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# Associations of middle-aged mother's but not father's body mass index with 18-year-old son's waist circumferences, birth weight, and serum hepatic enzyme levels

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**Abstract**

Mitochondrial dysfunction has been reported to contribute to insulin resistance (IR) in the elderly and type 2 diabetes. To test this hypothesis, we examined relations of insulin resistance in young men to their mother's body mass index (BMI) and compared with those to their father's BMI, because as a rule, mitochondrial DNA is exclusively maternally inherited and because mitochondria are fundamental in mediating effects on energy dissipation.

We measured heights, weights, waist circumference, systolic and diastolic blood pressure (BP), and biochemical variables in sera from 193 male college students aged 18 to 20 years after an overnight fast. Birth weight was available from 184 students. Self-reported heights and weights of their parents were obtained from 148 students. Insulin resistance and insulin secretion were estimated using homeostasis model assessment (HOMA-IR and HOMA-$\beta$, respectively). Mother's BMI was associated with their son's birth weight ($r = 0.23$, $P = .008$), BMI ($r = 0.37$, $P < .0001$), waist circumference ($r = 0.42$, $P < .0001$), fasting insulin ($r = 0.19$, $P = .02$), and HOMA-IR ($r = 0.18$, $P = .03$) but not with fasting glucose, HOMA-$\beta$, and systolic and diastolic BP. In addition, high-density lipoprotein cholesterol and lipoprotein(a) [Lp(a)] were inversely associated with mother's BMI ($r = -0.21$, $P = .01$ and $r = -0.17$, $P = .03$, respectively). Furthermore, there were significant associations with aspartate ($r = 0.20$, $P = .01$) and alanine ($r = 0.28$, $P = .0008$) aminotransferase and γ-glutamyl transpeptidase ($r = 0.30$, $P = .0003$), all of which are associated with mitochondrial function. In contrast, none of those variables were associated with father's BMI, except for Lp(a), which showed a significant and inverse association ($r = -0.17$, $P = .05$). After adjustment for sons' BMI, waist circumference and 3 hepatic enzymes were associated with mother's BMI, whereas Lp(a) was associated with both mother's and father's BMI. In multiple regression analysis for HOMA-IR as a dependent variable, BMI of their own ($\beta = .10$, $P < .0001$) and of their mothers ($\beta = .04$, $P = .10$) and birth weight ($\beta = -.27$, $P = .10$) emerged as determinants of HOMA-IR of the students($R^2 = 0.30$).

Our results are consistent with clinical observations of a greater risk of transmission of type 2 diabetes from the mother than the father and suggest that son's IR may be influenced by maternal effect as well as their adiposity.


## 1. Introduction

Metabolic syndrome has been coined to refer to clustering of risk factors associated with type 2 diabetes and cardiovascular disease [1-3]. Although the components of this syndrome include insulin resistance (IR)/hyperinsulinemia, hypertension, dyslipidemia, obesity, and glucose intolerance, IR is thought to be a primary physiological defect underlying this multiple metabolic disorders [1,2]. This concept is supported by many studies showing an association between IR and multiple disorders characteristics of metabolic syndrome in both children [4-6] and adults [7-11].

The underlying cause of IR is not known, although it is speculated that the primary defect may be genetic [2]. Genetic transmission [12-14] as well as familial aggregation [15-18] of IR has been reported. If this defect in turn accounted for the other metabolic abnormalities associated with IR, then the high correlations consistently observed

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between measures of IR and other metabolic abnormalities could be attributable to a common genetic pathway or set of pathways. Pedigree studies provide means for disentangling genetic and environmental sources of covariation among traits. An inspection of the significant familial patterns can lead to certain genetic and environmental inferences. For example, a pattern of significant correlations among siblings and between parents and offspring (who share about half their genes), but not between spouse (who share few genes assuming random mating), suggests a genetic heritability. Similarly, cross-trait familial correlations lead to the same type of genetic and environmental inferences. A pattern of significant cross-trait correlations between parents' body size and offspring's insulin level, and among siblings, but not spouses would suggest that a common gene (or genes) influences both traits. Mitochondrial dysfunction has recently been reported to contribute to IR in skeletal muscle of the elderly [19] and subjects with type 2 diabetes [20]. Mitochondrial DNA is exclusively maternally inherited, and mitochondria are fundamental in mediating effects on energy dissipation. In the present study, therefore, we examined relations of IR in young men to their mother's body mass index (BMI) and compared with those to their father's BMI. Because age is a factor known to affect mitochondrial function [19], we studied healthy, younger, and hence slim people as described below.

