SUPPLEMENTARY DATA

Age- and sex-specific causal effects of adiposity on cardiovascular risk factors
Fall *et al.*

Supplementary Table 1. Description of the participating studies

Study	Full name	Ethnicity	Country (Sample source)	Webpage
B58C	British 1958 Birth Cohort	White European	UK	http://www.b58cgene.sgul.ac.uk/
EGCUT_metabo	Estonian Genome Centre of the University of Tartu - Metabochip genotyping	Northern European (White, Caucasian)	Estonia	www.biobank.ee
EGCUT_omni	Estonian Genome Centre of the University of Tartu - Omni genotyping	Northern European (White, Caucasian)	Estonia	www.biobank.ee
FTC	FINNISH TWIN COHORT/Nicotine addiction families	Northern European (White, Caucasian)	Finland	
FR92	FINRISK 1992	Northern European (White, Caucasian)	Finland	Vartiainen E et al., Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol. 2010 Apr;39(2):504-18
FR97	FINRISK 1997	Northern European (White, Caucasian)	Finland	Vartiainen E et al., Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol. 2010 Apr;39(2):504-18
FR02	FINRISK 2002	Northern European (White, Caucasian)	Finland	Vartiainen E et al., Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol. 2010 Apr;39(2):504-18
FR07	FINRISK 2007	Northern European (White, Caucasian)	Finland	Vartiainen E et al., Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol. 2010 Apr;39(2):504-18
GOSH	Gender, Octo, SATSA, Harmony (Swedish Twin Register)	Northern European (White, Caucasian)	Sweden	http://ki.se/ki/jsp/polopoly.jsp?l=en&d=9610
GRAPHIC	Genetic Regulation of Arterial Pressure of Humans in the Community	White British	England	
H2000	Finnish Health survey 2000	Northern European (White, Caucasian)	Finland	www.terveys2000.fi/indexe.html
HELENA	HELENA	European	Greece, Germany, Belgium, France, Hungary, Italy, Sweden, Austria, Spain	http://www.helenastudy.com/
KORA F3	Cooperative Health Research in the Region of Augsburg, KOoperative Gesundheitsforschung in der Region Augsburg, F3	European (White, Caucasian)	Germany	http://www.helmholtz-muenchen.de/en/kora-en/kora-homepage/index.html
KORA F4	Cooperative Health Research in the Region of Augsburg, KOoperative Gesundheitsforschung in der Region	European (White, Caucasian)	Germany	http://www.helmholtz-muenchen.de/en/kora-en/kora-homepage/index.html

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	Augsburg , F4			
MONA LISA	MONA LISA LILLE	French (Caucasian)	French	
MONICA	MONICA LILLE	French (Caucasian)	French	http://www.thl.fi/monica/
MORGAM[1]	Monitoring of trends and determinants in Cardiovascular disease, Risk, Genetics, Archiving and Monograph	European White	Finland, Italy, France, UK (North Ireland)	www.thl.fi/morgam
MPP	Malmö Prevention Project	Northern European (White, Caucasian)	Sweden	http://www.ludc.med.lu.se/research-units/diabetes-and-endocrinology/sample-collections/malmoe-prevention-project-mpp/
NESDA	Netherlands Study of Depression and Anxiety	Northern European (White, Caucasian)	Netherlands	http://www.nesda.nl/en/
NFBC1966	Northern Finland Birth Cohort 1966	Northern European (White, Caucasian)	Finland	http:kelo.oulu.fi/NFBC/
NFBC1986	Northern Finland Birth Cohort 1986	Northern European (White, Caucasian)	Finland	http:kelo.oulu.fi/NFBC/
NTR	Netherlands Twin Register	Northern European (White, Caucasian)	Netherlands	www.tweelingenregister.org
PIVUS	Prospective Investigation of the Vasculature in Uppsala Seniors	Northern European (White, Caucasian)	Sweden	http://www.medsci.uu.se/pivus/pivus.htm
PPP	Prevalence, Prediction and Prevention of diabetes	Northern European (White, Caucasian)	Finland	http://www.botnia-study.org
QIMR-AUSTRALIA	Twin and family studies at the Queensland Institute of Medical Research	European	Australia	http://genepi.qimr.edu.au/
RS	Rotterdam Study	European (White, Caucasian)	Netherlands	http://www.epib.nl/research/ergo.htm
TWINGENE	TWINGENE	Northern European (White, Caucasian)	Sweden	http://ki.se/ki/jsp/polopoly.jsp?l=en&d=9610
TwinsUK	TwinsUK	White, Caucasian (UK)	United Kingdom	http://www.twinsuk.ac.uk/
ULSAM	Uppsala longitudinal study of adult men	Northern European (White, Caucasian)	Sweden	http://www.pubcare.uu.se/ULSAM
WTCCC-CAD	Wellcome Trust Case Control Consortium CAD Cases	White British	England	www.wtccc.org.uk

