Online Appendix to:

Joint Analysis of Individual Participants' Data from 17 Studies on the Association of the *IL6* Variant -174G>C with Circulating Glucose Levels, Body-Mass Index, and Interleukin-6 Levels

Research Design and Methods

Study Inclusion Criteria, Search Strategy, and Study Recruitment

All available published and unpublished studies fulfilling the following criteria were recruited for the *IL6*-T2DM consortium: 1) association study conducted in humans, 2) polymorphic genotype data for *IL6* -174G>C, 3) T2DM cases and nondiabetic controls, 4) published before September 2005 or unpublished, 5) availability of individual participant's data (IPD). Studies were excluded if the control group consisted only of individuals with pre-diabetes (one study),(1) or if ethnic admixture of unrelated study subjects was reported in the original publication (Pima Indian case-control study, reported in (2)).

Published studies were identified in the PUBMED database using the following search terms: (IL-6 OR IL6 OR interleukin-6) AND (diabetes OR T2DM OR NIDDM) AND (gene OR genes OR genet* OR polymorphism* OR allele*). To further extend the search, the reference lists from all identified original studies and review articles on this topic were examined. Unpublished studies were recruited by a call for participation at the symposium "Immunogenetic Contribution to Type 2 Diabetes and Parameters of the Metabolic Syndrome", which was held in September 2004 at the 40th Annual Meeting of the European Association for the Study of Diabetes, and by personally contacting investigators in the field.

Data Cleaning, Phenotyping and Genotyping Methods

The study center at the Helmholtz Zentrum München checked all incoming data for plausibility and for consistency with information provided by the investigators or the published article. Plausible and corrected data were converted into a standard format and incorporated into a central database.

Body-mass index was calculated as weight [kg] divided by squared height [m²] from measured anthropometric data, except for the RMIFAM and DANISH studies where self-reported data were used. An overview on methods used to quantify circulating interleukin-6 (IL-6) levels is presented in table A1.

A questionnaire was sent to all principal investigators to collect data on genotyping methods and quality. This information is also summarized in table A1. As *IL6* -174G>C is a G/C-polymorphism and allele G is complementary to allele C, the genotyping sequences and strands, assessed via the questionnaire, were compared with a reference to confirm that the allele labeling was performed consistently across all studies.

Further Details on the Statistical Analyses

Statistical analyses were performed using SAS software version 9.1 (Cary, N.C., USA). *IL6* -174G>C allele and genotype frequencies were estimated, accounting for the correlation in family data by use of an exchangeable structure in a generalized estimating equations approach (SAS PROC GENMOD). Hardy-Weinberg equilibrium (HWE) was tested in nondiabetic subjects (SAS PROC ALLELE); for family studies only one randomly drawn subject per family was included. In order to approximate a normal distribution, circulating IL-6 was logarithmically transformed. If a study featured less than 50 participants for a specific outcome, this study was not included in the joint analysis.

Publication bias was investigated by visual inspection of funnel plots and by the Egger's regression test (3). Funnel and forest plots were prepared using Review Manager software version 4.2 (Cochrane Collaboration, Copenhagen, DK).

Table A1 – Online Appendix. Methods Used for Quantifying Circulating IL-6 Levels and Genotyping *IL6* -174G>C (rs1800795 according to http://www.ncbi.nlm.nih.gov)

