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Common Variations in the Genes Encoding C-Reactive Protein, Tumor Necrosis Factor-α, and Interleukin-6, and the Risk of Clinical Diabetes in the Women's Health Initiative Observational Study

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BACKGROUND: Circulating concentrations of high-sensitivity C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) have been associated with an increased risk of diabetes.

METHODS: To examine the roles of genetic variation in the genes encoding CRP, TNF- α, and IL-6 in the development of diabetes, we conducted a prospective case–control study nested within the Women's Health Initiative Observational Study. We followed 82 069 postmenopausal women (50–79 years of age) with no history of diabetes for incident diabetes for a mean follow-up of 5.5 years. We identified 1584 cases and matched them with 2198 controls with respect to age, ethnicity, clinical center, time of blood draw, and length of follow-up. We genotyped 13 haplotype-tagging single-nucleotide polymorphisms (tSNPs) across 2.3 kb of the *CRP* (C-reactive protein, pentraxin-related) gene, 16 tSNPs across 2.8 kb of the *TNF* (tumor necrosis factor) gene, and 14 tSNPs across 4.8 kb of the *IL6* [interleukin 6 (interferon, beta 2)] gene. Plasma concentrations of TNF-α receptor 2 (TNF-α-R2) and IL-6 were measured.

RESULTS: After adjusting for matching factors, confounding variables, and multiple comparisons, we found 8 variants in the *TNF* gene to be associated with plasma TNF-α-R2 concentrations in white women ($q < 0.05$). After adjusting for multiple comparisons ($q > 0.05$), we found no association of any *IL6* gene variant with plasma IL-6 concentration, nor did we find any significant associations between any SNPs among these 3 genes and diabetes risk ($q > 0.05$).

CONCLUSIONS: We found modest associations between *TNF* variants and circulating concentrations of TNF-α-R2. Common variants of the *CRP*, *TNF*, and *IL6* genes were not significantly associated with risk of clinical diabetes in postmenopausal women.

Inflammatory markers such as high-sensitivity C-reactive protein (hsCRP),[11] tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) have been implicated as possible etiologic factors in the development of obesity, diabetes, and cardiovascular disease *(1–10)*. We previously reported that among postmenopausal women enrolled in the Women's Health Initiative Observational Study (WHI-OS) increased circulating concentrations of hsCRP, TNF-α, and IL-6 were significantly associated with an increased diabetes risk *(11)*. Recently, common genetic variants in the *CRP*[12] (C-reactive protein, pentraxin-related) gene were associated with their corresponding plasma marker concentrations in Europeans *(12)*, European Americans *(13, 14)*, African Americans *(7, 13)*, and Pima Indians *(15)*. To date, relatively few studies have investigated the associations of common variants in the genes encoding TNF-α and IL-6 with their plasma concentrations or looked for direct associations of *CRP*, *TNF*

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[11] Nonstandard abbreviations: hsCRP, high-sensitivity C-reactive protein; TNF-α, tumor necrosis factor α; IL-6, interleukin-6; WHI-OS, Women's Health Initiative Observational Study; TNF-α-R2, TNF-α receptor 2; tSNP, haplotype-tagging single-nucleotide polymorphism; NCBI dbSNP, National Center for Biotechnology Information database SNP; HWE, Hardy–Weinberg equilibrium; MET, metabolic equivalent; FDR, false-discovery rate.
[12] Human genes: *CRP*, C-reactive protein, pentraxin-related; *TNF*, tumor necrosis factor; *IL6*, interleukin 6 (interferon, beta 2).

(tumor necrosis factor), or *IL6* [interleukin 6 (interferon, beta 2)] gene variants with diabetes risk, especially in a multiethnic population.

We conducted a comprehensive assessment of the association of genetic variants for TNF-α and IL-6 with plasma concentrations of these 2 inflammation markers in a large case–control study nested within the WHI-OS. We also investigated the association of variations in the *CRP*, *TNF*, and *IL6* genes with diabetes risk in the same group of women.

Materials and Methods

PARTICIPANTS

Details regarding the case–control study design have been described elsewhere *(16, 17)*. The WHI-OS is a longitudinal study designed to examine the association of clinical, socioeconomic, behavioral, and dietary risk factors with the subsequent incidences of health outcomes, including diabetes and cardiovascular disease. In brief, 82 069 of the 93 676 postmenopausal women enrolled in the WHI-OS had no history of diabetes at baseline. We therefore assumed that the presence of diabetes had not influenced baseline plasma marker concentrations and baseline gene expression. Diabetes was self-reported by treatments with diet, oral hypoglycemic agents, or insulin. Incident diabetes cases were identified from postbaseline self-reports of first-time use of oral hypoglycemic agents or insulin or from hospitalizations for previously unreported diabetes. We followed the principle of risk-set sampling *(11)* to randomly select controls for each new case from women who remained free of diabetes at the time the case was identified during follow-up. We individually matched 1584 cases with 2198 controls by age ($\pm$2.5 years), racial/ethnic group, clinical center (geographic location), time of blood draw ($\pm$0.10 h), and length of follow-up. The ethnic groups represented in this study include American whites (n = 1936), American blacks (n = 1098), Hispanic/Latino Americans (n = 455), and Asian/Pacific Islanders (n = 293). A 1:2 matching ratio was used for minorities to strengthen the power in these case groups with smaller sample sizes *(17)*. Each control was identified and matched with a case only once in the analysis. The study was approved by the Institutional Review Board at the University of California Los Angeles.

