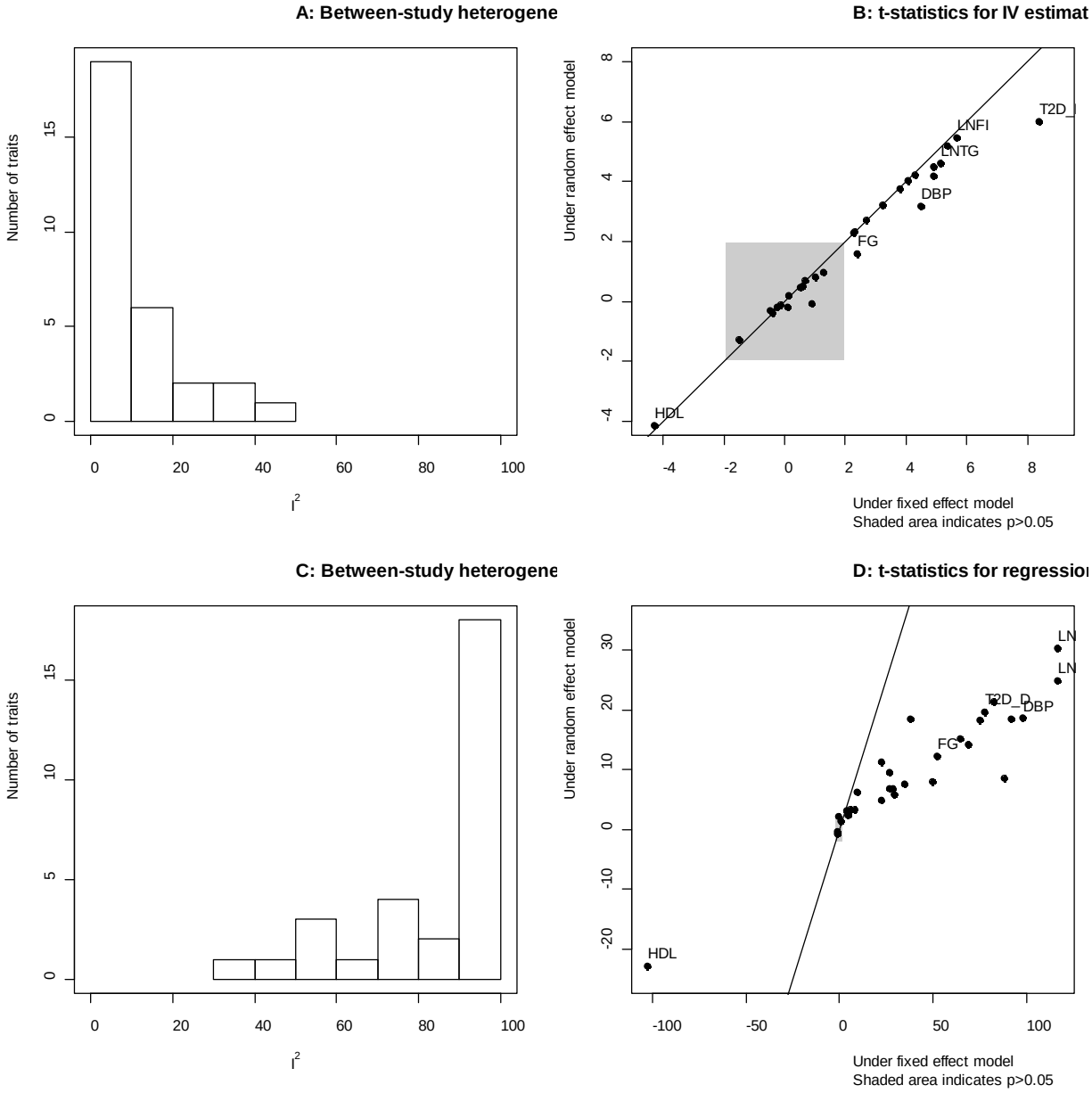

Figure S1. Distribution of I^2 (left) and relationship between fixed- and random effect Wald test statistics (right) for IV estimate of the causal effect of BMI on traits (top) and the conventional regression estimate for the effect of BMI on traits (bottom).
Panel A: histogram of I^2 for the meta-analysis of the effect of *FTO* on each of 30 traits evaluated from more than one study. Panel B: a scatter plot of Wald test statistics for the instrumental variable estimate of BMI on the same 30 traits as in A, with values based on a fixed effect model on the horizontal axis and values based on the random effect model on the vertical axis; each dot corresponds to one trait, with traits "Ever type-2 diabetes", diastolic blood pressure, fasting glucose, fasting insulin, triglycerides and HDL labelled for illustration. The grey square indicates the area where t-statistics are not significant at the conventional level α=0.05. Panel C: same as A, but for the effect of BMI on the traits. Panel D: same as B, but for the conventional regression estimate of the effect of BMI on traits.

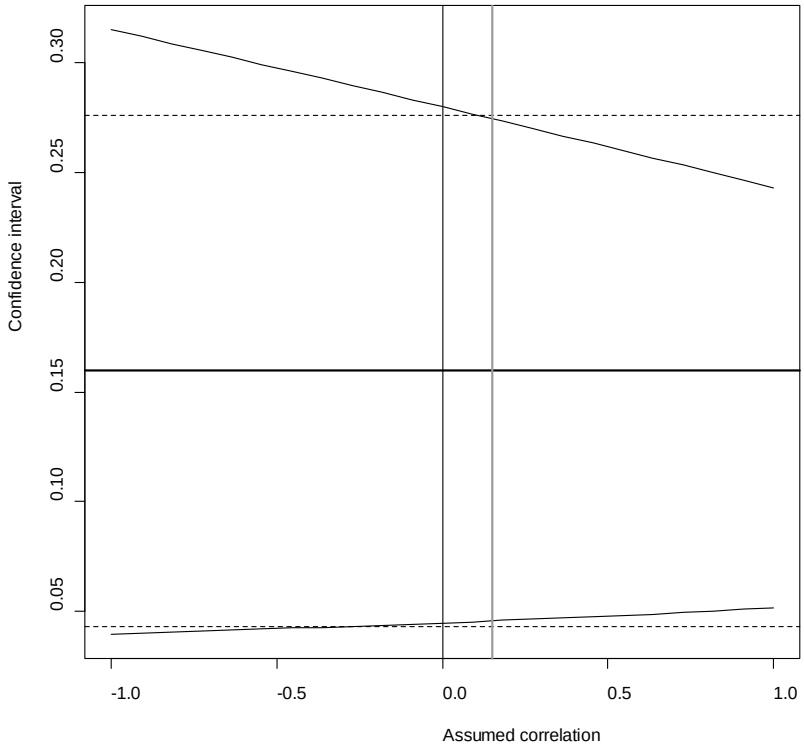

Figure S2. Illustration of sensitivity analysis for the instrumental variable estimator of the effect of BMI on a specific trait (here: "Ever heart failure"). On the horizontal axis, the range of possible correlations between and is displayed, on the vertical axis, the effect size (i.e. change of the log-odds ratio of heart failure for a one-point increase of BMI). The thick black horizontal line in the middle represents the reported estimate, the broken horizontal lines at the top and bottom indicate the 95% confidence interval based on the delta method; these do not take the possible correlation into account and are therefore constant in this plot. The curved thin lines at the top and at the bottom of the plot indicate the 95% confidence interval based on the Fieller theorem, which is clearly wider at the negative end than at the positive end of the correlation scale. The vertical reference lines indicate the width of the confidence intervals for uncorrelated estimates (thin black line at) and at the plug-in estimate of the correlation (thick grey line at). The worst case can clearly be seen at the left margin for .

Table S1. Phenotypic details of the participating cohorts. (Part 1)

Cohort	Full name of cohort	Software for analysis	Study sample reference	Website
DECODE	deCODE genetics sample set	R	PMID: 18445777, PMID: 17460697,PMID: 18438407, PMID: 19767754, 18991354,17478679	http://www.decode.com/
DGIcases	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research	STATA/SE 11.1	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research , et al. Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels. Science, 2007	http://www.broadinstitute.org/scientific-community/science/projects/diabetes-genetics-initiative/diabetes-genetics-initiative
DGIcontrols	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research	STATA/SE 11.1	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research, et al. Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels. Science 2007	http://www.broadinstitute.org/scientific-community/science/projects/diabetes-genetics-initiative/diabetes-genetics-initiative
DIL	Wellcome Trust Diabetes and Inflammation Laboratory	Plink and R	Todd, J.A., Walker, N.M., Cooper, J.D., Smyth, D.J. et al (2007) Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat. Genet.	www.wtccc.org.uk / www-gene.cimr.cam.ac.uk
EGCUT	Estonian Genome Centre of the University of Tartu	R	Nelis et al 2009 PLoS ONE	www.biobank.ee
ERF	Erasmus Rucphen Family (EUROSPAN)	R software	Aulchenko YS, et al. Linkage disequilibrium in young genetically isolated Dutch population. Eur J Hum Genet. 2004	
FINNTWIN12	Finnish Twin cohort / FT12 twins	R 2.12.1	Kaprio, J et al. Genetic and environmental factors in health-related behaviors: studies on Finnish twins and twin families. Twin Res. 5, 2002	www.twinstudy.helsinki.fi
FR02	Finnish Risk factor survey 2002	R 2.12.1	Vartiainen E, et al Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol. 2010	www.ktl.fi/finriski
FR07	Finnish Risk factor survey 2007	R 2.12.1	Vartiainen E, et al Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol. 2010	www.ktl.fi/finriski
FR92	Finnish Risk factor survey 1992	R 2.12.1	Vartiainen E,et al . Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol. 2010	www.ktl.fi/finriski
FR97	Finnish Risk factor survey 1997	R 2.12.1	Vartiainen E et al Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol. 2010	www.ktl.fi/finriski
FTC	FINNISH TWIN COHORT/Nicotine addiction families	Stata 11.2	Loukola A, et al Linkage of nicotine dependence and smoking behavior on 10q,7q and 11p in twins with homogeneous genetic background. Pharmacogenomics J. 2008 PMID: 17549066.	www.twinstudy.helsinki.fi
GODARTSDIAB	Genetics of Diabetes Audit and Research Study in Tayside Scotland	SAS/R	PMID:9329309	
GODARTSNONDIAB	Genetics of Diabetes Audit and Research Study in Tayside Scotland	SAS/R	PMID:9329309	
GOSH	Swedish twin registry: Gender, Octo, Satsa, Harmony	STATA 11	PMID: 17254424	http://ki.se/ki/jsp/polopoly.jsp?l=en&d=9610
GRAPHIC	Genetic Regulation of Arterial Pressure of Humans in the Community	Stata 11		
H2000	Finnish Health survey 2000	R 2.12.1	Methodology Report - Health 2000 Survey. In: Sami Heistaro, ed. Helsinki: National Public Health Institute; 2008.	www.terveys2000.fi/indexe.html
KORAF3	Cooperative Health Research in the Region of Augsburg, KOoperative Gesundheitsforschung in der Region Augsburg	R	Wichmann, H.-E.et al (2005): KORA-gen-resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen* 67	http://www.helmholtz-muenchen.de/en/kora-en/kora-homepage/index.html
KORAF4	Cooperative Health Research in the Region of Augsburg, KOoperative	R	Wichmann, H.-E.et al. (2005): KORA-gen-resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen* 67	http://www.helmholtz-muenchen.de/en/kora-en/kora-