Study	IL-6 Level Quantification	Genotyping Method	Call Rate [%]*
Botnia Study	n.a.	Allelic discrimination assay-by-design on ABI 7900 (Applied Biosystems)	100
Captopril Prevention Project	Sandwich ELISA, R&D Systems, Abingdon, UK	Dynamic allele specific hybridization (DASH)	100
Danish Study	n.a.	Chip-based MALDI-TOF MS (MassArray, Sequenom)	96
Ealing Diabetes Study of Coagulation	n.a.	Nla III RFLP, MADGE	97
European Prospective Investigation into Cancer and Nutrition Potsdam	Sandwich ELISA, R&D Systems, Abingdon, UK	SNuPE, MegaBACE 1000	100
The Finland-United States Investigation of NIDDM Genetics	n.a.	Illumina GoldenGate	98
Girona Genetics of Diabetes Study	Solid-phase, enzyme-labeled, chemiluminescent sequential immunometric assay, DPC DIPESA S.A., Madrid, Spain	SfaNI RFLP	99
KORA MI Family Study	Sandwich ELISA, R&D Systems, Abingdon, UK	Hsp92II RFLP, PAGE	97
KORA Survey S4	Sandwich ELISA, CLB, Amsterdam, Netherlands	Chip-based MALDI-TOF MS (MassArray, Sequenom)	97
KORA T2DM Family Study	n.a.	Chip-based MALDI-TOF MS (MassArray, Sequenom)	98
MONICA/KORA Case Cohort Study S123	Sandwich ELISA, CLB, Amsterdam, Netherlands	Chip-based MALDI-TOF MS (MassArray, Sequenom)	99
MONICA/KORA Survey S3	n.a.	Chip-based MALDI-TOF MS (MassArray, Sequenom)	99
Regensburg MI Family Study	n.a.	Hsp92II RFLP, PAGE	97
Second Northwick Park Heart Study	n.a.	PCR by MADGE, NIaIII RFLP	99
Tarraco Study	n.a.	SfaNI RFLP	99
University College Diabetes and Cardiovascular Study	Sandwich ELISA, R&D Systems, Abingdon, UK	PCR by MADGE, NIaIII RFLP	99

n.a. = not applicable; MI = Myocardial Infarction

* Successfully genotyped individuals in percent of all subjects intended for genotyping

Table A2 – Online Appendix. Description of Included Studies

Study Name (Official Abbreviation)	Study Description*
Botnia Study	The Botnia Study began in 1990 as a family-based study aiming to identify genes increasing susceptibility to T2DM. Type 2 diabetic subjects from the area of five health care centers in the Botnia region of Western Finland were invited to participate together with their family members. For the purpose of this joint analysis, unrelated individuals were genotyped for *IL6* -174G>C. According to a priori defined criteria, one type 2 diabetic individual per family was selected. Nondiabetic subjects comprise cases' spouses and unrelated individuals, all being 35 years or older.
Captopril Prevention Project (CAPPP)	CAPPP is a prospective randomized clinical trial conducted in Sweden and Finland during the 1990s. Patients aged 25–66 years, with a measured diastolic blood pressure of 100 mmHg or more on two occasions, were recruited at health centers and randomly assigned to captopril or conventional antihypertensive treatment. Exclusion criteria were secondary hypertension, serum creatinine concentration of more than 150 μmol/l and disorders that required treatment with ß-blockers. Cases had T2DM at baseline or were diagnosed during the follow-up. This joint analysis includes a substudy of the Swedish part of CAPPP, which has been genotyped for *IL6* -174G>C. This substudy comprises all patients that got myocardial infarction (MI), plus two control subjects without MI per patient, matched with respect to gender, age and smoking. Further details: (4).
Danish Study	The DANISH case-control study of T2DM involves all 4568 subjects with normal glucose tolerance (NGT) from the Inter99 cohort and 1389 unrelated type 2 diabetic patients recruited from the outpatient clinic at Steno Diabetes Center, Copenhagen and the Research Center for Prevention and Health through the Inter99 study. The Inter99 cohort is a population-based randomized non-pharmacological intervention study for prevention of cardiovascular disease done at the Research Center for Prevention and Health involving 6514 Caucasian subjects (6164 with data from an oral glucose tolerance test). Further details: (5).
Ealing Diabetes Study of Coagulation (EDSC)	The type 2 diabetic individuals of the EDSC study were recruited consecutively from the Ealing Hospital diabetes clinic in London, UK. Patients completed a questionnaire with details of age, ethnicity, smoking habit, fasting status, duration of diabetes, and other clinical details. Blood was collected for plasma and DNA analysis. Several further parameters, such as BMI, were measured. Type 2 diabetic individuals (n = 927) comprised primarily three ethnic groups, Indian Asian, n = 503, UK White, n = 331, Black Afro-Caribbean, n = 93. Further details: (6). To ensure comparability with the other Caucasian studies, only the White subjects were included in this joint analysis.
European Prospective Investigation into Cancer and Nutrition Potsdam (EPIC-Potsdam)	A nested case-control study was designed within the European Prospective Investigation into Cancer and Nutrition Potsdam cohort (EPIC-POTSDAM_nCC-T2DM), which is part of the European multicenter, population-based EPIC-study including 27548 subjects from the area around Potsdam, Germany (women aged 35–65 years and men aged 40–65 years). Baseline examination and blood sampling were conducted between 1994 and 1998. Data presented in this joint analysis are based on the first follow-up questionnaires sent to the study participants on average 2.3 years after baseline examination. Further details: (7). To ensure comparability with the other cross-sectional studies, only the nondiabetic control subjects were included in this joint analysis. Cases were free of T2DM at baseline and developed their incident T2DM during the follow-up. Analyses of their data are presented separately.

