Brief Genetics Report

IL6 Gene Promoter Polymorphisms and Type 2 Diabetes

Joint Analysis of Individual Participants' Data From 21 Studies

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Several lines of evidence indicate a causal role of the cytokine interleukin (IL)-6 in the development of type 2 diabetes in humans. Two common polymorphisms in the promoter of the IL-6 encoding gene *IL6*, −174G>C (rs1800795) and −573G>C (rs1800796), have been investigated for association with type 2 diabetes in numerous studies but with results that have been largely equivocal. To clarify the relationship between the two *IL6* variants and type 2 diabetes, we analyzed individual data on >20,000 participants from 21 published and unpublished studies. Collected data represent eight different countries, making this the largest association analysis for type 2 diabetes reported to date. The GC and CC genotypes of *IL6* −174G>C were associated with a decreased risk of type 2 diabetes (odds ratio 0.91, $P = 0.037$), corresponding to a risk modification of nearly 9%. No evidence for association was found between *IL6* −573G>C and type 2 diabetes. The observed association of the *IL6* −174 C-allele with a reduced risk of type 2 diabetes provides further evidence for the hypothesis that immune mediators are causally related to type 2 diabetes; however, because the association is borderline significant, additional data are still needed to confirm this finding. *Diabetes* 55:2915–2921, 2006

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FHS, Framingham Heart Study; HWE, Hardy-Weinberg equilibrium; IL, interleukin; IPD, individual participants' data.

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Recent studies have investigated the role of variants within genes encoding immune-related markers in mediating increased type 2 diabetes risk. One of the most widely studied immune genes is the interleukin (IL)-6 encoding gene *IL6*, which maps to chromosome 7p21. IL-6 exerts crucial effects not only in inflammation and infection but also within the nervous and endocrine systems (1). A vast number of epidemiological, genetic, rodent, and human in vivo and in vitro studies have investigated the putative role of IL-6 in the pathogenesis underlying type 2 diabetes. The impact of IL-6 on hepatocytes, skeletal muscle cells, β-cells, and the central nervous system has been described, and both protective and pathogenic activity of IL-6 in type 2 diabetes was suggested (2,3). Functional relevance has been ascribed to several *IL6* variants located in the promoter region, including −174G>C (rs1800795) and −573G>C (rs1800796, previously denoted as −572G>C), with in

vitro data demonstrating unequivocally that the *IL6* −174G>C sequence affects promoter strength (4,5). The relation between −174G>C and circulating IL-6 is not completely consistent in the literature. Whereas several studies indicate that −174G>C is associated with plasma levels of IL-6, particularly in inflammatory situations (6,7), no association between −174G>C and IL-6 was found within 718 nondiabetic women of the Nurses' Health Study (8).

Association between −174G>C and type 2 diabetes was first reported in U.S. Pima Indians and Spanish Caucasians (9), the C-allele being statistically significantly associated with a decreased risk of type 2 diabetes. One study subsequently replicated these initial findings (10), although most did not (11–14). The only major study on −573G>C was performed in Danish Caucasians and showed a significantly increased risk of type 2 diabetes by the C-allele, but the −573G>C control genotypes were not in Hardy-Weinberg equilibrium (HWE) (14). Because of the ambiguity in interpreting the role of *IL6* polymorphisms in type 2 diabetes susceptibility based on these disparate reports, we assembled an international *IL6*–type 2 diabetes consortium in order to perform a joint analysis.

The consortium utilized individual participants' data (IPD) and recruited all published and unpublished data on the association of the *IL6* −174G>C or −573G>C polymorphisms and type 2 diabetes. This approach overcomes many of the problems associated with meta-analyses of published estimates such as variability in study design, poor data quality, insufficient or heterogeneous confounder adjustment, and publication bias (15). As of late 2005, investigators from the U.S., Greece, Spain, Germany, U.K., Denmark, Sweden, and Finland participated in the consortium and contributed raw data on >30,000, mostly Caucasian, subjects. As such, this study is one of the largest genetic epidemiologic association studies on IPD ever conducted. The aim of this joint analysis is to provide conclusive evidence whether the two *IL6* variants, −174G>C and −573G>C, are associated with risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS

All available published and unpublished studies fulfilling the following criteria were included in this joint analysis: *1*) association study conducted in humans, *2*) polymorphic genotype data for *IL6* −174G>C or −573G>C, *3*) type 2 diabetic case and nondiabetic control subjects, *4*) published before September 2005 or unpublished, and *5*) availability of IPD. Studies were excluded if the control group consisted only of individuals with pre-diabetes (16) or if ethnic admixture of unrelated study subjects was reported in the original publication (Pima Indian case-control study, 9). Information on search strategy, study recruitment, data collection and cleaning, and genotyping methods is provided in the online appendix (available at http://diabetes.diabetesjournals.org).

Definition of analyzed samples. Included datasets were analyzed as discordant-sib or case-control comparisons. Participants of case-control comparisons were not related to each other or to participants of other included studies. Datasets were edited to ensure that case subjects with type 2 diabetes and control subjects had the same sex and age range. Control subjects consisted of nondiabetic subjects, excluding individuals with pre-diabetes (impaired fasting glucose or impaired glucose tolerance [17]) when glucose values were available (see study-specific details in online appendix Table A2).

Statistical analyses. Statistical analyses were performed using SAS software version 9.1 (Cary, NC). Allele and genotype frequencies were estimated, allowing for the correlation in family data (sibships) by use of an exchangeable structure in a generalized estimating equations approach (SAS Proc Genmod). Linkage disequilibrium was assessed by the squared correlation coefficient r^2, and HWE was tested separately for case and control subjects per study (SAS Proc Allele).

Study-specific odds ratios (ORs) with SEs for association between *IL6* variants and type 2 diabetes were estimated from the IPD by logistic regression for case-control comparisons (SAS Proc Logistic) and by conditional logistic regression for discordant-sib comparisons (SAS Proc Phreg). The correlation due to linkage between disease status and investigated variants among sibs sharing the same marker alleles was accounted for by a jackknife variance estimate (18). All analyses were adjusted for age, sex, and BMI. Effect modification by BMI (quantitative and dichotomized at 28 kg/m^2) and sex was tested.

As the CC genotype of *IL6* −573G>C was rare (<1.5% in all studies), C-allele carriers (CC and GC genotypes) were compared with GG subjects. For −174G>C, ORs comparing either CC or GC with the wild-type GG were calculated, according to which the appropriate genetic model was chosen for the main analysis. Between-study heterogeneity was tested by the χ^2-based Q-statistic, and its impact was quantified by I^2 (19).

For the summary OR, study-specific ORs were combined by using the inverse-variance fixed-effect and the DerSimonian and Laird random-effects models. As the heterogeneity between study-specific ORs was low in all main analyses, the two models provided identical or very similar results. Thus, only the fixed-effect results are reported. The summary ORs of all studies where the control group was in HWE are reported as main results.

Publication bias was investigated by visual inspection of funnel plots and formally tested using Egger's regression method (20). Funnel and forest plots were prepared using Review Manager software version 4.2 (Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

For the *IL6* −174G>C polymorphism, 10 published studies met the inclusion criteria. All of these studies, with the exception of the Framingham Heart Study (FHS) (21), provided IPD and were included in the joint analysis. Additionally, 12 unpublished studies were available for −174G>C and included in our analyses. For −573G>C, only one published study was available. However, data from eight unpublished studies met our inclusion criteria and were additionally used in our analyses. Data from 30,636 (−174G>C) and 21,352 (−573G>C) individuals were initially compiled in the central database; 22,626 and 17,305 subjects met the requirements for the analyzed samples, respectively. Except for one discordant-sib study on admixed Pima Indians, all studies consisted of Caucasian subjects.

