

# Supplementary Material

## The Construction of a Multidomain Risk Model of Alzheimer's Disease and Related Dementias

**Supplementary Table 1. Study Measures**

Variable	Values	Definition
<b>Claims-based diagnoses</b>		International Classification of Disease 9th Edition
<i>Alzheimer's disease</i>	0 before onset;	331.0
<i>Alzheimer's disease-related dementia</i>	1 after onset; date of onset based on the date of the associated claim.	331.0 331.11 331.19 331.2x 331.7x 797.xx 290.0x-290.3x 290.10-290.13 290.20 290.21 290.40-290.43 294.0x 294.2x 294.8x 294.10 294.11
<i>Myocardial infarction</i>		410.xx-412.xx
<i>Angina pectoris</i>		413.xx
<i>Heart failure</i>		428.xx
<i>Valvular heart disease</i>		746.xx
<i>Rheumatic heart disease</i>		393.xx-398.xx
<i>Arterial hypertension</i>		401.xx-405.xx
<i>Cardiac arrhythmias</i>		427.xx
<i>Ischemic stroke</i>		433.xx-435.xx
<i>Hemorrhagic stroke</i>		430.xx-432.xx
<i>Other cerebrovascular diseases</i>		436.xx-438.xx
<i>Systemic hypotension</i>		458.xx
<i>Chronic kidney disease</i>		581.xx-583.xx 585.xx-588.xx
<i>Chronic obstructive pulmonary disease</i>		490.xx-496.xx
<i>Diabetes mellitus</i>		250.xx
<i>Thyroid dysfunction</i>		240.xx-246.xx
<i>Metabolic syndrome</i>		277.7x
<i>Obstructive sleep apnea</i>		327.23
<i>Depression</i>		311.xx 300.4x 309.0x 309.1x 296.2x 296.3x 296.5x 298.0x V79.0x 309.28 301.12
<i>Traumatic brain injury</i>		800.xx-804.xx 850.xx-854.xx
<i>Chronic liver disease</i>		571.xx 572.2.x-572.4x 573.xx
<i>Solid malignant tumors</i>		14x.xx-19x.xx
<i>Nonsolid cancer</i>		20x.xx
<i>Cancer, unspecified</i>		235.xx-239.xx
<b>Self-reported diseases</b>		Has a doctor ever (since the last interview) told you that you have...
<i>Alzheimer's disease/Dementia</i>	0 before onset; 1 after onset;	...a memory-related disease such as Alzheimer's or Dementia?
<i>Hypertension</i>	date of onset	...high blood pressure or hypertension?
<i>Heart diseases</i>	based on the date of the	...heart attack, coronary heart disease, angina, congestive heart failure or other heart problems?

<i>Stroke</i>	associated	...stroke or transient ischemic attack?
<i>Lung diseases</i>	interview.	...chronic lung disease except asthma such as chronic bronchitis or emphysema?
<i>Cancer</i>		...cancer or a malignant tumor of any kind except skin cancer?
<i>Diabetes mellitus</i>		...diabetes or high blood sugar?
<i>Arthritis</i>		...arthritis or rheumatism?
<i>Psychiatric disorder</i>		...emotional, nervous, or psychiatric problems?
<i>Back pain</i>		...back pain?
<b>Number of ADL limitations;</b>	(0-5)	Because of a health or memory problem do you have any difficulty with...
<i>Bathing</i>	0 before onset;	...bathing or showering?
<i>Eating</i>	1 after onset;	...eating, such as cutting up your food?
<i>Dressing</i>	date of onset	...dressing, including putting on sock and shoes?
<i>Walk across room</i>	based on the	...walking across a room?
<i>Getting out of bed</i>	date of the	...getting in or out of bed?
	associated	
	interview.	
<b>Number of IADL limitation</b>	(0-5)	Because of a health or memory problem do you have any difficulty with...
<i>Use of telephone</i>	0 before onset;	...making phone calls?
<i>Taking medication</i>	1 after onset;	...taking medication?
<i>Handling money</i>	date of onset	...managing your money, such as paying your bills and keeping track of expenses?
	based on the	...shopping for groceries?
<i>Shopping</i>	date of the	...preparing a hot meal?
<i>Preparing a meal</i>	associated	
	interview.	
<b>Score on the CESD scale</b>	(0-8)	Much of the time during the past week, you felt...
<i>Depressed</i>	0 before onset;	...depressed.
<i>Effort</i>	1 after onset;	...that everything you did was an effort.
<i>Sleep</i>	date of onset	...your sleep was restless?
<i>Loneliness</i>	based on the	...felt lonely.
<i>Feeling Sad</i>	date of the	...felt sad.
<i>Low Energy</i>	associated	...could not get going.
<i>Happy</i>	interview when	...felt happy (inverted).
<i>Enjoying Life</i>	condition was	...enjoyed life (inverted).
	reported as	
	"most of the	
	time"	
<b>Other Health Issues</b>		
<i>Hearing Problems</i>	0 or 1	Individual reports fair or poor hearing.
<i>Vision Problems</i>	0 or 1	Individual reports fair or poor vision.
<i>Current smoker</i>	0 or 1	Individual reports smoking at time of interview.
<i>Past smoker</i>	0 or 1	Individual reports (has reported) smoking during his/her lifetime.
<i>Heavy alcohol consumption</i>	0 or 1	Individual reports consuming more than 21 alcoholic beverages per week.
<i>Lack of physical activity</i>	0 or 1	Individual reports that he/she does not engage in vigorous physical activity.
<i>Body Mass Index</i>	continuous	
<i>Obese</i> >=30	0 or 1	Body mass index>=30.
<i>Underweight</i> <18.5	0 or 1	Body mass index<18.5.
<i>Disability</i>	0 or 1	Individual reports receiving social security disability insurance.