	Gesundheitsforschung in der Region Augsburg			homepage/index.html
MDCCV	Malmö Diet and Cancer -cardiovascular cohort (MDC-CV)	SPSS 18	Hedblad et al: Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death. Diab Med 2002	www.med.lu.se/klinvetmalmo/mkc_mfm
MORGAM	Monitoring of trends and determinants in Cardiovascular disease, Risk, Genetics, Archiving and Monograph	R	Evans A, et al , for the MORGAM Project.). Int J Epidemiol 2005;34:21-27. [PubMed], Tunstall-Pedoe H, editor. Prepared by Tunstall-Pedoe et al The WHO MONICA Project. MONICA Monograph and Multimedia Sourcebook. Geneva: World Health Organization; 2003.	http://www.ktl.fi/morgam/
MPP	Malmö Prevention Project	STATA/SE 11.1	Berglund G et al. Cardiovascular risk groups and mortality in an urban Swedish male population: the Malmö Preventive Project. J Intern Med 1996; 239: 489–497	http://www.ludc.med.lu.se/research-units/diabetes-and-endocrinology/sample-collections/malmoe-prevention-project-mpp/
NESDA	Netherlands Study of Depression and Anxiety	R 2.12.0 / STATA SE 9.0 / PASW 18.0.0	Penninx, B.W.J.H. et al., 2008, The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods: Int.J.Methods Psychiatr. Res.	http://www.nesda.nl/en/
NFBC1966	Northern Finland Birth Cohort 1966	SAS 9.2 / R 2.12.2	Rantakallio P. Groups at risk in low birth weight infants and perinatal mortality. Acta Paediatr Scand. 1969;	http:kelo.oulu.fi/NFBC/
NFBC1986	Northern Finland Birth Cohort 1986	SAS 9.2 / R 2.12.2	Jarvelin MR et al. Labour induction policy in hospitals of different levels of specialisation. Br J Obstet Gynaecol 1993	http:kelo.oulu.fi/NFBC/
NTR	Netherlands Twin Register	R 2.12.0 / STATA SE 9.0 / PASW 18.0.0	Willemsen, G. et al., 2010, The Netherlands Twin Register biobank: a resource for genetic epidemiological studies: Twin Res.Hum.Genet	www.tweelingenregister.org
PIVUS	Prospective Investigation of the Vasculature in Uppsala Seniors	STATA 11	E. Ingelsson, J. Hulthe and L. Lind, Inflammatory markers in relation to insulin resistance and the metabolic syndrome, European Journal of Clinical Investigation Vol 38	http://www.medsci.uu.se/pivus/pivus.htm
PPP	Prevalence, Prediction and Prevention of diabetes	STATA/SE 11.1	Isomaa B, Forsén B, Lahti K, et al. A family history of diabetes is associated with reduced physical fitness in the Prevalence, Prediction and Prevention of Diabetes (PPP)–Botnia study. Diabetologia 2010	
QIMR-AUSTRALIA	Twin studies at the Queensland Instutite of Medical Research	Merlin, SPSS	Liu JZ, et al Genome-wide association study of height and body mass index in Australian twin families. Twin Research and Human Genetics 2010	http://genepi.qimr.edu.au/
RS	Rotterdam Study	SPSS	Hofman A, et al . The Rotterdam Study: 2010 objectives and design update. Eur J Epidemiol. 2009	http://www.epib.nl/research/ergo.htm
TWINGENE	Cardiovascular risk factor study of Swedish twin pairs	STATA 11	NA	http://ki.se/ki/jsp/polopoly.jsp?l=en&d=9610
TwinsUK	TwinsUK	STATA 10.1	Spector TD, Williams FM. The UK Adult Twin Registry (TwinsUK). Twin Res Hum Genet. 2006 Dec;9(6):899-906	http://www.twinsuk.ac.uk/
ULSAM	Uppsala longitudinal study of adult men	STATA 11	Zethelius B, et al Proinsulin and acute insulin response independently predict Type 2 diabetes mellitus in men--report from 27 years of follow-up study. Diabetologia 2003	http://www.pubcare.uu.se/ULSAM
WTCCCCases	Wellcome Trust Case Control Consortium CAD Cases	Stata 11 & Plink	WTCCC2 Nature. 2010;464;713-20. PMID: 20360734 DOI: 10.1038/nature08979	www.wtccc.org.uk
WTCCCCont	Wellcome Trust Case Control Consortium 1958 Birth Cohort	Stata 11 & Plink	WTCCC -58BC .C. Power, J. Elliott, Int. J. Epidemiol., 35, 34 (2006).	www.wtccc.org.uk
WTCCCT2D	Wellcome Trust Case Control Consortium - T2D	PLINK / R	WTCCC-T2D, Diabetes UK Warren 2 repository S. Wiltshire et al., Am. J. of Hum. Gen. 69, 553-569 (2001).	www.wtccc.org.uk

TableS1. Phenotypic details of the participating cohorts. (Part 2)

Cohort	Number of subjects with *FTO* and BMI data	Longitudinal data	Age at BMI	Mean BMI at baseline	Proportion women (%)	N with incident type 2 diabetes	N with ever type 2 diabetes	N with incident any stroke	N with ever any stroke
DECODE	36,896	No	59.1 (18.0)	27.2 (5.3)	63.8%	NA	2,126	NA	NA
DGIcases	1602	No	64.42 (10.32)	28.50 (4.40)	49.8%	NA	NA	NA	201
DGIcontrols	1508	No	58.61 (10.16)	26.70 (3.78)	52.2%	NA	NA	NA	26
DIL	2,589	No	45 (0)	27.5 (5.0)	51.3%	NA	NA	NA	NA
EGCUT	11,282	No	45.74 (18.34)	26.5 (5.52)	56.0%	NA	1,132	NA	323
ERF	2,725	No	48.9(14.3)	26.9 (4.7)	55.3%	NA	146	NA	NA
FINNTWIN12	419	No	22.9 (1.5)	22.84 (4.0)	49.2%	NA	NA	NA	NA
FR02	8,142	Yes	48.9(13.12)	26.91 (4.68)	53.3%	296	746	96	228
FR07	5,900	Yes	50.45 (13.93)	27.13 (4.88)	53.3%	67	567	18	121
FR92	5,536	Yes	44.39 (11,32)	26.13 (4.46)	53.9%	426	629	194	253
FR97	6,747	Yes	47.79 (13.22)	26.63 (4.61)	53.3%	429	818	188	303
FTC	1,109	Yes	55.01 (4.4.3)	26.09 (4.07)	38.1%	NA	55	NA	NA
GODARTSDIAB	8,171	No	66.11(11.28)	31.37(6.12)	44.0%	NA	NA	NA	629
GODARTSNONDIAB	6,768	No	60.73(13.09)	27.18(4.60)	49.9%	NA	8,178	NA	202
GOSH	1,346	Yes	54.17(12.00)	24.52(3.20)	50.1%	NA	62	289	316
GRAPHIC	2,024	No	39.29 (14.5)	26.11 (4.6)	49.6%	NA	21	NA	NA
H2000	3,480	Yes	56.21 (17.19)	26.81 (4.68)	56.9%	NA	311	93	261
KORAF3	2,976	No	56.92 (12.76)	27.61 (4.62)	52.3%	NA	238	NA	NA
KORAF4	3,009	No	56.08 (13.26)	27.62 (4.81)	51.5%	NA	214	NA	NA
MDCCV	5,901	No	57.47 (5.94)	25.77 (3.99)	58.0%	NA	420	NA	NA
MORGAM	3,745	Yes	59.28 (6.93)	26.75 (3.99)	4.6%	NA	267	356	139
MPP	13,616	No	45.2 (7.01)	24.28 (3.30)	33.3%	NA	NA	NA	NA
NESDA	1,927	No	41.90 (12.52)	25.65 (5.04)	67.6%	NA	95	NA	NA
NFBC1966	4,775	Yes	31.17 (0.35)	24.70 (4.28)	51.8%	NA	123	20	33
NFBC1986	5,285	Yes	16.00 (0.37)	21.22 (3.48)	51.0%	NA	NA	NA	NA
NTR	5,416	No	42.55 (14.76)	25.25 (4.30)	61.2%	NA	240	NA	NA
PIVUS	979	No	70.19 (0.17)	27.07 (4.3)	49.8%	NA	34	NA	35
PPP	4,355	No	47.90 (15.63)	26.31 (4.44)	53.8%	NA	160	NA	49
QIMR-AUSTRALIA	11,827	No	35.61 (17.41)	24.12 (5.12)	57.2%	NA	NA	NA	NA
RS	5,745	Yes	69.0 (8.80)	26.3 (3.69)	58.7%	547	1,178	618	149
TWINGENE	6,386	Yes	65.4(8.3)	26.2(4.2)	45.0%	NA	640	327	461
TwinsUK	4,829	No	52.8(14.42)	26.1 (5.06)	0.0%	NA	80	NA	NA
ULSAM	1,175	Yes	49.6 (0.6)	24.8 (3.0)	0.0%	226	48	274	274
WTCCCCases	2,966	No	51.27 (8.7)	28.02 (4.5)	19.9%	NA	260	NA	NA
WTCCCCont	5,443	No	46(0)	27.37 (4.8)	45.7%	NA	113	NA	NA
WTCCCT2D	1,903	No	48.71 (10.41)	28.23 (5.57)	47.4%	NA	1,903	NA	NA

Table S1. Phenotypic details of the participating cohorts. (Part 3)

Cohort	N with mortality events	N with incident metabolic syndrome	N with ever metabolic syndrome	N with incident ischemic stroke	N with ever ischemic stroke	N with incident hypertension	N with ever hypertension	N with incident hemorrhagic stroke	N with ever hemorrhagic stroke
DECODE	NA	NA	NA	NA	2,366	NA	8,248	NA	284
DGIcases	NA	NA	1,008	NA	NA	NA	1,101	NA	NA
DGIcontrols	NA	NA	353	NA	NA	NA	666	NA	NA
DIL	NA	NA	NA	NA	NA	NA	NA	NA	NA
EGCUT	281	NA	1,101	NA	128	NA	4,362	NA	10
ERF	NA	NA	403	NA	NA	NA	1,285	NA	NA
FINNTWIN12	NA	NA	NA	NA	NA	NA	NA	NA	NA
FR02	253	NA	NA	69	157	NA	3,569	NA	NA
FR07	36	NA	1,596	11	83	NA	2,874	NA	NA
FR92	493	NA	NA	140	175	NA	2,415	NA	NA
FR97	565	NA	NA	154	235	NA	3,191	NA	NA
FTC	57	NA	NA	NA	NA	NA	NA	NA	NA
GODARTSDIAB	NA	NA	NA	NA	181	NA	NA	NA	67
GODARTSNONDIAB	NA	NA	NA	NA	37	NA	NA	NA	41
GOSH	959	NA	NA	190	212	NA	1,189	55	56
GRAPHIC	NA	NA	NA	NA	NA	NA	577	NA	NA
H2000	558	NA	NA	75	225	NA	1,828	NA	NA
KORAF3	NA	NA	NA	NA	NA	NA	1,476	NA	NA
KORAF4	NA	NA	583	NA	NA	NA	1,158	NA	NA
MDCCV	NA	NA	1,450	NA	NA	NA	3,049	NA	NA
MORGAM	1,434	NA	NA	282	NA	NA	1,966	64	NA
MPP	NA	NA	24	NA	NA	NA	4,700	NA	NA
NESDA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NFBC1966	49	NA	664	8	13	NA	419	6	11
NFBC1986	21	NA	110	NA	NA	NA	17	NA	NA
NTR	NA	NA	NA	NA	NA	NA	NA	NA	NA
PIVUS	NA	NA	120	NA	NA	NA	144	NA	NA
PPP	NA	NA	1,034	NA	NA	NA	1,778	NA	NA
QIMR-AUSTRALIA	NA	NA	NA	NA	NA	NA	NA	NA	NA
RS	2,980	NA	1,291	340	NA	NA	3,273	56	NA
TWINGENE	276	NA	1,766	181	254	NA	3,771	48	68
TwinsUK	NA	NA	80	NA	NA	NA	572	NA	NA
ULSAM	735	458	76	167	167	600	438	51	51
WTCCCCases	NA	NA	NA	NA	NA	NA	1,228	NA	NA
WTCCCCont	NA	NA	NA	NA	NA	NA	1,427	NA	NA
WTCCCT2D	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table S1. Phenotypic details of the participating cohorts. (Part 4)

Cohort	N with incident heart failure	N with ever heart failure	N with incident dyslipidemia	N with ever dyslipidemia	N with incident coronary heart disease	N with ever coronary heart disease	N with total cholesterol	N with systolic blood pressure	N with triglycerites
DECODE	NA	NA	NA	NA	NA	3568	18,393	16,726	17,099
DGIcases	NA	NA	NA	1,038	NA	447	1,455	1,584	1,455
DGIcontrols	NA	NA	NA	616	NA	36	1,416	1,503	1,416
DIL	NA	NA	NA	NA	NA	NA	2,526	2,577	2,514
EGCUT	NA	804	NA	3,268	NA	537	2,362	11,277	1,868
ERF	NA	NA	NA	333	NA	NA	2,716	2,728	2,713
FINNTWIN12	NA	NA	NA	NA	NA	NA	416	NA	424
FR02	231	506	NA	3,074	162	383	7,549	8,142	7,549
FR07	65	284	NA	1,919	33	196	5,066	5,877	3,991
FR92	513	605	NA	2,142	331	410	5,451	5,537	5,450
FR97	467	711	NA	2,733	347	516	6,594	6,807	6,594
FTC	NA	NA	NA	NA	NA	NA	NA	NA	NA
GODARTSDIAB	NA	747	NA	NA	NA	1,030	7,679	8,077	5,724
GODARTSNONDIAB	NA	139	NA	NA	NA	262	6,407	6,760	5,529
GOSH	223	240	NA	477	96	102	1,374	1,344	1,102
GRAPHIC	NA	NA	NA	NA	NA	NA	2,020	2,020	1,961
H2000	308	745	NA	1,547	175	437	2,846	3,244	2,846
KORAF3	NA	NA	NA	397	NA	NA	231	2,985	231
KORAF4	NA	NA	NA	303	NA	NA	3,008	3,018	3,007
MDCCV	NA	NA	NA	2,089	NA	NA	5,210	5,901	5,210
MORGAM	NA	NA	NA	1,565	973	341	3,628	3,754	1,714
MPP	NA	NA	NA	NA	NA	NA	10,880	9,853	10,870
NESDA	NA	NA	NA	544	NA	NA	1,813	NA	1,810
NFBC1966	4	8	NA	1,031	14	17	4,566	4,769	4,565
NFBC1986	NA	NA	NA	1,030	NA	NA	5,110	5,281	5,110
NTR	NA	NA	NA	2,043	NA	NA	5,032	NA	5,032
PIVUS	NA	NA	NA	90	NA	27	784	975	784
PPP	NA	NA	NA	1,734	NA	210	3,923	4,355	3,924
QIMR-AUSTRALIA	NA	NA	NA	NA	NA	NA	8,315	NA	8,311
RS	717	894	NA	1,313	1056	1557	3,382	5,791	3,230
TWINGENE	142	174	NA	2,820	24	25	5,401	6,101	5,398
TwinsUK	NA	NA	NA	747	NA	NA	4,245	2,646	4,194
ULSAM	211	211	237	561	271	271	1,128	1,175	1,128
WTCCCCases	NA	NA	NA	NA	NA	NA	1,341	1,407	1,147
WTCCCCont	NA	NA	NA	NA	NA	NA	5,352	5,430	5,341
WTCCCT2D	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table S1. Phenotypic details of the participating cohorts. (Part 5)