The Finland-United States Investigation of NIDDM Genetics (FUSION)	The index probands in the FUSION study were identified primarily from the National Hospital Discharge Registry (NHDR), which includes records since 1970 of all hospitalized patients with diabetes, and from previous studies carried out by the National Public Health Institute in Finland. From the NHDR, all patients who were hospitalized with a diagnosis of T2DM in Finland during 1987–1993 were identified in the first wave of sampling (FUSION 1). In the second wave of sampling (FUSION 2), patients hospitalized with T2DM during 1994–1995 were identified. Potential families for FUSION 2 also included some identified during FUSION 1 but not invited to participate at that time due to distance from the study clinics. An index proband with his family was eligible for participation in the FUSION study if 1) the proband or another affected sibling was diagnosed with T2DM between 35 and 60 years of age, 2) there was no history of type 1 diabetes in first-degree relatives, 3) the proband had one or more living full siblings diagnosed with T2DM at any age, and 4) at least one parent was apparently nondiabetic, with preference given to families with living parents or parents who had lived a long life without known diabetes. Further details on FUSION 1: (8), on FUSION 2: (9). Participants of FUSION 1 and FUSION 2 were analyzed separately. “FUSION 1” in this joint analysis comprises one type 2 diabetic individual from each FUSION 1 family, and nondiabetic spouses of type 2 diabetic FUSION participants, as well as elderly subjects that were all born in 1925 and were normal glucose tolerant by oral glucose tolerance tests (OGTTs) at both ages 65 and 70. “FUSION 2” comprises the sibling generation of the FUSION 2 sampling wave.
Girona Genetics of Diabetes Study	The type 2 diabetic patients of the Girona Genetics of Diabetes Study were consecutively recruited subjects from the diabetes clinics at the Hospital of Girona, Spain. The nondiabetic subjects are unrelated healthy Caucasian middle-aged subjects recruited from the general population. Further details: (2).
KORA Studies in chronological order	KORA (Cooperative Health Research in the Region Augsburg) is a regional research platform in the German city of Augsburg and the two adjacent counties, for population-based studies, subsequent follow-up studies and family studies in the fields of epidemiology, health economics, and health care research. KORA was established in 1996 to expand the WHO (World Health Organization) MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) project in Augsburg. In the framework of MONICA, three independent cross-sectional population-representative surveys were conducted in 1984/85 (S1), 1989/90 (S2), and 1994/95 (S3) and a population-based acute myocardial infarction (AMI) registry was set up. The study subjects of all Augsburg MONICA and KORA surveys and the family studies on myocardial infarction and T2DM are of German nationality and were studied by physical examination, blood testing and a standardized interview in KORA study centers. All tests were carried out by specially trained personnel. Further details: (10-12). Some individuals were originally recruited for two or more studies, but were assigned to one of the included KORA studies for the purpose of this joint analysis according to a priori defined criteria.
MONICA /KORA Survey S3	The MONICA/KORA Survey S3 originally investigated 4856 individuals. Study participants that are included in the MONICA/KORA Case Cohort Study S123 were eliminated from subjects of the MONICA/KORA Survey S3 for this joint analysis.
KORA MI Family Study	Patients with MI prior to the age of 60 years and their siblings were identified through the AMI. The diagnosis of MI was established according to the MONICA diagnostic criteria. Of 1254 patients contacted, 609 agreed to participate in the study (532 men, aged 56.1 ± 0.3 years). Moreover, 540 siblings without MI (251 men, aged 54.6 ± 0.4 years from 325 families) were recruited and examined by the same protocol.