**Socioeconomics**

<i>Social isolation</i>	0 or 1	Volunteers (including helping friends and neighbors) zero times a year <b>AND</b> interacts with family less than once a month in a year;
<i>Married</i>	0 or 1	Individual reports being married or living with partner.
<i>Lost Spouse</i>	0 or 1	Individual reports being divorced, separated, or widowed.
<i>No high school degree</i>	0 or 1	Individual reports no high school diploma/GED.
<i>College education</i>	0 or 1	Individual reports at least some college education.
<i>Low income</i>	0 or 1	Reported household income <\$15,579.95 in 2010 dollars
<i>Low wealth</i>	0 or 1	Reported household wealth <\$54,638.95 in 2010 dollars
<i>Female sex</i>	0 or 1	Individual reports being biologically female.
<i>Black Race</i>	0 or 1	Individual reports identifying as Black.

**Environmental**

<i>Particulate matter</i>	continuous	Zip-level annual concentration of fine particulate matter in $\mu\text{g}/\text{m}^3$ averaged for 2000-2015.
<i>Ozone</i>	continuous	Zip-level annual concentration of ozone in parts per billion averaged for 2000-2015.
<i>Nitrogen dioxide</i>	continuous	Zip-level annual concentration of nitrogen dioxide in parts per billion averaged for 2000-2015.

**Genetic**

<i>PRS Amyl_React Pathway</i>	continuous	
<i>PRS Apopt_PosReg_GO Pathway</i>	continuous	
<i>PRS Apopt_NegReg_GO Pathway</i>	continuous	
<i>PRS NDea_NegReg_GO Pathway</i>	continuous	
<i>PRS Tau_Liter Pathway</i>	continuous	
<i>PRS Reactome_Dopa Pathway</i>	continuous	Constructed using HRS genetic data using SNPs from respective pathway (Supplementary Table s2) with p-value<0.01, and excluding SNPs associated with APOE
<i>PRS Nsig_KEGG Pathway</i>	continuous	
<i>PRS Reactome_Neuro_Receptor Pathway</i>	continuous	
<i>PRS Mitoch Pathway</i>	continuous	
<i>PRS BioMitoch Pathway</i>	continuous	
<i>PRS Infl_Hallm Pathway</i>	continuous	
<i>PRS Ninfl+ Pathway</i>	continuous	
<i>PRS (HRS, v.4, no APOE)</i>	continuous	PRS provided by HRS; constructed using all SNPs excluding SNPs associated with APOE
<i>PRS (HRS, 0.01 v.4, no APOE)</i>	continuous	PRS provided by HRS; constructed using SNPs with p-value<0.01 excluding SNPs associated with APOE
<i>PRS (HRS, v.4, with APOE)</i>	continuous	PRS provided by HRS; constructed using all SNPs
<i>PRS (HRS, 0.01 v.4, with APOE)</i>	continuous	PRS provided by HRS; constructed using SNPs with p-value<0.01
<i>rs12539172</i>		
<i>rs3851179</i>		
<i>rs405509 (APOE)</i>		
<i>rs769449 (APOE)</i>	Ordinal (0, 1, or 2)	Provided by HRS genetic data.
<i>rs2075650 (TOMM40)</i>		
<i>rs8106922 (TOMM40)</i>		
<i>rs6859 (NECTIN2)</i>		
<i>rs157580 (TOMM40)</i>		
<i>rs4311</i>		

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## **Supplementary Table 2. Genes Representing Pathways Relevant to AD/ADRD**

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### **Amyloid signaling [Amyl\_React]**

"HIST4H4 HIST2H3C HIST3H2BB CST3 FGA HIST1H2BA GSN HIST1H2AE HIST1H2AD H2AFX H2AFZ HIST1H2BD HIST1H2BB H3F3A H3F3B APCS HSPG2 HIST2H3A APOA1 IAPP H3F3AP5 APP INS LTF LYZ MFGE8 NPPA ODAM HIST2H4B PRL B2M SAA1 SEMG H3F3AP6 HIST2H3D SNCA TGFBI HIST2H2AA4 TTR LOC728320 LOC731820 CALCA HIST1H4I HIST1H2AJ HIST1H2AC HIST1H2AB HIST2H2AA3 HIST2H2AC HIST1H2BG HIST1H2BL HIST1H2BN HIST1H2BM HIST1H2BF HIST1H2BE HIST1H2BH HIST1H2BI HIST1H2BC HIST1H2BO HIST2H2BE HIST1H3A HIST1H3D HIST1H3C HIST1H3E HIST1H3I HIST1H3G HIST1H3J HIST1H3H HIST1H3B HIST1H4A HIST1H4D HIST1H4F HIST1H4K HIST1H4J HIST1H4C HIST1H4H HIST1H4B HIST1H4E HIST1H4L HIST2H4A HIST1H2BK HIST1H3F HIST1H2BJ ITM2B"

### **Positive regulation of neuronal apoptosis [Apopt\_PosReg\_GO]**

CASP3 EPHA7 CASP2 CDC42 CDK5R1 PAK3 DDIT3 CTNNB1 FBXW7 MAP2K7 MAP3K11 GRIK5 CCL3 HDAC4 ITGA1 ATF2 PIN1 FASLG CASP9 NQO1 TGFB2 PARK2 JUN PMAIP1 BAX ASCL1 AGER PCSK9 PAWR TFAP2A GSK3B AIFM1 CDK5 ATF4 MCL1 RAPSN FOXO3 SRPK2 GRIK2 TFAP2B ATM NF1 CDC34 BBC3 UBE2M BCL2L1 TP53

