 'E0013', 'E001z', 'E002.', 'E0020', 'E0021', 'E002z', 'E003.', 'XE1Xt', 'X00R0', 'E00z.', 'E041.', 'E04y.', 'Eu02.', 'XaKyY', 'Eu02y', 'X003A', 'XE1Z6', 'XE1Z6', 'E00z.', 'E00z.', 'Eu02z', 'Xa1GB', 'Eu02z', 'X00R2', 'XE1Z6', 'E00z.', 'Eu02z', 'XE1Xr', 'Eu041', 'F112.', 'F10y.', 'F10y0', 'F10y1', 'XaPws', 'F10yz', 'X0037', 'F11..', 'X003m', 'F11yz', 'Fyu31', 'XE1Xr', 'X00R2', 'X002w', '1461.', 'XaaeA', 'XaJBU', 'XaJBV', 'XaJBW', 'XaJBX', 'XaMJC', 'XaMGF', 'XabtQ', 'Xaefu', 'Xaefv', 'XaaiW', 'XacLx', 'XabEI', 'XaaBZ', 'XacIx', 'XacIy', 'XacIz', 'XacJ0', 'XabEk', 'XaYFR', 'XabEi', 'XacM2', 'XaLff', 'XaLfo', 'XaLFp', 'XaMFy', 'XaMG0', 'XaMGG', 'XaMGI', 'XaMGJ', 'XaMGK') OR read_2 IN ('F110.', 'F1100', 'F1101', 'Eu00.', 'Eu000', 'Eu001', 'Eu002', 'Eu00z', 'Fyu30', 'E004.', 'E0040', 'E0041', 'E0042', 'E0043', 'E004z', 'Eu01.', 'Eu010', 'Eu011', 'Eu012', 'Eu013', 'Eu01y', 'Eu01z', 'F21y2', 'G678.', 'Eu020', 'F111.', 'A411.', 'F11x7', 'E011.', 'E0110', 'E0111', 'E0112', 'E011z', 'E012.', 'E0120', 'Eu021', 'A4110', 'Eu022', 'Eu023', 'Eu024', 'F11x9', 'Eu106', 'E000.', 'E001.', 'E0010', 'E0011', 'E0012', 'E0013', 'E001z', 'E002.', 'E0020', 'E0021', 'E002z', 'E003.', 'E00y.', 'E00z.', 'E041.', 'E04y.', 'Eu02.', 'Eu025', 'Eu02y', 'F116.', 'Eu02z', 'Eu041', 'F112.', 'F10y.', 'F10y0', 'F10y1', 'F10y2', 'F10yz', 'F118.', 'F11y.', 'F11y2', 'F11yz', 'Fyu31', 'E00.', '1461.', '38C13', '3AE3.', '3AE4.', '3AE5.', '3AE6.', '66h.', '6AB.', '8BM02', '8BM50', '8BM60', '8BPa.', '8CMe0', '8CMG2', '8CMZ.', '8CMZ0', '8CMZ1', '8CMZ2', '8CMZ3', '8CSA.', '8Hla.', '8IAe0', '8IAe2', '9hD.', '9hD0.', '9hD1.', '9Ou.', '9Ou1.', '9Ou2.', '9Ou3.', '9Ou4.', '9Ou5.'

eMethods: Primary Outcomes

Cognitive Outcomes. Fluid intelligence, a 13-item task of problem-solving requiring logic and reasoning ability, was evaluated using a touch screen at UKB assessment center visits.¹³ This measure was available for all participants. Prospective Memory, a type of episodic memory, measures an individual's memory for future tasks and was assessed via touchscreen. Prior to other cognitive assessments, participants were given an instruction that they were later asked to recall after other cognitive assessments were complete (i.e., “At the end of the games we will show you four coloured shapes and ask you to touch the Blue Square. However, to test your memory, we want you to actually touch the Orange Circle instead”). Three possible scores are obtained: 0- Instruction not recalled, either skipped or incorrect; 1 - correct recall on first attempt; 2 - correct recall on second attempt. Values were coded as 1 for correct on the first attempt, and 0 otherwise.

Incident Dementia. Dementia diagnosis was ascertained using a combination of diagnoses obtained from primary care, hospital inpatient, death registered records, and self-report. Algorithmically defined dementia and First Occurrences Dementia and primary care records were merged. Only individuals with a confirmed primary care linkage were included in analyses with this outcome. We used the date of diagnosis at the earliest date of dementia codes recorded, irrespective of the source used. Similar merging with primary care records was performed for Alzheimer's disease and vascular dementia. Primary care records we queried with the following ICD10 and ICD9 codes for dementia, Alzheimer's disease, and vascular dementia . Dementia: F02, F03, G31, 331.0, 294.1, and 294.8, plus codes for Alzheimer's disease and vascular dementia. Alzheimer's disease: F00, G30, and 331.0. Vascular dementia: F01, and 290.4. Participant time in years was calculated from the date of handgrip strength assessment until the date of dementia diagnosis, date of loss to follow-up, date of death, censoring (December 4, 2020), or updating date of HGS.

Neuroimaging Outcomes. We utilized global and regional brain Imaging Derived Phenotypes (IDPs) provided by the UK Biobank brain imaging team. Details on imaging acquisition and the imaging processing are available elsewhere.¹³ The neuroimaging outcomes of interest for this study included: Total brain volume (TBV), defined as the sum of white and grey matter independent of cerebrospinal fluid, was ascertained using T1 structural brain MRI. (Analyses of TBV normalized for head size (Field 25009) are included in the appendix.) Hippocampal Volume was assessed using the T1 structural brain MRI. Main analyses consider total hippocampal volume while sensitivity analyses consider the right and left hippocampus separately. White matter hyperintensity volume (WMH) was ascertained using T1-weighted and T2 FLAIR volumes structural brain MRI (field 25781). Main analyses used total brain volume and hippocampal volume scaled by intracranial volume, such that scaled volume is given by crude volume divided by intracranial volume times mean intracranial volume. Appendix 3 provides results of these analyses using crude volumes. Given known differences in head size, we report all gender-stratified model results normalized for intracranial volume in Figure 4 and non-normalized results in the Appendix 4.

