Introduction

Abdominal obesity is strongly associated with the accumulation of metabolic disorders; subjects with abdominal obesity are likely to exhibit clustering of metabolic abnormalities\(^1\-^5\). Pathophysiologicaly, visceral fat accumulation is present upstream of a variety of metabolic abnormalities, and the concept is now well recognized as metabolic syndrome in clinical practice\(^1\-^2\).

On the other hand, it is also true that metabolic disorders do not only arise from visceral fat accumulation. In other words, visceral fat accumulation is not the one and only origin of the clustering of metabolic abnormalities\(^2\). Indeed, some subjects with accumulated metabolic abnormalities have a waist circumference within the normal limits\(^5\). In such subjects, metabolic abnormalities arise from etiologies other than visceral fat accumulation.

However, to date, little is known about to what extent visceral fat accumulation and its associated etiologies, e.g., a decreased circulating adiponectin level\(^6\), explain the clustering of metabolic abnormalities. Whether these factors account for a large portion of risk clustering remains to be elucidated.
Subjects treated for hypertension, diabetes mellitus, dyslipidemia and/or hyperuricemia were excluded from the current study. We also excluded patients who were pregnant and those with malignant neoplasms, renal failure and/or a history of heavy drinking (alcohol consumption ≥100 g per day).

Statistical Analysis
We performed a structural equation modeling (SEM) analysis to assess the contribution of visceral fat accumulation and the circulating adiponectin level to the clustering of metabolic abnormalities. We created a path diagram based on the concept of metabolic syndrome\(^1,2\), as shown in Fig. 1. In brief, we hypothesized that visceral adiposity and a decreased circulating adiponectin level lay upstream of the clustering of metabolic abnormalities, i.e., hypertension, hyperglycemia, a reduced high-density lipoprotein (HDL) cholesterol level, hypertriglyceridemia, hyperuricemia\(^9,10\) and an elevated alanine aminotransferase (ALT) level\(^11-13\). Based on this hypothesis, we developed a multiple indicator multiple cause (MIMIC) model with a latent variable termed “risk clustering,” as demonstrated in Fig. 1. In this model, an increased VFA, together with a decreased adiponectin level, would

Fig. 1. Designed path diagram.
The ellipse represents a latent variable, whereas the rectangles and circles indicate observed and error variables, respectively. e1 to e8 represent error variables. Log(x) represents log-transformed x. Adpn, adiponectin; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; PG, plasma glucose; SBP, systolic blood pressure; TG, triglycerides; UA, uric acid; VFA, visceral fat area.

Aim
The aim of the current study was to investigate the contribution of visceral fat accumulation and adiponectin to the clustering of metabolic abnormalities using a statistical analysis.

Methods
Study Population and Definitions
We used data obtained from the Amagasaki Visceral Fat Study, registered as UMIN000002391. The study was a cohort study approved by the human ethics committee of Osaka University. Written informed consent was obtained from all participants. In the current study, we analyzed a total of 1,989 Japanese employees of the city office of Amagasaki, Hyogo, who participated in health checkups at the office. During the health checkups, we additionally assessed visceral fat accumulation and the circulating adiponectin level. Visceral fat accumulation was assessed according to the bioelectrical impedance method and estimated as the visceral fat area (VFA) at the umbilical level\(^7\). The circulating adiponectin levels were measured using a latex particle-enhanced turbidimetric assay\(^8\). Subjects treated for hypertension, diabetes mellitus, dyslipidemia and/or hyperuricemia were excluded from the current study. We also excluded patients who were pregnant and those with malignant neoplasms, renal failure and/or a history of heavy drinking (alcohol consumption ≥100 g per day).
Abdominal Obesity and Risk Clustering

We investigated to what extent age and sex influence the clustering of metabolic abnormalities both directly and indirectly via visceral fat accumulation and the circulating adiponectin level. Second, we substituted the body mass index (BMI), a general index of obesity, for the log-transformed VFA in the original path diagram. Furthermore, we added the BMI as a competing factor with the log-transformed VFA to the original path diagram in order to compare the independent impact on “risk clustering” between the BMI and log-transformed VFA. Third, we added the low-density lipoprotein (LDL) cholesterol level as another phenotype of the pathological condition of “risk clustering” in the original path diagram. Previous studies have demonstrated that the LDL cholesterol level is less significantly associated with abdominal obesity than the HDL cholesterol and triglycerides levels. We hypothesized that the LDL cholesterol level less reflects “risk clustering” than other lipid profiles. The LDL cholesterol levels were calculated using the Friedewald formula. Since the LDL cholesterol levels were not calculated in the patients with a triglycerides level of ≥ 400 mg/dL, we performed the analysis using full information maximum likelihood (FIML) estimation.

