SUPPLEMENTARY MATERIAL

Effect of smoking on physical and cognitive capability in later life: A multi-cohort study using observational and genetic approaches

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Wave of outcome assessment in this analysis

Boyd Orr (BO)(1): Physical capability measures were assessed at the third wave (2002-03).

Caerphilly Prospective Study (CAPS) : Cognitive function measures were assessed at phase III, with follow up measures to calculate decline taken from phase V. Physical capability measures were assessed at phase V.

English Longitudinal Study of Ageing (ELSA)(2): Physical and cognitive capability were assessed at wave 2 (2004/5). Follow up cognitive measures for decline calculations were taken from wave 5(2010/11).

Hertfordshire Ageing Study (HAS) (3): Cognitive function was assessed at wave 1 (1994/5) with follow up measures for decline taken from wave 2 (2003/05). Grip strength was assessed at wave 1 and all other physical capability measures at wave 2.

Hertfordshire Cohort Study (HCS) (4): Grip strength was assessed at wave 1 (1999-2004) while TUG speed, walk speed, balance ability and chair rise speed were assessed at both waves 1 (1999-2004) and 2 (2004/05) with partial overlap in some tests and no overlap in others. These latter measures were combined across waves, with priority given to wave 1, and the covariates tailored as such.

Lothian Birth Cohort 1921 (LBC1921) (5): Physical and cognitive capability were assessed at wave 1age 79 years, with follow up cognitive capability measures for decline calculations taken from wave 3 age 87 years.

National Child Development Study (NCDS) (6): Cognitive capability was assessed at the 2008 follow up when the study members were 50 years old.

MRC National Survey of Health and Development (NSHD) (7): All cognitive capability measures were taken from the 1999 wave when the study members were 53 years, with follow up measures for cognitive decline taken when the study members were 60-64 years. All physical capability measures were taken from the 1999 wave with the exception of TUG, which was analysed when the study members were 60-64 years.

Whitehall II Study (WHII) (8): Walking speed was analysed at phase 7 (2002-04), while all cognitive outcomes were analysed at phase 5 (1997-99) with follow up measures taken from phase 7.

Analyses of the genotype-covariate and genotype-smoking associations took the covariate and smoking outcomes from the earliest wave at which they were analysed in the observational associations.

Measures of physical capability

Details of the ascertainment and harmonisation of the five measures of physical capability used in analyses are described in detail elsewhere(9) and are summarised here. The approach to harmonise chair rise times (5 or 10 rises) was to calculate chair rise speed in the current study.

Grip strength was tested in ELSA, HAS, HCS, LBC AND NSHD using handheld dynamometers (the specific devices used in each study are described elsewhere (9)). The maximum measure was used in each study (extracted from 3 measures of each hand in ELSA, HAS and HCS, 3 measures of the dominant hand in LBC and 2 measures in each hand in NSHD). If repeat measures were missing the existing measures were used to derive the maximum.

Standing balance was assessed in BO, CaPS, ELSA, HAS, HCS and NSHD. Owing to the heterogeneity in the way the test was administered across cohorts, the outcome used in analyses was a derived binary variable for inability to balance on one leg with eyes open for five seconds. In ELSA the tests administered were more complex as described by Cooper *et al*(9) and we derived the outcome in the same way, namely, inability to balance in full tandem with eyes open for 5 seconds with individuals who were not progressed to the next phase of testing classed as unable. Individuals who did not complete the balance test for health reasons were classed as unable in all analyses. If tests were conducted more than once the best performance was used to derive the outcome variable.

The timed walk test was conducted in LBC (6 metres as fast as possible), HAS and HCS (3 metres at normal pace), ELSA (8 feet at normal pace with 2 trials) and WHII (8 feet at

normal pace with 3 trials). To normalise the distribution and to make a higher outcome a healthier outcome, times were converted to speeds in metres per second and then averaged where repeat trials were available.

The timed get up and go test was performed in BO, HAS, HCS, CaPS and NSHD. In all cohorts, study members had to rise from a chair, walk 3 metres at a normal pace and return to a seated position in the chair. The test was repeated in BO and CaPS. Again all times were converted to speeds in metres per second and then averaged where the trial was conducted more than once.

Timed chair rises were assessed in HAS, HCS, ELSA and NSHD. All times were converted to chair rise speed in stands per second. The cohorts measured time to complete 5 or 10 chair rises as fast as possible. In ELSA, individuals under 69 years performed 10 rises while those aged 70 and over performed 5 rises. Time to complete 5 rises was measured in both age groups and this was used to derive chair rise speed.

Some physical performance measures were conducted in part of the HCS cohort in one wave and in the remaining cohort in a later wave. To maximise sample size, measures were pooled across waves and covariates were tailored according to the wave at which the outcome had been performed.

Measures of cognitive capability

The measures of cognition across the HALCyon cohorts were categorised into measures of crystallised ability and measures of fluid cognition.

Measures of crystallised cognitive function

The National Adult Reading Test (NART)(10) was available in LBC, CaPS and NSHD. This requires study members to read aloud 50 words with irregular pronunciation and the number of words pronounced correctly is used in analyses here. NART should reflect pre-morbid IQ.

The Mill Hill vocabulary test(11) was administered in HAS and WHII. Study members had to choose the correct synonym for 33 words out of 6 multiple choice answers with increasing difficulty. The number of correct answers is used in analyses.

Measures of fluid cognitive function

Semantic fluency was tested in ELSA, NSHD, NCDS and WHII via a verbal or written test where study members were asked to name as many animals as possible in 1 minute. The number of unique animals named were used in analyses.

Verbal memory was tested in ELSA, NSHD, NCDS and WHII via a word recall test. The numbers of words correctly recalled was used in analyses. In NSHD, we summed the total score for remembering the same 15 words in writing over three consecutive trials. The sum of two trials with a delay for the second trial for remembering 10 words verbally was analysed in ELSA and NCDS. 20 words were recalled in writing in WHII.