eMethods: Covariate Categorizations

Collapsed Race/Ethnicity Categories

White: British, White, Irish, Any other white background

Black: Black or Black British, White and Black Caribbean, White and Black African, African, Caribbean, Any other Black background

Asian: Asian or Asian British, Chinese, Indian, Pakistani, Bangladeshi, Any other Asian background

Mixed/Other: Mixed, Any other mixed background, Other ethnic group

High School or Equivalent Educational Categories

College or University degree

A levels/AS levels or equivalent

NVQ or HND or HNC or equivalent

Other professional qualifications e.g.: nursing, teaching

A levels/AS levels or equivalent

eMethods: Statistical Modeling Approach

Cox proportional hazard models were used to determine the relative hazard of dementia associated with decreased HGS, accounting for repeated HGS measures. Death, as obtained from the death registry data, was considered a competing event. Cox proportional hazard assumptions were met for all-cause dementia models at a significance threshold of 0.05 (see Appendix X).¹⁹ Stratification variables were selected in order to meet the proportionality assumption, which included stratification by age decile (all models), number of APOE-e4 alleles, and race (confounder and full models), and quartile of systolic blood pressure (full model). Overall health rating (good and excellent vs. other categories) and assessment centre (London area vs. other areas) were dichotomized due to no dementia diagnosis events within some strata of those variables. We employed generalized linear or logistic mixed effects models to examine the association between HGS and cognitive outcomes and MRI volumetric measures. All mixed effects models included a random intercept and fixed slope and adjusted for age and age squared as orthogonal polynomials.

eTable 3: Missingness in First Visit for the Entire Sample

	Total (N=497965)
No GP Registration	271152 (54.5%)
Missing HGS at BL	0 (0%)
Missing Assessment Center	0 (0%)
Missing TDI	614 (0.1%)
Missing Race	2365 (0.5%)
Missing Education	4238 (0.9%)
Missing APOE-e4	14016 (2.8%)
Missing Age	0 (0%)
Missing BMI	1183 (0.2%)
Missing Physical Activity	26465 (5.3%)
Missing Overall Health Rating	542 (0.1%)
Missing SBP	33364 (6.7%)
Missing Gender	0 (0%)

Additional Summaries of Sample Characteristics

eTable 4: Demographic Characteristics Among Individuals Completing Cognitive Testing

	Women (N=82363)	Men (N=71034)	Total (N=153397)
	Mean (SD) or N(%)	Mean (SD) or N(%)	Mean (SD) or N(%)
Age	56.43 (8.1)	57.00 (8.3)	56.69 (8.2)
High School Equivalent			
Yes	54373 (66.0%)	50142 (70.6%)	104515 (68.1%)
No	27990 (34.0%)	20892 (29.4%)	48882 (31.9%)
Race			
Asian	2745 (3.3%)	2876 (4.0%)	5621 (3.7%)
Black	2478 (3.0%)	1705 (2.4%)	4183 (2.7%)
Mixed	1322 (1.6%)	862 (1.2%)	2184 (1.4%)
White	75818 (92.1%)	65591 (92.3%)	141409 (92.2%)
BMI	26.94 (5.1)	27.78 (4.2)	27.33 (4.7)
Townsend Deprivation Index	-1.20 (2.9)	-1.17 (3.0)	-1.18 (2.9)
Days per week of moderate physical activity	3.79 (2.3)	3.69 (2.3)	3.75 (2.3)
Systolic blood pressure	138.03 (20.4)	142.98 (18.5)	140.32 (19.7)
Overall health rating			
Prefer not to answer	25 (0.0%)	25 (0.0%)	50 (0.0%)
Do not know	238 (0.3%)	190 (0.3%)	428 (0.3%)
Excellent	12473 (15.1%)	9769 (13.8%)	22242 (14.5%)
Good	49826 (60.5%)	40146 (56.5%)	89972 (58.7%)
Fair	16559 (20.1%)	17297 (24.4%)	33856 (22.1%)
Poor	3242 (3.9%)	3607 (5.1%)	6849 (4.5%)
APOE-e4 Carrier			
Yes	23138 (28.1%)	19911 (28.0%)	43049 (28.1%)
No	59225 (71.9%)	51123 (72.0%)	110348 (71.9%)
Baseline HGS	24.49 (6.3)	40.63 (8.9)	31.97 (11.1)

eTable 5: Demographic Characteristics Among Individuals With Neuroimaging Measures

	Women (N=20204)	Men (N=18439)	Total (N=38643)
	Mean (SD) or N(%)	Mean (SD) or N(%)	Mean (SD) or N(%)
Age	54.31 (7.4)	55.66 (7.6)	54.95 (7.5)
High School Equivalent			
Yes	15794 (78.2%)	15298 (83.0%)	31092 (80.5%)
No	4410 (21.8%)	3141 (17.0%)	7551 (19.5%)
Race			
Asian	238 (1.2%)	315 (1.7%)	553 (1.4%)
Black	183 (0.9%)	126 (0.7%)	309 (0.8%)
Mixed	150 (0.7%)	101 (0.5%)	251 (0.6%)
White	19633 (97.2%)	17897 (97.1%)	37530 (97.1%)
BMI	25.98 (4.5)	27.07 (3.7)	26.50 (4.2)
Townsend Deprivation Index	-1.87 (2.7)	-1.96 (2.7)	-1.91 (2.7)
Days per week of moderate physical activity	3.55 (2.3)	3.42 (2.2)	3.49 (2.3)
Systolic blood pressure	133.14 (19.1)	140.50 (17.4)	136.65 (18.7)
Overall health rating			
Prefer not to answer	4 (0.0%)	1 (0.0%)	5 (0.0%)
Do not know	26 (0.1%)	20 (0.1%)	46 (0.1%)
Excellent	5021 (24.9%)	4248 (23.0%)	9269 (24.0%)
Good	12411 (61.4%)	11079 (60.1%)	23490 (60.8%)
Fair	2406 (11.9%)	2777 (15.1%)	5183 (13.4%)
Poor	336 (1.7%)	314 (1.7%)	650 (1.7%)
APOE-e4 Carrier			
Yes	5680 (28.1%)	4971 (27.0%)	10651 (27.6%)
No	14524 (71.9%)	13468 (73.0%)	27992 (72.4%)
Baseline HGS	26.63 (6.1)	43.47 (8.5)	34.67 (11.2)

eTable 6: Demographic Characteristics Among Individuals With Gp Linkages, Stratified by Median HGS.