PLASMA MARKER MEASUREMENTS

Plasma concentrations of hsCRP, TNF-α receptor 2 (TNF-α-R2), and IL-6 were measured for each participant. TNF-α-R2 is measured more reliably in frozen samples than TNF-α itself, and TNF-α-R2 concentrations correlate well with TNF-α concentrations *(18, 19)*. The details of plasma marker measurements are described elsewhere *(11)*. In brief, the CVs were 1.6%, 3.5%, and 7.6% for hsCRP, TNF-α-R2, and IL-6, respectively.

HAPLOTYPE-TAGGING SINGLE-NUCLEOTIDE POLYMORPHISM SELECTION AND GENOTYPING METHODS

As described previously *(20, 21)*, we implemented a 2-stage approach for choosing haplotype-tagging single-nucleotide polymorphisms (tSNPs) for genotyping. In the first stage, we used the National Center for Biotechnology Information database SNP (NCBI dbSNP) and the HapMap database to conduct a comprehensive survey of common genetic variation. In the second stage, we identified tSNPs on the basis of linkage disequilibrium patterns among 61 individuals from each ethnic population. The rationale and method have previously been described in detail *(21, 22)*.

We genotyped selected SNPs with the TaqMan allelic-discrimination method. After PCR amplification, we read the end-point fluorescence with the Applied Biosystems Primer 7900HT Fast Real-Time PCR instrument and scored genotypes with the aid of SDS 2.2.2 Allelic Differentiation Software (Applied Biosystems). To evaluate reproducibility, we randomly selected 5% of the duplicated samples and genotyped them in a blinded fashion. We excluded SNPs with a higher rate of genotyping discordance, a higher rate of missing genotypes, or significant ($P < 0.001$) deviation from the Hardy–Weinberg equilibrium (HWE).

STATISTICAL ANALYSIS

We first assessed the allele frequency and HWE for each SNP among the controls for each ethnic group. Next, we used a χ^2 test to test for heterogeneity in genotype distributions across ethnic groups (SAS 9.2; SAS Institute). In multivariable regression models, we adjusted for matching factors (age, clinical center, time of blood draw, and ethnicity) and other potential confounders [body mass index, cigarette smoking (never, past, and current), alcohol intake (never, past, and current), family history of diabetes, hormone-replacement therapy use (never, past, and current), and the total metabolic equivalent (MET) value from the individual's recreational physical activity per week at baseline [1 MET (the energy expended by a person at rest) = 1 kcal $\cdot$ (kg body weight)$^{-1} \cdot$ h^{-1}]. To investigate the relationship between SNPs and plasma markers, we log-transformed the plasma marker data with skewed distributions to improve compliance with the normality assumption. We calculated the differences in the mean logarithms of plasma marker concentrations according to each genotyped tSNP by fitting general linear models that treated plasma marker concentrations as dependent variables and tSNPs as independent variables. An additive model was used. The results of this anal-

ysis were expressed as an increase or decrease in the difference in the mean logarithms of the plasma marker per each additional copy of the reference allele. Likelihood ratio tests were used to test for the effects of genotype–ethnicity interaction on inflammatory marker concentrations.

In assessing the relationship between each SNP and diabetes risk, we used multivariable logistic regression (conditional on matching) to calculate odds ratios and 95% CIs. Each SNP was coded as an additive genetic model in estimating allelic association with diabetes risk; the likelihood ratio test was used to test the effect of genotype–ethnicity interaction on diabetes risk.

To account in this study for potential false positives due to multiple comparisons, we calculated the false-discovery rate (FDR) by incorporating all *P* values from multiple tests performed for the association of SNPs and plasma markers. The FDR statistics were obtained for each *P* value, and FDR statistics with *q* values <0.05 were considered statistically significant *(23)*. The PROC MULTTEST procedure in SAS 9.2 was used to obtain *q* values.

Results

ESTIMATION OF ALLELE FREQUENCIES

The allele frequencies of 9 SNPs in the *TNF* gene and 13 SNPs in the *IL6* gene differed significantly by ethnicity (Table 1). The 13 SNPs in the *CRP* gene have been published elsewhere *(13)*. Figs. 1 and 2 schematically present the locations of the SNPs along the *TNF* and *IL6* genes according to the gene structure presented in NCBI Entrez Gene (http://www.ncbi.nlm.nih.gov/gene). In the *TNF* gene, rs2239704, rs1041981, and rs3093661 in white women deviated significantly from the HWE among the controls. None of the 14 SNPs in the *IL6* gene showed any statistically significant deviation from HWE among the controls of each ethnic group.

