Association of Adiposity Trajectories With Insulin Sensitivity and Glycemic Deterioration

A longitudinal study of rural Chinese twin adults

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OBJECTIVE—To evaluate associations between adiposity trajectories over time and insulin sensitivity and glucose deterioration in a Chinese twin cohort.

RESEARCH DESIGN AND METHODS—This study focused on 341 males and 292 females aged 20–50 years at baseline who had physical clinical examinations and oral glucose tolerance test at two time points with an average of 6 years apart. BMI, waist circumference, percent body fat (PBF), and percent trunk fat (PTF) trajectories were classified into five track groups based on age- and sex-specific tertiles at each visit. We calculated the odds of the insulin sensitivity index$_{(0,120)}$ [ISI$_{(0,120)}$] or glycemic deterioration at follow-up among five defined trajectories (tertile$_{baseline}$ → tertile$_{follow\text{-}up}$) using generalized estimate equation models. Additionally, we applied structural equation models to examine genetic and environmental influences on adiposity, adiposity change over time (ACO), ISI$_{(0,120)}$, and the interrelationships among them.

RESULTS—Participants with stable adiposity (BMI, waist circumference, PBF, and PTF) in the highest tertile or shifting to the highest tertile tended to have the lowest ISI$_{(0,120)}$ at follow-up or experience glycemic deterioration. Genetic factors exerted the major influence on adiposity, but environmental factors unique to each twin contributed more strongly to ISI and ACO. Correlations between adiposity/ACO and insulin sensitivity were mainly due to environmental influences.

CONCLUSIONS—When adiposity stays or becomes high, insulin sensitivity falls and risk of glycemic deterioration rises. Additionally, we found that genetic factors exerted the major influence on adiposity, while environmental factors played the principal role for ACO and insulin sensitivity.

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The paired epidemics of obesity and type 2 diabetes are evident in both developed and developing countries (1–6). In China, the prevalence of overweight (BMI ≥25 kg/m^2) in adults increased from 14.6 to 21.8% between 1992 and 2002 after rapid economic and social change (7). Similarly, the prevalence of diabetes in China rose from 5.5% in 2000–2001 to 9.7% in 2007–2008 (8). Studies have shown that adiposity accumulation leads to the dysregulation of adipocytokines, which participate in the pathogenesis of insulin resistance (9–12). Western and Eastern large population studies (8,13,14) have demonstrated that overweight/obesity is associated with increased prevalence of diabetes/prediabetes; however, most of these studies were focused on cross-sectional relationships. Fewer investigations have explored longitudinal associations between adiposity and indicators of type 2 diabetes or prediabetes (15,16). Even fewer such studies have been conducted in China, which now has overtaken India as home to the largest population with type 2 diabetes in the world (17). Furthermore, in most population studies, BMI has been commonly applied, although it has been criticized as an inadequate measure of adiposity, particularly in Asian populations. In fact, an Asian population study (18) has confirmed that the risk for type 2 diabetes starts at a lower BMI in Asians than in Europeans. But data are lacking regarding the relationship of adiposity, insulin, and diabetes with adiposity measured through more accurate methods.

Given these reasons and the current epidemics of obesity and type 2 diabetes in China, it is important to gain a deeper understanding of the relationship between adiposity trajectory on insulin function and glycemic deterioration. The Anqing Twin Cohort Study provides a unique opportunity to examine longitudinal trends of adiposity and associated change in insulin sensitivity and glucose homeostasis as well as estimate genetic and environmental contributions to adiposity, adiposity change over time (ACO), insulin sensitivity, and the correlations among them.

RESEARCH DESIGN AND METHODS

We used data from the longitudinal Anqing Twin Cohort Study, which has previously been described (19). No twins in this study were raised in two different families. Briefly, a baseline study was carried out in eight rural counties of Anqing from 1998 to 2000; follow-up data were collected from 2005 to 2006. Participants were invited to a central office and stayed overnight to complete an interview-based questionnaire, oral glucose tolerance test (OGTT), physical exam, and dual-energy X-ray absorptiometry (DEXA) scans at baseline and follow-up. Physical examinations were conducted by physicians specifically trained for the study. After exclusion of 34 subjects with outlier values (outside ±3 SD) in insulin sensitivity index$_{(0,120)}$ [ISI$_{(0,120)}$] (6) and 6 subjects whose glucose level at baseline met the study standard for diabetes, there were 633 adult twins aged 20–50 years at baseline who had available DEXA scan results, had OGTT at both time points, completed zygosity determination, and were eligible for this proposed study. The study protocol was approved by the institutional review boards of Children's Memorial Hospital, Chicago, Illinois, and the Institute of Biomedicine, Anhui Medical University, Hefei, China.