Study-specific descriptive statistics. Characteristics of included studies and participants are summarized in Table 1 and online appendix Table A2, respectively. Details on study design and conduct are presented in online appendix Table A3. The estimated r^2 coefficients between the two single nucleotide polymorphisms in control subjects ranged from 0.027 (KORA-T2DMFAM_CC study) to 0.048 (MONICA-S3_CC study). Control genotype frequencies of all studies were in HWE, except for the RMIFAM_DS and TGN_CC studies for *IL6* −174G>C and the Danish_CC study for *IL6* −573G>C (online appendix Table A2).

***IL6* −174G>C polymorphism and risk of type 2 diabetes.** Figure 1*A* shows the ORs and 95% CIs for 18 individual studies for the association between *IL6* −174 C-allele dominant and type 2 diabetes, adjusted for age, sex, and BMI. The pooled OR for 4,746 case and 16,230 control subjects was 0.91 ($P = 0.037$); I^2, the impact of heterogeneity, was 0% (95% CI 0–50). The dominant genetic model appeared most consistent with the data, the pooled model-free OR_{GCvsGG} and OR_{CCvsGG} being 0.92 (0.83–1.01) and 0.90 (0.80–1.01), respectively, and was thus chosen for the main analysis. Visual inspection of the funnel plot of all 18 studies showed that studies with high, as well as low, precision of the OR estimate were distributed symmetrically around the pooled OR (online appendix Figure A1). Thus, no publication bias is suggested, which was further supported by the nonsignificant Egger's regression test ($P = 0.71$).

TABLE 1
Characteristics of included studies

Study name	Contributing studies*	Country	Case/control subjects†	Data on −573G>C‡	Published§	Reference‖
BOTNIA_CC	Botnia Study	Finland	760/539	Yes	3a,b	NA
CAPPP_CC	Captopril Prevention Project	Sweden	45/414	Yes	2a,b	25
DANISH_CC	Danish Study	Denmark	1,094/4,507	Yes	1a,b	14
EDSC_CC	Case: Ealing Diabetes Study of Coagulation; Control: Second Northwick Park Heart Study	U.K.	85/1,326	No	Case: 3a; Control: 1a	Case: NA; Control: 10
EPIC-POTSDAM_CC	European Prospective Investigation into Cancer and Nutrition Potsdam	Germany	175/349	No	1a	12
FUSION_CC	The Finland-United States Investigation of NIDDM Genetics	Finland	506/353	No	3a	NA
FUSION_DS	The Finland-United States Investigation of NIDDM Genetics	Finland	227/132	No	3a	NA
GIRONA_CC	Girona Genetics of Diabetes Study	Spain	43/67	No	1a	9
GREEK_CC	Greek Study	Greece	30/37	No	1a	13
KORA-MIFAM_CC	KORA Myocardial Infarction Family Study	Germany	66/417	No	2a	26
KORA-MIFAM_DS	KORA Myocardial Infarction Family Study	Germany	27/39	No	2a	26
KORA-S4_CC	KORA Survey S4	Germany	230/460	Yes	1a, 3b	11
KORA-T2DMFAM_CC	Case: KORA Type 2 Diabetes Family Study; Control: additionally from KORA Survey S4	Germany	335/421	Yes	3a,b	NA
KORA-T2DMFAM_DS	KORA Type 2 Diabetes Family Study	Germany	344/358	Yes	3a,b	NA
MONICA/KORA-COHORT_CC	MONICA/KORA Case Cohort Study S123	Germany	488/1,585	Yes	3a,b	NA
MONICA-S3_CC	MONICA/KORA Survey S3	Germany	156/3,186	Yes	2a, 3b	26
PIMA_DS	Type 2 Diabetes Susceptibility in Pima Indians Study	U.S.	62/79	No	1a	9
RMIFAM_CC	Regensburg Myocardial Infarction Family Study	Germany	280/983	No	2a	26
RMIFAM_DS	Regensburg Myocardial Infarction Family Study	Germany	412/538	No	2a	26
TGN_CC	Tarraco Study	Spain	156/53	No	1a	9
UDACS_CC	Case: University College Diabetes and Cardiovascular Study; Control: Second Northwick Park Heart Study	U.K.	133/1,326	Yes	1a, 3b	10

IL6 −573G>C was not genotyped in the Ealing Diabetes Study of Coagulation. Thus, for the −573G>C analysis, the complete Second Northwick Park Heart Study (n = 2,652) was used as the control group for UDACS _CC. *For description of contributing studies see online appendix Table A2. †Number of type 2 diabetic case/nondiabetic control subjects included in age- and sex-adjusted analyses for *IL6* −174G>C and/or *IL6* −573G>C. ‡Yes = data on *IL6* −174G>C and −573G>C are available; no = only data on *IL6* −174G>C are available. §Detailed publication of 1a = *IL6* −174G>C, 1b = *IL6* −573G>C and type 2 diabetes; association between 2a = *IL6* −174G>C, 2b = *IL6* −573G>C and type 2 diabetes mentioned in publication with primary outcome other than type 2 diabetes, considered as "unpublished" (mostly, only part of the study participants have been mentioned); unpublished results for 3a = *IL6* −174G>C, 3b = *IL6* −573G>C and type 2 diabetes. ‖References of studies, for which the relationship between the *IL6* −174G>C or the *IL6* −573G>C and type 2 diabetes has been published in detail or mentioned in a publication with primary outcomes other than type 2 diabetes. NA, not applicable.

