Title: Metabolic rate of major organs and tissues in young adult South Asian women

Running title: Tissue-specific metabolic rate in South Asian women

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ABSTRACT

Background/Objectives: Major organ- and tissue-specific metabolic rate (K_i) values were initially estimated using *in vivo* methods, and values reported by Elia[1] were subsequently supported by statistical analysis. However, the majority of work to date on this topic has addressed individuals of European descent, whereas population variability in resting energy metabolism has been reported. We aimed to estimate K_i values in South Asian females.

Subjects/Methods: This cross-sectional study recruited 70 healthy young women of South Asian ancestry. Brain and organs were measured using magnetic resonance imaging, skeletal muscle mass by dual-energy X-ray absorptiometry, fat mass by the 4-component model, and whole-body resting energy expenditure by indirect calorimetry. Organ and tissue K_i values were estimated indirectly using regression analysis through the origin. Preliminary analysis suggested overestimation of heart mass, hence the modeling was repeated with a literature-based 22.5% heart mass reduction.

Results: The pattern of derived K_i values across organs and tissues matched that previously estimated *in vivo*, but the values were systematically lower. However, adjusting for the overestimation of heart mass markedly improved the agreement.

Conclusions: Our results support variability in K_i values among organs and tissues, where some are more metabolically 'expensive' than others. Initial

findings suggesting lower organ/tissue K_i values in South Asian women were likely influenced by heart mass estimation bias. The question of potential ethnic variability in organ- and tissue-specific energy metabolism requires further investigation.

INTRODUCTION

Resting energy expenditure (REE) is an important index of individual and population energy requirements. Whole-body REE (or, equivalently, resting metabolic rate) can be viewed as the sum of specific energy expenditures of individual body organs and tissues, which demonstrate considerable variability in magnitude. In 1992, for example, Elia[1] published tissue-specific expenditure, or 'K_i' values (kcal/kg/day) for the brain, heart, kidneys, liver, skeletal muscle mass (SMM), adipose tissue (AT), and a residual tissue component, based on arterio-venous catheterization studies. Whereas the energy expenditure of the heart and kidneys was estimated to be 440 kcal/kg/day, the equivalent metabolic rate of muscle at rest was just 13 kcal/kg/day. The relative contribution of different organs and tissues to whole-body lean mass therefore has major implications for total REE.

Measuring organ/tissue K_i values by *in vivo* arterio-venous methods in human subjects is technically difficult, [2,3] and has not subsequently been reported in the literature. With the use of indirect calorimetry and imaging methods, a number of authors have collected REE and organ size data and utilized indirect statistical

models to assess the applicability of Elia's K_i values in various cohorts of adult men and women.[3-7] In 2010, Wang and colleagues developed a stepwise univariable regression method, and reported validation of Elia's values in young adults recruited in Kiel, Germany.[3]

Ethnicity and/or geography-related REE variability has long been discussed in the literature, with, for example, the suggestion that tropical and non-tropical peoples differ in average REE.[8-11] Evidence also suggests ethnic differences in organ and tissue mass (e.g. smaller organ size in African Americans[12] and South Asians[13,14] than Europeans). Adjusting for tissue mass has been shown to reduce ethnic differences in REE.[12,15-17] However, the method developed by Wang et al.[3] to assess organ and tissue-specific resting energy rates has not been replicated in non-European populations. The present study aimed to utilize indirect calorimetry, state-of-the-art body composition methods, and the statistical method developed by Wang and coworkers to assess the applicability of Elia's K_i values to young women of South Asian ancestry.

MATERIALS AND METHODS

Participants

Power analysis demonstrated that at an alpha level of 0.05, a sample size of 70 would yield 80% power to detect a correlation of 0.33, which represents a medium effect size.[18]

We sought to recruit in London, UK women of South Asian (Indian, Pakistani, Bangladeshi, Sri Lankan) ancestry; aged 20-28 years; healthy; nulliparous; term-born; with body mass index (BMI) in the range 17-28 kg/m^2. Determination of ethnicity was based on subjects' self-identification and confirmed by maternal and paternal grandparents also being Indian, Pakistani, Bangladeshi or Sri Lankan. The age range and single sex were chosen to avoid phenotypic variability associated with sexual dimorphism, pubertal growth, and aging.

