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Insulin Sensitivity and Insulin Clearance are Heritable and Have Strong Genetic Correlation in Mexican Americans

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests relevant to this study.

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Abstract

Objective—We describe the GUARDIAN (Genetics UndeRlying DIAbetes in HispaNics) consortium, along with heritability estimates and genetic and environmental correlations of insulin sensitivity and metabolic clearance rate of insulin (MCRI).

Design and Methods—GUARDIAN is comprised of seven cohorts, consisting of 4336 Mexican-American individuals in 1346 pedigrees. Insulin sensitivity (S_I), MCRI, and acute insulin response (AIRg) were measured by frequently sampled intravenous glucose tolerance test in four cohorts. Insulin sensitivity (M, M/I) and MCRI were measured by hyperinsulinemic-euglycemic clamp in three cohorts. Heritability and genetic and environmental correlations were estimated within the family cohorts (totaling 3925 individuals) using variance components.

Results—Across studies, age and gender-adjusted heritability of insulin sensitivity (S_I, M, M/I) ranged from 0.23–0.48 and of MCRI from 0.35–0.73. The ranges for the genetic correlations were 0.91 to 0.93 between S_I and MCRI; and −0.57 to −0.59 for AIRg and MCRI (all $P<0.0001$). The ranges for the environmental correlations were 0.54 to 0.74 for S_I and MCRI (all $P<0.0001$); and −0.16 to −0.36 for AIRg and MCRI (P <0.0001−0.06).

Conclusions—These data support a strong familial basis for insulin sensitivity and MCRI in Mexican Americans. The strong genetic correlations between MCRI and S_I suggest common genetic determinants.

Keywords

insulin sensitivity; insulin clearance; heritability; genetic correlation; environmental correlation

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INTRODUCTION

Derangements in insulin sensitivity, insulin secretion, and insulin clearance contribute to the development of type 2 diabetes mellitus (T2D). Unlike insulin sensitivity and insulin secretion, the metabolic clearance rate of insulin (MCRI) has been relatively understudied in the pathophysiology of T2D. Emerging data suggest that reduction in insulin clearance, in addition to augmentation of insulin production, is an important contributor to the compensatory hyperinsulinemia that develops in response to insulin resistance (1). Insulin resistance and insulin clearance are inversely correlated (2,3). Weight gain results in a decrease in MCRI (4), and weight loss results in an increase in MCRI (3). Genetic factors also appear to contribute to variation in MCRI. Children with and without a family history of diabetes underwent clamp studies; the children with a positive family history had not only decreased insulin sensitivity but also decreased MCRI (5). Similar results were obtained in a study of non-diabetic, normal-glucose-tolerant adults with a first degree relative with diabetes (6). We found that MCRI is highly heritable in Mexican Americans (7,8). The physiologic importance and heritable nature of MCRI are just beginning to be recognized, necessitating an improved understanding of this novel trait and its genetic determinants.

In contrast to MCRI, for which the only heritability reports have been our own (7,8), there have been several reports on the heritability of insulin sensitivity and insulin secretion, using surrogate measures based on fasting or oral glucose tolerance tests (OGTT) as well as direct measures from detailed phenotyping by euglycemic-hyperinsulinemic clamps, hyperglycemic clamps, or frequently sampled intravenous glucose tolerance tests (FSIGT). The majority of such reports have been conducted in European-origin cohorts. Focusing on studies that utilized detailed phenotyping (9–16), the median heritability of insulin sensitivity is 0.38 (range 0.24 to 0.60) and of insulin secretion is 0.52 (range 0.35 to 0.76). The few studies in Mexican Americans have produced a similar picture of heritability for insulin sensitivity (median 0.40, range 0.21 to 0.63) (7,8,17,18); heritability of FSIGT-derived acute insulin secretion has been estimated as 0.5 (18). In addition to the need for more heritability studies in Mexican Americans, there have been no publications examining genetic and environmental correlations between insulin clearance and other glucose homeostasis traits.

The study described herein, Genetics UndeRlying Diabetes In hispANics, or GUARDIAN, was formed to eventually conduct a GWAS in seven Mexican-American cohorts of insulin sensitivity and insulin clearance directly quantified by the euglycemic clamp and FSIGT. The present report details the seven cohorts comprising GUARDIAN, describes the heritability of glucose homeostasis traits, and presents the genetic and environmental correlations of MCRI with insulin sensitivity, insulin secretion, and body mass index (BMI). Elucidation of the genetic architecture of these traits is a logical first step preceding the planned GWAS. In this paper, we emphasize MCRI because it is a relatively new trait examined in genetic epidemiology.