KORA Survey S4 (KORA S4)	The KORA S4 studied a population-representative sample of 4261 subjects, 25–74 years old, during the years 1999–2001. The sample design followed the guidelines of the three previous MONICA Augsburg surveys. In the age-range of 55–74 years, 1653 persons participated in an OGTT. These participants were genotyped for *IL6* -174G>C and included in this joint analysis. Further details: (13).
KORA T2DM Family Study (KORA T2DMFAM)	In 2001 / 2002, 605 nuclear families were enrolled in the KORA T2DM Family Study. Families were ascertained through an index proband with known T2DM, who had at least one full sib or both parents willing to participate in the study. All available members of the index probands' nuclear families, i.e. full sibs and parents, were included. Index probands were all from the city or region of Augsburg. They were recruited from T2DM patients of the Central Hospital of Augsburg, from earlier MONICA- and KORA-studies, from the AMI register or via public relations. All participants were living in Germany and all were of European origin. Most subjects were extensively phenotyped in the KORA study center, some were examined by their family doctor, who decided whether or not the subject had T2DM and took blood samples for DNA analyses. Data of the sibling generation was included in this joint analysis.
MONICA/ KORA Case Cohort Study S123	All participants of at least one of the three MONICA Augsburg surveys were prospectively followed for the MONICA/KORA Case Cohort Study S123. The study was restricted to participants aged 35–74 years at baseline, since the incidence of T2DM is low in younger subjects. A stratified random sample of the source population, containing 1885 subjects, was selected. A total of 555 incident cases of T2DM were observed between participants' study start dates and 31st of December 2002. Further details: (14). For the purposes of this joint analysis on quantitative phenotypes, the baseline data of the MONICA/KORA Case Cohort Study S123 (prevalent T2DM and nondiabetic subjects) without the participants who developed their incident T2DM during the follow-up was used to ensure comparability with the other cross-sectional studies (MONICA/KORA-BASE). Analyses of the subjects with incident T2DM are presented separately.
Regensburg MI Family Study	The kindreds of the Regensburg MI Family Study were ascertained through MI index patients, who were identified by screening 93,500 patient charts in seven cardiac in-hospital rehabilitation centers distributed throughout Germany. Index patients had all suffered from MI before 60 years. If at least one sibling had suffered from MI or had severe coronary artery disease or bypass surgery, the index patient with all available parents and siblings were contacted and invited to participate in the study. All participating individuals filled out a standardized questionnaire that focused on cardiovascular risk factors, medical diagnoses, life style and medication. Further details: (15). Data of the sibling generation was included in this joint analysis.
Second Northwick Park Heart Study (NPHS II)	For the NPHS II study 3012 unrelated healthy Caucasian middle-aged male subjects were recruited from nine general medical practices scattered throughout the UK and prospectively followed from 1989. Sixty-eight subjects with diabetes at baseline were excluded from analysis. Further details: (16).
Tarraco Study	For the Tarraco study 211 unrelated type 2 diabetic subjects were recruited from the outpatient clinic at Hospital Universitari de Tarragona "Joan XXIII" during the years 2000–2004. Simultaneously, 118 healthy subjects were recruited from the same hospital. Further details: (2).