	Women		Men		Total	
	At or Above Median (N=51428)	Below Median (N=51307)	At or Above Median (N=45338)	Below Median (N=42333)	At or Above Median (N=96766)	Below Median (N=93640)
Age	54.01 (7.9)	58.53 (7.3)	54.87 (8.1)	58.67 (7.8)	54.42 (8.0)	58.59 (7.5)
High School Equivalent						
Yes	35740 (69.5%)	29369 (57.2%)	33017 (72.8%)	27539 (65.1%)	68757 (71.1%)	56908 (60.8%)
No	15688 (30.5%)	21938 (42.8%)	12321 (27.2%)	14794 (34.9%)	28009 (28.9%)	36732 (39.2%)
Race						
Asian	580 (1.1%)	1464 (2.9%)	598 (1.3%)	1626 (3.8%)	1178 (1.2%)	3090 (3.3%)
Black	847 (1.6%)	541 (1.1%)	591 (1.3%)	410 (1.0%)	1438 (1.5%)	951 (1.0%)
Mixed	424 (0.8%)	538 (1.0%)	285 (0.6%)	429 (1.0%)	709 (0.7%)	967 (1.0%)
White	49577 (96.4%)	48764 (95.0%)	43864 (96.7%)	39868 (94.2%)	93441 (96.6%)	88632 (94.7%)
BMI	26.86 (5.0)	27.24 (5.2)	27.95 (4.0)	27.77 (4.4)	27.37 (4.6)	27.48 (4.8)
Townsend Deprivation Index	-1.62 (2.8)	-1.30 (3.0)	-1.68 (2.9)	-1.12 (3.1)	-1.65 (2.8)	-1.22 (3.0)
Days per week of moderate physical activity	3.65 (2.3)	3.62 (2.4)	3.67 (2.3)	3.58 (2.4)	3.66 (2.3)	3.60 (2.4)
Systolic blood pressure	136.03 (19.9)	138.59 (20.4)	143.01 (18.0)	143.04 (19.0)	139.30 (19.3)	140.60 (19.9)
Overall health rating						
Prefer not to answer	9 (0.0%)	18 (0.0%)	7 (0.0%)	19 (0.0%)	16 (0.0%)	37 (0.0%)
Do not know	128 (0.2%)	199 (0.4%)	116 (0.3%)	163 (0.4%)	244 (0.3%)	362 (0.4%)
Excellent	10454 (20.3%)	6926 (13.5%)	8057 (17.8%)	5478 (12.9%)	18511 (19.1%)	12404 (13.2%)
Good	31682 (61.6%)	29998 (58.5%)	26426 (58.3%)	23140 (54.7%)	58108 (60.1%)	53138 (56.7%)

Fair	8009 (15.6%)	11492 (22.4%)	9232 (20.4%)	10698 (25.3%)	17241 (17.8%)	22190 (23.7%)
Poor	1146 (2.2%)	2674 (5.2%)	1500 (3.3%)	2835 (6.7%)	2646 (2.7%)	5509 (5.9%)
APOE-e4 Carrier						
Yes	14754 (28.7%)	14348 (28.0%)	12960 (28.6%)	11916 (28.1%)	27714 (28.6%)	26264 (28.0%)
No	36674 (71.3%)	36959 (72.0%)	32378 (71.4%)	30417 (71.9%)	69052 (71.4%)	67376 (72.0%)
Dementia Dx in Follow-Up						
Yes	358 (0.7%)	855 (1.7%)	427 (0.9%)	996 (2.4%)	785 (0.8%)	1851 (2.0%)
No	51070 (99.3%)	50452 (98.3%)	44911 (99.1%)	41337 (97.6%)	95981 (99.2%)	91789 (98.0%)

Regression Coefficients for a 5-kg Decrement in Hand-Grip Strength

Note: All tables give results for models 1, 2, and 3 in the corresponding columns.

eTable 7: Gender-stratified linear regression coefficients for a 5-kg decrement in hand-grip strength and fluid intelligence and prospective memory.

	Model 1	Model 2	Model 3
Men: Fluid Intelligence	-0.028 (-0.032, -0.024)	-0.006 (-0.010, -0.002)	-0.007 (-0.010, -0.003)
	p < 0.001	p = 0.002	p = 0.0003
Observations	95,935	95,935	95,935
Women: Fluid Intelligence	-0.068 (-0.073, -0.064)	-0.047 (-0.051, -0.042)	-0.043 (-0.047, -0.038)
	p < 0.001	p < 0.001	p < 0.001
Observations	108,002	108,002	108,002
Men: Prospective Memory	0.876 (0.867, 0.886)	0.912 (0.902, 0.922)	0.910 (0.900, 0.921)
	p < 0.001	p < 0.001	p < 0.001
Observations	98,502	98,502	98,502
Women: Prospective Memory	0.851 (0.839, 0.864)	0.880 (0.867, 0.894)	0.888 (0.874, 0.901)
	p < 0.001	p < 0.001	p < 0.001
Observations	110,609	110,609	110,609

eTable 8: Gender-Stratified Hazard Ratios for the Association Between Handgrip Strength and Incident All-Cause, Alzheimer, and Vascular Dementia.