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METHODS AND PROCEDURES

Description of the Discovery Cohorts

Seven cohorts are included in the GWAS phase of the GUARDIAN study: five family-based studies (IRAS Family, BetaGene, MACAD, HTN-IR, NIDDM-Athero; total 3925 individuals) and two non-family based studies (IRAS, TRIPOD; total 411 individuals). Only the family-based studies were used in heritability and genetic and environmental correlation analyses reported herein. All cohorts are of self-reported Mexican ancestry. Persons with self-reported and laboratory confirmed diabetes are not included. Four studies measured insulin sensitivity by FSIGT (IRAS, IRAS Family, BetaGene, TRIPOD) and three by euglycemic clamp (MACAD, HTN-IR, NIDDM-Athero). The primary traits of interest in the GUARDIAN GWAS are insulin resistance and insulin clearance. Individuals from the cohorts who had neither of these traits measured are not included.

The institutional review boards at the clinical centers, laboratory centers, and coordinating center approved the GUARDIAN Study.

IRAS—The Insulin Resistance Atherosclerosis Study (IRAS) was an epidemiologic cohort study designed to examine the relationship between insulin resistance and carotid atherosclerosis across a range of glucose tolerance (19). Individuals of self-reported Mexican-American ethnicity were recruited in San Antonio, TX and San Luis Valley, CO. Recruitment was balanced across age and glucose tolerance status. GUARDIAN includes 194 individuals from the IRAS. Insulin sensitivity was obtained by FSIGT. Other phenotypes include OGTT and carotid intima-media thickness by B-mode ultrasonography.

IRAS Family Study—The IRAS Family Study was a family study designed to examine the genetic and epidemiologic basis of glucose homeostasis traits and abdominal adiposity; details of the IRAS Family Study are described elsewhere (20). Briefly, self-reported Mexican pedigrees were recruited in San Antonio, TX and San Luis Valley, CO. Probands with large families were recruited from the initial non-family-based IRAS Study (19), which was modestly enriched for impaired glucose tolerance and T2D. GUARDIAN includes 1040 individuals in 88 pedigrees from the IRAS Family Study. Insulin sensitivity was obtained by FSIGT. Other phenotypes include abdominal fat areas measured by computed tomography scan and total body fat by dual X-ray absorptiometry (DXA) scan.

BetaGene—BetaGene was a family study designed to identify genetic determinants of β-cell function (21). BetaGene recruited non-diabetic women with a history of gestational diabetes mellitus (GDM), their adult family members, and women without history of GDM. GUARDIAN includes 1217 of these individuals in 390 pedigrees, 238 families of probands with previous GDM and 152 families of probands with normal pregnancies. Recruitment occurred in the Los Angeles area. Insulin sensitivity was obtained by FSIGT. Other phenotypes include OGTT and total body fat by DXA scan.

TRIPOD—The Troglitazone in the Prevention of Diabetes (TRIPOD) study was designed to address the impact of troglitazone treatment on β-cell function and glucose levels in women with prior GDM (22). TRIPOD recruited non-diabetic women with history of GDM in the

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Los Angeles area; family members were not recruited. GUARDIAN includes baseline (pre-intervention) data from 217 of these individuals. Insulin sensitivity was obtained by tolbutamide-modified FSIGT. Other phenotypes include OGTT and carotid intima-media thickness by B-mode ultrasonography.

HTN-IR—The Hypertension-Insulin Resistance Family Study (HTN-IR) was designed as a family study to examine the genetic basis of hypertension and insulin resistance (23). Family members of probands with documented hypertension were recruited in the Los Angeles area. GUARDIAN includes 708 of these individuals from 156 families. Insulin sensitivity was obtained by euglycemic clamp. Other phenotypes include OGTT, carotid intima-media thickness by B-mode ultrasonography, and salt sensitivity.

