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Total Energy Expenditure and Requirements in Children with Chronic Kidney Disease

by

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ABSTRACT

HUMAN DEVELOPMENT AND HEALTH

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TOTAL ENERGY EXPENDITURE AND REQUIREMENTS FOR CHILDREN WITH CHRONIC KIDNEY DISEASE

Caroline Elizabeth Anderson

There is uncertainty and some confusion about the energy requirements (ER) of children with chronic kidney disease (CKD), and this is problematic for dietetic practice which is based on limited and poor quality evidence. The aim of this thesis was to examine the hypothesis that total energy expenditure (TEE) and ER are reduced compared to health, and are related to the severity of CKD. To do this a systematic literature review was undertaken, followed by a detailed study examining the ER of children with CKD and healthy controls. The study used both traditional methods (activity diaries, calorimetry, food diaries, dietary energy reference values) and a novel device (Intelligent Device for Energy Expenditure and Activity (IDEEA)) for measuring TEE and physical activity energy expenditure (PAEE). IDEEA was tested for validity so that it could be used to gather data to inform routine dietetic practice. Kidney function, growth status and body composition were also assessed.

The literature search on ER failed to find any studies that measured TEE in children with CKD. Three studies measured or predicted basal metabolic rate (BMR), but the lack of controls in some studies and the inconsistent results with potentially biased methods of expressing them (BMR/kg, BMR/kg Fat Free Mass (FFM), BMR/cm) made it difficult to draw any firm conclusions. Therefore, a study of 20 children with CKD (age 11.9 ± 3.4 years; estimated glomerular filtration rate (eGFR), 33.7 ± 20.5 ml/min/1.73²) and 20 age and gender matched controls was undertaken. Those with CKD had a growth deficit (Z score: weight -0.31 ± 1.17 $p=0.008$; BMI -0.13 ± 1.06 $p=0.023$) and a tendency towards less FFM (swept frequency impedance, skinfolds, and plethysmography), without significant differences in hydration status. BMR (kcal/day; adjusted for age, gender, weight and height) and % predicted (Schofield) BMR did not differ significantly between groups, but in the CKD group it was inversely related to eGFR ($-r=0.518$, $p=0.019$). IDEEA was found to have good precision and validity under controlled conditions in both groups. However, in 12 free living healthy children it showed poor agreement with doubly labelled water (up to 153 ± 651 kcal difference) with no significant advantages over activity diaries, dietary intake or estimated average ER. Some implausible results were also found in both groups.

Although BMR was inversely related to kidney function, it alone does not reflect ER which also depends on PA (probably the most variable part of TEE in CKD), and the energy required for catch up growth (or energy deficit in obesity). The hope that IDEEA would provide a valid basis for assessing ER in free living conditions did not materialise and the hypothesis could not be formally tested. The thesis identified the need to improve the evidence base, using valid novel methods for measuring TEE, that would help establish a structured approach to consider, the effects of age, stage of disease and growth status. Meanwhile, it is reasonable to continue to use methods currently used in dietetic practice despite, their limitations as identified by this work.

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DECLARATION OF AUTHORSHIP

I, Caroline Elizabeth Anderson

declare that the thesis entitled

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and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- parts of this work have been published as: Published abstracts and posters
– see Appendix 3

Signed:

Date:.....

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Definitions and Abbreviations

AD	Activity diary
ADP	Air displacement plethysmography
AFA	Arm fat area
AMA	Arm muscle area
ASPEN	American Society for Parenteral and Enteral Nutrition
BAPEN	British Society for Parenteral and Enteral Nutrition
BIA	Bioelectrical impedance
BIVA	Bioelectrical impedance vector analysis
BF	Body fat
BMI	Body mass index
BMR	Basal metabolic rate
SchBMR	Basal metabolic rate estimated by Schofield equation
BSK	Bicep skinfold
CKD	Chronic kidney disease
CHO	Carbohydrate
CO ₂	Carbon dioxide
CV	Coefficient of variation
D	Density
Db	Body density
DEI	Dietary energy intake
DEXA	Dual energy x ray absorption
DoH	Department of Health
DH	Diet history

DLW	Doubly labelled water
DNI	Dietary nutrient intake
DRV	Dietary reference value
EAR	Estimated average requirement
ECF	Extra cellular fluid
EDR	Estimated dietary record
EE	Energy expenditure
EI	Energy intake
FAO/WHO/UNU	Food and Agriculture Organisation/World Health Organisation/ United Nations University
FEI	Food energy intake
FFM	Fat free mass
FM	Fat mass
FFQ	Food frequency questionnaire
FSA	Food standards agency
eGFR	estimated Glomerular filtration rate
GRF	Glomerular filtration rate
^2H	Deuterium
HFA	Height for age
HAZ	Height for age Z score
HD	Haemodialysis
HRM	Heart rate monitoring
Ht	Height
ICF	Intracellular fluid

