Waist Circumference Adjusted for Body Mass Index and Intra-Abdominal Fat Mass

Tina Landsvig Berentzen1, Lars Ångquist1, Anna Kotronen2,3, Ronald Borra4,5, Hannele Yki-Järvinen2, Patricia Iozzo6,4, Riitta Parkkola4,5, Pirjo Nuutila4,7, Robert Ross8, David B Allison9, Steven B Heymsfield10, Kim Overvad11,12, Thorkild I. A. Sørensen1, Marianne Uhre Jakobsen11

1 Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark, 2 Division of Diabetes, Department of Medicine, University of Helsinki, Helsinki, Finland, 3 Minerva Medical Research Institute, Helsinki, Finland, 4 Turku PET Centre, University of Turku, Turku, Finland, 5 Departments of Radiology, University of Turku and Turku University Hospital, Turku, Finland, 6 Institute of Clinical Physiology, National Research Council, Pisa, Italy, 7 Departments of Medicine, University of Turku and Turku University Hospital, Turku, Finland, 8 Division of Endocrinology and Metabolism, School of Kinesiology and Health Studies, Department of Medicine, Queen’s University, Kingston, Ontario, Canada, 9 Section on Statistical Genetics, Department of Biostatistics, University of Alabama at Birmingham, Birmingham, Alabama, United States, 10 Pennington Biomedical Research Center, Baton Rouge, Louisiana, United States, 11 Department of Epidemiology, School of Public Health, Aarhus University, Aarhus, Denmark, 12 Department of Cardiology, Center for Cardiovascular Research, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark

Abstract

**Background:** The association between waist circumference (WC) and mortality is particularly strong and direct when adjusted for body mass index (BMI). One conceivable explanation for this association is that WC adjusted for BMI is a better predictor of the presumably most harmful intra-abdominal fat mass (IAFM) than WC alone. We studied the prediction of abdominal subcutaneous fat mass (ASFM) and IAFM by WC and by addition of BMI as an explanatory factor.

**Methodology/Principal Findings:** WC, BMI and magnetic resonance imaging data from 742 men and women who participated in clinical studies in Canada and Finland were pooled. Total adjusted squared multiple correlation coefficients (R²) of ASFM and IAFM were calculated from multiple linear regression models with WC and BMI as explanatory variables. Mean BMI and WC of the participants in the pooled sample were 30 kg/m² and 102 cm, respectively. WC explained 29% of the variance in ASFM and 51% of the variance in IAFM. Addition of BMI to WC added 28% to the variance explained in ASFM, but only 1% to the variance explained in IAFM. Results in subgroups stratified by study center, sex, age, obesity level and type 2 diabetes status were not systematically different.

**Conclusion/Significance:** The prediction of IAFM by WC is not improved by addition of BMI.

Introduction

Several studies suggest that the association between anthropometric measures of obesity, such as body mass index (BMI) and waist circumference (WC), and mortality is U-shaped [1–3]. However, recent large-scale studies have consistently shown that the association between WC and mortality is particularly strong and direct when adjusted for BMI [1,4–8]. The explanation behind this direct association is not established, but one conceivable explanation is that WC adjusted for BMI is a better predictor than WC alone of intra-abdominal fat mass (IAFM), which is presumed to be the most harmful fat depot [9,10].

We pooled anthropometric and magnetic resonance imaging (MRI) data from European and American samples, and studied the prediction of abdominal subcutaneous fat mass (ASFM) and IAFM by WC alone and by addition of BMI as an explanatory factor.

Materials and Methods

Subjects

Subjects (Table S1) were white men and women with no chronic illness, except for type 2 diabetes and a small subset of subjects with stress related angina pectoris symptoms [11]. Subjects were recruited mainly via the general media to participate in clinical studies in Canada [12–15] and two sites of Finland; Helsinki [16] and Turku [11,17–20] in the late 1990’s and up to 2010. Written informed consent was obtained from each participant in accordance with the local ethical guidelines and with the Helsinki Declaration II.
Explanatory variables were BMI (kg/m²) and WC (cm). In all centres, height was measured with a height ruler, and body weight was measured with participants wearing light clothes and no shoes. In Canada, WC was measured at the superior edge of the iliac crest or at the level of the lowest rib. In Helsinki, WC was measured midway between spina iliaca superior and the lower rib margin. In Turku, WC was measured at the level of the umbilicus. In all centres, BMI was calculated as weight in kilograms divided by the square of height in meters.

