SUPPLEMENTARY DATA

Sixty-five common genetic variants and prediction of type 2 diabetes
Talmud et al

UCLEB consortium study members

Northwick Park Heart Study II (NPHS II): Philippa J Talmud[1], Steve E Humphries[1], Jackie A Cooper[1]

British Regional Heart Study (BRHS) Richard Morris[2], Peter Whincup[3], Goya Wannamethee[2], Barbara Jefferis[2]

British Women's Health and Heart Study: Caroline Dale[4], Antoinette Amuzu[4], Tom Gaunt[5,6] , Teri-Louise Davies[5,6], Debbie A Lawlor[5,6], Ian N Day[5,6]

Medical Research Council National Survey of Health and Development (MRC NSHD): Andrew Wong[7], Ken Ong[7,8], Marcus Richards[7], Rebecca Hardy[7], Diana Kuh[7]

Whitehall II Study (WHII): Mika Kivimaki[9,] Meena Kumari[9] Claudia Langenberg[8,9]

English Longitudinal Study of Ageing (ELSA): Meena Kumari[9]

1958 Birth cohort (1958BC) Christine Power[10], Elina Hypponen[10,11,12]

Caerphilly prospective study (CaPS): Yoav Ben-Shlomo[5], Ian N Day[5,6]

Edinburgh Artery Study (EAS); Edinburgh Type 2 Diabetes Study (ET2DS); Asymptomatic

Atherosclerosis Aspirin Trial (AAAT); Edinburgh Heart Disease Prevention Study (EHDPS) : Stela McLachlan[13], Mark WJ Strachan[14], Jacqueline Price[13]

Tina Shah[9] Jorgen Engmann[9] Jon White[15] Claudia Giambartolomei[15], Delilah Zabaneh[15,] Michael V Holmes[9,16] Daniel I Swerdlow[9] , Reecha Sofat[17], Mark Caulfield[18], Shah Ebrahim[4], Nicholas Wareham[8], Vincent Plagnol[15], Frank Dudbridge[4], John C Whittaker[19], Juan P Casas[4, 9] Aroon D Hingorani[9, 17]

[1] Centre for Cardiovascular Genetics, Dept. of Medicine, British Heart Foundation Laboratories, Rayne Building, Royal Free and University College Medical School, London, UK
[2] Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
[3] University College London Genetics Institute, Department of Genetics, Environment and Evolution, London[4]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
[5] School of Social and Community Medicine, University of Bristol, Bristol, UK
[6] MRC Integrative Epidemiology Unit at the University of Bristol, UK
[7]MRC Unit for Lifelong Health and Ageing, London, UK
[8]MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK
[9]Department of Epidemiology & Public Health, UCL Institute of Epidemiology & Health Care, University College London, London, UK

SUPPLEMENTARY DATA

[10] Centre for Paediatric Epidemiology and Biostatistics, University College London Institute of Child Health, London
[11] School of Population Health and Sansom Institute, University of South Australia, Adelaide, Australia
[12]South Australian Health and Medical Research Institute, Adelaide, Australia
[13] Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK
[14] Metabolic Unit, Western General Hospital, Edinburgh, UK
[15]University College London Genetics Institute, Department of Genetics, Environment and Evolution, London, UK
[16]Division of Transplant Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
[17]Centre for Clinical Pharmacology, University College London, London, UK
[18]William Harvey Research Institute, Barts and the London. Queen Mary's School of Medicine and Dentistry, London, UK
[19] Genetics Division, Research and Development, GlaxoSmithKline, Harlow, UK

Supplementary Research Design

Details of the Prospective cohorts used in this analysis

British Regional Heart Study (BRHS): (1) From 1978 to 1980, 7735 men aged 40-59 were recruited from general practices across the UK. A wide range of phenotypic measures is available for established risk markers such as lipids, blood pressure and inflammatory and haemostatic markers. Most of these measures were taken both at recruitment and re-examination, which occurred in 1998-2000 when men were aged 60-79. At this re-examination 4252 participants attended and DNA was extracted for 3945. A case-control sample was selected using 1095 cases with prevalent data at re-examination or incident cases of CHD or stroke over the next 8 years and 1358 controls. The controls were frequency matched based on being in the same town and within the same fixed 5-year age band as the cases. Data on important behavioural variables such as cigarette and alcohol consumption, as well as physical activity, have been regularly collected through follow up. Well validated outcome variables such as major coronary heart disease, stroke, diabetes, and revascularisation, as well as cause-specific mortality, continue to be collected from medical records almost 30 years after recruitment. (http://www.ucl.ac.uk/pcph/research-groups-themes/brhs-pub)

SUPPLEMENTARY DATA

British Women's Heart and Health Study (BWHHS): (2) The British Women's Heart & Health Study (BWHHS) is a prospective cohort study of 4,286 women aged between 60 and 79 at baseline in 1999-2001. Participants were randomly selected from general practice registers in 23 towns across England, Wales and Scotland. The criteria for the sampling frame and clinic protocols were very similar to the 20 year follow-up of BRHS. Baseline measurements included biomarkers and blood samples for DNA extraction taken by research nurses as well as ascertainment of a wide range of phenotypic measures. Follow-up by postal questionnaire was undertaken in 2003, 2007 and 2010-2011. Of the 4,278 participants who gave consent for genetic studies, 15 were defined by the examining nurse as being non-white and were excluded from further analysis. Of the remaining 4,263 women, 3,800 (89%) had DNA available for genotyping. Survival status is obtained from the Data Linkage Service, Health and Social Care Information Centre, London and CVD events have been prospectively studied by biennial review of primary care medical records with validation checks. The UCLEB case-control sample was selected based on 523 cases with prevalent or incident CHD or stroke. 1501 controls were frequency matched based on being in the same town and within the same fixed 5-year age band as the cases. For these analyses prevalent T2D was ascertained from either self-report, medical record review, use of glucose lowering medication, and/or a fasting glucose >7mmol/L. Incident T2D to 2007 was determined by self-report, medical record review or use of glucose lowering medication. Ethical approval was granted for the BWHHS from the London Multi-Centre Research Ethics Committee and 23 Local Research Ethics Committees.

Medical Research Council National Survey of Health and Development (MRC NSHD): (3) This is an on-going prospective birth cohort study consisting of all births in England, Scotland and Wales in one week in March 1946. The sample includes single, legitimate births whose fathers were in non-manual or agricultural occupations and a randomly selected one in four of all others, whose fathers were in manual labour. The original cohort, now 68 years of age, comprised 2,547 women and 2,815 men who have been followed-up over 20 times since their birth. The data collected to date include repeat cognitive function, physical, lifestyle and anthropomorphic measures, as well as blood analytes and other measures. The cohort recently completed a particularly intensive phase of clinical assessment and biological sampling with blood and urine sampling and analysis, and cardiac and vascular imaging [29](4). DNA was extracted from blood samples collected in 1999 (5). Follow-up for disease outcomes is by self-reports of doctor diagnosed events that have been validated against General Practice (GP) records. (http://www.nshd.mrc.ac.uk/).

Edinburgh Artery Study (EAS): (6) At baseline (August 1987-September 1988), an age-stratified random sample of men and women, aged 55-74 years, was selected from the age-sex registers of ten general practices with catchment populations spread geographically and socioeconomically throughout the city of Edinburgh. Subjects were excluded if they were unfit to participate (e.g. due to severe mental illness or terminal disease). These exclusions were replaced by other randomly sampled subjects. The study population is almost exclusively European. DNA was extracted at 5 years follow-up. Physical examinations were performed by specially trained research nurses using standardised operating procedures. The quality of clinical measurements were checked before and during the study by repeat measurements taken intermittently by the study co-ordinator. Individual observer measurements were assessed for drift. Blood assays were performed in accredited laboratories using international standards. Subjects have been followed up for 20 years for cardiovascular events, using repeat self-reporting questionnaires, record linkage for hospitalisations and deaths, and validation of events against pre-specified criteria through searching of hospital and GP notes. Comprehensive clinical examination was repeated at 5 and 12 years after commencement of the study, resulting in repeat measurements of several key variables.

SUPPLEMENTARY DATA

Whitehall II Study (WHII): (7) Whitehall II recruitment of 10,308 participants (70% men) between 1985 and 1988 involved 20 London based Civil service departments. Genetic samples were collected in 2004 from over 6,000 participants. The study is highly phenotyped for cardiovascular and other ageing related health outcomes, with 9 phases of follow up (5 with clinical assessment and biological sampling), over 20 years of follow up. A wide variety of health behaviour and 7 environmental data are also collected and the participants are consented for linkage to recorded clinical data such as Hospital Episode Statistics (HES), the Office of National Statistics mortality data and the national registry of acute coronary syndromes in England and Wales (Myocardial Ischaemia National Audit Project). (http://www.ucl.ac.uk/whitehallII/)

English Longitudinal Study of Ageing (ELSA): (8) This is a national cohort of participants (48% men) aged over 50 years recruited from the Health Surveys for England in 1998, 1999 and 2001. Genetic data were collected at Wave 2 of the study (2004/5). A wide range of phenotypic measures relevant to ageing are available. These measures were made at Wave 0 of the study (1998, 1999 and 2001) and at follow up (2004/5). Data on health behaviours and a wide range of health outcomes are available. Nearly all participants (97%) are also consented to linkage to routine data such as HES, which allows for the assessment of health outcomes and cause specific mortality. A case-control sample was selected using 412 cases and 1573 controls. Controls and cases were matched by sex and 5-year age bands at Wave 2. (http://www.ifs.org.uk/elsa/)**.** Age in ELSA was collapsed at 90+ (and coded 90).

Caerphilly prospective study (CaPS):(9) This study is based on men aged between 45 to 59 years who resided in the small South Wales town of Caerphilly between the examination dates of 1979 &1983. Of the 2818 eligible, 2512, (89%) were recruited. The men were studied at baseline (Phase 1) and each subsequent 5 year period (Phase 2–5) and have therefore been followed up for around 20 years. An additional 447 patients were recruited at phase 2. The cohort has a wide range of cardiovascular phenotypes and at phase 3, cognitive function was also assessed, which has been supplemented with clinical dementia and cognitive impairment at phase 5. DNA was extracted from blood samples collected in 1992–1994. Follow-up for disease outcomes is by self-report from participants, who are also linked to hospital episode discharge summaries for validation checks to comply with WHO criteria, as well as death certificates for fatal events.

SUPPLEMENTARY DATA

Supplementary Table 1. Details of published T2D risk variants (10) used in the risk analysis and their internal and external odds ratios

RS number	CHR	Chr position (hg18)	Gene	Risk allele/Other	Risk allele freq	external OR -effect from published data	internal OR - effect from combined studies
rs10923931	1	120,319,482	*NOTCH2*	T/G	0.12	1.08	1.13
rs2075423	1	212,221,342	*PROX1*	G/T	0.62	1.07	1.07
rs780094	2	27,594,741	*GCKR*	C/T	0.61	1.06	1.07
rs10203174	2	43,543,534	*THADA*	C/T	0.89	1.14	1.10
rs243088	2	60,422,249	*BCL11A*	T/A	0.45	1.07	1.04
rs7569522	2	161,054,693	*RBMS1*	A/G	0.44	1.05	1.06
rs13389219	2	165,237,122	*GRB14*	C/T	0.60	1.07	1.07
rs2943640	2	226,801,829	*IRS1*	C/A	0.63	1.1	1.14
rs1801282	3	12,368,125	*PPARG*	C/G	0.86	1.13	1.05
rs1496653	3	23,429,794	*UBE2E2*	A/G	0.75	1.09	0.93
rs12497268	3	64,065,403	*PSMD6*	G/C	0.80	1.03	1.04
rs6795735	3	64,680,405	*ADAMTS9*	C/T	0.59	1.08	0.98
rs11717195	3	124,565,088	*ADCY5*	T/C	0.77	1.11	1.07
rs4402960	3	186,994,381	*IGF2BP2*	T/G	0.33	1.13	1.18
rs17301514	3	188,096,103	*ST64GAL1*	A/G	0.13	1.05	1.01
rs6819243	4	1,283,245	*MAEA*	T/C	0.96	1.07	1.32
rs4458523	4	6,340,887	*WFS1*	G/T	0.57	1.1	1.07
rs459193	5	55,842,508	*ANKRD55*	G/A	0.70	1.08	1.03
rs6878122	5	76,463,067	*ZBED3*	G/A	0.28	1.1	0.98
rs7756992	6	20,787,688	*CDKAL1*	G/A	0.29	1.17	1.19
rs4299828	6	38,285,645	*ZFAND3*	A/G	0.79	1.04	0.96
rs3734621	6	39,412,189	*KCNK16*	C/A	0.03	1.07	1.27
rs17168486	7	14,864,807	*DGKB*	T/C	0.19	1.11	1.02
rs849135	7	28,162,938	*JAZF1*	G/A	0.52	1.11	1.14
rs10278336	7	44,211,888	*GCK*	A/G	0.50	1.07	1.00
rs17867832	7	126,784,073	*GCC1*	T/G	0.91	1.09	0.94
rs13233731	7	130,088,229	*KLF14*	G/A	0.51	1.05	0.99
rs516946	8	41,638,405	*ANK1*	C/T	0.76	1.09	0.99
rs7845219	8	96,006,678	*TP53INP1*	T/C	0.52	1.06	1.11
rs3802177	8	118,254,206	*SLC30A8*	G/A	0.66	1.14	1.09
rs10758593	9	4,282,083	*GLIS3*	A/G	0.42	1.06	0.95