Using this path diagram, we performed an SEM analysis according to the maximum likelihood method, to calculate the squared multiple correlation ($R^2$). The $R^2$ of a variable indicates the proportion of the variable’s variance accounted for by its predictors. We also performed the analysis after stratifying the study population by sex, as previous studies have reported sex difference in the characteristics of metabolic syndrome.

We additionally designed the following three path diagrams. First, we added sex and age as variables to the original path diagram. Although the concept of metabolic syndrome itself is universal across both age and sex, it is known that an older age and male sex are associated with an increased risk of metabolic abnormalities. We investigated to what extent age and sex influence the clustering of metabolic abnormalities both directly and indirectly via visceral fat accumulation and the circulating adiponectin level. Second, we substituted the body mass index (BMI), a general index of obesity, for the log-transformed VFA in the original path diagram. Furthermore, we added the BMI as a competing factor with the log-transformed VFA to the original path diagram in order to compare the independent impact on “risk clustering” between the BMI and log-transformed VFA. Third, we added the low-density lipoprotein (LDL) cholesterol level as another phenotype of the pathological condition of “risk clustering” in the original path diagram. Previous studies have demonstrated that the LDL cholesterol level is less significantly associated with abdominal obesity than the HDL cholesterol and triglycerides levels. We hypothesized that the LDL cholesterol level less reflects “risk clustering” than other lipid profiles. The LDL cholesterol levels were calculated using the Friedewald formula. Since the LDL cholesterol levels were not calculated in the patients with a triglycerides level of ≥ 400 mg/dL, we performed the analysis using full information maximum likelihood (FIML) estimation.

The data are provided as the mean ± SD or number (percentage), except for the VFA and levels of adiponectin, glucose, triglycerides and transaminase, which are presented as the median (interquartile range). The LDL cholesterol levels were calculated using the Friedewald formula in the patients with a triglyceride level of < 400 mg/dL ($n = 1,961$).

### Table 1. Characteristics of the study population

| Distribution | Prevalence of abnormality |
|--------------|---------------------------|
| Male sex     | 1440 (72%)                |
| Age (year)   | 46 ± 11                   |
| Body mass index (kg/m²) | 23.4 ± 3.3               |
| VFA (cm²)    | 74 (48-110)               |
| Systolic blood pressure (mmHg) | 121 ± 16               |
| Diastolic blood pressure (mmHg) | 74 ± 11                |
| Glucose (mg/dL) | 93 (88-110)              |
| HDL cholesterol (mg/dL) | 61 ± 15                 |
| Triglycerides (mg/dL) | 87 (61-136)             |
| LDL cholesterol (mg/dL)* | 119 ± 31               |
| Uric acid (mg/dL) | 5.6 ± 1.4               |
| Aspartate aminotransferase (U/L) | 20 (17-24)             |
| Alanine aminotransferase (U/L) | 19 (14-27)            |
| Adiponectin ($\mu$g/mL) | 7.2 (5.1-9.9)           |
|                  | Distribution              |
|                  | 1440 (72%)                |
|                  | 46 ± 11                   |
|                  | 23.4 ± 3.3                |
|                  | 74 (48-110)               |
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|                  | 87 (61-136)               |
|                  | 119 ± 31                  |
|                  | 5.6 ± 1.4                 |
|                  | 20 (17-24)                |
|                  | 19 (14-27)                |
|                  | 7.2 (5.1-9.9)             |

The data are presented as the mean ± SD or number (percentage), except for the VFA and levels of adiponectin, glucose, triglycerides and transaminase, which are presented as the median (interquartile range). *The LDL cholesterol levels were calculated using the Friedewald formula in the patients with a triglyceride level of < 400 mg/dL ($n = 1,961$).
The goodness-of-fit index (GIF) was 0.954, the adjusted goodness-of-fit index (AGIF) was 0.913, the comparative fit index (CFI) was 0.916 and the root mean square error of approximation (RMSEA) was 0.097. These statistical fit measurements indicate that the model had a fairly good and permissible fitness.

As shown in Fig. 2, the log-transformed VFA and adiponectin levels exhibited a considerable association with “risk clustering,” with \( R^2 \) values equal to 0.73, meaning that the measurements of the VFA and adiponectin level (see Fig. 2).