## 2. Methods

### 2.1. Participants

One hundred ninety-three of 195 men, who entered Kobe University of Mercantile Marine, Kobe, Japan, in 2001, underwent anthropometric, blood pressure (BP), and blood tests. Of those, 148 students provided self-reported heights and weights of their biologic parents, and 184 students provided their birth weight either through maternal and child health notebook records (issued by each municipal office). However, maternal body weight and weight change during pregnancy were not available, and birth weights were not corrected for pregnancy term. They were all Japanese, and 98% were aged 18 years.

### 2.2. Procedures

Students were asked to fast overnight and to refrain from smoking and alcohol overnight before attending the Center. Stature was measured to the nearest millimeter using a field anthropometer. Body weights and percent body fat were measured after they voided. This was done using an impedance fat meter (TBF-202, Tanita Corp, Tokyo, Japan). TBF-202 employs 2-foot pad electrodes with a corresponding digital scale, as previously reported [21,22]. Body mass index was calculated as weight in kilograms divided by the square of height in meters. A flexible fiberglass tape was used to obtain minimum waist circumference at the natural indentation.

BP was measured with an automated sphygmomanometer (TM-2711, A&D, Tokyo, Japan), which was standardized against a standard mercury sphygmomanometer, after the students had rested at least 5 minutes.

Alcohol consumption and smoking habits were determined by an interview at the time of each participant's physical examination. Data with respect to diet and exercise were not available. Nobody received any medications.

Venous blood was sampled after an overnight fast and centrifuged at 3000 rpm for 30 minutes at 4°C. Aspartate and alanine aminotransferase (AST and ALT, respectively) and γ-glutamyl transpeptidase (GGT) were measured using an autoanalyzer. Cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), and apolipoproteins were measured as previously reported [20]. Low-density lipoprotein cholesterol (LDL-C) was calculated using the formula of Friedwald et al [21]. Plasma glucose was measured by the glucose oxidase method. Insulin was assayed using a commercially available kit (Pharmacia, Tokyo, Japan). Insulin resistance and secretion ($\beta$ cell) determined by homeostasis model assessment [23] (HOMA) were calculated using fasting plasma glucose

Table 1
Descriptive data of 193 young male college students and their parental age and BMI