Cohort	N with interleukine 6	N with gamma-glytamyl-transferase	N with fasting insulin	N with c-reactive protein	N with C-peptide	N with alanine aminotransferase	N with LDL cholesterol	N with HDL cholesterol
DECODE	NA	NA	3,103	24,128	NA	NA	16,297	17,009
DGIcases	NA	NA	NA	NA	NA	NA	426	1,414
DGIcontrols	NA	NA	1,345	NA	NA	NA	710	1,406
DIL	NA	NA	NA	2,475	NA	NA	2,373	2,519
EGCUT	NA	859	NA	NA	NA	859	1,872	1,921
ERF	NA	NA	2,125	2,090	NA	NA	2,699	2,716
FINNTWIN12	NA	NA	NA	NA	NA	NA	424	424
FR02	NA	8,138	NA	8,119	NA	NA	7,454	7,549
FR07	NA	5,900	3,865	5,900	NA	NA	3,990	3,991
FR92	NA	5,524	NA	932	NA	NA	5,330	5,451
FR97	NA	6,811	NA	6,457	NA	NA	6,480	6,594
FTC	NA	NA	NA	NA	NA	NA	NA	NA
GODARTSDIAB	NA	NA	NA	NA	NA	NA	5,172	7,343
GODARTSNONDIAB	NA	NA	1,642	NA	NA	NA	5,365	6,307
GOSH	NA	310	109	282	NA	NA	856	1,166
GRAPHIC	NA	NA	NA	NA	NA	NA	1,961	2,020
H2000	NA	NA	2,577	NA	NA	NA	2,831	2,846
KORAF3	1,537	2,996	NA	243	NA	2,994	231	231
KORAF4	NA	3,017	2,981	3,018	NA	3,017	3,007	3,007
MDCCV	NA	NA	4,755	NA	NA	NA	5,077	5,156
MORGAM	NA	NA	NA	NA	NA	NA	1,663	3,628
MPP	NA	13,563	NA	NA	NA	12,318	NA	243
NESDA	1,905	1,877	NA	1,901	NA	NA	1,795	1,806
NFBC1966	NA	NA	4,297	4,755	NA	NA	4,551	4,566
NFBC1986	NA	NA	4,879	5,247	NA	NA	5,110	5,110
NTR	4,804	5,052	4,707	4,958	NA	4,855	5,021	5,030
PIVUS	961	975	892	972	NA	975	782	784
PPP	NA	NA	4,142	NA	1,195	4,333	3,881	3,923
QIMR-AUSTRALIA	NA	8,241	NA	NA	NA	8,242	7,962	8,278
RS	599	4,309	3,414	5,567	NA	4,314	3,140	3,331
TWINGENE	NA	NA	NA	6,489	NA	NA	5,322	5,401
TwinsUK	398	3,546	2,272	4,035	NA	3,761	4,183	4,247
ULSAM	1,021	NA	913	1,082	NA	1,086	917	917
WTCCCCases	NA	NA	NA	NA	NA	NA	1,103	1,103
WTCCCCont	NA	NA	NA	2,687	NA	NA	5,041	5,345
WTCCCT2D	NA	NA	NA	NA	NA	NA	NA	NA

Table S1. Phenotypic details of the participating cohorts. (Part 6)

Cohort	N with HbA1c	N with fasting glucose	N with diastolic blood pressure	N with 2h post OGTT glucose	Glucose: mean (SD) / mmol/L	Insulin: mean (SD) /pmol/L	HbA1c: mean (SD)/%	2hG: mean (SD) / mmol/L	C-peptide: mean (SD) / nmol/l	HDL-C: mean (SD) / mmol/L	LDL-C: mean (SD) / mmol/L
DECODE	NA	12,017	NA	NA	5.25 (0.60)	63.6 (55.1)	NA	NA	NA	1.45 (0.42)	3.69 (1.08)
DGIcases	NA	NA	1,583	NA	NA	NA	NA	NA	NA	1.20 (0.31)	3.96 (1.04)
DGIcontrols	505	1,387	1,502	1,017	5.32 (0.52)	39.47 (32.41)	5.37 (0.52)	5.64 (1.32)	NA	1.39 (0.34)	4.03 (0.92)
DIL	2,532	NA	2,577	NA	NA	NA	5.21 (0.64)	NA	NA	1.56 (0.40)	3.41 (0.91)
EGCUT	NA	1,757	11,277	301	5.38 (0.79)	NA	NA	5.92 (1.20)	NA	1.36 (0.70)	3.60 (1.63)
ERF	NA	2,703	2,728	NA	4.66 (1.15)	13.26 (7.51)	NA	NA	NA	1.28 (0.37)	3.72 (0.98)
FINNTWIN12	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.76 (0.41)	1.68 (0.47)
FR02	NA	NA	8,142	NA	NA	NA	NA	NA	NA	1.51 (0.42)	3.45 (0.95)
FR07	NA	3,872	5,874	3,827	5.72 (0.46)	42.42 (25.31)	NA	6.16 (1.65)	NA	1.46 (0.35)	3.28 (0.82)
FR92	NA	NA	5,536	NA	NA	NA	NA	NA	NA	1.40 (0.35)	3.55 (0.99)
FR97	NA	NA	6,808	NA	NA	NA	NA	NA	NA	1.40 (0.36)	3.48 (0.92)
FTC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GODARTSDIAB	NA	NA	8,077	NA	9.58 (3.55)	NA	7.20(1.44)	NA	NA	1.26 (0.67)	2.71 (1.01)
GODARTSNONDIAB	6,728	3,388	6,760	NA	5.13 (0.91)	78.06 (60.00)	5.52 (0.42)	NA	NA	1.59 (0.57)	3.10 (0.97)
GOSH	375	102	1,344	NA	6.3(0.55)	63.5(34.1)	5.51(1.00)	NA	NA	1.43(0.41)	3.75(1.00)
GRAPHIC	NA	NA	2,020	NA	NA	NA	NA	NA	NA	1.63 (0.4)	2.89 (0.8)
H2000	NA	2,660	3,244	NA	5.94 (0.46)	53.62 (36.55)	NA	NA	NA	1.33 (0.38)	3.74 (1.06)
KORAF3	2,999	231	2,985	NA	6.41 (1.18)	NA	5.36 (0.52)	NA	NA	1.51 (0.46)	3.48 (0.91)
KORAF4	3,024	2,990	3,018	2,724	6.17 (1.20)	65.09 (249.2)	5.55 (0.62)	7.06 (2.47)	NA	1.44 (0.37)	3.51 (0.90)
MDCCV	4,895	4,914	5,901	NA	5.85 (1.56)	47.93 (45.22)	4.91 (0.77)	NA	NA	1.38 (0.37)	4.17 (0.99)
MORGAM	NA	NA	3,754	NA	NA	NA	NA	NA	NA	1.21 (0.39)	3.81 (0.95)
MPP	202	13,615	9,858	7,370	5.46 (0.554)	NA	4.83 (0.49)	5.64 (1.47)	NA	1.55 (0.37)	NA
NESDA	NA	1,722	NA	NA	5.03 (0.58)	NA	NA	NA	NA	1.63 (0.44)	3.13 (1.00)
NFBC1966	NA	4,322	4,762	NA	5.70 (0.63)	58.47 (28.71)	NA	NA	NA	1.55 (0.38)	3.00 (0.89)
NFBC1986	NA	4,789	5,281	NA	5.18 (0.73)	76.10 (49.32)	NA	NA	NA	1.40 (0.29)	2.25 (0.57)
NTR	4,725	4,821	NA	NA	5.35 (0.53)	63.03 (42.14)	5.31 (0.57)	NA	NA	1.42 (0.38)	3.10 (0.95)
PIVUS	NA	855	975	NA	5.57 (0.56)	51.0 (30.6)	NA	NA	NA	1.52 (0.43)	3.40 (0.84)
PPP	NA	4,173	4,355	4,144	5.28 (0.57)	45.83 (34.66)	NA	5.24 (1.59)	0.64 (0.26)	1.42 (0.39)	3.30 (0.944)
QIMR-AUSTRALIA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.52 (0.42)	3.31 (0.93)
RS	NA	3,295	5,790	NA	5.88 (1.32)	96.1 (253.1)	NA	NA	NA	1.34 (0.37)	3.75 (0.88)
TWINGENE	6,484	5,657	6,044	NA	5.40 (0.60)	NA	4.80 (0.07)	NA	NA	1.4(0.41)	3.90 (0.93)
TwinsUK	NA	4,517	2,646	966	4.66 (0.58)	49.53 (34.40)	NA	6.78 (0.40)	NA	1.47 (0.40)	3.41 (1.09)
ULSAM	288	1,123	1,175	908	5.50 (0.50)	73.40 (39.70)	7.10 (0.99)	6.90 (1.80)	NA	1.40 (0.40)	5.20 (1.20)
WTCCCCases	NA	NA	934	NA	NA	NA	NA	NA	NA	1.11 (0.40)	2.95 (0.90)
WTCCCCont	2,714	NA	5,430	NA	NA	NA	5.27 (0.69)	NA	NA	1.11 (0.40)	2.95 (0.90)
WTCCCT2D	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table S1. Phenotypic details of the participating cohorts. (Part 7)

Cohort	Total cholesterol: mean (SD) / mmol/L	Systolic blood pressure: mean (SD) / mmHg	Diastolic blood pressure: mean (SD) / mmHg	ALT: mean (SD) / U/L	GGT: mean (SD) / U/L	Interleukine-6: mean (SD) / pg/mL	CRP: mean (SD) / mg/L
DECODE	5.82 (1.17)	135.4 (20.4)	NA	NA	NA	NA	38.7 (65.8)
DGIcases	5.81 (1.18)	149.2 (20.8)	84.1 (10.2)	NA	NA	NA	NA
DGIcontrols	5.93 (1.09)	135.9 (18.8)	81.5 (9.9)	NA	NA	NA	NA
DIL	5.88 (1.10)	126.8 (16.4)	79.0 (10.8)	NA	NA	NA	2.12 (3.80)
EGCUT	5.50 (1.18)	130.81 (21.75)	80.52 (12.92)	24.3 (17.3)	21.5 (20.3)	NA	NA
ERF	5.56 (1.10)	140.30 (20.44)	80.46 (10.03)	NA	NA	NA	3.36 (8.12)
FINNTWIN12	4.64 (0.82)	NA	NA	NA	NA	NA	NA
FR02	5.60 (1.07)	137.13 (22.02)	80.46 (12.53)	NA	34.67 (51.55)	NA	2.49 (5.23)
FR07	5.32 (0.99)	138.92 (22.69)	81.01 (12.55)	NA	33.36 (47.18)	NA	2.43 (5.03)
FR92	5.62 (1.11)	136.84 (20.98)	82.18 (12.93)	NA	27.64 (40.77)	NA	4.05 (7.63)
FR97	5.54 (1.05)	137.63 (21.78)	83.52 (12.47)	NA	35.23 (53.19)	NA	2.38 (5.91)
FTC	NA	NA	NA	NA	NA	NA	NA
GODARTSDIAB	5.66 (1.27)	141.50(18.55)	76.28 (11.09)	NA	NA	NA	NA
GODARTSNONDIAB	5.58 (1.04)	135.90 (19.36)	79.28 (9.95)	NA	NA	NA	NA
GOSH	6.3(1.35)	154.3(25.1)	84.3(12.5)	NA	0.53(0.57)	NA	7.23(5.8)
GRAPHIC	5.08 (1.1)	119.47 (11.4)	72.15 (8.1)	NA	NA	NA	NA
H2000	5.96 (1.13)	140.47 (25.21)	84.79 (12.97)	NA	NA	NA	NA
KORAF3	5.81 (1.02)	135.21 (22.48)	84.95 (11.61)	20.78 (12.57)	38.2 (58.01)	2.85 (10.45)	0.45 (0.85)
KORAF4	5.58 (1.02)	126.94 (21.19)	78.25 (10.95)	25.69 (12.24)	40.4 (77.23)	NA	0.25 (0.53)
MDCCV	6.17 (1.10)	141.33 (19.04)	86.98 (9.47)	NA	NA	NA	NA
MORGAM	5.92 (1.06)	142 (21)	86 (12)	NA	NA	NA	NA
MPP	5.61 (1.04)	127.1 (14.2)	83.9 (8.8)	0.367 (0.210)	0.497 (0.410)	NA	NA
NESDA	5.11 (1.06)	NA	NA	NA	25.50 (29.47)	1.64 (16.21)	2.84 (5.13)
NFBC1966	5.06 (0.99)	125.21 (13.88)	77.69 (11.60)	NA	NA	NA	2.01 (3.66)
NFBC1986	4.26 (0.79)	115.48 (12.73)	67.69 (7.58)	NA	NA	NA	0.99 (2.85)
NTR	5.12 (1.06)	NA	NA	10.33 (6.14)	32.02 (34.39)	1.90 (4.31)	3.30 (6.54)
PIVUS	5.4 (0.98)	149.7 (22.7)	78.8 (10.2)	20.2 (13.5)	29.9 (30.0)	30.4 (85.3)	3.2 (4.8)
PPP	5.30 (1.06)	129.3 (17.2)	79.1 (9.9)	27.9 (19.9)	NA	NA	NA
QIMR-AUSTRALIA	5.67 (1.05)	NA	NA	24.46 (17.32)	29.32 (35.69)	NA	NA
RS	6.59 (1.22)	139.2 (22.3)	73.7 (11.5)	18.0 (11.4)	29.9 (28.6)	2.827 (4.03)	3.38 (6.8)
TWINGENE	5.94(1.1)	139.3(19.8)	81.6(10.5)	NA	NA	NA	3.42(7.4)
TwinsUK	5.44 (1.23)	121.41 (15.91)	76.60 (10.56)	28.55 (13.68)	27.04 (24.70)	23.29 (26.59)	2.65 (4.70)
ULSAM	6.8 (1.3)	131.4 (16.8)	82.6 (10.5)	25.8(15.3)	NA	5.85(9.2)	3.3 (4.7)
WTCCCCases	5.00 (1.1)	139.46 (24.0)	81.14 (13.4)	NA	NA	NA	NA
WTCCCCont	5.00 (1.1)	139.46 (24.0)	81.14 (13.4)	NA	NA	NA	2.20 (4.32)
WTCCCT2D	NA	NA	NA	NA	NA	NA	NA