MACAD—The Mexican-American Coronary Artery Disease (MACAD) Study was designed as a family study to examine the genetic basis of coronary artery disease and insulin resistance (24). Family members of probands with documented coronary artery disease were recruited from the Los Angeles area. GUARDIAN includes 772 of these individuals from 208 families. Insulin sensitivity was obtained by euglycemic clamp. Other phenotypes include OGTT, carotid intima-media thickness by B-mode ultrasonography, total body fat by DXA scan, and post-heparin lipase activity assessment.

NIDDM-Athero—The NIDDM-Atherosclerosis Study was designed as a family study to examine the genetic basis of subclinical atherosclerosis and diabetes (25). Family members of probands with T2D were recruited in the Los Angeles area. GUARDIAN includes 188 of these individuals from 93 families. Insulin sensitivity was obtained by euglycemic clamp. Other phenotypes include OGTT and carotid intima-media thickness by B-mode ultrasonography.

Phenotyping

Euglycemic clamp—Insulin sensitivity and MCRI were measured by euglycemic clamp in MACAD, HTN-IR, and NIDDM-Athero under an identical protocol. During the hyperinsulinemic-euglycemic clamp (26), a priming dose of human insulin (Novolin, Clayton, NC) was given and followed by infusion for 120 minutes at a constant rate (60 mU m^{-2} min^{-1}) to establish hyperinsulinemia. Blood was sampled every 5 minutes, and the rate of 20% dextrose co-infused was adjusted to maintain plasma glucose concentrations at 95 to 100 mg/dL. The glucose infusion rate (M value, mg m^{-2} min^{-1}) over the last 30 minutes of steady-state insulin and glucose concentrations reflects glucose uptake by all tissues of the body (primarily insulin-mediated glucose uptake in muscle) and is therefore directly correlated with tissue insulin sensitivity (26). The insulin sensitivity index (mg m^{-2} min^{-1} μIU^{-1} mL) was calculated as M/I, where I is the steady-state insulin level. In this study, to clearly distinguish between insulin sensitivity and insulin clearance, we relied on M as an approximation for insulin sensitivity in our correlation analyses because the calculations of M/I and insulin clearance both use steady-state insulin in the denominator. The metabolic clearance rate of insulin (MCRI, mL m^{-2} min^{-1}) was calculated as the insulin infusion rate divided by the steady state plasma insulin level of the euglycemic clamp, as previously described (7,26).

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Frequently sampled intravenous glucose tolerance test (FSIGT)—Insulin sensitivity and MCRI were measured by FSIGT in the IRAS, IRAS-Family, BetaGene, and TRIPOD studies. Insulin-related traits were assessed by the FSIGT with minimal model analyses (27). Two modifications of the original protocol were used. An injection of insulin was used in all studies (with the exception of TRIPOD, which injected tolbutamide) to ensure adequate plasma insulin levels for the accurate computation of insulin resistance across a broad range of glucose tolerance (28). Also, the reduced sampling protocol (which requires 12 rather than 30 plasma samples and shows similar results to the full protocol (29)) was used because of the large number of individuals. Glucose in the form of a 50% solution (0.3 g/kg) and regular human insulin (0.03 units/kg) were injected through an intravenous line at 0 and 20 min, respectively. Blood was collected at −5, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min for plasma glucose and insulin concentrations. The insulin sensitivity index (S_I) was calculated by mathematical modeling methods using the MINMOD program (version 3.0 [1994]). Acute insulin response to glucose (AIRg) was calculated as the increase in insulin concentrations at 2–8 min above the basal (fasting) insulin level. MCRI was calculated as the ratio of the insulin dose over the incremental area under the curve of insulin from 20 minutes to infinity (30), using the following equation:

$$\text{Clearance}\,(\text{L}/\,\text{min})=\frac{\text{Dose}\times 1000}{\int_{t=20}^{\infty}(\text{Ins}(\text{t})-\text{Ins}(0))}$$

Here *Dose* is the amount of insulin injected at 20 min. *Ins(t)* is the plasma insulin concentration in standard units (μU/ml) at each FSIGT sampling point and *Ins(0)* is the fasting plasma insulin concentration determined prior to the FSIGT glucose injection.