| | | Mean ± SD | Range |
|---|---|---|---|
| Father* | Age (y) | 49 ± 4 | 40-61 |
| | Body mass (kg) | 67 ± 8 | 52-90 |
| | Height (cm) | 170 ± 5 | 155-183 |
| | BMI (kg/m$^2$) | 23.2 ± 2.5 | 18.6-31.5 |
| Mother† | Age (y) | 46 ± 3 | 39-56 |
| | Body mass (kg) | 53 ± 7 | 39-80 |
| | Height (cm) | 156 ± 5 | 143-169 |
| | BMI (kg/m$^2$) | 21.8 ± 2.7 | 16.8-32.9 |
| Son | Body mass (kg) | 62.9 ± 9.5 | 46.9-109.1 |
| | Height (cm) | 171.9 ± 5.5 | 156.7-188.3 |
| | BMI (kg/m$^2$) | 21.3 ± 3.3 | 15.6-36.8 |
| | Waist circumference (cm) | 72.0 ± 8.0 | 59.0-108.0 |
| | Percentage body fat (%) | 17.0 ± 5.5 | 8.1-36.0 |
| | Systolic BP (mm Hg) | 121 ± 12 | 95-154 |
| | Diastolic BP (mm Hg) | 70 ± 8 | 52-93 |
| | Fasting glucose (mmol/L) | 4.7 ± 0.3 | 3.6-5.6 |
| | Fasting insulin (pmol/L) | 32 ± 19 | 18-116 |
| | HOMA-IR | 1.1 ± 0.7 | 0.2-4.6 |
| | HOMA-$\beta$ | 5.0 ± 2.8 | 1.2-16.5 |
| | Birth weight‡ (kg) | 3.3 ± 0.3 | 2.3-4.5 |
| | Total cholesterol (mg/dL) | 167 ± 30 | 110-257 |
| | LDL-C (mg/dL) | 96 ± 29 | 44-187 |
| | HDL-C (mg/dL) | 61 ± 12 | 31-102 |
| | Triglyceride (mg/dL) | 52 ± 22 | 20-138 |
| | Lp(a) (mg/dL) | 15 ± 15 | 1.0-89.0 |
| | Apolipoprotein B (mg/dL) | 74 ± 19 | 43-143 |
| | AST (U/L) | 22 ± 8 | 11-75 |
| | ALT (U/L) | 24 ± 20 | 6-147 |
| | GGT (U/L) | 23 ± 11 | 11-80 |

* n = 139.
† n = 136.
‡ n = 184.

Table 2
Correlations of parental and son's body mass indices with anthropometric, BP, and biochemical data in 148 sons aged 18 years

| | BMI | | |
|---|---|---|---|
| | Father | Mother | Son |
| Father's BMI | 1 | 0.02 | −0.08 |
| Mother's BMI | 0.02 | 1 | 0.37*** |
| Son's BMI | −0.08 | 0.37***† | 1 |
| Waist circumference | 0.05 | 0.41***‡† | 0.86*** |
| Percentage body fat | 0.01 | 0.35***† | 0.80*** |
| Systolic BP | 0.04 | 0.15† | 0.39*** |
| Diastolic BP | 0.07 | 0.13 | 0.33*** |
| Fasting glucose | −0.09 | 0.15 | 0.21* |
| Fasting insulin | 0.03 | 0.19†* | 0.44*** |
| HOMA-IR | 0.01 | 0.18†* | 0.43*** |
| HOMA-$\beta$ | 0.09 | 0.11 | 0.29** |
| Birth weight | 0.01 | 0.23‡* | 0.05 |
| Total cholesterol | 0.02 | 0.02 | 0.13 |
| LDL-C | 0.03 | 0.11 | 0.21* |
| HDL-C | −0.02 | −0.21†* | −0.27* |
| Triglyceride | 0.05 | 0.1 | 0.31** |
| Lp(a) | −0.17*‡ | −0.17*‡† | −0.03 |
| Apolipoprotein B | 0.00 | 0.09 | 0.25* |
| AST | −0.08 | 0.20*‡† | 0.20* |
| ALT | −0.12 | 0.28*‡† | 0.31** |
| GGT | −0.11 | 0.30**‡† | 0.27* |

*** $P < .001$.
† $P < .05$ or less after adjustment for son's birth weight.
‡ $P < .05$ or less after adjustment for son's body mass index.
* $P < .05$.
** $P < .01$.

and insulin levels in each participant. HOMA-IR has been validated by comparison with results of glucose clamp studies [23,24], intravenous glucose tolerance test [23,25], and continuous infusion of glucose with minimal model assessment [25]. The HOMA–$\beta$ cell method has been validated by comparison with the intravenous glucose with minimal model assessment [26]. Application of HOMA has also been used in epidemiological studies [23,27,28].

### 2.3. Statistical analysis

This was performed with the SAS statistical software system (SAS Institute, Cary, NC). Spearman correlation coefficients were calculated to determine the relationship between parent's BMI and BP, and anthropometric and metabolic variables of their sons. Partial Spearman correlation coefficients adjusting for son's BMI and birth weight were used to ascertain the direct relationship between parent's BMI and other variables. Finally, multiple regression analysis with backward elimination procedure was carried out to discriminate variables affecting HOMA-IR in young men. $P$ values of $<.05$ were considered significant.