rs16927668	9	8,359,533	*PTPRD*	T/C	0.24	1.04	1.11
rs10811661	9	22,124,094	*CDKN2A/B*	T/C	0.82	1.18	1.18
rs17791513	9	81,095,410	*TLE4*	A/G	0.91	1.12	1.43
rs2796441	9	83,498,768	*TLE1*	G/A	0.57	1.07	1.08
rs11257655	10	12,347,900	*CDC123/CAMK1D*	T/C	0.23	1.07	1.05
rs12242953	10	70,535,348	*VPS26A*	G/A	0.93	1.07	0.96
rs12571751	10	80,612,637	*ZMIZ1*	A/G	0.52	1.08	1.11
rs1111875	10	94,452,862	*HHEX/IDE*	C/T	0.58	1.11	1.02
rs7903146	10	114,748,339	*TCF7L2*	T/C	0.27	1.39	1.32
rs2334499	11	1,653,425	*DUSP8*	T/C	0.43	1.04	1.07
rs163184	11	2,803,645	*KCNQ1*	G/T	0.50	1.09	1.11
rs5215	11	17,365,206	*KCNJ11*	C/T	0.41	1.07	1.16
rs1552224	11	72,110,746	*ARAP1 (CENTD2)*	A/C	0.81	1.11	1.14
rs10830963	11	92,348,358	*MTNR1B*	G/C	0.31	1.1	1.07
rs11063069	12	4,244,634	*CCND2*	G/A	0.21	1.08	1.04
rs10842994	12	27,856,417	*KLHDC5*	C/T	0.80	1.1	1.11
rs2261181	12	64,498,585	*HMGA2*	T/C	0.10	1.13	1.04
rs7955901	12	69,719,560	*TSPAN8/LGR5*	C/T	0.45	1.07	0.93
rs12427353	12	119,911,284	*HNF1A (TCF1)*	G/C	0.79	1.08	1.08
rs1359790	13	79,615,157	*SPRY2*	G/A	0.72	1.08	1.08
rs4502156	15	60,170,447	*C2CD4A*	T/C	0.52	1.06	1.06
rs7177055	15	75,619,817	*HMG20A*	A/G	0.68	1.08	1.09
rs11634397	15	78,219,277	*ZFAND6*	G/A	0.64	1.05	1.08
rs2007084	15	88,146,339	*AP3S2*	G/A	0.92	1.02	1.07
rs12899811	15	89,345,080	*PRC1*	G/A	0.31	1.08	0.97
rs9936385	16	52,376,670	*FTO*	C/T	0.41	1.13	1.18
rs7202877	16	73,804,746	*BCAR1*	T/G	0.89	1.12	1.00
rs2447090	17	2,245,724	*SRR*	A/G	0.62	1.04	0.95
rs11651052	17	33,176,494	*HNF1B (TCF2)*	A/G	0.44	1.1	1.02
rs12970134	18	56,035,730	*MC4R*	A/G	0.27	1.08	1.08
rs10401969	19	19,268,718	*CILP2*	C/T	0.08	1.13	1.05
rs8182584	19	38,601,550	*PEPD*	T/G	0.38	1.04	1.08
rs8108269	19	50,850,353	*GIPR*	G/T	0.31	1.07	1.03
rs4812829	20	42,422,681	*HNF4A*	A/G	0.19	1.06	1.09

SUPPLEMENTARY DATA

Supplementary Table 2. Odds ratios by study for the Framingham Offspring T2D score, the externally weighted gene score and the two combined for each of the seven studies

	BRHS	BWHHS	EAS	MRC NSHD	WHII	ELSA	CAPS	Total
FORS								
OR per SD increase (95% CI) P value	2.47 (2.05-2.98) $5.46x10^{-21}$	3.16 (2.40-4.16) $2.21x10^{-16}$	1.87 (1.10-3.17) 0.02	3.45 (2.60-4.59) $1.23x10^{-17}$	2.53 (2.20-2.92) $5.83x10^{-38}$	2.34 (1.80-3.03) $2.02x10^{-10}$	3.11 (2.52-3.84) $9.60x10^{-26}$	2.70 (2.48-2.93) $P=5.4x10^{-121}$
OR Top vs. bottom quintile (95% CI) P value	25.40 (6.19-104.19) 7.12x10-6	12.52 (3.04-51.60) 0.0005	*	23.87 (3.31-172.40) 0.002	17.37 (10.73-28.12) $3.26x10^{-31}$	19.44 (4.58-82.50) 0.00006	22.33 (7.93-62.91) 4.10x10-9	21.07 (14.86-29.88) $1.48x10^{-65}$
Externally weighted gene score								
OR per SD increase (95% CI) P value	1.41 (1.19-1.67) 0.00008	1.39 (1.14-1.70) 0.001	1.59 (0.98-2.57) 0.06	1.53 (1.27-1.85) $9.00x10^{-6}$	1.25 (1.09-1.44) 0.001	1.60 (1.27-2.01) 0.0001	1.63 (1.35-1.98) $4.42x10^{-7}$	1.43 (1.33-1.54) $P=2.25x10^{-22}$
OR Top vs. bottom quintile (95% CI) P value	2.42 (1.36-4.30) 0.003	2.46 (1.33-4.57) 0.004	1.78 (0.29-10.84) 0.53	4.01 (1.99-8.11) 0.0001	1.99 (1.28-3.09) 0.002	3.72 (1.66-8.35) 0.001	3.72 (1.94-7.13) 0.00008	2.70 (2.12-3.43) $P=7.03x10^{-16}$
FORS+ externally weighted gene score								
OR per SD increase (95% CI) P value	2.62 (2.17-3.17) 3.77x10-23	3.34 (2.54-4.38) 4.32x10-18	2.10 (1.23-3.57) 0.006	3.85 (2.90-5.11) 1.16x10-20	2.53 (2.19-2.91) 1.27x10-37	2.61 (2.00-3.39) 1.00x10-12	3.29 (2.65-4.07) 1.79x10-27	2.83 (2.61-3.08) 3.08x10-132
OR Top vs. bottom quintile (95% CI) P value	60.29 (8.34-435.59) 0.00005	25.15 (3.47-182.35) 0.001	-	13.21 (3.22-54.12) 0.0003	16.02 (9.88-25.98) $2.32x10^{-29}$	25.31 (6.05-105.94) $9.87x10^{-6}$	33.55 (10.35-108.78) $4.92x10^{-9}$	22.59 (15.75-32.41) $1.24x10^{-63}$

*****Not calculated because of zero counts in the bottom quintile

SUPPLEMENTARY DATA

Supplementary Table 3. Association of the 65 T2D risk SNPs with traits of interest (significance level p<0.0008 after Bonferroni correction).

After correction for multiple testing, eight of the variants contributing to the T2D genetic risk score were also associated with non-genetic variables included in the FORS algorithm*:* *MC4R* and *FTO* with BMI, GCK, *SLC30A8* and *TCF7L2* with fasting glucose, *IRS1* with HDL-cholesterol, *GCKR* and *CILP2* with triglyceride concentration.

a) Body Mass Index

Nearest gene(s)	SNP	Effect allele	b	se	P value
FTO	rs9936385	C	0.238	0.05	$1.94x10^{-6}$
MC4R	rs12970134	A	0.229	0.055	$3.13x10^{-5}$
THADA	rs10203174	C	-0.195	0.076	0.01
SLC30A8	rs3802177	G	-0.129	0.052	0.014
C2CD4A	rs4502156	T	-0.11	0.049	0.024
AP3S2	rs2007084	G	0.192	0.086	0.025
MAEA	rs6819243	T	0.313	0.159	0.05
CDKAL1	rs7756992	G	-0.101	0.055	0.066
ANKRD55	rs459193	G	-0.093	0.055	0.094
IGF2BP2	rs4402960	T	-0.076	0.053	0.15
VPS26A	rs12242953	G	-0.133	0.098	0.177
SPRY2	rs1359790	G	0.071	0.053	0.18
GRB14	rs13389219	C	-0.065	0.049	0.188
ANK1	rs516946	C	-0.071	0.057	0.21
HMG20A	rs7177055	A	0.065	0.054	0.226
DGKB	rs17168486	T	-0.077	0.064	0.229
KLF14	rs13233731	G	-0.057	0.049	0.242
GCKR	rs780094	C	0.058	0.05	0.245
KCNQ1	rs163184	G	0.054	0.048	0.262
TSPAN8/LGR5	rs7955901	C	-0.054	0.049	0.268
CDC123/CAMK1D	rs11257655	T	0.064	0.06	0.289
UBE2E2	rs1496653	A	-0.061	0.06	0.308
GCK	rs10278336	A	-0.048	0.049	0.33
ADCY5	rs11717195	T	-0.054	0.056	0.336
GLIS3	rs10758593	A	-0.042	0.049	0.386
ADAMTS9	rs6795735	C	-0.042	0.049	0.392
RBMS1	rs7569522	A	-0.041	0.048	0.395
ZFAND6	rs11634397	G	-0.041	0.051	0.423
KLHDC5	rs10842994	C	-0.047	0.06	0.431
JAZF1	rs849135	G	-0.036	0.048	0.457
TP53INP1	rs7845219	T	0.035	0.048	0.467
CILP2	rs10401969	C	-0.065	0.091	0.478

SUPPLEMENTARY DATA

CCND2	rs11063069	G	-0.041	0.059	0.482
KCNJ11	rs5215	C	-0.035	0.051	0.485
PEPD	rs8182584	T	0.033	0.05	0.505
HHEX/IDE	rs1111875	C	-0.028	0.049	0.571
ZMIZ1	rs12571751	A	0.024	0.048	0.621
MTNR1B	rs10830963	G	0.026	0.054	0.631
ST64GAL1	rs17301514	A	0.036	0.078	0.648
DUSP8	rs2334499	T	-0.022	0.049	0.657
HNF4A	rs4812829	A	0.029	0.066	0.664
HMGA2	rs2261181	T	0.035	0.083	0.669
TCF7L2	rs7903146	T	-0.022	0.053	0.681
IRS1	rs2943640	C	-0.017	0.05	0.743
CDKN2A/B	rs10811661	T	0.02	0.064	0.761
HNF1B (TCF2)	rs11651052	A	0.014	0.048	0.765
TLE4	rs17791513	A	0.028	0.1	0.779
WFS1	rs4458523	G	-0.011	0.049	0.83
KCNK16	rs3734621	C	0.033	0.156	0.831
GIPR	rs8108269	G	0.011	0.054	0.839
BCL11A	rs243088	T	-0.01	0.048	0.841
ARAP1 (CENTD2)	rs1552224	A	-0.013	0.067	0.842
HNF1A (TCF1)	rs12427353	G	-0.01	0.061	0.869
NOTCH2	rs10923931	T	0.013	0.078	0.87
PSMD6	rs12497268	G	0.01	0.064	0.872
BCAR1	rs7202877	T	0.013	0.082	0.877
PROX1	rs2075423	G	-0.007	0.051	0.896
SRR	rs2447090	A	0.005	0.05	0.921
PTPRD	rs16927668	T	0.006	0.06	0.922
GCC1	rs17867832	T	0.01	0.119	0.933
PPARG	rs1801282	C	-0.006	0.073	0.933
TLE1	rs2796441	G	-0.004	0.049	0.937
ZBED3	rs6878122	G	-0.004	0.052	0.94
ZFAND3	rs4299828	A	0.002	0.061	0.977
PRC1	rs12899811	G	0.001	0.053	0.979

