Associations of Different Adipose Tissue Depots with Insulin Resistance: A Systematic Review and Meta-analysis of Observational Studies

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Fat distribution is strongly associated with insulin resistance, a risk factor for type 2 diabetes and cardiovascular diseases. However, associations of different adipose tissue depots with insulin resistance have not been systematically evaluated. In this study we examined associations of different adipose tissue depots/obesity indices with insulin resistance, as measured by homeostatic model assessment of insulin resistance (HOMA-IR) in observational studies. A total of 40 studies with 56 populations and 29 adipose tissue depots/obesity indices were included in the meta-analysis. There were strong correlation between HOMA-IR and visceral fat mass ($r = 0.570$, 95% confidence interval(CI): 0.424–0.687), total fat mass ($r = 0.492$, 95%CI: 0.407–0.570), body mass index ($r = 0.482$, 95%CI: 0.445–0.518) and waist circumference ($r = 0.466$, 95%CI: 0.432–0.500), except lower extremity fat ($r = 0.088$, 95%CI: −0.116–0.285). Sample size, diabetic status, gender, mean of body mass index, and race contributed to heterogeneity of these associations. This study showed a positive correlation between insulin resistance and most adipose tissue depots/obesity indices, and the strongest association is for visceral fat mass.

Insulin resistance, a key determinant of metabolic syndrome1–3, is an important risk factor for type 2 diabetes1 and cardiovascular diseases4,5. Adiposity, a major determinant of insulin resistance6–8, and its distribution measures have been shown to be associated with insulin resistance by a number of studies7,9–19. However, to what extent various adipose tissue depots and obesity indices are associated with insulin resistance has not been systematically evaluated.

Among insulin resistance indices, homeostatic model assessment of insulin resistance (HOMA-IR) is the most commonly used in population studies20,21. In this meta-analysis, we systematically examined the associations of HOMA-IR with different indices of adiposity and body fat distribution, such as body mass index (BMI)12–14, waist circumference15,16, trunk fat mass17–19, visceral fat22,23, and total fat mass23,24 to identify which of the adipose tissue depots/obesity indices has the best association with insulin resistance.

Result

Basic characteristics of the included studies. A total of 29 adipose indices were reportedly associated with HOMA-IR. 17/29 indices were not included in the meta-analysis because they were reported only once or twice (Table 1). The remaining 12 adipose tissue depots/obesity indices that were reported more than three times were analyzed with meta-analysis.

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The correlations between HOMA-IR and the 17 adipose indices that were excluded from the meta-analysis.

Apart from retroperitoneal adipose tissue and suprailiac skinfold thickness, 15/17 adipose tissue depots/obesity indices showed significant correlations with HOMA-IR (Table 1). There were significant correlations between HOMA-IR and abdominal fat, intra-abdominal fat, subscapular skinfold thickness, intra-peritoneal fat ratio, and subcutaneous fat ratio.

The correlations between HOMA-IR and the 12 adipose indices revealed by meta-analysis.

11/12 adipose tissue depots/obesity indices except leg or lower extremity fat mass showed significant correlation with HOMA-IR (Table 2). The strongest correlation was for visceral fat ($r = 0.570$, 95%CI: 0.424–0.687), followed by total fat mass ($r = 0.492$, 95%CI: 0.407–0.570) and body mass index ($r = 0.482$, 95% CI: 0.445–0.518).