	Model 1	Model 2	Model 3
Men: All-Cause Dementia	1.18 (1.14, 1.21)	1.16 (1.12, 1.20)	1.14 (1.10, 1.18)
	p < 0.001	p < 0.001	p < 0.001
Observations	100,384	100,384	100,384
Women: All-Cause Dementia	1.17 (1.12, 1.23)	1.14 (1.09, 1.20)	1.10 (1.05, 1.15)
	p = 0. p < 0.001	p < 0.001	p < 0.001
Observations	115,787	115,787	115,787
Men: Alzheimer's Disease	1.11 (1.06, 1.17)	1.11 (1.05, 1.16)	1.10 (1.04, 1.15)
	p < 0.001	p < 0.001	p < 0.001
Observations	100,384	100,384	100,384
Women: Alzheimer's Disease	1.15 (1.07, 1.24)	1.13 (1.05, 1.21)	1.10 (1.02, 1.18)
	p < 0.001	p = 0.002	p = 0.02
Observations	115,787	115,787	115,787
Men: Vascular Dementia	1.24 (1.17, 1.32)	1.23 (1.15, 1.31)	1.20 (1.12, 1.28)
	p < 0.001	p < 0.001	p < 0.001
Observations	100,384	100,384	100,384
Women: Vascular Dementia	1.24 (1.11, 1.39)	1.20 (1.07, 1.35)	1.12 (1.00, 1.26)
	p < 0.001	p = 0.002	p = 0.06
Observations	115,787	115,787	115,787

eTable 9: Linear Regression Coefficients for the Association of a 5-kg Decrement in Handgrip Strength With Normalized and Nonnormalized Total Brain, Hippocampal, and White Matter Hyperintensity Volume, Stratified by Gender. *TBV: total brain volume; HV: hippocampal volume; HVR: hippocampal volume, right; HVL: hippocampal volume, left; WMHI: white matter hyperintensity volume.*

	Model 1	Model 2	Model 3
Men: Crude TBV	-5,879.71 (-6,731.46, -5,027.95)	-5,163.70 (-6,012.91, -4,314.48)	-5,110.34 (-5,966.62, -4,254.07)
	p < 0.001	p < 0.001	p < 0.001
Observations	18,438	18,438	18,438
Women: Crude TBV	-7,064.74 (-8,088.62, -6,040.87)	-6,760.95 (-7,794.56, -5,727.34)	-6,747.66 (-7,791.96, -5,703.35)
	p < 0.001	p < 0.001	p < 0.001
Observations	20,204	20,204	20,204
Men: Normalized TBV	-255.20 (-660.49, 150.09)	-223.67 (-630.73, 183.38)	-322.42 (-732.56, 87.72)
	p = 0.22	p = 0.29	p = 0.13
Observations	18,438	18,438	18,438
Women: Normalized TBV	630.19 (111.71, 1,148.67)	329.23 (-196.28, 854.73)	296.09 (-235.73, 827.91)
	p = 0.02	p = 0.22	p = 0.28
Observations	20,204	20,204	20,204
Men: Normalized HV	3.97 (-3.90, 11.84)	0.27 (-7.68, 8.23)	-0.64 (-8.67, 7.39)
	p = 0.33	p = 0.95	p = 0.88
Observations	18,438	18,438	18,438
Women: Normalized HV	13.74 (3.90, 23.57)	9.35 (-0.70, 19.40)	10.27 (0.10, 20.43)
	p = 0.01	p = 0.07	p = 0.05
Observations	20,204	20,204	20,204

	Model 1	Model 2	Model 3
Men: Crude HV	-33.20 (-41.12, -25.29)	-32.44 (-40.44, -24.44)	-32.34 (-40.42, -24.26)
	p < 0.001	p < 0.001	p < 0.001
Observations	18,438	18,438	18,438
Women: Crude HV	-39.12 (-48.32, -29.92)	-39.33 (-48.70, -29.95)	-38.27 (-47.76, -28.79)
	p < 0.001	p < 0.001	p < 0.001
Observations	20,204	20,204	20,204
Men: Crude HVL	-17.37 (-21.75, -13.00)	-16.94 (-21.37, -12.51)	-17.13 (-21.60, -12.66)
	p < 0.001	p < 0.001	p < 0.001
Observations	18,438	18,438	18,438
Women: Crude HVL	-17.12 (-22.23, -12.01)	-17.11 (-22.31, -11.90)	-16.80 (-22.07, -11.53)
	p < 0.001	p < 0.001	p < 0.001
Observations	20,204	20,204	20,204
Men: Crude HVR	-15.83 (-20.37, -11.30)	-15.51 (-20.10, -10.92)	-15.22 (-19.86, -10.58)
	p < 0.001	p < 0.001	p < 0.001
Observations	18,438	18,438	18,438
Women: Crude HVR	-21.98 (-27.14, -16.82)	-22.21 (-27.47, -16.95)	-21.46 (-26.79, -16.14)
	p < 0.001	p < 0.001	p < 0.001
Observations	20,204	20,204	20,204
Men: Normalized HVL	1.12 (-3.21, 5.46)	-0.63 (-5.02, 3.75)	-1.30 (-5.72, 3.13)
	p = 0.62	p = 0.78	p = 0.57
Observations	18,438	18,438	18,438
Women: Normalized HVL	8.96 (3.46, 14.46)	6.90 (1.27, 12.52)	7.18 (1.49, 12.88)
	p = 0.002	p = 0.02	p = 0.02
Observations	20,204	20,204	20,204

	Model 1	Model 2	Model 3
Men: Normalized HVR	2.85 (-1.56, 7.25)	0.91 (-3.55, 5.37)	0.66 (-3.84, 5.17)
	p = 0.21	p = 0.70	p = 0.78
Observations	18,438	18,438	18,438
Women: Normalized HVR	4.77 (-0.65, 10.19)	2.45 (-3.10, 7.99)	3.07 (-2.54, 8.69)
	p = 0.09	p = 0.39	p = 0.29
Observations	20,204	20,204	20,204
Men: WMHI	23.19 (-37.12, 83.50)	49.42 (-11.67, 110.51)	92.22 (31.09, 153.35)
	p = 0.46	p = 0.12	p = 0.004
Observations	18,438	18,438	18,438
Women: WMHI	41.32 (-26.99, 109.63)	72.46 (2.78, 142.14)	83.56 (13.54, 153.58)
	p = 0.24	p = 0.05	p = 0.02
Observations	20,204	20,204	20,204

eTable 10: Age Less Than 65: Gender-Stratified Linear Regression Coefficients for a 5-kg Decrement in Hand-Grip Strength and Fluid Intelligence and Prospective Memory.