[1]The MORGAM cohort (Monitoring of trends and determinants in Cardiovascular disease, Risk, Genetics, Archiving and Monograph) is a consortium of cohort studies, whose data have been harmonized into one database for joint analysis1. For the current analysis, MORGAM includes the following cohorts: Brianza 01, 02 and 03 (Italy); the placebo cohort of the ATBC Study (Finland); Lille, Strasbourg and Toulouse cohorts of the PRIME study (France); and Belfast cohort of the PRIME study (Northern Ireland). The analyses performed in MORGAM used the cohort as covariate to reduce possible cohort specific confounding.

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Supplementary Table 2. Age, sex and body mass index of the participating cohorts

Study	Age (years) at measurement: mean (SD)	Sex: N men / N women	BMI (kg/m^2): mean (SD)
B58C	45.16 (0.39)	3,226/3,255	27.39 (4.88)
EGCUT_metabo	58.43 (11.45)	868 / 1,402	28.07 (6.47)
EGCUT_omni	48.98 (20.17)	4,591 / 5,255	26.53 (5.28)
FTC	55.01 (4.43)	686/423	26.09 (4.07)
FR92	44.39 (11,32)	2,552 / 2,984	26.13 (4.46)
FR97	47.79 (13.22)	3,150 / 3,598	26.63 (4.61)
FR02	47.96 (13.12)	3,800 / 4,342	26.91 (4.68)
FR07	50.45 (13.93)	2,753 / 3,147	27.13 (4.88)
GOSH	54.1(11.8)	756/741	24.5 (3.2)
GRAPHIC	39.29 (14.5)	1,021/1,003	26.11 (4.6)
H2000	56.21 (17.19)	1,501 / 1,979	26.81 (4.68)
HELENA	14.7 (1.4)	549/595	21.3 (3.8)
KORA F3	56.92 (12.76)	1,419/1,557	27.61 (4.62)
KORA F4	56.08 (13.26)	1,459/1,550	27.62 (4.81)
MONA LISA	55.4 (11.4)	772/771	27.0 (5.0)
MONICA	51.2 (8.4)	582/567	26.6 (5.0)
MORGAM	58.03 (8.54)	5,448/1,087	27.21 (4.22)
MPP	45.5 (6.90)	10,294 / 5,571	24.25 (3.29)
NESDA	42.07 (12.83)	745 / 1,489	25.64 (5.03)
NFBC1966	31.17 (0.35)	2,137 / 2,298	24.70 (4.28)
NFBC1986	16.00 (0.37)	2,591 / 2,694	21.22 (3.48)
NTR	41.87 (15.09)	2,599 / 4,155	24.67 (4.09)
PIVUS	70.19 (0.17)	491/488	27.07 (4.3)
PPP	47.90 (15.63)	2,017 / 2,349	26.31 (4.44)
QIMR-AUSTRALIA	35.61 (17.42)	5,059/6,737	24.11 (5.12)
RS	69.0 (8.80)	2,372/3,373	26.3 (3.69)
TWINGENE	65.4(8.3)	3,021/2,470	26.2(4.2)
TwinsUK	52.80 (14.42)	0/4,829	26.06 (5.06)

SUPPLEMENTARY DATA

ULSAM	49.6 (0.6)	1,175/ 0	24.8 (3.0)
WTCCC-CAD	51.27 (8.7)	2,376/590	28.02 (4.5)

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Supplementary Table 3. Lead SNPs and proxy SNPs used to create the genetic score instrument. All lead SNPs were available (genotyped or imputed) in studies B58C, EGCUTomni, FR02, FR07, FR92, FR97, H2000, QIMR-AUSTRALIA, RS and WTCCC-CAD, and these studies are not included in the table.