Table S2. Cohort-specific genotyping details

	SNP	EFFECT ALLELE	NON EFFECT ALLELE	EAF	HWE p-value	Call rate	IMP	In silico/ De novo	Genotyping platform & SNP panel	Genotyping centre	Genotyping calling algorithm
DECODE	rs9939609	A	T	0.41	0.54	.	0	De novo/ In silico	Centaurus (Nanogen)	DeCode	-
DGIcases	rs9939609	A	T	0.42	0.64	1	0	In silico	Affymetrix GeneChip® Human Mapping 500K Array Set	Broad Institute	BRLMM
DGIcontrols	rs9939609	A	T	0.40	0.24	1	0	In silico	Affymetrix GeneChip® Human Mapping 500K Array Set	Broad Institute	BRLMM
DIL	rs3751812	T	G	0.40	0.77	0.999	0	De novo /In Silico (IC;ICQ; OQ; Metabo)	TaqMan & rs9939609	Wellcome Trust Sanger Institute	Applied Biosystems SDS
EGCUT	rs9939609	A	T	0.44	0.56	1	0	In silico	Illumina 318K, 370K, Affymetrix 250K	Erasmus MC	BEADSTUDIO, BRLMM
ERF	rs9939609	A	T	0.43	NA	NA	1	In silico	Illumina Human670-QuadCustom	Wellcome Trust Sanger Institute	
FINNTWIN12	rs3751812	T	G	0.41	0.95	0.998	0	In silico	Illumina Human670-QuadCustom	Wellcome Trust Sanger Institute	
FR02	rs9939609	A	T	0.41	0.65	0.999	0	De novo	Sequenom	Institute for Molecular Medicine Finland (FIMM)	Manually curated
FR07	rs9939609	A	T	0.39	0.19	0.999	0	De novo	Sequenom	Institute for Molecular Medicine Finland (FIMM)	Manually curated
FR92	rs9939609	A	T	0.40	0.11	0.999	0	De novo	Sequenom	Institute for Molecular Medicine Finland (FIMM)	Manually curated
FR97	rs9939609	A	T	0.40	0.63	0.999	0	De novo	Sequenom	Institute for Molecular Medicine Finland (FIMM)	Manually curated
FTC	rs3751812	T	G	0.41	0.85	0.987	0	In silico	Illumina Human670-QuadCustom	Wellcome Trust Sanger Institute	
GODARTSDIAB	rs9939609	A	T	0.42	0.30	1	0	In silico	Affymetrix 6.0/Cardio-Metabo BeadChip (Illumina 200K)	Sanger	CHIAMO/genosnp
GODARTSNONDIAB	rs9939609	A	T	0.40	0.13	1	0	In silico	Affymetrix 6.0/Cardio-Metabo BeadChip (Illumina 200K)	Sanger	CHIAMO/genosnp
GOSH	rs9939609	A	T	0.39	0.24	1	0	In silico	Cardio-Metabo BeadChip (Illumina 200K)	DeCode	GenCall algorithm, GenomeStudio, Illumina
GRAPHIC	rs9939609	A	T	0.40	0.04	1	0	In silico	HumanCVD 50K BeadChip	Leicester	GenCall
H2000	rs9939609	A	T	0.40	0.51	0.993	0	De novo	Sequenom	Institute for Molecular Medicine Finland (FIMM)	Manually curated
KORAF3	rs11075989	T	C	0.40	0.97	1	0	In silico	Cardio-Metabo BeadChip (Illumina 200K)	Munich	GenCall algorithm, GenomeStudio, Illumina
KORAF4	rs11075989	T	C	0.40	0.97	0.999	0	In silico	Cardio-Metabo BeadChip (Illumina 200K)	Munich	GenCall algorithm, GenomeStudio, Illumina
MDCCV	rs9939609	A	T	0.41	0.83	0.976	0	De novo	Taqman Assay (Applied Biosystems)	Lund University Diabetes center	
MORGAM	rs11075989	T	C	0.41	0.11	1	0	In silico	Cardio-Metabo BeadChip (Illumina 200K)	Wellcome Trust Sanger Institute	GenCall algorithm, GenomeStudio, Illumina
MPP	rs9939609	A	T	0.41	0.92	0.99	0	De novo	Taqman Assay (Applied Biosystems)	Lund University Diabetes Centre	SDS v 2.2
NESDA	rs9939609	A	T	0.40	NA	NA	1	In silico	Illumina 660K / Affymetrix (660K/907K)	Perlegen (USA), Tgene (USA)	Affymetrix proprietary, Birdsuite

NFBC1966	rs9939609	A	T	0.39	0.62	0.96	0	De novo	TaqMan® SNP genotyping assay (Applied Biosystems, Warrington, UK)	Oxford Centre for Diabetes Endocrinology and Metabolism	
NFBC1986	rs1421085	C	T	0.41	0.61	0.994	0	De novo	Taqman Assay (Applied Biosystems)	Institute of Biology, Pasteur Institute, Lille, France, CNRS-UMR8090	7900 HT SDS 3.2 (Applied Biosystems)
NTR	rs9939609	A	T	0.38	NA	NA	1	In silico	In silico: Illumina (907K/660K/370K) / Affymetrix (660K/1M); De novo: Sequenom MassARRAY iPLEX Platform	In silico: various; De novo: Moleculaire Epidemiologie, Leiden University	In silico: Affymetrix proprietary, Birdsuite; De novo: MassARRAY Analyzer 4 System
PIVUS	rs9939609	A	T	0.41	1	1	0	In silico	Cardio-Metabo BeadChip (Illumina 200K)	Uppsala SNP Technology Platform	GenCall algorithm, GenomeStudio, Illumina
PPP	rs9939609	A	T	0.38	0.36	0.95	0	De novo	Taqman Assay (Applied Biosystems)	Lund University Diabetes Centre	SDS v 2.2
QIMR-AUSTRALIA	rs9939609	A	T	0.40	NA	NA	1	In silico	Illumina 317K, Illumina 370K, Illumina 610K chip	University of Helsinki, DeCode	
RS	rs9939609	A	T	0.38	NA	NA	1	In silico	Version 3 Illumina Infinium II HumanHap 550 SNP chip array	Genetic Laboratory Dept Internal Medicine, Erasmus MC, The Netherlands	BeadStudio, Genecall
TWINGENE	rs9939609	A	T	0.41	0.52	1	0	De novo	Centaurus (Nanogen)	DeCode	
TwinsUK	rs3751812	T	G	0.39	0.70	1	0	In silico	Illumina	WTSI,CIDR	Illluminus
ULSAM	rs9939609	A	T	0.39	0.24	1	0	In silico	Cardio-Metabo BeadChip (Illumina 200K)	Uppsala SNP Technology Platform	GenCall algorithm, GenomeStudio, Illumina
WTCCCCases	rs11075989	T	C	0.41	0.52	1	0	In silico	Cardio-Metabo BeadChip (Illumina 200K)	Sanger	GenCall algorithm, GenomeStudio, Illumina
WTCCCCont	rs11075989	T	C	0.39	0.76	1	0	In silico	Cardio-Metabo BeadChip (Illumina 200K)	Sanger	GenCall algorithm, GenomeStudio, Illumina
WTCCCT2D	rs9939609	A	T	0.45	0.10	1	0	In silico	Affymetrix / 500k (T2C cases) /6.0 (NBS & 58BC controls)	Oxford	

Table S3. List of proxies with r2>0.9 for *FTO* variant rs9939609 at chr 16, position 52378028, alleles T/A.

Proxies	Alleles on (+) strand	Position hg18	Distance from index SNP	r^2 to best SNP
rs11075990	A/G	52377394	634	1
rs11075989	C/T	52377378	650	1
rs3751812	G/T	52375961	2067	1
rs9935401	G/A	52374339	3689	1
rs8051591	A/G	52374253	3775	1
rs8050136	C/A	52373776	4252	1
rs8043757	A/T	52370951	7077	1
rs17817449	T/G	52370868	7160	1
rs7202116	A/G	52379116	1088	0.967
rs9923233	C/G	52376699	1329	0.967
rs7185735	A/G	52380152	2124	0.967
rs17817964	C/T	52385567	7539	0.967
rs7193144	T/C	52368187	9841	0.967
rs9936385	T/C	52376670	1358	0.935
rs1558902	T/A	52361075	16953	0.934
rs1421085	T/C	52358455	19573	0.934
rs12149832	G/A	52400409	22381	0.934

Table S4A. Definitions of outcomes

Trait	Definition	Exclusion for logistic models	Exclusion for Cox regression models
Coronary heart disease (acute myocardial infarction or unstable angina)	Either defined from hospital discharge registry or cause of death registry (main diagnosis); or from validated events ICD-8 codes: 410, 411 , ICD-9 codes: 410, 411B, ICD-10 codes: I20.0, I21, I22, *Note: Self-reported events are considered not useful.*	None	Free of any major CVD (coronary heart disease, stroke *and* heart failure) at BMI measurement, as defined in middle column
Ischemic stroke	Either defined from hospital discharge registry or cause of death registry (main diagnosis); or from adjudicated events ICD-8 codes: 432-434, ICD-9 codes: 433-434, ICD-10 codes: I63, *Note: Self-reported events are considered not useful.*	None	Free of any major CVD (coronary heart disease, stroke *and* heart failure) at BMI measurement, as defined in middle column
Hemorrhagic stroke	Either defined from hospital discharge registry or cause of death registry (main diagnosis); or from adjudicated events ICD-8 codes: 430-431, ICD-9 codes 430-432, ICD-10 codes: I60-I62, *Note: Self-reported events are considered not useful*	None	Free of any major CVD (coronary heart disease, stroke and heart failure) at BMI measurement, as defined in middle column
Any acute stroke or transient ischemic attack	Either defined from hospital discharge registry or cause of death registry (main diagnosis); or from adjudicated events ICD-8 codes: 430-436, ICD-9 codes: 430-436, ICD-10 codes: I60-I64+G45, *Note: Self-reported events are considered not useful*	None	Free of any major CVD (coronary heart disease, stroke and heart failure) at BMI measurement, as defined in middle column
Heart failure	Either defined from hospital discharge registry or cause of death registry (main diagnosis); or from adjudicated events, ICD-8 codes: 427.00, 427.10, ICD-9 codes: 428, ICD-10 codes: I50, *Note: Self-reported events are considered not useful*	None	Free of any major CVD (coronary heart disease, stroke and heart failure) at BMI measurement, as defined in middle column
Type 2 diabetes	Fasting blood glucose ≥7 mmol/L or anti-diabetic treatment. Self-reported diabetes	Type I diabetics, pregnant at blood sampling	Free of T2D at BMI measurement, as defined in middle column type 1 diabetes, pregnant at blood sampling
Hypertension	Systolic blood pressure ≥140, diastolic blood pressure ≥90, or on anti-hypertensive treatment	None	Free of hypertension at BMI measurement, as defined in middle column
Dyslipidemia	Serum triglycerides ≥1.7 mmol/L, HDL-cholesterol < 1.0 mmol/L in men and <1.3 mmol/L in women, or treatment with nicotinic acid or fibrates	None	Free of dyslipidemia at BMI measurement, as defined in middle column
Metabolic Syndrome	At least 3 out of 5 criteria should be present: . waist circumference (men, ≥102 cm; women, ≥88 cm), . elevated triglycerides (≥1.7 mmol/l), . reduced HDL cholesterol (men, <1.03 mmol/l; women, <1.29 mmol/l), . blood pressure (systolic ≥130 mmHg or diastolic ≥85mmHg), . fasting glucose (≥5.6 mmol/l).	None	Free of METS at BMI measurement, as defined in middle column

Table S4B. Definitions of quantative outcomes and transformations

Trait	Unit	transformation	exclusion
Glucose	mmol/l	if measured in blood, convert to plasma scale	Exclude all individuals with diabetes (T2D, T1D) from datasets ('diagnosed', on diabetes treatment (oral and insulin), and/or FPG >=7 mmol/L), non-fasting or pregnant
Insulin	pmol/l	Natural log-transformed	Same as above
HbA1c	%	use the NGSP definition	Same as above PLUS Exclude samples with major blood abnormalities (thalassemia, sickle cell anemia, etc). Exclude samples who have had a blood transfusion in the previous 2-3 months
2h post OGTT glucose	mmol/l		Same as for FG
C-peptide	nmol/l	Natural log-transformed	Same as for FG
High-density-lipoprotein cholesterol	mmol/l		Non-fasting, Patients on lipid-lowering medication
Low-density-lipoprotein cholesterol	mmol/l		Non-fasting, Patients on lipid-lowering medication
Triglycerides	mmol/l	Natural log-transformed	Non-fasting, Patients on lipid-lowering medication
Total cholesterol	mmol/l		Non-fasting, Patients on lipid-lowering medication
Systolic blood pressure	mmHg		None
Diastolic blood pressure	mmHg		None
Alanine aminotransferase	U/l	Natural log-transformed	Known liver disease
Gamma-glutamyl transferase	U/l	Natural log-transformed	Known liver disease
Interleukin-6	pg/ml	Natural log-transformed	Known inflammatory disease or acute infection (at time of blood sampling)
C-reactive protein	mg/l	Natural log-transformed, measured using high-sensitivity assays	Known inflammatory disease or acute infection (at time of blood sampling)

Table S5. Specifications of assays used for quantitative traits and study-specific definitions of binary traits. (Part 1)