University College Diabetes and Cardiovascular Study (UDACS)	The UDACS Study comprises 1011 consecutive subjects recruited from the diabetes clinic at University College London Hospitals NHS Trust (UCLH) between the years 2001 and 2002. Patients completed a questionnaire with details of age, ethnicity, smoking habit, fasting status, duration of diabetes, and other clinical details. Blood was collected for plasma and DNA analysis. Several further parameters, such as BMI, were measured. No subjects requiring renal dialysis were recruited. Further details: (16).

* The numbers of participants presented for the original studies do not always match the numbers used in the analyses of this joint analysis. The reason is that some subjects of the original studies were not included in the joint analysis because of study overlap, missing genotype data, or missing phenotype data.

Table A3. References of Included Studies and Overview on Analyzed Outcomes

Study	No. T2DM / Nondiab*	Outcome†				Reference‡
		Fasting Glucose	2h-Glucose	BMI	IL-6 Level	
BOTNIA	731 / 557	3	3	3	4	n.a.
CAPPP	42 / 424	2	4	1	2	(4)
DANISH	1212 / 4399	1	3	1	4	(5)
EDSC	299 / 0	3	4	3	4	n.a.
EPIC-POTSDAM	0 / 348	4	4	2	2	(7)
FUSION 1	508 / 367	3	3	3	4	n.a.
FUSION 2	437 / 201	3	3	3	4	n.a.
GIRONA	42 / 123	3	3	3	3	(2)
KORA-MIFAM	95 / 881	4	4	2	2	(17)
KORA-S4	225 / 1190	3	3	1	1	(18)
KORA-T2DMFAM	776 / 513	3	3	3	4	n.a.
MONICA/ KORA-BASE	101 / 1744	4	4	3	3	n.a.
MONICA-S3	151 / 3551	4	4	2	4	(17)
NPHS II	0 / 2652	4	4	1	4	(16)
RMIFAM	662 / 2614	4	4	2	4	(17)
TGN	166 / 64	4	4	3	4	(2)
UDACS	560 / 0	4	4	1	3	(16)

n.a. = not applicable

* Number of type 2 diabetic (T2DM) / nondiabetic subjects included in analyses of the outcome BMI

† Publication of analyses on association between *IL6* -174G>C and outcomes fasting glucose, 2-h glucose, body-mass index (BMI), or interleukin-6 (IL-6) levels 1 = as main outcome, 2 = as additional outcome. 3 = Completely unpublished before study recruitment for joint analysis. 4 = No or not enough outcome data available for analysis.

‡ References of association studies between *IL6* -174G>C and circulating glucose or IL-6 levels, BMI, or T2DM

Table A4 – Online Appendix. Overview on Studies and Number of Participants Included in the Analyses of the Quantitative Traits Fasting Glucose, 2-h Glucose, Body-Mass Index, and Circulating Interleukin-6 Levels

	Fasting Glucose			2-h Glucose			Body-Mass Index			Circulating IL-6 Levels		
Study	**Nondiab***	**T2DM***	**Full***	**Nondiab**	**T2DM**	**Full**	**Nondiab**	**T2DM**	**Full**	**Nondiab**	**T2DM**	**Full**
CAPPP	286	*(37)*†	323				424	*(42)*†	466	420	*(42)*†	462
DANISH	4397	1139	5536	4396	366	4762	4399	1212	5611			
EDSC		106						299	299			
EPIC-POTSDAM	65						348		348	346		346
FUSION1	358	486	844	359	*(37)*†	396	367	508	875			
FUSION2	194	397	591	192	78	270	201	437	638			
GIRONA	123	*(41)*†	164	89	*(12)*†	101	123	*(42)*†	165	84	*(30)*†	114
KORA-MIFAM							881	95	976	872	94	966
KORA-S4	1186	132	1318	1190	118	1308	1190	225	1415	1183	222	1405
KORA-T2DMFAM	512	152	664	505	56	561	513	776	1289			
MONICA/KORA-BASE							1744	101	1845	1716	101	1817
MONICA-S3	299						3551	151	3702			
NPHS II							2652		2652			
RMIFAM							2614	662	3276			
UDACS								560	560		549	549
Sum Main Analyses	**7420**	**2412**	**9440**	**6731**	**618**	**7398**	**19007**	**5026**	**24117**	**4621**	**966**	**5659**
Studies with HWE-Violation (included in sensitivity analyses):												
BOTNIA	557	728	1285	539	462	1001	557	731	1288			
TGN		52					64	166	230			
Sum All Studies	**7977**	**3192**	**10725**	**7270**	**1080**	**8399**	**19628**	**5923**	**25635**	**4621**	**966**	**5659**