ASSOCIATIONS OF GENETIC VARIANTS WITH PLASMA BIOMARKERS AND DIABETES RISK

Half of the 16 SNPs in the *TNF* gene were associated with plasma TNF-α-R2 concentrations in white women (Table 2). For 4 SNPs, carriers of each additional copy of the reference allele had lower TNF-α-R2 concentrations [range for the decrease in mean logarithm per allele (SE), −0.03 (0.01) to −0.04 (0.02); all adjusted *q* values were <0.05 after FDR]. In contrast, carriers of the reference alleles for the 4 other SNPs (rs909253, rs1041981, rs1800629, and rs2256974) had higher TNF-α-R2 concentrations [range of the increase in mean logarithm per allele (SE), 0.04 (0.01) to 0.05 (0.01); all adjusted *q* values were <0.05 after FDR]. After adjusting for multiple testing, we found no significant association between any of the *IL6* gene variants and IL-6 concentration.

After adjusting for matching factors, other potential confounders, and multiple comparisons, we found no evidence of any significant associations between any of the SNPs among the 3 genes (*CRP*, *TNF*, and *IL6*) and diabetes risk (all *q* values were >0.05; Table 3). Our findings were confirmed in our analysis of 4 additional models with various covariates (particularly the effect of controlling for family history of diabetes and body mass index) to investigate the potential independent associations of the inflammation marker variants of interest with diabetes risk (data not shown).

Discussion

In this large multiethnic cohort of postmenopausal women, 8 common variants of the gene encoding TNF-α were associated with the plasma TNF-α-R2 concentration in whites, whereas we found no association between common variants of the *IL6* gene and the plasma IL-6 concentration. No variants of the *CRP*, *TNF*, or *IL6* genes were significantly associated with increased diabetes risk after we corrected for multiple comparisons.

One of the 8 SNPs (rs1800629) in the *TNF* gene that we found to be associated with plasma TNF-α concentrations in whites was associated in a prior study with TNF-α concentration in the same ethnic group *(24)*. The null findings for a relationship between common variants of the same gene and diabetes risk were consistent with results from previous studies of European and Chinese populations *(25–28)*. The presence of the A allele of SNP rs1800629 in the *TNF* gene among Brazilian individuals older than 48 years has been associated with increased hsCRP concentrations *(29)*. Although our results were not statistically significant, the direction of the association between this *TNF* variant and hsCRP concentration was the same in our samples. Furthermore, as we demonstrated in our prior study, increased hsCRP concentrations were associated with an increased diabetes risk *(11)*. Therefore, if this *TNF* variant is in fact associated with increased hsCRP concentrations, then it may play an indirect role in the pathogenesis of type 2 diabetes. A metaanalysis has indicated that individuals who carry this TNF-α variant are at higher risk of developing obesity than control individuals, suggesting that the *TNF* gene is involved in the pathogenesis of the metabolic syndrome *(30)*. Obesity is a well-known risk factor for the development of type 2 diabetes. On the other hand, another study indicated that this TNF-α variant was not associated with insulin resistance in young Asian Indians *(31)*. Taken together, the data indicate that the

Table 1. Location and allele frequencies of genotyped tSNPs in *TNF* and *IL6* genes in controls.