Outcome variables were ASFM and IAFM obtained using MRI. In Canada, abdominal fat mass was determined using 4–5 images acquired from the region extending from 5 cm below to 15 cm above the L4 and L5 intervertebral space using the method described previously [21]. IAFM was defined as intra-peritoneal+retroperitoneal fat mass. In Helsinki, abdominal fat mass was determined by a series of 16 T1-weighted transaxial images acquired from the region extending from 8 cm above to 8 cm below the L4 and L5 intervertebral space using the method described previously [22]. IAFM was defined as intra-peritoneal fat mass. In Turku, abdominal fat mass was determined from a single 10-mm thick axial image at the level of the intervertebral disc L2–L3 using the method described previously [23]. IAFM was defined as intra-peritoneal fat mass, and retroperitoneal fat mass was also assessed. In all centres, an adipose tissue density of 0.9196 g/ml was used to convert the measured volumes into kilos.

Covariates were study centre, sex, age and type 2 diabetes. Type 2 diabetes status was assessed from oral glucose tolerance tests or fasting glucose obtained according to standard protocols in the local centers [11–20].

Heterogeneity and pooling of the data

Differences between the study centres, as partly illustrated in Table S1, were addressed by three strategies. First, differences in the measurements of abdominal fat masses were taken into account by converting ASFM and IAFM into centre-specific z-scores. Differences, second, in the definitions of IAFM were taken into account by performing the statistical analyses in three different pooled data sets A) pooled data from Canada/Turku using z-scores of IAFM defined as intra-peritoneal + retroperitoneal fat mass, B) pooled data from Helsinki/Turku using z-scores of IAFM defined as intra-peritoneal fat mass, C) pooled data from Canada/Helsinki/Turku using z-scores of IAFM defined as intra-peritoneal + retroperitoneal fat mass in Canada and intra-peritoneal fat mass in Helsinki and Turku. Data from each study centre was also analysed separately using z-scores of the centre specific definitions of IAFM. Third, other differences, e.g. in the measurement site of WC, were taken into account by including centre as a covariate in analyses including all centres.

Statistical analyses

Analyses were conducted in Stata version 11.2 (Stata Corporation, College Station, Texas; www.stata.com).

The variance explained in ASFM by BMI was calculated as the total adjusted squared multiple correlation coefficient ($R^2$) [24] of ASFM obtained from a multiple linear regression model with BMI as explanatory variable. WC was included as an explanatory variable in a second step. Likelihood ratio tests were used to compare the model with BMI with the model with BMI+WC. Similar analyses were conducted for BMI and IAFM, and for WC with BMI added in the second step. Analyses were also conducted with study centre, sex, age and type 2 diabetes included as explanatory factors in a third step. Furthermore, the residuals from each of these models of BMI, WC and their combination were plotted across the distributions of WC and BMI.

To investigate whether the associations between the anthropometric measures and abdominal fat depots were equal across study center, sex, age (cut-off at 30 years), obesity level (cut-off at BMI ≥30 kg/m²) and type 2 diabetes status (yes/no), regression analyses were stratified according to each of these factors. Differences between groups were tested by including cross-product terms in the analyses.

Linearity of BMI and WC in the regression analyses was evaluated by restricted cubic splines, and the fit of the models to the data was found acceptable by evaluating the standardized residuals of each model in residual and probit-plots.

Results

Table 1 provides the basic description of the participants in each of the pooled samples.

Table 2 shows the variance explained in abdominal fat depots by BMI, WC and their combination in each of the pooled samples. The absolute value of $R^2$ varied in the samples due to differences in sample characteristics and distribution of the explanatory variables. BMI explained 47%, 65% and 56% of the variance in ASFM, and 11%, 37% and 25% of the variance in IAFM in Canada/Turku, Helsinki/Turku and Canada/Helsinki/Turku, respectively (Table 2, crude models). Addition of WC to BMI added 2%, 1% and 1% to the variance explained in ASFM and 40%, 17% and 27% to the variance explained in IAFM in Canada/Turku, Helsinki/Turku and Canada/Helsinki/Turku, respectively (Table 2, crude models). WC explained 11%, 43% and 29% of the variance in ASFM and 49%, 54%, 51% of the variance in IAFM in Canada/Turku, Helsinki/Turku and Canada/Helsinki/Turku, respectively (Table 2, crude models). Addition of BMI to WC added 38%, 23% and 28% to the variance explained in ASFM and 2%, 0% and 1% to the variance explained in IAFM in Canada/Turku, Helsinki/Turku and Canada/Helsinki/Turku, respectively (Table 2, crude models). Inclusion of study center, sex, age, and type 2 diabetes increased the proportion of variance explained in ASFM and IAFM in all samples (Table 2, adjusted models). As in the crude models, addition of WC to BMI added to the variance explained in IAFM, but only marginally to the variance explained in ASFM. Addition of BMI to WC added to the variance explained in ASFM, but not to the variance explained in IAFM (Table 2, adjusted models). The residuals from the model of BMI, WC and their combination in relation to ASFM and IAFM were similar across the distribution of WC and BMI. So these results were in accordance with the results based on $R^2$ (Figure S1 and S2).