Lead SNP			**Proxies used**			**Studies**														
SNP id	Locus	EA	Proxy 1	Proxy 2	Proxy 3	EGCUT metabo	FTC	GOSH	GRAPHIC	KORAF3	KORAF4	MORGAM	NESDA	NFBC1966	NFBC1986	NTR	PIVUS	TWIN-GENE	TwinsUK	ULSAM
rs4836133	*ZNF608*	A	rs6864049			1		1	1	1	1	1	1	1	1	1	1	1	1	1
rs4929949	*RPL27A*	C	rs7127684	rs9300091		1			2	1	1	1			1		2	2	2	2
rs4771122	*MTIF3*	G	rs1006353	rs12016871	rs4771122	1	3		2	1	1	1			1		2	2		2
rs713586	*RBJ*	C	rs10182181	rs713587	rs6752378	3		1	2	1	1	1			1		2	2		2
rs10767664	*BDNF*	A	rs2030323	rs988748		1		1	2	1	1	1			1		2	2		2
rs10150332	*NRXN3*	C	rs17109256	rs7144011		1			1	1	1	2			1		1	1		1
rs1555543	*PTBP2*	C	rs11165643	rs10489741		1			2	1	1	1			1		1	1		1
rs1558902	*FTO*	A	rs1421085	rs11075989		1			1	1	1	2			1		1	1		1
rs2890652	*LRP1B*	C				NA				NA	NA				NA		NA	NA		NA
rs887912	*FANCL*	T	rs1016287	rs759250					1				1			1	1	1	2	1
rs9816226	*ETV5*	T				NA				NA	NA				NA		NA	NA		NA
rs11847697	*PRKD1*	T				NA				NA	NA				NA		NA	NA		NA
rs7359397	*SH2B1*	T	rs3888190	rs7498665	rs4788102				3				2			2	1	1		1
rs29941	*KCTD15*	G	rs29942						1								1	1		1
rs2112347	*FLJ35779*	T	rs10057967						1								1	1		1
rs3817334	*MTCH2*	T	rs4752856						1								1	1		1
rs3810291	*TMEM160*	A	rs2303108	rs10408163		2		1				1								
rs1514175	*TNNI3K*	A	rs3845344										1			1				
rs10938397	*GNPDA2*	G	rs12641981						1						1					
rs2241423	*MAP2K5*	G	rs16951304										1			1				
rs13078807	*CADM2*	G	rs9852859						1											
rs2287019	*QPCTL*	C																		

SUPPLEMENTARY DATA

rs543874	*SEC16B*	G																		
rs2815752	*NEGR1*	A																		
rs7138803	*FAIM2*	A																		
rs571312	*MC4R*	A																		
rs12444979	*GPRC5B*	C																		
rs10968576	*LRRN6C*	G																		
rs2867125	*TMEM18*	C																		
rs206936	*NUDT3*	G																		
rs13107325	*SLC39A8*	T																		
rs987237	*TFAP2B*	G																		

EA, effect allele

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Supplementary Table 4. Measurement methods used for glycemic traits