| Variables                  | Number of studies | $z$ value$^a$ | $r$ value$^b$ |
|----------------------------|-------------------|---------------|---------------|
| **Abdominal fat**          |                   |               |               |
| Mass                       | 87                | 0.585         | <0.001        |
| Area                       | 51                | 0.530         | <0.001        |
| **Intra-abdominal fat**    |                   |               |               |
| Mass                       | 51                | 0.110         | >0.05         |
| Area                       | 51                | 0.360         | <0.01         |
| **Subcutaneous anterior fat** |               |               |               |
| Mass                       | 51                | 0.390         | <0.01         |
| Area                       | 51                | 0.360         | <0.01         |
| **Subcutaneous posterior fat** |              |               |               |
| Mass                       | 51                | 0.288         | <0.01         |
| Area                       | 51                | 0.195         | >0.05         |
| **Upper extremity fat**    |                   |               |               |
| Mass                       | 30                | 0.620         | 0.003         |
| Area                       | 30                | 0.550         | 0.011         |
| **Intraperitoneal fat ratio** |               |               |               |
| Mass                       | 1579              | 0.460         | <0.0001       |
| **Subcutaneous fat ratio** |                   |               |               |
| Mass                       | 30                | 0.480         | <0.0001       |
| Area                       | 30                | 0.482         | <0.001        |
| **Liver attenuation**      |                   |               |               |
| Mass                       | 5291              | −0.310        | <0.0001       |
| Area                       | 5291              | 0.440         | <0.0001       |
| **Pericardial adipose tissue** |             |               |               |
| Mass                       | 55                | 0.515         | <0.001        |
| Area                       | 272               | 0.254         | <0.001        |
| **Subscapular skinfold thickness** |           |               |               |
| Mass                       | 55                | 0.595         | <0.001        |
| Area                       | 55                | 0.413         | <0.01         |
| **Intra-peritoneal fat ratio** |             |               |               |
| Mass                       | 55                | 0.288         | <0.01         |
| Area                       | 55                | 0.195         | >0.05         |
| **Subcutaneous fat ratio** |                   |               |               |
| Mass                       | 55                | 0.347         | 0.010         |
| Area                       | 55                | 0.296         | 0.028         |
| **Truncal subcutaneous fat** |                 |               |               |
| Mass                       | 783               | 0.480         | <0.0001       |

Table 1. Correlation coefficients between HOMA-IR and the 17-adipose indices that were not included in the Meta-analysis.

| Variables                  | Number of studies | $z$ value$^a$ | $r$ value$^b$ |
|----------------------------|-------------------|---------------|---------------|
| Visceral fat               |                   |               |               |
| Mass                       | 3                 | 0.648 (0.453, 0.843) | 0.570 (0.424, 0.687) |
| Area                       | 9                 | 0.438 (0.390, 0.487) | 0.412 (0.371, 0.452) |
| Subcutaneous fat           |                   |               |               |
| Mass                       | 3                 | 0.344 (0.149, 0.539) | 0.331 (0.148, 0.492) |
| Area                       | 8                 | 0.412 (0.265, 0.558) | 0.390 (0.259, 0.506) |
| Total fat                  |                   |               |               |
| Mass                       | 7                 | 0.539 (0.432, 0.647) | 0.492 (0.407, 0.570) |
| Area                       | 2                 | 0.338 (0.188, 0.489) | 0.326 (0.186, 0.453) |
| Fat mass percentage        | 6                 | 0.436 (0.343, 0.529) | 0.410 (0.330, 0.485) |
| Leg/lower extremity fat mass| 7                 | 0.088 (−0.117, 0.293) | 0.088 (−0.116, 0.285) |
| Body mass index            | 30                | 0.526 (0.479, 0.574) | 0.482 (0.445, 0.518) |
| Waist circumference        | 40                | 0.505 (0.462, 0.549) | 0.466 (0.432, 0.500) |
| Hip circumference          | 10                | 0.436 (0.391, 0.481) | 0.410 (0.372, 0.447) |
| Waist/Hip circumference     | 14                | 0.351 (0.290, 0.413) | 0.337 (0.282, 0.391) |
| Waist circumference to height ratio | 6 | 0.460 (0.402, 0.519) | 0.430 (0.382, 0.477) |
| Leg to trunk ratio         | 4                 | −0.376 (−0.672, −0.081) | −0.359 (−0.586, −0.081) |
| Trunk fat mass             | 7                 | 0.371 (0.186, 0.555) | 0.355 (0.183, 0.504) |

Table 2. Pooled correlation coefficients between HOMA-IR and adipose indices and 95% confidence interval estimated with random model by Meta-analysis. *Fisher transformation from correlation coefficient, $z = \frac{1}{2} \ln \left( \frac{1 + r}{1 - r} \right)$, $^b$correlation coefficient from $z$ value, $r = \frac{\exp(z^2) - 1}{\exp(z^2) + 1}$.