SUPPLEMENTARY DATA

b) Glucose

Nearest gene(s)	SNP	Effect allele	b	se	P value
TCF7L2	rs7903146	T	0.052	0.011	$2.28x10^{-}$
GCK	rs10278336	A	0.041	0.01	$4.13x10^{-5}$
SLC30A8	rs3802177	G	0.039	0.011	0.000392
GLIS3	rs10758593	A	0.035	0.01	0.001
PROX1	rs2075423	G	0.031	0.011	0.003
MTNR1B	rs10830963	G	0.034	0.011	0.003
BCL11A	rs243088	T	0.027	0.01	0.008
JAZF1	rs849135	G	0.027	0.01	0.009
CDKAL1	rs7756992	G	0.03	0.011	0.009
KLHDC5	rs10842994	C	0.033	0.013	0.01
HNF1A (TCF1)	rs12427353	G	0.031	0.013	0.014
UBE2E2	rs1496653	A	0.031	0.012	0.014
KCNQ1	rs163184	G	0.023	0.01	0.023
IRS1	rs2943640	C	0.024	0.011	0.026
ADCY5	rs11717195	T	0.023	0.012	0.049
CDKN2A/B	rs10811661	T	0.025	0.013	0.059
TP53INP1	rs7845219	T	0.019	0.01	0.063
THADA	rs10203174	C	0.027	0.016	0.088
HMG20A	rs7177055	A	0.017	0.011	0.12
ANKRD55	rs459193	G	0.018	0.012	0.122
ARAP1 (CENTD2)	rs1552224	A	0.022	0.014	0.123
GCKR	rs780094	C	0.015	0.01	0.165
SRR	rs2447090	A	-0.013	0.01	0.224
TLE1	rs2796441	G	0.012	0.01	0.231
HNF4A	rs4812829	A	-0.017	0.014	0.234
ZBED3	rs6878122	G	0.012	0.011	0.269
TSPAN8/LGR5	rs7955901	C	-0.011	0.01	0.276
SPRY2	rs1359790	G	-0.011	0.011	0.302
HMGA2	rs2261181	T	-0.018	0.017	0.302
FTO	rs9936385	C	0.011	0.01	0.302
PSMD6	rs12497268	G	-0.013	0.013	0.332
HNF1B (TCF2)	rs11651052	A	0.01	0.01	0.34
ANK1	rs516946	C	0.011	0.012	0.346
C2CD4A	rs4502156	T	-0.009	0.01	0.384
CCND2	rs11063069	G	-0.011	0.012	0.393
GIPR	rs8108269	G	0.009	0.011	0.402
CDC123/CAMK1D	rs11257655	T	0.01	0.013	0.411
DUSP8	rs2334499	T	-0.008	0.01	0.412
HHEX/IDE	rs1111875	C	0.008	0.01	0.422

SUPPLEMENTARY DATA

TLE4	rs17791513	A	0.016	0.021	0.459
NOTCH2	rs10923931	T	-0.012	0.016	0.465
PRC1	rs12899811	G	-0.008	0.011	0.488
VPS26A	rs12242953	G	0.014	0.021	0.509
KCNJ11	rs5215	C	-0.007	0.011	0.526
PPARG	rs1801282	C	0.01	0.015	0.531
ZFAND3	rs4299828	A	-0.008	0.013	0.555
IGF2BP2	rs4402960	T	0.006	0.011	0.557
GRB14	rs13389219	C	0.005	0.01	0.636
MAEA	rs6819243	T	-0.015	0.033	0.659
ST64GAL1	rs17301514	A	-0.007	0.016	0.681
DGKB	rs17168486	T	0.005	0.013	0.683
ADAMTS9	rs6795735	C	-0.004	0.01	0.718
WFS1	rs4458523	G	0.003	0.01	0.796
ZMIZ1	rs12571751	A	0.003	0.01	0.796
BCAR1	rs7202877	T	0.004	0.017	0.833
ZFAND6	rs11634397	G	0.002	0.011	0.86
RBMS1	rs7569522	A	-0.002	0.01	0.863
KLF14	rs13233731	G	-0.002	0.01	0.867
GCC1	rs17867832	T	0.004	0.025	0.872
MC4R	rs12970134	A	-0.002	0.011	0.874
KCNK16	rs3734621	C	-0.004	0.033	0.91
PTPRD	rs16927668	T	-0.001	0.013	0.911
AP3S2	rs2007084	G	0.001	0.018	0.943
CILP2	rs10401969	C	-0.001	0.019	0.952
PEPD	rs8182584	T	0	0.01	0.996

SUPPLEMENTARY DATA

c) HDL

Nearest gene(s)	SNP	Effect allele	b	se	p-value
IRS1	rs2943640	C	-0.021	0.005	2.67×10^{-5}
ANKRD55	rs459193	G	-0.016	0.005	0.002
GCK	rs10278336	A	-0.011	0.005	0.013
C2CD4A	rs4502156	T	0.01	0.005	0.023
SPRY2	rs1359790	G	0.008	0.005	0.11
HMG20A	rs7177055	A	-0.008	0.005	0.111
KCNQ1	rs163184	G	-0.007	0.005	0.145
WFS1	rs4458523	G	-0.007	0.005	0.146
JAZF1	rs849135	G	0.006	0.005	0.18
PPARG	rs1801282	C	-0.009	0.007	0.181
BCAR1	rs7202877	T	-0.01	0.008	0.207
AP3S2	rs2007084	G	0.01	0.008	0.208
NOTCH2	rs10923931	T	0.009	0.007	0.211
TSPAN8/LGR5	rs7955901	C	0.006	0.005	0.217
ZMIZ1	rs12571751	A	-0.006	0.004	0.217
GCKR	rs780094	C	-0.006	0.005	0.229
PRC1	rs12899811	G	0.006	0.005	0.235
TP53INP1	rs7845219	T	-0.005	0.005	0.238
MTNR1B	rs10830963	G	0.006	0.005	0.251
CCND2	rs11063069	G	-0.006	0.005	0.252
ST64GAL1	rs17301514	A	-0.007	0.007	0.309
UBE2E2	rs1496653	A	0.006	0.006	0.309
KLF14	rs13233731	G	-0.004	0.005	0.338
HNF1A (TCF1)	rs12427353	G	0.005	0.006	0.354
MC4R	rs12970134	A	-0.005	0.005	0.357
ADCY5	rs11717195	T	0.005	0.005	0.373
FTO	rs9936385	C	-0.004	0.005	0.378
KLHDC5	rs10842994	C	0.005	0.006	0.382
DGKB	rs17168486	T	0.005	0.006	0.39
THADA	rs10203174	C	0.006	0.007	0.406
CILP2	rs10401969	C	-0.007	0.008	0.423
ZFAND3	rs4299828	A	0.004	0.006	0.427
DUSP8	rs2334499	T	-0.004	0.005	0.435
HNF4A	rs4812829	A	-0.005	0.006	0.444
VPS26A	rs12242953	G	-0.007	0.009	0.473
SRR	rs2447090	A	0.003	0.005	0.492
PTPRD	rs16927668	T	0.004	0.006	0.516
GIPR	rs8108269	G	-0.003	0.005	0.547
HNF1B (TCF2)	rs11651052	A	0.003	0.004	0.547

SUPPLEMENTARY DATA

TLE4	rs17791513	A	0.006	0.009	0.549
ADAMTS9	rs6795735	C	-0.003	0.005	0.552
KCNJ11	rs5215	C	-0.003	0.005	0.575
GLIS3	rs10758593	A	0.002	0.005	0.614
ANK1	rs516946	C	0.002	0.005	0.649
CDC123/CAMK1D	rs11257655	T	-0.002	0.006	0.661
SLC30A8	rs3802177	G	0.002	0.005	0.673
CDKN2A/B	rs10811661	T	-0.002	0.006	0.679
ARAP1 (CENTD2)	rs1552224	A	0.002	0.006	0.694
CDKAL1	rs7756992	G	0.002	0.005	0.716
BCL11A	rs243088	T	-0.002	0.004	0.727
KCNK16	rs3734621	C	-0.005	0.015	0.735
MAEA	rs6819243	T	0.005	0.015	0.75
GCC1	rs17867832	T	0.003	0.011	0.775
PEPD	rs8182584	T	-0.001	0.005	0.781
ZFAND6	rs11634397	G	0.001	0.005	0.789
HMGA2	rs2261181	T	-0.002	0.008	0.807
GRB14	rs13389219	C	-0.001	0.005	0.846
PROX1	rs2075423	G	-0.001	0.005	0.872
PSMD6	rs12497268	G	0.001	0.006	0.901
TCF7L2	rs7903146	T	-0.001	0.005	0.917
IGF2BP2	rs4402960	T	0	0.005	0.931
TLE1	rs2796441	G	0	0.005	0.938
RBMS1	rs7569522	A	0	0.005	0.963
HHEX/IDE	rs1111875	C	0	0.005	0.988
ZBED3	rs6878122	G	0	0.005	0.995

SUPPLEMENTARY DATA

d) Systolic Blood pressure

Nearest gene(s)	SNP	Effect allele	b	se	p-value
FTO	rs9936385	C	0.768	0.262	0.003
IRS1	rs2943640	C	0.765	0.266	0.004
IGF2BP2	rs4402960	T	0.757	0.277	0.006
PRC1	rs12899811	G	-0.6	0.278	0.031
RBMS1	rs7569522	A	0.388	0.255	0.128
MAEA	rs6819243	T	1.261	0.839	0.133
TLE1	rs2796441	G	0.384	0.259	0.138
ADCY5	rs11717195	T	-0.41	0.295	0.164
KCNK16	rs3734621	C	-1.098	0.821	0.181
KLF14	rs13233731	G	-0.34	0.257	0.185
TP53INP1	rs7845219	T	0.329	0.255	0.197
CDKAL1	rs7756992	G	0.357	0.288	0.216
SLC30A8	rs3802177	G	0.313	0.276	0.256
AP3S2	rs2007084	G	-0.505	0.453	0.265
GRB14	rs13389219	C	0.274	0.26	0.292
TLE4	rs17791513	A	0.534	0.527	0.311
SRR	rs2447090	A	0.242	0.264	0.36
HMGA2	rs2261181	T	-0.392	0.436	0.369
ANK1	rs516946	C	0.27	0.3	0.369
BCL11A	rs243088	T	-0.224	0.253	0.376
CCND2	rs11063069	G	0.272	0.31	0.381
HHEX/IDE	rs1111875	C	-0.224	0.259	0.389
KCNJ11	rs5215	C	-0.219	0.267	0.411
MTNR1B	rs10830963	G	-0.228	0.285	0.425
HNF1B (TCF2)	rs11651052	A	-0.199	0.254	0.435
MC4R	rs12970134	A	-0.222	0.288	0.441
BCAR1	rs7202877	T	0.326	0.431	0.449
DUSP8	rs2334499	T	0.188	0.258	0.466
HMG20A	rs7177055	A	-0.204	0.283	0.469
CILP2	rs10401969	C	-0.347	0.481	0.47
CDKN2A/B	rs10811661	T	0.244	0.339	0.472
GLIS3	rs10758593	A	-0.176	0.258	0.494
PROX1	rs2075423	G	-0.18	0.268	0.502
PTPRD	rs16927668	T	-0.207	0.317	0.514
TCF7L2	rs7903146	T	0.184	0.282	0.515
TSPAN8/LGR5	rs7955901	C	-0.163	0.256	0.524
CDC123/CAMK1D	rs11257655	T	0.201	0.316	0.525
PSMD6	rs12497268	G	-0.211	0.335	0.53
DGKB	rs17168486	T	-0.213	0.339	0.53

SUPPLEMENTARY DATA

SPRY2	rs1359790	G	-0.16	0.279	0.565
ADAMTS9	rs6795735	C	-0.146	0.258	0.573
NOTCH2	rs10923931	T	-0.225	0.413	0.585
GIPR	rs8108269	G	0.154	0.285	0.59
PPARG	rs1801282	C	-0.203	0.385	0.598
WFS1	rs4458523	G	0.117	0.258	0.65
HNF1A (TCF1)	rs12427353	G	-0.14	0.321	0.663
VPS26A	rs12242953	G	-0.208	0.519	0.689
ARAP1 (CENTD2)	rs1552224	A	-0.137	0.352	0.697
JAZF1	rs849135	G	-0.088	0.255	0.73
KLHDC5	rs10842994	C	-0.107	0.317	0.736
UBE2E2	rs1496653	A	0.106	0.314	0.736
PEPD	rs8182584	T	0.085	0.264	0.747
GCKR	rs780094	C	0.084	0.263	0.751
GCC1	rs17867832	T	0.176	0.625	0.778
KCNQ1	rs163184	G	-0.069	0.255	0.788
ANKRD55	rs459193	G	0.074	0.292	0.801
GCK	rs10278336	A	0.063	0.258	0.807
C2CD4A	rs4502156	T	0.059	0.258	0.819
ST64GAL1	rs17301514	A	-0.079	0.41	0.846
ZFAND6	rs11634397	G	0.051	0.268	0.851
ZFAND3	rs4299828	A	-0.056	0.32	0.862
ZBED3	rs6878122	G	-0.012	0.274	0.964
ZMIZ1	rs12571751	A	0.009	0.254	0.972
THADA	rs10203174	C	-0.011	0.399	0.978
HNF4A	rs4812829	A	0.003	0.35	0.994