Individuals born at ≥37 weeks' gestation were recruited to control for the possibility that variability in body composition and/or metabolism outcomes would have developed in association with pre-term birth. Individuals were excluded if they reported health conditions with the potential to affect growth or metabolism; smoking; or contraindications for magnetic resonance imaging (MRI). The BMI range was set to avoid very underweight or obese women. In general, Asian populations demonstrate lower median BMI compared to non-Asians,[19] and increased adiposity or altered metabolism may occur below a BMI of 30 kg/m^2,[19,20] therefore the upper BMI cutoff for recruitment was set at 28 kg/m^2.

Flyers, posters and online advertisements were used in recruitment. Data were collected from March 2015 to May 2016 at UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust, London, UK. Ethical approval was granted by the Camden and Kings Cross NHS

Research Ethics Committee of the Health Research Authority. Upon joining the study all participants gave written, informed consent.

Height and weight

Duplicate measures of height were taken to the nearest 0.1cm using a wall-mounted stadiometer (Holtain, Dyfed, UK), with subjects standing barefoot. Weight was taken in duplicate to the nearest 0.01kg.

Fat mass and skeletal muscle mass

Fat mass (FM) was derived using the 4-component model of body composition assessment, as described previously.[21] Dual-energy X-ray absorptiometry (DXA; Lunar Prodigy, GE Medical Systems, Madison, WI, USA) was used to quantify SMM. Subjects underwent a scan of approximately 5 minutes' duration, with the mass of lean, non-fat tissue in the arms and legs provided directly by the DXA system software (Encore, v14.10.022). The basis for using these data as a measure of whole-body SMM, and further details of the method, have been described previously.[22]

Resting energy expenditure

A Deltatrac II indirect calorimeter (Datex-Engstrom Corp, Helsinki, Finland) was used to measure subjects' whole-body REE in a post-absorptive state, in a thermoneutral environment. Subjects were not measured at a specified point in their menstrual cycle. However, day-of-cycle at data collection (estimated using

subject-reported information on recent menstruation and general cycle length) was found not to be associated with measured REE, and thus rejected as a potential confounder.

Following gas calibration of the metabolic cart, O_2 consumption and CO_2 production were assessed continuously for 25 minutes as subjects rested, supine, on a hospital cot under a ventilated plastic canopy. Using these data, REE was calculated in kcal/24hr units using the equation of Weir: (3.941 x $V O_2$) + (1.106 x $V CO_2$).[23]

MRI acquisition

High-resolution 3D imaging of the brain, chest and abdomen was undertaken using a 3T Siemens Magnetom Prisma scanner (Siemens, Erlangen, Germany). The following were acquired: a T1-weighted MPRAGE sequence for brain volume (TR = 2000ms, TE = 2.74ms, flip angle = 8º, voxel size = 1.0 x 1.0 x 1.0mm isotropic, slices = 240, duration = 5min); a T2-weighted, turbo spin echo SPACE sequence for the abdomen (TR = 2000ms, TE = 220ms, flip angle = variable, voxel size = 1.5 x 1.5 x 1.5mm isotropic, slices = 144, duration = 7min); and for the chest, a T2-weighted TrueFISP sequence with breath-hold (TR = 475ms, TE = 1.53ms, flip angle = 47º, voxel size = 1.5 x 1.5 x 4.0mm, gap = 0, slices = 42, duration = 20sec).

Brain and body organ volumes

To derive brain volume (summed cerebral and cerebellar gray and white matter, and subcortical structures including the amygdala, hippocampus, pallidum, thalamus and striatum), T1-weighted MR images were processed and segmented with FreeSurfer (v5.3) and FIRST (FMRIB Software Library v5.0), as described in detail elsewhere.[24-26] Specifically, FIRST was used to segment subcortical structures, due to limitations of FreeSurfer for this purpose.

The heart, kidneys and liver were manually segmented by MKS from raw MRI data using the open-source OsiriX DICOM viewer (v8.5).[27] Regions of interest were drawn around the organs of interest in contiguous image slices in each subject dataset. The software automatically calculated organ volume by summing the voxels in the regions of interest and multiplying by the slice thickness. Duplicate organ volumes were derived on different days, and averaged. The technical error of measurement[28] for the duplicate measures was 1.9% for the heart, 1.1% for the left kidney, 0.7% for the right kidney, and 0.7% for the liver.