Anthropometry

Height was measured without shoes to the nearest 0.1 cm on a portable stadiometer. Weight was measured without shoes to the nearest 0.1 kg with the subject standing motionless in the center of a calibrated scale. Waist circumference was measured as the minimum circumference between the interior margin of the rib cage and the crest of the ileum. The mean value of three measurements was used. A standard whole-body DEXA (20) scan was performed to determine both percent body fat (PBF) and percent trunk fat (PTF). Adiposity and ACO from baseline to follow-up were defined as follows:

$$\text{BMI} = \text{weight (kilograms)/height squared (meters squared)}$$

$$\text{PTF} = \text{trunk fat mass (kilograms)/body weight (kilograms)} \times 100$$

$$\text{PBF} = \text{body fat mass (kilograms)/body weight (kilograms)} \times 100$$

$$\Delta\text{BMI} = \text{BMI}_{\text{follow-up}} - \text{BMI}_{\text{baseline}}$$

$$\Delta\text{WC} = \text{WC}_{\text{follow-up}} - \text{WC}_{\text{baseline}}$$

$$\Delta\text{PBF} = \text{PBF}_{\text{follow-up}} - \text{PBF}_{\text{baseline}}$$

$$\Delta\text{PTF} = \text{PTF}_{\text{follow-up}} - \text{PTF}_{\text{baseline}}$$

Adiposity trajectories

For each adiposity measure, we first determined age- and sex-specific tertiles at baseline and follow-up, which led to nine possible trajectories. We then regrouped these trajectories into five levels based on patterns of ISI$_{(0,120)}$ (6) at follow-up across nine strata (Supplementary Table 1). Specifically, the five trajectories identified in Table 1 are as follows: *1*) reference: stable in lowest tertile, middle tertile falling to lowest tertile, stable in middle tertile, or highest tertile falling to lowest tertile; *2*) 1R (low rising slightly): lowest tertile at baseline, middle tertile at follow-up; *3*) 1/2R (low/middle rising): lowest or middle tertile at baseline, highest at follow-up; *4*) 3F (high falling slightly): highest tertile at baseline, middle tertile at follow-up; and *5*) 3S (high and stable): highest tertile at both baseline and follow-up.

Insulin sensitivity and glucose deterioration assessments

OGTT was conducted using standard procedures (World Health Organization,1985) in all subjects. A 75-g oral glucose equivalent load was administered after 12–14 h fasting. Blood specimens were obtained at 0 and 2 h for determination of plasma glucose and serum insulin concentration. Laboratory assay methods have previously been described (21). We used ISI$_{(0,120)}$ as a measure of insulin sensitivity, which estimates the disposition of plasma glucose given body weight and ambient insulin levels. The ISI$_{(0,120)}$ formula is as follows:

$$\text{ISI}_{(0,120)} = M/\text{MPG}/\log\text{MSI}$$

$$M \text{ (glucose uptake in peripheral tissue)} = [75{,}000 \text{ mg} + (0 \text{ min glucose} - 120 \text{ min glucose}) \times 0.19 \times \text{body weight}]/120 \text{ min}$$

where MPG is mean plasma glucose of the 0- and 120-min glucose values from the OGTT and MSI is mean insulin of the 0- and 120-min insulin values.

Type 2 diabetes was defined based on self-reported history or OGTT results of fasting plasma glucose ≥7.0 mmol/L and/or 2-h plasma glucose ≥11.1 mmol/L.

Prediabetes was defined to include any of three indicators of abnormal glucose tolerance according to American Diabetes Association diagnostic criteria (22): isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), or combined IFG and IGT (IFG&IGT).

Glycemic deterioration was ascertained for subjects with any change of the following: *1*) normal glucose at baseline but abnormal (IGT, IFG, IGT&IFG, or type 2 diabetes) at follow-up, *2*) IGT or IFG at baseline and IGT&IFG at follow-up, and *3*) IGT, IFG, or IGT&IFG at baseline and type 2 diabetes at follow-up.

Zygosity identification

Zygosity of each twin was determined using DNA fingerprint technology by genotyping 10 microsatellite markers with high heterozygosity (>70%) that were located on different somatic chromosomes as previously described (19).

Statistical analysis

PBF and PTF variables were normalized by natural logarithm for all statistical testing, as the original values were skewed. Student *t* test was used to compare differences between means of continuous variables. χ^2 tests were used to compare differences in proportions of categorical variables.

Taking advantage of the longitudinal design of the cohort, we examined the association between adiposity trajectory and prediabetes indicators, using the adiposity trajectory categories described above. For each of four defined trajectories, we compared the odds of the lower tertile of ISI$_{(0,120)}$ or glycemic deterioration with the reference trajectory. Generalized estimating equation models were applied to account for intratwin pair correlation. All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC).

Taking advantage of the twin design of the cohort, we estimated genetic and environmental contributions to each adiposity measure, ACO, and ISI$_{(0,120)}$ at follow-up as well as to adiposity/ACO-ISI$_{(0,120)}$ correlations. As the variance estimation did not support collapse over sex groups (data not shown), we performed bivariate Cholesky structural equation models (SEMs) by sex using Mx software (http://www.psy.vu.nl/mxbib). Age-adjusted residuals of adiposity, ACO, and ISI were used in all the SEM analyses. Variance component estimates were based on the most parsimonious unconstrained model. Because of the small number of dizygotic twins with different sex, SEM analyses only focused on 208 monozygotic and 102 same-sex dizygotic twin pairs.