IDEEA	Intelligent device for energy expenditure and activity
kcal	kilocalorie
KDOQI	Kidney Dialysis Outcomes Quality Initiative
kg	Kilogram
kj	kilojoule
LBM	lean body mass
MAC	Mid-arm circumference
MAMC	Mid-arm muscle circumference
MUST	Malnutrition Universal Screening Tool
mBMR	Measured Basal metabolic rate
MR	Metabolic rate
NHANES	National health and nutrition examination survey
NKF	National kidney federation
O ₂	Oxygen
O ¹⁸	Oxygen enriched with isotope
PA	Physical activity
PAB	Physical activity behaviour
PAEE	Physical activity energy expenditure
PAL	Physical activity level
PAR	Physical activity ratio
pBMR	Predicted basal metabolic rate
REE	Resting energy expenditure
R ₅₀	Resistance @ 50kHz
R _l	R infinity

RMR	Resting metabolic rate
R_z	R zero
RQ	Respiratory quotient
SACN	Scientific Advisory Committee on Nutrition
Sds	Standard deviation score
SI	Suprailiac skinfold
SKF	Skinfold thickness
SOP	Standard operating procedure
SPA	Spontaneous physical activity
SS	Subscapular skinfold
TBW	Total body water
TDEI	Total dietary energy intake
TEE	Total energy expenditure
TEF	Thermic effect feeding
TSK	Tricep skinfold
WDR	Weighed dietary record
Wt	Weight
WTCRF	Wellcome Trust Clinical Research Facility
WFA	Weight for age
WFH	Weight for height
WHZ	Weight for height Z score
Xc50	Reactance @ 50kHz
24HR	Twenty four hour record

1. Background

Nutrition is important in the clinical management of childhood chronic kidney disease (CKD) for optimal growth, wellbeing and clinical outcome. The cornerstone of any nutritional intervention is energy intake, and, unless energy needs are met, other nutritional interventions cannot be effective. There is a paucity of data on energy requirements in children with CKD¹⁻³, from which recommendations for energy intake are determined in clinical practice. This raises a basic question: how confident are we in current clinical practice, both in regard to the evidence base and the methods used to estimate total energy expenditure (TEE) and/or physical activity in CKD?

This thesis arose from the need to address the uncertainty about the prescription of dietary energy in clinical practice for children with CKD. More specifically, it emerged from a series of inter-related questions. Firstly, what are the energy requirements of children with CKD?; Secondly, do energy needs differ with type of treatment and disease stage?; Thirdly, do energy needs differ from health?; Fourthly, should we continue to use estimated average requirement (EAR) to estimate energy requirements for children with CKD? and finally, should these energy requirements differ between those who are malnourished and those who are not?

To help put this thesis into clinical context, CKD will first be defined and classified into disease stage, and then dietetic practice will be reviewed with respect to four issues:

1. the aims and importance of nutritional management;
2. current clinical practice for estimation of energy requirements and problems associated with establishing and implementing them in clinical practice;
3. the role of the paediatric renal dietitian;
4. what tools are available to help estimate the energy requirements of children with CKD in clinical practice.

The gaps in evidence based practice will be identified for examination in more detail in subsequent chapters.

1.1 Chronic kidney disease terminology

CKD has been defined by the National Kidney Federation (NKF)¹¹ as either kidney damage or decreased kidney function for 3 or more months⁴. Kidney function in children can be assessed by measuring glomerular filtration rate (GFR), or estimated using the Schwartz formula⁵, (Chapter 3 provides details on how to estimate GFR). Normal GFR is approximately 90 to 130 ml/min per 1.73 m² ⁴. To help classify CKD, the NKF has categorised the severity of disease into five stages (stages 1–5); stage 5 representing severe and end stage disease⁴. A description of all stages of disease is provided in the methodology in Chapter 3.

Children can be diagnosed with CKD antenatally or at any stage during their life. CKD can also present itself at any stage of disease. Prompt diagnosis and optimal treatment can help improve clinical outcome, health and wellbeing of the child. The type of treatment varies with the stage of disease and the needs of the individual child, which means that a structured approach is required to ensure valuable clinical resources are targeted to achieve optimum clinical outcome. One important part of the overall treatment is nutritional management, which requires a multidisciplinary team approach. Figure 1.1 below provides an overview of key nutritional management issues in children with CKD. This highlights the need for accurate assessment when formulating treatment plans.