Gene	dbSNP ID[a]	Location	Allele[b]	Allele frequency, %					P^c
				Whites	Blacks	Hispanics	Asian/Pacific Islanders	Total	
TNF				(n = 939)	(n = 737)	(n = 275)	(n = 156)	(n = 2107)	
	rs2239705	5′ flanking	C(T)	18.12	13.07	25.63	20.00	17.48	<0.0001
	rs2230365	5′ flanking	C(T)	15.09	6.68	17.63	25.15	13.26	<0.0001
	rs2009658	5′ flanking	C(G)	16.02	13.11	18.18	17.38	15.39	0.048
	rs2239704	5′ flanking	G(T)	41.77	28.21	39.96	40.30	36.71	<0.0001
	rs909253	5′ flanking	T(C)	34.22	48.59	36.05	37.35	39.73	<0.0001
	rs2857713	5′ flanking	T(C)	26.70	28.36	26.71	22.26	26.93	0.28
	rs1041981	5′ flanking	C(A)	33.58	48.25	35.61	38.04	39.27	<0.0001
	rs1799964	5′ flanking	T(C)	21.59	18.18	21.22	20.86	20.30	0.11
	rs1799724	5′ flanking	C(T)	10.74	3.95	16.91	17.38	9.69	<0.0001
	rs1800750	5′ flanking	G(A)	1.78	2.28	1.26	0	1.75	0.17
	rs1800629	5′ flanking	G(A)	15.88	12.72	9.39	2.42	12.90	<0.0001
	rs361525	5′ flanking	G(A)	5.67	4.62	3.06	3.44	4.80	0.22
	rs3093661	Intron 1	G(A)	3.98	4.10	2.36	3.46	3.77	0.50
	rs3093662	Intron 1	A(G)	8.15	8.67	6.27	3.61	7.73	0.045
	rs769178	3′ flanking	C(A)	10.15	4.03	17.33	16.67	9.45	<0.0001
	rs2256974	3′ flanking	G(T)	18.21	34.26	25.45	36.54	26.13	<0.0001
IL6				(n = 928)	(n = 738)	(n = 276)	(n = 163)	(n = 2105)	
	rs1880242	5′ flanking	G(T)	53.17	79.22	56.34	26.52	60.69	<0.0001
	rs10499563	5′ flanking	C(T)	77.32	82.02	80.88	82.08	79.81	0.0069
	rs2069824	5′ flanking	C(T)	91.08	85.79	91.82	99.08	89.92	<0.0001
	rs1800797	5′ flanking	A(G)	62.2	90.34	78.88	96.04	76.88	<0.0001
	rs1800796	5′ flanking	C(G)	93.66	90.39	78.52	30.49	85.59	<0.0001
	rs1800795	5′ flanking	C(G)	61.29	90.19	78.68	97.26	76.58	<0.0001
	rs2069830	Exon 2	C(T)	0.05	9.14	0.36	0	3.26	<0.0001
	rs2069838	Intron 3	C(T)	0.32	6.65	1.08	0	2.62	<0.0001
	rs2069840	Intron 3	C(G)	34.72	18.71	31.93	7.72	26.59	<0.0001
	rs2069842	Intron 4	A(G)	99.79	92.81	99.09	100	97.26	<0.0001
	rs2069845	Intron 4	A(G)	42.00	34.35	29.86	3.05	34.7	<0.0001
	rs2069861	3′ flanking	C(T)	8.27	1.96	3.97	0.31	4.88	<0.0001
	rs1524106	3′ flanking	C(A)	67.4	47.1	45.31	8.84	52.84	<0.0001
	rs1524103	3′ flanking	G(C)	25.54	41.6	31.52	19.63	31.5	<0.0001

[a] From the NCBI dbSNP.
[b] Reference alleles are indicated in parentheses.
[c] *P* values were estimated by a χ^2 test ($df = 3$) for genotype distribution across the 4 ethnic groups.

TNF gene may not lead directly to the development of diabetes, but it may play an interactive role with other factors, such as CRP, in the pathogenesis of diabetes.

We observed no significant associations in our samples between *IL6* variants and the plasma IL-6 concentration. One study showed the genetic variant rs10499563 to be significantly associated with increased IL-6 concentrations in individuals in an acute inflammatory state *(30)*. The presence of acute inflammation may affect the association between this genetic variant and the plasma IL-6 concentration. In general, we presume that the women in our study did not have acute inflammation at the time of blood draw, which may account for this discrepancy. A study of 1953 Ko-

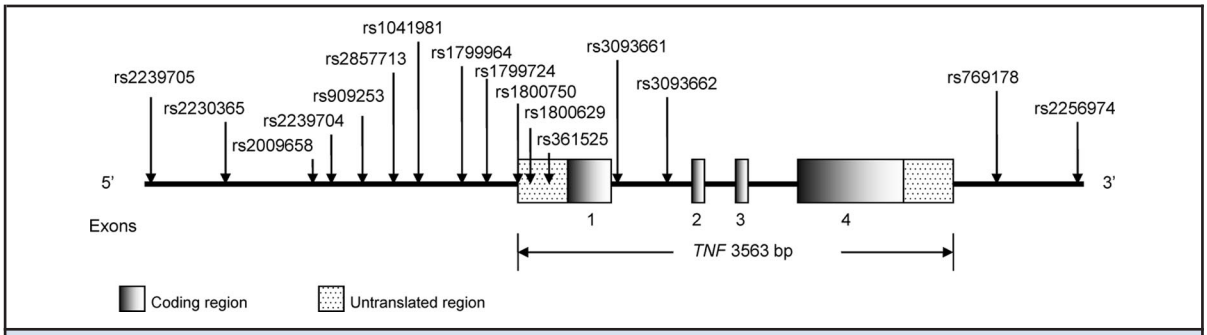

Fig. 1. Human *TNF* gene (chromosome 6p21.3) and SNP locations.

rean men and women found that the rs1800796 G/G genotype was associated with increased serum IL-6 concentrations *(32)*. This result is consistent with our analysis, which showed that carriers of each additional copy of the G allele in this SNP were associated with increased IL-6 concentrations in the Asian population, although our result was not statistically significant. Inconsistent findings regarding the association between this gene and diabetes risk have been reported previously in several case–control, prospective population-based studies and metaanalyses *(33–37)*. A joint analysis of the data for the individual participants from 21 studies observed that the C allele of the rs1800795 SNP in the *IL6* gene was associated with a reduced risk of diabetes *(34)*, whereas a metaanalysis indicated a null association between the same SNP in the *IL6* gene and diabetes risk *(36)*. In general, the literature lacks reports of studies that have examined the associations of common variants in the *TNF* and *IL6* gene regions with the corresponding plasma marker concentrations and diabetes risk, particularly in a multiethnic cohort.