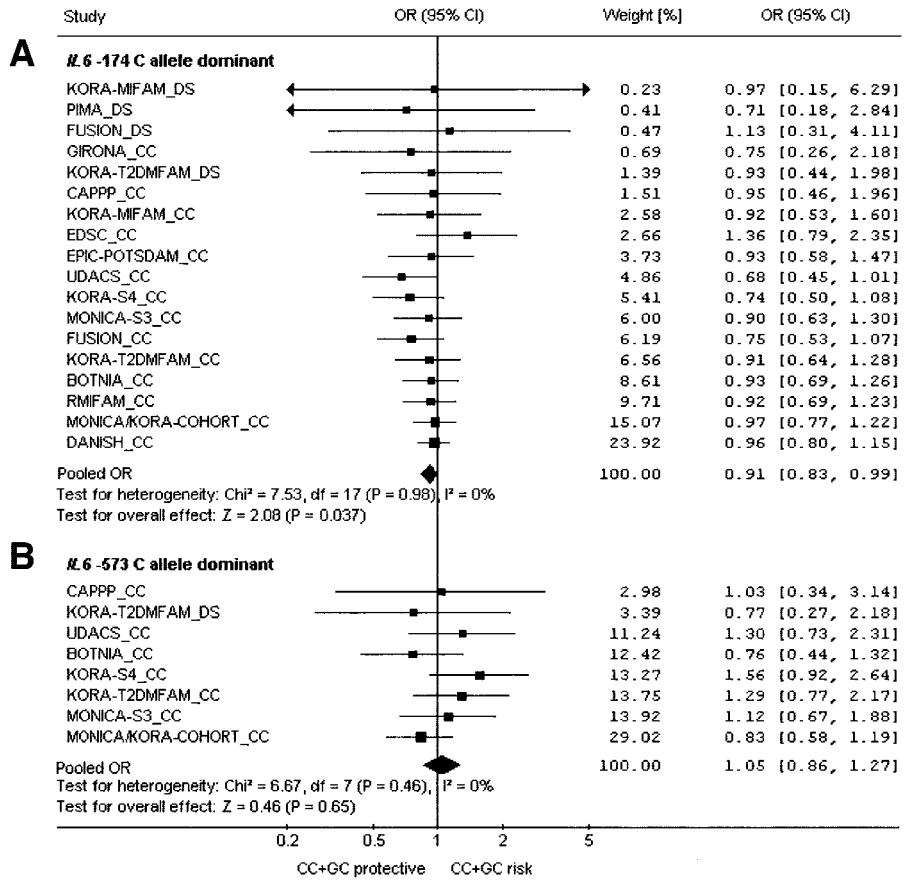

FIG. 1. Forest plot, illustrating the study-specific ORs and 95% CIs for the association between *IL6* −174G>C (*A*) and *IL6* −573G>C (*B*) and type 2 diabetes, dominant model for the C-allele, adjusted for age, sex, and BMI. Additionally, the pooled fixed-effect OR is shown. All studies where the genotypes of control subjects are in HWE, and where the covariates age, sex, and BMI are available, are included. The addenda behind the abbreviated study names denote case-control (CC) and discordant-sib (DS) studies. The studies are sorted according to the weight with which they contribute to the pooled OR estimate. I^2 measures the impact of inconsistency across studies and can range between 0 and 100%.

Two studies were not included in the main analysis due to HWE violation in the control groups and one (GREEK_CC study) because BMI adjustment was not possible. Their study-specific ORs were 1.9 (95% CI 1.2–3.0) for the RMIFAM_DS study, 0.6 (0.3–1.3) for the TGN_CC study (adjusted for age, sex, and BMI), and 2.2

TABLE 2
Pooled ORs of association between *IL6* variants and type 2 diabetes

Analysis type	Studies	Case/control subjects	OR (95% CI)*	*P* for heterogeneity	I^2 (%)
IL6 −174 C-allele dominant					
Main analysis†	18	4,746/16,230	0.91 (0.83–0.99)	0.98	0.0
Influence of studies that are not included in main analysis and of BMI adjustment					
All studies recruited for this joint analysis	21	5,606/17,020	0.94 (0.87–1.02)‡	0.31	11.7
Studies in HWE§	19	5,038/16,429	0.92 (0.85–1.00)‡	0.88	0.0
HWE, BMI available (main analysis but not adjusted for BMI)‖	18	5,008/16,392	0.92 (0.85–1.00)‡	0.93	0.0
IL6 −573 C-allele dominant					
Main analysis†	8	2,392/9,265	1.05 (0.86–1.27)	0.46	0.0
Influence of DANISH_CC study (not included in main analysis), and of BMI adjustment					
All studies recruited for this joint analysis	9	3,509/13,796	1.14 (0.99–1.32)‡	0.07	44.8
Studies in HWE (main analysis but not adjusted for BMI)¶	8	2,458/9,414	1.02 (0.86–1.22)‡	0.19	30.0

I^2 is the measure of heterogeneity and can range between 0 and 100%. *Fixed-effect OR estimate with 95% CI, adjusted for age, sex, and BMI. †All studies with control subjects in HWE, adjusted for age, sex, and BMI. ‡Adjusted for age and sex. §The RMIFAM_DS and the TGN_CC studies are excluded, as the genotypes of the control subjects of these studies are not in HWE for *IL6* −174G>C. ‖GREEK_CC study is excluded, as this study does not have data on BMI for control subjects. ¶DANISH_CC study is excluded, as genotypes of control subjects of this study are not in HWE for *IL6* −573G>C.

(0.7–7.1) for the GREEK_CC study (adjusted for age and sex). Sensitivity analyses, including these studies or showing the impact of BMI adjustment, are presented in Table 2. Further sensitivity analyses are presented in online appendix Table A4; no major difference was found between case-control/discordant-sib studies, between studies which originally were designed/not designed as type 2 diabetes studies, between studies which used/did not use an oral glucose tolerance test to exclude subjects with impaired glucose tolerance from the control subjects, between studies enriched/not enriched for myocardial infarction patients, and between published/unpublished studies, respectively. Analyzing men and women separately also did not appreciably affect the size of the pooled OR. Likewise, there was no major change when excluding each study at a turn, with the pooled ORs ranging between 0.89 (0.81–0.99) and 0.92 (0.84–1.01) (online appendix Figure A2 A). There was no evidence that BMI ($P > 0.4$, no evidence for heterogeneity between studies) or sex ($P = 0.93$, no heterogeneity) significantly modified the relationship between *IL6* −174G>C and type 2 diabetes.

IL6 −573G>C polymorphism and risk of type 2 diabetes. Figure 1*B* shows the ORs and 95% CIs for eight individual studies for the association between *IL6* −573 C-allele dominant and type 2 diabetes, adjusted for age, sex, and BMI. The pooled OR for 2,392 case and 9,265 control subjects was 1.05 ($P = 0.65$); I^2 was estimated as 0% (95% CI 0–68). The DANISH_CC study (OR 1.7 [95% CI 1.3–2.2]) was not included in this main analysis because control genotypes for −573G>C were not in HWE. Sensitivity analyses, presented in Table 2, show that heterogeneity between studies was substantially reduced by eliminating the DANISH_CC study and by adjusting for BMI (reduction from $I^2 = 44.8\%$ [$P = 0.07$] to $I^2 = 0.0\%$ [$P = 0.46$]). Further sensitivity analyses for subgroups of studies and stratification for sex show no remarkable change in the pooled result (online appendix Table A5). Removing each study at a turn yielded pooled ORs ranging between 0.98 and 1.15 with 95% CIs that always included unity, indicating that the pooled OR was not unduly influenced by any single study (online appendix Figure A2 B). There was no effect modification of BMI ($P > 0.6$) or sex ($P = 0.28$) on the relationship between −573G>C and type 2 diabetes.

DISCUSSION

The results presented here, based on IPD from 5,601 type 2 diabetic case and 17,019 control subjects and representing 21 association studies, provide evidence that the *IL6* −174G>C polymorphism is associated with type 2 diabetes and that individuals carrying the C-allele have a 9% lower odds of suffering from type 2 diabetes compared with individuals with the GG genotype ($P = 0.037$). We did not find a statistically significant relationship between *IL6* −573G>C and type 2 diabetes. It is plausible that the shown association of −174G>C with type 2 diabetes reflects a true modulating effect of −174G>C or another variant in linkage disequilibrium with −174G>C. The closest known gene (*TOMM7*) is situated about 100 kb from *IL6* and is located within a different linkage disequilibrium block (http://www.hapmap.org).

Putative impact of unincluded studies. Except for the FHS with data on *IL6* −174G>C (21), all studies investigating the relationship between −174G>C or −573G>C and type 2 diabetes published before September 2005 and fulfilling the inclusion criteria were incorporated in this joint analysis. With only 64 type 2 diabetic cases, the FHS corresponds to a weight of ~2% in this joint analysis. Thus, inclusion of the FHS would have had no major impact on the pooled OR.

Since the deadline for inclusion of newly published studies has elapsed until today (June 2006), only two large studies (>500 participants) fulfilling the inclusion criteria for our joint analysis have been published (8). Their study-specific ORs for association between *IL6* −174 C-allele dominant and type 2 diabetes, adjusted for age and BMI, were 0.95 (95% CI 0.82–1.10) for the Nurses' Health Study (1,315 female case and 2,265 female control subjects) and 0.95 (0.77–1.17) for the Health Professional Follow-up Study (885 male case and 894 male control subjects) (Dr. Lu Qi, personal communication). The pooled OR for the joint analysis, including these studies, was 0.92 (0.86–0.99) and had a slightly lower *P* value of 0.030 than our main analysis.