Table 1—*Sample characteristics* (N = 633‡)

	Baseline		Follow-Up	
	Male	Female	Male	Female
n	341	292	341	292
Age (years)	34.7 (7.5)	33.2 (6.2)[a]	41.3 (7.4)	3 9.8 (6.3)[a]
BMI (kg/m^2)	21.2 (2.0)	21.4 (2.4)	21.9 (2.5)	22.4 (2.7)[a]
Waist circumference (cm)	70.6 (6.1)	69.4 (6.4)[b]	74.8 (8.1)	73.6 (8.2)
PBF (%)	10.1 (5.1)	24.2 (5.7)[a]	13.8 (7.6)	28.8 (6.3)[a]
PTF (%)	5.3 (2.9)	11.8 (3.5)[a]	7.8 (4.8)	15.0 (4.2)[a]
Fasting plasma glucose (mmol/L)	4.5 (0.6)	4.5 (0.5)	5.4 (0.7)	5.4 (0.6)
2HPG (mmol/L)	4.2 (1.2)	4.8 (1.0)[a]	5.2 (1.7)	6.3 (1.9)[a]
$ISI_{(0,120)}$ (mg · L^2 · mmol^{-1} · mU^{-1})	77.1 (35.8)	62.0 (25.6)[a]	62.2 (30.3)	40.4 (11.6)[a]
Overweight, *n* (%)#	18 (5.3)	13 (4.5)	32 (9.4)	44 (15.1)
Obesity, *n* (%)#	0 (0.0)	2 (0.7)	1 (0.3)	4 (1.4)
Prediabetes, *n* (%)	12 (3.5)	14 (4.8)	105 (30.8)	101 (34.5)
Type 2 diabetes, *n* (%)	—	—	7 (2.1)	8 (2.7)

Data are means (SD) unless otherwise indicated. 2HPG, 2-h postprandial glucose. $ISI_{(0,120)}$ = *M*/MPG/logMSI; *M* (glucose uptake in peripheral tissue) = [75,000 mg + (0 min glucose − 120 min glucose) × 0.19 × body weight]/120 min, where MPG is mean plasma glucose of the 0- and 120-min glucose values from the OGTT and MSI is the mean insulin of the 0- and 120-min insulin values. ‡Subjects with type 2 diabetes (*n* = 3) at baseline were excluded. [a]$P < 0.05$ compared with male at same time point. [b]$P < 0.01$ compared with male at same time point. #World Health Organization classification of adult overweight and obesity: overweight, BMI ≥25 kg/m^2; obese, BMI ≥30 kg/m^2.

RESULTS—The distribution of demographic and anthropometric characteristics, plasma glucose, ISI, and glucose tolerance among 633 study subjects is presented in Table 1. The mean age at follow-up was 41.3 years for males and 39.8 years for females. As expected, all adiposity measures and glucose levels were significantly higher at follow-up than at baseline in both sexes. Insulin sensitivity decreased over the 6-year period in parallel with marked rises in prediabetes (3.5–30.8% for males; 4.8–34.5% for females). During the same period, in this relatively lean population (average BMI ~21–22 kg/m^2), varying with subgroup (time points and sex), overweight/obesity climbed modestly for males (~5–9.7%) but drastically for females (~5–16.7%).

The proportion of prediabetes at baseline was just 4%. At follow-up, 200 (32%) subjects met criteria for prediabetes, of whom 186 converted from normal glucose tolerance at baseline. There were only 15 (2.4%) newly developed cases of type 2 diabetes at follow-up, 11 of which transformed from normal glucose tolerance (Supplementary Table 2).

Table 2 presents the odds ratios (ORs) for lower $ISI_{(0,120)}$ and glycemic deterioration at follow-up in relation to adiposity trajectory, as defined in RESEARCH DESIGN AND METHODS. Compared with the reference, subjects stable in or shifting to the highest tertile were more likely to have lower $ISI_{(0,120)}$ and experience glycemic deterioration at follow-up. For instance, the ORs of lower $ISI_{(0,120)}$ and glycemic deterioration at follow-up were 2.7 (95% CI 1.8–4.3) and 2.1 (1.4–3.3), respectively, for subjects whose BMI remained in the highest tertile compared with the reference trajectory. Meanwhile, the ORs of lower $ISI_{(0,120)}$ and glycemic deterioration at follow-up were 1.8 (1.0–3.1) and 2.2 (1.2–3.8), respectively, for subjects whose BMI status shifted from low/middle to the highest tertile compared with the reference. Similar significant associations were observed for PBF, PTF, and waist circumference trajectories. No increased risk of lower $ISI_{(0,120)}$ or glycemic deterioration was observed for other trajectories, with two exceptions. For the 3F trajectories (highest tertile falling to middle tertile) of PBF and PTF, a higher risk of glycemic deterioration was observed, with ORs of 2.0 (1.1–3.6) and 2.2 (1.3–3.9), respectively. Furthermore, the results of our analysis remained the same even after adjustment for smoking, alcohol consumption, education, physical activity levels, and menopause at follow-up (data not shown).