* Number of 'Nondiab' = nondiabetic subjects, 'T2DM' = type 2 diabetic subjects, 'Full' = nondiabetic and type 2 diabetic subjects combined (used for full data analysis)

† These type 2 diabetic subjects were not included in the T2DM status-specific analysis because there were less than 50 type 2 diabetic subjects in this study with data on the respective outcome

Table A5 – Online Appendix. Characteristics of Study Participants in the Joint Analysis

Study	Sta-tus*	T2DM Diagnosis†	No.‡	% Male	Mean ± Standard Error		*IL6* -174G>C		
					Age [years]	BMI [kg/m²]	% GC	% CC	P HWE§
BOTNIA	1	4, 10	731	53	60 ± 10	29 ± 5	53	25	0.18
	2	2, 3, 4, 6	557	48	53 ± 12	26 ± 4	55	24	0.03
CAPPP	1	5, 7, 10	42	81	58 ± 5	30 ± 4	45	26	0.55
	2	4	424	72	57 ± 7	27 ± 4	45	24	0.11
DANISH	1	3, 4, 5, 6, 10	1212	59	57 ± 11	30 ± 5	48	23	0.28
	2	5, 7	4399	47	45 ± 8	26 ± 4	48	23	0.06
EDSC	1	3, 4, 10	299	63	63 ± 14	30 ± 6	45	22	0.13
	2	n.a.							
EPIC-POTSDAM	1	n.a.							
	2	1, 2	348	59	55 ± 7	27 ± 4	55	18	0.07
FUSION 1	1	3, 4, 5, 6, 10	508	55	63 ± 7	30 ± 5	47	30	0.15
	2	2, 3, 4, 7	367	41	66 ± 6	27 ± 4	50	30	1.00
FUSION 2	1	3, 4, 5, 6, 10	437	55	64 ± 9	30 ± 5	49	29	0.89
	2	2, 3, 4, 6	201	38	58 ± 9	27 ± 4	52	28	0.30
GIRONA	1	5, 6, 10	42	76	53 ± 10	31 ± 5	50	10	0.73
	2	4, 6	123	82	47 ± 13	26 ± 4	50	24	1.00
KORA-MIFAM	1	1, 3, 8	95	85	58 ± 6	30 ± 5	50	15	0.66
	2	1, 2, 8	881	67	55 ± 8	28 ± 4	47	17	0.71
KORA-S4	1	2, 3, 5, 6, 10	225	59	65 ± 5	31 ± 5	54	16	0.17
	2	1, 2, 4, 6	1190	51	64 ± 5	28 ± 4	52	17	0.06
KORA-T2DMFAM	1	2, 3, 5, 6, 10	776	58	61 ± 10	31 ± 5	52	16	0.02
	2	1, 2, 4, 6	513	43	58 ± 11	28 ± 5	52	16	0.17
MONICA/ KORA-BASE	1	2, 10	101	66	62 ± 7	30 ± 4	49	21	0.85
	2	1	1744	53	52 ± 10	27 ± 4	49	17	0.55
MONICA-S3	1	2, 3, 8, 10	151	58	63 ± 8	30 ± 4	46	23	0.33
	2	1, 2, 8	3551	51	48 ± 14	27 ± 4	50	19	0.26
NPHSII	1	n.a.							
	2	1	2652	100	56 ± 3	26 ± 3	50	18	0.47
RMIFAM	1	1, 9	662	70	61 ± 7	28 ± 4	51	18	0.26
	2	1, 9	2614	68	58 ± 9	27 ± 3	48	19	0.52
TGN	1	1, 4	166	34	60 ± 10	29 ± 5	50	08	0.16
	2	1, 3, 4, 6	64	41	49 ± 14	30 ± 5	61	08	0.04
UDACS	1	4, 10	560	59	66 ± 11	30 ± 6	45	13	0.85
	2	n.a.							