Study	Glucose	Insulin	HbA1c
B58C	NA	NA	Ion exchange HPLC using the TOSOH A1c2.2 analyser
EGCUT_metabo	NA	NA	NA
EGCUT_omni	NA	NA	NA
FTC	NA	NA	NA
FR92	NA	NA	NA
FR97	NA	NA	NA
FR02	NA	NA	NA
FR07	Enzymatic, hexokinase (fasting time >= 8 hours)	CMIA, Chemiluminescent Microparticle Immuno Assay (measured from serum)	NA
GOSH	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet
GRAPHIC	NA	NA	NA
H2000	Glucose, Hexokinase (4-11 hour fasting time)	Microparticle enzyme immunoassay (4-11 hour fasting time)	NA
HELENA	Enzyme assays on the Dimension RxL clinical chemistry system (Dade Behring, Schwalbach, Germany) .	Insulin was measured by a solid-phase two-site chemiluminescent immunometric assay with an Immulite 2000 analyzer (DPC Biermann GmbH, Bad Nauheim, Germany).	NA
KORA F3	GLU Flex (Dade Behring); Hexokinase/G6P-DH	NA	turbidimetric immunologic inhibition assay (TINIA; HA1C Kit Dade Behring)
KORA F4	GLU Flex (Dade Behring); Hexokinase/G6P-DH	ELISA	HPLC (Menarini HA-8160)
MONA LISA	Glucose was measured using the standard glucose hexokinase method (DuPont Dimension, Brussels, Belgium).	Plasma insulin was measured with an enzyme immunoassay (Beckman Coulter) or an immunoradiometric assay (Immunotech) .	HbA1c was measured by HPLC (ChromSystems, Munich, Germany).
MONICA	Plasma glucose was measured using the standard glucose hexokinase method (DuPont Dimension, Brussels, Belgium).	Plasma insulin was measured by radio-immunoassay (Medgenix Diagnostics, Brussels, Belgium).	NA
MORGAM	NA	NA	NA
MPP	Hexokinase method (routine methods at the Department of Clinical Chemistry, University Hospital)		Routine methods at the Department of Clinical Chemistry, University Hospital
NESDA	Hexokinase method (Gluco-quant) (Modular analytics, Roche diagnostics, Mannheim, Germany)	NA	NA
NFBC1966	Blood glucose was analysed by a glucose dehydrogenase method (Granutest 250, Diagnostica Merck, Darmstadt, Germany)	Serum insulin was analysed by RIA (Pharmacia Diagnostics, Uppsala, Sweden)	NA
NFBC1986	Plasma glucose concentrations were analysed by	Serum insulin was determined by radioimmunoassay	NA

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	Cobas Integra 700 automatic analyser (Roche Diagnostics, Basel, Switzerland)	(Pharmacia Diagnostics, Uppsala, Sweden)	
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)
PIVUS	Reference method at Uppsala University Hospital	Enzymatic-immunological assay at Uppsala University Hospital	NA
PPP	Glucose dehydrogenase method (Hemocue, Ängelholm, Sweden)	Serum insulin by fluoroimmunometric assay (Delfia, Perkin Elmer, Turku, Finland)	Local laboratories
QIMR-AUSTRALIA	NA	NA	NA
RS	Glucose levels were measured using the glucose hexokinase method (Instruchemie)	Serum insulin was determined by metric assay (Biosource Diagnostics, Camarillo, CA, USA).	NA
TWINGENE	Reference method at Karolinska Institutet	NA	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
ULSAM	Glucose dehydrogenase method (Gluc-DH, Merck, Darmstadt, Germany)	Immunoreactive insulin: Enzymatic-immunological assay (Enzymun, Boehringer Mannheim)	HPLC with gradient system (BIO-RAD Laboratories)
WTCCC-CAD	NA	NA	NA

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Supplementary Table 5. Measurement methods used for lipids