Analysis strategy. As recommended by Thakkinstian et al. (22), studies with HWE violation in the control group were excluded from the main analyses. This reduced heterogeneity between study-specific ORs for both *IL6* variants. Strikingly, two of the three studies with HWE violation showed ORs that were not compatible with the results of this joint analysis, as their 95% CIs and the 95% CIs of the pooled ORs did not overlap. Koushik et al. (23) investigated the reasons for heterogeneity in the published ORs on the association between the p53 codon 72 polymorphism and cervical neoplasia; the most important factor that contributed to heterogeneity was whether the genotype frequencies of the control groups were in HWE. Several reasons may account for HWE violation, including genotyping error, ethnic admixture in the control group, or chance. The decision to adjust the main analyses not only for age and sex but also for BMI arose from the fact that heterogeneity was remarkably reduced for *IL6* −573G>C.

Strengths and limitations of this joint analysis. This study represents the first joint analysis of IPD designed to address the role of *IL6* variants in type 2 diabetes susceptibility. Using a consortium-based strategy, this analysis was strengthened by the high compliance of investigators to contribute their published and unpublished data. To our knowledge, the present work is the largest IPD study that has been conducted to date to address the role of candidate gene variants in type 2 diabetes susceptibility.

Joint analyses based on IPD have several advantages compared with meta-analyses that are based on published estimates or summary data (15). Here, standardized methods were applied, incoming data were checked and cleaned, genotypes were tested for HWE violation, putative confounders for type 2 diabetes were uniformly adjusted for, stratified and interaction analyses were performed, and a consistent genetic model was applied. The observed low heterogeneity among studies may have resulted from these standardized procedures.

The greatest limitation of any meta-analysis is the risk of publication bias. To avoid this bias, we have strived to include all existing data involving the *IL6* −174G>C and −573G>C variants and type 2 diabetes susceptibility and managed to include predominantly unpublished data. Nevertheless, we conducted analyses to assess the effect of publication bias on our results for −174G>C. Utilizing the funnel plot and Egger's regression test, there was no evidence for publication bias, suggesting that our study sample is comprised of a representative dataset.

Although this study including >20,000 subjects is among the largest genetic association studies performed to date on IPD, the observed inverse association of the *IL6* −174 C-allele with type 2 diabetes, showing a *P* value of 0.037, is borderline significant. Bonferroni correction for the two analyzed single nucleotide polymorphisms would turn the result to statistical nonsignificance. However, the ORs of the recently published Nurses' Health Study and Health Professional Follow-up Study point in the same direction as our joint analysis, thus adding strength to the reported association of −174G>C with type 2 diabetes. The weak OR of 0.91 is plausible, as type 2 diabetes is a complex disease whose etiology is dependent upon multiple genetic and environmental factors and consistent with estimates obtained in other genes that affect susceptibility to type 2 diabetes (24).

In conclusion, this joint analysis is the largest association study on the genetics of type 2 diabetes published to date. We have assessed the role of two widely studied polymorphisms in the *IL6* gene, using IPD from published and unpublished studies, and did not find evidence for an association between *IL6* −573G>C and type 2 diabetes. In contrast, we determined that the GC and CC genotypes of *IL6* −174G>C show an OR of 0.91 for association with type 2 diabetes, which corresponds to a risk reduction of nearly 9%. However, because the association between the *IL6* −174G>C polymorphism and type 2 diabetes is borderline significant, a secondary analysis including additional data is critical. Thus, the present work represents a crucial first step toward elucidating the extent to which the *IL6* −174G>C plays a role in type 2 diabetes susceptibility and provides additional evidence supporting a direct relationship between chronic subclinical inflammation and type 2 diabetes etiology.

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Online Appendix to:

IL6 Promoter Polymorphisms and Type 2 Diabetes Mellitus: Joint Analysis of Individual Participants' Data from 21 Studies

Research Design and Methods

Search Strategy, Study Recruitment, and Data Collection

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.

All participating studies have been conducted according to the principles expressed in the Declaration of Helsinki. Individual studies had either written informed consent for all participants for genetic analyses or approval from their institutional review board for genetic analyses.

Data were collected on the *IL6* variants -174G>C or -573G>C, T2DM status, age and sex (required). Body mass index (BMI), ethnicity, familial relationships, and plasma glucose values were gathered where available.

Data Cleaning and Genotyping Methods

The study center at GSF 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.

A questionnaire was sent to all principal investigators to collect data on genotyping methods and quality. This information is summarized in table A1. As both variants are G/C-polymorphisms 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.

Table A1 – online appendix

Methods used for genotyping the *IL6* promoter polymorphisms -174G>C and -573G>C

Study Name	Genotyping Method	Call Rate[a] -174 [%]	Call Rate[a] -573 [%]
Botnia Study	Allelic discrimination assay-by-design method on ABI 7900 (Applied Biosystems)	100	100
Captopril Prevention Project	Dynamic allele specific hybridization (DASH)	100	98
Danish Study	Chip-based MALDI-TOF MS (MassArray, Sequenom)	96	95
Ealing Diabetes Study of Coagulation	Nla III RFLP, MADGE	97	n.a.[b]
European Prospective Investigation into Cancer and Nutrition Potsdam	SNuPE, MegaBACE 1000	100	n.a.
The Finland-United States Investigation of NIDDM Genetics	Illumina GoldenGate	98	n.a.
Girona Genetics of Diabetes Study	SfaNI RFLP	99	n.a.
Greek Study	PCR with sequence specific primers, cytokine genotyping kit (One Lambda, USA.)	99	n.a.
KORA MI[c] Family Study	Hsp92II RFLP, PAGE	97	n.a.
KORA Survey S4	Chip-based MALDI-TOF MS (MassArray, Sequenom)	97	97
KORA T2DM Family Study	Chip-based MALDI-TOF MS (MassArray, Sequenom)	98	97
MONICA/KORA Case Cohort Study S123	Chip-based MALDI-TOF MS (MassArray, Sequenom)	99	99
MONICA/KORA Survey S3	Chip-based MALDI-TOF MS (MassArray, Sequenom)	99	99
Regensburg MI Family Study	Hsp92II RFLP, PAGE	97	n.a.
Second Northwick Park Heart Study	PCR by MADGE, NIaIII RFLP (*IL6* -174G>C), MblI RFLP (*IL6* -573G>C)	99	98
Tarraco Study	SfaNI RFLP	99	n.a.
T2DM Susceptibility in Pima Indians Study	Pyrosequencing	97	n.a.
University College Diabetes and Cardiovascular Study	PCR by MADGE, NIaIII RFLP (*IL6* -174), MblI RFLP (*IL6* -573G>C)	99	98

[a] Successfully genotyped individuals in percent of all subjects intended for genotyping