n.a. = not applicable

* 1 = type 2 diabetic subjects, 2 = nondiabetic subjects

† Type of type 2 diabetes mellitus (T2DM)-diagnosis for type 2 diabetic subjects: 1 = interview question; 2 = interview question with diabetes confirmation by doctor; 3 = diabetes medication; 4 = doctor diagnosis; 5 = fasting glucose ≥ 7.0 mmol/l; 6 = oral glucose tolerance test with 2-hour glucose ≥ 11.1 mmol/l (WHO-OGTT); 7 = WHO-OGTT in some participants to confirm diagnosis; 8 = random glucose ≥ 11.1 mmol/l; 9 = HbA1c ≥ 6.2%; 10 = exclusion of subjects with type 1 diabetes

Type of "No T2DM"-diagnosis for nondiabetic subjects: 1 = interview question; 2 = no diabetes medication; 3 = doctor diagnosis; 4 = fasting glucose < 7.0 mmol/l; 5 = fasting glucose < 6.1 mmol/l; 6 = oral glucose tolerance test (OGTT) with 2-hour glucose < 11.1 mmol/l; 7 = OGTT with 2-hour glucose < 7.8 mmol/l; 8 = random glucose < 11.1 mmol/l; 9 = HbA1c < 6.2%

‡ Number of individuals included in analyses for association between *IL6* -174G>C and BMI

§ P value of exact test for Hardy-Weinberg equilibrium (HWE), using 10,000 Monte Carlo permutations. In the four family-studies FUSION 2, KORA-MIFAM, KORA-T2DMFAM, and RMIFAM, HWE was calculated, including only one randomly drawn type 2 diabetic, or nondiabetic subject, respectively, per family.

Table A6 – Online Appendix. Sensitivity Analyses, Excluding Published Studies*

Outcome	Egger's Test†	Excluded Studies	Individual N	Individual B-Estimates [95% CI]	Summary N‡	Summary B-Estimate [95% CI]‡
Full Data Analyses: C-Allele Dominant Model						
Fasting Glucose [mmol/L]§	0.12	DANISH	5536	-0.08 [-0.20, 0.03]	3904	-0.09 [-0.19, -0.002]
2-h Glucose [mmol/L]§	0.23	n.a.	n.a.	n.a.	7398	-0.08 [-0.20, 0.05]
BMI‖	0.06	CAPPP	466	1.03 [0.26, 1.81]	13413	0.01 [-0.14, 0.16]
		DANISH	5611	0.04 [-0.22, 0.29]		
		KORA-S4	1415	0.13 [-0.35, 0.60]		
		NPHS II	2652	0.22 [-0.06, 0.50]		
		UDACS	560	0.86 [-0.05, 1.77]		
Analysis in Type 2 Diabetic Subjects: CC- versus GG-Genotype						
Ln IL-6 [pg/ml]§	0.62	KORA-S4	222	0.15 [-0.20, 0.51]	744	0.14 [-0.02, 0.30]

n.a.=not applicable (because all studies were unpublished)

* Published for the respective outcome as a main result at the time of study recruitment

† P-value of Egger's regression test for publication bias including all studies of main analysis