Phonemic fluency was analysed in LBC and WHII. In LBC, study members were given three 1 minute trials to name as many words as possible beginning with F, L and C. The total

number of words is used in analyses. In WHII, study members wrote as many words as possible in 1 minute beginning with S.

Search speed was tested in ELSA (780 letters), NSHD (600 letters) and NCDS (780 letters) whereby participants must cross out particular letters in a large grid of letters. The number of letters searched per minute was used in analyses.

The Alice Heim 4-I test (AH4)(12) was available for analyses in CaPS, HAS and WHII. This involves 65 verbal and mathematical questions. The total score achieved in 10 minutes was used in analyses here.

Choice reaction time was assessed in CaPS via a computer test in which the study members had to press one of four key pads depending on which box a stimulus appeared in on screen.

Wechsler logical memory(13) was tested in LBC. The participants were asked to recall two stories immediately and following a delay for each. The total sum of the scores for each story were progressed to analysis.

Raven's Progressive Matrices(14) were used in LBC, in which study members were given 20 minutes to complete 60 multiple choice "complete the pattern" questions. The total score was used in the analysis.

Deriving a score for General Fluid Ability (Gf)

Where available, three fluid cognitive measures were included from each cohort to produce the factor. These were semantic fluency, AH4 and inverse transformed FCRT in CaPS; word recall, semantic fluency and natural log transformed search speed in NSHD and ELSA;

semantic fluency, ravens progressive matrices and logical memory in LBC; semantic fluency, word recall and AH4 in WHII.

Derivation of covariates

Disease status was defined as a binary variable. Individuals were assigned "case" status if they had a history of heart disease, stroke or diabetes. The definition of a case varied across cohorts depending on the availability of information. The numbers of cases by cohort are described in Supplementary Table 2.

Socio-economic position was classified according to the Registrar-General's Social Classes (RGSC) system and included in analyses as a categorical variable. This is based on a study member's current or most recent occupation. Individuals who did not have information were coded as missing while individuals with occupations beyond the classification system were coded in an "unclassifiable" category. As the classification differed across cohorts slightly, to assess the association between genotype and socio-economic position to test the Mendelian Randomization assumptions, individuals who had a valid RGSC coding (I-V) were binarised into Professional & Managerial or other.

Individuals aged 90 years or over are not assigned an exact age in ELSA data releases. As such, we estimated the age of these individuals using a representative estimate of the mean age of individuals aged 90 and over in England and Wales in 2005 (the year of wave 2 assessment). To calculate this estimate, we used the England and Wales Mid-Year Population Estimates of the Very Elderly, 2002-2010, demographic table "Mid-2010 Estimates of the very elderly (including centenarians) England and Wales; estimated resident population" which was part of the Population Estimates of the Very Elderly, 2010 Office for National Statistics release (release date 29 September 2011, date accessed 5 February 2014 from http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-223697). The estimated age used in analyses was 92.62 years.

Genotyping

The rs16969968 SNP was genotyped by KBioscience (http://www.lgcgenomics.com/) in CaPS, BO, HCS, HAS, ELSA and WHII. In LBC, the genotype data came from the Illumina 610-Quadv1 array (rs1051730) and in NCDS from a combination of the T1DGC(15) array (rs1051730) and the WTCCC2 array (rs16969968, Illumina 1.2M chip). The rs16969968 and the rs1051730 SNPs are used interchangeably and thus genotypes from these SNPs were pooled for the NCDS analysis. Genotype data for rs16969968 in NSHD came from a previous genotyping performed by KBioscience. For SNPs genotyped by HALCyon, call rate, clustering and duplicate concordance were examined where possible. Departures from HWE and MAF were examined in all cohorts. The whole analysis was restricted to unrelated individuals of European ancestry where this information was available. Further information on the genotyping quality is provided in Supplementary Table 1.

Supplementary Table 1: Genotype Quality

Cohort	SNP	Call Rate (%)	Duplicate Concordance Rate (%)
BO	rs16969968	97.50	97.87
CaPS	rs16969968	98.04	100
ELSA	rs16969968	99.38	99.76
HAS	rs16969968	94.79	Not available
HCS	rs16969968	97.06	Not available
LBC	rs1051730	NA	NA
NCDSa*	rs16969968	NA	NA
NCDSb*	rs1051730	NA	NA
NSHD	rs16969968	NA	NA
WHII	rs16969968	98.48	97.12

Notes:
*In NCDS we analysed a combination of the rs16969968 and the rs1051730 genotype depending on availability. As these SNPs are used interchangeably, each individual was classified according to their number of minor alleles of either SNP

Supplementary Table 2: Disease status by cohort

Cohort	% Individuals classed as a case
BO	29.14
CaPS	42.25
ELSA	19.94
HAS	23.75
HCS	15.33
LBC	35.51
NCDS	2.66
NSHD	8.14
WHII	10.31

Notes:
Based on individuals included in the observational analysis using the earliest wave analysed to calculate %

Supplementary Table 3: Genotype frequencies by cohort

Cohort	C/C	C/T	T/T	HWE p-value**	Total
BO	214	198	42	0.69	454
CaPS	593	569	125	0.50	1287
ELSA	2494	2404	589	0.79	5487
HAS	214	235	68	0.78	517
HCS	1191	1211	310	0.93	2712
LBC*	231	239	43	0.08	513
NCDS*	2099	2133	566	0.50	4798
NSHD	1222	1164	255	0.36	2641
WHII	1747	1750	423	0.62	3920
TOTAL	10005	9903	2421	0.73	22329

Notes:
Numbers based on all individuals with age, sex, smoking status and genotype. The earliest cohort phase or wave utilised in the analyses was used to extract data, and to perform the meta-analysis in Figures 1-4 (main paper)
*Cohort analysis uses rs1051730 as a proxy. NCDS analysis combines rs16969968 with rs1051730. Results represent pooled SNPs here.
**Based on chi-squared test with 1 degree of freedom

Supplementary Table 4: Observational sample size by outcome and cohort (Model M1)