Preliminary analysis demonstrated unexpectedly high values for heart mass in comparison with published data.[5,29,30] Heart mass/volume measurement bias may vary across autopsy/dissection or *in vivo* MRI protocols, thus potentially resulting in outcomes which are not comparable across studies. Moreover, preliminary statistical modeling indicated that Elia's K_i values lay outside the 95%

confidence intervals (CIs) associated with our organ/tissue K_i values, which could be due to our overestimation of heart mass relative to Elia's protocol.

Few studies have compared MRI with autopsy-derived organ volumes, however one such study by Prodhomme and colleagues[31] reported MRI-derived heart volume in infants at post-mortem imaging to be 22.5% greater on average than 'real heart volume' measured at autopsy. As we could not change our measurement protocol for heart mass, we explored the effect of reducing measured heart mass by 22.5%, to see how it affected the K_i values.

Statistics

Brain, heart, liver and kidney volumes were converted to mass using the following published density values in g/cm^3: 1.036 (brain); 1.06 (heart and liver); and 1.05 (kidneys).[32]

We followed the statistical approach developed by Wang and colleagues[3] to assess the applicability of Elia's published K_i values. First, body mass was treated as the sum of 7 body components:

$$\mathrm{BM} = M_{brain} + M_{heart} + M_{liver} + M_{kidneys} + M_{SMM} + M_{FM} + M_{residual} \quad (1)$$

where *M* is the mass of the specific body component. In contrast to Wang et al.,[3] we used a measure of FM, rather than AT. Previous authors have used FM

197 rather than AT in similar models.[5,33] Residual mass comprises tissues including
198 blood, bone, skin, stomach and intestines, connective tissue, and lungs.[3,4] It was
199 calculated as body mass minus the sum of masses for brain, heart, liver, kidneys,
200 SMM and FM.
201
202 By definition, whole-body REE is the sum of the products of each body
203 component mass and its corresponding K_i value:
204

$$\mathrm{REE} = \Sigma(K_i \times M_i) \tag{2}$$

205
206 where K_i is the specific resting metabolic rate in kcal/kg/day for body component
207 *i*, and M_i is the mass of the component in kilograms. Hence the resting energy
208 expenditure for organ *i* is given by
209

$$\mathrm{REE_i} = REE - \sum_{-i}(K_i \times M_i) \tag{2a}$$

210
211 where the summation omits element *i*.
212
213 Energy expenditure for each organ/tissue was calculated using measured
214 masses and Elia's K_i values, for example:
215

$$\mathrm{REE}_{brain} = \mathrm{REE} - (200M_{liver} + 440M_{heart} + 440M_{kidneys} + 13M_{SMM} + 4.5M_{FM} + 12M_{residual}) \tag{3}$$

Following Wang et al.[3], least-squares univariable regression through the origin was then used to estimate K_i:

$$\mathrm{REE}_{brain} = K_{brain} \times M_{brain} + residual\ variance \quad (4)$$

The estimate of K_i could then be compared with Elia's value, of e.g. 240 kcal/kg/day for brain. These steps (Equations 3 and 4) were repeated for each organ and tissue.

Statistical analyses were performed using the R language for statistical computing[34] in RStudio (v1.1.419) with two-tailed significance tests at an alpha level of 0.05.

RESULTS

Seventy women were recruited, the majority of them students attending universities in and around London. Fifty-one percent of the sample reported Indian ethnicity, 11% Pakistani, 11% Bangladeshi and 11% Sri Lankan; the remainder reported mixed South Asian ancestry.

Two subjects misreported their height and weight at recruitment, resulting in a measured BMI range of 17-30 kg/m^2. One subject reported a gestational age of 34 weeks; all other participants were born at 37-42 weeks' gestation.

Table 1 details descriptive characteristics for the sample. Heart mass was missing for one subject, and REE for two subjects.