COHORT	Glucose	Insulin	HbA1c	C-peptide	HDL-C	LDL-C
DECODE	Roche diagnostics and Technicon auto-analyser or the Hitachi 912 clinical chemistry auto-analyser	Insulin electrochemiluminescence immunoassay	NA	NA	Enzymatic techniques. Data derived from 2 labs (Landspitali University Hospital and RAM).	Data derived from two labs (Landspitali University Hospital and RAM). Most data derived through Friedewald's formula. Minority directly measured.
DGIcases	Plasma glucose was measured with a glucose oxidase method (Beckman Glucose Analyzer, Beckman Instruments, Fullerton, CA)	Radioimmunoassay (Pharmacia, Uppsala, Sweden), enzyme linked immunoassay (DAKO Diagnostics Ltd, Cambridgeshire, UK), and fluoroimmunometric assay (AutoDelfia, Perkin Elmer Finland, Turku, Finland)	Local laboratories	Human C-peptide RIA-kit (Linco Research, St. Charles, Missouri, USA)	Cobas Mira analyzer (Hoffmann La Roche, Basel, Switzerland) in the Finnish cohort, Hitachi 911 (Boehringer Mannheim, Mannheim, Germany) in the Southern Swedish cohort and Technicon DAX 48 (Bayer Sweden AB, Gothenburg, Sweden) in the Skara cohort	Friedewald formula
DGIcontrols	Plasma glucose was measured with a glucose oxidase method (Beckman Glucose Analyzer, Beckman Instruments, Fullerton, CA)	Radioimmunoassay (Pharmacia, Uppsala, Sweden), enzyme linked immunoassay (DAKO Diagnostics Ltd, Cambridgeshire, UK), and fluoroimmunometric assay (AutoDelfia, Perkin Elmer Finland, Turku, Finland)	Local laboratories	Human C-peptide RIA-kit (Linco Research, St. Charles, Missouri, USA)	Cobas Mira analyzer (Hoffmann La Roche, Basel, Switzerland) in the Finnish cohort, Hitachi 911 (Boehringer Mannheim, Mannheim, Germany) in the Southern Swedish cohort and Technicon DAX 48 (Bayer Sweden AB, Gothenburg, Sweden) in the Skara cohort	Friedewald formula
DIL	NA	NA	ion exchange HPLC	NA	autoanalyser	NA
EGCUT	Reference method at Tartu University Hospital	NA	Reference method at Tartu University Hospital	NA	Reference method at Tartu University Hospital	Reference method at Tartu University Hospital
ERF	assay info na / measured in serum	assay info na / measured in serum	NA	NA	assay info na / measured in serum	NA
FINNTWIN12	NA	NA	NA	NA	NMR	NMR
FTC	NA	NA	NA	NA	NA	NA
FR92	NA	NA	NA	NA	Dextran-MgCl2 precipitation (average 4-hour fasting time)	LDL cholesterol was calculated using Friedewald's formula: LDL=serum cholesterol-HDL-(0.45.serum triglycerides), Average 4-hour fasting time.
FR97	NA	NA	NA	NA	Dextran-MgCl2 precipitation (average 4-hour fasting time)	LDL cholesterol was calculated using Friedewald's formula: LDL=serum cholesterol-HDL-(0.45.serum

						triglycerides), Average 4-hour fasting time.
FR02	NA	NA	NA	NA	Direct, polyethylene glycol-modified enzyme (PEG) (average 4-hour fasting time)	LDL cholesterol was calculated using Friedewald's formula: LDL=serum cholesterol-HDL-(0.45.serum triglycerides), Average 4-hour fasting time.
FR07	Enzymatic, hexokinase (fasting time >= 8 hours)	CMIA, Chemiluminescent Microparticle Immuno Assay (measured from serum)	NA	NA	Accelerator selective detergent	Lipid Selective Detergent
GODARTS	Gluco-quant Glucose / HK, Roche Diagnostics	ELISA assay (Mercodia)	Reference method at NHS Tayside	NA	Reference method at NHS Tayside	Friedewald calculated
GOSH	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet	NA	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet
GRAPHIC	NA	NA	NA	NA	Abbott Aeroset 2.0 Analyser	Abbott Aeroset 2.0 Analyser
H2000	Glucose, Hexokinase (4-11 hour fasting time)	Microparticle enzyme immunoassay (4-11 hour fasting time)	NA	NA	HDL-C Plus (4-11 hour fasting time)	LDL-C Plus (4-11 hour fasting time)
KORA F3	GLU Flex (Dade Behring); Hexokinase/G6P-DH	NA	turbidimetric immunologic inhibition assay (TINIA; HA1C Kit Dade Behring)	NA	AHDL Flex method (Dade-Behring)	direct method (ALDL, Dade-Behring).
KORA F4	GLU Flex (Dade Behring); Hexokinase/G6P-DH	ELISA	HPLC (Menarini HA-8160)	NA	AHDL Flex method (Dade-Behring)	direct method (ALDL, Dade-Behring).
MDCCV	whole blood glucose, hexokinase method	radioimmunoassay	standars procedures (Dept Clincal Chemistry, Malmö University Hospital)	NA	standars procedures (Dept Clincal Chemistry, Malmö University Hospital)	Friedewalds
MORGAM	NA	NA	NA	NA	Dextran sulphate-Mg++ method, phosphotungstate-Mg++ method, or updated phosphotungstate-Mg++ method after the Boehringer-Ms.	Calculated using Friedewald's formula.
MPP	Hexokinase method (routine methods at the Department of Clinical Chemistry, University Hospital)	NA	routine methods at the Department of Clinical Chemistry, University Hospital	NA	routine methods at the Department of Clinical Chemistry, University Hospital	Friedewald formula
NESDA	Hexokinase method (Gluco-quant) (Modular analytics, Roche diagnostics, Mannheim, Germany)	NA	NA	NA	Enzymatic colorimetric assay (HDL-C plus) (Modular analytics, Roche diagnostics, Mannheim, Germany)	LDL cholesterol was calculated using Friedewald's formula (only if triglycerides < 5.0mmol/L): LDL=cholesterol-HDL-(0.45.triglycerides).
NFBC1966	Blood glucose was analysed by a glucose dehydrogenase method	Serum insulin was analysed by RIA	NA	NA	NA	Serum LDL was calculated by the Friedewald formula

	(Granutest 250, Diagnostica Merck, Darmstadt, Germany)	(Pharmacia Diagnostics, Uppsala, Sweden)				if the serum TG level was less than 354 mg/dL; if the TG level was greater than equal 354 mg/dL, LDL was determined by precipitating LD-lipoproteins with heparin and measuring cholesterol in the liquid phase and subtracting it from TC
NFBC1986	Plasma glucose concentrations were analysed by Cobas Integra 700 automatic analyser (Roche Diagnostics, Basel, Switzerland)	Serum insulin was determined by radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden)	NA	NA	High-density lipoprotein (HDL)-cholesterol concentrations were analysed by Cobas Integra 700 automatic analyser (Roche Diagnostics, Basel, Switzerland)	Low-density lipoprotein (LDL)-cholesterol concentrations were analysed by Cobas Integra 700 automatic analyser (Roche Diagnostics, Basel, Switzerland)
NTR	Vitros 250 Glucose assay (Johnson & Johnson, Rochester, USA; measured in heparin plasma)	Immulite 1000 Insulin Method (Diagnostic Product Corporation, Los Angeles, USA; measured in heparin plasma)	Nyocard HbA1c assay (Axis-Shield, Oslo, Norway; measured in EDTA whole blood)	NA	Vitros 250 direct HDL cholesterol assay (Johnson & Johnson, Rochester, USA; measured in heparin plasma)	LDL cholesterol was calculated using Friedewald's formula: LDL=plasma cholesterol-HDL-(0.20.plasma triglycerides).
PIVUS	Reference method at Uppsala University Hospital	Enzymatic-immunological assay at Uppsala University Hospital	NA	NA	Reference method at Uppsala University Hospital	Reference method at Uppsala University Hospital
PPP	Glucose dehydrogenase method (Hemocue, Ängelholm, Sweden)	Serum insulin by fluoroimmunometric assay (Delfia, Perkin Elmer, Turku, Finland)	Local laboratories	Human C-peptide RIA-kit (Linco Research, St. Charles, Missouri, USA)	Enzymatic method (Konelab 60i analyser; Thermo Electron Oy, Vantaa, Finland)	Friedewald formula
QIMR-AUSTRALIA	NA	NA	NA	NA	Direct Assay, Roche Cholesterol Oxidase	Friedewald Calculation
RS	Glucose levels were measured using the glucose hexokinase method (Instruchemie)	Serum insulin was determined by metric assay (Biosource Diagnostics, Camarillo, CA, USA).	NA	NA	HDL-c was determined enzymatically, using an automated procedure	LDL cholesterol was calculated using Friedewald's formula: LDL=serum cholesterol-HDL-(0.45.serum triglycerides).
TWINGENE	Reference method at Karolinska Institutet	NA	Reference method at Karolinska Institutet	NA	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet
TwinsUK	Ektachem 700 multichannel analyzer using an enzymatic colorimetric slide assay (Johnson and Johnson Clinical Diagnostic Systems, Amersham, U.K.)	immunoassay (Abbott Laboratories, Maidenhead, U.K.)	NA	NA	precipitation with magnesium chloride/phosphotumgstate and thereafter as TC	LDL cholesterol was calculated using Friedewald's formula: LDL=serum cholesterol-HDL-(0.45.serum triglycerides).
ULSAM	Glucose dehydrogenase method (Gluc-DH, Merck, Darmstadt,	Immunoreactive insulin: Enzymatic-	HPLC with gradient system (BIO-RAD	NA	precipitation with magnesium chloride/phosphotumgstate and	LDL cholesterol was calculated using

	Germany)	immunological assay (Enzymun, Boehringer Mannheim)	Laboratories)		thereafter as TC	Friedewald's formula: LDL=serum cholesterol-HDL-(0.45.serum triglycerides).
WTCCCCont	NA	NA	ion exchange HPLC	NA	Abbott Aeroset 2.0 Analyser	Abbott Aeroset 2.0 Analyser
WTCCC Cases	NA	NA	NA	NA	Abbott Aeroset 2.0 Analyser	Abbott Aeroset 2.0 Analyser
WTCCCT2D	NA	NA	NA	NA	NA	NA

Table S5. Specifications of assays used for quantitative traits and study-specific definitions of binary traits. (Part 2)

COHORT	Triglycerides	Total cholesterol	Alanine aminotransferase (ALT)	Gamma-glytamyl-transferase (GGT)	Interleukine-6	CRP
DECODE	Enzymatic techniques. Data derived from 2 labs (Landspitali University Hospital and RAM).	Enzymatic techniques. Data derived from 2 labs (Landspitali University Hospital and RAM).	NA	NA	NA	Reference method at Landspitali University and RAM.
DGIcases	Cobas Mira analyzer (Hoffmann La Roche, Basel, Switzerland) in the Finnish cohort, Hitachi 911 (Boehringer Mannheim, Mannheim, Germany) in the Southern Swedish cohort and Technicon DAX 48 (Bayer Sweden AB, Gothenburg, Sweden) in the Skara cohort	Cobas Mira analyzer (Hoffmann La Roche, Basel, Switzerland) in the Finnish cohort, Hitachi 911 (Boehringer Mannheim, Mannheim, Germany) in the Southern Swedish cohort and Technicon DAX 48 (Bayer Sweden AB, Gothenburg, Sweden) in the Skara cohort	NA	NA	NA	NA
DGIcontrols	Cobas Mira analyzer (Hoffmann La Roche, Basel, Switzerland) in the Finnish cohort, Hitachi 911 (Boehringer Mannheim, Mannheim, Germany) in the Southern Swedish cohort and Technicon DAX 48 (Bayer Sweden AB, Gothenburg, Sweden) in the Skara cohort	Cobas Mira analyzer (Hoffmann La Roche, Basel, Switzerland) in the Finnish cohort, Hitachi 911 (Boehringer Mannheim, Mannheim, Germany) in the Southern Swedish cohort and Technicon DAX 48 (Bayer Sweden AB, Gothenburg, Sweden) in the Skara cohort	NA	NA	NA	NA
DIL	autoanalyser	autoanalyser	NA	NA	NA	nephelometry (Dade Behring) on citrated plasma samples after one thaw cycle.
EGCUT	Reference method at Tartu University Hospital	Reference method at Tartu University Hospital	Reference method at Tartu University Hospital	Reference method at Tartu University Hospital	NA	NA
ERF	assay info na / measured in serum	assay info na / measured in serum	NA	NA	NA	assay info na / measured in serum
FINNTWIN12	NMR	NMR	NA	NA	NA	NA
FTC	NA	NA	NA	NA	NA	NA
FR92	Enzymatic, GPO-PAP (average 4-hour fasting time)	Enzymatic, CHOD-PAP, (average 4-hour fasting time)	NA	NA	NA	NA
FR97	Enzymatic, GPO-PAP (average 4-hour fasting time)	Enzymatic, CHOD-PAP (average 4-hour fasting time)	NA	NA	NA	NA
FR02	Enzymatic, GPO-PAP (average 4-hour fasting time)	Enzymatic, CHOD-PAP (average 4-hour fasting time)	NA	NA	NA	NA
FR07	Enzymatic, GPO	Enzymatic, CHOD-PAP	NA	NA	NA	NA
GODARTS	Reference method at NHS Tayside	Reference method at NHS Tayside	NA	NA	NA	NA
GOSH	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet	NA	Reference method at Karolinska Institutet	NA	Reference method at Karolinska Institutet
GRAPHIC	Abbott Aeroset 2.0 Analyser	Abbott Aeroset 2.0 Analyser	NA	NA	NA	NA
H2000	Triglycerides, GPO PAP (4-	Cholesterol, CHOD PAP (4-	NA	NA	NA	NA