Study	HDL-C	LDL-C	Triglycerides	Total cholesterol
B58C	Abbott AU2700 autoanalyser	Estimated by Friedewald's formula	Abbott AU2700 autoanalyser	Abbott AU2700 autoanalyser
EGCUT_metabo	NA	NA	NA	NA
EGCUT_omni	NA	NA	NA	NA
FTC				
FR92	Dextran-MgCl2 precipitation (average 4-hour fasting time)	LDL cholesterol was calculated using Friedewald's formula. Average 4-hour fasting time.	Enzymatic, GPO-PAP (average 4-hour fasting time)	Enzymatic, CHOD-PAP, (average 4-hour fasting time)
FR97	Dextran-MgCl2 precipitation (average 4-hour fasting time)	LDL cholesterol was calculated using Friedewald's formula, Average 4-hour fasting time.	Enzymatic, GPO-PAP (average 4-hour fasting time)	Enzymatic, CHOD-PAP (average 4-hour fasting time)
FR02	Direct, polyethylene glycol-modified enzyme (PEG) (average 4-hour fasting time)	LDL cholesterol was calculated using Friedewald's formula, Average 4-hour fasting time.	Enzymatic, GPO-PAP (average 4-hour fasting time)	Enzymatic, CHOD-PAP (average 4-hour fasting time)
FR07	Accelerator selective detergent	Lipid Selective Detergent	Enzymatic, GPO	Enzymatic, CHOD-PAP
GOSH	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet
GRAPHIC	Abbott Aeroset 2.0 Analyser	Abbott Aeroset 2.0 Analyser	Abbott Aeroset 2.0 Analyser	Abbott Aeroset 2.0 Analyser
H2000	HDL-C Plus (4-11 hour fasting time)	LDL-C Plus (4-11 hour fasting time)	Triglycerides, GPO PAP (4-11 hour fasting time)	Cholesterol, CHOD PAP (4-11 hour fasting time)
HELENA	Enzyme assays on the Dimension RxL clinical chemistry system (Dade Behring, Schwalbach, Germany) .	Enzyme assays on the Dimension RxL clinical chemistry system (Dade Behring, Schwalbach, Germany)	Enzyme assays on the Dimension RxL clinical chemistry system (Dade Behring, Schwalbach, Germany) .	Enzyme assays on the Dimension RxL clinical chemistry system (Dade Behring, Schwalbach, Germany) .
KORA F3	AHDL Flex method (Dade-Behring)	Direct method (ALDL, Dade-Behring).	TGL Flex (Dade-Behring),	cholesterol-esterase method (CHOL Flex, Dade-Behring)
KORA F4	AHDL Flex method (Dade-Behring)	Direct method (ALDL, Dade-Behring).	TGL Flex (Dade-Behring),	cholesterol-esterase method (CHOL Flex, Dade-Behring)
MONA LISA	HDL-cholesterol was measured after sodium phosphotungstate/magnesium chloride precipitation (Olympus).	Friedewald formula	Triglycerides were measured with enzyme assays (Olympus).	Total cholesterol levels were measured with enzyme assays (Olympus).
MONICA	HDL- cholesterol was measured after sodium phosphotungstate/magnesium chloride precipitation (Boehringer Mannheim, Mannheim, Germany).	Friedewald formula	Triglyceride levels were measured using enzyme assays (Boehringer Mannheim, Mannheim, Germany).	Cholesterol levels were measured using enzyme assays (Boehringer Mannheim, Mannheim, Germany).
MORGAM	HDL- cholesterol was measured after phosphotungstate/magnesium chloride precipitation: http://www.thl.fi/publications/morgam/qa/baseline/chol/table9.htm	Calculated using Friedewald's formula.	Enzymatic	http://www.thl.fi/publications/morgam/qa/baseline/chol/table9.htm

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MPP	routine methods at the Department of Clinical Chemistry, University Hospital		routine methods at the Department of Clinical Chemistry, University Hospital	routine methods at the Department of Clinical Chemistry, University Hospital
NESDA	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)	Enzymatic colorimetric assay (GPO-PAP) (Modular analytics, Roche diagnostics, Mannheim, Germany)	Enzymatic colorimetric assay (CHOD-PAP) (Modular analytics, Roche diagnostics, Mannheim, Germany)
NFBC1966		Serum LDL was calculated by the Friedewald formula 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	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)
NFBC1986	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)	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)
NTR	Vitros 250 direct HDL cholesterol assay (Johnson & Johnson, Rochester, USA; measured in heparin plasma)	LDL cholesterol was calculated using Friedewald's formula	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)
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
PPP	Enzymatic method (Konelab 60i analyser; Thermo Electron Oy, Vantaa, Finland)	Friedewald formula	Enzymatic method (Konelab 60i analyser; Thermo Electron Oy, Vantaa, Finland)	Enzymatic method (Konelab 60i analyser; Thermo Electron Oy, Vantaa, Finland)
QIMR-AUSTRALIA	Direct Assay, Roche Cholesterol Oxidase	Friedewald formula	Enzymatic, Roche Method	Enzymatic, Roche Method
RS	HDL-c was determined enzymatically, using an automated procedure	LDL cholesterol was calculated using Friedewald's formula	Triglycerides were determined enzymatically, using an automated procedure	Total cholesterol was determined enzymatically, using an automated procedure
TWINGENE	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet	Reference method at Karolinska Institutet
TwinsUK	precipitation with magnesium chloride/phosphotumgstate and thereafter as TC	LDL cholesterol was calculated using Friedewald's formula	colorimetric enzymatic method	colorimetric enzymatic method
ULSAM	precipitation with magnesium chloride/phosphotumgstate and thereafter as TC	LDL cholesterol was calculated using Friedewald's formula	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
WTCCC-CAD	Abbott Aeroset 2.0 Analyser	Abbott Aeroset 2.0 Analyser	Abbott Aeroset 2.0 Analyser	Abbott Aeroset 2.0 Analyser