### **Negative regulation of neuronal apoptosis [Apopt\_NegReg\_GO]**

EN2 AMBRA1 AXL NONO LIG4 FAM134B DLX1 CHL1 DNAJC5 CORO1A NTRK2 ISL1 NR4A2 NTRK1 HIPK2 ILK STAR NGFR CLCF1 KIF14 TYRO3 MTNR1B FOXB1 XRCC2 CNTF NR4A3 ZNF259 PSEN1 TGFB3 NES GRIK2 CCL2 GPI FYN HYOU1 BAX CRLF1 SIX4 KRAS OXR1 FGF8 NAIP TP73 TOX3 MSH2 GABRB3 BHLHB9 VSTM2L ITSN1 SET CEBPB NTF3 PIN1 STXBP1 TFAP2D MT3 JUN HIF1A C5AR1 LRP1 RASA1 FAIM2 UNC5B SOD2 PPARGC1A GCLM CNTFR SYNGAP1 POU4F1 PPT1 WFS1 STAMBP KDM2B EPOR HMOX1 NRBP2 MAP2K4 ERBB3 LGMN AGAP2 NRP1 BCL2L1 BARHL1 ADAM8 BTG2 SNCA ALKBH1 MEF2C EN1 ANGPT1 NEFL PTK2B BDNF PIK3CA BRAF SOD1 NDNF NTF4 PINK1 JAK2 GCLC MAP3K12 HSP90AB1 TFAP2B CITED1 GABRB2 GFRAL CLN3 SNCB C1orf187 GDNF MECP2 GDF5 ROCK1 VEGFB PARK7 CPEB4 CACNA1A SIX1 PRKCG HRAS AARS PARK2 NGF GRIN1 PRKCI ADNP F2R PRDX2 MDK UBE2V2 GABRA5 BCL2 PCP4

### **Negative regulation of neuronal death [NDea\_NegReg\_GO]**

PSEN1 TGFB3 ZNF259 NR4A3 GRIK2 NES CNTF AKT1 FYN HYOU1 IKBKG C12orf5 CCL2 GPI SIX4 OXR1 KRAS PM20D1 BAX CRLF1 CREB1 ATF4 TOX3 CHMP4B TP73 NAIP PPP5C FGF8 VSTM2L GABRB3 BHLHB9 SET ITSN1 MSH2 TFAP2D JUN MT3 NTF3 CEBPB PIN1 IL13 STXBP1 RASA1 LRP1 FAIM2 HIF1A C5AR1 UNC5B SOD2 AMBRA1 HDAC7 EN2 GNB2L1 FAM134B DLX1 NONO AXL LIG4 NTRK2 CORO1A ISL1 DNAJC5 CHL1 NR4A2 STAR ILK STAT3 HIPK2 NTRK1 KIF14 TYRO3 PSMC1 BTBD10 REL NGFR CLCF1 FOXB1 XRCC2 MTNR1B CCL5 TRAF2 GABRB2 CITED1 HSP90AB1 TFAP2B MAP3K12 GCLC SIRT1 EPO CLN3 SNCB GFRAL IL6 GDNF C1orf187 GDF5 ROCK1 CDK5 SERPINF1 VEGFB MECP2 PARK7 HRAS AARS PARK2 NGF CPEB4 PRKCG SIX1 CACNA1A F2R GRIN1 ADNP PRKCI BCL2 GABRA5 PCP4 PRDX2 UCN CSF3 UBE2V2 MDK IGF1 POU4F1 PPT1 CNTFR GCLM PPARGC1A SYNGAP1 EPOR HMOX1 WFS1 CD34 STAMBP KDM2B HTRA2 LRRK2 ERBB3 NRP1 BCL2L1 LGMN AGAP2 MAP2K4 ESR2 NRBP2 BTG2 C19orf6 ADAM8 BARHL1 MEF2C

SNCA ALKBH1 CTNNB1 ESR1 EN1 PPARA NEFL ANGPT1 SORL1 SOD1 BRAF NDNF  
PIK3CA BDNF PTK2B CHMP4A NTF4 PINK1 JAK2 CHGA

**Tau phosphorylation [Tau\_Liter]**

FYN GSK3B NGFR TXNIP TLR9 AMPK DUSP1 PPP2R4 SUMO1 NGF MAPK14 mTOR  
BDNF AKAP5 CALM1 DLG4 TSC1 TSC2 ATG7 RPS6KB1 PP1 PP2A AKT CDK5R1

**Dopamine release [Reactome\_Dopa]**

JUN FRS2 CALM2 CALM1 PDPK1 RPS6KA6 TP73 MAP3K5 RPS6KA5 BRAF MAP3K1  
MAP3K3 IKBKB ABL1 AKT1 SHC4 AKT2 NRAS AKT3 SH2B1 NFKB1 NFKBIB NFKBIA  
NFKBIE PIK3R5 MAPK14 NGFRAP1 MAPK12 RELA KRAS SHC3 TRAF6 NGF CALML5  
BDNF NGFR SH2B3 CSK CAMK4 YWHAB BCL2 CAMK2A CAMK2B CAMK2D FOXO3  
CAMK2G IRS2 SORT1 CALML3 CRK SH2B2 CRKL PLCG1 PLCG2 YWHAZ ARHGDIA  
CALM3 YWHAH ARHGDIB YWHAG YWHAE CDC42 SOS2 PTPN11 RAF1 SHC1 RIPK2  
RHOA BAD IRAK4 PRKCD MAPK9 MAPK10 MAGED1 MAPK11 MAP2K2 MAPK13  
MAP2K1 BAX MAP2K7 MAP2K5 RPS6KA2 RAPGEF1 RPS6KA3 GRB2 MAPK3  
RPS6KA4 MAPK7 KIDINS220 RAC1 SOS1 MAPK1 RPS6KA1 YWHAQ HRAS MAPK8  
PRDM4 MAPKAPK2 GSK3B PSEN1 NTF4 IRAK2 NTF3 IRAK1 RAP1A PIK3R3 RAP1B  
IRAK3 TP53 PIK3CA PIK3CB PIK3CD GAB1 FASLG SHC2 ATF4 IRS1 ZNF274 NTRK2  
PIK3CG IRS4 NTRK1 PIK3R1 PIK3R2 CALML6 NTRK3