	11 hour fasting time)	11 hour fasting time)				
KORA F3	TGL Flex (Dade-Behring),	cholesterol-esterase method (CHOL Flex, Dade-Behring)	UV test; IFCC with pyridoxal phosphate activation (Roche/Hitachi cobas)	Enzymatic calorimetric assay; HiCo Gamma-glutamyltransferase liquid (Roche/Hitachi cobas) against IFCC	sandwich ELISA (CLB, Amsterdam, The Netherlands)	high-sensitivity immunoradiometric assay (IMRA)
KORA F4	TGL Flex (Dade-Behring),	cholesterol-esterase method (CHOL Flex, Dade-Behring)	UV test; IFCC with pyridoxal phosphate activation (Roche/Hitachi cobas)	Enzymatic calorimetric assay; HiCo Gamma-glutamyltransferase liquid (Roche/Hitachi cobas) against IFCC	sandwich ELISA (CLB, Amsterdam, The Netherlands)	high-sensitivity immunoradiometric assay (IMRA)
MDCCV	standars procedures (Dept Clincal Chemistry, Malmö University Hospital)	standars procedures (Dept Clincal Chemistry, Malmö University Hospital)	NA	NA	NA	NA
MORGAM	NA	Dextran sulphate-Mg++ method, phosphotungstate-Mg++ method, or updated phosphotungstate-Mg++ method after the Boehringer-Ms.	NA	NA	NA	NA
MPP	routine methods at the Department of Clinical Chemistry, University Hospital	routine methods at the Department of Clinical Chemistry, University Hospital	NA	NA	NA	NA
NESDA	Enzymatic colorimetric assay (GPO-PAP) (Modular analytics, Roche diagnostics, Mannheim, Germany)	Enzymatic colorimetric assay (CHOD-PAP) (Modular analytics, Roche diagnostics, Mannheim, Germany)	NA	Enzymatic IFCC (Modular analytics, Roche diagnostics, Mannheim, Germany; measured in heparin plasma)	IL-6 ELISA HS (Pelikine Compact ELISA, Sanquin, Amsterdam, The Netherlands; measured in plasma)	CRP ELISA HS (Dako, Glostrup, Denmark; measured in plasma)
NFBC1966	Fasting serum triglycerides were determined using an Hitachi 911 automatic analyzer and commercial reagents (Roche, Mannheim, Germany)	Fasting serum total cholesterol was determined using an Hitachi 911 automatic analyzer and commercial reagents (Roche, Mannheim, Germany)	NA	NA	NA	Serum CRP concentrations were determined by immunoenzymometric assay (Medix Biochemica, Espoo, Finland)
NFBC1986	Triglyceride concentrations were analysed by Cobas Integra 700 automatic analyser (Roche Diagnostics, Basel, Switzerland)	Serum total cholesterol concentrations were analysed by Cobas Integra 700 automatic analyser (Roche Diagnostics, Basel, Switzerland)	NA	NA	NA	Serum CRP concentrations were determined by immunoenzymometric assay (Medix Biochemica, Espoo, Finland)
NTR	Vitros 250 Triglycerides assay (Johnson & Johnson, Rochester, USA; measured in heparin plasma)	Vitros 250 total cholesterol assay (Johnson & Johnson, Rochester, USA; measured in heparin plasma)	Vitros ALT assay (Johnson & Johnson, Rochester, USA; measured in heparin plasma)	Vitros GGT assay (Johnson & Johnson, Rochester, USA; measured in heparin plasma)	Quantikine human Interleukine-6 kit (R&D systems; measured in EDTA plasma)	Immulite 1000 CRP assay (Diagnostic Product Corporation, USA; measured in heparin plasma)
PIVUS	Reference method at Uppsala University Hospital	Reference method at Uppsala University Hospital	Reference method at Uppsala University Hospital	Reference method at Uppsala University Hospital	Evidence® array biochip analyser (Randox Laboratories Ltd, Crumlin, UK)	Ultra sensitive particle enhanced immunoturbidimetric assay (Orion Diagnostica, Espoo,

						Finland)
PPP	Enzymatic method (Konelab 60i analyser; Thermo Electron Oy, Vantaa, Finland)	Enzymatic method (Konelab 60i analyser; Thermo Electron Oy, Vantaa, Finland)	Local laboratories	NA	NA	NA
QIMR-AUSTRALIA RS	Enzymatic, Roche Method Triglycerides were determined enzymatically, using an automated procedure	Enzymatic, Roche Method Total cholesterol was determined enzymatically, using an automated procedure	Roche, IFCC Method Automated biochemistry spectrophotometric analyzer (ELAN-Fully Selective Analyzer, Eppendorf- Merck, Hamburg, Germany)	Roche, IFCC Method Automated biochemistry spectrophotometric analyzer (ELAN-Fully Selective Analyzer, Eppendorf- Merck, Hamburg, Germany)	NA enzyme immuno assays according to the instructions of the manufacture (Medgenix, Amersfoort, the Netherlands). The lower detection limit of the assay was 3 pg/ml.	NA Rate Near Infrared Particle Immunoassay (Immage® Immunochemistry System, Beckman Coulter, USA).
TWINGENE	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet	NA	NA	NA	Reference method at Karolinska Institutet, half of the cohort analyzed with "high-sensitive" assay. Models adjusted for 2 different methods
TwinsUK	colorimetric enzymatic method	colorimetric enzymatic method	kinetic rate method on a Synchron LX20 automated multi channel analyzer (Beckman Coulter, Fulleton, CA) multi channel analyzer (Beckman Coulter, Fulleton, CA)	kinetic rate method on a Synchron LX20 automated multi channel analyzer (Beckman Coulter, Fulleton, CA) multi channel analyzer (Beckman Coulter, Fulleton, CA)	hIL-6 Ultra-Sensitivity ELISA (BioSource, Nivelles, Belgium)	Human Cardiovascular Disease (CVD) Panel 2 (acute-phase proteins) LINCOplex Kit (HCVD2-67BK) from Linco (Millipore) and with the Extracellular Protein Buffer Reagent Kit (LHB0001) from Invitrogen
ULSAM	Enzymatic techniques using IL Test Cholesterol Trinders's Method and IL Test Enzymatic-colorimetric Method	Enzymatic techniques using IL Test Cholesterol Trinders's Method and IL Test Enzymatic-colorimetric Method	Greiner 300 analyser, enzymatic method	NA	IL-6 ELISA HS, R&D Systems, Minneapolis, MN	Latex enhanced reagent;Behring BN ProSpec analyzer
WTCCCCont	Abbott Aeroset 2.0 Analyser	Abbott Aeroset 2.0 Analyser	NA	NA	NA	nephelometry (Dade Behring) on citrated plasma samples after one thaw cycle.
WTCCC Cases	Abbott Aeroset 2.0 Analyser	Abbott Aeroset 2.0 Analyser	NA	NA	NA	NA
WTCCCT2D	NA	NA	NA	NA	NA	NA

Table S5. Specifications of assays used for quantitative traits and study-specific definitions of binary traits. (Part 3)

COHORT	Coronary heart disease (acute myocardial infarction or unstable angina)	Ischemic stroke	Hemorrhagic stroke	Any acute stroke or transient ischemic attack
DECODE	registry-based (ICD9+10)	validated medical records	validated medical records	validated medical records
DGIcases	Registry-based	NA	NA	Registry-based
DGIcontrols	Registry-based	NA	NA	Registry-based
DIL	NA	NA	NA	NA
EGCUT	registry-based/self-reported (ICD10)	registry-based/self-reported (ICD10)	registry-based/self-reported (ICD10)	registry-based/self-reported (ICD10)
ERF	NA	NA	NA	NA
FINNTWIN12	NA	NA	NA	NA
FTC	NA	NA	NA	NA
FR92	Registry for social welfare and healthcare: I200, I21, I22 [ICD-10] / 410, 4110 [ICD-8/9]; causes of death registry: I20–I25, I46, R96, R98 [ICD-10] / 410-414, 798 (not 7980A) [ICD-8/9]	Registry for social welfare and healthcare: I63–I64 (not I636) [ICD -10] / 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 [ICD-9] / 433, 434, 436 [ICD-8] as S_PAADG, S_PAADGE, S_DG2, S_DG2E, S_DG3, S_DG3E, S_DG4	NA	I60–I64 (not I636) [ICD -10] / 430, 431, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 [ICD-9] / 430, 431 (except 43101, 43191) 433, 434, 436 [ICD-8]
FR97	Registry for social welfare and healthcare: I200, I21, I22 [ICD-10] / 410, 4110 [ICD-8/9]; causes of death registry: I20–I25, I46, R96, R98 [ICD-10] / 410-414, 798 (not 7980A) [ICD-8/9]	Registry for social welfare and healthcare: I63–I64 (not I636) [ICD -10] / 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 [ICD-9] / 433, 434, 436 [ICD-8] as S_PAADG, S_PAADGE, S_DG2, S_DG2E, S_DG3, S_DG3E, S_DG4	NA	I60–I64 (not I636) [ICD -10] / 430, 431, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 [ICD-9] / 430, 431 (except 43101, 43191) 433, 434, 436 [ICD-8]
FR02	Registry for social welfare and healthcare: I200, I21, I22 [ICD-10] / 410, 4110 [ICD-8/9]; causes of death registry: I20–I25, I46, R96, R98 [ICD-10] / 410-414, 798 (not 7980A) [ICD-8/9]	Registry for social welfare and healthcare: I63–I64 (not I636) [ICD -10] / 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 [ICD-9] / 433, 434, 436 [ICD-8] as S_PAADG, S_PAADGE, S_DG2, S_DG2E, S_DG3, S_DG3E, S_DG4	NA	I60–I64 (not I636) [ICD -10] / 430, 431, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 [ICD-9] / 430, 431 (except 43101, 43191) 433, 434, 436 [ICD-8]
FR07	Registry for social welfare and healthcare: I200, I21, I22 [ICD-10] / 410, 4110 [ICD-8/9]; causes of death registry: I20–I25, I46, R96, R98 [ICD-10] / 410-414, 798 (not 7980A) [ICD-8/9]	Registry for social welfare and healthcare: I63–I64 (not I636) [ICD -10] / 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 [ICD-9] / 433, 434, 436 [ICD-8] as S_PAADG, S_PAADGE, S_DG2, S_DG2E, S_DG3, S_DG3E, S_DG4	NA	I60–I64 (not I636) [ICD -10] / 430, 431, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 [ICD-9] / 430, 431 (except 43101, 43191) 433, 434, 436 [ICD-8]

GODARTS	registry-based (ICD9+10)	registry-based (ICD9+10)	registry-based (ICD9+10)	registry-based (ICD9+10)
GOSH	registry-based (ICD9+10)	registry-based (ICD9+10)	registry-based (ICD9+10)	registry-based (ICD9+10)
GRAPHIC	NA	NA	NA	NA
H2000	Registry for social welfare and healthcare: I200, I21, I22 [ICD-10] / 410, 4110 [ICD-8/9]; causes of death registry: I20–I25, I46, R96, R98 [ICD-10] / 410-414, 798 (not 7980A) [ICD-8/9]	Registry for social welfare and healthcare: I63–I64 (not I636) [ICD -10] / 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 [ICD-9] / 433, 434, 436 [ICD-8] as S_PAADG, S_PAADGE, S_DG2, S_DG2E, S_DG3, S_DG3E, S_DG4	NA	I60–I64 (not I636) [ICD -10] / 430, 431, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 [ICD-9] / 430, 431 (except 43101, 43191) 433, 434, 436 [ICD-8]
KORA F3	NA	NA	NA	NA
KORA F4	NA	NA	NA	NA
MDCCV	NA	NA	NA	NA
MORGAM	registry-based (ICD9+10)	NA	NA	registry-based (ICD9+10)
MPP	Registry-based	NA	NA	Registry-based
NESDA	NA	NA	NA	NA
NFBC1966	registry-based (ICD8+9+10)	registry-based (ICD8+9+10)	registry-based (ICD8+9+10)	registry-based (ICD8+9+10)
NFBC1986	registry-based (ICD8+9+10)	registry-based (ICD8+9+10)	registry-based (ICD8+9+10)	registry-based (ICD8+9+10)
NTR	NA	NA	NA	NA
PIVUS	validated medical records	NA	NA	validated medical records
PPP	Registry-based	NA	NA	Registry-based
QIMR-AUSTRALIA	NA	NA	NA	NA
RS	registry-based (ICD10)	NA	NA	adjudicated events based on medical records and neuroimaging
TWINGENE	registry-based (ICD9+10)	registry-based (ICD9+10)	registry-based (ICD9+10)	registry-based (ICD9+10)
TwinsUK	NA	NA	NA	NA
ULSAM	registry-based (ICD9+10)	registry-based (ICD9+10)	registry-based (ICD9+10)	registry-based (ICD9+10)
WTCCCCont	NA	NA	NA	NA
WTCCC Cases	NA	NA	NA	NA
WTCCCT2D	NA	NA	NA	NA

Table S5. Specifications of assays used for quantitative traits and study-specific definitions of binary traits. (Part 4)