[Table 1 near here]

Table 1 also presents previously published average organ masses for five all-female cohorts and one mixed-sex cohort for comparison with the current study. Our average liver mass was smaller, and heart mass larger, than the results of Illner et al.,[5] Grandmaison et al.,[28] and Davis et al.,[29] whilst kidney mass was similar across studies. Our average heart mass was approximately double that reported in two female South Asian cohorts[35,36] and nearly double that of the mixed-sex cohort of Wang et al.[3] Age, height, weight, FM and SMM differed somewhat across the cohorts (in particular the mixed-sex cohort[3], as would be expected), although BMI averages were similar.

Table 2 shows organ/tissue K_i value estimates and their associated 95% CIs.

[Table 2 near here]

Table 2 also provides results from the sensitivity analysis, where measured heart mass was reduced by 22.5% (ref. 31). With this reduction, mean heart mass was

0.41 ± 0.07 kg. Our K_i values better matched Elia's when using adjusted heart mass, as shown in Figure 1.

[Figure 1 near here]

Finally, Figure 2 is a pie chart demonstrating the percentage contribution of each of the 7 organs and tissues to total REE, following calculation of the products of K_i and M_i. The contribution of brain and liver to REE is roughly double that of fat and the kidneys, which demonstrate the smallest contribution of the 7 body components.

[Figure 2 near here]

DISCUSSION

This study has extended the analysis by Wang and colleagues[3] to test the applicability of Elia's[1] K_i values to young South Asian women in the UK. Our K_i values demonstrated a similar pattern to Elia's, in that they ranked the organs and tissues in the same order (i.e. values for heart, kidney, brain and liver were larger than those for SMM, which was in turn larger than FM). However, our values were significantly lower.

Of the internal organs measured for this study, the heart was the most difficult to extract from MR images using manual segmentation due to relatively ambiguous boundaries with surrounding tissues. As this may have led to over-estimation of MRI heart volume, we tried reducing our estimates by 22.5% based on previously published data.[31] The latter study involved infants at post mortem and hence was not ideally matched to the present study of adults. However, it does provide clear evidence of the bias in heart volume based on MRI.

Our average heart mass was greater than that reported in previous female cohorts of both South Asian and European ethnicity, and also greater than that reported in a mixed-sex cohort (see Table 1). These comparisons would suggest that heart mass in our cohort is double that reported for South Asian women of similar age, and nearly double that for males and females of European origin (who, as noted above, have been suggested to in fact have larger organ size on average than South Asians).[13,14] At the same time, the comparison studies demonstrated larger values than ours for the brain and the liver, and similar values for the kidneys.[3,5,29,30,36]

Of course, comparisons among these studies also have limitations. The studies in South Asian women (both from the Chandigarh region of Northwest India) rely on autopsy data, which may be particularly difficult to compare with MRI studies due to differences in technique and protocol. With respect to the heart, MRI and 'real' volume outcomes may differ due to the presence of blood in the

ventricles.[31,37] Comparing MRI studies to one another may similarly be difficult when variation exists in sample size, body size/composition, and the software and protocols utilized to extract organ mass. Our average measured heart mass, for example, was 77% larger than that reported by Illner et al.[5] and Wang et al.[3], but just 21% larger than that reported by Davis and colleagues.[30] Finally, it is problematic to compare body composition between an all-female sample and a mixed-sex sample, although this was done here with a focus on heart mass to consider the possibility of overestimation.

Assuming that heart mass was overestimated using our protocol, we explored whether reducing heart mass by 22.5% (ref. 31) altered the results of our K_i value analysis. Indeed, repeating Wang et al.'s analysis following heart mass adjustment yielded K_i values very similar to Elia's published values.

Reports from the 1930s indicated ethnic and/or geographical variability in REE,[9,38] for example Tamil women in South India having lower average metabolism than white American women.[39] Individuals of Japanese, Filipino and Bengalese ethnicity demonstrated negative deviations in REE, as assessed against contemporary normative standards, of 6.4%, 8.3% and 9%, respectively.[40] Henry and Rees[11] concluded that individuals in tropical regions could be characterized generally as having lower REE than individuals in temperate regions.