**Neurotrophin signaling [Nsig\_KEGG]**

RIMS1 RAB3A SLC18A2 SNAP25 STX1A STXBP1 VAMP2 SYN1 SYN2 SYT1 SYN3

**Neurotransmitter receptor binding/synapse function [Reactome\_Neuro\_Receptor]**

AKAP9 CACNG3 CACNG2 GNB5 ADCY1 ADCY2 ADCY3 ADCY5 ADCY6 ADCY7  
CHRNA1 CHRNA2 CHRNA3 CHRNA4 CHRNA5 CHRNA7 ADCY8 CHRNB2 CHRNB3  
CHRNB4 CHRND CHRNE CHRNG ADCY9 AP2M1 AP2S1 CREB1 AP2A1 AP2A2 AP2B1  
DLG1 DLG3 ADCY4 EPB41L1 ARHGEF9 PLCB1 GABBR1 GABRA1 GABRA2 GABRA3  
GABRA4 GABRA5 GABRA6 GABRB1 GABRB2 GABRB3 GABRG2 GABRG3 GABRR1  
GABRR2 CACNG4 RPS6KA6 GNAI1 GNAI2 GNAI3 GNAL GNB1 GNB2 GNB3 GNG3  
GNG4 GNG5 GNG7 GNG10 GNG11 GNGT1 GNGT2 GRIA1 GRIA2 GRIA3 GRIA4 GRIK1  
GRIK2 GRIK3 GRIK4 GRIK5 GRIN1 GRIN2A GRIN2B GRIN2C GRIN2D HRAS KCNJ2  
KCNJ3 KCNJ4 KCNJ5 KCNJ6 KCNJ9 KCNJ10 KCNJ12 KCNJ15 KCNJ16 MDM2 MYO6  
NEFL NSF PDPK1 GNG13 PLCB2 PLCB3 GNG2 CHRNA9 PRKACB PRKCA PRKCB  
PRKCG MAPK1 GNG12 RAF1 RASGRF1 RASGRF2 CACNG8 GNB4 RPS6KA1 RPS6KA2  
RPS6KA3 RRAS LOC651907 BRAF LOC732445 CALM1 CALM2 CALM3 GRIP2 CAMK4  
CAMK2A CAMK2B CAMK2D NCALD CAMKK1 ACTN2 CHRNA6 CHRFAM7A GNG8  
PICK1 AKAP5 GABBR2

**Mitochondrial (dys)function [Mitoch]**

NFE2L2 DNM1L APE1 TFAM DNAJA3 HSPD1 HSPE1 CLPP YME1L1 TXN2 RCAN1  
HIGD1A

**Mitochondrial pathway, generic [BioMitoch]**

CASP9 CASP8 CASP7 BCL2 BID BIK BCL2L1 BIRC2 APAF1 BAX BIRC3 XIAP CASP6  
CASP3 DFFA DIABLO CYCS DFFB ENDOG BAK1 AIFM1

**Hallmark Inflammatory Response [Infl\_Hallm]**

CXCL10 CCL2 CCL5 FPR1 CCL20 IL1A IL8 CCL7 CCL22 CXCL11 CCR7 EDN1 CD40  
CXCL9 IL6 IL1B TLR2 IL1R1 CD69 ICAM1 CCRL2 AQP9 EREG C3AR1 GNA15 CMKLR1  
PTGER4 LIF IL15 NAMPT OPRK1 ITGB8 PTAFR ADM PLAUR NFKB1 INHBA OSM  
TNFSF10 TNFSF15 IFNGR2 EMR1 IL12B CSF1 CXCL6 TNFRSF9 LYN ACVR2A LDLR

BDKRB1 HRH1 F3 BST2 PTGIR CD55 CALCRL CSF3 GPR132 IL4R NLRP3 IL15RA  
ADORA2B GCH1 OLR1 PTGER2 CSF3R MYC RELA TNFAIP6 IL7R IL18 GABBR1 CD82  
TNFSF9 NMUR1 IL2RB TLR1 LPAR1 IRAK2 RIPK2 MMP14 P2RX7 SLC11A2 SELL  
P2RY2 ABCA1 FFAR2 PROK2 GNAI3 TACR1 SLC7A1 CDKN1A CYBB TIMP1 HBEGF  
SCARF1 EBI3 NFKBIA SRI SLC7A2 CCL17 TLR3 APLNR OSMR IL10RA PSEN1 GPR183  
ATP2B1 TNFRSF1B BEST1 GPC3 SCN1B ACVR1B HPN SEMA4D KLF6 CD48 CXCR6  
SLC1A2 GP1BA TAPBP RGS16 SLAMF1 LCK HIF1A AHR NMI RHOG TPBG NPFFR2  
IFNAR1 ICOSLG RASGRP1 IFITM1 KCNJ2 LY6E IL18R1 IL10 KCNA3 HAS2 DCBLD2  
LAMP3 VIP CD70 RGS1 SLC31A1 ADRM1 KCNMB2 SERPINE1 MXD1 AXL MEFV PVR  
CCL24 PDE4B LCP2 PDPN IRF7 MET ATP2A2 SLC31A2 FZD5 ITGA5 SGMS2 MARCO  
CD14 EIF2AK2 ROS1 ATP2C1 NDP BTG2 MSR1 PTPRE RNF144B PCDH7 SPHK1  
IL18RAP RTP4 RAF1 CHST2 ITGB3 KIF1B SELE NOD2 C5AR1 EMP3 CLEC5A TACR3  
SLC4A4 MEP1A SELS LTA PIK3R5 STAB1 IRF1 ICAM4 P2RX4 ABI1 CX3CL1 SLC28A2  
**Neuro-inflammation and myelin clearance [Ninfl\_plus]**  
CRP IL4 IL6 TGFB1 TNF LGALS3 CLU APOA1 CD68 CXCL1 CXCL8 CXCL10 GSPG4  
CLU2 TAK1 CD137 BAGE1 NRG1

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The genes were selected based on MSigDB (Molecular Signatures Database) online resource of annotated gene sets (<http://www.gsea-msigdb.org/gsea/msigdb/index.jsp>), as well as on the literature.