SUPPLEMENTARY DATA

e) Triglycerides

Nearest gene(s)	SNP	Effect allele	b	se	p-value
GCKR	rs780094	C	-0.103	0.014	$1.88x10^{-13}$
CILP2	rs10401969	C	-0.108	0.026	$3.27x10^{-5}$
HNF4A	rs4812829	A	0.045	0.019	0.018
CDKAL1	rs7756992	G	0.035	0.016	0.022
GRB14	rs13389219	C	0.03	0.014	0.03
MAEA	rs6819243	T	0.092	0.045	0.041
ANKRD55	rs459193	G	0.031	0.016	0.052
PEPD	rs8182584	T	0.027	0.014	0.056
GCC1	rs17867832	T	-0.062	0.034	0.066
HNF1A (TCF1)	rs12427353	G	0.031	0.017	0.071
HMGA2	rs2261181	T	0.042	0.024	0.077
HNF1B (TCF2)	rs11651052	A	0.024	0.014	0.083
KCNQ1	rs163184	G	0.022	0.014	0.102
KLF14	rs13233731	G	0.022	0.014	0.113
DUSP8	rs2334499	T	0.022	0.014	0.116
SLC30A8	rs3802177	G	0.023	0.015	0.13
KCNK16	rs3734621	C	0.061	0.044	0.172
CCND2	rs11063069	G	0.023	0.017	0.174
PRC1	rs12899811	G	-0.02	0.015	0.178
PPARG	rs1801282	C	0.026	0.021	0.21
DGKB	rs17168486	T	-0.022	0.018	0.223
ADCY5	rs11717195	T	-0.019	0.016	0.232
IRS1	rs2943640	C	0.016	0.014	0.254
MTNR1B	rs10830963	G	0.017	0.015	0.258
ANK1	rs516946	C	0.018	0.016	0.268
ADAMTS9	rs6795735	C	0.015	0.014	0.278
HHEX/IDE	rs1111875	C	-0.015	0.014	0.291
ARAP1 (CENTD2)	rs1552224	A	-0.019	0.019	0.31
TLE4	rs17791513	A	-0.028	0.028	0.33
C2CD4A	rs4502156	T	-0.013	0.014	0.361
SRR	rs2447090	A	0.013	0.014	0.37
CDC123/CAMK1D	rs11257655	T	0.015	0.017	0.372
PTPRD	rs16927668	T	-0.015	0.017	0.375
VPS26A	rs12242953	G	-0.024	0.028	0.395
HMG20A	rs7177055	A	0.011	0.015	0.458
IGF2BP2	rs4402960	T	-0.011	0.015	0.469
TLE1	rs2796441	G	-0.009	0.014	0.506
THADA	rs10203174	C	0.013	0.022	0.531
PROX1	rs2075423	G	-0.009	0.014	0.532

SUPPLEMENTARY DATA

GIPR	rs8108269	G	-0.009	0.015	0.567
TSPAN8/LGR5	rs7955901	C	0.008	0.014	0.567
WFS1	rs4458523	G	-0.008	0.014	0.579
BCL11A	rs243088	T	0.007	0.014	0.588
PSMD6	rs12497268	G	-0.009	0.018	0.6
KCNJ11	rs5215	C	-0.007	0.014	0.616
GLIS3	rs10758593	A	-0.007	0.014	0.616
SPRY2	rs1359790	G	-0.006	0.015	0.669
AP3S2	rs2007084	G	-0.01	0.024	0.674
TP53INP1	rs7845219	T	-0.005	0.014	0.703
CDKN2A/B	rs10811661	T	0.007	0.018	0.717
TCF7L2	rs7903146	T	0.005	0.015	0.723
BCAR1	rs7202877	T	0.008	0.023	0.724
UBE2E2	rs1496653	A	-0.006	0.017	0.739
ZFAND3	rs4299828	A	0.006	0.017	0.74
ZBED3	rs6878122	G	-0.004	0.015	0.791
MC4R	rs12970134	A	0.004	0.016	0.811
ZMIZ1	rs12571751	A	0.003	0.014	0.84
NOTCH2	rs10923931	T	-0.004	0.022	0.851
FTO	rs9936385	C	-0.002	0.014	0.893
JAZF1	rs849135	G	0.001	0.014	0.931
ZFAND6	rs11634397	G	-0.001	0.014	0.967
ST64GAL1	rs17301514	A	-0.001	0.022	0.968
KLHDC5	rs10842994	C	-0.001	0.017	0.972
RBMS1	rs7569522	A	0	0.014	0.993
GCK	rs10278336	A	0	0.014	0.996

SUPPLEMENTARY DATA

Supplementary Table 4. Area under the receiver operator curve for T2D gene scores for each study.

Study	N Cases/controls	Externally weighted	Unweighted
BRHS	150/2167	0.592 (0.545-0.638)	0.593 (0.546-0.640)
BWHHS	103/1751	0.588 (0.529-0.648)	0.575 (0.519-0.632)
EAS	16/687	0.672 (0.559-0.785)	0.580 (0.447-0.713)
MRC NSHD	118/2292	0.618 (0.568-0.669)	0.609 (0.560-0.657)
WHII	219/2826	0.556 (0.516-0.597)	0.555 (0.515-0.594)
ELSA	74/1611	0.639 (0.571-0.706)	0.612 (0.546-0.678)
CAPS	124/1156	0.646 (0.595-0.696)	0.605 (0.555-0.654)
Combined studies (fixed effect)	804/12490	0.602 (0.582-0.622)	0.587 (0.567-0.607)
Combined studies (random effect)	804/12490	0.607 (0.578-0.636)	0.587 (0.567-0.607)

Test for heterogeneity between studies in ROC area (p=0.08 externally weighted and p=0.59 unweighted).

Supplementary Table 5. . Detection rates at 5% and 10% false positive rates (FPR) for the individual studies and the combined study.

	5% FPR FORS	10% FPR FORS	5% FPR FORS + Gene score	10% FPR FORS + Gene score
BRHS	15.33%	32.00%	24.67%	38.00%
BWHHS	18.45%	29.13%	22.33%	37.86%
EAS	6.25%	12.50%	12.50%	12.50%
MRC NSHD	14.41%	20.34%	20.34%	38.98%
WHII	25.11%	34.25%	25.11%	34.70%
ELSA	12.16%	32.43%	16.22%	39.19%
CAPS	29.84%	41.13%	29.84%	43.55%
All- fixed effects	18.56%	30.67%	23.14%	37.28%
(95% CI)	(15.90 - 21.22)	(27.51 -33.82)	(20.23-26.05)	(33.95 - 40.61)
All - random effects (95% CI)	18.14% (12.98 - 23.29)	30.10% (24.26 - 35.95)	22.97% (19.57 - 26.36)	37.11% (32.65 - 41.57)

SUPPLEMENTARY DATA

Supplementary Table 6. Calibration of 10 year risk categories for T2D for Framingham Offspring Score with and without the externally weighted gene score.

	Predicted risk			
Score (overall)	<5%	5-9.9%	10-14.9%	≥15%
FORS	3.1%	6.1%	12.2%	19.3%
FORS+ Externally weighted gene score	3.1%	5.6%	11.9%	19.8%

Observed and predicted risks adjusted to 10 years follow-up

Supplementary Table 7. Effect of adding genetic information to model fit and calibration (overall model).

Model	L-R test	BIC	Hosmer-Lemeshow
FORS	-	5465.88	P=0.65
FORS+EW	$P=1.34x10^{-16}$	5406.15	P=0.10

Supplementary Table 8. Area under the ROC curve for Framingham variables and Framingham + externally weighted gene score by BMI tertiles.

	Combined studies	BMI<24.5	BMI 24.5-27.4	BMI>=27.5	P value
FORS	ROC (95% CI)	0.697 (0.645-0.748)	0.753 (0.724-0.782)	0.696 (0.672-0.719)	
FORS+EW	ROC (95% CI)	0.739 (0.690-0.787)	0.752 (0.722-0.783)	0.713 (0.689-0.737)	
	Difference (FORS+EW)-FORS	0.037 (0.018-0.056) P=0.0001	0.017 (0.004-0.031) P=0.01	0.013 (0.002-0.023) P=0.02	P=0.02

SUPPLEMENTARY DATA

Supplementary Table 9. Net Reclassification index by tertiles of age ≤ 53 years, 54-59 year and ≥ 60, based on addition of gene score to FORS, calculated using risk cut offs of 5%, 10%, 15% for ten year risk.

a)

Age<=53	No. of people						
	Plus the externally weighted gene score – **T2D free** (n=7520.25)				Reclassified		
Predicted risk FORS	<5	5-9.9	10-14.9	>=15	Increased risk	Decreased risk	Net correctly reclassified
<5	4447.32	280.99	14.85	4	758.71	672.18	-1.2% (02.1 to -0.2)
5-9.9	330.24	723.48	232.03	64.4			
10-14.9	13.79	196.48	208.35	200.73			
>=15	0	23.84	118.07	626.9			
	Plus the externally weighted gene score- **Incident T2D** (n=478.36)						
	<5	5-9.9	10-14.9	>=15			
<5	142.21	16	1	0	80.99	31.6	10.3% (6.0 to 14.7)
5-9.9	12	36.67	23.75	12.82			
10-14.9	0	13.60	29.36	27.42			
>=15	0	2	4	157.53			
NRI (95% CI)* =9.2% (4.7 to 13.6) $p=5.49x10^{-5}$							

SUPPLEMENTARY DATA

b)

Age 54-59	No. of people						
	Plus the externally weighted gene score – **T2D free** (n=2382.50)				Reclassified		
Predicted risk FORS	<5	5-9.9	10-14.9	>=15	Increased risk	Decreased risk	Net correctly reclassified
<5	1615.68	115.12	9.2	0	226.63	142.07	-3.5% (-5.1 to -2.0)
5-9.9	81.91	187.44	47.04	14.81			
10-14.9	0	33.37	48.39	40.46			
>=15	0	3.75	23.04	162.29			
	Plus the externally weighted gene score – **Incident T2D** (n=182.35)						
	<5	5-9.9	10-14.9	>=15			
<5	58.36	11	0	0	27	17.66	5.1% (-2.1 to 12.3)
5-9.9	9.52	18.25	2	2			
10-14.9	0	6	7	12			
>=15	0	0	2.14	54.08			
NRI (95% CI)* =1.6% (-5.8 to 8.9) p=0.68							

c)

Age>=60	No. of people						
	Plus the externally weighted gene score – **T2D free** (n=8813.05)				Reclassified		
Predicted risk FORS	<5	5-9.9	10-14.9	>=15	Increased risk	Decreased risk	Net correctly reclassified
<5 5-9.9 10-14.9 >=15	4343.63 652.37 21.38 6.55	185.89 1056.37 417.38 51.30	12.22 286.88 373.61 175.39	0 46.62 265.28 918.18	796.89	1324.37	6.0% (5.0 to 7.0)
	Plus the externally weighted gene score – **Incident T2D** (n=461.14)						
	<5	5-9.9	10-14.9	>=15			
<5 5-9.9 10-14.9 >=15	78.44 15.27 0 0	7.13 26.28 26.33 9.73	0 30.22 34.88 15.89	0 1 39.62 176.35	77.97	67.22	2.3% (-2.8 to 7.5)
NRI (95% CI)* =8.3% (3.1 to 13.5) p=0.002							

Supplementary Table 10. Area under the ROC curve for Framingham variables and Framingham + externally weighted gene score by gender.