	BO	CaPS	ELSA	HAS	HCS	LBC	NCDS	NSHD	WHII
Grip strength	0	0	5374(587)	635(87)	2803(239)	536(35)	0	2831(645)	0
Chair rise speed	0	0	4654(490)	244(16)	1516(105)	0	0	2721(608)	0
Walk speed	0	0	3442(312)	260(16)	2176(167)	534(35)	0	0	5319(278)
TUG speed	279(33)	999(123)	0	263(16)	2180(168)	0	0	1849(189)	0
Inability to balance on one leg for 5s	279(33)	1002(124)	5385(589)	265(17)	1569(106)	0	0	2860(648)	0
Mill Hill	0	0	0	633(86)	0	0	0	0	4563(354)
NART	0	1804(479)	0	0	0	540(36)	0	2812(646)	0
Gf	0	1698(450)	5306(582)	0	0	531(35)	0	2856(653)	4486(348)
AH4	0	1798(482)	0	621(85)	0	0	0	0	4552(357)
Semantic fluency	0	1820(485)	5418(594)	0	0	0	7652(1570)	2928(674)	4537(353)
Phonemic fluency	0	0	0	0	0	538(35)	0	0	4543(353)
Search speed	0	0	5306(582)	0	0	0	7521(1538)	2918(672)	0
Word recall	0	0	5411(591)	0	0	0	7600(1565)	2866(655)	4541(355)
Four choice reaction time	0	1722(459)	0	0	0	0	0	0	0
Logical memory	0	0	0	0	0	540(36)	0	0	0
Raven's Progressive Matrices	0	0	0	0	0	536(36)	0	0	0
Mill Hill decline	0	0	0	228(20)	0	0	0	0	4510(350)
NART decline	0	1021(218)	0	0	0	202(8)	0	0	0
AH4 decline	0	1003(211)	0	254(20)	0	0	0	0	4505(353)
Semantic fluency decline	0	1044(224)	3713(380)	0	0	0	0	0	4484(349)
Phonemic fluency decline	0	0	0	0	0	203(7)	0	0	4478(349)
Search speed decline	0	0	0	0	0	0	0	2055(383)	0
Word recall decline	0	0	3714(380)	0	0	0	0	2005(372)	4482(351)
Four choice reaction time decline	0	960(202)	0	0	0	0	0	0	0
Logical memory decline	0	0	0	0	0	204(8)	0	0	0
Raven's Progressive Matrices decline	0	0	0	0	0	198(8)	0	0	0

Notes: Numbers based on all individuals with age, sex, socio-economic position and the outcome measure. Numbers with smoking status are provided with numbers with CPD in brackets. Smoking status was analysed as binary variables in separate analyses comparing classes of smoker. Some regressions were not possible due to small sample size, and on some occasions individuals were removed from the analysis automatically by the software

Supplementary Table 5: Genetic sample size by outcome and cohort

	BO	CaPS	ELSA	HAS	HCS	LBC	NCDS	NSHD	WHII
Grip strength	0	0	764(587)/2647/1963	85(74)/233/143	324(224)/1090/1234	32(32)/252/223	0	593(588)/1200/727	0
Chair rise speed	0	0	634(490)/2279/1741	18(15)/101/54	126(96)/560/736	0	0	558(554)/1154/712	0
Walk speed	0	0	412(312)/1774/1256	19(15)/107/57	207(154)/828/1019	32(32)/251/222	0	0	495(214)/1877/1854
TUG speed	40(30)/108/106	129(91)/409/144	0	19(15)/109/58	208(155)/829/1021	0	0	171(167)/914/517	0
Inability to balance on one leg for 5s	40(30)/108/106	131(93)/411/146	768(589)/2643/1974	19(15)/109/59	127(97)/579/764	0	0	596(591)/1212/737	0
Mill Hill	0	0	0	84(73)/232/143	0	0	0	0	512(279)/1427/1656
NART	0	406(314)/571/203	0	0	0	33(33)/253/223	0	591(586)/1191/719	0
Gf	0	386(297)/542/191	759(582)/2617/1930	0	0	32(32)/248/222	0	599(594)/1206/738	506(273)/1406/1622
AH4	0	407(314)/569/201	0	84(73)/225/143	0	0	0	0	515(282)/1423/1647
Semantic fluency	0	410(317)/576/203	775(594)/2665/1978	0	0	0	960(957)/1516/2179	616(611)/1235/750	511(278)/1416/1648
Phonemic fluency	0	0	0	0	0	32(32)/251/224	0	0	511(278)/1419/1650
Search speed	0	0	759(582)/2617/1930	0	0	0	938(935)/1488/2140	614(609)/1232/748	0
Word recall	0	0	771(591)/2664/1976	0	0	0	959(956)/1505/2162	601(596)/1209/742	513(280)/1426/1641
Four choice reaction time	0	391(302)/550/195	0	0	0	0	0	0	0
Logical memory	0	0	0	0	0	33(33)/252/224	0	0	0
Raven's Progressive Matrices	0	0	0	0	0	33(33)/252/222	0	0	0
Mill Hill decline	0	0	0	19(15)/88/55	0	0	0	0	506(276)/1417/1633
NART decline	0	228(168)/359/151	0	0	0	6(6)/92/94	0	0	0
AH4 decline	0	217(161)/360/147	0	19(15)/99/62	0	0	0	0	509(279)/1413/1630
Semantic fluency decline	0	232(172)/369/153	492(380)/1785/1436	0	0	0	0	0	505(275)/1405/1625
Phonemic fluency decline	0	0	0	0	0	5(5)/92/96	0	0	505(275)/1405/1619

Search speed decline	0	0	0	0	0	0	0	360(356)/930/561	0
Word recall decline	0	0	492(380)/1786/1436	0	0	0	0	350(346)/907/550	506(276)/1412/1618
Four choice reaction time decline	0	213(158)/345/142	0	0	0	0	0	0	0
Logical memory decline	0	0	0	0	0	6(6)/92/96	0	0	0
Raven's Progressive Matrices decline	0	0	0	0	0	6(6)/90/92	0	0	0

Notes: Numbers based on all individuals with age, sex, genotype, smoking status and the outcome measure, and are restricted to those also in the observational analysis. Numbers provided are current smokers (number with CPD)/ex smokers/never smokers. Numbers reflect the data progressed to regression analyses, irrespective of whether the regression was possible.