However, subsequent studies suggested that differences in body composition (i.e. variation in the relative proportion of high-metabolic rate organs and lower-metabolic rate SMM and FM) could explain ethnic/geographical REE differences.[12,16,40-43] Whereas ethnic differences in REE tend to persist when controlling for overall weight or BMI, they are abolished when fat-free mass, which includes SMM and organs, is taken into account. Differences in average REE between Indian females and Australian females of European descent were rendered non-significant with adjustment for both fat-free mass and FM.[16]

It is possible that organ/tissue K_i values vary by ethnic ancestry and/or geography for reasons unrelated to body composition. Our initial results suggest that K_i values, or the metabolic 'cost' of six organs and tissues and a residual component, might indeed be different in South Asian women compared to other cohorts. It is more likely, however, that bias in the estimation of heart mass, or potentially another organ or tissue, explains inconsistencies between our estimated values and Elia's.

In conclusion, we cannot definitively determine whether our K_i values for South Asian women are inconsistent with those reported by Elia, as we have shown that potential error in the measurement of organ mass may impact results when using the method of Wang and coworkers.[3] Despite the difficulties of *in vivo* K_i value assessment, such methods may be necessary to more firmly elucidate ethnic variability in tissue-specific metabolic rates, if it exists.

The current results suggest that the heart may be the least reproducible organ to determine with MRI using manual measurements. Software designed to assist segmentation and/or the use of advanced imaging methods (e.g. ref. 44) may increase accuracy in heart volume/mass estimation, even as investigators must remain cautious when comparing MRI with autopsy-derived measurements.

Nevertheless, our results support the rankings in Elia's reported K_i values, irrespective of the heart mass variable used: organs and tissues appear variably 'expensive', with the brain and visceral organs demonstrating higher specific metabolic rates than SMM, FM or residual mass. High-cost organs such as the heart and kidney have a specific REE more than 30 times greater than an equivalent amount of muscle tissue at rest (although it has not been sufficiently appreciated that skeletal muscle comprises a greater proportion of total REE than the kidneys when mass is taken into account; see Figure 2). Variability in the size of organ/tissue components therefore contributes to variability in energy expenditure associated with fat-free mass, which in turn accounts for much of the variance in whole-body REE.[45] This suggests that patterns of growth and development in early life may influence adult REE, as shown previously in an elderly European population.[46]

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CONFLICT OF INTEREST: The authors declare no conflicts of interest.

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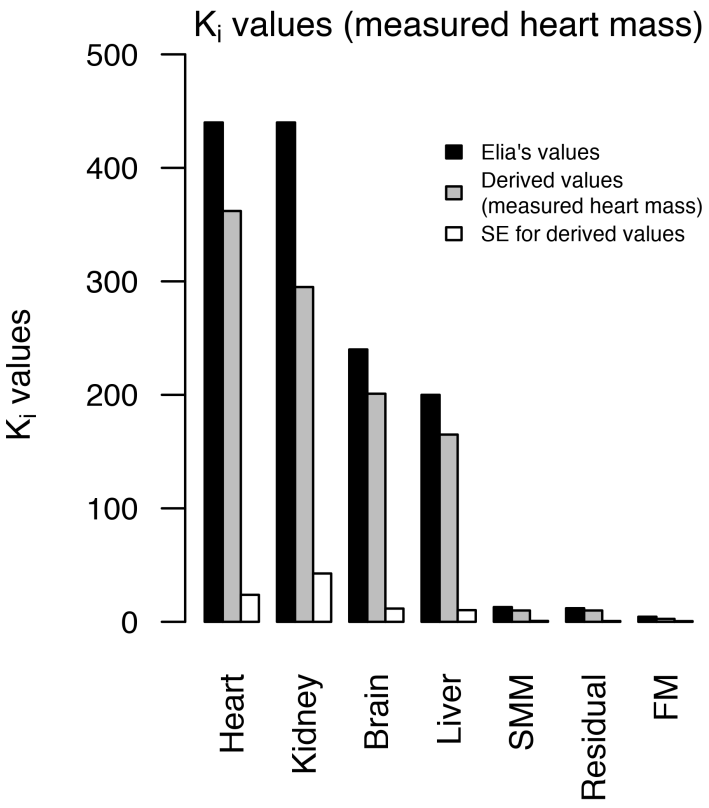
Figure 1. K_i values (kcal/kg/day) derived using measured heart mass and heart mass minus 22.5%, compared with Elia's values

Figure 2. Percentage contribution of organs and tissues to total resting energy expenditure (kcal/day) in females, calculated using K_i values reported by Elia and masses measured in the current study, including adjusted heart mass