	Combined studies	Men	Women	P value
FORS	ROC (95% CI)			
FORS+EW	ROC (95% CI)			
	Difference (FORS+EW)-FORS	0.012 (0.004-0.019) P=0.003	0.016 (0.003-0.029) P=0.02	P=0.59

SUPPLEMENTARY DATA

Supplementary Table 11. Net -reclassification index based on addition of gene score to FORS, calculated using risk cut offs of 5%, 10%, 15% for ten year risk.

a) Male

Male	No. of people						
	Plus externally weighted gene score- No DIABETES (n=10530.36)				**Reclassified**		
Predicted risk FORS	<5	5-9.9	10-14.9	>=15	Increased risk	Decreased risk	Net correctly reclassified
<5	6593.68	396.59	24.06	0	982.2	906.47	-0.7% (-1.5 to 0.1)
5-9.9	467.02	902.8	258.31	64.75			
10-14.9	8.79	263.6	309.52	238.49			
>=15	3.13	35.96	127.97	835.69			
	Plus externally weighted gene score- INCIDENT DIABETES (n=705.96)						
Predicted risk FORS	<5	5-9.9	10-14.9	>=15			
<5	223.2	27	1	0	122.61	52.39	9.9% (6.3 to 13.6)
5-9.9	22.65	55.05	37.87	12.82			
10-14.9	0	18.6	32.48	43.92			
>=15	0	4	7.14	220.23			
NRI (95% CI)= 9.2% (5.5 to 13.0) p=1.52x10-6							

b) Female

Female	No. of people						
	Plus externally weighted gene score- No DIABETES (n=8185.42)				**Reclassified**		
Predicted risk FORS	<5	5-9.9	10-14.9	>=15	Increased risk	Decreased risk	Net correctly reclassified
<5	3812.94	185.41	12.22	0	800.02	1232.18	5.3% (4.3 to 6.4)
5-9.9	597.5	1064.46	284.25	53.49			
10-14.9	26.38	383.63	372.86	264.65			
>=15	3.42	42.93	178.32	902.96			
	Plus externally weighted gene score- INCIDENT DIABETES (n=415.89)						
Predicted risk FORS	<5	5-9.9	10-14.9	>=15			
<5	55.81	7.13	0	0	63.35	64.09	-0.2% (-5.5 to 5.1)
5-9.9	14.14	26.15	18.1	3			
10-14.9	0	27.33	38.76	35.12			
>=15	0	7.73	14.89	167.73			
NRI (95% CI)= 5.1% (-0.3 to 10.5) p=0.07							

SUPPLEMENTARY DATA

Supplementary Table 12. Analysis of the original 20 SNPS reported in (11)

a) NRI (combined studies)

ALL	No. of people						
	Plus EW gene score- No DIABETES (n=15989.79)				Reclassified		
Predicted risk FORS	<5	5-9.9	10-14.9	>=15	Increased risk	Decreased risk	Net correctly reclassified
<5	8702.28	551.46	49.64	5.6	1737.28	2383.08	4.0%
5-9.9	1178.83	1283.48	505.69	206.85			
10-14.9	101.83	601.48	432.98	418.04			
>=15	1	147.24	352.7	1450.69			
	Plus EW gene score- INCIDENT DIABETES (n=1069.46)						
	<5	5-9.9	10-14.9	>=15			
<5	240.05	42.57	5.42	0	190.52	170.44	1.9%
5-9.9	48.62	68.94	34.06	28.72			
10-14.9	5.13	55.22	51.74	79.75			
>=15	3.26	21.72	36.49	347.77			
NRI (95% CI)* =5.9% (2.3 to 9.5) p=0.001 NRI (95% CI) † 4.3% (0.8 to 7.8) p=0.02 NRI (95% CI) ‡ 5.0% (0.2 to 9.9) p=0.04							

*no adjustment for study

† results from fixed effects meta-analysis of individual study results. I-squared=40.7%, p value for heterogeneity p=0.12.

‡ results from random effects meta-analysis of individual study results.

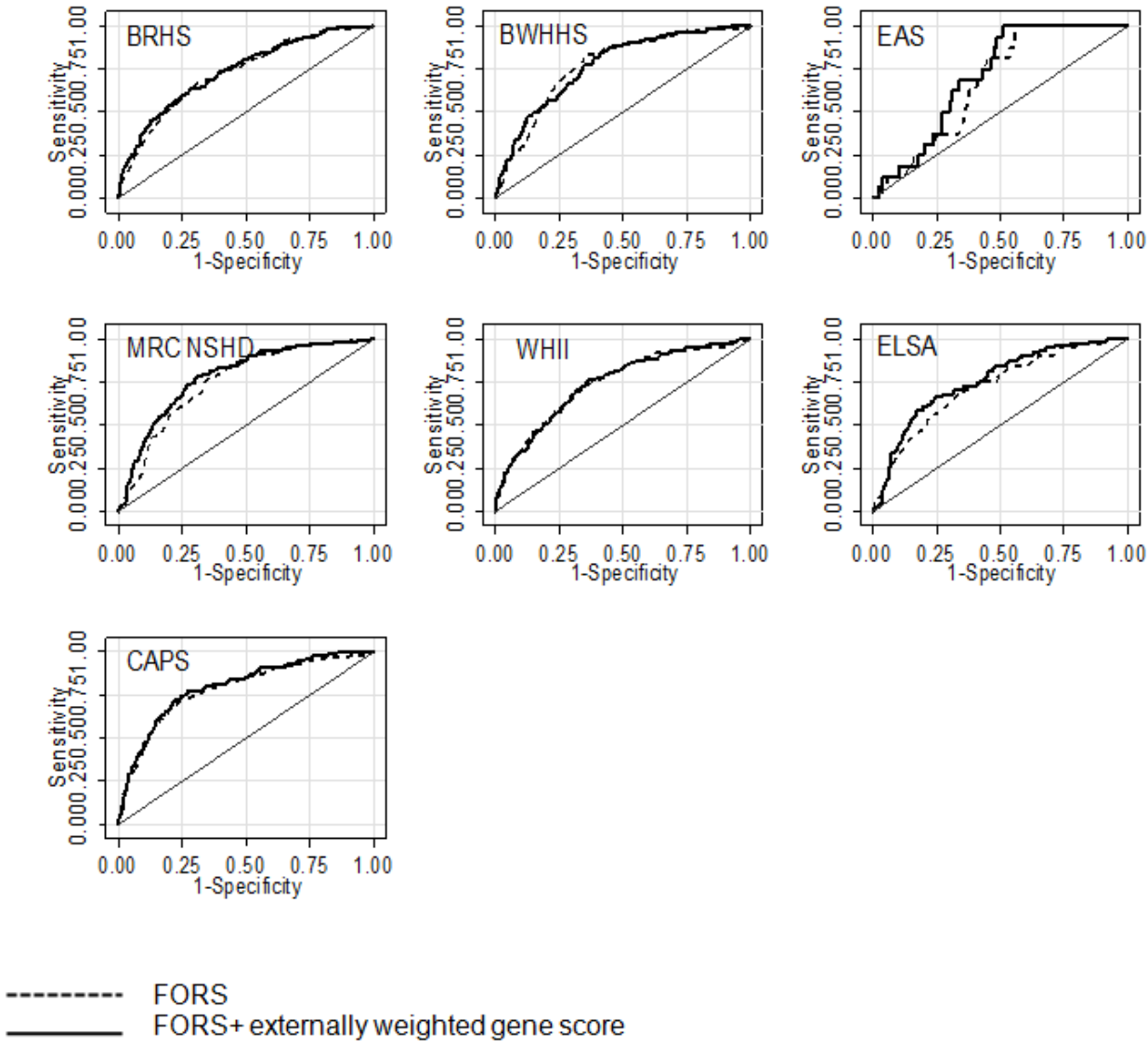
b) $A_{ROC\ s}$ of the combined seven studies

		Combined
FORS	A_{ROC} (95% CI)	0.75 (0.74-0.80)
FORS+ EW	A_{ROC} (95% CI) p value vs. FORS	0.76 (0.74 0-0.78) p=0.23

Difference (FORS+EW) – FORS: 0.005 (-0.003 to 0.013) p=0.23

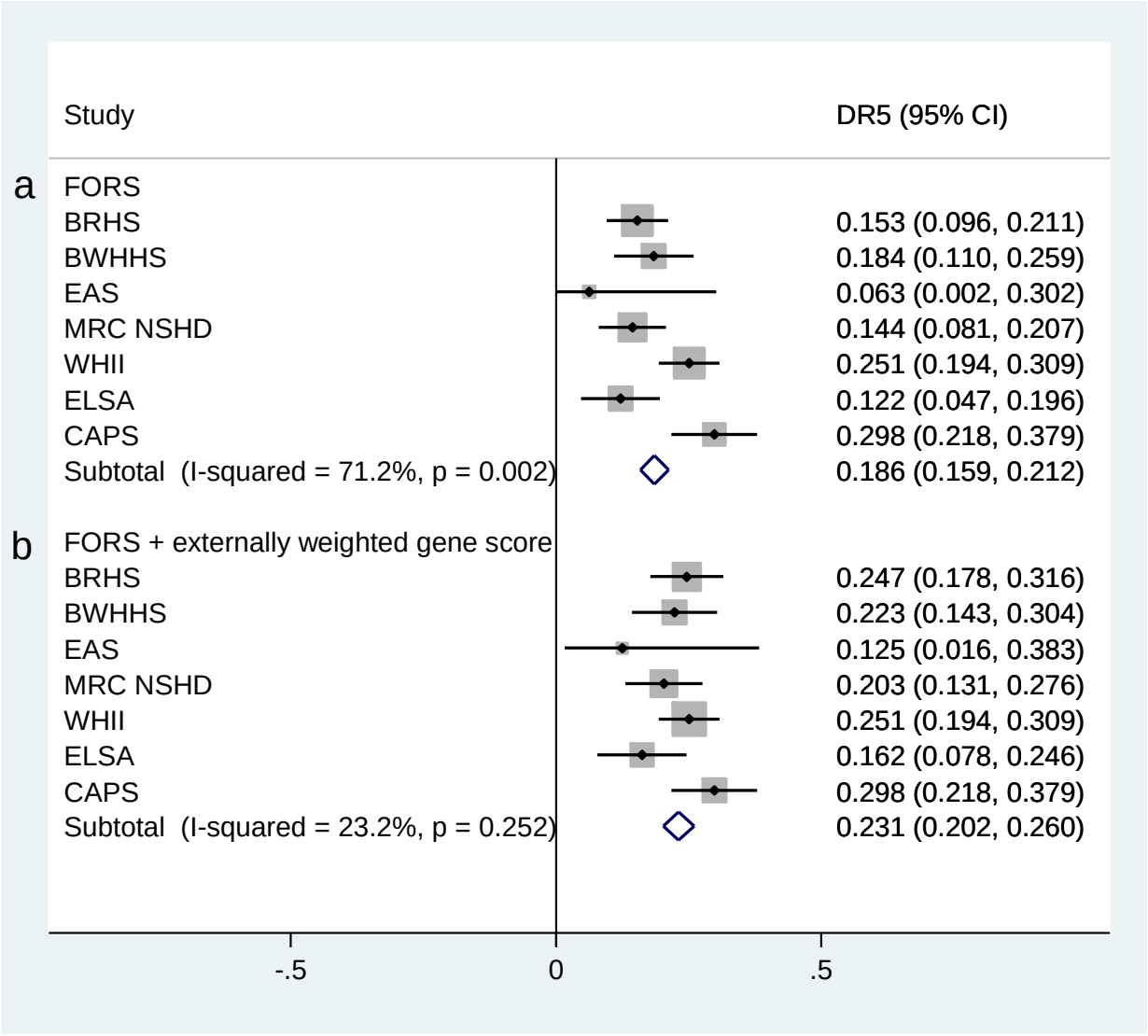
SUPPLEMENTARY DATA

Supplementary Figure 1. Receiver operating characteristic (ROC) curves for the seven UCLEB studies in the analysis.