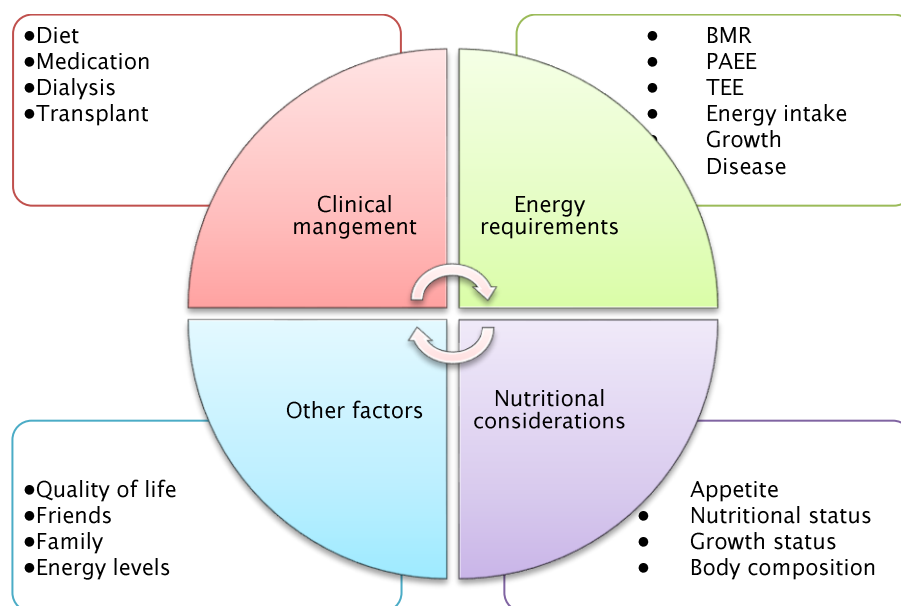


Figure 1–1 Overview of nutritional management issues for children with CKD

BMR = basal metabolic rate; PAEE = physical activity energy expenditure; TEE = total energy expenditure

1.2 Nutritional management of children with CKD.

The nutritional management of children with CKD encompasses five key areas⁶⁻⁸:

1. to provide adequate nutrition for growth and development;
2. to maintain / improve nutritional status;
3. to optimise plasma biochemistry;
4. to delay progression of kidney disease
5. to reduce the risk of chronic morbidities and mortality in later life (adulthood).

To address these issues, regular assessments (both nutritional and medical) are required. Dietary advice and/or nutritional supplementation also need to be tailored to the individual needs of the child^{9 10 8}. In nutritional terms, this means ensuring that adequate energy and micronutrient intakes are achieved, together with adjustments in dietary energy, protein, phosphate, sodium, potassium and fluid, according to the clinical need^{6-8 11}. The importance of nutrition in childhood CKD.

1.2.1 The importance of nutrition in childhood CKD

Nutrition has long been recognised as an integral part of the management of infants, children and adolescents with CKD^{6 8}. Nutrition has previously been defined as the maintenance of normal growth and body composition¹², although a more up to date definition also includes a functional component¹³ to ensure nutritional requirements are optimal for health and wellbeing. In addition, children with CKD require the appropriate level of nutrition to aid kidney function, delay the progression of renal dysfunction^{6 14} and reduce clinical morbidity and mortality. Whether this nutrition alters with stage of disease and type of treatment remains uncertain.

In clinical practice, dietary manipulation to aid biochemical status and delay progression of disease often results in the alteration of energy and other nutrients^{15 8} and potentially leads to under and over nutrition. This is why it is essential to monitor children with CKD closely, and provide appropriate and timely nutritional supplementation. More specifically, a reduction in energy intake without appropriate dietary compensation can lead to catabolism and growth failure (especially if associated with a reduced dietary protein intake)^{15 16}. In turn, this can adversely affect clinical outcomes.

1.2.2 The importance of energy intake in children with CKD

Energy intake (EI) has been recognised as having a key role in the nutritional management of childhood CKD since the 1970's. The provision of sufficient energy has been recognised in the prevention of growth retardation^{17 18 19 20}, and has a role in improving or delaying deteriorating kidney function, and can slow down the progression of disease^{15 21-25}. Conversely, insufficient dietary EI leading to poor nutritional status and short stature, has been linked to more rapid progression of disease, an earlier requirement for dialysis, and increased mortality and morbidity²⁶⁻³⁰. However, it remains unclear as to whether these issues are a cause or an effect. In addition, chronic under nutrition and weight loss in children can also lead to the loss of muscle and/or fat mass (FM), vitamin and mineral deficiencies, and can adversely affect functional capacity, including cognition and mobility, bone mineralisation and immunity^{31 32}.