**Supplementary Table 3. Summary statistics**

<b>Variable</b>	<b>Alzheimer's Disease</b>	<b>Alzheimer's Disease Related Dementias</b>
<b>N</b>	8,094	8,084
<b>N AD/ADR</b>	375	919
<b>Follow-up duration (y)</b>	10.69 (4.83)	10.48 (4.81)
<b>Age at baseline, mean (STD)</b>	67.49 (3.98)	67.48 (3.97)
<b>Age at baseline, median (Interquartile Range)</b>	65.0 (65.0,69.0)	65.0 (65.0,69.0)
<i>Female sex, N (%)</i>	4643 (57.4%)	4639 (57.4%)
<i>Black Race, N (%)</i>	1118 (13.8%)	1114 (13.8%)
<i>White Race, N (%)</i>	6811 (84.1%)	6805 (84.2%)
<i>Deceased, N (%)</i>	1646 (20.3%)	1331 (16.5%)
<b>Claims-based diagnoses</b>		
<i>Myocardial infarction</i>	16.0 (36.6)	15.5 (36.2)
<i>Angina pectoris</i>	10.3 (30.4)	10.1 (30.1)
<i>Heart failure</i>	19.7 (39.8)	18.9 (39.1)
<i>Valvular heart disease</i>	1.4 (11.7)	1.4 (11.6)
<i>Rheumatic heart disease</i>	4.5 (20.7)	4.3 (20.3)
<i>Arterial hypertension</i>	70.2 (45.8)	69.8 (45.9)
<i>Cardiac arrhythmias</i>	31.8 (46.6)	31.0 (46.3)
<i>Ischemic stroke</i>	19.9 (39.9)	19.3 (39.4)
<i>Hemorrhagic stroke</i>	2.1 (14.3)	1.9 (13.5)
<i>Other cerebrovascular diseases</i>	12.0 (32.5)	11.0 (31.3)
<i>Systemic hypotension</i>	8.8 (28.3)	8.0 (27.1)
<i>Chronic kidney disease</i>	16.8 (37.4)	16.0 (36.6)
<i>Chronic obstructive pulmonary disease</i>	28.3 (45.1)	27.8 (44.8)
<i>Diabetes mellitus</i>	29.6 (45.6)	29.1 (45.4)
<i>Thyroid dysfunction</i>	25.0 (43.3)	24.6 (43.1)
<i>Metabolic syndrome</i>	0.8 (8.9)	0.8 (8.9)
<i>Obstructive sleep apnea</i>	8.2 (27.4)	7.9 (27.0)
<i>Depression</i>	18.9 (39.2)	17.6 (38.1)
<i>Traumatic brain injury</i>	2.8 (16.6)	2.6 (16.0)
<i>Chronic liver disease</i>	5.4 (22.7)	5.3 (22.3)
<i>Solid malignant tumors</i>	32.3 (46.8)	31.8 (46.6)
<i>Nonsolid cancer</i>	2.8 (16.4)	2.7 (16.2)
<i>Cancer, unspecified</i>	18.4 (38.8)	18.1 (38.5)
<b>Self-reported diseases</b>		
<i>Heart diseases</i>	22.7 (34.1)	22.7 (34.1)
<i>Stroke</i>	5.9 (18.6)	5.9 (18.6)
<i>Lung diseases</i>	9.8 (24.4)	9.8 (24.4)
<i>Cancer</i>	13.4 (28.6)	13.4 (28.6)
<i>Diabetes mellitus</i>	16.6 (31.2)	16.6 (31.2)
<i>Arthritis</i>	58.9 (39.8)	58.9 (39.8)
<i>Psychiatric disorder</i>	15.4 (30.3)	15.4 (30.3)
<i>High Blood Pressure</i>	53.9 (41.4)	53.9 (41.4)
<b>Other Health-Related Measures</b>		
<i>Number of ADL limitations</i>	0.2 (0.5)	0.2 (0.5)
<i>Number of IADL limitations</i>	0.2 (0.4)	0.2 (0.4)
<i>Score on the CESD scale</i>	1.3 (1.4)	1.3 (1.4)
<i>Hearing Problems</i>	18.9 (29.1)	18.9 (29.1)
<i>Vision Problems</i>	18.0 (26.3)	18.0 (26.3)
<i>Current smoker</i>	13.9 (30.4)	13.9 (30.4)
<i>Heavy alcohol consumption</i>	0.8 (9.1)	0.8 (9.1)
<i>Lack of physical activity</i>	62.5 (29.1)	62.5 (29.2)

<i>Body Mass Index</i>	27.7 (5.1)	27.7 (5.1)
<b>Socioeconomics</b>		
<i>Social isolation</i>	14.7 (18.0)	14.7 (18.0)
<i>No high school degree</i>	27.1 (33.9)	27.1 (33.9)
<i>Low income</i>	16.7 (37.3)	16.7 (37.3)
<b>Environmental</b>		
<i>Particulate matter 2.5 (µg/m<sup>3</sup>)</i>	10.3 (2.3)	10.3 (2.3)
<i>Ozone (parts per billion)</i>	38.9 (3.8)	38.9 (3.8)
<i>Nitrogen dioxide (parts per billion)</i>	19.1 (8.8)	19.1 (8.8)
<b>Genetic</b>		
<i>PRS Amyl_React Pathway</i>	-0.039 (1.003)	-0.039 (1.003)
<i>PRS Apopt_PosReg_GO Pathway</i>	0.008 (1.002)	0.008 (1.002)
<i>PRS Apopt_NegReg_GO</i>	-0.036 (0.999)	-0.037 (0.999)
<i>PRS NDea_NegReg_GO Pathway</i>	-0.048 (0.994)	-0.049 (0.994)
<i>PRS Tau_Liter Pathway</i>	-0.022 (1.004)	-0.022 (1.004)
<i>PRS Reactome_Dopa Pathway</i>	0.049 (0.995)	0.048 (0.996)
<i>PRS Nsig_KEGG Pathway</i>	0.051 (0.994)	0.051 (0.995)
<i>PRS Reactome_Neuro_Receptor</i>	0.038 (0.997)	0.038 (0.997)
<i>PRS Mitoch Pathway</i>	0.046 (1.009)	0.046 (1.009)
<i>PRS BioMitoch Pathway</i>	-0.040 (0.996)	-0.040 (0.997)
<i>PRS Infl_Hallm Pathway</i>	0.005 (1.006)	0.005 (1.006)
<i>PRS Ninfl+ Pathway</i>	-0.035 (1.006)	-0.035 (1.006)
<i>PRS (HRS, v.4, no APOE)</i>	-0.021 (0.992)	-0.022 (0.992)
<i>PRS (HRS, 0.01 v.4, no APOE)</i>	-0.012 (0.998)	-0.012 (0.998)
<i>PRS (HRS, v.4, with APOE)</i>	-0.021 (0.992)	-0.021 (0.992)
<i>PRS (HRS, 0.01 v.4, with APOE)</i>	-0.010 (0.997)	-0.010 (0.996)
<i>rs12539172</i>	28.3 (32.4)	28.3 (32.4)
<i>rs3851179</i>	33.3 (33.7)	33.3 (33.7)
<i>rs405509 (APOE)</i>	44.3 (35.7)	44.3 (35.7)
<i>rs769449 (APOE)</i>	10.0 (21.3)	10.0 (21.3)
<i>rs2075650 (TOMM40)</i>	13.7 (24.3)	13.7 (24.2)
<i>rs8106922 (TOMM40)</i>	38.1 (34.7)	38.1 (34.7)
<i>rs6859 (NECTIN2)</i>	41.6 (34.9)	41.6 (34.8)
<i>rs157580 (TOMM40)</i>	35.2 (34.3)	35.2 (34.3)
<i>rs4311</i>	44.2 (35.9)	44.2 (35.9)