The results stratified by study center and according to sub-groups of sex, age, obesity level and type 2 diabetes status were not systematically different from the results in the pooled samples (Table S2, S3, S4, S5, S6, S7, S8, S9, S10, S11, S12, S13, S14, crude and adjusted models).

Discussion

The present study showed, in contrast to the expectation, that the prediction of IAFM by WC was not improved by addition of BMI as an explanatory factor. WC explained a modest proportion of the variation in IAFM, but the proportion was larger than the proportion explained by BMI. Accordingly, the prediction of IAFM by BMI was improved by addition of WC as an explanatory factor. These results were consistent across the different pooled samples and study centers, and in subgroups of sex, age, obesity level and type 2 diabetes status.
Strengths of our study include the use of advanced and precise non-invasive measures of ASFM and IAFM in a large data sample. Abdominal fat masses and WC were measured differently in the study centres, but despite these differences, results were consistent across the study centres. We do therefore not believe that these measurement differences have influenced our results despite some [25], but not other [26] studies suggesting that such measurement differences could have an influence. Due to the large data sample, we could address whether the results differed among sub-groups defined according to sex, age, obesity level and type 2 diabetes status, and results were consistent across these factors. However, limited information on covariates was available, all participants had the same ethnic background, and the majority was overweight and obese. We used $R^2$ to assess whether WC adjusted for BMI was a better predictor of IAFM than WC alone. $R^2$ is dependent on the distribution of the explanatory variables, and, accordingly, the absolute value of $R^2$ varied in the different samples. However, the prediction of IAFM by WC was not improved by addition of BMI as an explanatory factor in any of the samples, which suggests that predictive value of WC and WC adjusted for BMI was not influenced by differences in the distribution of the explanatory variables.

Several large-scale studies have shown that the association between WC and mortality is particularly strong and direct when adjusted for BMI [1,4–8]. One conceivable explanation for this association has been that WC adjusted for BMI is a better predictor of IAFM than WC alone. The variation in WC is believed to originate from variation in ASFM and IAFM, whereas

### Table 1. Characteristics of the study participants in each of the samples pooled.

|                      | Canada/Turku (n = 383) | Helsinki/Turku (n = 502) | Canada/Helsinki/Turku (n = 742) |
|----------------------|------------------------|--------------------------|---------------------------------|
|                      | Median (10–90%-tile)   | Median (10–90%-tile)    | Median (10–90%-tile)           |
| Age                  | 57 (38; 72)            | 48 (25.8; 64)            | 49 (27.68)                      |
| Body mass index (kg/m²) | 30.6 (26.6; 35.8)    | 29.7 (23.5; 36.6)        | 30.2 (24.2; 35.9)              |
| Waist Circumference (cm) | 103.8 (91; 115.5)    | 101.1 (83.5; 118)        | 102.3 (86; 117.5)              |
| Abdominal Subcutaneous Fat Mass (kg) | 4.6 (2.9; 7.2) | 3.9 (1.8; 6.9)           | 4.2 (2.1; 7.0)                 |
| Intra-Abdominal Fat Mass (kg) | 3.0 (1.6; 4.8)* | 1.5 (0.5; 3.2)†          | 1.9 (0.6; 4.1)†                |
| Women in the sample  | 46.7% (179)            | 49.8% (250)              | 50.3% (373)                     |
| Subjects with type 2 diabetes | 27.1% (104) | 36.7% (184)              | 25.9% (192)                     |

*Intra-Abdominal Fat Mass = intra-peritoneal fat mass+retroperitoneal fat mass.
†Intra-Abdominal Fat Mass = intra-peritoneal fat mass.
¤Intra-Abdominal Fat Mass = intra-peritoneal fat mass+retroperitoneal fat mass in Canada and intra-peritoneal fat mass in Helsinki and Turku.