[b] Not applicable

[c] Myocardial infarction

Table A2 – online appendix

Characteristics of included study participants

Study Name[a]	Status[b]	Diagnosis[c]	No.[d]	% Male	Mean ± Standard Error		*IL6* -174G>C			*IL6* -573G>C		
					Age [years]	BMI [kg/m²]	% GC	% CC	P HWE[e]	% GC	% CC	P HWE[e]
BOTNIA_CC	1	4, 10	760	53	60 ± 10	29 ± 5	52	25	0.18	5	0.1	0.41
	2	2, 3, 5, 7	539	48	53 ± 12	26 ± 4	54	25	0.08	6	0.4	0.13
CAPPP_CC	1	5, 7, 10	45	80	58 ± 5	30 ± 4	47	24	0.76	9	0.0	1.00
	2	4	414	71	58 ± 6	27 ± 4	46	24	0.12	9	0.7	0.10
DANISH_CC	1	3, 4, 5, 6, 10	1094	63	52 ± 8	30 ± 6	46	24	0.02	10	0.4	0.54
	2	5, 7	4507	46	45 ± 8	26 ± 4	48	23	0.06	7	0.5	0.0001
EDSC_CC	1	3, 4, 10	85	100	55 ± 6	30 ± 6	58	19	0.20	.	.	.
	2	1	1326	100	56 ± 3	26 ± 3	50	18	0.34	.	.	.
EPIC-POTSDAM _CC	1	4	175	58	55 ± 7	31 ± 5	55	17	0.12	.	.	.
	2	1, 2	349	58	55 ± 7	27 ± 4	55	18	0.053	.	.	.
FUSION_CC	1	3, 4, 5, 6, 10	506	54	63 ± 7	30 ± 5	47	30	0.18	.	.	.
	2	2, 3, 5, 7	353	41	66 ± 6	27 ± 4	50	30	0.92	.	.	.
FUSION_DS	1	3, 4, 5, 6, 10	227	58	64 ± 9	30 ± 5	50	24	0.79	.	.	.
	2	2, 3, 5, 7	132	35	58 ± 9	27 ± 4	49	28	0.86	.	.	.
GIRONA_CC	1	5, 6, 10	43	77	53 ± 10	31 ± 5	51	9	0.52	.	.	.
	2	5, 7	67	84	47 ± 9	26 ± 3	48	27	0.81	.	.	.
GREEK_CC	1	3, 4, 10	30	23	57 ± 8	28 ± 4	33	10	0.38	.	.	.
	2	1, 2, 3	37	62	52 ± 9	n.a.[f]	27	8	0.32	.	.	.
KORA-MIFAM_CC	1	1, 3, 8	66	88	58 ± 6	30 ± 5	50	12	0.79	.	.	.
	2	1, 2, 8	417	73	58 ± 6	28 ± 4	47	18	0.61	.	.	.
KORA-MIFAM_DS	1	1, 3, 8	27	78	59 ± 6	30 ± 4	51	18	1.00	.	.	.
	2	1, 2, 8	39	46	61 ± 6	28 ± 4	58	11	0.31	.	.	.
KORA-S4_CC	1	2, 3, 5, 6, 10	230	59	65 ± 5	31 ± 5	54	15	0.13	13	0.0	0.60
	2	1, 2, 5, 7	460	47	63 ± 5	28 ± 4	53	20	0.19	9	0.7	0.11
KORA-T2DMFAM_CC	1	2, 3, 5, 6, 10	335	60	61 ± 8	31 ± 5	50	17	0.82	13	0.3	1.00
	2	1, 2, 5, 7	421	48	64 ± 6	28 ± 4	52	16	0.19	9	0.2	0.61
KORA-T2DMFAM_DS	1	2, 3, 5, 6, 10	344	59	60 ± 10	31 ± 5	53	16	0.08	9	0.0	1.00
	2	1, 2, 5, 7	358	40	58 ± 10	27 ± 4	53	16	0.10	11	0.3	1.00
MONICA/KORA-COHORT_CC	1	2, 10	488	62	64 ± 9	30 ± 4	48	18	0.78	10	0.2	1.00
	2	1	1585	53	63 ± 10	27 ± 4	50	16	0.37	12	0.3	0.83
MONICA-S3_CC	1	2, 3, 8, 10	156	58	63 ± 8	30 ± 5	45	22	0.33	11	1.3	0.14
	2	1, 2, 8	3186	51	50 ± 13	27 ± 4	50	19	0.24	11	0.3	1.00
PIMA_DS	1	5, 6, 11	62	35	35 ± 12	38 ± 9	7	0	1.00	.	.	.
	2	3, 4, 6	79	44	34 ± 13	35 ± 10	9	0	1.00	.	.	.
RMIFAM_CC	1	1, 9	280	64	64 ± 9	28 ± 4	50	15	0.54	.	.	.
	2	1, 9	983	61	62 ± 9	27 ± 4	47	20	0.13	.	.	.
RMIFAM_DS	1	1, 9	412	69	60 ± 7	28 ± 4	52	17	0.19	.	.	.
	2	1, 9	538	61	61 ± 8	27 ± 3	43	18	0.02[g]	.	.	.
TGN_CC	1	1, 4	156	37	59 ± 9	29 ± 5	49	9	0.22	.	.	.
	2	1, 3, 5, 7	53	43	50 ± 12	30 ± 4	62	8	0.04	.	.	.
UDACS_CC	1	4, 10	133	100	57 ± 5	31 ± 5	48	12	0.85	12	0.8	0.45
	2	1	1326[h]	100	56 ± 3	26 ± 3	49	19	1.00	9[h]	0.2[h]	1.00[h]

[a] Study name, used in this publication.; _CC = case-control study, _DS = discordant-sib study

[b] Case-control status within this study: 1 = Type 2 diabetes mellitus (T2DM) cases, 2 = non-diabetic controls

[c] Type of T2DM-diagnosis for cases: 1 = interview question; 2 = interview question with diabetes confirmation by doctor; 3 = diabetes medication; 4 = doctor diagnosis; 5 = fasting plasma glucose ≥ 7.0 mmol/l; 6 = oral glucose tolerance test with 2-hour plasma glucose ≥ 11.1 mmol/l (WHO-OGTT); 7 = WHO-OGTT in some participants to confirm diagnosis; 8 = random plasma glucose ≥ 11.1 mmol/l; 9 = HbA1c ≥ 6.2%; 10 = exclusion of subjects with type 1 diabetes; 11 = type 1 diabetes is virtually non-existent in PIMA Indians

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

[d] Number of individuals included in age- and sex-adjusted analyses for *IL6* -174G>C and / or *IL6* -573G>C

[e] P-value of exact test for Hardy-Weinberg equilibrium (HWE), using 10,000 Monte Carlo permutations

[f] Not applicable

[g] The P-value remains 0.02 when including only one randomly drawn control per family

[h] *IL6* -573G>C was not genotyped in the Ealing Diabetes Study of Coagulation. Thus, for the -573G>C analysis, the complete Second Northwick Park Heart Study (n = 2652) was used as control group for UDACS_CC

Table A3 – online appendix

Short description of included studies

Study Name (official abbreviation)	Study Description [a]
Botnia Study	The Botnia Study began in 1990 as a family-based study aiming to identify genes increasing susceptibility to T2DM. Subjects with T2DM from the area of five health care centres 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 the two *IL6*-variants -174G>C and -573G>C. According to a priori defined criteria, one T2DM individual per family was selected. Controls comprise cases' spouses and unrelated controls, 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 the two *IL6*-variants -174G>C and -573G>C. This substudy comprises all patients that got myocardial infarction, plus two controls per case, matched with respect to gender, age and smoking. Further details: (1).
Danish Study	The DANISH case-control study of T2DM involves all 4,568 subjects with normal glucose tolerance (NGT) from the Inter99 cohort as controls and 1,389 unrelated T2DM patients recruited from the outpatient clinic at Steno Diabetes Center, Copenhagen and the Research Centre for Prevention and Health through the Inter99 study as cases. The Inter99 cohort is a population-based randomized non-pharmacological intervention study for prevention of cardiovascular disease done at the Research Centre for Prevention and Health involving 6,514 Caucasian subjects (6,164 with data from an oral glucose tolerance test). Further details: (2).
Ealing Diabetes Study of Coagulation (EDSC)	The subjects of the EDSC study were recruited consecutively from the Ealing Hospital diabetes clinic in London. 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. Patients with T2DM (n = 927) comprised primarily three ethnic groups, Indian Asians, n = 503, UK White, n = 331, Black Afro-Caribbean, n = 93. Further details: (3). As the NPHS II study of healthy male individuals serves as control group, only white male EDSC subjects were included in this joint analysis.
European Prospective Investigation into Cancer and Nutrition (EPIC) Potsdam	A nested case-control study was designed within the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort, which is part of the European multicenter, population-based EPIC-study including 27,548 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 is based on the first follow-up questionnaires sent to the study participants on average 2.3 years after baseline examination. Cases were free of T2DM at baseline and developed their incident T2DM during the follow-up. Further details: (4).