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**Supplementary Table 4.** ADRD hazard ratios evaluated in univariable analyses for i) overall population of older adults (All) with 95% confidence intervals (Lo.CI, Up.CI), ii) for sex-specific subpopulations (Male, Female), iii) Black population, and iv) for models with 1, 3, and 5 years of lag (Lag1, Lag3, and Lag5).

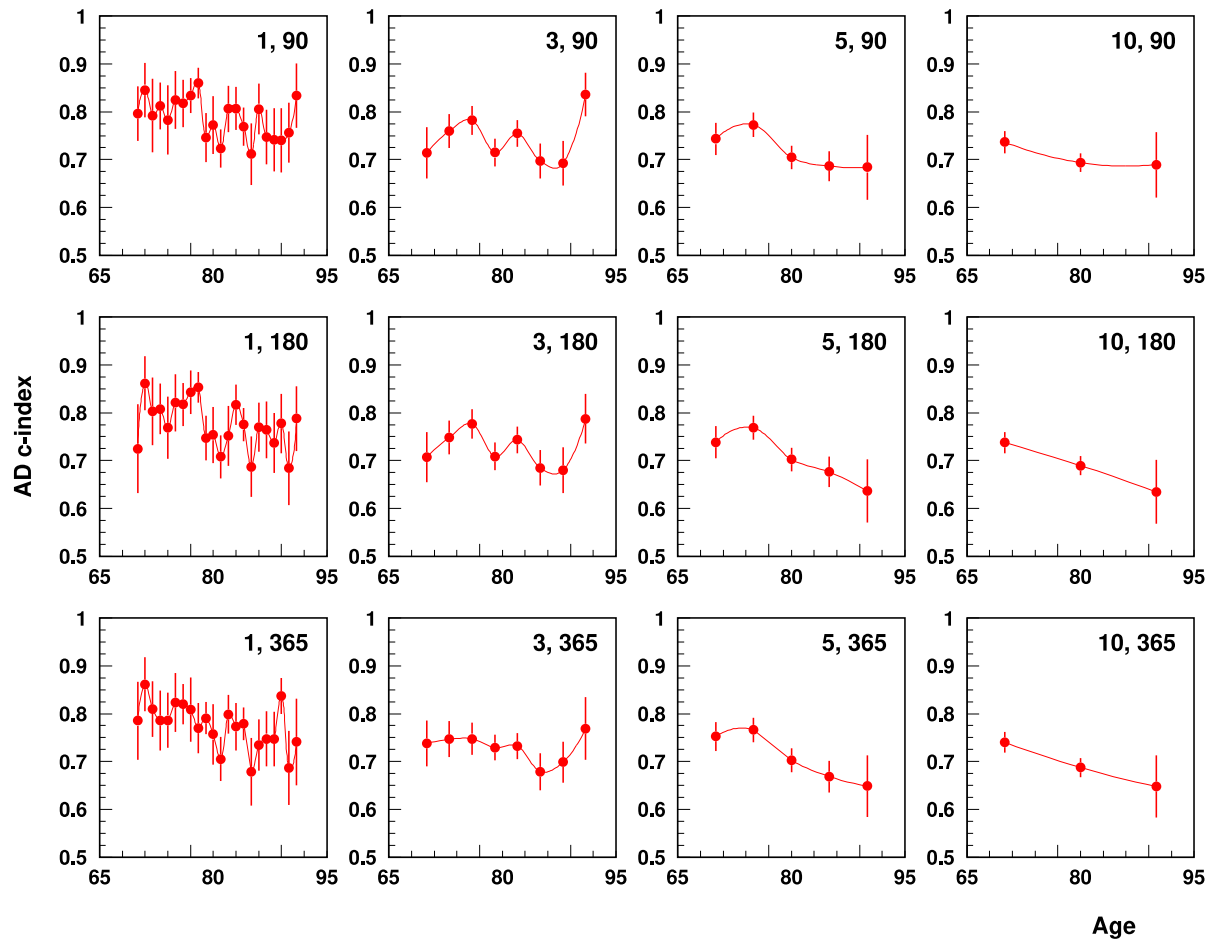
Predictors	Hazard Ratios						
	AD (HR with CI)	Male	Female	Black	Lag1	Lag3	Lag5
Myocardial infarction	1.74 (1.50,2.03)	1.62	1.88	1.30	1.66	1.65	1.47
Angina pectoris	1.64 (1.38,1.94)	1.69	1.59	0.82	1.55	1.50	1.47
Heart failure	2.48 (2.15,2.87)	2.53	2.44	2.54	2.17	2.03	1.95
Valvular heart disease	1.81 (1.21,2.72)	1.78	1.79	1.07	1.82	1.71	1.48
Rheumatic heart disease	2.24 (1.76,2.85)	1.82	2.56	2.56	1.99	2.40	2.47
Arterial hypertension	2.87 (2.35,3.51)	2.72	3.02	5.93	1.94	1.69	1.59
Cardiac arrhythmias	2.00 (1.75,2.29)	2.16	1.91	1.94	1.62	1.63	1.56
Ischemic stroke	2.87 (2.50,3.29)	2.66	3.04	3.50	2.16	1.97	1.80
Hemorrhagic stroke	4.06 (2.95,5.59)	3.22	4.90	7.25	2.92	3.06	3.58
Other cerebrovascular disease	3.79 (3.27,4.40)	3.55	4.03	3.89	2.75	2.47	2.50
Systemic hypotension	2.65 (2.17,3.24)	3.14	2.26	2.91	1.93	1.68	1.45
Chronic kidney disease	2.43 (2.07,2.86)	2.24	2.62	1.85	1.66	1.53	1.21
COPD	1.88 (1.65,2.16)	2.07	1.76	1.77	1.56	1.60	1.49
Diabetes mellitus	1.83 (1.60,2.09)	1.81	1.85	1.44	1.70	1.64	1.65
Thyroid dysfunction	1.45 (1.26,1.67)	1.54	1.46	1.68	1.33	1.22	1.29
Metabolic syndrome	0.89 (0.33,2.38)	0.46	1.32	0.67	0.75	1.00	0.47
Obstructive sleep apnea	2.11 (1.63,2.74)	2.42	1.71	1.12	1.94	1.79	1.93
Depression	3.55 (3.09,4.07)	4.96	3.06	3.20	2.34	2.17	2.07
Traumatic brain injury	3.26 (2.51,4.24)	4.54	2.73	2.14	2.66	2.32	1.96