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Supplementary Table 6. Measurement methods used for inflammation and liver markers

Study	Alanine aminotransferase (ALT)	Gamma-glytamyl-transferase (GGT)	Interleukine-6	CRP
B58C	NA	NA	NA	Nephelometry using latex particles coated with monoclonal human anti-CRP, analysed by BN Prospec protein analyser
EGCUT_metabo	NA	NA	NA	NA
EGCUT_omni	NA	NA	NA	NA
FTC	NA	NA	NA	NA
FR92	NA	GGT was determined using a kinetic method (J.T. Baker Chemicals B.V., Denventer, Holland or Oy Medix Biochemica Ab, Kauniainen, Finland)	NA	CRP was determined from serum by latex immunoassay CRP16 (Abbott, Architect c8000, Abbott Laboratories, Chicago, IL). The intra-assay and inter-assay CVs were 0.83% and 0.93%, respectively
FR97	NA	GGT was determined using a kinetic method (J.T. Baker Chemicals B.V., Denventer, Holland or Oy Medix Biochemica Ab, Kauniainen, Finland)	NA	CRP was determined from serum by latex immunoassay CRP16 (Abbott, Architect c8000, Abbott Laboratories, Chicago, IL). The intra-assay and inter-assay CVs were 0.83% and 0.93%, respectively
FR02	NA	kinetic method (ECCLS, ThermoElektron Oy, Finland)	NA	immunoturbidometric method sensitivized to low concentration range (Orion Diagnostica, Finland)
FR07	NA	kinetic method (Abbott Laboratories. Abbott Park, Illinois, U.S.A)	NA	latex-immunoturbidometric method (Sentinel Diagnostics, Milan, Italy).
GOSH	NA	Reference method at Karolinska Institutet	NA	Reference method at Karolinska Institutet
GRAPHIC	NA	NA	NA	NA
H2000	NA	NA	NA	NA
HELENA	Serum alanine aminotransferase levels were measured on the Dimension RxL clinical chemistry system (Dade Behring, Schwalbach, Germany) with enzymatic methods.	Serum gamma GT levels were measured on the Dimension RxL clinical chemistry system (Dade Behring, Schwalbach, Germany) with enzymatic methods.	IL-6 secretion was measured in the cell culture media by cytometric bead array and detected by flow cytometry (Facscan, BD, Sunnyvale, CA).	CRP was measured in serum by immunoturbidimetry (AU2700 biochemistry analyzer; Olympus, Watford, UK).

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KORA F3	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)	CRP was measured with nephelometry using latex particles coated with monoclonal human anti-CRP, analyzed on a BNII from Siemens, Eschborn, Germany
KORA F4	UV test; IFCC with pyridoxal phosphate activation (Roche/Hitachi cobas)	Enzymatic calorimetric assay; HiCo Gamma-glutamyltransferase liquid (Roche/Hitachi cobas) against IFCC	Quantikine HS ELISA kit from R&D Systems	CRP was measured with nephelometry using latex particles coated with monoclonal human anti-CRP, analyzed on a BNII from Siemens, Eschborn, Germany
MONA LISA	NA	Enzymatic colorimetric assay (Olympus).	NA	Concentrations of ultra-sensitive CRP were measured by Behring kits and nephelometry (BN Prospec, Behring Diagnostics, Westwood, MA
MONICA	NA	Gamma GT levels were measured with enzymatic reagents on automated analyser (Hitachi 912, Roche diagnostics, Meylan France).	NA	NA
MORGAM	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
NESDA	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	NA	NA	NA	Serum CRP concentrations were determined by immunoenzymometric assay (Medix Biochemica, Espoo, Finland)
NFBC1986	NA	NA	NA	Serum CRP concentrations were determined by immunoenzymometric assay (Medix Biochemica, Espoo, Finland)
NTR	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	Evidence® array biochip analyser (Randox Laboratories Ltd, Crumlin, UK)	Ultra sensitive particle enhanced immunoturbidimetric assay (Orion Diagnostica, Espoo, Finland)
PPP	Local laboratories	NA	NA	NA
QIMR-AUSTRALIA	Roche, IFCC Method	Roche, IFCC Method	NA	NA
RS	Automated biochemistry spectrophotometric analyzer (ELAN-Fully Selective Analyzer, Eppendorf-Merck, Hamburg, Germany)	Automated biochemistry spectrophotometric analyzer (ELAN-Fully Selective Analyzer, Eppendorf-Merck, Hamburg, Germany)	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.	Rate Near Infrared Particle Immunoassay (Immage® Immunochemistry System, Beckman Coulter, USA).