Supplementary Table 6: Observational estimates for the associations between smoking and cognitive capabilities - single cohort analyses

Outcome	Cohort	Modelψ	Cigarette per day β (95% CI)	Current vs. ex smoker β (95% CI)	Current vs. never smoker β (95% CI)	Ever vs. never smoker β (95% CI)
Four choice reaction time#	CaPS	M1	0.008(-0.002,0.017)	-0.159**(-0.260,-0.058)	-0.050(-0.185,0.085)	0.044(-0.074,0.162)
		M2	0.007(-0.004,0.017)	-0.203***(-0.310,-0.096)	-0.063(-0.210,0.083)	0.061(-0.069,0.190)
Logical memory	LBC	M1	0.023(-0.049,0.095)	0.138(-0.220,0.496)	0.192(-0.161,0.545)	0.031(-0.140,0.202)
		M2	0.024(-0.049,0.098)	0.123(-0.240,0.485)	0.185(-0.170,0.540)	0.037(-0.137,0.210)
Raven's progressive matrices	LBC	M1	-0.015(-0.081,0.051)	-0.160(-0.501,0.180)	-0.094(-0.426,0.237)	0.009(-0.155,0.173)
		M2	-0.011(-0.077,0.056)	-0.163(-0.507,0.181)	-0.086(-0.420,0.248)	0.009(-0.157,0.175)

Notes:
ψModels: (M1) age, sex and SEP adjusted, (M2) M1 + disease adjusted
#Inverse transformed
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Supplementary Table 7: Observational estimates for the associations between smoking and measures of cognitive decline.

	Outcome	Modelψ	Cigarette per day OR (95% CI)	Current vs. ex smoker OR (95% CI)	Current vs. never smoker OR (95% CI)	Ever vs. never smoker OR (95% CI)
Crystallized	Mill Hill	M1	1.003(0.980,1.027)	1.002(0.691,1.452)	1.121(0.915,1.375)	1.099(0.961,1.258)
		M2	1.004(0.980,1.028)	0.997(0.666,1.491)	1.117(0.911,1.371)	1.100(0.960,1.259)
	NART	M1	0.993(0.961,1.027)##	1.065(0.786,1.443)	1.134(0.777,1.655)	1.008(0.752,1.353)
		M2	0.998(0.962,1.036)##	1.030(0.742,1.430)	1.183(0.781,1.792)	1.053(0.765,1.451)
Fluid Measures	AH4	M1	0.998(0.979,1.017)	1.265*(1.047,1.527)	1.271(0.746,2.165)	1.058(0.778,1.439)
		M2	0.996(0.977,1.016)	1.283**(1.076,1.531)	1.370(0.806,2.328)	1.120(0.870,1.442)
	Semantic fluency	M1	1.019(0.992,1.046)	1.090(0.912,1.302)	1.167(0.883,1.544)	1.068(0.939,1.215)
		M2	1.023(0.992,1.056)	1.092(0.924,1.290)	1.188(0.898,1.573)	1.071(0.937,1.225)
	Phonemic fluency	M1	1.003(0.979,1.028)#	1.042(0.843,1.286)	0.990(0.805,1.218)	0.973(0.851,1.112)
		M2	1.002(0.978,1.027)#	1.038(0.840,1.283)	0.993(0.808,1.222)	0.984(0.860,1.125)
	Word recall	M1	0.997(0.969,1.026)	1.233**(1.077,1.412)	1.219**(1.061,1.401)	1.020(0.898,1.157)
		M2	0.997(0.969,1.025)	1.230**(1.074,1.409)	1.213**(1.055,1.395)	1.021(0.893,1.167)

Notes:
ψModels: (M1) age, sex and SEP adjusted, (M2) M1 + disease adjusted
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001
#analysis in WHII only
##analysis in CAPS only

Supplementary Table 8: Observational estimates for the associations between smoking and measures of cognitive decline - single cohort analyses

Outcome	Cohort	Modelψ	Cigarette per day OR (95% CI)	Current vs. ex smoker OR (95% CI)	Current vs. never smoker OR (95% CI)	Ever vs. never smoker OR (95% CI)
Search speed	NSHD	M1	1.001(0.978,1.025)	1.364*(1.043,1.784)	1.170(0.871,1.571)	0.934(0.751,1.161)
		M2	1.005(0.982,1.029)	1.359*(1.039,1.777)	1.174(0.874,1.577)	0.938(0.754,1.166)
Four choice reaction timeγ	CaPS	M1	1.021(0.990,1.054)	1.825***(1.295,2.572)	1.742*(1.128,2.690)	1.125(0.774,1.635)
		M2	1.017(0.981,1.054)	1.854**(1.281,2.684)	1.742*(1.082,2.803)	1.111(0.737,1.676)
Logical memory	LBC	M1	#	0.427(0.046,3.982)	0.409(0.046,3.650)	1.118(0.576,2.172)
		M2	#	0.419(0.044,4.026)	0.393(0.043,3.588)	1.236(0.624,2.448)
Raven's progressive matrices	LBC	M1	#	1.325(0.285,6.165)	2.668(0.545,13.052)	2.128*(1.074,4.219)
		M2	#	1.187(0.250,5.644)	2.990(0.588,15.191)	2.322*(1.153,4.677)

Notes:
ψModels: (M1) age, sex and SEP adjusted, (M2) M1 + disease adjusted
#Analysis not possible due to small sample size
γDecline in four choice reaction time was calculated using the bottom 25% decliners so that the outcome represents decline in cognitive ability over time
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Supplementary Table 9: Association between rs16969968 and covariates

Covariate	Effect (95% CI)	I^2 (p-value$^{\tau}$)
Age (years)	-0.000(-0.010,0.010)	0.00(0.455)
BMI	-0.019(-0.139,0.101)	20.82(0.264)
Height (cm)	-0.003(-0.203,0.197)	0.00(0.957)
Sex	1.016(0.974,1.059)	0.00(0.600)
Disease status	1.029(0.971,1.092)	0.00(0.935)
SEP (binary RGSC codes I or II versus RGSC codes III-V)	1.031(0.987,1.077)	0.00(0.984)

Effect sizes are regression coefficients for continuous outcome measures and odds ratios for binary measures.
τ: I^2 is the percentage of the variation across studies that is due to heterogeneity rather than chance(16). The p-value is for Cochran's Q statistic.