Statistical analysis

The demographic and glucose homeostasis traits were examined for implausible values and multivariate outliers. Differences in phenotype across cohorts were tested using the Wilcoxon rank sum test for continuous traits and chi square test for categorical traits (gender). Within each cohort, each trait was examined for departure from conditional normality (conditional on age, gender and BMI) and homogeneity of variance. If necessary, winsorization or a transformation was applied that best approximated the distributional assumptions of conditional normality and homogeneity of variance; except for MCRI, for traits warranting transformation, the same transformation was computed across all cohorts. Transformations included natural logarithm of the trait plus a constant (S_I), natural logarithm (BMI, MCRI derived from FSIGT, fasting insulin), and square root (AIRg, M/I, M); fasting glucose and MCRI derived from clamp were not transformed. All analyses reported adjust for age and gender unless stated otherwise; the IRAS Family Study also adjusts for the clinic site (San Antonio and San Luis Valley).

Estimates of heritability (h^2) were computed for each trait using the variance components approach as implemented by SOLAR (31) in the five family-based cohorts (BetaGene, IRAS Family, HTN-IR, MACAD, NIDDM-Athero). Here, the residual phenotypic variance, after accounting for covariates (age, gender, ± BMI), is partitioned into additive genetic and non-

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genetic (environmental) components and tested using maximum likelihood methods. Similarly, common genetic (ρ_g) and environmental (ρ_e) correlations between traits were calculated using the bivariate variance component approach implemented in SOLAR (31). Statistical significance was determined via maximum likelihood tests. Heritability of MCRI and M/I, as well as genetic and environmental correlations, were not computed in NIDDM-Athero because its sample size did not allow for reliable estimation.

RESULTS

Clinical characteristics of the seven cohorts are shown in Table 1. There is a broad range in these characteristics, reflecting differences in the cohorts. The greater pedigree size of IRAS Family reflects the design of that study, which purposely sought large families. Individuals in the IRAS and IRAS Family cohorts are older than those in the other cohorts. By design, the BetaGene and TRIPOD studies have a markedly higher proportion of women. While statistically different, BMI and fasting glucose are quantitatively fairly similar across cohorts, while measures of insulin sensitivity and insulin clearance exhibit moderate variation between studies.

Heritability estimates are displayed in Table 2. Substantial heritability was observed for all glucose homeostasis traits. The heritability of MCRI in the two FSIGT cohorts (IRAS Family, BetaGene: 0.35–0.40) was lower than the heritability observed in the two clamp cohorts (MACAD, HTN-IR: 0.67–0.73). Heritability of S_I and M/I was similar in three of the four cohorts (0.39–0.44); the heritability of M/I in MACAD was slightly lower (0.23). The heritability of M, an unadjusted index of insulin sensitivity, spanned a similar range of heritability values as S_I and M/I. The heritability of AIRg was very similar between the two FSIGT cohorts (0.48–0.51). Heritabilities of the glucose homeostasis traits were similar whether or not BMI was included as a covariate (Table 2).

Table 3 lists the results of genetic and environmental correlations of MCRI with insulin sensitivity, AIRg, and BMI; these analyses are adjusted for age and gender. Within the FSIGT cohorts, strong positive genetic and environmental correlations were observed between MCRI and S_I. On the other hand, in the clamp cohorts, the pattern was less consistent, with weaker genetic and environmental correlations in HTN-IR, and non-significant genetic correlation in MACAD. Similarly, in the FSIGT cohorts, strong negative genetic and environmental correlations were seen between MCRI and BMI. In the clamp cohorts, comparable negative environmental correlations were observed, whereas the genetic correlations were essentially null. Significant negative genetic and environmental correlations were observed between MCRI and AIRg. In models additionally adjusted for BMI, the genetic and environmental correlations between MCRI and insulin sensitivity indexes (S_I and M) and between MCRI and AIRg were quantitatively similar to the results described above (data not shown).

Table 4 displays genetic and environmental correlations of AIRg with insulin sensitivity and BMI in the FSIGT cohorts. The genetic correlations in both cases were greater than the environmental correlations.

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DISCUSSION

We assembled the GUARDIAN Consortium to address knowledge gaps concerning the increased risk of T2D observed in Mexican Americans compared to European populations. Ethnic differences in the pre-clinical predictors of diabetes have been documented (32), which may arise from differences in lifestyle, physiology, and/or genetic predisposition. Yet, little data exist to fully explore potential genetic differences. The ranges of heritability for insulin sensitivity (0.23 to 0.48) and insulin secretion (0.48 to 0.51) found in the GUARDIAN cohorts are similar to those already reported for Europeans (9–16). There are no published heritability data on MCRI in Europeans for comparison to current results in Mexican Americans. Heritability of fasting glucose and fasting insulin was substantial and varied widely between cohorts, consistent with prior reports (7, 8, 11, 14, 16, 17, 20, 33, 34).