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: (5), on FUSION 2: (6). For the purpose of this joint analysis, the FUSION study was split in two parts. One T2DM individual from each FUSION 1 family was chosen as case for the FUSION_CC study. Controls for the FUSION_CC study include normoglycemic (NGT) spouses of FUSION T2DM individuals, and elderly controls that were all born in 1925 and were NGT by oral glucose tolerance tests (OGTTs) at both, ages 65 and 70. All FUSION 2 sibships discordant for T2DM were included in the FUSION_DS study.
Girona Genetics of Diabetes Study	The control subjects of the Girona Genetics of Diabetes Study were unrelated healthy Caucasian middle-aged subjects recruited from the general population. The T2DM patients were consecutively recruited subjects from the diabetes clinics at the Hospital of Girona, Spain. Further details: (7).
Greek Study	The diabetic subjects of the Greek study were recruited between the years 1998 and 2001, by screening the records of the diabetes clinic at “Evagelismos” hospital in Athens, and selecting individuals aged between 30 and 60 years with initial diagnosis different from type 1 diabetes mellitus. Since non-obese individuals at the age of 30 or older with good metabolic control on diet or oral hypoglycaemic therapy may initially be misclassified as T2DM patient, although they suffer from Latent Autoimmune Diabetes of Adults (LADA), the subjects were checked for the presence of serum antibodies against glutamic acid decarboxylase (GAD65), since these antibodies represent a specific marker for the presence of LADA diabetes. Finally, these patients were stratified into two groups: patients with latent autoimmune diabetes of adults (LADA) and patients with T2DM. Patients with negative GAD65 antibodies were used as T2DM cases in this joint analysis. Blood was collected for plasma and DNA analysis. Several other clinical and immunological parameters, such as BMI, C-peptide levels, cytokines intracellular and serum levels, were also measured. Healthy individuals without clinical and laboratory evidence and without family history of diabetes served as controls and were used in this joint analysis. Further details: (8).

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: (9-11). 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. These included higher priorities for families with discordant sibs and for studies where both investigated *IL6* SNPs have been genotyped.
MONICA /KORA Survey S3	The MONICA/KORA Survey S3 originally investigated 4,856 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 myocardial infarction (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 1,254 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. For the purpose of this joint analysis, the study was split in two parts. All for T2DM discordant sibships were included in the KORAMIFAM_DS study. Of the remaining families with T2DM individuals, one T2DM individual per family was chosen as case for the KORAMIFAM_CC study according to a priori defined criteria. Controls for the KORAMIFAM_CC study comprise one subject per family from families without T2DM individuals.
KORA Survey S4 (KORA S4)	The KORA S4 studied a population-representative sample of 4,261 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, 1,653 persons participated in an OGTT. Further details: (12). The prevalent T2DM and the NGT-individuals of the OGTT-substudy were used in this joint analysis. The NGT-individuals of the KORA S4 were divided in two subgroups, to serve in the joint analysis as control group for both, the T2DM individuals of the KORA S4 (KORA-S4_CC; two controls per case randomly selected) and the unrelated T2DM individuals of the KORA-T2DMFAM (KORA-T2DMFAM_CC; the remainder of the controls).

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. For the purpose of this joint analysis, the study was split in two parts. All for T2DM discordant sibships were included in the KORA-T2DMFAM_DS study. Of the remaining families with T2DM individuals, one T2DM individual per family was chosen as case for the KORA-T2DMFAM_CC study according to a priori defined criteria (n = 351). Controls for the KORA-T2DMFAM_CC study comprise one subject per family from families without T2DM individuals (n = 13) and the randomly selected normoglycemic individuals of the KORA S4, that are not used in the KORA-S4_CC study (n = 406).
MONICA/ KORA Case Cohort Study S123	The MONICA/KORA Case Cohort Study S123 was turned into a nested case-control study for the purpose of this joint analysis. All participants of at least one of the three MONICA Augsburg surveys were prospectively followed. The case cohort study was restricted to participants aged 35–74 years at baseline, since the incidence of T2DM is low in younger subjects. For the case-cohort study, a stratified random sample of the source population, containing 1,885 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: (13).
Regensburg MI Family Study	The kindreds of the Regensburg MI Family Study were ascertained through myocardial infarction (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: (14). For the purpose of this joint analysis, the study was split in two parts. All for T2DM discordant sibships were included in the RMIFAM_DS study. Of the remaining families with T2DM individuals, one T2DM individual per family was chosen as case for the RMIFAM_CC study according to a priori defined criteria. Controls for the RMIFAM_CC study were selected from families without T2DM individuals (one per family).
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. The participants of the NPHSII study were randomly divided in two equally sized subgroups, to serve in the joint analysis as control group for both, the EDSC and the UDACS study. Further details: (15).

Tarraco Study	For the Tarraco study 211 unrelated T2DM 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 as control subjects. Further details: (7).
T2DM Susceptibility in Pima Indians Study	PIMA subjects were participants in ongoing longitudinal studies of T2DM conducted among members of the Gila River Indian Community in Arizona since 1965. For the joint analysis, the family-based association study of sibships, which is robust to confounding by ethnic admixture or other sources of population stratification, was used. Further details: (7).
University College Diabetes and Cardiovascular Study (UDACS)	The UDACS Study comprises 1,011 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: (15). As the NPHS II study of healthy male individuals serves as control group, only male UDACS subjects were included in this joint analysis.

[a] The numbers presented for the original studies do not always match the numbers presented in table 1. The reason is that some subjects of the original studies were not included in the joint analysis because of study overlap, missing genotype data, missing T2DM status or because the sex- or age-range of cases and controls did not match according to the sample requirements described in the methods section.