Supplementary Table 10: Associations between rs16969968 and outcomes stratified by smoking status - single cohort analyses

Outcome Category	Outcome	Cohort	Current smokers β (95% CI)	Never smokers β (95% CI)	Ever smokers β (95% CI)
Cognitive capability	Four choice reaction time##	CaPS	0.053(-0.097,0.204)	-0.068(-0.283,0.148)	0.031(-0.065,0.127)
	Logical memory	LBC	0.240(-0.547,1.027)	0.095(-0.116,0.305)	0.125(-0.062,0.313)
	Raven's progressive matrices	LBC	0.375(-0.360,1.111)	-0.124(-0.328,0.080)	-0.010(-0.193,0.174)
			Current smokers OR (95% CI)	Never smokers OR (95% CI)	Ever smokers OR (95% CI)
Cognitive capability decline	Search speed	NSHD	1.029(0.712,1.486)	0.997(0.747,1.330)	1.003(0.824,1.222)
	Four choice reaction time γ	CaPS	1.736*(1.131,2.664)	1.008(0.528,1.924)	1.263(0.945,1.690)
	Logical memory	LBC	#	1.541(0.720,3.297)	1.630(0.759,3.500)
	Raven's progressive matrices	LBC	#	1.057(0.425,2.630)	1.401(0.696,2.821)

Notes:
#Analysis not possible due to small sample size
##Inverse transformed
γDecline in four choice reaction time was calculated using the bottom 25% decliners so that the outcome represents decline in cognitive ability over time
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001
Models adjusted for age and sex.

Supplementary Table 11: Comparison of observational with instrumental variable estimates - single cohorts analyses

Observational association of interest			Observational estimate, β_O (95% CI)	IV estimate, β_{IV} (95% CI)
Smoking behaviour	Outcome	Cohort		
Current vs ex smoker	Four choice reaction time#	CaPS	-0.159**(-0.260,-0.058)	-11.376(-212.414,189.661)

Notes: IV: instrumental variable;
As explained in the methods, sample used to calculate observed and IV estimates differs according to the availability of variables
#Inverse transformed
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Heterogeneity statistics for meta-analysed estimates

Supplementary Table 12: Heterogeneity statistics for the observational estimates for the associations between smoking and physical capabilities (Table 2, main paper)

Outcome	Model$^{\psi}$	I^2 (p-value$^{\tau}$)			
		Cigarette per day$^{\delta}$	Current vs. ex smoker	Current vs. never smoker	Ever vs. never smoker
Grip strength	M1	0.00(0.576)	1.27(0.399)	57.83(0.050)	60.15(0.040)
	M2	0.00(0.710)	0.00(0.584)	54.30(0.068)	54.34(0.067)
	M3	0.00(0.684)	0.00(0.871)	34.55(0.191)	53.93(0.070)
Chair rise speed	M1	0.00(0.766)	30.01(0.232)	30.07(0.232)	0.00(0.403)
	M2	0.00(0.997)	22.13(0.278)	38.10(0.183)	18.51(0.298)
	M3	0.00(0.757)	20.50(0.287)	45.16(0.140)	5.02(0.368)
Walk speed	M1	37.14(0.174)	62.67(0.030)	36.02(0.181)	0.00(0.908)
	M2	17.97(0.300)	59.21(0.044)	29.22(0.227)	0.00(0.868)
	M3	56.98(0.054)	66.38(0.018)	57.23(0.053)	0.00(0.764)
TUG speed	M1	12.17(0.336)	6.29(0.371)	0.00(0.901)	57.69(0.051)
	M2	9.21(0.354)	0.00(0.740)	0.00(0.931)	52.83(0.076)
	M3	47.16(0.109)	0.00(0.791)	0.00(0.994)	29.08(0.228)
Inability to balance on one leg for 5s	M1	0.00(0.683)	0.00(0.672)	19.26(0.288)	0.00(0.709)
	M2	0.00(0.673)	0.00(0.833	0.00(0.423)	0.00(0.730)
	M3	0.00(0.778)	0.00(0.836)	13.18(0.330)	0.00(0.611)

Notes:
ψModels: (M1) age, sex and SEP adjusted, (M2) M1 + disease adjusted, (M3) M2 + height, BMI adjusted
δAssociation is for 1 CPD for comparison with genotypic analysis
τ I^2 is the percentage of the variation across studies that is due to heterogeneity rather than chance(16). The p-value is for Cochran's Q statistic.