### Table 2. Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in each of the pooled samples.

|                      | Canada/Turku # | Helsinki/Turku # | Canada/Helsinki/Turku # |
|----------------------|----------------|------------------|--------------------------|
|                      |                |                  |                          |
| ASFM                 |                |                  |                          |
| Crude $R^2$          | 0.47           | 0.11             | 0.49                     |
| Adjusted* $R^2$      | 0.60           | 0.56             | 0.62                     |
| BMI                  |                |                  |                          |
| WC                   | 0.11           | 0.43             | 0.66                     |
| BMI+WC               | 0.49           | 0.66             | 0.78                     |
| IAFM                 |                |                  |                          |
| Crude $R^2$          | 0.11           | 0.37             | 0.51                     |
| Adjusted* $R^2$      | 0.52           | 0.64             | 0.59                     |

Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index. IAFM, intra-abdominal fat mass. $R^2$, adjusted squared multiple correlation coefficients.

WC, waist circumference.

*Regression models adjusted for study center, sex, age, type 2 diabetes status.
†Intra-abdominal fat mass = intra-peritoneal fat mass+retroperitoneal fat mass.
¤Intra-abdominal fat mass = intra-peritoneal fat mass.

p<0.05 for WC and BMI in all models, except for BMI in where p>0.05.

doi:10.1371/journal.pone.0032213.t001

doi:10.1371/journal.pone.0032213.t002
the variation in BMI is believed to originate primarily from variation in subcutaneous fat mass, both at the abdomen and elsewhere. By adjusting WC for BMI, the hypothesis has been that the variation in ASFM is removed from the variation in WC, whereby the variation left in WC adjusted for BMI may directly reflect the variation in IAFM. Our data do not confirm this hypothesis, as addition of BMI to WC did not add to the variance explained in IAFM. Similar to our results, a previous study on white men and women found that addition of BMI to WC added to the variance explained in ASFM, but not to the variance explained in IAFM [27]. The increased mortality risk associated with a high WC in a model adjusted for BMI may, however, not only reflect the effects of high amounts of (intra) abdominal fat mass, but also the effects of low amounts of beneficial body compartments, such as gluteofemoral fat mass or lean body mass [28–30]. More studies of WC and WC adjusted for BMI in relation to imaging measurements of fat distribution and body composition are needed to understand the mechanism behind the strong, direct and replicated association between WC adjusted for BMI and mortality [1,4–8].

In conclusion, our results do not support the hypothesis that WC adjusted for BMI is a better predictor of IAFM than WC alone. Therefore, the assumption that WC adjusted for BMI is a better predictor of IAFM than WC alone should be reconsidered.

Supporting Information

**Table S1** Characteristics of the study participants in each of the included samples. * Intra-abdominal fat mass = intra-peritoneal+retroperitoneal fat mass. # Intra-abdominal fat mass = intra-peritoneal fat mass.

**Table S2** Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in each study sample. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R 2, adjusted squared multiple correlation coefficients. WC, waist circumference. # Regression models adjusted for sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass+−retroperitoneal fat mass. $ Intra-abdominal fat mass = intra-peritoneal fat mass.

**Table S3** Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in the pooled Canada/Helsinki/Turku sample by sex. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R 2, adjusted squared multiple correlation coefficients. WC, waist circumference. # Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass+−retroperitoneal fat mass in Canada and intra-peritoneal in Helsinki and Turku.

**Table S4** Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in the pooled Canada/Helsinki/Turku sample by age. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R 2, adjusted squared multiple correlation coefficients. WC, waist circumference. # Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass+−retroperitoneal fat mass in Canada and intra-peritoneal in Helsinki and Turku.

**Table S5** Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in the pooled Canada/Helsinki/Turku sample by obesity level. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R 2, adjusted squared multiple correlation coefficients. WC, waist circumference. # Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass+−retroperitoneal fat mass in Canada and intra-peritoneal in Helsinki and Turku.

**Table S6** Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in the pooled Canada/Helsinki/Turku sample by type 2 diabetes status. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R 2, adjusted squared multiple correlation coefficients. WC, waist circumference. # Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass+−retroperitoneal fat mass in Canada and intra-peritoneal in Helsinki and Turku.

**Table S7** Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in the pooled Canada/Turku sample by sex. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R 2, adjusted squared multiple correlation coefficients. WC, waist circumference. # Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass+−retroperitoneal fat mass in Canada and intra-peritoneal in Helsinki and Turku.