The correlations between HOMA-IR and the 17 adipose indices that were excluded from the meta-analysis. Apart from retroperitoneal adipose tissue and suprailiac skinfold thickness, 15/17 adipose tissue depots/obesity indices showed significant correlations with HOMA-IR (Table 1). There were significant correlations between HOMA-IR and abdominal fat, intra-abdominal fat, subscapular skinfold thickness, intra-peritoneal fat ratio, and subcutaneous fat ratio.

The correlations between HOMA-IR and the 12 adipose indices revealed by meta-analysis. 11/12 adipose tissue depots/obesity indices except leg or lower extremity fat mass showed significant correlation with HOMA-IR (Table 2). The strongest correlation was for visceral fat ($r = 0.570$, 95%CI: 0.424–0.687), followed by total fat mass ($r = 0.492$, 95%CI: 0.407–0.570) and body mass index ($r = 0.482$, 95% CI: 0.445–0.518).
Table 3. Summary of Meta-regression analysis of z value. \(^a\)Fisher transformation of correlation coefficient, \(z = \frac{1}{2} \ln(\frac{1 + r}{1 - r})\). \(^b\)Pearson correlation with logarithm transformation, – Sample size in the subgroup is not enough for regression analysis.

### Sensitivity analyses.
No study appears to drive the pooled estimation as dropping any of the studies did not materially change the pooled estimation.

### Meta-regression analysis on correlation coefficients' related factors.
The Meta-regression analysis identified a number of factors that were associated with the correlation between adipose tissue depots/obesity indices and HOMA-IR, including sample size of population, gender, race, diabetic status and mean of BMI (Table 3). In detail, sample size of population was found to be associated with correlation between visceral fat and HOMA-IR while gender was associated with correlation between subcutaneous fat or waist to hip circumference ratio and HOMA-IR. In addition, race was associated with correlation between body mass index and HOMA-IR and correlation between waist circumference and HOMA-IR while diabetic status, mean of BMI and race were associated with correlation between intraperitoneal fat ratio and HOMA-IR. In addition, diabetic status, gender, mean BMI, and race were associated with correlation between visceral fat and HOMA-IR. In all, race was associated with correlation between body mass index and HOMA-IR and correlation between waist circumference and HOMA-IR while diabetic status, mean of BMI and race were associated with correlation between intraperitoneal fat ratio and HOMA-IR.

### Statistical tests of publication bias.
No publication bias was found for the 12 indices included in the meta-analyses by Begg's test (\(P > 0.05\), Table 4). Using Egger's test, we found that 2/12 \(P\) values for leg (or lower extremity fat) and trunk fat respectively, fell lower than 0.05 (Table 4).

### Discussion
This meta-analysis study is the first to assess correlation between different adipose tissue depots/obesity indices and insulin resistance. We found significant correlations between most adipose tissue depots/obesity indices and insulin resistance. Among these indices, visceral fat mass showed the strongest correlation with HOMA-IR, followed by total fat mass, BMI and waist circumference. Notably, the leg fat (or lower extremity fat) had no significant correlation with HOMA-IR. In addition, diabetic status, gender, mean BMI, and race were associated with correlation estimates in meta-regression analysis. These findings may have important clinical and public health implications for prevention and treatment of diabetes.

In this study visceral fat mass showed the strongest correlation with HOMA-IR, followed by total fat mass, BMI and waist circumference. Other studies, which were not included in this meta-analysis, also reported significant correlation between HOMA-IR and intraperitoneal fat ratio\(^{23}\), intra-abdominal fat\(^{23}\), abdominal fat\(^{23}\) and sagittal abdominal diameter\(^{14,27}\) with correlation coefficients around 0.5. Visceral adipose tissue appeared to be the best predictor of insulin resistance\(^{24-30}\), measured by the clamp technique. Kelley et al.\(^{30}\) reported that insulin-stimulated
Table 4. Statistical tests of publication bias.