Assuming an additive model, we observed no significant associations between the variants in the *CRP* gene and the risk of clinical diabetes, a result consistent with prior findings *(38)*. Although these genetic variants have substantial and independent associations with the plasma hsCRP concentration *(13)*, our prospective data do not support a direct heritable role for CRP in the development of diabetes.

The lack of significant genetic associations in the current study may be due to insufficient statistical power, especially among the Hispanic and Asian women. Nevertheless, our study was well powered to detect effects for alleles shared across all ethnic groups. In fact, we had >80% power to detect a relative risk of ≥1.25 for risk alleles with frequencies from 10% to 70%. Additionally, our study included only postmenopausal women, and therefore our results may not be generalized to men or younger women.

In conclusion, 8 common genetic variants of the *TNF* gene were associated with the plasma TNF-α-R2 concentration among whites in this large multiethnic case–control study of postmenopausal women, although these common *TNF* variants were not associated with a risk of clinical diabetes. Common *IL6* variants were not associated with IL-6 concentration or diabetes risk, nor were common *CRP* variants associated with the risk of clinical diabetes. Our data indicate modest associations between *TNF* gene variants and circulating concentrations of TNF-α-R2. Common variants of the genes encoding

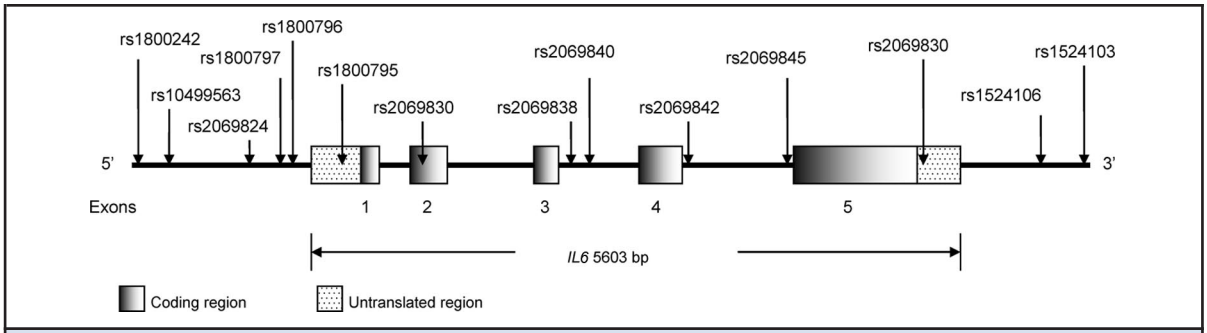

Fig. 2. Human *IL6* gene (chromosome 7p21) and SNP locations.

Table 2. Differences in mean logarithms in plasma concentrations according to corresponding SNPs stratified by ethnicity.