Figures 1 and 2 present estimated genetic and environmental contributions to adiposity measures (BMI, PBF, waist circumference, and PTF), $ISI_{(0,120)}$ at follow-up, ACO, and the correlations among them. For BMI, PBF, waist circumference, and PTF at follow-up, genetic factors contributed much more than environmental factors, with heritability estimates of 64–70% in both sexes. However, for ACO and $ISI_{(0,120)}$ at follow-up, variances were more attributable to environmental than to genetic factors. For ACO, heritability was 23–41% for males and 13–37% for females, except for ΔBMI for males (heritability ~60%). Similarly, the heritability for $ISI_{(0,120)}$ was only 38% for males and 23% for females.

Each pair correlation linking adiposity to $ISI_{(0,120)}$ was slightly stronger than the corresponding pair correlation between adiposity variation and $ISI_{(0,120)}$. For example, the correlation coefficient for BMI-$ISI_{(0,120)}$ was −0.23, while that of ΔBMI-$ISI_{(0,120)}$ was −0.15. Bivariate Cholesky decomposition models showed that each adiposity/adiposity variation–$ISI_{(0,120)}$ was modestly environmentally correlated, indicating that these paired traits share some environmental factors. Weak genetic correlations ($r_{TP} < 0.40$) were not statistically significant.

CONCLUSIONS—To our knowledge, this study provides unique information regarding how adiposity trajectories are associated with insulin sensitivity and impaired glucose tolerance in a lean Chinese rural population. The current study is the first to estimate genetic and environmental contributions to adiposity and adiposity variations at the same time.

Three main findings

First, the data were collected during a 6-year interval of significant change in adiposity among the study population. The prevalence of prediabetes in this lean Chinese rural population increased from a low level at baseline (3.5% in males; 4.8% in females) to >30%, which slightly exceeded the reported prevalence of prediabetes in rural Koreans (23) in 2003 (26.1% in males; 20.5% in females). This discovery is also in line with the recent report of the 2007–2008 national prevalence of type 2 diabetes and prediabetes in China (8). The result from this national survey suggests that the level of economic development and associated lifestyle and diet change made the main contribution to the high prevalence of type 2 diabetes/prediabetes in China. In China between 1992 and 2002, the per capita gross domestic product rose by more than 10-fold, which is paralleled with the proportion of energy intake from animal foods elevated from 9.3 to 13.7%

Table 2—*Risk of low ISI and glycemic deterioration by adiposity trajectory in a Chinese twin study* (N = 633)

	Lowest $ISI_{(0,120)}$ tertile at follow-up		Glycemic deterioration[a]	
Adiposity trajectory^	*n* (%)	OR (95%CI)	*n* (%)	OR (95%CI)
BMI				
Reference	307 (25.4)	1.0	307 (26.4)	1.0
3S	144 (48.6)	2.7 (1.8–4.3)#	144 (41.0)	2.2 (1.4–3.4)#
1/2R	67 (37.3)	1.8 (1.0–3.1)	67 (41.8)	2.1 (1.2–3.8)‡
1R	60 (26.7)	1.1 (0.6–2.1)	60 (33.3)	1.3 (0.7–2.4)
3F	55 (36.4)	1.6 (0.8–3.1)	55 (34.5)	1.3 (0.7–2.4)
PBF				
Reference	308 (22.4)	1.0	308 (27.6)	1.0
3S	145 (53.5)	3.8 (2.4–6.0)#	145 (39.3)	2.1 (1.3–3.2)‡
1/2R	66 (42.4)	2.3 (1.3–4.2)‡	66 (42.4)	2.2 (1.3–4.0)‡
1R	61 (32.8)	1.8 (1.0–3.2)	61 (23.0)	1.0 (0.6–1.6)
3F	53 (28.3)	1.3 (0.7–2.5)	53 (43.4)	1.9 (1.0–3.4)*
Waist circumference				
Reference	299 (25.1)	1.0	299 (28.1)	1.0
3S	126 (53.2)	3.3 (2.1–5.3)#	126 (43.7)	2.2 (1.2–3.4)#
1/2R	85 (40.0)	2.0 (1.2–3.3)‡	85 (38.8)	2.0 (1.2–3.4)*
1R	67 (31.3)	1.3 (0.8–2.4)	67 (28.4)	1.1 (0.6–2.0)
3F	56 (23.2)	1.0 (0.6–1.9)	56 (28.6)	1.1 (0.6–2.0)
PTF				
Reference	314 (22.9)	1.0	314 (27.1)	1.0
3S	150 (55.3)	4.0 (2.6–6.2)#	150 (38.0)	1.8 (1.1–2.7)‡
1/2R	61 (42.6)	2.4 (1.3–4.4)‡	61 (41.0)	2.3 (1.3–4.1)‡
1R	58 (28.1)	1.3 (0.7–2.5)	57 (26.3)	1.0 (0.6–1.8)
3F	51 (23.5)	1.0 (0.5–2.0)	51 (49.0)	2.1 (1.3–3.9)*