Table 13: Heterogeneity statistics for the observational estimates for the associations between smoking and cognitive capabilities (Table 3, main paper)

	Outcome	Modelψ	I^2 (p-value$^{\tau}$)			
			Cigarette per day	Current vs. ex smoker	Current vs. never smoker	Ever vs. never smoker
Crystallized measures	Mill Hill	M1	0.00(0.871)	0.00(0.737)	0.00(0.686)	0.00(0.355)
		M2	0.00(0.840)	0.00(0.871)	0.00(0.555)	0.00(0.323)
	NART	M1	0.00(0.942)	38.31(0.198)	35.77(0.211)	0.00(0.897)
		M2	0.00(0.951)	13.95(0.313)	45.40(0.160)	0.00(0.856)
Fluid Measures	Gf	M1	72.99(0.005)	23.31(0.266)	34.84(0.189)	0.00(0.721)
		M2	70.30(0.009)	25.15(0.254)	40.81(0.149)	0.00(0.492)
	AH4	M1	40.59(0.186)	0.00(0.718)	0.00(0.562)	0.00(0.883)
		M2	45.68(0.159)	0.00(0.583)	0.22(0.367)	0.00(0.650)
	Semantic fluency	M1	55.00(0.064)	0.00(0.696)	55.18(0.063)	51.82(0.081)
		M2	52.97(0.075)	0.00(0.766)	57.00(0.054)	52.01(0.080)
	Phonemic fluency	M1	0.00(0.349)	71.96(0.059)	72.86(0.055)	0.00(0.954)
		M2	0.00(0.345)	61.60(0.107)	76.07(0.041)	0.00(0.688)
	Search speed#	M1	0.00(0.432)	52.72(0.121)	74.32(0.020)	32.00(0.230)
		M2	0.00(0.690)	58.19(0.091)	73.57(0.023)	22.52(0.275)
	Word recall	M1	43.43(0.151)	75.93(0.006)	49.89(0.112)	0.00(0.901)
		M2	40.73(0.167)	76.49(0.005)	52.38(0.098)	0.00(0.793)

Notes:
ψModels: (M1) age, sex and SEP adjusted, (M2) M1 + disease adjusted
#Natural log transformed
τ I^2 is the percentage of the variation across studies that is due to heterogeneity rather than chance(16). The p-value is for Cochran's Q statistic.

Table 14: Heterogeneity statistics for the observational estimates for the associations between smoking and measures of cognitive decline (Supplementary Table 7)

	Outcome	Modelψ	I^2 (p-value$^{\tau}$)			
			Cigarette per day	Current vs. ex smoker	Current vs. never smoker	Ever vs. never smoker
Crystallized	Mill Hill	M1	0.00(0.899)	14.36(0.280)	0.00(0.537)	0.00(0.790)
		M2	0.00(0.738)	17.00(0.272)	0.00(0.417)	0.00(0.758)
	NART	M1	##	0.00(0.523)	0.00(0.857)	0.00(0.484)
		M2	##	0.00(0.613)	0.00(0.692)	0.00(0.537)
Fluid Measures	AH4	M1	0.00(0.693)	6.08(0.345)	73.87(0.022)	59.08(0.087)
		M2	0.00(0.586)	0.00(0.379)	69.77(0.037)	38.88(0.195)
	Semantic fluency	M1	62.52(0.069)	33.15(0.224)	67.20(0.047)	31.28(0.233)
		M2	69.96(0.036)	22.29(0.276)	65.30(0.056)	33.50(0.222)
	Phonemic fluency	M1	#	0.00(0.741)	0.00(0.938)	0.00(0.775)
		M2	#	0.00(0.950)	0.00(0.871)	0.00(0.841)
	Word recall	M1	74.55(0.020)	0.00(0.824)	0.00(0.470)	41.37(0.182)
		M2	73.47(0.023)	0.00(0.857)	0.00(0.478)	46.72(0.153)

Notes:
ψModels: (M1) age, sex and SEP adjusted, (M2) M1 + disease adjusted
#analysis in WHII only
##analysis in CAPS only
τ I^2 is the percentage of the variation across studies that is due to heterogeneity rather than chance(16). The p-value is for Cochran's Q statistic.

Table 15: Heterogeneity statistics for the associations between rs16969968 and outcomes stratified by smoking status (Table 4, main paper)

Outcome Category	Outcome	I^2 (p-value$^{\tau}$)		
		Current smokers	Never smokers	Ever smokers
Physical capability	Grip strength	20.54(0.284)	55.79(0.060)	0.00(0.999)
	Chair rise speed	47.63(0.126)	49.81(0.113)	18.21(0.300)
	Walk speed	64.53(0.024)	0.00(0.623)	0.00(0.643)
	TUG speed	0.00(0.455)	0.00(0.681)	0.00(0.496)
Cognitive capability	Mill Hill	0.00(0.684)	0.00(0.619)	73.28(0.053)
	NART	0.00(0.885)	1.34(0.363)	0.00(0.484)
	Gf	0.00(0.803)	0.00(0.897)	0.00(0.702)
	AH4	0.00(0.784)	0.00(0.561)	0.00(0.511)
	Semantic fluency	40.45(0.152)	0.00(0.832)	0.00(0.551)
	Phonemic fluency	0.00(0.744)	0.00(0.739)	86.59(0.006)
	Search speed#	23.73(0.270)	44.80(0.163)	0.00(0.941)
	Word recall	0.00(0.509)	26.06(0.255)	0.00(0.813)
Physical capability	Inability to balance on one leg for 5s	26.86(0.233)	0.00(0.556)	0.00(0.987)
Cognitive capability decline	Mill Hill	33.46(0.220)	0.00(0.913)	0.00(0.603)
	NART	ψψ	0.00(0.674)	0.00(0.681)
	AH4	0.00(0.436)	0.00(0.444)	0.00(0.557)
	Semantic fluency	44.00(0.168)	75.69(0.016)	0.00(0.771)
	Phonemic fluency	ψ	22.18(0.257)	71.80(0.060)
	Word recall	0.00(0.819)	0.00(0.486)	0.00(0.708)

Notes: #Natural log transformed
ψanalysis in WHII only
ψψanalysis in CAPS only
Models adjusted for age and sex.
τ I^2 is the percentage of the variation across studies that is due to heterogeneity rather than chance(16). The p-value is for Cochran's Q statistic.