Gene	SNP ID	Difference in mean logarithms (SE)[a]					*P* for ethnic interaction[b]
		Whites	Blacks	Hispanics	Asian/Pacific Islanders	Total	
TNF		(n = 1592)	(n = 912)	(n = 328)	(n = 209)	(n = 3041)	
	rs2239705	−0.02 (0.01)	−0.03 (0.02)	0.002 (0.03)	0.04 (0.04)	0.003 (0.01)	0.03
	rs2230365	−0.04 (0.01)[c]	−0.04 (0.03)	−0.02 (0.03)	−0.06 (0.03)	−0.02 (0.01)	0.86
	rs2009658	−0.03 (0.01)	−0.04 (0.02)	0.01 (0.03)	−0.05 (0.04)	−0.02 (0.01)	0.73
	rs2239704	−0.02 (0.01)	−0.002 (0.02)	−0.005 (0.02)	−0.01 (0.03)	0.001 (0.01)	0.25
	rs909253	0.04 (0.01)[d]	0.01 (0.02)	0.02 (0.02)	0.06 (0.03)	0.02 (0.01)	0.70
	rs2857713	−0.03 (0.01)[e]	−0.02 (0.02)	0.001 (0.03)	−0.07 (0.04)	−0.03 (0.01)[k]	0.38
	rs1041981	0.05 (0.01)[f]	0.003 (0.02)	0.01 (0.02)	0.06 (0.03)	0.02 (0.01)	0.51
	rs1799964	−0.03 (0.01)[g]	−0.02 (0.02)	0.01 (0.03)	−0.07 (0.04)	−0.02 (0.01)	0.65
	rs1799724	−0.03 (0.02)	−0.08 (0.04)	−0.01 (0.03)	0.05 (0.04)	−0.002 (0.01)	0.01
	rs1800750	0.03 (0.04)	0.04 (0.05)	0.08 (0.08)	−0.35 (0.31)	0.03 (0.03)	0.93
	rs1800629	0.04 (0.01)[h]	−0.01 (0.02)	0.03 (0.04)	0.01 (0.08)	0.02 (0.01)	0.07
	rs361525	−0.03 (0.02)	0.02 (0.04)	−0.02 (0.06)	−0.09 (0.08)	−0.02 (0.02)	0.58
	rs3093661	−0.04 (0.02)	−0.03 (0.04)	−0.08 (0.08)	−0.08 (0.08)	−0.05 (0.02)	0.44
	rs3093662	−0.04 (0.02)	0.01 (0.03)	−0.05 (0.05)	−0.10 (0.08)	−0.03 (0.01)	0.44
	rs769178	−0.03 (0.02)	−0.07 (0.04)	−0.01 (0.03)	0.04 (0.04)	−0.001 (0.01)	0.02
	rs2256974	0.04 (0.01)[i]	0.01 (0.02)	0.02 (0.03)	0.05 (0.03)	0.01 (0.01)	0.54
IL6		(n = 1608)	(n = 918)	(n = 327)	(n = 207)	(n = 3060)	
	rs1880242	−0.01 (0.01)	−0.03 (0.03)	−0.06 (0.04)	−0.01 (0.05)	−0.01 (0.01)	0.64
	rs10499563	−0.003 (0.01)	−0.003 (0.02)	0.003 (0.03)	0.02 (0.05)	−0.002 (0.01)	0.69
	rs2069824	−0.01 (0.02)	−0.01 (0.03)	−0.02 (0.05)	−0.08 (0.09)	−0.01 (0.01)	0.28
	rs1800797	−0.05 (0.03)	−0.05 (0.07)	−0.10 (0.08)	−0.28 (0.26)	−0.04 (0.02)	0.02
	rs1800796	0.03 (0.05)	0.06 (0.07)	−0.10 (0.07)	0.02 (0.10)	0.04 (0.03)	0.07
	rs1800795	−0.04 (0.03)	−0.05 (0.07)	−0.10 (0.08)	−0.23 (0.27)	−0.03 (0.02)	0.01
	rs2069830	−0.32 (0.50)	0.05 (0.07)	−0.06 (0.53)	—[j]	0.09 (0.06)	0.62
	rs2069838	0.05 (0.27)	0.005 (0.08)	−0.36 (0.38)	—[j]	0.04 (0.07)	0.57
	rs2069840	−0.01 (0.03)	0.08 (0.05)	−0.17 (0.06)	−0.06 (0.17)	−0.01 (0.02)	0.66
	rs2069842	−0.16 (0.27)	−0.05 (0.08)	0.46 (0.26)	—[j]	−0.08 (0.06)	0.17
	rs2069845	0.04 (0.03)	−0.001 (0.04)	0.12 (0.07)	0.10 (0.40)	0.04 (0.02)	0.01
	rs2069861	0.05 (0.05)	0.13 (0.15)	0.21 (0.14)	—[j]	0.07 (0.04)	0.04
	rs1524106	0.03 (0.03)	0.05 (0.04)	−0.01 (0.06)	−0.02 (0.15)	0.03 (0.02)	0.04
	rs1524103	−0.03 (0.03)	−0.03 (0.04)	−0.05 (0.07)	0.002 (0.12)	−0.01 (0.02)	0.50

[a] The difference in mean logarithms and the SE per additional reference allele of each SNP were calculated by means of general linear regression models with adjustment for matching factors (age, clinical center, and time of blood draw), incidence of diabetes, and other confounders, including body mass index, hormone-replacement therapy, alcohol consumption, cigarette smoking, family history of diabetes, and physical activity.

[b] *P* value was estimated with a log-likelihood ratio test for the effect of the interaction of each genotype and ethnicity on plasma concentrations.

[c] $P = 0.003$, with $q = 0.01$ after FDR.

[d] $P = 0.000041$, with $q = 0.0003$ after FDR.

[e] $P = 0.005$, with $q = 0.02$ after FDR.

[f] $P = 0.000006$, with $q < 0.0001$ after FDR.

[g] $P = 0.007$, with $q = 0.02$ after FDR.

[h] $P = 0.006$, with $q = 0.02$ after FDR.

[i] $P = 0.004$, with $q = 0.01$ after FDR.

[j] Result is difficult to interpret because of small sample size within strata.

[k] $P =$ was 0.0009, with $q = 0.01$ after FDR.

Table 3. The multivariable adjusted odds ratio (95% CI) for diabetes risk associated with genetic variants, as calculated with the additive effect model.