Table A4 – online appendix

Sensitivity analyses: Pooled ORs of association between *IL6* -174 C allele dominant and T2DM

Type of sensitivity analysis	No. of Studies	No. of Cases / Controls	OR (95% CI)[a]	P Het[b]	I^2 [%][c]
Studies included as in main analysis[d], stratified by study type					
Published studies[e]	6	1,551 / 6,672	0.88 (0.76–1.01)	0.61	0.0
Unpublished studies	12	3,195 / 9,558	0.93 (0.83–1.04)	0.98	0.0
Case-control studies	14	4,140 / 15,720	0.91 (0.83–1.00)	0.89	0.0
Discordant-sib studies	4	606 / 510	0.93 (0.53–1.63)	0.97	0.0
Originally T2DM study	13	4,184 / 11,250	0.91 (0.82–1.00)	0.82	0.0
Originally not T2DM study[f]	5	562 / 4,980	0.92 (0.75–1.12)	1.00	0.0
Studies with OGTT[g]	8	3,254 / 6,602	0.90 (0.79–1.01)	0.90	0.0
Studies without OGTT	10	1,492 / 9,628	0.93 (0.81–1.05)	0.87	0.0
Studies not enriched for MI	12	3,699 / 13,731	0.91 (0.82–1.00)	0.76	0.0
Studies enriched for MI[h]	6	1,047 / 2,499	0.92 (0.76–1.11)	1.00	0.0
Studies included as in main analysis[d], original data stratified by sex					
Women[i]	13	1,852 / 6,330	0.91 (0.78–1.06)	0.35	9.2
Men[j]	16	2,962 / 9,261	0.93 (0.83–1.05)	0.39	5.5

[a] Fixed effect odds ratio estimate with 95% confidence interval, adjusted for age, sex and body mass index (BMI)

[b] P-value of Q-test for heterogeneity

[c] Measure of heterogeneity, can range between 0 and 100%

[d] All studies with controls in Hardy-Weinberg equilibrium (HWE), adjusted for age, sex and BMI

[e] The following studies are published: DANISH_CC, EPIC-POTSDAM_CC, GIRONA_CC, KORA-S4_CC, PIMA_DS, UDACS_CC

[f] The following studies originally were not designed as T2DM studies: CAPPP_CC, KORAMIFAM_CC, KORAMIFAM_DS, MONICA-S3_CC, RMIFAM_CC

[g] The following studies used an oral glucose tolerance test (OGTT) to exclude subjects with impaired glucose tolerance from the controls: BOTNIA_CC, DANISH_CC, FUSION_CC, FUSION_DS, GIRONA_CC, KORA-S4_CC, KORA-T2DMFAM_CC, KORA-T2DMFAM_DS

[h] The following studies are enriched for myocardial infarction (MI) patients: CAPPP_CC, KORAMIFAM_CC, KORAMIFAM_DS, KORA-T2DMFAM_CC, KORA-T2DMFAM_DS, RMIFAM_CC

[i] The following studies are not included because they comprise no or too few female participants: CAPPP_CC, EDSC_CC, GIRONA_CC, KORAMIFAM_DS, UDACS_CC

[j] The following studies are not included because they comprise too few male participants: KORAMIFAM_DS, PIMA_DS

Table A5 – online appendix

Sensitivity analyses: Pooled ORs of association between *IL6* -573 C allele dominant and T2DM

Type of sensitivity analysis	No. of Studies	No. of Cases / Controls	OR (95% CI)[a]	P Het[b]	I^2 [%][c]
Studies included as in main analysis[d], stratified by study type					
Case-control studies[e]	7	2,076 / 9,007	1.06 (0.87–1.29)	0.39	5.1
Originally T2DM study[f]	6	2,198 / 5,735	1.03 (0.84–1.28)	0.25	24.0
Studies with OGTT[g]	4	1,583 / 1,648	1.13 (0.84–1.51)	0.24	28.2
Studies without OGTT	4	809 / 7,617	0.99 (0.77–1.27)	0.56	0.0
Studies not enriched for MI	5	1,726 / 8,209	1.02 (0.82–1.27)	0.23	29.2
Studies enriched for MI[h]	3	666 / 1,056	1.14 (0.75–1.76)	0.67	0.0
Studies included as in main analysis[d], original data stratified by sex					
Women[i]	6	892 / 3,074	1.18 (0.85–1.63)	0.49	0.0
Men	8	1,352 / 5,951	1.01 (0.79–1.28)	0.56	0.0

[a] Fixed effect odds ratio estimate with 95% confidence interval, adjusted for age, sex and body mass index (BMI)

[b] P-value of Q-test for heterogeneity

[c] Measure of heterogeneity, can range between 0 and 100%

[d] All studies with controls in Hardy-Weinberg equilibrium (HWE), adjusted for age, sex and BMI

[e] KORA-T2DMFAM_DS is not included here, being the only discordant-sib study

[f] CAPPP_CC and MONICA-S3_CC are not included here, being the only studies which originally were not designed as T2DM studies

[g] The following studies used an oral glucose tolerance test (OGTT) to exclude subjects with impaired glucose tolerance (IGT) from the controls: BOTNIA_CC, KORA-S4_CC, KORA-T2DMFAM_CC, KORA-T2DMFAM_DS

[h] The following studies are enriched for myocardial infarction (MI) patients: CAPPP_CC, KORA-T2DMFAM_CC, KORA-T2DMFAM_DS

[i] The following studies are not included because they comprise no or too few female participants: CAPPP_CC, UDACS_CC

Figure Legends – online appendix

Figure A1

Funnel plot for the association between *IL6* -174G>C and T2DM. For each study, the odds ratio (OR) of the dominant model for the C allele, adjusted for age, sex and BMI, is plotted against the standard error of its log OR (SE(logOR)) as a measure of study precision. All studies with *IL6* -174G>C genotypes of control individuals in HWE, where the covariates age, sex and BMI are available, are included. Black circles represent published studies, white circles represent unpublished studies. The vertical line marks the pooled OR (0.91).

Figure A2

Sensitivity analysis for the association between **A** *IL6* -174G>C, or **B** *IL6* -573G>C and T2DM, dominant model for the C allele, adjusted for age, sex and BMI. Pooled fixed effect odds ratios (ORs) with 95% confidence intervals (95% CIs) are displayed for the main analysis (all studies in HWE with BMI available) and after alternate omission of individual studies. The addenda _CC and _DS behind the abbreviated study names denote case-control and discordant-sib studies, respectively. The studies are sorted according to the weight with which they contribute to the pooled OR estimate. The vertical line marks unity (1.0).