[a]Glycemic deterioration is defined as subjects whose glucose tolerance was normal at baseline but abnormal (IGT, IFG, or type 2 diabetes) at follow-up and subjects who were IGT or IFG at baseline but had combined IGT and IFG or type 2 diabetes at follow-up. ^Age- and sex-specific tertiles were calculated for all adiposity measures. #$P < 0.001$. ‡$P < 0.01$. *$P < 0.05$.

and that from fats from 22 to 29.8% (4). Urbanization and universal use of automobiles have caused many Chinese to shift from a physically active lifestyle to a sedentary lifestyle. Increasing numbers of Chinese are employed in less labor-demanding occupations as China's growing economy becomes an important part of the global economy. The drastic rise in prevalence of prediabetes/type 2 diabetes in our study may also be due to twin-specific features in our study population, such as low birth weight and exposure to undernutrition in utero. Insults or stresses during the intrauterine period can lead to permanent changes in structure, metabolism, and physiology through altered expression of the genome without changes in the DNA codes, i.e., epigenetics (24). Other population studies have also shown that early life events relate to later susceptibility to diabetes (25,26).

Second, two types of adiposity trajectories were observed to be associated with falling insulin sensitivity and deteriorating glucose tolerance: stable in the highest tertile and shifting to the highest tertile. These findings indicate that either maintaining or achieving unfavorable adiposity status can contribute to the pathophysiology of insulin resistance and diabetes. Such results from our study are consonant with a recent report that showed that baseline waist circumference and the long-term increment in waist circumference were associated with worsening insulin resistance in African American and white adult populations (16). The findings are also in line with the theory that adiposity, especially central adiposity, contributes to metabolic deregulation and diabetogenesis. Our findings clarify the relationship between adiposity trajectory and insulin sensitivity and glucose tolerance and thus enhance the body of knowledge on adiposity-diabetes associations. The mechanisms underlying this association of adiposity and diabetes may include dysregulation of adipocytokines and other active molecules produced by adipocytes, which increase with higher adiposity accumulations (27,28). The more counterintuitive finding—that a modest fall from the highest adiposity level for PBF or PTF is associated with increased risk of glycemic deterioration—may indicate the impact of high adiposity level at baseline on glucose tolerance and possibly increased lipolysis; the latter always in parallel with uncontrolled glucose in preobese subjects with newly developed diabetes results in a fall in adiposity.

Finally, this study has shown that insulin sensitivity is principally determined by environmental factors, while adiposity measures are mainly influenced by genetic factors. Intriguingly, adiposity variation is also under more environmental than genetic influence. The finding on adiposity heritability is in agreement with our previous study (29,30), which suggests that the majority of variance in BMI, waist circumference, and PBF is attributable to genetic influence. However, our estimation of heritability of insulin sensitivity in adults is lower than in an earlier British study (31), where the heritability of quantitative insulin sensitivity check index was >50%. We speculate that the difference is due to the gene-obesity interaction discovered by Wang et al. (31), i.e., that gene-obesity interactions result in different heritability estimates at different BMI levels. According to this theory, it is possible that our lean Chinese subjects (BMI 21.9 kg/m^2 in males and 22.4 kg/m^2 in females) confine the expression of genes relevant to insulin resistance, leading to low heritability estimation for insulin sensitivity. This would be consistent with studies showing that BMI or obesity status can modify the associations between interleukin-6, ectonucleotide pyrophosphatase/phosphodiesterase 1, angiotensin-converting enzyme, and insulin receptor substrate-1 genotypes and insulin resistance or the risk of diabetes (29–31).

This study has several strengths. DEXA-based adiposity measures were used, allowing for highly accurate adiposity assessment. We applied a dynamic insulin function index, $ISI_{(0,120)}$, derived from both the fasting and postload glucose and insulin concentrations, which is highly correlated with insulin sensitivity as measured by the gold standard euglycemic-hyperinsulinemic clamp method and is the best available surrogate measure of insulin resistance for prediction of type 2 diabetes (32). Additionally, thus far this is the first report to estimate the heritability of ACO. On the other hand, since we have only two data collection points, we cannot assess complex adiposity fluctuations.