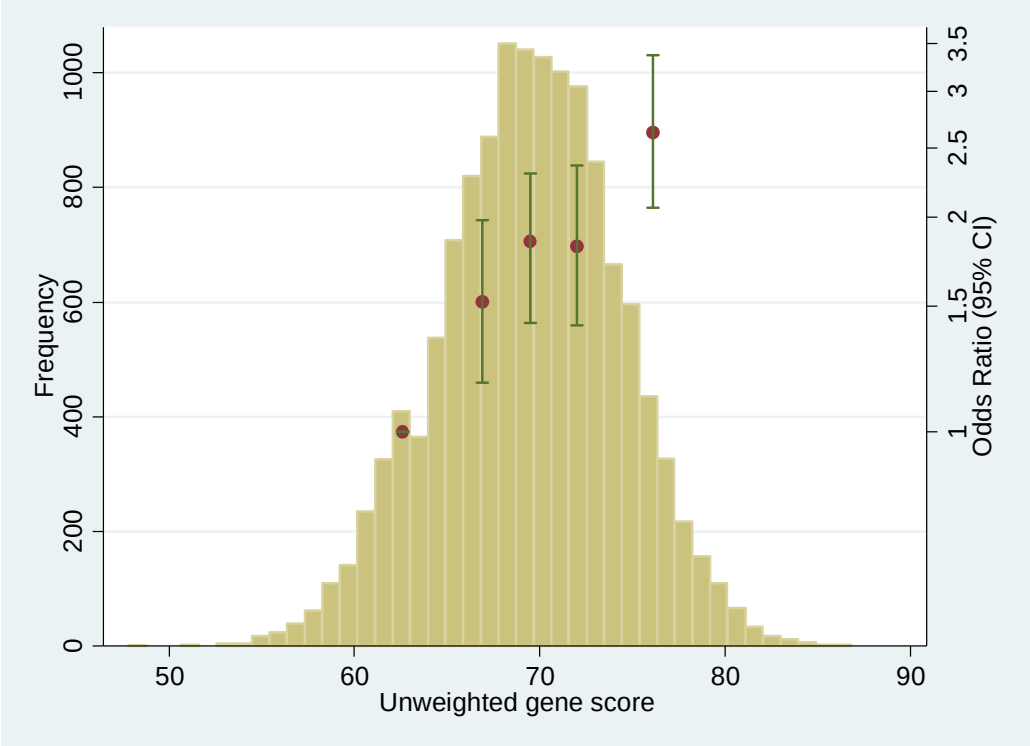
SUPPLEMENTARY DATA

Supplementary Figure 2. Forest plot for the detection rate (5% FPR) for each of the seven studies for the Framingham phenotypic score alone and (b) Framingham score plus the weighted gene score.



SUPPLEMENTARY DATA

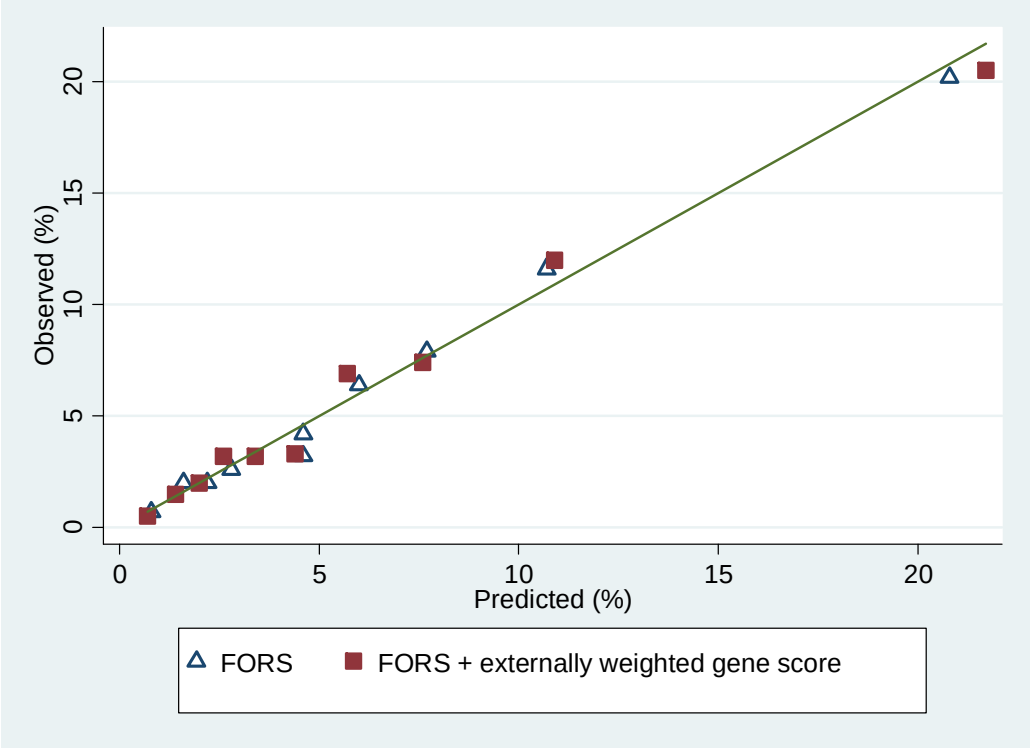
Supplementary Figure 3. Distribution of unweighted gene score and odds ratios for association with T2D.



The OR for T2D among individuals in the top vs bottom quintile of the gene score distribution was 2.63 (2.06-3.37) $p=1.16 \times 10^{-14}$ for the un-weighted gene score. The A_{ROC} for the un-weighted gene score was 0.586 (0.566-0.606).

SUPPLEMENTARY DATA

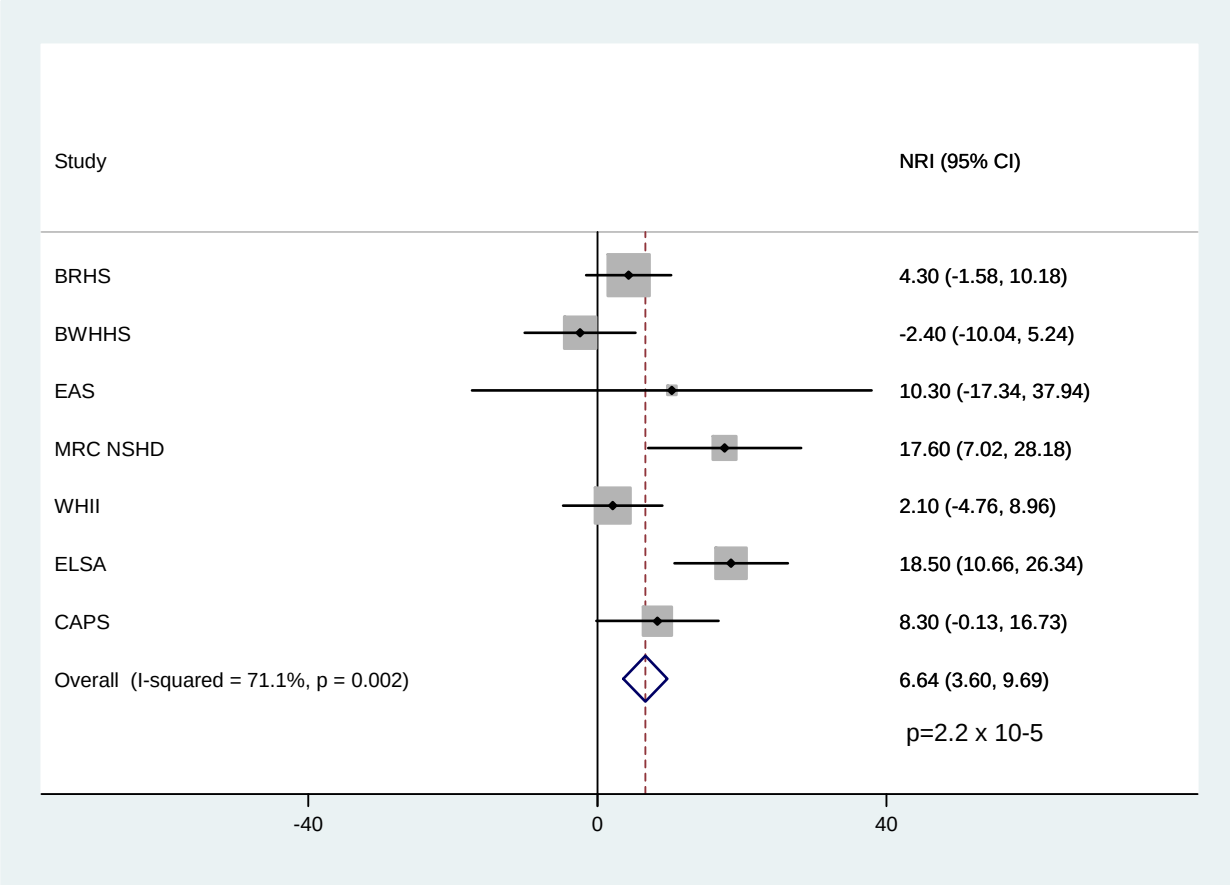
Supplementary Figure 4. Hosmer-Lemeshow calibration plot showing observed against predicted values by decile of predicted risk.



Hosmer-Lemeshow p=0.65 FORS and p=0.10 FORS + externally weighted gene score.

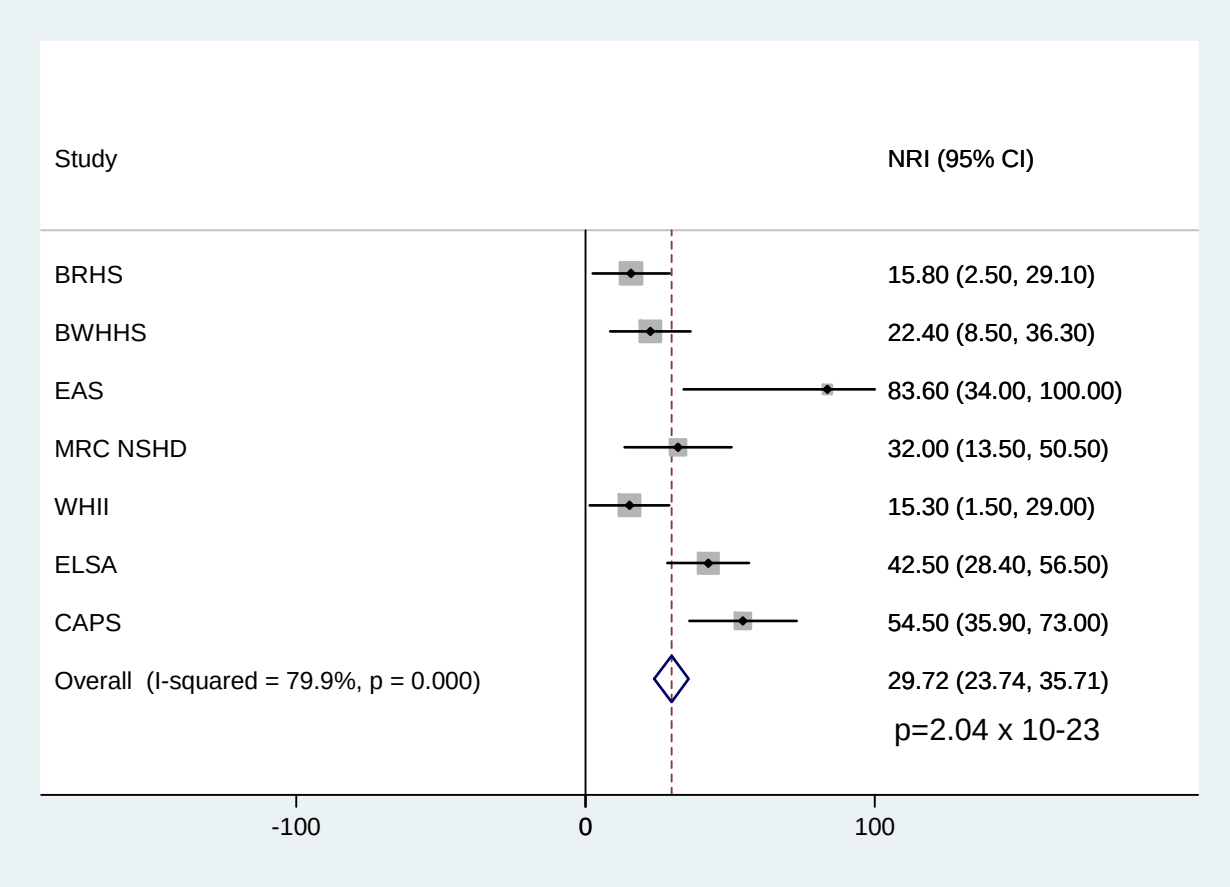
SUPPLEMENTARY DATA

Supplementary Figure 5. The Net Reclassification Index by Study.