Figures – online appendix

Figure A1 – online appendix

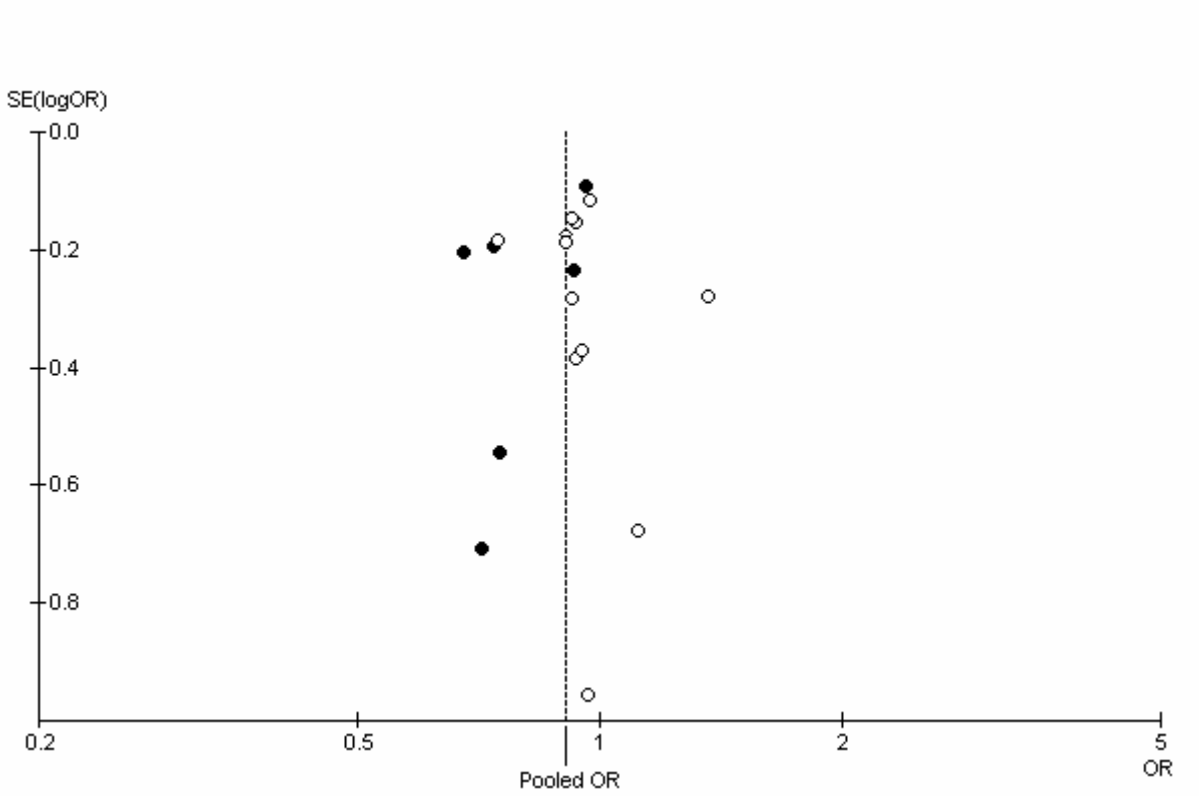


Figure A2 A – online appendix

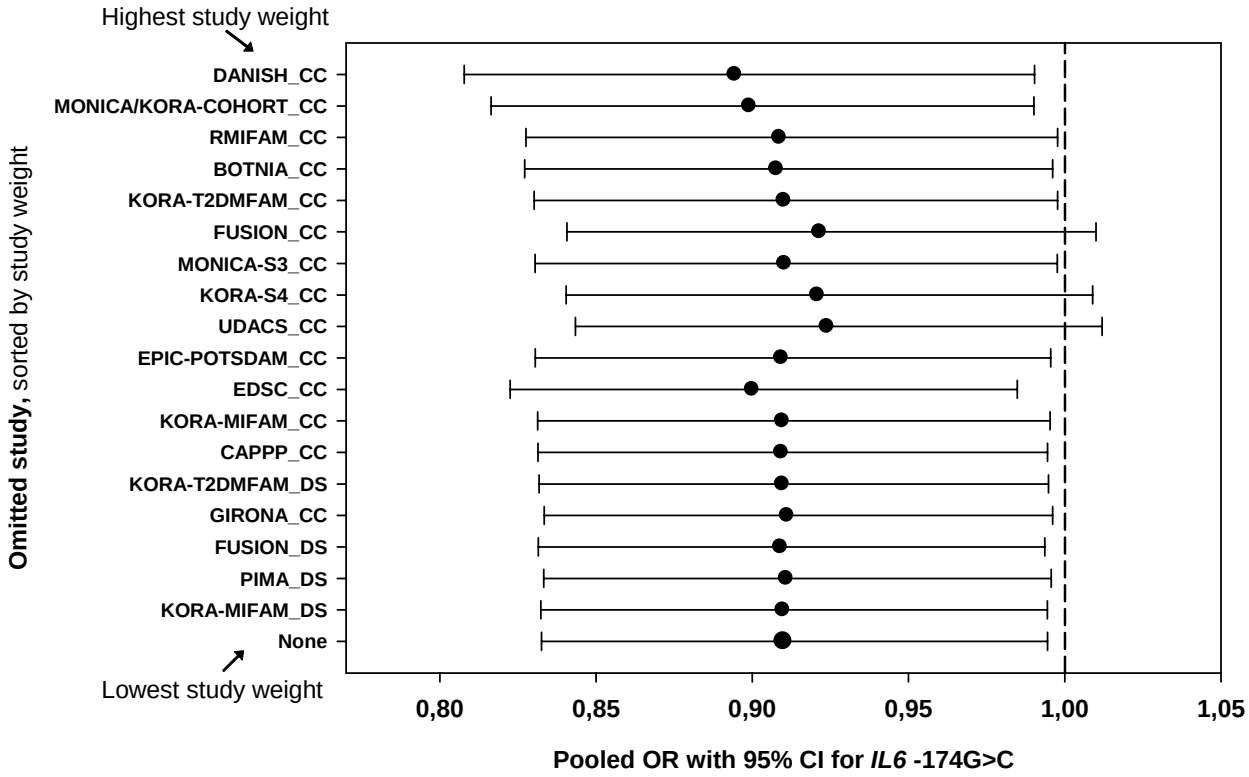
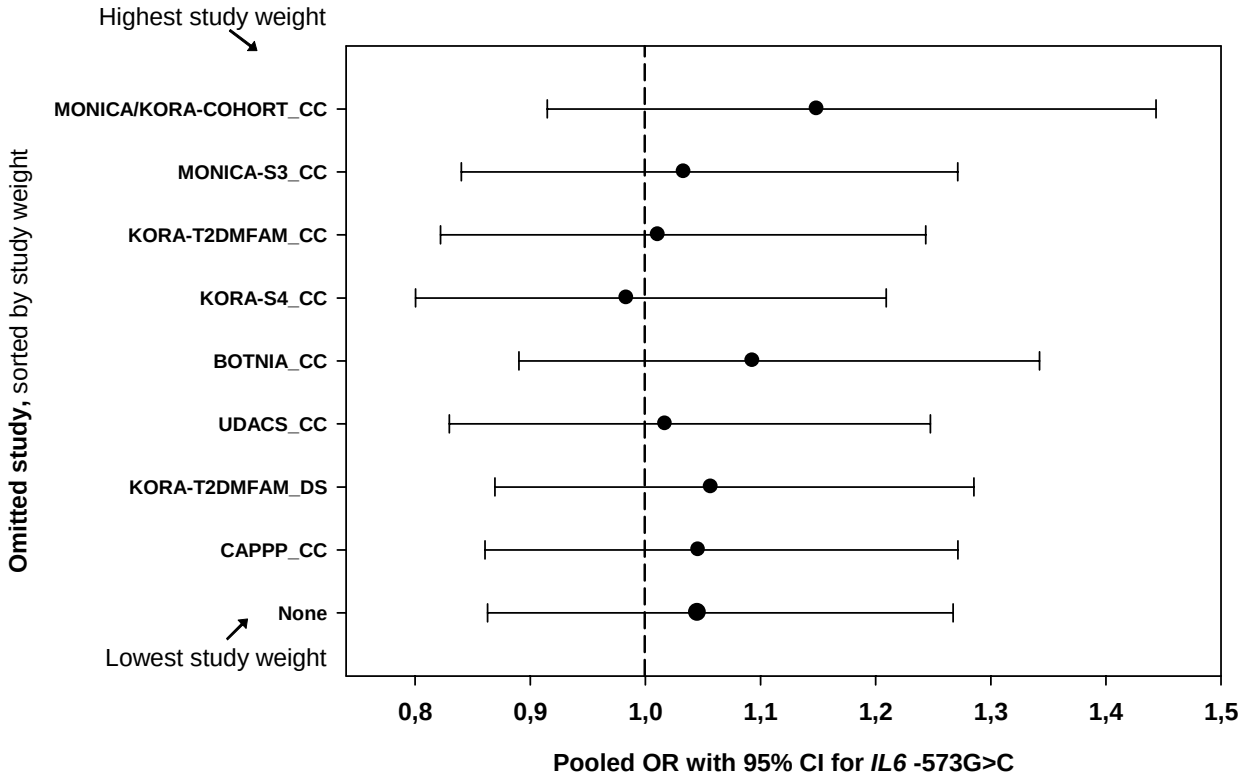


Figure A2 B – online appendix



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