K_i values (measured heart mass)
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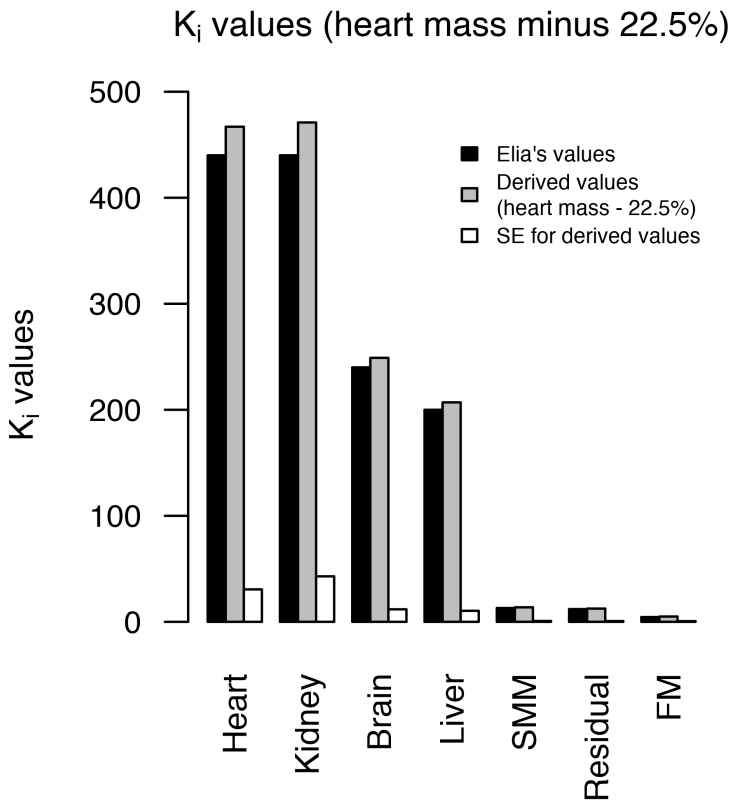
Derived values
(measured heart mass)
SE for derived values
Heart
Kidney
Brain
Liver
SMM
Residual
FM


K_i values (heart mass minus 22.5%)
K_i values
500
400
300
200
100
0
Elia's values
Derived values
(heart mass - 22.5%)
SE for derived values
Heart
Kidney
Brain
Liver
SMM
Residual
FM

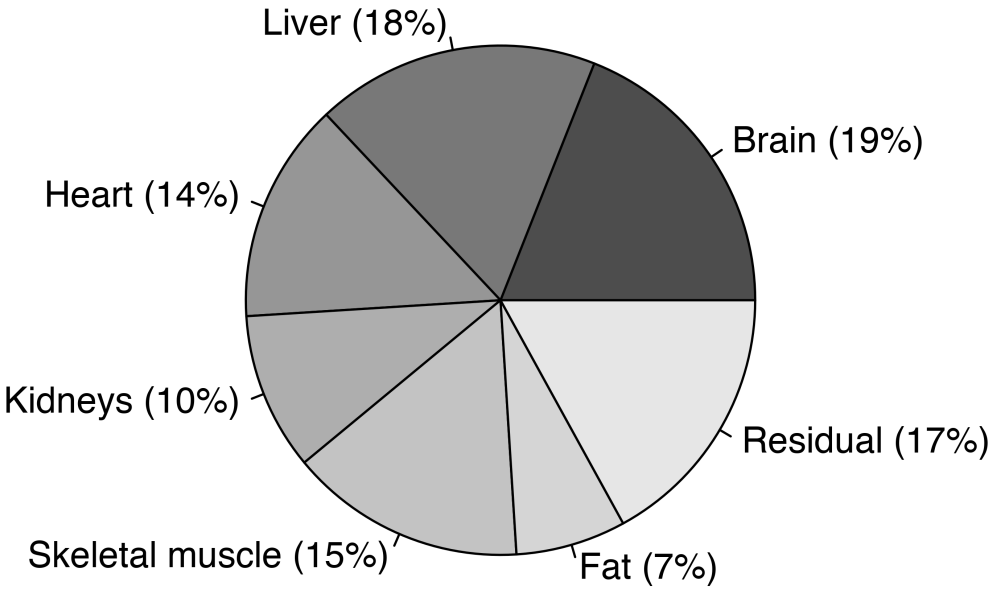

Liver (18%)
Brain (19%)
Heart (14%)
Kidneys (10%)
Residual (17%)
Skeletal muscle (15%)
Fat (7%)