**Table S8** Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in the pooled Canada/Turku sample by age. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R 2, adjusted squared multiple correlation coefficients. WC, waist circumference. # Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass+−retroperitoneal fat mass in Canada and intra-peritoneal in Helsinki and Turku.

**Table S9** Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in the pooled Canada/Turku sample by age and sex.
Waist, BMI and Intra-Abdominal Fat Mass

in the pooled Canada/Turku sample by obesity level. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R^2, adjusted squared multiple correlation coefficients. WC, waist circumference. * Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # and WC in □ where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass+retroperitoneal fat mass.

Table S10 Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in the pooled Canada/Turku sample by type 2 diabetes status. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R^2, adjusted squared multiple correlation coefficients. WC, waist circumference. * Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # and WC in □ where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass+retroperitoneal fat mass.

Table S11 Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in the pooled Helsinki/Turku sample by sex. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R^2, adjusted squared multiple correlation coefficients. WC, waist circumference. * Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # and WC in □ where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass.

Table S12 Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in the pooled Helsinki/Turku sample by age. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R^2, adjusted squared multiple correlation coefficients. WC, waist circumference. * Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # and WC in □ where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass.

Table S13 Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in the pooled Helsinki/Turku sample by obesity level. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R^2, adjusted squared multiple correlation coefficients. WC, waist circumference. * Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # and WC in □ where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass.

Table S14 Variance explained in abdominal subcutaneous fat mass and intra-abdominal fat mass by body mass index, waist circumference and their combination in the pooled Helsinki/Turku sample by type 2 diabetes status. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index- IAFM, intra-abdominal fat mass. R^2, adjusted squared multiple correlation coefficients. WC, waist circumference. * Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # and WC in □ where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass.

Figure S1 The association between waist circumference, body mass index and the residuals of abdominal subcutaneous fat mass in the pooled Canada/Helsinki/ Turku sample. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index. CAN, Canada. HEL, Helsinki. TUR, Turku. WC, waist circumference. The residuals in the upper panel are derived from a model with WC (left) or BMI (right) as explanatory variables. The residuals in the lower panel are derived from a model with WC and BMI as explanatory variables.

Figure S2 The association between waist circumference, body mass index and the residuals of intra-abdominal fat mass in the pooled Canada/Helsinki/ Turku sample. Abbreviations: ASFM, abdominal subcutaneous fat mass. BMI, body mass index. CAN, Canada. HEL, Helsinki. IAFM, intra-abdominal fat mass. TUR, Turku. WC, waist circumference. Intra-abdominal fat mass = intra-peritoneal fat mass+retroperitoneal fat mass in Canada and intra-peritoneal mass in Helsinki and Turku. The residuals in the upper panel are derived from a model with WC (left) or BMI (right) as explanatory variables. The residuals in the lower panel are derived from a model with WC and BMI as explanatory variables.

Author Contributions
Conceived and designed the experiments: TLB KO TIAS MUJ. Performed the experiments: AK RB HYJ PI RP PN RR DBA SBH. Analyzed the data: TLB LA. Contributed reagents/materials/analysis tools: TLB LA AK RB HYJ PI RP PN RR DBA SBH KO TIAS MUJ. Wrote the paper: TLB. Assisted the interpretation and discussion of the results and made a critical revision of the manuscript for its intellectual content: TLB LA AK RB HYJ PI RP PN RR DBA SBH KO TIAS MUJ.