Chronic liver disease	2.11 (1.62,2.74)	1.51	2.50	1.44	1.98	1.84	2.07
Solid malignant tumors	1.16 (1.01,1.33)	1.34	1.03	1.18	1.03	1.05	1.06
Nonsolid cancer	1.42 (0.92,2.19)	2.45	0.60	1.96	1.10	0.83	0.83
Cancer, unspecified	1.14 (0.97,1.34)	1.30	1.01	1.07	1.09	1.07	1.08
Heart diseases (SR)	1.22 (1.07,1.39)	1.19	1.25	1.02	1.28	1.33	1.30
Stroke (SR)	2.42 (2.06,2.84)	2.39	2.46	1.96	2.37	2.33	2.32
Lung diseases (SR)	1.24 (1.02,1.49)	1.02	1.40	1.37	1.26	1.33	1.38
Cancer (SR)	0.86 (0.73,1.01)	0.81	0.90	0.86	0.82	0.89	0.96
Diabetes (SR)	1.38 (1.19,1.60)	1.40	1.37	1.12	1.49	1.49	1.60
Arthritis (SR)	0.91 (0.79,1.05)	0.93	0.89	1.01	1.04	1.19	1.24
Depression (SR)	1.85 (1.58,2.17)	2.09	1.77	1.14	1.88	1.82	1.73
Back pain (SR)	1.08 (0.94,1.24)	1.02	1.14	0.91	1.11	1.14	1.22
Disability (ADL)	1.45 (1.38,1.53)	1.54	1.40	1.28	1.43	1.34	1.36
Instrumental ADL	1.63 (1.56,1.70)	1.69	1.59	1.44	1.56	1.42	1.35
CESD scale	1.17 (1.13,1.20)	1.19	1.16	1.13	1.15	1.16	1.16
Current smoking	1.39 (1.08,1.79)	1.37	1.39	1.17	1.39	1.34	1.29
Hard drinking	1.31 (0.59,2.92)	1.44	0.92	n/a	1.31	1.31	1.31
Body mass index	0.97 (0.95,0.98)	0.98	0.96	0.99	0.97	0.99	1.00
No physical activities	1.74 (1.48,2.06)	1.91	1.64	1.68	1.71	1.78	1.68
Hearing problems	1.25 (1.09,1.44)	1.28	1.24	1.45	1.26	1.23	1.36
Vision problems	1.62 (1.41,1.87)	1.62	1.62	1.40	1.59	1.51	1.61
Social isolation	1.44 (1.24,1.67)	1.34	1.50	1.13	1.22	1.25	1.17
Low income	1.84 (1.61,2.10)	1.74	2.00	1.53	1.58	1.48	1.41
Low education	1.35 (1.16,1.57)	1.34	1.35	1.13	1.35	1.35	1.35
Female	0.99 (0.87,1.13)	.	.	1.14	0.99	0.99	0.99
Black	1.65 (1.38,1.97)	1.51	1.75	.	1.65	1.65	1.65
PM 2.5	1.06 (1.03,1.09)	1.11	1.03	1.06	1.06	1.06	1.06
Ozone	1.01 (0.99,1.02)	1.01	1.01	0.99	1.01	1.01	1.01
NO2	1.00 (1.00,1.01)	1.01	1.00	1.00	1.00	1.00	1.00