COHORT	Heart failure	Type 2 diabetes	Dyslipidemia	Hypertension	Metabolic Syndrome
DECODE	NA	self-reported, diabetes medication and glucose measurements	NA	measurements and blood pressure medication	NA
DGIcases	NA	WHO 98	lipid medication and lipid measurements	measurements and blood pressure medication	according to definition in document
DGIcontrols	NA	WHO 98	lipid medication and lipid measurements	measurements and blood pressure medication	according to definition in document
DIL	NA	NA	NA	NA	NA
EGCUT	registry-based/self-reported (ICD10)	registry-based/self-reported (ICD10), diabetes medication and glucose measurements	registry-based/self-reported (ICD10), lipid medication and lipid measurements	registry-based/self-reported (ICD10), measurements and blood pressure medication	measurements
ERF	NA	glucose measurement and diabetes medication	lipid measurements and lipid medication	BP measurements and htn medication	measurements
FINNTWIN12	NA	NA	NA	NA	NA
FTC	NA	self-report of diabetes and type of treatment, pure insulin users excluded	NA	NA	NA
FR92	I50, I110, I130, I132 [ICD -10] / 4029B, 4148, 428 [ICD-9], 42700, 42710, 428 [ICD-8]	Self-reported or diagnosed T2D, fasting blood-glucose >= 7 or anti-diabetic treatment	Any type of lipid medication and lipid measurements	Measurements and blood pressure medication	NA
FR97	I50, I110, I130, I132 [ICD -10] / 4029B, 4148, 428 [ICD-9], 42700, 42710, 428 [ICD-8]	Self-reported or diagnosed T2D, fasting blood-glucose >= 7 or anti-diabetic treatment	Any type of lipid medication and lipid measurements	Measurements and blood pressure medication	NA
FR02	I50, I110, I130, I132 [ICD -10] / 4029B, 4148, 428 [ICD-9], 42700, 42710, 428 [ICD-8]	Self-reported or diagnosed T2D, fasting blood-glucose >= 7 or anti-diabetic treatment	Any type of lipid medication and lipid measurements	Measurements and blood pressure medication	NA
FR07	I50, I110, I130, I132 [ICD -10] / 4029B, 4148, 428 [ICD-9], 42700, 42710, 428 [ICD-8]	Self-reported or diagnosed T2D, fasting blood-glucose >= 7 or anti-diabetic treatment	Any type of lipid medication and lipid measurements	Measurements and blood pressure medication	ATP III
GODARTS	registry-based (ICD9+10)	validated journal study	NA	NA	NA
GOSH	registry-based (ICD9+10)	self-reported, diabetes medication and glucose measurements	lipid medication and lipid measurements	measurements and blood pressure medication	measurements
GRAPHIC	NA	Self reported	NA	BP measures or treatment	NA
H2000	I50, I110, I130, I132 [ICD -10] / 4029B, 4148, 428 [ICD-9], 42700, 42710, 428 [ICD-8]	Self-reported or diagnosed T2D, fasting blood-glucose >= 7 or anti-diabetic treatment	Any type of lipid medication and lipid measurements	Measurements and blood pressure medication	NA
KORA F3	NA	Diabetes definition based on self-reported diabetes or diabetic treatment	Serum triglycerides ≥1.7 mmol/L and HDL-cholesterol < 1.0 mmol/L in men and <1.3 mmol/L in women, or treatment with fibrates. For KORA F4 nearly all individuals were fasting and for KORA F3 most individuals were non fasting. We do not use fasting	Systolic blood pressure ≥140, diastolic blood pressure ≥90, or on anti-hypertensive treatment	NA

			individuals only for definition of dyslepidemia		
KORA F4	NA	Diabetes definition based on self-reported diabetes or diabetic treatment	Serum triglycerides ≥1.7 mmol/L and HDL-cholesterol < 1.0 mmol/L in men and <1.3 mmol/L in women, or treatment with fibrates. For KORA F4 nearly all individuals were fasting and for KORA F3 most individuals were non fasting. We do not use fasting individuals only for definition of dyslepidemia	Systolic blood pressure ≥140, diastolic blood pressure ≥90, or on anti-hypertensive treatment	NCEP definition (lipids and glucose in mg/dl): At least 3 out of 5 criteria should be present: . waist circumference (men, =102 cm; women, =88 cm), . elevated triglycerides (=150 mg/dl), . reduced HDL cholesterol (men, <40 mg/dl; women, <50 mg/dl), . blood pressure (systolic =130 mmHg or diastolic =85mmHg), . fasting glucose (=110,g/dl).
MDCCV	NA	selfreported diagnosis, self-reported medication or measured fasting glucose <7	selfreported lipid medication or lipid measurements	measurements or antihypertensive medication	measurements
MORGAM	NA	self-reported	lipid measurements	measurements of blood pressure	NA
MPP	NA	NA	NA	measurements and blood pressure medication	according to definition in document
NESDA	NA	self-reported, diabetes medication and glucose>=7 mmol/L (no distinction between type I and type II)	lipid medication and lipid measurements	NA	NA
NFBC1966	registry-based (ICD8+9+10)	self-reported, diabetes medication and glucose measurements	lipid measurements	measurements and blood pressure medication	measurements
NFBC1986	registry-based (ICD8+9+10)	diabetes medication and glucose measurements	lipid measurements	measurements	measurements
NTR	NA	medication or glucose >= 7	medication or cholesterol profile	NA	NA
PIVUS	NA	self-reported, diabetes medication and glucose measurements	lipid medication and lipid measurements	measurements and blood pressure medication	measurements
PPP	NA	WHO 98	lipid medication and lipid measurements	measurements and blood pressure medication	according to definition in document
QIMR-AUSTRALIA	NA	NA	NA	NA	NA
RS	registry-based (ICD10)	Diabetes medication and abnormal fasting or random glucose	lipid medication and lipid measurements	measurements and blood pressure medication	measurements
TWINGENE	registry-based (ICD9+10)	self-reported, diabetes medication and glucose measurements	lipid medication and lipid measurements	measurements and blood pressure medication	measurements
TwinsUK	NA	self-reported, diabetes medication and glucose measurements (OGTT)	lipid medication and lipid measurements	measurements and blood pressure medication	measurements
ULSAM	registry-based (ICD9+10)	self-reported, diabetes medication and glucose measurements (OGTT)	lipid medication and lipid measurements	measurements and blood pressure medication	measurements
WTCCCCont	NA	Self reported	NA	BP measures or treatment	NA
WTCCC Cases	NA	Self reported	NA	BP measures or treatment	NA
WTCCCT2D	NA	Validation of the diagnosis of diabetes in the index sib pair was based on either current prescribed	NA	NA	NA

treatment
with sulfonyl ureas, biguanides, and/or insulin
or, in the
case of individuals treated with diet alone,
historical or
contemporary laboratory evidence of
hyperglycemia (as
defined by World Health Organization [1985]
guidelines
in place at the time of recruitment). Diagnosis
between age 25 and 75

Table S6. Confidence intervals (CIs) for the estimates for different traits (on the logit/log scale for binary traits). The delta method corresponds to the CI reported in Tables 1 and 2 of the paper. The plugin CI is based on the between-cohort estimate of the correlation between β[*FTO*-TRAIT] and β[*FTO*-BMI]. The worst case CI is based on the widest CI possible under any correlation. F1 is the length of the plugin CI divided by the length of the reported CI; F2 is the length of the worst case CI divided by the reported CI (all on the regression scale).

	Delta method	Plug-in	Worst case	F1	F2
Ever coronary heart disease	-0.129/0.119	-0.136/0.114	-0.148/0.105	1.01	1.02
Incident coronary heart disease	-0.15/0.121	-0.156/0.118	-0.172/0.107	1.01	1.03
Ever heart failure	0.0432/0.276	0.0457/0.274	0.0399/0.315	0.98	1.18
Incident heart failure	0.0242/0.326	0.0261/0.328	0.023/0.372	1.00	1.16
Ever haemorrhagic stroke	-0.421/0.334	-0.429/0.333	-0.483/0.295	1.01	1.03
Incident haemorrhagic stroke	-1.03/0.219	-1.02/0.223	-1.18/0.192	0.99	1.10
Ever ischemic stroke	-0.161/0.117	-0.159/0.12	-0.185/0.103	1.00	1.04
Incident ischemic stroke	-0.131/0.312	-0.125/0.333	-0.116/0.358	1.03	1.07
Ever stroke	-0.144/0.127	-0.14/0.134	-0.166/0.113	1.01	1.03
Incident stroke	-0.142/0.229	-0.134/0.247	-0.125/0.263	1.03	1.05
Ever type 2 diabetes	0.21/0.414	0.228/0.396	0.193/0.466	0.82	1.34
Incident type 2 diabetes	0.116/0.48	0.137/0.424	0.106/0.546	0.79	1.21
Ever dyslipidaemia	0.0686/0.188	0.0719/0.186	0.0629/0.213	0.96	1.26
Incident dyslipidaemia	-0.43/0.627	-	-0.381/0.72	-	1.04
Ever hypertension	0.068/0.173	0.0706/0.173	0.0623/0.196	0.97	1.27
Incident hypertension	-0.243/0.419	-	-0.215/0.481	-	1.05
Ever metabolic syndrome	0.165/0.368	0.161/0.393	0.152/0.415	1.15	1.30
Incident metabolic syndrome	-0.0173/0.723	-	-0.0129/0.827	-	1.13
Incident mortality	-0.103/0.0685	-0.104/0.0687	-0.118/0.0607	1.01	1.04
2h post OGTT glucose	0.0128/0.162	0.0129/0.172	0.0121/0.185	1.07	1.16
Fasting glucose	-0.00446/0.0393	-0.00429/0.0404	-0.00385/0.045	1.02	1.12
HbA1c	-0.0129/0.0269	-0.0133/0.0264	-0.0114/0.0308	1.00	1.06
Fasting insulin	0.0358/0.076	0.0379/0.0743	0.0329/0.0857	0.90	1.31
Diastolic blood pressure	0.187/0.793	0.197/0.786	0.172/0.903	0.97	1.21
Systolic blood pressure	0.475/1.31	0.497/1.3	0.435/1.48	0.96	1.26
HDL-C	-0.0261/-0.00941	-0.0257/-0.0099	-0.0295/-0.00861	0.95	1.26
LDL-C	-0.0122/0.0346	-0.0124/0.0344	-0.0107/0.0396	1.00	1.08
ALT	0.0161/0.0517	0.0162/0.0536	0.0147/0.0588	1.05	1.24
CRP	0.0343/0.1	0.0359/0.0994	0.0314/0.114	0.97	1.25
GGT	0.0187/0.0547	0.0214/0.0497	0.0172/0.0621	0.79	1.25
IL-6	-0.0517/0.0615	-0.0507/0.0639	-0.0458/0.0707	1.01	1.03
Triglycerides	0.0162/0.0403	0.0172/0.0396	0.0149/0.0457	0.93	1.28
Total cholesterol	-0.0177/0.0296	-0.0176/0.0301	-0.0157/0.0339	1.01	1.05

Table S7. Confidence intervals (CIs) for the difference between the instrumental variable estimates β[IV] and the conventional regression estimates β[BMI_TRAIT] for different traits (on the logit/log scale for D/ITraits). The delta method corresponds to the CI reported in Tables 1 and 2 of the paper. The plugin CI is based on the between-cohort estimate of correlations. The worst case CI is based on the widest CI possible under any correlation. F1 is the length of the plugin CI divided by the length of the reported CI; F2 is the length of the worst case CI divided by the reported CI (all on the regression scale).

	Delta method	Plug-in	Worst case	F1	F2
Ever coronary heart disease	-0.159/0.0907	-0.164/0.0956	-0.178/0.109	1.04	1.15
Incident coronary heart disease	-0.196/0.0767	-0.196/0.0768	-0.213/0.094	1.00	1.13
Ever heart failure	-0.041/0.197	-0.0523/0.208	-0.0801/0.236	1.10	1.33
Incident heart failure	-0.0694/0.234	-0.0755/0.24	-0.107/0.271	1.04	1.25
Ever haemorrhagic stroke	-0.409/0.348	-0.407/0.345	-0.447/0.386	0.99	1.10
Incident haemorrhagic stroke	-1.02/0.233	-0.997/0.206	-1.13/0.34	0.96	1.17
Ever ischemic stroke	-0.186/0.0944	-0.2/0.108	-0.209/0.117	1.10	1.16
Incident ischemic stroke	-0.166/0.28	-0.183/0.297	-0.2/0.314	1.08	1.15
Ever stroke	-0.157/0.117	-0.164/0.123	-0.177/0.137	1.05	1.15
Incident stroke	-0.166/0.206	-0.169/0.209	-0.19/0.229	1.01	1.13
Ever type 2 diabetes	0.0682/0.274	0.0897/0.253	0.0237/0.319	0.79	1.43
Incident type 2 diabetes	-0.0329/0.332	0.0202/0.279	-0.0837/0.383	0.71	1.28
Ever dyslipidaemia	-0.0739/0.0513	-0.0659/0.0432	-0.102/0.0798	0.87	1.46
Incident dyslipidaemia	-0.481/0.56	-	-0.543/0.621	-	1.12
Ever hypertension	-0.0522/0.0553	-0.051/0.0542	-0.0742/0.0773	0.98	1.41
Incident hypertension	-0.28/0.372	-	-0.323/0.414	-	1.13
Ever metabolic syndrome	-0.117/0.0935	-0.132/0.108	-0.168/0.144	1.14	1.48
Incident metabolic syndrome	-0.206/0.52	-	-0.278/0.592	-	1.20
Incident mortality	-0.119/0.0546	-0.127/0.0619	-0.136/0.071	1.08	1.19
2h post OGTT glucose	-0.0532/0.104	-0.0671/0.118	-0.0832/0.134	1.18	1.38
Fasting glucose	-0.0331/0.0116	-0.0359/0.0143	-0.0394/0.0179	1.12	1.28
HbA1c	-0.0357/0.00658	-0.0382/0.00904	-0.0426/0.0134	1.12	1.32
Fasting insulin	-0.0249/0.0164	-0.0234/0.015	-0.0343/0.0259	0.93	1.46
Diastolic blood pressure	-0.439/0.181	-0.419/0.16	-0.552/0.293	0.93	1.36
Systolic blood pressure	-0.439/0.418	-0.396/0.375	-0.615/0.594	0.90	1.41
HDL-C	-0.0038/0.0133	-0.00298/0.0125	-0.00732/0.0168	0.90	1.41
LDL-C	-0.0305/0.0172	-0.0327/0.0193	-0.0363/0.023	1.09	1.24
ALT	-0.0117/0.0264	-0.0136/0.0283	-0.0203/0.0351	1.10	1.46
CRP	-0.0531/0.0228	-0.0554/0.0251	-0.0726/0.0423	1.06	1.51
GGT	-0.0138/0.0231	-0.0115/0.0208	-0.0213/0.0306	0.87	1.40
IL-6	-0.0863/0.0279	-0.0827/0.0243	-0.0944/0.0361	0.94	1.14
Triglycerides	-0.0177/0.00685	-0.0164/0.00557	-0.0226/0.0118	0.90	1.40
Total cholesterol	-0.0342/0.014	-0.036/0.0158	-0.0394/0.0193	1.07	1.22

Text S1.Extended Methods

Software used for imputation in studies
Standard software packages IMPUTE and MACH were used for imputation[1,2].