Despite these nutritional concerns, the literature suggests that spontaneous dietary energy intake is less than the estimated average requirement (EAR) or recommended dietary intake^{2 14 24 33 34 12 25 35}. This is especially the case in children with severe CKD^{24 8}, in whom energy intake is reduced to a greater extent, and which has been progressively deteriorating over time^{10 36}. However, some studies suggest that, although energy intake is reduced, it may be normal, relative to the reduced body size (indicated by inadequate growth). Since this thesis was undertaken, the NKF through the work of Kidney Dialysis Outcome Quality Initiative (KDOQI) has suggested also that there is no evidence that energy requirements differ from healthy children⁸, but recognises that the evidence base is limited. This mirrors findings published in children with other chronic diseases regarding energy requirements³⁷. Unfortunately, previous EI studies in children with CKD have not adequately validated the assessment of dietary energy intake and methodology, so confidence in these findings can be questioned. This lack of validation, coupled with the limited number of studies examining dietary intake and energy requirements in children with CKD, resonates with local clinical experience, and raises several questions: Firstly, do children with CKD have the same energy requirements as healthy children?; Secondly, is EAR suitable as the basis for prescriptions of energy?; and finally, should different energy requirements be used at different stages of disease and be modified further by the presence of malnutrition?

In recent years, increasing evidence has also emerged suggesting that over nutrition and obesity have detrimental effects on both kidney function and cardiovascular disease^{8 38-40 41}. This means that, apart from the need to avoid underfeeding for the aforementioned reasons, it is also necessary to avoid overfeeding. The challenge to the paediatric nephrology team is how to achieve an adequate energy intake to accomplish nutritional management aims when the evidence base is uncertain.

1.2.3 Challenges to the paediatric nephrology team

Providing the appropriate amount of nutrition (and, in particular dietary energy to avoid the consequences of under and over nutrition), is crucial to the clinical management of children with CKD²⁴. As already indicated, one of the key problems is failure to achieve a sufficient energy intake, which can also be a source of frustration for the children and their families/carers¹⁵. The development of obesity is another problem. The following five key challenges relating to estimating energy requirements face the paediatric nephrology team:

1. establishing clear outcome goals for energy requirements (energy balance/growth and/or improved clinical outcome);
2. identifying and understanding the individual components of energy requirements;
3. identifying and understanding the factors that may affect these components (including body composition, malnutrition, disease stage and treatment);
4. accurately measuring and interpreting the components of energy requirements, whilst taking into account any alterations in hydration status (which in itself is difficult to determine with any degree of certainty);
5. translating and monitoring energy requirements in clinical practice, which is further hindered by the lack of data on body composition (fat and lean body mass).

Furthermore, the extent to which an increase in body mass is due to accretion of tissues necessary for normal growth, or excess fluid and fat (which, in the long-term leads to overweight and obesity) is unknown. This uncertainty makes the current practice of estimation of energy requirements insecure. Figure 1.2 provides an overview of the complex considerations that need to be taken into account when estimating the energy requirements for children with CKD.