In GUARDIAN, insulin sensitivity data comes from two techniques, the euglycemic clamp and the FSIGT. In individuals of varying insulin resistance, there is a strong correlation between S_I measures from the FSIGT and from the clamp (35,36). The two variables reflect a single physiological process: the ability of insulin to enhance glucose disposal in the body (35). Multiple reports of strong correlation between minimal-model and clamp-based assessment of insulin action, and reports that S_I is genetically determined (7,16,18,23) lend credence to the idea that we will be able to utilize both measurements in a combined analysis. In support of this is the observation that the heritability estimates for the various insulin sensitivity measures (S_I, M/I, M) fell within a fairly narrow range (0.23–0.48).

MCRI from the euglycemic clamp and FSIGT both reflect fractional hepatic insulin extraction, insulin distribution kinetics, and tissue uptake of insulin. Realizing the possible limitations of heritability calculations (37), we observed that clamp-derived MCRI had greater heritability than FSIGT-derived MCRI. Thus, subtle differences in what is actually being measured may exist. For example, euglycemic clamps are performed in a hyperinsulinemic steady state, while the FSIGT reflects a dynamically changing state. With its prolonged insulin infusion, the clamp-derived MCRI, while still predominantly reflecting hepatic insulin clearance (50%), reflects substantial contributions from other tissues such as the kidneys (30%) and skeletal muscle (10%) (38), and is essentially a measure of whole-body insulin clearance. On the other hand, the FSIGT-derived MCRI of the acute insulin injection reflects mainly hepatic insulin clearance, as there is little time for the insulin to distribute widely. If renal and/or muscle insulin clearance has a greater genetic basis then hepatic clearance, this might explain the higher heritability observed in the clamp studies. Differences in pedigree structure and sample size between studies may also contribute to differences in heritability estimates for the same trait. In our study of the effect of pedigree size on estimates of heritability, we used a resampling scheme to lead us to the observation that sibpairs and smaller pedigrees tend to increase the estimate of heritability; equally important, smaller pedigrees had increased standard errors (39). Although not strictly observed here, the variation of the heritability estimates and standard errors are consistent with this observation.

The positive genetic and environmental correlations between MCRI and S_I, and the negative correlations between MCRI and BMI are consistent with prior physiologic studies (2–4).

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Within the clamp cohorts, genetic correlations between MCRI and M and between MCRI and BMI were less consistent, possibly reflecting the measurement issues discussed above. Another possible explanation may be differences in ascertainment; probands had a family history of hypertension in HTN-IR while probands in MACAD had a family history of coronary artery disease. Of note, hypertension has been associated with reduced insulin clearance (40). The negative genetic and environmental correlations between MCRI and AIRg may simply indicate that increased insulin clearance blunts the acute insulin response to glucose. The negative correlations may also stem from the opposite responses of these traits to insulin resistance, wherein insulin clearance drops and insulin secretion rises to produce compensatory hyperinsulinemia (1). Compensatory insulin secretion may explain the negative and positive correlations between AIRg and S_I and AIRg and BMI, respectively; these correlations appear to have a stronger genetic than environmental basis (Table 4). Given differences in genetic architecture observed herein, the planned GWAS for insulin sensitivity and insulin clearance will consist of association analyses conducted within each cohort separately, followed by meta-analysis.

A limitation of our study concerns the accuracy of our measurements of MCRI. Because we did not measure C-peptide levels during the euglycemic clamps to document suppression of endogenous insulin secretion, it is possible that our estimates of insulin clearance may underestimate the true values. However, because the proportion of steady state plasma insulin represented by residual insulin secretion is expected to be small during hyperinsulinemic infusion, we are confident that this had a minimal effect on our results. We also did not measure C-peptide during the FSIGT studies. To partially account for residual endogenous insulin production, our FSIGT-based calculation of MCRI utilizes the area under the curve of insulin above the basal insulin level.