In summary, in this lean, rural Chinese twin adult sample, we found that

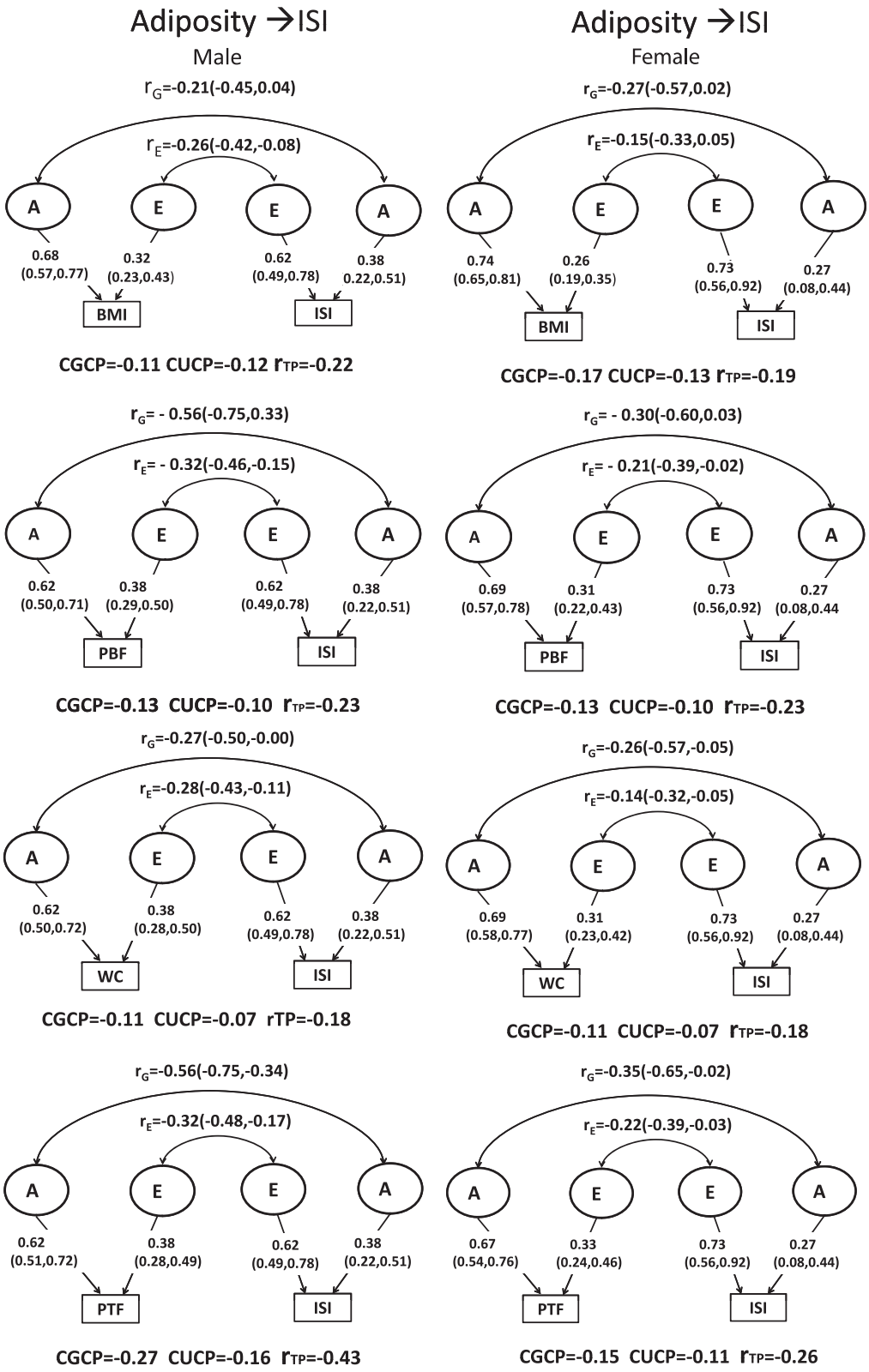

Figure 1—*Estimates of genetic (r_G) and environmental (r_E) correlations between adiposity measures (BMI, waist circumference [WC], PBF, and PTF) and ISI$_{(0,120)}$ at follow up. A, genetic variance component; CGCP, genetic contribution to the correlation between two phenotypes; CUCP, unique environmental contribution to the correlation between two phenotypes; E, environmental variance component; r_G, genetic correlation between two phenotypes; r_E, unique environmental correlation between two phenotypes; r_{TP}, phenotype correlation between insulin sensitivity and adiposity measures.*