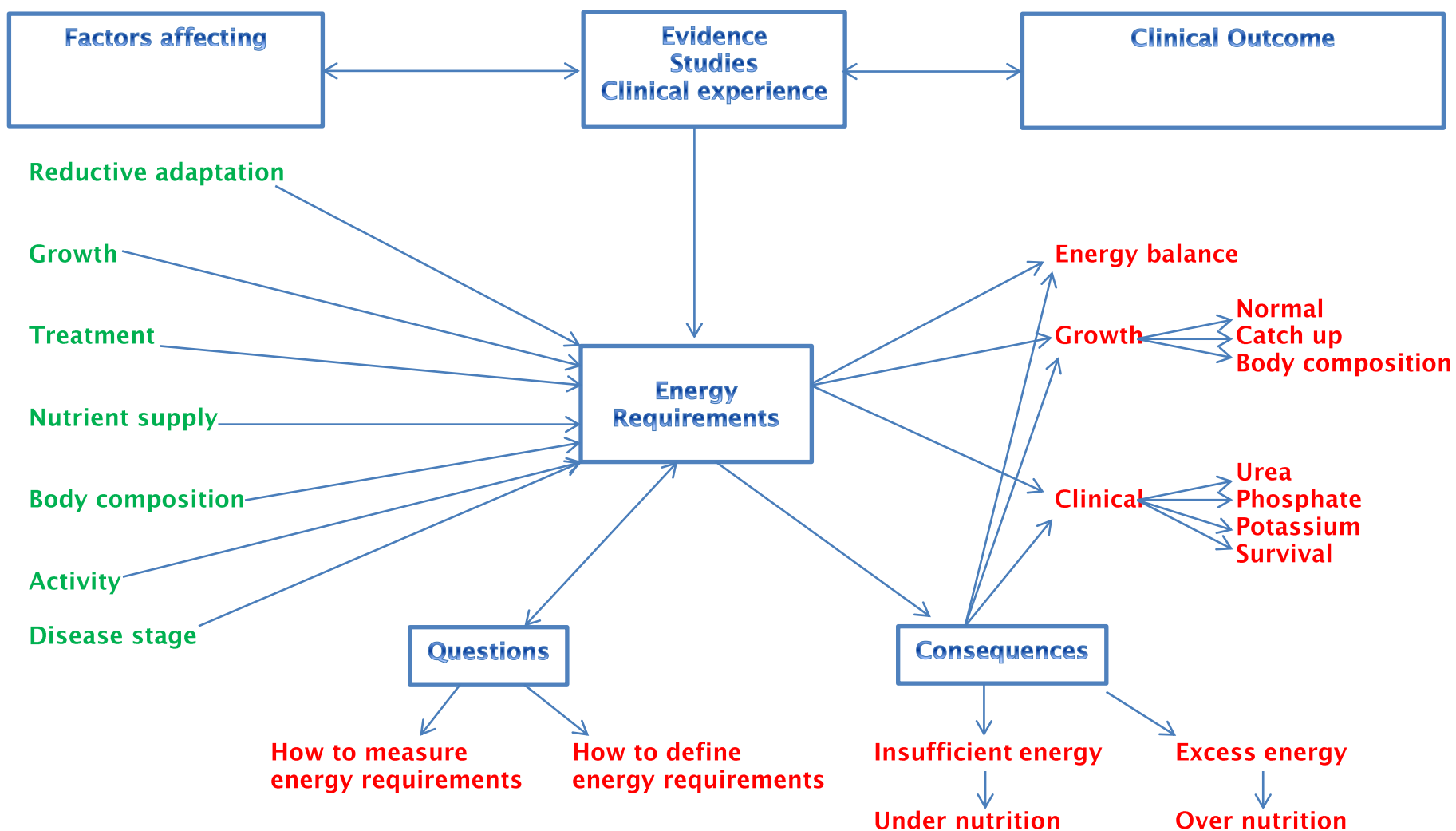


Figure 1-2 Overview of the complex considerations that need to be taken into account when estimating energy requirements

1.3 Current clinical practice used to estimate energy requirements for children with CKD

Current clinical practice of estimating the energy requirements of children with CKD in the UK is based on expert opinion, which is informed by a limited number of studies. Calculations are often based on the UK estimated average requirement (EAR)^{6 42} for energy for healthy groups of children according to their chronological age or height-age^{6 14}. This estimated value is generally used as the basis of the initial energy prescription^{6 7}, although a theoretical upper range (based on expert opinion⁶) is also taken into account. This upper range varies with age, clinical problems / symptoms and the type of treatment the child is undergoing.

Similar national recommendations are used as the basis for estimating energy requirements in Australia, the USA & Canada and in the rest of Europe^{43 8 11 44 45}. The above approach for estimating energy requirements is based on the three key principles, which are summarised below together with their limitations.

The calculation of energy requirements of children with CKD using the EAR for healthy children (UK Dietary Reference Values (DRV's)⁴² is based on three steps:

- 1) Estimating resting energy expenditure (REE);
- 2) Estimating physical activity (PA);
- 3) Combining the above two to estimate EAR (typically calculated as multiples of REE based on physical activity levels (PAL)).

Unfortunately, these principles are not as robust as they might appear for a variety of reasons. One of these is that the concept of EAR was originally intended for groups of healthy children rather than individuals with disease such as CKD^{6 42 46}. Another limitation is that resting energy expenditure (REE) and physical activity (PA) (which form the basis of EAR) can be affected by kidney disease. Unfortunately, there are limited data on direct measurements of REE in children with CKD^{11 44} and no studies seem to take into account the influence of physical activity. Furthermore, the results are conflicting and confusing because they were established using different methodologies using different control groups, and are complicated further by expressing the results in different ways (e.g. kcal/cm, kcal/kg, kcal/LBM/day, kcal/day). In some studies, REE was not measured but established from predictive equations¹⁻³. Additionally, height has

been used as the basis for calculating REE and requirements,^{13 47 48} but this may not be the most appropriate parameter, since kidney disease can cause growth failure^{6 8 46}. Lastly, current methodologies for estimating energy needs do not take into account the most variable component of energy expenditure, which is PA. The identification of these problems again raises the question of how secure are we in the use of EAR for the estimation of energy requirements for children with CKD. Figure 1.3 summarised the components of energy requirements for children with CKD and their associated factors, highlighting how much remains unknown. The next section will then discuss the dietitians' role in nutritional management.