Per-study analysis: motivation
For modelling the relationships between *FTO* genotype, the intermediate phenotype BMI and the different cardiometabolic traits as seen in Figure 1 of the manuscript, we distinguish between continuously scaled or quantitative traits (QTraits), dichotomous outcomes (DTraits, marked as "Ever" in Table 1 of the manuscript) and incident or survival outcomes (ITraits, marked as "Incident" in Table 1). Except for overall mortality, each ITrait has a corresponding DTrait in this study. We model the relationship between any predictor variable (*FTO* or BMI) and a QTrait as outcome via linear regression (possibly after logarithmizing the QTrait); for DTraits, we use logistic regression and for ITraits, Cox proportional hazard regression, as detailed below.

The purpose of the parallel analysis of prevalent and incident cases is to combine the benefits of the two approaches: survival analysis exploits time-to-event data more thoroughly and is easier to interpret causally, but is only available for a subset of cohorts for each of the D/ITraits; logistic regression ignores time scale, but is applicable to all cohorts with prevalent data, and has consequently more power to detect significant associations. For our study, the results from both approaches support each other well, with close effect estimates throughout (Table 1 of the manuscript).

Model definitions for per-cohort analysis
The following models were used to assess the relationship between (a) *FTO* and BMI, (b) BMI and traits, and (c) between *FTO* and traits. *Study specific covariates* below include, among others, study centres, sub-cohorts or principal components for population stratification.

(a) Analysis of association between *FTO* and BMI. Model: *linear regression*
BMI = SNP + sex + age + other study specific covariates
Age was defined as the age at baseline (time of the BMI measurement).

(b) Analysis of associations between BMI and the traits
(b.1) Quantitative traits (QTrait). Model: *linear regression*
QTrait = BMI+ sex + age+ other study specific covariates
Age was defined as the age at the time of measurement of the QTrait.

(b.2) Dichotomous traits (DTrait). Model: *logistic regression*
DTrait = BMI + sex + age + other study specific covariates
Age was defined as the age at event for DTrait in those who ever have the event, whereas in non-affected individuals, age was the latest known age (age at death or loss-to-follow-up).

(b.3) Incidence traits (ITrait). Model: *Cox proportional hazard regression*
ITrait = BMI+ sex [+ age at baseline] + other study specific covariates
Baseline refered to the time of BMI measurement. Individuals that did not reach the endpoint were censored at time of death or other loss-of-follow up.

(c) Analysis of *FTO* and outcome trait association with and without BMI adjustment
(c.1) Quantitative traits (QTrait). Model: *linear regression*
QTrait = SNP + sex + age + other study specific covariates
Age was defined as the age at the time of measurement of the QTrait.

(c.2) Dichotomous traits (DTrait). Model: *logistic regression*
DTrait = SNP + sex + age + other study specific covariates
Age was defined as the age at event for DTrait in those who ever have the event, whereas in non-affected individuals age was the latest known age (age at death or loss-to-follow-up).

(c.3) Incidence traits (ITrait). Model: *Cox proportional hazard regression*
ITrait = SNP + sex + age at baseline + other study specific covariates
Baseline refered to the time of BMI measurement.

Quality Control of Cohort-Specific Results
All genotypes were inspected for strand, lead- or proxy marker and effect allele reported. For all regression results, inverse standard errors were plotted by trait over the square-root of effective sample size [eff_n = 2/((1/n_cases)+(1/n_controls))] to ensure absence of trait transformation errors.

Meta-analysis and between-study heterogeneity
We assessed between-cohort heterogeneity via Cochrane's Q-statistic and I^2-statistics.[3-5] Histograms of the distribution of I^2 in associations between BMI and traits and associations between *FTO* and traits are shown in Panels A and C of Figure S1. For the proposed cut-off of $I^2>0.25$, we found non-negligible heterogeneity between studies for many associations, in particular among the BMI-trait associations, but also for the association between *FTO* and BMI (I2 = 0.55). As a consequence, we used random-effects meta-analysis throughout. The results presented in Tables 1 and 2 of the manuscript are estimates of the *average* effect of BMI on the traits investigated rather than the common effect.[6]

Different reasons for the variation between cohorts are possible: the relationship between BMI and cardiometabolic traits is of course famously confounded with other genetic and life style factors that vary systematically between cohorts. This may be driven by varying subject age, sex and disease distribution between contributing cohorts, and by differences in the outcome measurement methods among contributing cohorts. We analysed our aggregate data with meta-regression of betas with mean age as a covariate to assess the impact of cohort age on the effect sizes of *FTO*-trait and BMI-trait. The results show that [BMI-trait] betas are significantly ($p<0.01$) decreasing with cohort mean age for LDL cholesterol, triglycerides and total cholesterol. On the other hand, when examining the effect of cohort age on the *FTO*-trait betas, no effect was observed.

Figure S1 also shows the effect of choosing the random-effects model instead of the fixed-effects model on the Wald-statistics for both the IV estimator and the conventional regression estimator (Panel B): for the IV estimates, we see moderate shrinkage of the Wald test statistics, with only fasting glucose (labelled as FG) being significant at $\alpha=0.05$ for fixed, but not random effects; arguably, even though the random effects model leads to slightly more conservative estimates, both models indicate comparable strength of evidence, in good agreement with the moderate I^2 values seen in the corresponding histogram in Panel A, and the consistent estimate for the *FTO*-BMI association (under both fixed and random effects). This effect size is similar to earlier reported effect sizes of *FTO* on BMI.[7]

For the estimates of BMI with trait, however, the use of the random effects model leads to severe shrinkage of the Wald test statistics and a reduction of their range by a factor of four in Panel D. This is clearly driven by the large amount of between-cohort variability shown in the corresponding histogram of I^2 values in Panel C. Here, the use of the fixed effect estimates would overstate the strength of our case significantly, and this is the most pressing reason for our using the random effects model throughout.

Standard errors and inference for the instrumental variable (IV) estimator
After meta-analysis, the IV estimator for the effect of BMI on a trait was calculated as the ratio of the regression coefficients *FTO*-TRAIT and *FTO*-BMI:

(Eq. 1)

The standard error is calculated via the delta method as

(Eq. 2)

Based on these estimates, we appeal to standard-normal asymptotics, with the resulting Wald test statistic and 95% confidence intervals given as

The p-value for the : was derived from the standard normal distribution. For the odds ratios and hazard ratios associated with DTraits and ITraits, the 95% CI estimates were back-transformed through the antilogit and exponentiation, respectively.

For comparing the IV estimate and the conventional estimate , we consider the difference
(Eq. 3)

The corresponding standard error is
(Eq. 4)

We use again standard normal asymptotics for the difference, viz.

The p-value for the : was derived from the standard normal distribution, and the confidence intervals for odds/hazard ratios are back-transformed as above.

Methodolocical considerations

Apart from the assumptions described in the main paper, additional assumptions are required for unbiased causal estimates (providing quantification as opposed to testing only), specifically about the shape of the association between intermediate phenotype and outcome [8,9]); we have assumed linearity throughout, for which there is reasonable evidence [10]). Estimates are also sensitive towards epigenetic and GxE modifications of the relationship between *FTO* and BMI. There is preliminary evidence that environmental factors such as physical activity and fat intake may influence the association of *FTO* with BMI and potentially metabolic outcomes [4], but the observed effect amounts to only modest modification of the *FTO*-BMI relationship, and does not imply a direct association between *FTO* and physical activity/fat intake.

These possible interactions and epigenetic changes should not affect the causal interpretation per se, but could affect the precision of our estimates. Based on reported effect sizes of GxE-interactions, we expect the loss of power and the corresponding effect on causal estimates to be fairly small.

Sensitivity analysis for the IV inference

Correlations between the regression coefficients can affect the estimation of the standard errors for the quantities and given in Eq. 1 and 3 above. The formulas for the standard errors underlying the results reported in the paper, given in Eq. 2 and 4, do not take this possibility into account. Given that the per-cohort regression coefficients underlying the meta-analysis are estimated on the same data, there is no *prima facie* reason to rule out that they are in fact correlated. As we do not have per-cohort estimates for the correlations between regression coefficients that would allow us to calculate a joint estimate through meta-analysis, we have evaluated the possible impact of such correlations through sensitivity analysis. Essentially, we compare the reported confidence intervals and p-values with two modified estimates:

1. Using the between-cohort estimate of the correlation between and , and between and , respectively, to adjust the confidence intervals. We refer to this as the meta-regression or *plugin*-estimate.
2. Using the widest confidence interval possible under any correlation in the interval ±1; we refer to this as the *worst-case* estimate.

For the IV estimator , we use Fieller's theorem to derive confidence limits that not only explicitly include the effect of correlation, but also provide a check on the quality of the delta method approximation.[5]Figure S2 shows a graphical summary of the results for the dichotomous trait “Ever heart failure” (variable HF_D), where the thick horizontal line represents the estimated effect (on the logit scale); the broken horizontal lines show the 95% confidence interval based on the standard error given in Eq. 2, which is also reported in Table 1 of the paper (back-transformed via antilogit). These values are independent of the range of possible correlations between and shown on the x-axis of the plot, whereas the confidence interval based on Fieller’s theorem is shown as two curves that are more distant for negative correlations than for positive correlations. We find that:

1. the confidence interval for an assumed correlation of is almost identical to the interval arrived at via the delta method,
2. the plugin-estimate for the confidence interval, assuming that the observed correlation between and can be estimated via the between-cohort correlation of (shown as vertical thick grey line), is actually somewhat tighter than the reported confidence interval, and
3. the worst-case confidence interval can be seen at , and is ca. 30% wider than the reported CI; however, the extension is almost exclusively at the upper limit of the confidence interval, so the impact on comparing with zero is negligible.

Corresponding plots for the other traits (not shown) look similar and lead to very similar conclusions. Table S6 shows a summary of the reported, the plug-in and the worst-case confidence intervals, supporting the same conclusions, viz. that possible correlations have little effect for our inference on the IV estimator.
For the confidence interval of the difference from Eq. 3, the standard error in Eq. 4 can in principle be affected both through correlation between and (and consequently inflated) as well as through correlation between and . Note, however that the latter is unlikely from the outset, because the standard error in Eq. 4 is dominated by , which is considerably larger than (range of ratio = 1.7-13.3, median of ratio = 5.5). Accordingly, the extra covariance term in the correlation-adjusted formula for the standard error

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will have little effect on the total standard error, regardless of the strength of the correlation between and .

This is also evident from Table S7 that presents the confidence intervals adjusted for the effect of both possible correlations: the plugin-estimate is based on using the between-cohort estimate of correlation for both and , as well as and . The worst case estimate is based on combining the worst-case scenarios for both standard errors. As in Table S6, we find that a) the possible effect of correlations is small, b) the plugin confidence intervals tend to be narrower than the reported confidence intervals, and c) even under the worst case scenario, we do not need to change our conclusions.

A small technical wrinkle in the derivation of the adjusted version of above is that Fieller's theorem does not provide an estimate for per se, but only lower and upper confidence limits. We have side-stepped this issue by applying the correction factors based on the relative lengths of the confidence intervals listed in Table S6 to the standard errors based on Eq. 2.

According to Burgess and Thompson[11] some bias may be anticipated in the meta-analysis, compared to the analysis at individual level. In addition, *FTO* as a relatively weak instrument may also lead to biases. Therefore we have run extensive simulation studies to assess the bias and precision of the estimator in the settings of our study, by setting the association parameters between *FTO* and BMI to what has been observed here and varying the magnitude of the true causal effect.

As a result, quantitative trait analysis using the linear IV estimator did not lead to any biases, but for binary trait analysis, the Wald ratio led to somewhat biased estimates of the causal odds ratio. Realistically the bias can reach a maximum of 10 % for traits with high prevalence and greatest difference between the conventional BMI-trait association measure and the IV estimate, such as type 2 diabetes. However, given the fact that the IV estimate is further from the null value than the conventional estimate in this study for all dichotomous outcomes, the bias is always in the conservative direction: the true causal effect estimate is likely to be further from the null than the obtained IV estimate. Although there has been reported a possibility of bias away from the null in meta-analysis results, caused by the use of a large number of small studies, we were not able to reproduce any bias in a simulation study using the parameters corresponding to the observed effect sizes and sizes of cohorts involved in the present study.

In summary, the obtained IV estimates (Wald ratios) are less biased for the true causal effect between BMI and trait than the possibly confounded conventional BMI-trait association measures.

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