References
1. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, et al. (2008) General and abdominal adiposity and risk of death in Europe. N Engl J Med 359: 2105–2120.
2. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, et al. (2009) Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 373: 1083–1096.
3. Berrington de GA, Hartge P, Cerhan JR, Flint AJ, Hannan L, et al. (2010) Body-mass index- IAFM, intra-abdominal fat mass. R^2, adjusted squared multiple correlation coefficients. WC, waist circumference. * Regression models adjusted for study center, sex, age, type 2 diabetes status. p<0.05 for WC and BMI in all models, except for BMI in # and WC in □ where p>0.05. || Intra-abdominal fat mass = intra-peritoneal fat mass.
4. Bigaard J, Tjonneland A, Thomsen BL, Overvad K, Heitmann BL, et al. (2003) Waist circumference, BMI, smoking, and mortality in middle-aged men and women. Obes Res 11: 895–903.
5. Janssen I, Katzmarzyk PT, Ross R (2005) Body mass index is inversely related to mortality in older people after adjustment for waist circumference. J Am Geriatr Soc 53: 2112–2118.
6. Kanaya AM, Vittinghoff E, Shlipak MG, Resnick HE, Visser M, et al. (2003) Association of total and central obesity with mortality in postmenopausal women with coronary heart disease. Ann J Epidemiol 158: 1161–1170.
7. Zhang C, Rexrode KM, Van Dam RM, Li TY, Hu FB (2008) Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women. Circulation 117: 1658–1667.
8. Jacobs EJ, Newton CC, Wang Y, Patel AV, McGillough ML, et al. (2010) Waist Circumference and All-Cause Mortality in a Large US Cohort. Arch Intern Med 170: 1293–1301.
9. Arner P (1998) Not all fat is alike. Lancet 351: 1301–1302.
10. Bjorntorp P (1997) Obesity. Lancet 350: 423–426.
11. Lautamaki R, Borra R, Issoz P, Komu M, Lehtimaki T, et al. (2006) Liver steatosis coexists with myocardial insulin resistance and coronary dysfunction in patients with type 2 diabetes. Am J Physiol Endocrinol Metab 291: E282–E290. [pii]:10.1152/ajpendo.00604.2005 [doi].
12. Lee S, Hudson R, Kilpatrick K, Graham TE, Ross R (2005) Caffeine ingestion is associated with reductions in glucose uptake independent of obesity and type 2 diabetes before and after exercise training. Diabetes Care 28: 566–572. 28/3/566 [pii].
13. Davidson LE, Hudson R, Kilpatrick K, Kuk JL, McMillan K, et al. (2009) Effects of exercise modality on insulin resistance and functional limitation in older adults: a randomized controlled trial. Arch Intern Med 169: 122–131.
14. Ross R, Janssen I, Dawson J, Kungl AM, Kuk JL, et al. (2004) Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial. Obes Res 12: 789–798.
15. Ross R, Dagnone D, Jones PJ, Smith H, Paddags A, et al. (2000) Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. A randomized, controlled trial. Ann Intern Med 133: 92–103.
16. Kotronen A, Peltonen M, Hakkarainen A, Sevastianova K, Bergholm R, et al. (2009) Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. Gastroenterology 137: 865–872. S0016-5085(09)00913-5 [pii];10.1053/j.gastro.2009.06.005 [doi].
17. Borra R, Lastamaki R, Parkkola R, Komu M, Sijens PE, et al. (2000) Inverse association between liver fat content and hepatic glucose uptake in patients with type 2 diabetes mellitus. Metabolism 57: 1445–1451. S0026-0495(00)00201-4 [pii];10.1016/j.metabol.2000.05.015 [doi].
18. Bucci M, Borra R, Nagren K, Parkka JP, Del RS, et al. (2011) Trimetazidine Reduces Endogenous Free Fatty Acid Oxidation and Improves Myocardial Efficiency in Obese Humans. Cardiovasc Thromb;10.1111/j.1755-5922.2011.00275.x [doi].
19. Viljanen AP, Issoz P, Borra R, Kankaanpaa M, Karmi A, et al. (2009) Effect of weight loss on liver free fatty acid uptake and hepatic insulin resistance. J Clin Endocrinol Metab 94: 50–55. Jc.2008-1689 [pii];10.1210/jc.2008-1689 [doi].
20. Virtanen KA, Hallsten K, Parkkola R, Janatuinen T, Lounpoist P, et al. (2003) Differential effects of rosiglitazone and metformin on adipose tissue distribution and glucose uptake in type 2 diabetic subjects. Diabetes 52: 263–290.
21. Ross R, Rissanen J, Bradley AJ, Janssen I, Kahn HS, et al. (2008) Does the relationship between waist circumference, morbidity and mortality depend on measurement protocol for waist circumference? Obes Rev 9: 312–325.
22. Janssen I, Heymsfield SB, Allison DB, Kotler DP, Ross R (2002) Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fat. Am J Clin Nutr 75: 683–688.
23. Draper N, Smith H (1981) Applied Regression Analysis Wiley.
24. Bigaard J, Frederiksen K, Tjonneland A, Thomsen BL, Overvad K, et al. (2004) Waist and hip circumferences and all-cause mortality: usefulness of the waist-to-hip ratio? Int J Obes Relat Metab Disord 28: 741–747.
25. Manolopoulos KN, Karpe F, Frayn KN (2010) Gluteofemoral body fat as a determinant of metabolic health. Int J Obes (Lond) 34: 949–959.