|                        | Begg’s test | Egger’s test |
|------------------------|-------------|--------------|
|                        | z value     | P value      | bias | P value |
| Visceral fat           | 1.83        | 0.067        | −0.5812 | 0.392   |
| Subcutaneous fat       | −0.96       | 0.337        | −0.9006 | 0.362   |
| Total fat              | 0.42        | 0.677        | −1.1902 | 0.398   |
| Fat mass percentage    | 0.19        | 0.851        | −0.6610 | 0.617   |
| Leg/lower extremity fat| −1.05       | 0.293        | −6.1400 | 0.015   |
| Body mass index        | −0.39       | 0.695        | −0.9814 | 0.296   |
| Waist circumference    | −0.08       | 0.935        | −1.0613 | 0.186   |
| Hip circumference      | −0.27       | 0.788        | −0.3973 | 0.763   |
| Waist/Hip circumference | 0.05        | 0.956        | −0.0496 | 0.972   |
| Waist circumference to height ratio | −0.19 | 0.851 | −0.1624 | 0.911   |
| Leg to trunk ratio     | −0.68       | 0.497        | −0.4371 | 0.956   |
| Trunk fat              | 0.45        | 0.652        | −3.6389 | 0.026   |

In conclusion, we found significant positive correlation between most adipose tissue depots/obesity indices and insulin resistance, as measured by HOMA-IR. Visceral fat showed the strongest correlation whereas lower extremity fat had no correlation with insulin resistance. Diabetic status, gender, race/ethnicity, and mean BMI contributed to the heterogeneity of the overall estimates.

Methods

**Literature collection.** We systematically searched PubMed, Web of Science, and Dissertation Theses to identify all relevant reports that met our inclusion criteria (see below) until September 2014. “Body mass index”, “waist circumference”, “waist to hip ratio”, “waist to height ratio”, “abdominal height”, “fat mass”, “skinfold”, “adiposity”, “adipose tissue”, “fatness”, “body fat distribution” and “insulin resistance” in Title or Abstract, as well as MeSH terms “Body Fat Distribution”, “Body Mass Index”, “Waist Circumference”, “Adipose Tissue”, “Skinfold Thickness” and “Insulin Resistance” were used as search terms. We also performed a manual search of references cited in published original and review articles.

The inclusion criteria were as follows: (1) the study was observational, either cross-sectional or of a case-control design; (2) conducted in humans; and (3) correlation coefficients between HOMA-IR and fat indices and their variance were reported. Studies were excluded if (1) the sample was under 19-year old; (2) the sample had chronic conditions such as cancer, heart failure, chronic kidney disease, and infectious disease. Studies of type 2 diabetes with no severe complication were included in this work.

**Data retrieval.** All data were independently retrieved by two investigators (Zhang, M and Zhou, L) according to a standardized protocol and data-collection form. Disagreements were resolved by discussion with the third investigator (Zhang, S). First author’s name and year of publication, study design (case-control or cross-sectional), characteristics of the study subjects including sample size, mean age, mean BMI, sex, race, diabetic status, indices of adiposity, HOMA-IR transformation, and measures of associations (correlation coefficient and P value) were recorded. The schematic view for data retrieval is presented in Fig. 1. A total of 40 studies including 29 adipose depots or adipose indices were identified. Twelve adipose indices with at least 3 individual results were analyzed with meta-analysis.

**Data analysis.** Z value from Fisher’s z-transformation of correlation coefficient by equation (1) \[ z = \frac{1}{2} \ln \left( \frac{1 + r}{1 - r} \right) \] was served as effect size, and standard error of z value was calculated with equation (2)
\[ z_{se} = \frac{1}{N - 3} \] The pooled z value and 95% confidence interval was transformed into correlation coefficient and 95% CI with equation (3) \( r = \frac{\exp(2z) - 1}{\exp(2z) + 1} \). Fixed and random effect models were used to combine z values for those with more than 3 populations. Heterogeneity of z values was assessed by \( I^2 \). Meta regression was performed to investigate the association between z values and sample characteristics while Begg's and Egger's tests were used to assess publication bias.

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**Author Contributions**

Z.M. conducted the literature search, designed the study, decided the data exclusion and inclusion criteria, retrieved data from published studies, performed data analysis and drafted the manuscript; H.T. extracted data from retrieved studies; Z.S. decided the data exclusion and inclusion criteria; Z.L. conducted the literature search. All authors reviewed the paper and approved the final manuscript.

**Additional Information**

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