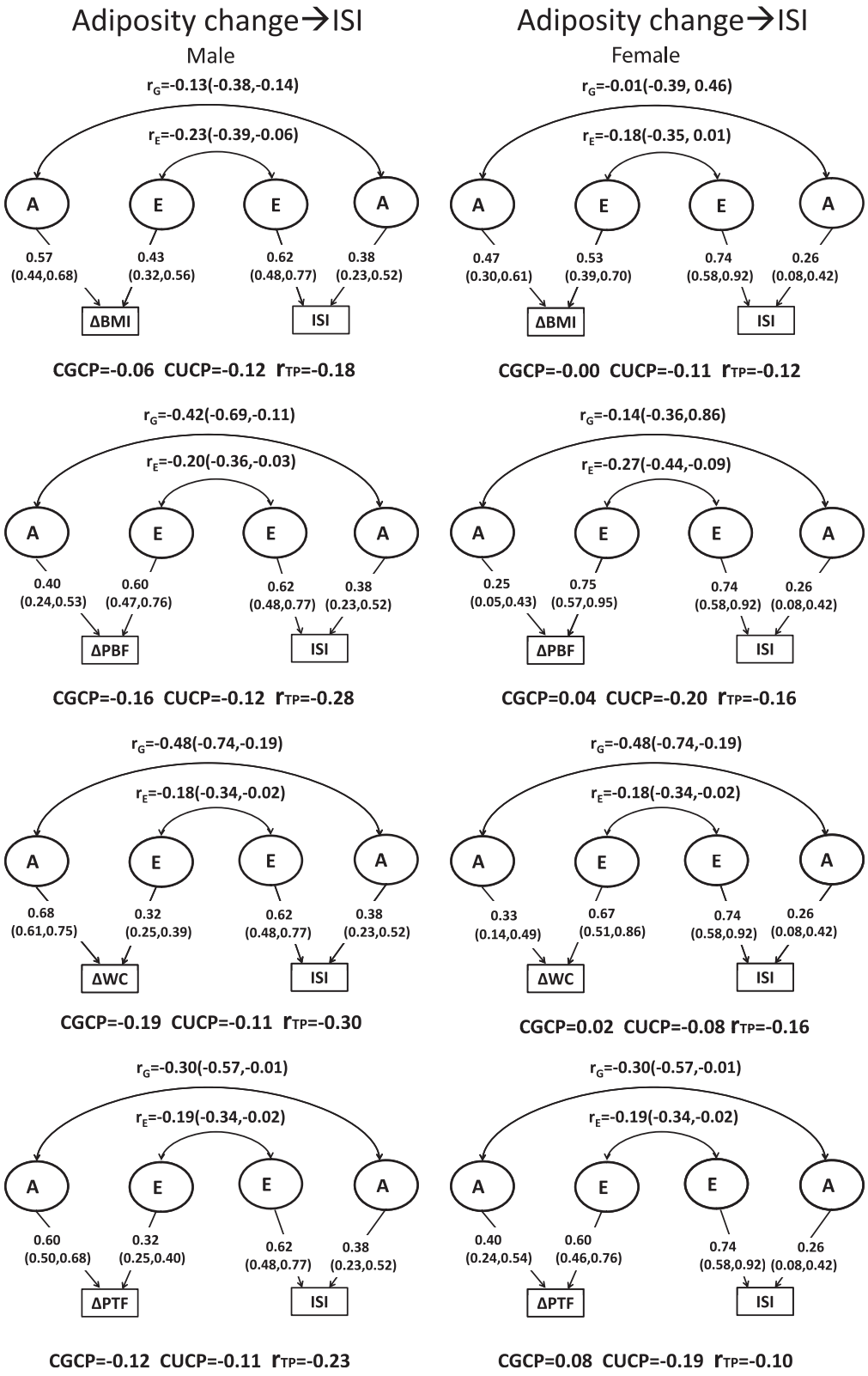

Figure 2—*Estimates of genetic (r_G) and environmental (r_E) correlations between ACO (ΔBMI, ΔPBF, ΔPTF, or Δwaist circumference [WC]) and $ISI_{(0,120)}$ at follow-up. A, genetic variance component; $\Delta BMI = BMI_{follow\text{-}up} - BMI_{baseline}$; CGCP, genetic contribution to the correlation between two phenotypes; CUCP, unique environmental contribution to the correlation between two phenotypes; E, environmental variance component; ΔPBF, $PBF_{follow\text{-}up} - PBF_{baseline}$; ΔPTF, $PTF_{follow\text{-}up} - PTF_{baseline}$; r_E, unique environmental correlation between two phenotypes; r_G, genetic correlation between two phenotypes; r_{TP}, phenotype correlation between insulin sensitivity and adiposity change measures; ΔWC, $WC_{follow\text{-}up} - WC_{baseline}$.*

when adiposity stays or becomes high, insulin sensitivity falls and risk of glycemic deterioration rises. In addition, we found that genetic factors exerted the major influence on adiposity, while environmental factors played the principal role in adiposity variation and insulin sensitivity. These results shed light on the possibility that the susceptibility to type 2 diabetes determined by genetic factors can be counteracted by environmental factors such as diet and exercise, indicating that strategies to constrain levels of adiposity and a rise in adiposity may improve insulin sensitivity and reduce the risk of diabetes.