		Adjusted odds ratio (95% CI)[a]					
Gene	SNP ID	Whites	Blacks	Hispanics	Asian/Pacific Islanders	All	*P* for ethnic interaction[c]
CRP		(n = 870/865)[b]	(n = 303/638)	(n = 115/242)	(n = 67/154)	(n = 1355/1899)	
	rs4275453	0.87 (0.71–1.07)	0.85 (0.67–1.09)	0.93 (0.57–1.52)	1.04 (0.51–2.15)	0.85 (0.74–0.98)[i]	0.92
	rs2808634	0.82 (0.66–1.03)	0.74 (0.51–1.07)	0.84 (0.48–1.49)	1.93 (0.73–5.11)	0.81 (0.68–0.97)[j]	0.34
	rs3093059	0.86 (0.59–1.25)	1.17 (0.88–1.56)	0.62 (0.30–1.25)	0.76 (0.32–1.80)	1.03 (0.84–1.26)	0.38
	rs2794521	0.82 (0.65–1.02)	0.78 (0.54–1.14)	0.76 (0.41–1.38)	1.66 (0.66–4.19)	0.81 (0.68–0.97)[k]	0.43
	rs1417938	1.03 (0.84–1.28)	1.36 (0.93–2.00)	1.07 (0.65–1.76)	0.75 (0.23–2.47)	1.09 (0.92–1.28)	0.91
	rs1800947	1.25 (0.85–1.84)	0.52 (0.15–1.81)	1.46 (0.40–5.31)	1.00 (0.33–2.96)	1.18 (0.86–1.63)	0.55
	rs1130864	1.09 (0.88–1.35)	1.18 (0.86–1.63)	0.91 (0.56–1.48)	1.15 (0.40–3.31)	1.09 (0.93–1.28)	0.76
	rs1205	1.10 (0.89–1.37)	0.80 (0.59–1.10)	1.19 (0.74–1.92)	0.82 (0.43–1.56)	1.01 (0.86–1.17)	0.61
	rs3093075	0.90 (0.61–1.32)	1.17 (0.88–1.55)	0.57 (0.28–1.16)	1.09 (0.47–2.51)	1.06 (0.87–1.31)	0.76
	rs3093068	0.81 (0.59–1.13)	1.30 (0.97–1.73)	0.84 (0.42–1.66)	1.11 (0.47–2.61)	1.05 (0.86–1.28)	0.62
	rs2808629	1.15 (0.93–1.43)	0.73 (0.54–0.99)[d]	1.30 (0.81–2.10)	0.72 (0.39–1.35)	1.00 (0.86–1.16)	0.34
	rs2369146	0.79 (0.62–1.00)	0.96 (0.74–1.24)	1.23 (0.76–2.00)	2.19 (0.80–5.97)	0.92 (0.78–1.08)	0.02[l]
	rs1470515	1.21 (0.99–1.48)	0.70 (0.52–0.94)[e]	0.97 (0.62–1.53)	0.95 (0.50–1.83)	1.01 (0.87–1.17)	0.29
TNF		(n = 867/882)	(n = 306/638)	(n = 115/244)	(n = 68/155)	(n = 1356/1919)	
	rs2239705	1.02 (0.79–1.31)	0.74 (0.50–1.09)	0.96 (0.61–1.53)	0.75 (0.31–1.79)	0.92 (0.76–1.10)	0.39
	rs2230365	1.06 (0.81–1.40)	0.91 (0.53–1.54)	0.77 (0.42–1.44)	0.86 (0.47–1.55)	0.96 (0.78–1.17)	0.79
	rs2009658	0.96 (0.73–1.27)	0.90 (0.60–1.33)	0.75 (0.42–1.33)	0.92 (0.44–1.94)	0.92 (0.76–1.11)	0.75
	rs2239704	1.09 (0.90–1.31)	0.79 (0.59–1.07)	1.33 (0.92–1.92)	0.66 (0.35–1.23)	1.00 (0.88–1.15)	0.36
	rs909253	0.99 (0.81–1.21)	1.40 (1.06–1.85)	0.83 (0.54–1.28)	1.77 (0.92–3.38)	1.09 (0.95–1.25)	0.52
	rs2857713	0.84 (0.67–1.05)	0.94 (0.70–1.27)	0.90 (0.55–1.46)	0.97 (0.50–1.91)	0.90 (0.77–1.05)	0.27
	rs1041981	1.02 (0.83–1.24)	1.39 (1.06–1.83)	0.84 (0.55–1.28)	1.79 (0.93–3.43)	1.11 (0.97–1.28)	0.60
	rs1799964	0.89 (0.70–1.13)	0.86 (0.61–1.20)	1.01 (0.60–1.72)	1.01 (0.50–2.03)	0.91 (0.76–1.07)	0.28
	rs1799724	1.04 (0.76–1.43)	0.62 (0.30–1.28)	1.14 (0.67–1.94)	0.80 (0.34–1.92)	0.97 (0.77–1.23)	0.57
	rs1800750	0.51 (0.24–1.09)	1.22 (0.55–2.69)	2.58 (0.55–12.2)	—[g]	0.90 (0.54–1.50)	0.01[m]
	rs1800629	0.91 (0.70–1.18)	1.24 (0.86–1.78)	1.19 (0.56–2.52)	6.29 (1.14–34.8)[h]	1.04 (0.85–1.27)	0.02[n]
	rs361525	0.74 (0.49–1.11)	1.04 (0.57–1.87)	2.23 (0.77–6.46)	1.56 (0.39–6.17)	0.93 (0.69–1.26)	0.09
	rs3093661	0.79 (0.50–1.26)	0.66 (0.33–1.32)	1.56 (0.44–5.50)	0.48 (0.08–2.92)	0.79 (0.56–1.12)	0.95
	rs3093662	0.87 (0.62–1.23)	0.70 (0.43–1.12)	1.09 (0.47–2.52)	1.24 (0.33–4.63)	0.84 (0.66–1.08)	0.61
	rs769178	1.06 (0.77–1.47)	0.58 (0.28–1.20)	1.09 (0.64–1.86)	0.94 (0.39–2.27)	0.98 (0.77–1.24)	0.70
	rs2256974	1.10 (0.85–1.42)	1.26 (0.96–1.67)	0.80 (0.49–1.30)	1.49 (0.76–2.93)	1.14 (0.97–1.34)	0.71
IL6		(n = 876/888)	(n = 304/641)	(n = 115/244)	(n = 67/154)	(n = 1362/1927)	
	rs1880242	1.01 (0.90–1.13)	1.04 (0.89–1.22)	1.14 (0.74–1.76)	1.14 (0.81–1.60)	1.03 (0.95–1.12)	0.36
	rs10499563	0.97 (0.88–1.08)	0.96 (0.83–1.11)	0.97 (0.76–1.23)	0.80 (0.58–1.11)	0.95 (0.89–1.03)	0.36
	rs2069824	0.93 (0.81–1.08)	1.06 (0.89–1.27)	0.66 (0.45–0.98)[f]	—[g]	0.98 (0.89–1.09)	0.57
	rs1800797	1.10 (0.90–1.34)	0.84 (0.57–1.26)	1.12 (0.62–2.04)	0.66 (0.09–4.77)	1.04 (0.89–1.23)	0.82
	rs1800796	1.18 (0.79–1.76)	1.34 (0.88–2.04)	1.02 (0.60–1.73)	0.90 (0.52–1.55)	1.10 (0.89–1.37)	0.66
	rs1800795	1.06 (0.87–1.29)	0.93 (0.61–1.41)	1.35 (0.76–2.41)	0.31 (0.01–6.92)	1.05 (0.89–1.23)	0.77
	rs2069830	1.81 (0.09–38.7)	0.99 (0.62–1.56)	—[g]	—[g]	1.00 (0.64–1.57)	0.66
	rs2069838	0.76 (0.15–3.88)	1.22 (0.76–1.97)	—[g]	—[g]	1.08 (0.69–1.69)	0.76
	rs2069840	1.16 (0.93–1.43)	0.89 (0.65–1.23)	0.94 (0.61–1.44)	0.64 (0.24–1.69)	1.06 (0.91–1.23)	0.28