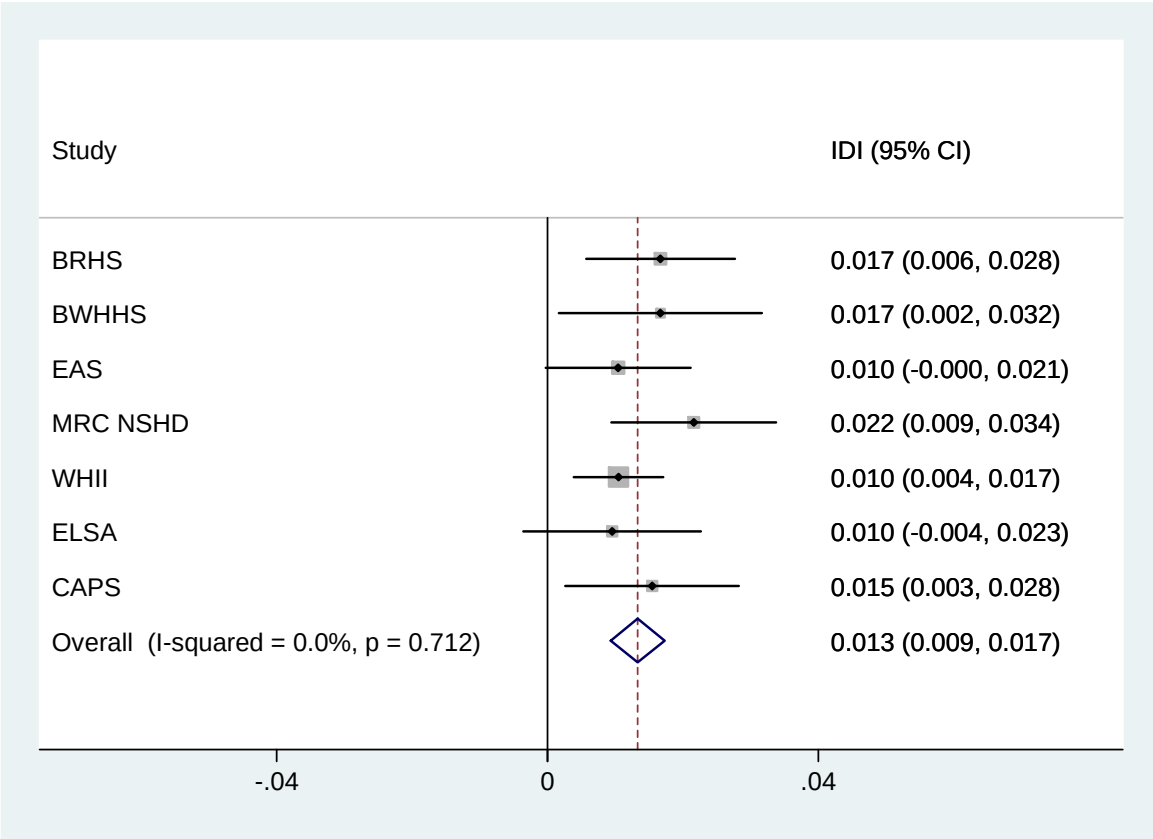
SUPPLEMENTARY DATA

Supplementary Figure 6. The continuous Net Reclassification Index for the seven studies individually and combined.
The continuous NRI(12) , which is independent of cut points, also indicated an improvement in prediction after adding the gene score, continuous NRI=29.7% (95%CI 23.7-35.7) $p=2.04x10^{-23}$ fixed effects and 34.7% (20.9 – 48.6) $p=8.65x10^{-07}$ random effects model.



SUPPLEMENTARY DATA

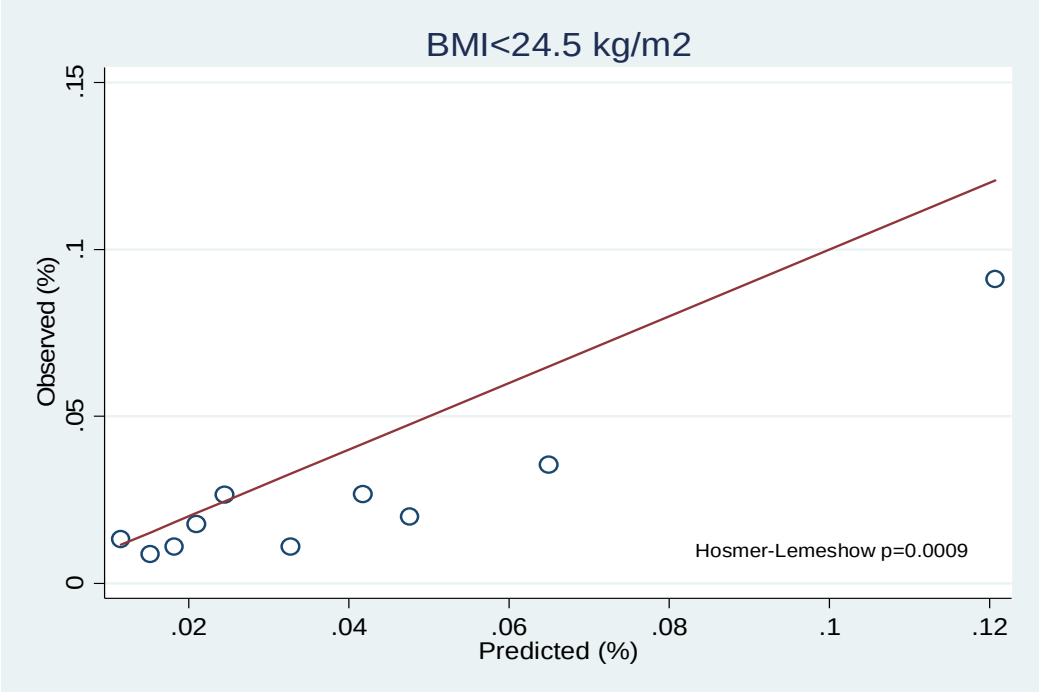
Supplementary Figure 7. The Integrated Discrimination improvement for the seven studies individually and combined.
The Integrated Discrimination Improvement (IDI), which is independent of cut points, also indicated a marginal improvement in prediction after adding the gene score, of 0.013 (0.009 to 0.017) p=6.15 x 10^{-11}.



SUPPLEMENTARY DATA

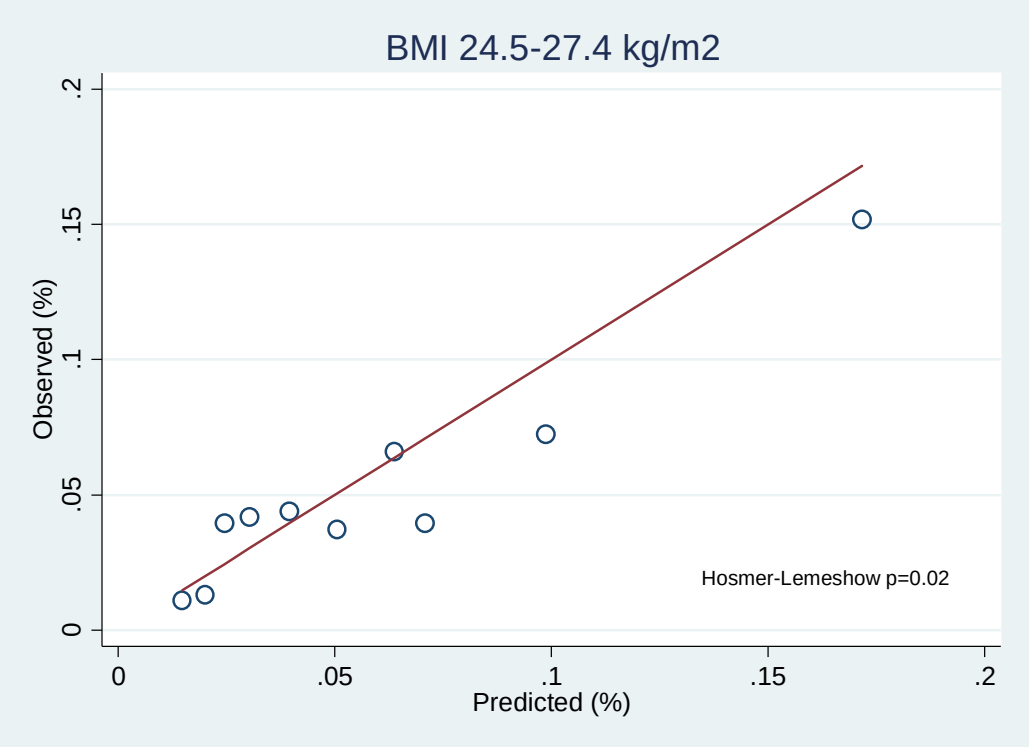
Supplementary Figure 8. Calibration plots for FORS+ externally weighted gene score by tertile of BMI.

a)

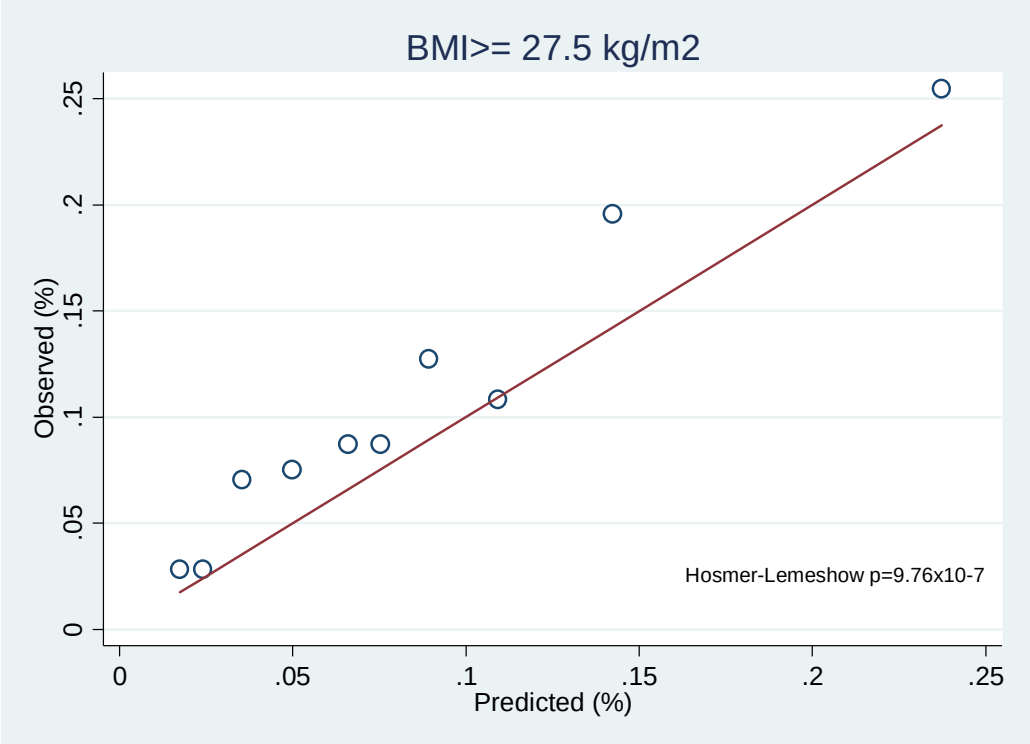


SUPPLEMENTARY DATA

b)



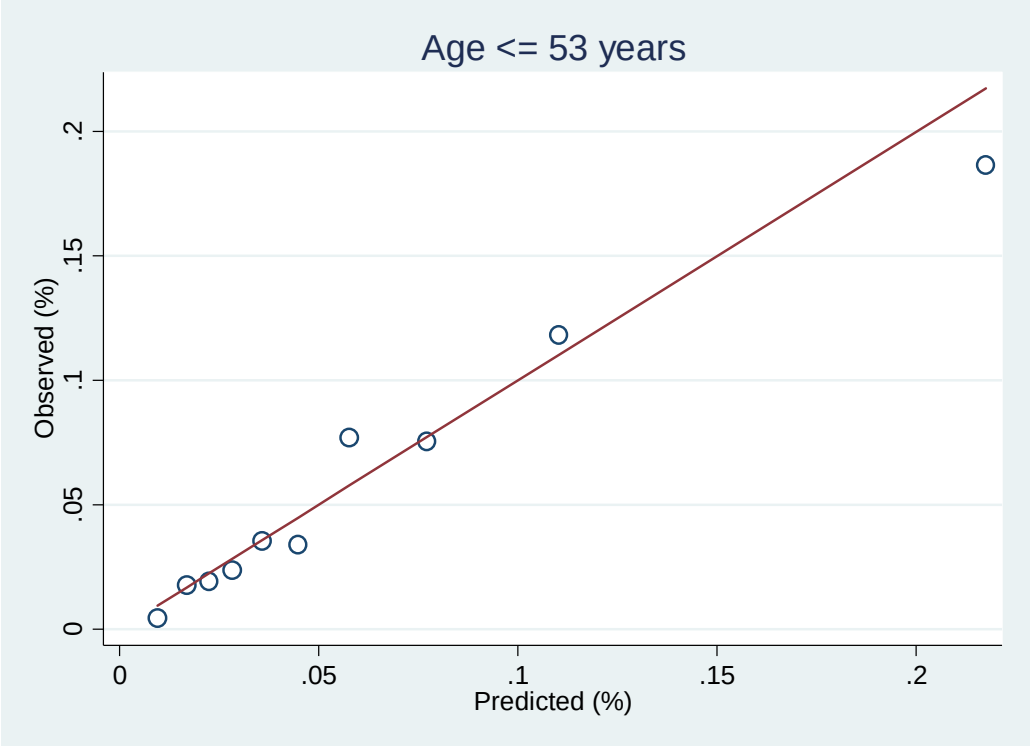
c)