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TWINGENE	NA	NA	NA	Reference method at Karolinska Institutet, half of the cohort analyzed with "high-sensitive" assay. Models adjusted for 2 different methods
TwinsUK	kinetic rate method on a Synchron LX20 automated multi channel analyzer (Beckman Coulter, Fulleton, CA)	kinetic rate method on a Synchron LX20 automated 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	Greiner 300 analyser, enzymatic method	NA	IL-6 ELISA HS, R&D Systems, Minneapolis, MN	Latex enhanced reagent;Behring BN ProSpec analyzer
WTCCC-CAD	NA	NA	NA	NA

SUPPLEMENTARY DATA

Supplementary Table 7. *FTO* analysis: Instrumental variable analysis of the association of adiposity with cardiovascular risk factors[a], non-stratified analysis.

	IV analysis (*FTO*)		
	n	β (95%CI)	*P*
Diastolic blood pressure	115,891	0.17(0.06-0.27)	0.002
Systolic blood pressure	116,443	0.21(0.10-0.31)	7.3E-05
Fasting glucose	67,589	0.05(-0.13-0.22)	0.60
2-h-post-OGTT-glucose	21,747	0.24(-0.01-0.50)	0.06
HbA1c	29,173	0.17(-0.04-0.38)	0.11
ln Fasting insulin	39,023	0.41(0.22-0.59)	1.8E-05
ln C-reactive protein	72,055	0.24(0.11-0.38)	0.001
ln Interleukin-6	11,789	0.02(-0.30-0.34)	0.92
HDL-cholesterol	97,482	-0.22(-0.34--0.09)	0.001
LDL-cholesterol	91,054	0.08(-0.06-0.23)	0.26
Total cholesterol	111,903	0.06(-0.07-0.20)	0.35
ln Triglycerides	105,867	0.25(0.11-0.39)	0.001
ln ALT	50,202	0.29(0.12-0.45)	0.001
ln GGT	77,023	0.24(0.12-0.36)	4.0E-04

[a]All models were adjusted for sex and age.
Abbreviations: β (95% CI), effect per standard deviation change of BMI on trait (SD-scale); OGTT, oral glucose tolerance test; ALT, alanine aminotransferase; GGT, gamma-glutamyl-transferase; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; ln, transformed to natural logarithm scale

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Supplementary Table 8. *FTO* analysis: Age-stratified instrumental variable analysis of the association of adiposity with cardiovascular risk factors[a].