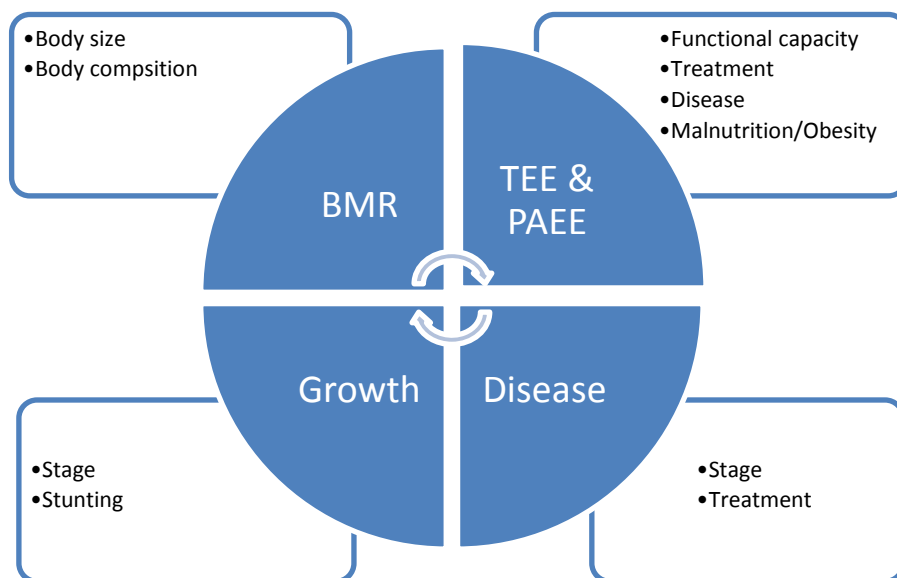


Figure 1-3 Components of energy requirements and related factors
BMR = basal metabolic rate; PA = physical activity

1.4 The role of the paediatric dietitian in the nutritional management of children with CKD

This thesis arose from questions raised when I first started working in paediatric nephrology as the dietitian. This section provides the context in which the questions were raised and the challenges that face the dietitian in the nutritional management of a child with CKD.

The role of the paediatric renal dietitian in the nutritional management of a child with CKD can be broken down into three key areas:

1. to assess nutritional status and growth;
2. to estimate nutritional requirements;
3. to design, advise, implement and monitor nutritional care plans tailored to the child and their family.

Each area requires careful consideration of the diagnosis and treatment, both of which affect nutritional requirements^{37 13}. To enable this to be done accurately and efficiently, there is a requirement to liaise closely with other members of the multidisciplinary team, and to use the appropriate tools, which are discussed below.

1.4.1 Tools used to guide/help this clinical practice

Before discussing the tools used to help a paediatric dietitian achieve the goals of nutritional management, it is helpful first to clarify the difference between nutritional screening and nutritional assessment, both of which have been defined by the British Association of Parenteral and Enteral Nutrition (BAPEN) through the Malnutrition Universal Screening Tool (MUST)⁴⁹ and more recently by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N)⁵⁰. Nutritional screening can be defined as: “a rapid, simple and general screening procedure to detect those at significant risk of nutritional problems, so that clear guidelines for action can be implemented,”⁴⁹ or “a process to identify an individual who is malnourished or who is at risk of malnutrition to determine if a detailed nutrition assessment is indicated”.⁵⁰ Nutritional screening can be carried out at a ward level by nurses and nursing care assistants, although any health professional who examines a child could conduct such a procedure^{49 50}. Meanwhile, nutritional assessment can be defined as “a more detailed, more specific, and in-depth evaluation of a patient’s nutritional state, typically by an individual/team with nutritional expertise,”⁴⁹ or “a comprehensive approach to diagnosing nutrition problems that use a combination of the following: medical, nutrition, and medication histories; physical examination; anthropometric measurements; and laboratory data.”⁵⁰. Nutritional assessment is then used to help guide clinical management by identifying any nutrient changes that are needed to improve clinical outcomes and nutritional status and, ideally, should provide the basis for any nutrition intervention^{49 50}. Different aspects of nutritional assessment can be carried out by a number of health care professionals, including paediatric dietitians’ and doctors, and involves a

multidisciplinary approach. The tools used to facilitate nutritional assessment rely upon a combination of clinical skill, resource availability, and setting^{51 50}. Chapter 2 provides a review of methods used for nutritional assessment, whilst subsequent chapters provide further details of measurements used in this thesis (Chapters 3–8).

Locally, the tools currently used to assess nutritional status and growth of children with CKD involve visual and clinical assessment of the child, together with the UK/WHO percentile growth charts^{52 53} for weight and height/length, the details of which can be found in Chapters 2 and 5. On occasion, indices of weight and height (BMI, percentage of weight-for-height (WFH) and height-for-age (HFA)) are also used (details can be found in Chapters 2 and 5). A more in-depth assessment of nutritional status and growth can be made using Z scores and by assessment of fat and muscle mass (details can be found in Chapters 2 and 5). However, these tools have not been available readily in clinical practice and, in the case of body composition, require appropriate resource and expertise to accurately interpret findings.

To estimate EI, dietitians' utilise 24 hour dietary recalls or 3 day diet diaries, the details of which can be found in Chapters 2 and 4. The adequacy of the dietary energy intake assessments are then determined by comparison with the estimated requirements provided by the UK dietary reference values for healthy children⁴². Clinical guidelines^{54 55 6} and assessments of nutritional status and growth further support this estimation.