**Supplementary Table 5.** Effects of Genetic Risk Factors on AD risk. AD hazard ratios (HR) were evaluated in univariable analyses of total sample of older adults (All) with 95% confidence intervals (Lo.CI, Up.CI), and for male, female, and Black populations.

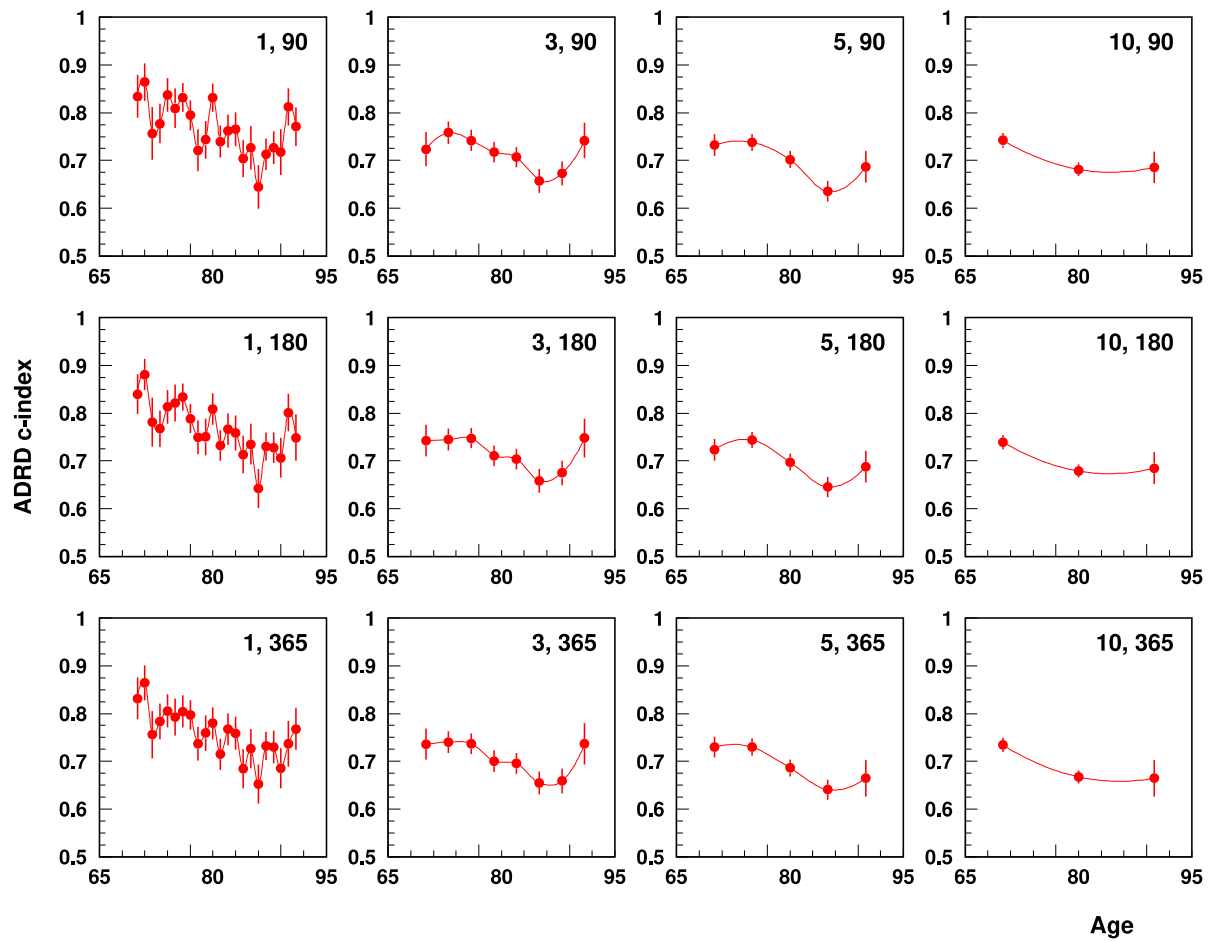
<b>Genetic Risk Factors</b> (PRS for pathways*, PRS for all genotyped SNPs, and Individual SNPs**)	<b>Hazard Ratios</b>			
	AD (HR with CI)	Male	Female	Black
PRS Amyl_React Pathway	0.96 (0.90,1.03)	0.94	0.98	0.96
PRS Apopt_PosReg_GO Pathway	0.98 (0.91,1.04)	0.92	1.01	1.04
PRS Apopt_NegReg_GO	1.00 (0.93,1.06)	0.87	1.09	1.01
PRS NDea_NegReg_GO Pathway	1.00 (0.94,1.07)	0.86	1.11	1.04
PRS Tau_Liter Pathway	1.06 (0.99,1.13)	1.04	1.07	1.09
PRS Reactome_Dopa Pathway	1.01 (0.95,1.08)	1.02	1.00	1.06
PRS Nsig_KEGG Pathway	0.99 (0.92,1.05)	0.98	0.99	1.10
PRS Reactome_Neuro_Recept	0.98 (0.92,1.05)	1.01	0.96	0.94
PRS Mitoch Pathway	1.02 (0.95,1.08)	1.02	1.01	0.97
PRS BioMitoch Pathway	1.07 (1.00,1.14)	0.97	1.14	1.19
PRS Infl_Hallm Pathway	1.10 (1.03,1.17)	1.05	1.14	0.94
PRS Ninfl+ Pathway	0.98 (0.92,1.04)	0.93	1.01	0.98
PRS (HRS, v.4, no APOE)	1.05 (0.98,1.12)	1.02	1.07	0.92
PRS (HRS, 0.01 v.4, no APOE)	1.10 (1.03,1.17)	1.02	1.16	0.97
PRS (HRS, v.4, with APOE)	1.06 (1.00,1.13)	1.03	1.09	0.92
PRS (HRS, 0.01 v.4, with APOE)	1.17 (1.10,1.25)	1.09	1.24	0.99
rs12539172	0.88 (0.80,0.98)	0.95	0.85	0.96
rs3851179	0.97 (0.88,1.07)	0.90	1.02	0.82
rs405509 (APOE)	1.12 (1.03,1.23)	1.06	1.17	1.21
rs769449 (APOE)	1.73 (1.52,1.96)	1.62	1.80	1.91
rs2075650 (TOMM40)	1.57 (1.39,1.76)	1.56	1.58	1.22
rs8106922 (TOMM40)	0.84 (0.77,0.93)	0.88	0.82	0.87
rs6859 (NECTIN2)	1.20 (1.10,1.32)	1.08	1.29	1.14
rs157580 (TOMM40)	0.81 (0.73,0.89)	0.84	0.79	0.97
rs4311	0.92 (0.84,1.01)	0.93	0.92	0.91

\*Sets of genes included in these pathways are provided in Supplementary Table 2

\*\* SNPs included as in Table 2



**Supplementary Figure 1.** C-index for AD risk for one, three, five, and ten years of follow-up for three algorithms of reconstruction of onsets. The first number at each plot shows the number of follow-up years and the second number shows the algorithm used for onset reconstruction (i.e., 90, 180, or 365 day-period used for confirmation of the original record with ICD-9 code). Using death as a confirmatory record add only several cases and does not impact the conclusions.



**Supplementary Figure 2.** C-index for ADRD risk for one, three, five, and ten years of follow-up for three algorithms of reconstruction of onsets. The first number at each plot shows the number of follow-up years and the second number shows the algorithm used for onset reconstruction (i.e., 90, 180, or 365 day-period used for confirmation of the original record with ICD-9 code).