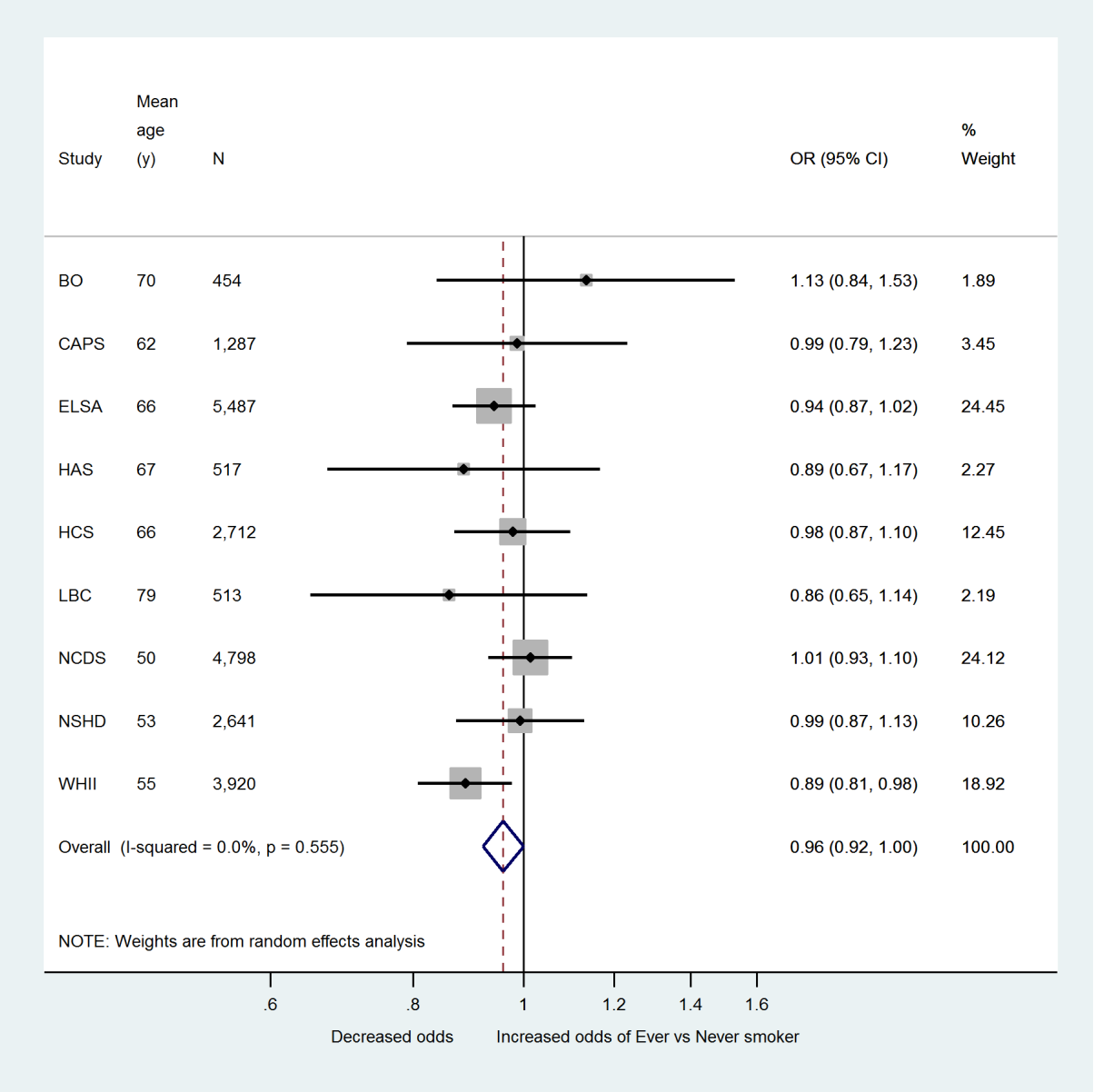
Table 16: Heterogeneity statistics for the IV estimates (Table 5, main paper)

Observational association of interest		I^2 (p-value$^{\tau}$)
Smoking behaviour	Outcome	
Cigarettes per day	Search speed#	27.95(0.250)
Current vs ex smoker	Grip strength	0.00(0.988)
	Walk speed	0.00(0.959)
	TUG speed	0.00(0.969)
	Chair rise speed	0.00(0.895)
	NART	0.00(0.818)
	Mill Hill	0.00(0.887)
	Gf	0.00(0.974)
	Semantic fluency	0.00(0.820)
	AH4	0.00(0.979)
	Word recall	0.00(0.973)
	Search speed#	0.00(0.984)