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R.L. contributed to the study concept, data analysis, interpretation, manuscript drafting, critical review, and revision of the manuscript. W.J.B., K.K.C, and X.L. contributed to the study concept, interpretation, critical review, and revision of the manuscript. G.W. and L.A. contributed to the study concept, data analysis, and interpretation. S.Z. and B.W. researched data. D.Z. contributed to the study concept, data analysis, and interpretation. X.X. contributed to the development of the twin cohort, secured funding, and researched data. Z.L. and H.X. researched data. X.W. contributed to the development of the twin cohort, secured funding, and contributed to the study concept and data analysis. X.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Imbeault P, Haman F, Blaise JM, et al. Obesity and type 2 diabetes prevalence in adults from two remote first nations communities in Northwestern Ontario, Canada. J Obes 2011; 2011:267509
2. Sundborn G, Metcalf PA, Gentles D, et al. Overweight and obesity prevalence among adult Pacific peoples and Europeans in the Diabetes Heart and Health Study (DHAHS) 2002-2003, Auckland New Zealand. N Z Med J 2010;123:30–42
3. Mohan V, Mathur P, Deepa R, et al. Urban rural differences in prevalence of self-reported diabetes in India—the WHO-ICMR Indian NCD risk factor surveillance. Diabetes Res Clin Pract 2008;80:159–168
4. Wang Y, Mi J, Shan XY, Wang QJ, Ge KY. Is China facing an obesity epidemic and the consequences? The trends in obesity and chronic disease in China. Int J Obes (Lond) 2007;31:177–188
5. Goodpaster BH, Thaete FL, Kelley DE. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. Am J Clin Nutr 2000;71:885–892
6. Gutt M, Davis CL, Spitzer SB, et al. Validation of the insulin sensitivity index (ISI (0,120)): comparison with other measures. Diabetes Res Clin Pract 2000;47:177–184
7. Gu D, Reynolds K, Wu X, et al.; InterASIA Collaborative Group. Prevalence of the metabolic syndrome and overweight among adults in China. Lancet 2005;365: 1398–1405
8. Yang W, Lu J, Weng J, et al.; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. N Engl J Med 2010;362:1090–1101
9. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259:87–91
10. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature 1998;395:763–770
11. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 1998;83:847–850
12. Whitehead JP, Richards AA, Hickman IJ, Macdonald GA, Prins JB. Adiponectin—a key adipokine in the metabolic syndrome. Diabetes Obes Metab 2006;8:264–280
13. Gregg EW, Cadwell BL, Cheng YJ, et al. Trends in the prevalence and ratio of diagnosed to undiagnosed diabetes according to obesity levels in the U.S. Diabetes Care 2004;27:2806–2812
14. Liu S, Wang W, Zhang J, et al. Prevalence of diabetes and impaired fasting glucose in Chinese adults, China National Nutrition and Health Survey, 2002. Prev Chronic Dis 2011;8:A13
15. Lawlor DA, Benfield L, Logue J, et al. Association between general and central adiposity in childhood, and change in these, with cardiovascular risk factors in adolescence: prospective cohort study. BMJ 2010;341:c6224
16. Park K, Lee DH, Erickson DJ, Himes JH, Shikany JM, Jacobs DR Jr. Association of long-term change in waist circumference with insulin resistance. Obesity (Silver Spring) 2010;18:370–376
17. New diabetes figures in China [article online], 2010. Brussels, Belgium, International Diabetes Federation. Available from http://www.idf.org/node/23563. Accessed 25 September 2011
18. Huxley R, James WP, Barzi F, et al.; Obesity in Asia Collaboration. Ethnic comparisons of the cross-sectional relationships between measures of body size with diabetes and hypertension. Obes Rev 2008;9(Suppl. 1):53–61
19. Wang B, Necheles J, Ouyang F, et al. Monozygotic co-twin analyses of body composition measurements and serum lipids. Prev Med 2007;45:358–365
20. DeVita MV, Stall SH. Dual-energy X-ray absorptiometry: a review. J Ren Nutr 1999; 9:178–181
21. Wang G, Liu X, Christoffel KK, et al. Prediabetes is not all about obesity: association between plasma leptin and prediabetes in lean rural Chinese adults. Eur J Endocrinol 2010;163:243–249
22. American Diabetes Association. Standards of medical care in diabetes—2011. Diabetes Care 2011;34(Suppl. 1):S11–S61
23. Lee JE, Jung SC, Jung GH, et al. Prevalence of diabetes mellitus and prediabetes in Dalseong-gun, Daegu City, Korea. Diabetes Metab J 2011;35:255–263
24. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 2008;359:61–73
25. Mi J, Law C, Zhang KL, Osmond C, Stein C, Barker D. Effects of infant birthweight and maternal body mass index in pregnancy on components of the insulin resistance syndrome in China. Ann Intern Med 2000;132:253–260
26. Yajnik CS, Fall CH, Vaidya U, et al. Fetal growth and glucose and insulin metabolism in four-year-old Indian children. Diabet Med 1995;12:330–336
27. Spiegelman BM, Flier JS. Obesity and the regulation of energy balance. Cell 2001; 104:531–543
28. Fasshauer M, Paschke R. Regulation of adipocytokines and insulin resistance. Diabetologia 2003;46:1594–1603
29. Ouyang F, Christoffel KK, Brickman WJ, et al. Adiposity is inversely related to insulin sensitivity in relatively lean Chinese adolescents: a population-based twin study. Am J Clin Nutr 2010;91:662–671
30. Zhang S, Liu X, Yu Y, et al. Genetic and environmental contributions to phenotypic components of metabolic syndrome: a population-based twin study. Obesity (Silver Spring) 2009;17:1581–1587
31. Wang X, Ding X, Su S, et al. Heritability of insulin sensitivity and lipid profile depend on BMI: evidence for gene-obesity interaction. Diabetologia 2009;52:2578–2584
32. Hanley AJ, Williams K, Gonzalez C, et al.; San Antonio Heart Study; Mexico City Diabetes Study; Insulin Resistance Atherosclerosis Study. Prediction of type 2 diabetes using simple measures of insulin resistance: combined results from the San Antonio Heart Study, the Mexico City Diabetes Study, and the Insulin Resistance Atherosclerosis Study. Diabetes 2003;52:463–469