## 3. Results

Characteristics of young students and their biologic parents were shown in Table 1. Body mass index averaged less than 25.0 kg/m$^2$ in the 3 groups. Strength of the current report is the relatively narrow age range of the parents and the restriction of the study to 18-year-old sons.

As shown in Table 2, mother's BMI was associated with their son's BMI ($r = 0.37$, $P < .0001$), waist circumference ($r = 0.42$, $P < .0001$), fasting insulin ($r = 0.19$, $P = .02$), HOMA-IR ($r = 0.18$, $P = .03$), and birth weight ($r = 0.23$, $P = .008$) but not with fasting glucose, HOMA-$\beta$, and systolic and diastolic BP. As shown in Fig. 1, BMI of sons increased in linear fashion from the lowest to the highest quartile of BMI of their mothers. In addition, HDL-C and lipoprotein(a) [Lp(a)] were inversely associated with mother's BMI ($r = -0.21$, $P = .01$ and $r = -0.17$, $P = .03$, respectively). Furthermore, there were significant associations with AST ($r = 0.20$, $P = .01$), ALT ($r = 0.28$, $P = .0008$), and GGT ($r = 0.30$, $P = .0003$), all of which are synthesized in the mitochondria. In contrast, none of those variables were associated with father's BMI, except for Lp(a), which showed a significant and inverse association ($r = -0.17$, $P = .05$). After adjustment for son's BMI (Table 2), waist circumference, birth weight and 3 hepatic enzymes were associated with mother's BMI, and Lp(a) was associated with both mother's and father's body mass indices. After adjustment for son's birth weight (Table 2), associations still remained significant with son's BMI, percentage body fat, systolic BP, fasting insulin, HOMA-IR, HDL-C, Lp(a), and 3 mitochondrial enzymes. As expected, BMI of the students showed significant associations with their systolic and diastolic BP, and anthropometric and biochemical variables but not with their birth weight. There was no association between mothers' and fathers' body mass indices.

In multiple regression analysis for HOMA-IR as a dependent variable, which included BMI of their own and their parent, waist circumference, birth weight, and systolic BP, BMI of their own ($\beta = .10$, $P < .0001$) and of their mothers ($\beta = .04$, $P = .10$) and birth weight ($\beta = -.27$, $P = .10$) emerged as independent determinants of HOMA-IR of the students($R^2 = 0.30$). In a model excluding mother's BMI, son's BMI and birth weight were independent determinants of HOMA-IR, whereas son's and mother's body mass indices were independent determinants of HOMA-IR in a model excluding birth weight. Waist

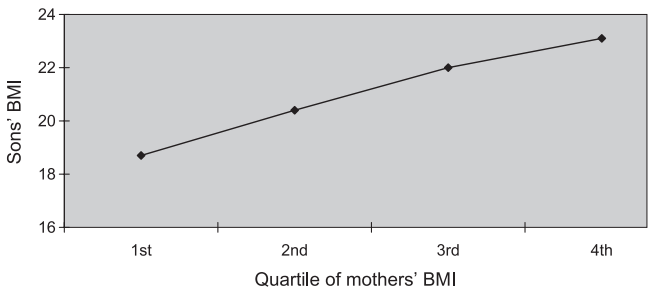


Fig. 1. A plot of sons' BMIs by quartile of mothers' BMIs. Mean BMIs of the mothers were 18.7, 20.7, 22.5, and 25.3 kg/m$^2$ in the first, second, third, and fourth quartiles, respectively.

circumference, however, did not emerge as a determinant of HOMA IR.