‡ Of unpublished studies

§ Adjusted for age, sex, and BMI

‖ Adjusted for age, sex, and T2DM

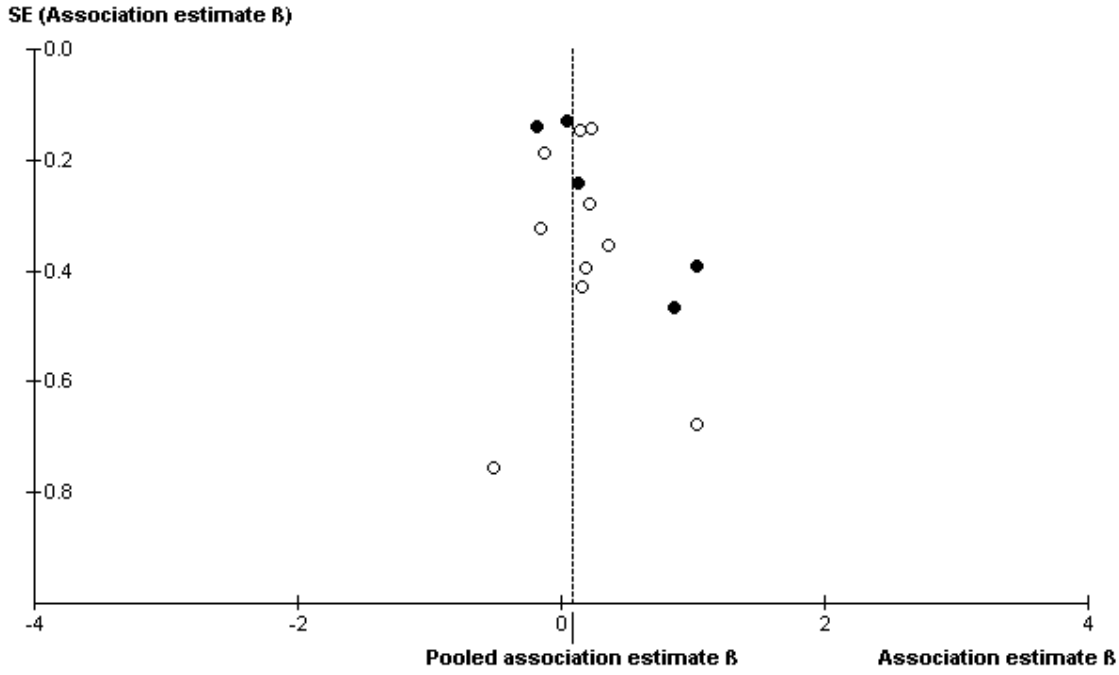
Table A7 – Online Appendix. Full Data Sensitivity Analyses, Additionally Including Studies showing HWE Violation in Nondiabetic Subjects (C-Allele Dominant Model)

Outcome	Additionally Included Studies	Individual N	Individual B-Estimates (95% CI)	Summary N	Summary B-Estimate (95% CI)
Fasting Glucose [mmol/L]*	BOTNIA	1285	0.01 [-0.38, 0.39]	10725	-0.09 [-0.16, -0.02]
2-h Glucose [mmol/L]*	BOTNIA	1001	0.44 [-0.37, 1.25]	8399	-0.06 [-0.19, 0.06]
BMI†	BOTNIA	1288	-0.02 [-0.58, 0.55]	25635	0.08 [-0.03, 0.19]
	TGN	230	-0.27 [-1.52, 0.99]		

* Adjusted for age, sex, and BMI

† Adjusted for age, sex, and T2DM

Figure A1 – Online Appendix



Funnel plot for the association between *IL6* -174G>C and BMI. For each study, the ß-coefficient of the dominant model for the C-allele, adjusted for age, sex and type 2 diabetes status, is plotted against its standard error as a measure of study precision. All studies with *IL6* -174G>C genotypes of nondiabetic individuals in HWE are included. Black circles represent for BMI published studies, white circles represent for BMI unpublished studies. The vertical line marks the pooled ß-coefficient (0.09).

References

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