In this report, the GUARDIAN Consortium has provided new insight in the genetic architecture of insulin resistance and MCRI. Our data support a strong familial basis for these traits in Mexican Americans. The strong genetic correlations between MCRI and S_I suggest common genetic determinants. The GUARDIAN GWAS will yield further insights into these two important traits in the development of T2D.

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What is already known about this subject

- Studies have reported heritability estimates ranging from 0.24 to 0.60 for insulin sensitivity, 0.35 to 0.76 for insulin secretion, and 0.58 to 0.73 for insulin clearance.
- Most heritability studies have been conducted in cohorts of European origin, highlighting the need for more studies in Mexican Americans.

What this study adds

- This study presents the structure of the GUARDIAN (Genetics UndeRlying DIAbetes in HispaNics) Consortium.
- Substantial heritability of insulin sensitivity and insulin clearance are observed in Mexican-American cohorts.
- Insulin clearance exhibits strong genetic and environmental correlations with insulin sensitivity and insulin secretion.

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Table 1

Clinical characteristics of the seven cohorts comprising GUARDIAN (mean and standard deviation, or percentage)

	FSIGT cohorts					Clamp cohorts				Overall *P* value
	BetaGene	**TRIPOD***	**IRAS***	**IRAS Family**	***P* value**	**HTN-IR**	**MACAD**	**NIDDM-Athero**	***P* value**	
Sample Size	1217	217	194	1040	-	708	772	188	-	-
Number of Pedigrees	390	217	194	88	-	156	208	93	-	-
Pedigree Size†	2 (1–12)	1	1	11 (2–30)	-	4 (1–17)	3 (1–17)	2 (1–5)	-	-
Age (yr)	34.6±8.0	34.4±6.5	58.9±8.4	40.6±13.7	<0.0001	37.3±14.1	34.5±8.9	31.7±9.59	<0.0001	<0.0001
Women (%)	72.0	100.0	58.2	59.0	<0.0001	58.9	56.7	56.9	0.68	<0.0001
BMI (kg/m^2)	29.5±6.1	30.4±5.4	28.8±5.1	28.3±5.7	<0.0001	28.7±5.5	28.9±5.1	28.5±5.9	0.39	<0.0001
Fasting Glucose (mmol/l)	5.10±0.63	5.37±0.51	5.36±0.55	5.18±0.53	<0.0001	5.30±0.54	5.12±0.57	4.87±0.71	<0.0001	<0.0001
Fasting Insulin (pmol/l)	55.8±39.6	103.8±51.6	109.8±69.0	88.8±64.2	<0.0001	93.0±63.0	96.0±54.0	88.2±51.6	0.0011	<0.0001
AIRg (pmol/l)	3457±2947	3030±2612	4093±4217	4561±3896	<0.0001	NA	NA	NA	-	-
MCRI (L/min)	10.1±5.7	NA‡	4.2±2.1	5.5±2.4	<0.0001	NA	NA	NA	-	-
MCRI ($ml\ m^{-2}\ min^{-1}$)	NA	NA	NA	NA	-	458.3±111.6	472.2±113.7	415.2±139.5	<0.0001	-
S_I ($\times 10^{-4}\ min^{-1}\ mIU^{-1}\ ml^{-1}$)	3.03±1.62	2.47±1.74	1.33±1.24	2.15±1.86	<0.0001	NA	NA	NA	-	-
M ($\mu mol\ m^{-2}\ min^{-1}$)	NA	NA	NA	NA	-	1274±546	1356±646	1252±531	0.10	-
M/I ($mg\ m^{-2}\ min^{-1}\ \mu IU^{-1}\ ml$)	NA	NA	NA	NA	-	1.82±1.01	1.94±1.07	1.64±0.97	0.013	-

P values compare trait values across FSIGT cohorts, clamp cohorts, and all cohorts. NA, not available

*TRIPOD and IRAS are studies of unrelated individuals; these studies did not contribute to the heritability estimates or genetic and environmental correlations

†Median pedigree size, with range in parentheses when applicable

‡MCRI is not available for TRIPOD because that study used tolbutamide in the FSIGT

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Table 2

Heritability (± standard error) of glucose homeostasis traits for the five family-based cohorts in GUARDIAN