IV analysis (*FTO*)							
	<55 years			≥55 years			
	n	β (95%CI)	*P*	n	β (95%CI)	*P*	P_{diff}
Diastolic blood pressure	70,409	0.23(0.10-0.36)	4.0E-04	46,595	0.06(-0.10-0.22)[b]	0.48	
Systolic blood pressure	70,574	0.21(0.10-0.32)	2.0E-04	46,982	0.20(0.02-0.38)	0.03	
Fasting glucose	43,714	0.03(-0.17-0.23)	0.79	24,813	0.04(-0.26-0.34)	0.80	
2-h-post-OGTT-glucose	13,591	0.25(0.02-0.49)	0.04	8,156	0.27(-0.25-0.80)	0.31	
HbA1c	14,792	0.14(-0.13-0.41)	0.31	14,152	0.15(-0.15-0.46)	0.33	
ln Fasting insulin	25,334	0.41(0.19-0.63)[b]	3.0E-04	14,583	0.36(0.06-0.66)	0.02	
ln C-reactive protein	42,058	0.30(0.13-0.47)	7.0E-04	29,981	0.15(-0.11-0.40)	0.25	
ln Interleukin-6	6,719	-0.26(-0.91-0.40)	0.44	5,070	0.17(-0.31-0.65)	0.48	
HDL-cholesterol	61,034	-0.27(-0.41--0.13)	1.0E-04	37,183	-0.14(-0.32-0.04)	0.12	
LDL-cholesterol	59,591	0.22(0.08-0.36)	0.002	32,468	-0.13(-0.38-0.12)	0.30	0.01
Total cholesterol	72,804	0.18(0.04-0.31)	0.01	40,112	-0.12(-0.32-0.08)	0.26	0.02
ln Triglycerides	71,842	0.33(0.15-0.50)	2.0E-04	35,060	0.07(-0.13-0.28)	0.48	
ln ALT	31,850	0.27(0.01-0.52)	0.04	18,352	0.18(-0.05-0.42)	0.13	
ln GGT	51,205	0.23(0.09-0.37)	0.001	25,818	0.23(-0.03-0.50)	0.08	

[a]All models were adjusted for sex and age.
[b]Significant difference ($P<0.05$) between IV analysis and observational analysis.

Abbreviations: β (95% CI), effect per standard deviation change of BMI on trait (SD-scale); P_{diff}, difference between age strata (only significant P-values are shown); OGTT, oral glucose tolerance test; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; ln, transformed to natural logarithm scale

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Supplementary Table 9. *FTO* analysis: Sex-stratified instrumental variable analysis of the association of adiposity with cardiovascular risk factors[a].

IV analysis (*FTO*)							
	Women			Men			
	n	β (95%CI)	*P*	n	β (95%CI)	*P*	P_{diff}
Diastolic blood pressure	59,581	0.08(-0.05-0.21)[b]	0.20	56,310	0.26(0.09-0.42)	0.002	
Systolic blood pressure	59,702	0.15(0.02-0.28)	0.02	56,741	0.28(0.11-0.45)	0.001	
Fasting glucose	35,589	0.03(-0.18-0.24)	0.81	32,000	0.11(-0.18-0.41)	0.45	
2-h-post-OGTT-glucose	10,032	0.28(-0.17-0.72)	0.22	11,715	0.28(-0.03-0.58)	0.08	
HbA1c	15,635	-0.02(-0.27-0.22)	0.85	13,538	0.40(0.05-0.75)	0.02	
ln Fasting insulin	21,962	0.19(-0.03-0.42)[b]	0.09	17,061	0.70(0.38-1.02)	1.8E-05	0.011
ln C-reactive protein	40,143	0.22(-0.01-0.45)	0.06	31,912	0.24(0.03-0.45)	0.02	
ln Interleukin-6	6,652	-0.12(-0.53-0.30)	0.58	5,137	0.19(-0.38-0.76)	0.52	
HDL-cholesterol	52,991	-0.12(-0.27-0.03)[b]	0.12	44,464	-0.34(-0.53--0.14)	8.0E-04	
LDL-cholesterol	50,604	0.12(-0.06-0.30)	0.21	40,450	0.04(-0.18-0.27)	0.71	
Total cholesterol	58,238	0.08(-0.08-0.25)	0.32	53,665	0.03(-0.19-0.24)	0.82	
ln Triglycerides	55,885	0.21(0.05-0.36)	0.01	49,982	0.29(0.08-0.50)	0.01	
ln ALT	26,849	0.18(-0.08-0.43)	0.18	23,353	0.39(0.13-0.64)	0.003	
ln GGT	41,138	0.25(0.09-0.40)	0.001	35,885	0.21(0.01-0.41)	0.04	

[a]All models were adjusted for age.
[b]Significant difference ($P<0.05$) between IV analysis and observational analysis.
Abbreviations: P_{diff}, difference between women and men (only significant P-values are shown); OGTT, oral glucose tolerance test; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; ln, transformed to natural logarithm scale