	Model 1	Model 2	Model 3
Men: Fluid Intelligence	-0.025 (-0.029, -0.021)	-0.002 (-0.007, 0.002)	-0.004 (-0.008, 0.001)
	p < 0.001	p = 0.266	p = 0.085
Observations	67,472	67,472	67,472
Women: Fluid Intelligence	-0.073 (-0.078, -0.067)	-0.050 (-0.055, -0.045)	-0.046 (-0.051, -0.041)
	p < 0.001	p < 0.001	p < 0.001
Observations	82,031	82,031	82,031
Men: Prospective Memory	0.870 (0.858, 0.881)	0.913 (0.901, 0.926)	0.911 (0.899, 0.924)
	p < 0.001	p < 0.001	p < 0.001
Observations	69,028	69,028	69,028
Women: Prospective Memory	0.843 (0.829, 0.858)	0.878 (0.862, 0.893)	0.883 (0.868, 0.899)
	p < 0.001	p < 0.001	p < 0.001
Observations	83,701	83,701	83,701

eTable 11: Age Less Than 65: Linear Regression Coefficients for the Association of a 5-kg Decrement in Handgrip Strength With Normalized and Nonnormalized Total Brain, Hippocampal, and White Matter Hyperintensity Volume, Stratified by Gender. *TBV*: total brain volume; *HV*: hippocampal volume; *HVR*: hippocampal volume, right; *HVL*: hippocampal volume, left; *WMHI*: white matter hyperintensity volume.

	Model 1	Model 2	Model 3
Men: Crude TBV	-5,951.13 (-6,857.86, -5,044.40)	-5,219.49 (-6,123.92, -4,315.07)	-5,138.99 (-6,051.61, -4,226.38)
	p < 0.001	p < 0.001	p < 0.001
Observations	16,088	16,088	16,088
Women: Crude TBV	-6,991.77 (-8,063.81, -5,919.72)	-6,694.68 (-7,776.43, -5,612.92)	-6,669.55 (-7,763.02, -5,576.08)
	p < 0.001	p < 0.001	p < 0.001
Observations	18,475	18,475	18,475
Men: Normalized TBV	-237.75 (-671.22, 195.72)	-205.72 (-641.81, 230.37)	-331.53 (-771.12, 108.06)
	p = 0.29	p = 0.36	p = 0.14
Observations	16,088	16,088	16,088
Women: Normalized TBV	805.56 (267.24, 1,343.87)	482.38 (-63.86, 1,028.63)	426.62 (-126.26, 979.50)
	p = 0.004	p = 0.09	p = 0.14
Observations	18,475	18,475	18,475

	Model 1	Model 2	Model 3
Men: Normalized HV	3.84 (-4.44, 12.11)	0.26 (-8.12, 8.64)	-0.77 (-9.23, 7.70)
	p = 0.37	p = 0.96	p = 0.86
Observations	16,088	16,088	16,088
Women: Normalized HV	16.92 (6.78, 27.05)	12.31 (1.94, 22.67)	13.35 (2.86, 23.84)
	p = 0.002	p = 0.02	p = 0.02
Observations	18,475	18,475	18,475
Men: Crude HV	-34.08 (-42.43, -25.73)	-33.10 (-41.55, -24.65)	-32.73 (-41.27, -24.19)
	p < 0.001	p < 0.001	p < 0.001
Observations	16,088	16,088	16,088
Women: Crude HV	-37.00 (-46.56, -27.44)	-37.31 (-47.06, -27.56)	-35.93 (-45.80, -26.06)
	p < 0.001	p < 0.001	p < 0.001
Observations	18,475	18,475	18,475
Men: Crude HVL	-17.76 (-22.39, -13.13)	-17.17 (-21.86, -12.49)	-17.18 (-21.92, -12.45)
	p < 0.001	p < 0.001	p < 0.001
Observations	16,088	16,088	16,088
Women: Crude HVL	-16.04 (-21.36, -10.72)	-16.05 (-21.48, -10.62)	-15.64 (-21.14, -10.14)
	p < 0.001	p < 0.001	p < 0.001
Observations	18,475	18,475	18,475
Men: Crude HVR	-16.33 (-21.12, -11.54)	-15.93 (-20.78, -11.08)	-15.55 (-20.46, -10.65)
	p < 0.001	p < 0.001	p < 0.001
Observations	16,088	16,088	16,088
Women: Crude HVR	-20.94 (-26.30, -15.58)	-21.25 (-26.72, -15.78)	-20.29 (-25.83, -14.74)
	p < 0.001	p < 0.001	p < 0.001
Observations	18,475	18,475	18,475

	Model 1	Model 2	Model 3
Men: Normalized HVL	1.09 (-3.48, 5.66)	-0.57 (-5.20, 4.06)	-1.25 (-5.93, 3.43)
	p = 0.65	p = 0.81	p = 0.60
Observations	16,088	16,088	16,088
Women: Normalized HVL	10.61 (4.91, 16.31)	8.46 (2.63, 14.30)	8.76 (2.85, 14.66)
	p < 0.001	p = 0.005	p = 0.004
Observations	18,475	18,475	18,475
Men: Normalized HVR	2.75 (-1.89, 7.39)	0.84 (-3.87, 5.54)	0.49 (-4.26, 5.24)
	p = 0.25	p = 0.73	p = 0.84
Observations	16,088	16,088	16,088
Women: Normalized HVR	6.30 (0.71, 11.89)	3.83 (-1.89, 9.56)	4.58 (-1.21, 10.38)
	p = 0.03	p = 0.19	p = 0.13
Observations	18,475	18,475	18,475
Men: WMHI	18.30 (-37.03, 73.62)	38.87 (-17.22, 94.97)	81.29 (25.21, 137.37)
	p = 0.52	p = 0.18	p = 0.005
Observations	16,088	16,088	16,088
Women: WMHI	66.28 (2.15, 130.42)	90.85 (25.40, 156.30)	102.21 (36.48, 167.95)
	p = 0.05	p = 0.01	p = 0.003
Observations	18,475	18,475	18,475

eTable 12: Age 65 and Older: Gender-Stratified Linear Regression Coefficients for a 5-kg Decrement in Hand-Grip Strength and Fluid Intelligence and Prospective Memory.