Study	MCRI	S_I or M/I	M	AIRg	Fasting Glucose	Fasting Insulin
Adjusted for age and gender						
BetaGene*	0.40±0.07 (<0.0001)	0.44±0.07 (<0.0001)	NA	0.51±0.07 (<0.0001)	0.69±0.07 (<0.0001)	0.66±0.07 (<0.0001)
IRAS Family*	0.35±0.07 (<0.0001)	0.39±0.07 (<0.0001)	NA	0.48±0.07 (<0.0001)	0.25±0.06 (<0.0001)	0.30±0.07 (<0.0001)
HTN-IR†	0.67±0.10 (<0.0001)	0.43±0.10 (<0.0001)	0.34±0.10 (<0.0001)	NA	0.50±0.11 (<0.0001)	0.31±0.11 (0.0006)
MACAD†	0.73±0.10 (<0.0001)	0.23±0.09 (0.0004)	0.48±0.10 (<0.0001)	NA	0.54±0.10 (<0.0001)	0.57±0.12 (<0.0001)
NIDDM-Athero†	NA‡	NA‡	0.41±0.18 (0.0084)	NA	0.63±0.19 (0.0007)	0.13±0.21 (0.26)
Adjusted for age, gender, and BMI						
BetaGene*	0.28±0.07 (<0.0001)	0.33±0.07 (<0.0001)	NA	0.46±0.07 (<0.0001)	0.69±0.07 (<0.0001)	0.64±0.07 (<0.0001)
IRAS Family*	0.35±0.07 (<0.0001)	0.34±0.06 (<0.0001)	NA	0.47±0.07 (<0.0001)	0.28±0.06 (<0.0001)	0.25±0.06 (<0.0001)
HTN-IR†	0.59±0.10 (<0.0001)	0.54±0.10 (<0.0001)	0.51±0.10 (<0.0001)	NA	0.49±0.11 (<0.0001)	0.39±0.10 (<0.0001)
MACAD†	0.71±0.10 (<0.0001)	0.28±0.09 (0.0004)	0.40±0.10 (<0.0001)	NA	0.51±0.10 (<0.0001)	0.60±0.12 (<0.0001)
NIDDM-Athero†	NA‡	NA‡	0.33±0.18 (0.023)	NA	0.65±0.20 (0.0005)	0.29±0.23 (0.086)

P values are in parentheses. NA, not available *FSIGT studies

†Clamp studies

‡Unable to estimate due to sample size

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Table 3

Genetic and environmental correlations (± standard error) for MCRI with insulin sensitivity, AIRg and BMI

	Insulin sensitivity (S_I or M)		AIRg		BMI	
Cohort	**Genetic**	**Environmental**	**Genetic**	**Environmental**	**Genetic**	**Environmental**
BetaGene*	0.91±0.05 (<0.0001)	0.54±0.05 (<0.0001)	−0.59±0.10 (<0.0001)	−0.16±0.08 (0.060)	−0.73±0.06 (<0.0001)	−0.53±0.11 (<0.0001)
IRAS Family*	0.93±0.03 (<0.0001)	0.74±0.03 (<0.0001)	−0.57±0.10 (<0.0001)	−0.36±0.07 (<0.0001)	−0.70±0.07 (<0.0001)	−0.66±0.05 (<0.0001)
HTNIR†	0.38±0.16 (0.017)	0.25±0.12 (0.048)	NA	NA	0.02±0.19 (0.85)	−0.43±0.12 (0.0003)
MACAD†	−0.27±0.15 (0.057)	0.60±0.17 (0.0005)	NA	NA	−0.04±0.13 (0.72)	−0.55±0.16 (0.0007)

Analyses adjusted for age and gender. *P* values in parentheses. NA, not available

*FSIGT studies

†Clamp studies

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Table 4

Genetic and environmental correlations (± standard error) for AIRg with insulin sensitivity and BMI

	Insulin sensitivity (S_I)		BMI	
Cohort	**Genetic**	**Environmental**	**Genetic**	**Environmental**
BetaGene*	−0.62±0.10 (<0.0001)	−0.33±0.07 (<0.0001)	0.37±0.08 (<0.0001)	−0.05±0.18 (0.78)
IRAS Family*	−0.44±0.11 (0.0002)	−0.10±0.07 (0.14)	0.30±0.11 (0.0057)	0.19±0.10 (0.045)

Analyses adjusted for age and gender. *P* values in parentheses.

*FSIGT studies