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 points within 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 at (ISI0,120) or glycemic deterioration at follow-up among five defined trajectories (tertile baseline → tertile follow-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), ISI0,120, 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 ISI0,120 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.

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/m²) 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 (8,13,14) studies 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.
**Adiposity trajectories, insulin sensitivity, and glycemic deterioration**

**RESEARCH DESIGN AND METHODS AND PROCEDURE**—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 \( \text{ISI}_{[0,120]} \) (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, OGTT at both time points, and 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:

\[
\text{BMI} = \frac{\text{weight (kilograms)}}{\text{height (meters squared)}}
\]

\[
\text{PTF} = \frac{\text{trunk fat mass (kilograms)}}{\text{body weight (kilograms) \times 100}}
\]

\[
\text{PBF} = \frac{\text{body fat mass (kilograms)}}{\text{body weight (kilograms) \times 100}}
\]

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

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

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

\[
\Delta WC = WC_{\text{follow-up}} - WC_{\text{baseline}}
\]

**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 \( \text{ISI}_{0,120} \) (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 \( \text{ISI}_{0,120} \) as a measure of insulin sensitivity, which estimates the disposition of plasma glucose given body weight and ambient insulin levels. The \( \text{ISI}_{0,120} \) formula is as follows:

\[
\text{ISI}_{0,120} = \frac{M}{\text{MPG} \times \text{logMSI}}
\]

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

where MPG is mean plasma glucose of the 0- and 120-min glucose values from the OGTT and MS1 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%) and 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. \( \chi^2 \) 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 \( \text{ISI}_{0,120} \) 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 \( \text{ISI}_{0,120} \) at follow-up as well as to adiposity/ACO-\( \text{ISI}_{0,120} \) 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.psych.uva.nl/mxlib). Age-adjusted residuals of adiposity, ACO, and \( \text{ISI}_{0,120} \) 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.
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 ages at follow-up were 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/m²), varying with subgroup (time points and sex), overweight/obesity climbed modestly for males (~5.9–7.7%) 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) 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 (rtp < 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 for the high prevalence of type 2 diabetes/prediabetes in China. In China between 1992 and 2002, the per capita gross domestic product had raised by more than 10-fold, which is paralleled with the proportion of energy intake from animal foods elevated from 9.3 to 13.7%
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 also have 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 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/m² in males and 22.4 kg/m² 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 (IL-6), ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1), angiotensin-converting enzyme (ACE), and insulin receptor substrate-1 (IRS-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.
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; ΔBMI = BMIfollow-up − BMIbaseline; CGCP, genetic contribution to the correlation between two phenotypes; CUCP, unique environmental contribution to the correlation between two phenotypes; E, environmental variance component; ΔPBF, PBFfollow-up − PBFbaseline; ΔPTF, PTFfollow-up − PTFbaseline; rE, unique environmental correlation between two phenotypes; rG, genetic correlation between two phenotypes; rTP, phenotype correlation between insulin sensitivity and adiposity change measures; ΔWC, WCfollow-up − WCbaseline.
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 like 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 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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