	Model 1	Model 2	Model 3
Men: Fluid Intelligence	-0.037 (-0.044, -0.030)	-0.014 (-0.020, -0.007)	-0.013 (-0.020, -0.007)
	p < 0.001	p < 0.001	p = 0.0002
Observations	28,463	28,463	28,463
Women: Fluid Intelligence	-0.063 (-0.073, -0.054)	-0.040 (-0.049, -0.031)	-0.037 (-0.046, -0.027)
	p < 0.001	p < 0.001	p < 0.001
Observations	25,971	25,971	25,971
Men: Prospective Memory	0.892 (0.875, 0.909)	0.910 (0.892, 0.929)	0.911 (0.892, 0.929)
	p < 0.001	p < 0.001	p < 0.001
Observations	29,474	29,474	29,474
Women: Prospective Memory	0.875 (0.851, 0.899)	0.890 (0.864, 0.916)	0.900 (0.874, 0.926)
	p < 0.001	p < 0.001	p < 0.001
Observations	26,908	26,908	26,908

eTable 13: Age 65 and Older: Gender-Stratified Hazard Ratios for a 5-kg Decrement in Hand-Grip Strength and Incident All-Cause, Alzheimer, and Vascular Dementia.

	Model 1	Model 2	Model 3
Men: All-Cause Dementia	1.16 (1.12, 1.21)	1.15 (1.10, 1.20)	1.14 (1.09, 1.19)
	p < 0.001	p < 0.001	p < 0.001
Observations	24,287	24,287	24,287
Women: All-Cause Dementia	1.14 (1.06, 1.21)	1.12 (1.05, 1.20)	1.08 (1.01, 1.15)
	p = 0.0002	p = 0.001	p = 0.04
Observations	23,242	23,242	23,242
Men: Alzheimer's Disease	1.10 (1.03, 1.18)	1.10 (1.03, 1.18)	1.10 (1.02, 1.18)
	p = 0.004	p = 0.01	p = 0.02
Observations	24,287	24,287	24,287
Women: Alzheimer's Disease	1.15 (1.04, 1.26)	1.13 (1.03, 1.25)	1.10 (1.00, 1.22)
	p = 0.005	p = 0.02	p = 0.05
Observations	23,242	23,242	23,242
Men: Vascular Dementia	1.18 (1.09, 1.28)	1.18 (1.09, 1.28)	1.17 (1.07, 1.28)
	p = 0.0001	p = 0.0002	p = 0.0004
Observations	24,287	24,287	24,287
Women: Vascular Dementia	1.17 (1.02, 1.35)	1.14 (0.99, 1.32)	1.08 (0.94, 1.25)
	p = 0.03	p = 0.07	p = 0.29
Observations	23,242	23,242	23,242

eTable 14: Age 65 and Older: Linear Regression Coefficients for the Association of a 5-kg Decrement in Handgrip Strength With Normalized and Nonnormalized Total Brain, Hippocampal, and White Matter Hyperintensity Volume, Stratified by Gender. *TBV*: total brain volume; *HV*: hippocampal volume; *HVR*: hippocampal volume, right; *HVL*: hippocampal volume, left; *WMHI*: white matter hyperintensity volume.

	Model 1	Model 2	Model 3
Men: Crude TBV	-5,249.93 (-7,749.19, -2,750.67)	-4,533.32 (-7,033.07, -2,033.56)	-4,684.67 (-7,201.14, -2,168.21)
	p = 0.0001	p = 0.0004	p = 0.0003
Observations	2,350	2,350	2,350
Women: Crude TBV	-7,997.20 (-11,446.90, -4,547.49)	-7,359.67 (-10,909.58, -3,809.76)	-7,385.65 (-10,954.15, -3,817.16)
	p = 0.0000	p = 0.0001	p = 0.0001
Observations	1,729	1,729	1,729
Men: Normalized TBV	-388.77 (-1,533.93, 756.40)	-237.01 (-1,378.18, 904.16)	-121.27 (-1,270.09, 1,027.55)
	p = 0.51	p = 0.69	p = 0.84
Observations	2,350	2,350	2,350
Women: Normalized TBV	-1,482.83 (-3,383.00, 417.34)	-1,540.45 (-3,477.77, 396.88)	-1,258.34 (-3,216.14, 699.46)
	p = 0.13	p = 0.12	p = 0.21
Observations	1,729	1,729	1,729