SUPPLEMENTARY DATA

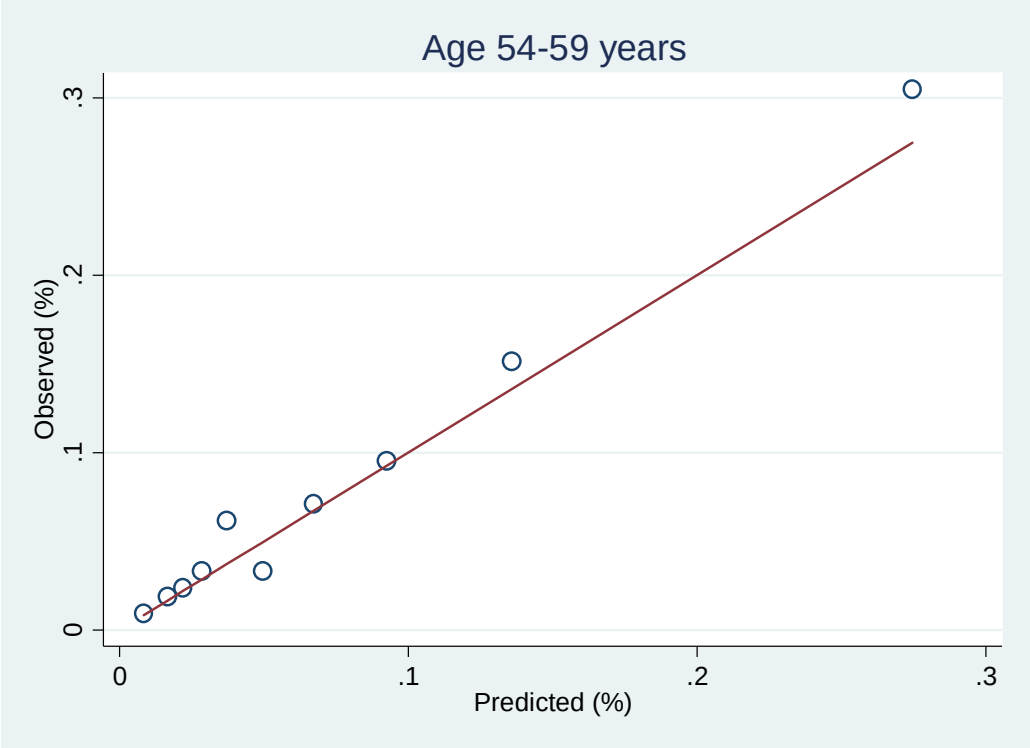
Supplementary Figure 9. Calibration plots for FORS plus externally weighted gene score by tertiles of age.

a)

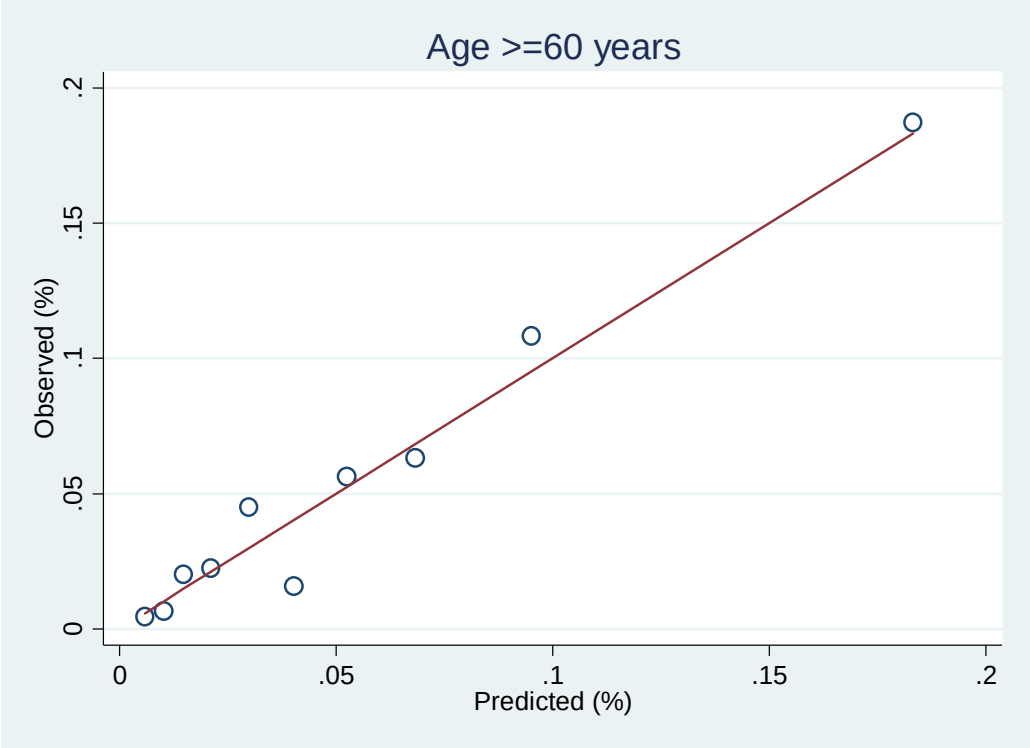


SUPPLEMENTARY DATA

b)



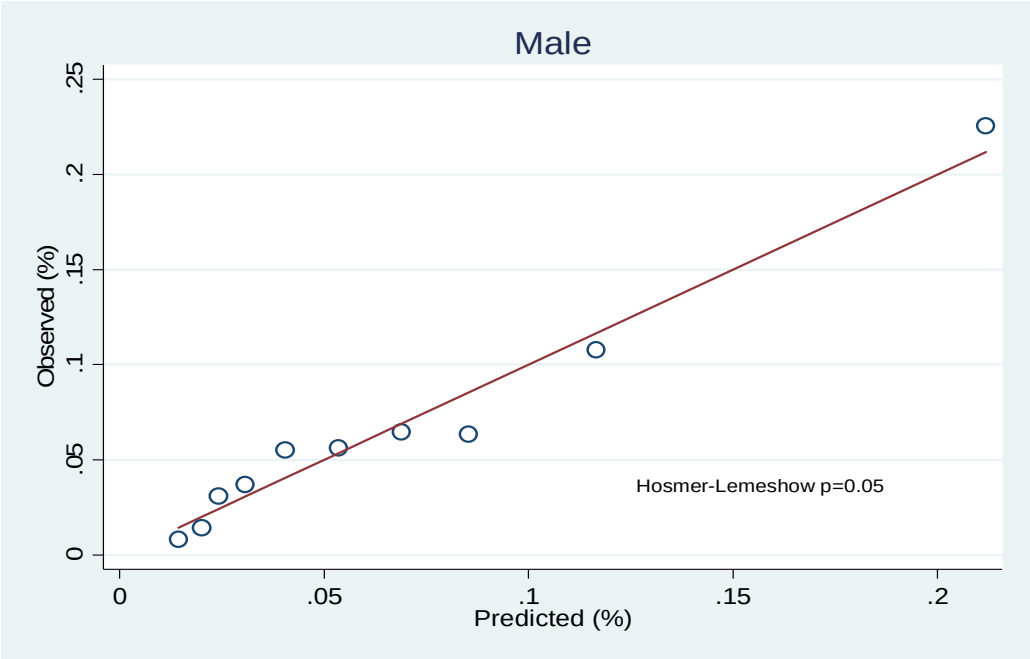
c)



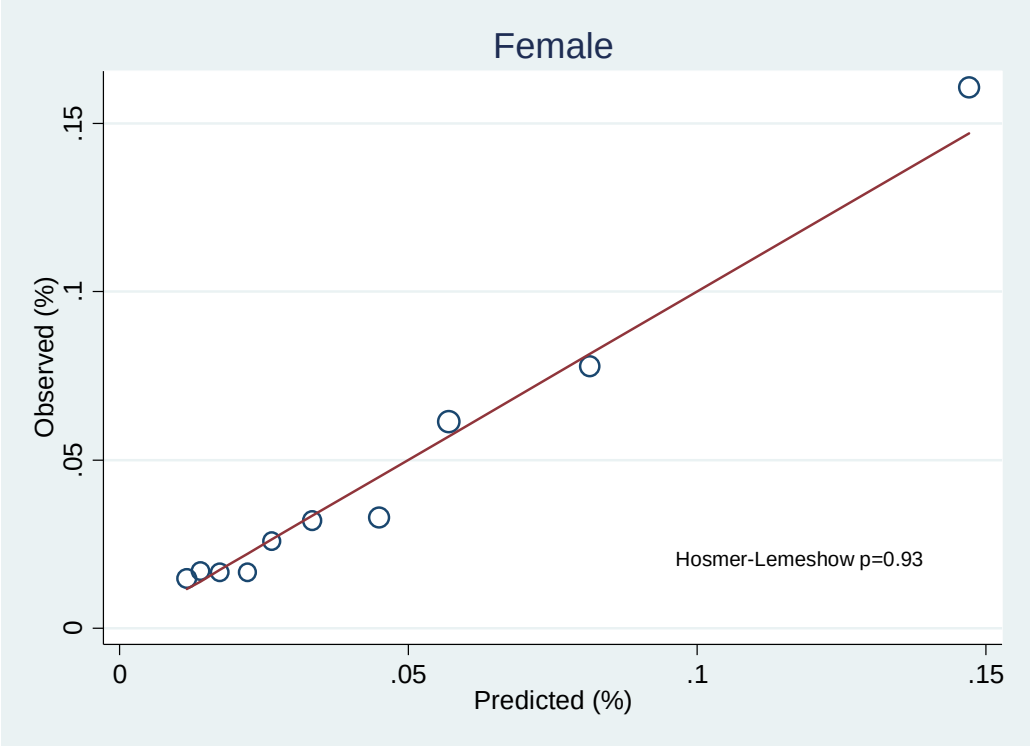
SUPPLEMENTARY DATA

Supplementary Figure 10 . Calibration plots for FORS+ externally weighted gene score by gender.

a) male



b) female



SUPPLEMENTARY DATA

References

1. Shaper AG, Pocock SJ, Walker M, Cohen NM, Wale CJ, Thomson AG. British Regional Heart Study: cardiovascular risk factors in middle-aged men in 24 towns. Br Med J 1981;283:179-186,
2. Lawlor DA, Bedford C, Taylor M, Ebrahim S. Geographical variation in cardiovascular disease, risk factors, and their control in older women: British Women's Heart and Health Study. J Epidemiol Community Health 2003;57:134-140,
3. Wadsworth M, Kuh D, Richards M, Hardy R. Cohort Profile: The 1946 National Birth Cohort (MRC National Survey of Health and Development). Int J Epidemiol 2006;35:49-54,
4. Kuh D, Pierce M, Adams J, Deanfield J, Ekelund U, et al. Cohort profile: updating the cohort profile for the MRC National Survey of Health and Development: a new clinic-based data collection for ageing research. Int J Epidemiol 2011;40:e1-e9,
5. Rousseau K, Byrne C, Griesinger G, Let al. Allelic association and recombination hotspots in the mucin gene (MUC) complex on chromosome 11p15.5. Ann Hum Genet 2007;71:561-569,
6. Fowkes FG, Housley E, Cawood EH, Macintyre CC, et al. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 1991;20:384-392,
7. Marmot MG, Smith GD, Stansfeld S, Patel C, et al. Health inequalities among British civil servants: the Whitehall II study. Lancet 1991;337:1387-1393,
8. Marmot MG, Banks J, Blundell R, Lessof C, and Nazroo J. Health, Wealth and Lifestyles of the Older Population in England: The 2002 English Longitudinal Study of Ageing. 2003;Institute for Fiscal Studies.
9. Bainton D, Miller NE, Bolton CH, Yarnell JW, et al. Plasma triglyceride and high density lipoprotein cholesterol as predictors of ischaemic heart disease in British men. The Caerphilly and Speedwell Collaborative Heart Disease Studies. Br Heart J 1992;68:60-66,
10. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segre AV, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nat Genet 2012;44:981-990,
11. Talmud PJ, Hingorani AD, Cooper JA, Marmot MG, et al. Utility of genetic and non-genetic risk factors in prediction of type 2 diabetes: Whitehall II prospective cohort study. B M J 2010;340:b4838,
12. Pencina MJ, D'Agostino RB, Sr., Demler OV. Novel metrics for evaluating improvement in discrimination: net reclassification and integrated discrimination improvement for normal variables and nested models. Stat Med 2012;31:101-113,