Assessment of body composition is rarely done in routine clinical practice, and so current practice provides an incomplete nutritional assessment in terms of fat and lean body mass (LBM). This is of concern because both fat and LBM have been shown to be altered in CKD⁵⁶, the latter being a major determinant of energy requirements¹³. In addition, hydration is also known to be altered in CKD and this can further complicate interpretation of body mass and body composition assessments. Furthermore, alterations in fat and lean mass can affect strength and function of the body and its tissues. For example, alterations in weight could be due to a change in fat and/or lean mass and/or hydration, which could affect both energy requirements and clinical outcomes.

1.5 Summary

This chapter has summarised two aspects of current dietetic practice in the management of children with CKD, specifically, nutritional assessment and energy intake assessment.

It suggests that malnutrition is a feature of CKD but the basis of current practice for managing the energy requirements of children with CKD is insecure. For example, it is not clear whether the energy requirements differ from healthy children and the extent to which they are linked to body composition and body function.

The next chapter aims to examine whether there is a sufficiently strong evidence base on these issues to inform routine dietetic practice.

2. Methods for measuring energy requirements

Chapter 1 reviewed dietetic practice with respect to the estimation of energy requirements in children with CKD, and suggested that the use of EAR as the basis of energy prescriptions is insecure. This chapter will now explore the methods used for measuring energy requirements and the evidence in the literature that formed the basis of current clinical practice. This will focus on three issues:

1. Is there a difference in energy requirements for children with CKD compared to health?
2. Do these requirements change with disease stage?
3. Are these requirements linked to body composition and body function?

An overview of energy requirements (Section 2.1) will be outlined, followed by two major approaches used to estimate energy requirements (energy expenditure (Section 2.2) and energy intake (Section 2.3)). In addressing the aforementioned issues, the need for catch-up growth and body composition will also be explored.

This information will then be used to identify gaps in knowledge, and, in turn, these will be used to formulate the aims, objectives and hypothesis of this thesis.

2.1 Estimating energy requirements for children

Current clinical practice for estimating energy requirements for children with CKD is to use EAR taken from the UK 1991 DRV⁴². In addition, the factorial method has also been used ($BMR + PAL = TEE + growth$).

2.1.1 Definitions

Energy requirements have been defined most recently by Scientific Advisory Committee on Nutrition (SACN)¹³ as the 'level of food energy intake required to maintain a healthy body weight in otherwise healthy people at existing levels of PA to allow for any specific needs'. The addition of 'levels of PA' differentiates this definition from previous versions.

Energy requirements for children are made up of several components: BMR / REE; PA; TEE; thermogenesis (thermic effect of food (TEF)) and growth¹³. Each are defined in Section 2.2 below. The TEF has been said to have a fairly constant contribution to energy requirements, whereas PA can vary considerably¹³ and, therefore, can alter the energy needs of an individual or group. A number of factors can also affect energy requirements: age, sex, body size (weight, height), body composition (lean body mass (LBM)), the energy cost of different activities, hormones, illness and ambient temperature. These factors need consideration when energy requirements are being assessed, especially when estimating requirements by the factorial method which is often used⁴².

Energy requirements have been estimated using the EAR taken from the UK DRV's⁴². DRV can be defined as 'a term used to define various expressions of estimated dietary requirements'.¹³ Dietary reference values have three levels of intake; lower reference nutrient intake (LRNI); EAR and reference nutrient intake (RNI). EAR can be defined as the level of intake whereby usually half the population need more than and half need less¹³. RNI can be defined as the level of intake that is usually enough for 97% of the population to ensure that the risk of deficiency is very small¹³. These values work on the assumption that nutrients are normally distributed with EAR as the mean and RNI or LRNI being two standard deviations above or below this assumed mean. Although RNI has been used for estimating the requirements of most nutrients (i.e. the requirements of 97.5% of the population are met), this is not used for energy. In the case of dietary energy, it is EAR that has been considered as the safe recommendation for energy and has been used for estimating the energy requirements for groups of healthy individuals. This is because an EI more than EAR is likely to lead to overweight or obesity, whilst an intake below EAR is likely to lead to a negative energy balance and weight loss. Individuals could, however, also be in energy balance if they have either a reduced EI or energy expenditure (EE), or increased EI or EE, which may not be optimum for health and wellbeing.

2.1.2 Methods used to estimate energy requirements in health and disease

The estimation of energy requirements for healthy groups of individuals who are in energy balance can be estimated by two approaches:

1. Estimation of EE
2. Estimation of EI

EE on the one hand can be estimated by the summation of its individual components (BMR, PA, TEF) or by estimation of TEE. However, these estimations do not consider energy required for the deposition of tissues, which is a component of normal growth. EI, on the other hand, includes energy deposition for growth and can be estimated directly. Figure 2.1 illustrates the relationship between the two approaches used to estimate energy requirements.