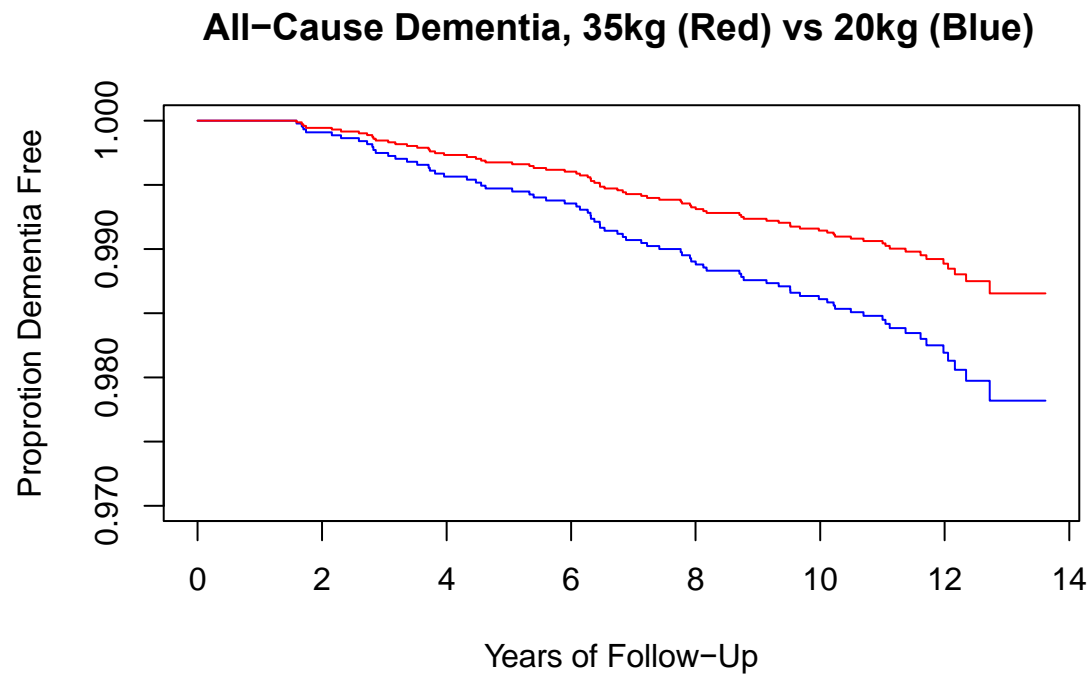
	Model 1	Model 2	Model 3
Men: Normalized HV	5.52 (-19.50, 30.53)	1.94 (-23.24, 27.11)	2.60 (-22.76, 27.95)
	p = 0.67	p = 0.89	p = 0.85
Observations	2,350	2,350	2,350
Women: Normalized HV	-23.30 (-61.95, 15.35)	-19.76 (-59.44, 19.92)	-20.87 (-60.97, 19.23)
	p = 0.24	p = 0.33	p = 0.31
Observations	1,729	1,729	1,729
Men: Crude HV	-25.32 (-49.90, -0.75)	-25.21 (-50.12, -0.30)	-26.23 (-51.36, -1.10)
	p = 0.05	p = 0.05	p = 0.05
Observations	2,350	2,350	2,350
Women: Crude HV	-64.01 (-97.69, -30.34)	-56.15 (-90.68, -21.62)	-59.02 (-93.94, -24.11)
	p = 0.0002	p = 0.002	p = 0.001
Observations	1,729	1,729	1,729
Men: Crude HVL	-13.90 (-27.22, -0.57)	-13.86 (-27.39, -0.34)	-14.74 (-28.39, -1.09)
	p = 0.05	p = 0.05	p = 0.04
Observations	2,350	2,350	2,350
Women: Crude HVL	-29.56 (-47.73, -11.39)	-25.57 (-44.19, -6.94)	-26.81 (-45.65, -7.98)
	p = 0.002	p = 0.01	p = 0.01
Observations	1,729	1,729	1,729
Men: Crude HVR	-11.43 (-25.46, 2.61)	-11.35 (-25.59, 2.90)	-11.49 (-25.87, 2.88)
	p = 0.12	p = 0.12	p = 0.12
Observations	2,350	2,350	2,350
Women: Crude HVR	-34.43 (-53.18, -15.67)	-30.56 (-49.91, -11.22)	-32.19 (-51.75, -12.64)
	p = 0.0004	p = 0.002	p = 0.002
Observations	1,729	1,729	1,729

	Model 1	Model 2	Model 3
Men: Normalized HVL	1.61 (-11.89, 15.10)	-0.13 (-13.75, 13.50)	-0.12 (-13.84, 13.61)
	p = 0.82	p = 0.99	p = 0.99
Observations	2,350	2,350	2,350
Women: Normalized HVL	-10.03 (-30.74, 10.68)	-7.98 (-29.23, 13.28)	-8.28 (-29.76, 13.19)
	p = 0.35	p = 0.47	p = 0.45
Observations	1,729	1,729	1,729
Men: Normalized HVR	3.89 (-10.04, 17.82)	2.05 (-12.00, 16.10)	2.71 (-11.44, 16.85)
	p = 0.59	p = 0.78	p = 0.71
Observations	2,350	2,350	2,350
Women: Normalized HVR	-13.28 (-34.48, 7.91)	-11.79 (-33.65, 10.08)	-12.60 (-34.69, 9.50)
	p = 0.22	p = 0.30	p = 0.27
Observations	1,729	1,729	1,729
Men: WMHI	55.97 (-245.23, 357.17)	130.11 (-174.84, 435.07)	178.70 (-126.32, 483.72)
	p = 0.72	p = 0.41	p = 0.26
Observations	2,350	2,350	2,350
Women: WMHI	-238.23 (-653.51, 177.04)	-121.82 (-553.63, 309.99)	-116.93 (-550.69, 316.82)
	p = 0.27	p = 0.59	p = 0.60
Observations	1,729	1,729	1,729

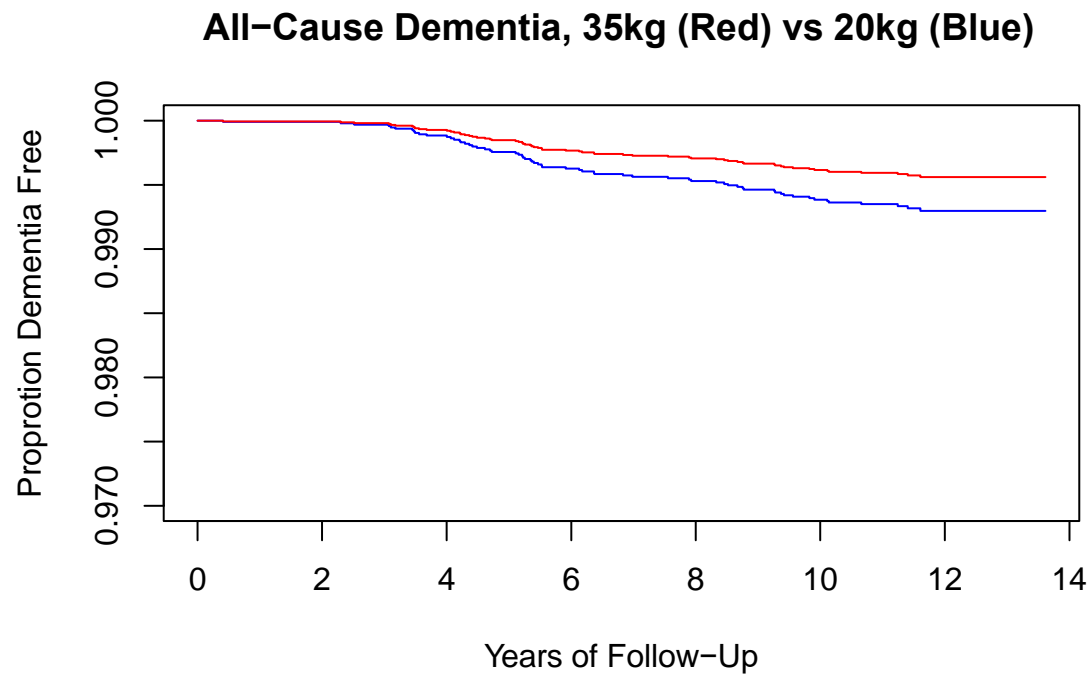
eTable 15: Gender-Stratified Hazard Ratios for the Association Between Handgrip Strength and Incident All-Cause Dementia Including Whether Job Involves Manual Labor as a Confounder in Models 2 and 3. Extent of manual labor was classified as always, usually, sometimes, and rarely/never (field 816). Model 1 with the same number of observations as complete case counts used for models 2 and 3 is given for comparison.