**Table 2.** Direct and indirect effects of the log-transformed VFA values on risk clustering

| Effect                  | Standardized estimates |
|-------------------------|------------------------|
| Direct effect           | 0.65 [95% CI: 0.61 to 0.68] |
| Indirect effect         | 0.16 [95% CI: 0.14 to 0.18] |
| Total effect            | 0.81 [95% CI: 0.78 to 0.83] |

The data are standardized estimates with 95% confidence intervals (CI) obtained using Bayesian estimation. The indirect effect is via the circulating adiponectin level (see Fig. 2).

Results

The characteristics of the study population are shown in Table 1. The mean age of the subjects was 46 ± 11 years old, and 72% of the participants were men. A total of 646 subjects (32%) had a VFA of ≥ 100 cm².

**Influence of VFA and Adiponectin on Risk Clustering**

Fig. 2 shows the main results of the SEM analysis. All estimates in the path diagram were statistically significant (all \( p < 0.001 \)). The goodness-of-fit index
Fig. 3. Impact of visceral fat accumulation and adiponectin on the clustering metabolic of abnormalities in men (A) and women (B).

The SEM analysis was performed after stratifying the study population by sex. The data reflect standardized regression weights (along arrows) and $R^2$ values. The ellipses represent latent variables, whereas the rectangles and circles indicate observed and error variables, respectively. $e_1$ to $e_8$ represent error variables. Log(x) represents log-transformed x. Adpn, adiponectin; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; PG, plasma glucose; SBP, systolic blood pressure; TG, triglycerides; UA, uric acid; VFA, visceral fat area.
ponectin levels explained 73% of the “risk clustering.” On the other hand, the $R^2$ values between “risk clustering” and its clinical phenotypes (i.e., systolic blood pressure, log-transformed glucose, log-transformed triglycerides, HDL cholesterol, uric acid and log-transformed ALT) ranged from 0.14 to 0.54. These findings indicate that these clinically measurable metabolic profiles reflect the pathological changes of “risk clustering” in vivo within a range of 14% to 54%.

Table 2 shows the direct and indirect effects of log-transformed VFA on “risk clustering.” The standardized direct effect was much larger than the standardized indirect effect, indicating that visceral fat accumulation influenced the clustering of metabolic abnormalities mainly directly rather than indirectly via the circulating adiponectin level.

We supplementarily calculated the estimated standardized factor score of the risk clustering in each subject. As a result, the standardized factor score, distributed with a mean of 0 and a variance of 1 in the entire population, was distributed with a mean of 0.36 and a variance of 0.70 in men and a mean of −0.90 and a variance of 0.60 in women. This finding indicates that men are more likely subject to risk clustering than women and that the variable of sex provides substantial information regarding risk clustering. Indeed, a supplemental path diagram in which sex was set as the one and only variable upstream of risk clustering revealed that sex by itself explained 46% of the variance in risk clustering. On the other hand, another path diagram in which age was set as the only variable upstream of risk clustering showed that age explained 14% of the variance in risk clustering.

### Stratification of the Study Population by Sex

Fig. 3 shows the results of the SEM analysis following stratification by sex. All estimates in the path diagram were again statistically significant in both sexes (all $p<0.001$). The statistical fit measurements after stratification were as follows: a GIF of 0.951, an AGIF of 0.908, a CFI of 0.861 and an RMSEA of 0.069. As shown in Fig. 3, the $R^2$ of risk clustering was 0.58 in the male subgroup and 0.64 in the female subgroup. The standardized estimates of the direct, indirect and total effects of the log-transformed VFA values on “risk clustering” were 0.57 [95% CI: 0.52 to 0.62], 0.13 [95% CI: 0.10 to 0.15] and 0.70 [95% CI: 0.65 to 0.74] in the male subgroup and 0.71 [95% CI: 0.64 to 0.78], 0.07 [95% CI: 0.04 to 0.10] and 0.78 [95% CI: 0.71 to 0.83] in the female subgroup, respectively.

| Table 3. Direct and indirect effects of age and sex on risk clustering |
|-----------------------------|-----------------------------|
| Effect of age on the risk clustering | Standardized estimates |
| Direct effect | 0.12 [95% CI: 0.08 to 0.16] |
| Indirect effect | 0.15 [95% CI: 0.12 to 0.18] |
| Total effect | 0.27 [95% CI: 0.22 to 0.31] |
| Effect of sex on the risk clustering | Standardized estimates |
| Direct effect | 0.31 [95% CI: 0.27 to 0.35] |
| Indirect effect | 0.33 [95% CI: 0.30 to 0.36] |
| Total effect | 0.64 [95% CI: 0.60 to 0.68] |

The data are presented as the standardized estimates with 95% confidence intervals (CI) obtained using Bayesian estimation. The indirect effect is via the log-transformed VFA and circulating adiponectin levels.