## 4. Discussion

We found a significant association of 18-year-old son's BMI, a surrogate of total body fat, with their middle-aged mother's BMI. In addition, son's waist circumference, a surrogate of abdominal fat, was also associated with their mother's BMI. Furthermore, of note was an association between son's HOMA-IR, a measure of IR, with their middle-aged mother's BMI. In contrast with mother's BMI, father's BMI had nothing to do with their son's anthropometric and biochemical variables . Because abdominal fat [29] and IR [30] have been shown to be independent predictors of type 2 diabetes, results of the present study may be consistent with clinical observations of a greater risk of transmission of type 2 diabetes from the mother than the father [31-34]. It is noted that the majority of populations (parents and sons) did not have metabolic syndrome, type 2 diabetes, and IR, but rather were slim, younger, and healthy people.

The underlying mechanisms of this phenomenon remain to be elucidated. As smoking and alcohol drinking are much more common in Japanese men than women, it is also possible that variability in paternal smoking and alcohol drinking abolishes a father-son relationship in BMI which might otherwise be observed. We cannot rule out the possibility of genetic imprinting. Sex-linked genetic transmission and the influence of the intrauterine milieu of the fetal development are probably major factors. Mitochondrial dysfunction has recently been reported to contribute to IR in skeletal muscle of the elderly [19] and subjects with type 2 diabetes [20]. Because as a rule, mitochondrial DNA is exclusively maternally inherited [35] and because mitochondria are fundamental in mediating effects on energy dissipation [36], our results suggest that their mother's but not their father's mitochondrial function may influence son's IR and abdominal fat. Age [37] and exercise [38] are major factors known to affect the size and/or function of mitochondria in skeletal muscle. We, therefore, examined a homogeneous cohort of young healthy Japanese people. The mothers studied were only, on average, 28 years old when they passed their mitochondria on to their sons, who were only 18 years old. Therefore, characteristics of these mitochondria should not be attributed to aging. In addition, 18- to 20-year-old college students could not be sedentary as compared to middle-aged individuals in the general population.

Not only decreased insulin secretion but also IR has been demonstrated in patients with the 3243 mutation of the mitochondrial DNA [39]. Sequential follow-up of such patients documented decreased insulin sensitivity before the development of insulin deficiency [39]. Furthermore, a common mitochondrial DNA variant has been demonstrated to be associated with IR in adult life [40]. These observations may be compatible with our finding that middle-aged mother's BMI was associated with their son's IR.

The present study, however, cannot discern genetic effects from common shared environmental influences on mother-son association, and hence, another potential explanation is a maternal effect. It is conceivable that there are intrauterine effects on the growth of the fetus that lead to lasting differences in BMI in later life [41]. In multiple regression analysis in the present study, however, IR was associated with birth weight, which is a crude marker of intrauterine nutritional condition and has been shown to be associated with IR [29]. We, therefore, believe that son's IR may be influenced by their mother's mitochondrial function as well as intrauterine nutritional condition.

Associations of mother's BMI with their son's AST and ALT may be compatible with the fact that aminotransferase reactions are associated with the citric acid cycle, which takes place in mitochondria. We have no explanation for significant associations between son's Lp(a) and their parental BMI, although serum Lp(a) concentrations were known to be influenced by genetic factors [42].

There are many studies on parent-offspring weight relationship [43]. Stunkard et al [44] showed a strong association in weight between adoptees and their biological fathers and mothers but no association with adoptive parent weight.

The results in this article are subject to several limitations. The cross-sectional design of the present study complicates the drawing of causal inferences, and a single measurement of biochemical variables may be susceptible to short-term variation, which would bias the results toward the null. Third, self-reported height and weight used to calculate BMI of parents are not an optimal index, although self-reported BMI is likely to be highly correlated with measured BMI [45]. Finally, we used several surrogates in the present study, which may be less accurate.

In conclusion, our findings are consistent with clinical observations of a greater risk of transmission of type 2 diabetes from the mother than the father and suggest that son's IR may be influenced by the maternal effect as well as their adiposity. Our results need to be complemented by studies where IR is measured directly and also in prospective studies of relatives of diabetic patients. Genes coded by mitochondrial DNA should continue to be investigated to elucidate where there is a molecular origin of the maternal effect.

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