	Model 1	Model 2	Model 3
Men: All-Cause Dementia	1.14 (1.07, 1.21)	1.12 (1.05, 1.19)	1.11 (1.04, 1.18)
	p = 0.0001	p = 0.001	p = 0.003
Observations	58,291	58,291	58,291
Women: All-Cause Dementia	1.14 (1.02, 1.27)	1.13 (1.01, 1.27)	1.11 (0.99, 1.24)
	p = 0.02	p = 0.03	p = 0.08
Observations	61,522	61,522	61,522

eFigure 1. Example Kaplan-Meier Curves for All-Cause Dementia for the 5th Age-Decile in Men

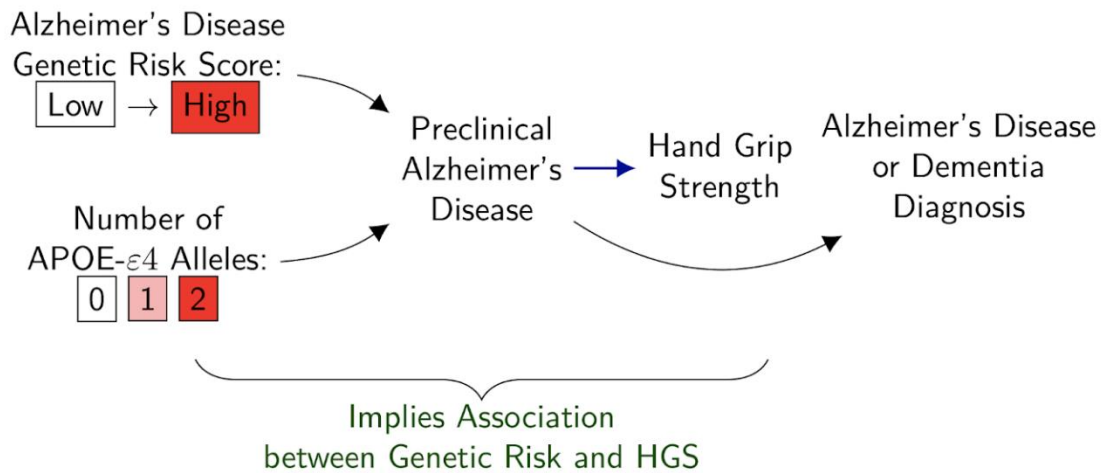


eFigure 2. Example Kaplan-Meier Curves for All-Cause Dementia for the 5th Age-Decile in Women

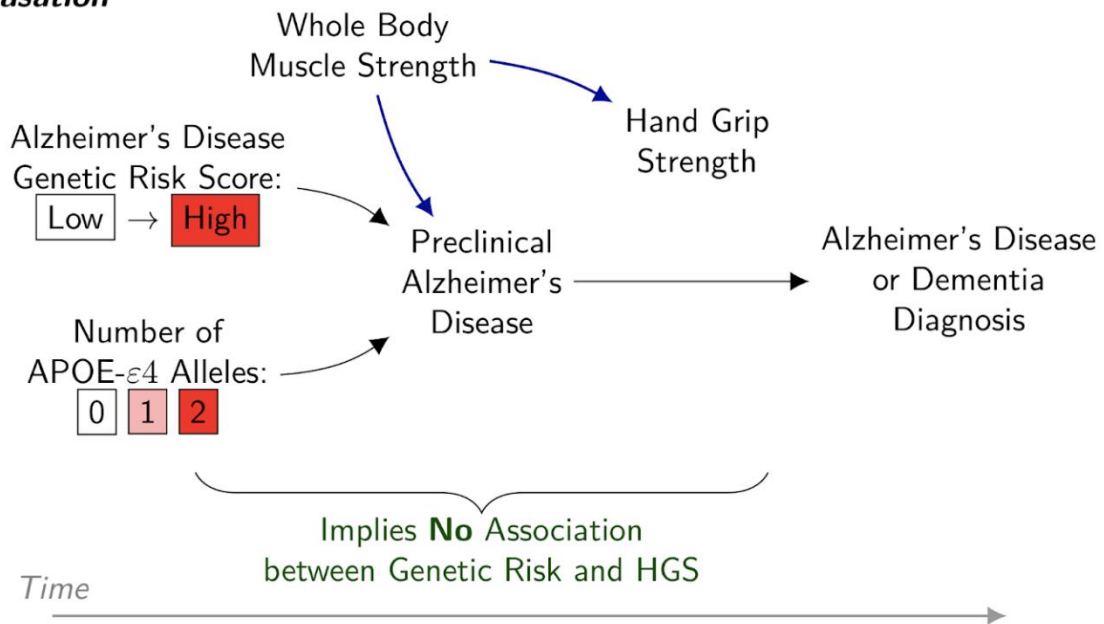


eFigure 3: Reverse Causation Schematic

**Reverse
Causation**



Causation



eTable 16: Associations Between Polygenetic Risk Score (PGS), APOE-e4 Alleles And Handgrip Strength Stratified by Gender and Age.

	Men under 65	Women under 65	Men under 65	Women under 65	Men 65+	Women 65+	Men 65+	Women 65+
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
PGS Score (+SD increase)	0.012	0.020			-0.016	-0.028		
	(-0.029, 0.054)	(-0.006, 0.046)			(-0.082, 0.050)	(-0.077, 0.020)		
	p = 0.564	p = 0.125			p = 0.638	p = 0.250		
APOE-e4 (+Allele)			-0.029	0.010			-0.019	-0.110*
			(-0.111, 0.052)	(-0.040, 0.060)			(-0.148, 0.111)	(-0.204, -0.016)
			p = 0.480	p = 0.696			p = 0.776	p = 0.022
Observations	179,994	221,349	179,994	221,349	61,376	60,369	61,376	60,369