### Direct and Indirect Influence of Age and Sex on Risk Clustering

We subsequently investigated to what extent age and sex influence “risk clustering” directly and indirectly via the log-transformed VFA and adiponectin levels. For this purpose, we additionally drew a total of six arrows from age and sex to log-transformed VFA, the log-transformed adiponectin levels and the latent variable “risk clustering” in the original path diagram. As a result, the $R^2$ of risk clustering improved from 0.73 in the original model (see Fig. 2) to 0.82 in the current model. These findings indicate that age and sex additionally explain 82%−73%=9% of risk clustering. Table 3 shows the direct and indirect effects of age and sex. The direct effects were similar to the respective indirect effects, indicating that approximately half of the influence of age and sex on risk clustering was via visceral fat accumulation and the circulating adiponectin level.

### Impact of BMI on Risk Clustering

Fig. 4A shows the results of the SEM analysis
Fig. 4. Impact of body mass index on the clustering of metabolic abnormalities.

The SEM analysis was performed after substituting BMI for log-transformed VFA in the original path diagram (A) and adding BMI as a competing factor with log-transformed VFA to the original path diagram (B). The data reflect standardized regression weights (along arrows) and $R^2$ values. The ellipses represent latent variables, whereas the rectangles and circles indicate observed and error variables, respectively. $e_1$ to $e_8$ represent error variables. Log(x) represents log-transformed x. Adpn, adiponectin; ALT, alanine aminotransferase; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; PG, plasma glucose; SBP, systolic blood pressure; TG, triglycerides; UA, uric acid; VFA, visceral fat area.
Table 4. Impact of risk clustering on the clinical phenotypes

| Clinical phenotype                | Standardized regression weights |
|----------------------------------|---------------------------------|
| LDL cholesterol                  | 0.26 [95% CI: 0.22 to 0.30]     |
| Systolic blood pressure          | 0.44 [95% CI: 0.40 to 0.48]     |
| Log-transformed glucose          | 0.37 [95% CI: 0.33 to 0.41]     |
| HDL cholesterol                  | −0.54 [95% CI: −0.57 to −0.50]  |
| Log-transformed triglycerides    | 0.74 [95% CI: 0.71 to 0.76]     |
| Uric acid                        | 0.53 [95% CI: 0.49 to 0.56]     |
| Log-transformed ALT              | 0.59 [95% CI: 0.56 to 0.61]     |

The data are standardized estimates with 95% confidence intervals (CI) obtained using Bayesian estimation. The indirect effect is via the log-transformed VFA and circulating adiponectin levels.

Impact of LDL Cholesterol as a Phenotype of Risk Clustering

We then assessed to what extent the LDL cholesterol level reflects risk clustering. To this end, we added the variable of the LDL cholesterol level as a phenotype of “risk clustering” to the original path diagram. The results are summarized in Table 4. Although “risk clustering” was significantly associated with the LDL cholesterol level ($p < 0.001$), the impact was relatively small compared to that observed for the other lipid profiles (i.e., the HDL cholesterol and log-transformed triglycerides levels). Indeed, the $R^2$ of risk clustering to LDL cholesterol was only 0.07. These results indicate that the LDL cholesterol level, as a clinical phenotype, less reflects the pathological changes of “risk clustering” than the other lipid profiles.

Discussion

In the current study, we performed a structural equation modeling analysis to assess the contribution of visceral fat accumulation and adiponectin to risk clustering. As a result, the log-transformed measurements of the VFA and circulating adiponectin level explained as much as 73% of the variance in risk clustering (Fig. 2). The subsequent analysis showed that as much as half of the impact of age and sex on risk clustering was via VFA and the circulating adiponectin level (Table 3). We also confirmed that the LDL cholesterol level less reflected the risk clustering than the HDL cholesterol and triglycerides levels (Table 4). Although visceral fat accumulation and a decreased adiponectin level are closely linked to the development of metabolic abnormalities, they are not the one and only origin of metabolic abnormalities. Some subjects suffer from metabolic abnormalities although they are free from abdominal obesity. The proportions with which visceral fat accumulation and adiponectin contribute to risk clustering remain to be elucidated. To the best of our knowledge, this is the first report to evaluate the contribution of visceral fat accumulation and adiponectin to risk clustering.