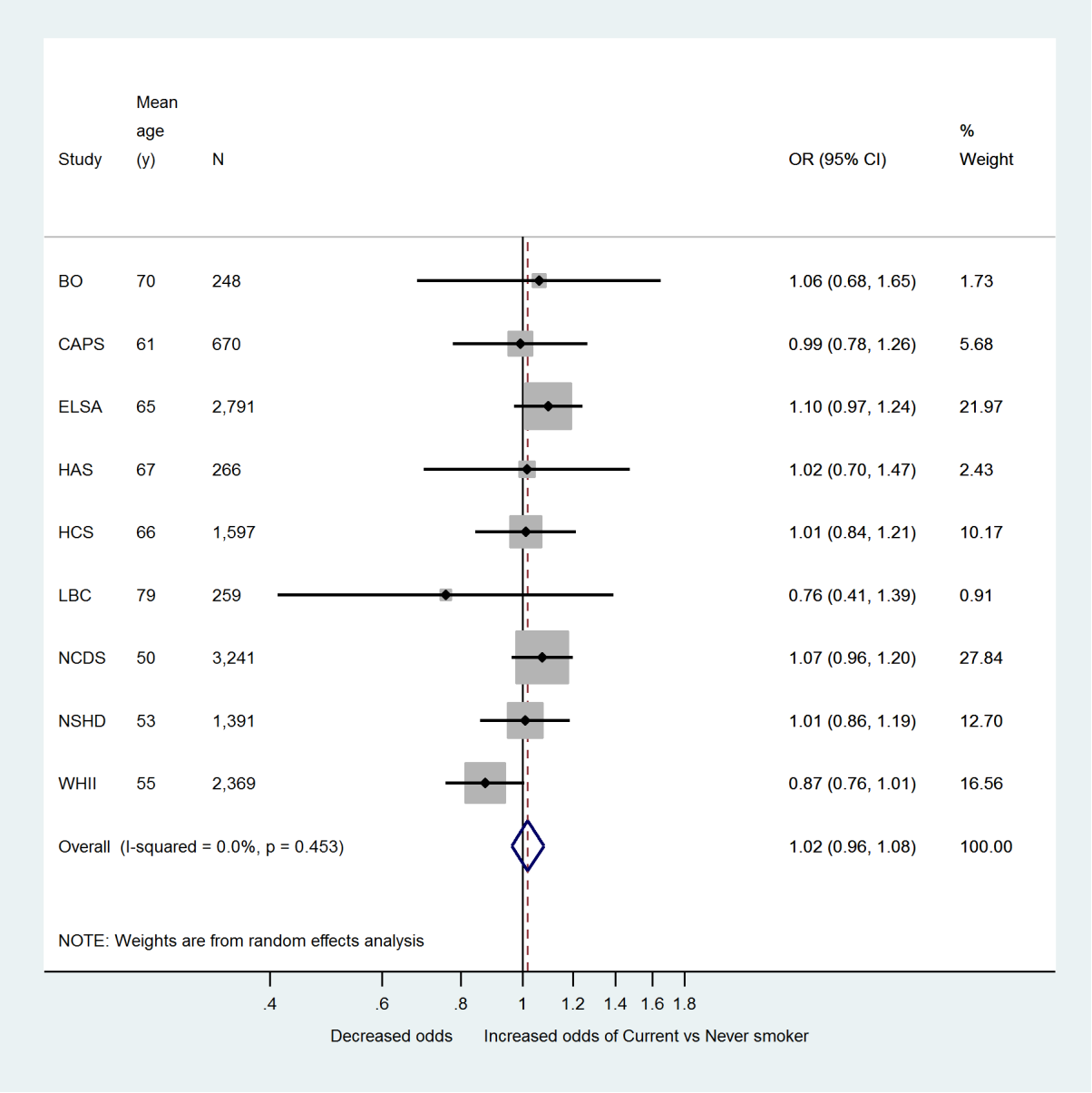
Notes:
#Natural log transformed
τ I^2 is the percentage of the variation across studies that is due to heterogeneity rather than chance(16). The p-value is for Cochran's Q statistic.

Supplementary Figures

Supplementary Figure 1: Meta-analysis of minor allele - ever versus never smoker association



Supplementary Figure 2: Meta-analysis of minor allele - current versus never smoker association



Cohort and other funding information

Cohorts

1958BC (NCDS) WTCCC: DNA collection was funded by MRC grant G0000934 and cell-line creation by Wellcome Trust grant 068545/Z/02. This study makes use of data generated by the Wellcome Trust Case-Control Consortium. A full list of investigators who contributed to generation of the data is available from the Wellcome Trust Case-Control Consortium website. Funding for the project was provided by the Wellcome Trust under the award 076113. Great Ormond Street Hospital/University College London, Institute of Child Health receives a proportion of funding from the Department of Health's National Institute for Health Research (NIHR) ('Biomedical Research Centres' funding).

1958BC (NCDS) T1DGC: DNA collection was funded by MRC grant G0000934 and cell-line creation by Wellcome Trust grant 068545/Z/02. This research used resources provided by the Type 1 Diabetes Genetics Consortium, a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases, National Human Genome Research Institute, National Institute of Child Health and Human Development, and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. Great Ormond Street Hospital/University College London, Institute of Child Health receives a proportion of funding from the Department of Health's National Institute for Health Research (NIHR) ('Biomedical Research Centres' funding).

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Samples from the English Longitudinal Study of Ageing (ELSA) DNA Repository (EDNAR), received support under a grant (AG1764406S1) awarded by the NIA. ELSA was developed by a team of researchers based at the National Centre for Social Research, University College London and the Institute of Fiscal Studies. The data were collected by the National Centre for Social Research.

BO: The Wellcome Trust funded R.M.M. to undertake the clinical third wave of follow-up of Boyd Orr (2002-03) as part of a research training fellowship in clinical epidemiology (grant GR063779FR).

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apply to access the NSHD data via a standard application procedure (further details available at: http://www.nshd.mrc.ac.uk/data.aspx).

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Researchers

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Cohort Ethical Approval

NCDS: Ethical approval for the 1958 birth cohort 45y survey (when DNA was collected) was obtained from South East Multi-centre Research Ethics Committee (ref. 01/1/44) and the Joint UCL/UCLH Committees on the Ethics of Human Research (Committee A) Ref: 08/H0714/40.

NSHD: Ethical approval for the NSHD data collection at 53 years was approved by the North Thames Multi-Centre Research Ethics Committee (ref. MREC 98/1/121). At 60–64 years ethical approval was obtained from the Central Manchester Local Research Ethics Committee (ref. 07/H1008/245) and the Scotland A Research Ethics Committee (ref. 08/MRE00/12). Written informed consent was obtained from study members at each stage of data collection.

English Longitudinal Study of Ageing (ELSA): ELSA has been approved by the National Research Ethics Service and all participants have given informed consent.

Whitehall II: All participants provided written consent and the University College London ethics committee approved the study.

BO: Ethical approval for the clinical third wave of follow-up of Boyd Orr (2002-03) was obtained from Multi-centre Research Ethics Committee Scotland. All participants gave informed consent.

LBC1921: Ethical approval for the Lothian Birth Cohort 1921 study was given by the Lothian Research Ethics Committee.

CAPS: Ethical approval for genotypic analyses was provided by South East Wales Local Research Ethics Committee Panel B (05/WSE02/131). The original CaPS project received ethical approval from the former South Glamorgan Area Health Authority.

HCS/HAS: Ethical approval for the Hertfordshire studies was obtained from the Hertfordshire Local Research Ethics Committee.

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