Table 1. Sample statistics for age, anthropometry, organ mass and resting er
and a mixed-sex sample

| | This study | | All-female studies (
Mean ± SD or Rang |
|---|---|---|---|
| **Subject characteristic** | ***n*** | **Mean ± SD** | **Sahni et al., 1994[1]**
***n* = 87** |
| Age (yr) | 70 | 24 ± 2 | 21 - 25 |
| Weight (kg) | 70 | 57.8 ± 9.3 | 48.1 ± 7.6 |
| Height (cm) | 70 | 161.2 ± 6.6 | |
| BMI (kg/m^2) | 70 | 22.3 ± 3.5 | |
| Fat mass (kg) | 70 | 20.3 ± 6.7 | |
| Skeletal muscle mass (kg) | 70 | 15.3 ± 2.2 | |
| Brain (kg) | 70 | 1.08 ± 0.08 | |
| Heart (kg) | 69 | 0.53 ± 0.09 | 0.23 ± 0.04 |
| Liver (kg) | 70 | 1.21 ± 0.21 | |
| Kidneys (kg) | 70 | 0.29 ± 0.05 | |
| Residual mass (kg) | 69 | 19.2 ± 2.1 | |
| Resting energy expenditure (kcal/24hr) | 68 | 1337 ± 184 | |

[1]Autopsy study; [2]MRI study

ıergy expenditure in this study, and in previously-reported all-female study samples (South

(South Asian):

ıe	**All-female studies (European): Mean ± SD**		
Singh et al., 2004[1] ***n*** **= 204**	**Illner et al., 2000[2]** ***n*** **= 13**	**De la Grandmaison et al., 2001[1]** ***n*** **= 329**	**Davis et al., 2015[2]** ***n*** **= 14**
21 - 30	25 ± 2	49 ± 20	37 ± 12
	62.8 ± 9.5	58.0 ± 13.2	53.9 ± 6.4
	170.0 ± 6.0	161.0 ± 7.5	155.0 ± 7.0
	22.1 ± 2.5	22.5 ± 4.5	22.4 ± 2.6
	19.2 ± 6.0		
	17.9 ± 2.5		
1.21 ± 0.11	1.5 ± 0.1		
0.24 ± 0.05	0.3 ± 0.0	0.31 ± 0.08	0.44 ± 0.04
1.3 ± 0.2	1.5 ± 0.2	1.48 ± 0.36	1.3 ± 0.23
0.26 ± 0.05	0.2 ± 0.0	0.27 ± 0.08	0.25 ± 0.04
	19.7 ± 2.1		
	1372 ± 163		

ı Asian or European cohorts)

Mixed-sex study (European): Mean ± SD
Wang et al., 2010[2] *n* = 43 (f=27)
26 ± 2.0
70.0 ± 11.3
174.0 ± 6.0
23.0 ± 2.7
16.6 ± 6.7
25.0 ± 5.9
1.33 ± 0.11
0.31 ± 0.09
1.35 ± 0.23
0.28 ± 0.06
22.8 ± 3.9
1547 ± 241

Table 2. Estimates of organ- and tissue-specific metabolic rate (K_i) values (kcal/kg/day), and effect of heart mass adjustment

Organ/tissue	K_i value (95% CI)	K_i value (95% CI) (heart mass less 22.5%, following Prodhomme et al.)	K_i value (Elia)
Heart	362 (315, 409)	467 (406, 528)	440
Kidneys	295 (210, 380)	471 (385, 556)	440
Brain	201 (178, 224)	249 (226, 273)	240
Liver	165 (144, 185)	207 (186, 228)	200
Skeletal muscle mass	10 (8.7, 12.0)	13.7 (12.1, 15.4)	13
Fat mass	2.6 (1.4, 3.8)	5.0 (3.8, 6.2)	4.5
Residual mass	10 (8.5, 11.1)	12.5 (11.2, 13.8)	12