We developed the MIMIC model according to the concept of metabolic syndrome and performed an SEM analysis. As a result, the log-transformed measurements of the VFA and circulating adiponectin levels were found to be considerably associated with risk clustering, with $R^2$ values equal to 0.73 (Fig. 2). This finding indicates that these factors explain as much as 73% of the variance in risk clustering. The $R^2$ of a variable reflects the proportion of the variable's vari-
ance that is accounted for by its predictors, and, mathematically, the index can be 100%. However, in the clinical setting, it is quite rare that clinical measurements or clinically evaluable phenotypes perfectly explain underlying pathological changes in the body. It should be also noted that two variables that are clinically considered to be strongly linked with each other do not always have a mathematically large value of $R^2$. For instance, systolic blood pressure and diastolic blood pressure are clinically considered to be strongly correlated with each other. In the current study population, the Pearson’s correlation coefficient ($r$) of these parameters was as high as $0.78$ ($p<0.001$) (data not shown). The $r$ in turn corresponded to an $R^2$ of 0.60, which may not seem mathematically large. Similarly, the HDL cholesterol and log-transformed triglycerides levels, another pair of parameters considered to exhibit a clinically sufficient correlation, had an $r$ of $-0.48$ ($p<0.001$), which corresponded to an $R^2$ of 0.23 (data not shown). Compared to these clinical findings, we believe that an $R^2$ of 0.73 is not small in the clinical setting. Indeed, an of $R^2$ 0.73 between two variables indicates a correlation coefficient $r$ of 0.85.

The subsequent sex-stratified analysis demonstrated that all estimates in the path diagram had statistical significance (all $p<0.001$) in both sexes, indicating that each component in the diagram plays a significant role, regardless of sex. However, the $R^2$ value of risk clustering was smaller in each sex than that observed in the original analysis of the entire population (Fig. 3). One possible explanation for this finding is that the variable of sex provides much information regarding the association (Table 3) and that stratification by sex decreases the variance of risk clustering. Indeed, sex by itself explained as much as 46% of the variance in risk clustering in the entire population, and the estimated factor score of risk clustering for the whole population was distributed with its variance decreased by 30% in men and 40% in women following stratification.

In the current study, we also investigated the direct and indirect effects of age and sex. Numerous studies have demonstrated that age and sex are associated with metabolic abnormalities. It is also well known that abdominal obesity is more likely observed in older populations and men. However, little is known regarding to what extent these factors influence risk clustering via visceral fat accumulation and the adiponectin level. We assessed the direct and indirect effects of these parameters and found that the indirect effects were no smaller than the respective direct effects (Table 3). These findings indicate that visceral fat accumulation and a decreased adiponectin level account for as much as half of the influence of age and sex on risk clustering.

The current study also confirmed that the BMI was inferior to VFA with respect to the impact on risk clustering (Fig. 4). It is true that BMI, a general index of obesity, was found to be strongly correlated with the log-transformed VFA values, thus indicating that the BMI substantially reflects visceral fat accumulation. However, when we compared the direct impact of these parameters on risk clustering, log-transformed VFA, rather than the BMI, had a substantial impact on risk clustering. These findings support the concept that abdominal obesity, rather than general obesity, influences the accumulation of metabolic abnormalities.

Another finding of the current study is that the LDL cholesterol levels less reflected the pathological changes of risk clustering than the HDL cholesterol and triglycerides levels (Table 4). This finding partly validates and supports the current diagnostic criteria for metabolic syndrome, in which the HDL cholesterol and triglyceride levels, but not the LDL cholesterol level, are included.

The current study had some limitations. First, subjects under treatment for hypertension, diabetes mellitus, dyslipidemia and hyperuricemia were excluded simply because their metabolic profiles would have been modified by their medications. It remains to be elucidated whether visceral fat accumulation and adiponectin have a similar impact on risk clustering in these subjects, whose metabolic abnormalities are considered to be advanced. Second, the current study did not assess insulin resistance, which is often described as an important feature of metabolic syndrome. Indeed, previous studies have demonstrated that insulin resistance is associated with abdominal obesity. The addition of an index of insulin resistance may have improved the model fitness and affected the $R^2$ values of risk clustering. Furthermore, no other obesity-related biomarkers, such as leptin, were assessed in the current study. Such biomarkers may also influence the model fitness and $R^2$. Third, the prevalence of a male sex was high, and a relatively small number of women were included. Although the current sex-stratified analysis demonstrated that all estimates in the original path diagram were statistically significant in both sexes and therefore confirmed that all components play significant roles regardless of sex, it remains to be clarified whether there are any sex differences in the magnitudes of these roles. Future studies with larger sample sizes, particularly of women, are needed to examine such sex differences.
Conclusion
The log-transformed measurements of VFA and circulating adiponectin level explain as much as 73% of the variance in risk clustering.

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Conflicts of Interest
There are no conflicts of interest associated with this manuscript.

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