Continued on page 324

Table 3. The multivariable adjusted odds ratio (95% CI) for diabetes risk associated with genetic variants, as calculated with the additive effect model. *(Continued from page 323)*

Gene	SNP ID	Adjusted odds ratio (95% CI)[a]					
		Whites	Blacks	Hispanics	Asian/Pacific Islanders	All	*P* for ethnic interaction[c]
	rs2069842	1.07 (0.11–10.4)	1.43 (0.87–2.37)	1.07 (0.14–8.55)	—[g]	1.26 (0.79–2.02)	0.98
	rs2069845	0.91 (0.75–1.11)	1.13 (0.87–1.48)	0.82 (0.51–1.32)	—[g]	0.95 (0.82–1.09)	0.49
	rs2069861	0.88 (0.62–1.25)	1.12 (0.43–2.91)	1.16 (0.43–3.16)	—[g]	0.98 (0.73–1.33)	0.92
	rs1524106	0.86 (0.70–1.06)	1.13 (0.88–1.44)	0.87 (0.58–1.31)	0.97 (0.40–2.34)	0.95 (0.83–1.10)	0.53
	rs1524103	1.17 (0.93–1.47)	0.94 (0.73–1.20)	1.16 (0.73–1.85)	0.75 (0.38–1.47)	1.02 (0.88–1.18)	0.33

[a] The odds ratio (OR) per additional reference allele of each SNP was calculated for the additive genetic effect model; ORs were estimated with conditional logistic regression models adjusted for matching factors (age, clinical center, time of blood draw, and ethnicity), body mass index, cigarette smoking, alcohol intake, hormone-replacement therapy, family history of diabetes, and physical activity.
[b] Sample sizes for each ethnic group are presented for each plasma marker as cases/controls.
[c] *P* value was estimated with a log-likelihood ratio test for the effect of the interaction of each genotype and ethnicity on diabetes risk.
[d] $P = 0.04$, with $q = 0.28$ after FDR.
[e] $P = 0.02$, with $q = 0.25$ after FDR.
[f] $P = 0.04$, with $q = 0.56$ after FDR.
[g] Result was difficult to interpret because of small sample size within strata.
[h] $P = 0.04$, with $q = 0.46$ after FDR.
[i] $P = 0.03$, with $q = 0.12$ after FDR.
[j] $P = 0.02$, with $q = 0.12$ after FDR.
[k] $P = 0.02$, with $q = 0.12$ after FDR.
[l] The *P* value became 0.24 after FDR.
[m] The *P* value became 0.15 after FDR.
[n] The *P* value became 0.15 after FDR.

CRP, TNF-α, and IL-6 were not significantly associated with the risk of clinical diabetes in postmenopausal women.

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