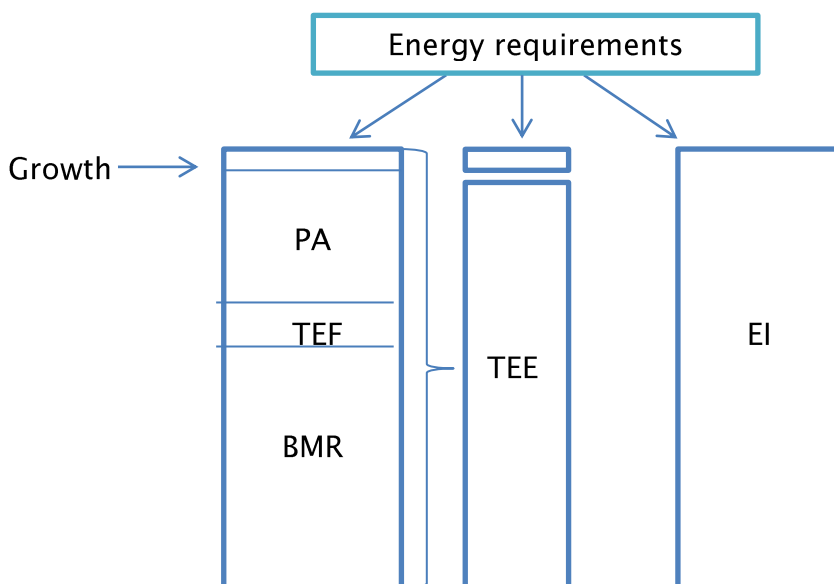


Figure 2–1 Approaches to estimating energy requirements for children.

PA= physical activity. PA=physical activity; TEF=thermic effect of feeding; BMR=basal metabolic rate; TEE=total energy expenditure; EI=energy intake.

2.1.3 Application of methods

Chapter 1 highlighted that EAR for healthy children may not be appropriate as the basis for calculating the energy requirements of children with disease in whom the components of energy requirements (EE and PA) are disturbed. Inappropriate provision of energy may lead to a child becoming underweight or overweight which can have detrimental effects on health.

In 2011, SACN¹³ published updated energy requirement recommendations for healthy groups of adults and children in the UK. This was in response to the

growing epidemic of obesity, the revision of predictive equations and the limitations of previous recommendations.

A number of key points were highlighted. Despite the increasing prevalence of overweight in the UK population, the average EI according to national diet and nutrition survey series⁵⁷ was substantially less than EAR, raising concerns about the accuracy of dietary intake methodology. The previous 1991 COMA⁴² recommendations were based on limited evidence, and provided little information on healthy or desirable PAL that could be used to achieve a healthy weight for different age groups. SACN therefore indicated the need to develop prescriptive recommendations for energy in the UK using a healthy weight, and suggested the Henry equations⁴⁸ could be used to do this in preference to the Schofield equations⁴⁷, which were recommended previously⁴². With this modification, attempts were made to establish age-related PAL guidelines that included high and low activity levels that were not necessarily normally distributed about the mean. The report also advocated the use of doubly labelled water (DLW) studies to estimate TEE in representative samples of the population¹³. These new recommendations have not been completely incorporated in UK clinical practice for healthy children or for children with chronic disease, although they are now under review by some national groups involved with clinical practice. One key reason for this is the problem with how to quantify low, median or high activity for children of different ages that relate to the three PAL levels (quartile (Q) Q25, Q75 and the median PAL) provided by SACN¹³.

2.1.4 Literature review

A systematic search of the literature was conducted in 2005 (and updated on 25th February 2013) to identify research investigating the energy requirements of children with CKD. Potential relevant studies were identified by searching electronic databases. The databases searched included PubMed, Web of Science, Web of Knowledge, and Medline. The search terms and mesh headings used included the following: children, adolescents, teenagers, chronic kidney disease/failure, chronic renal/kidney disease/failure, Dialysis*, estimated glomerular filtration rate*, creatinine clearance, EE*, BMR, resting metabolic rate, PA*, TEE, energy requirements*, EI, EAR, recommended daily intake, and healthy controls. In addition, a manual search of review articles and reference manuals

was undertaken. Studies were initially screened by reading the abstract, and then full articles were reviewed when appropriate.

Studies were deemed suitable if they met predetermined inclusion and exclusion criteria. To investigate the energy requirements and expenditure of children with CKD, the following inclusion criteria was developed: English language; children aged 6–17.99 years; CKD; stable for three months; and human only studies. Studies for children under 6 years and with acute kidney failure were excluded. Figure 2.2 shows a diagram of the literature search, and Table 2.1 shows a summary of the studies included for a full review.

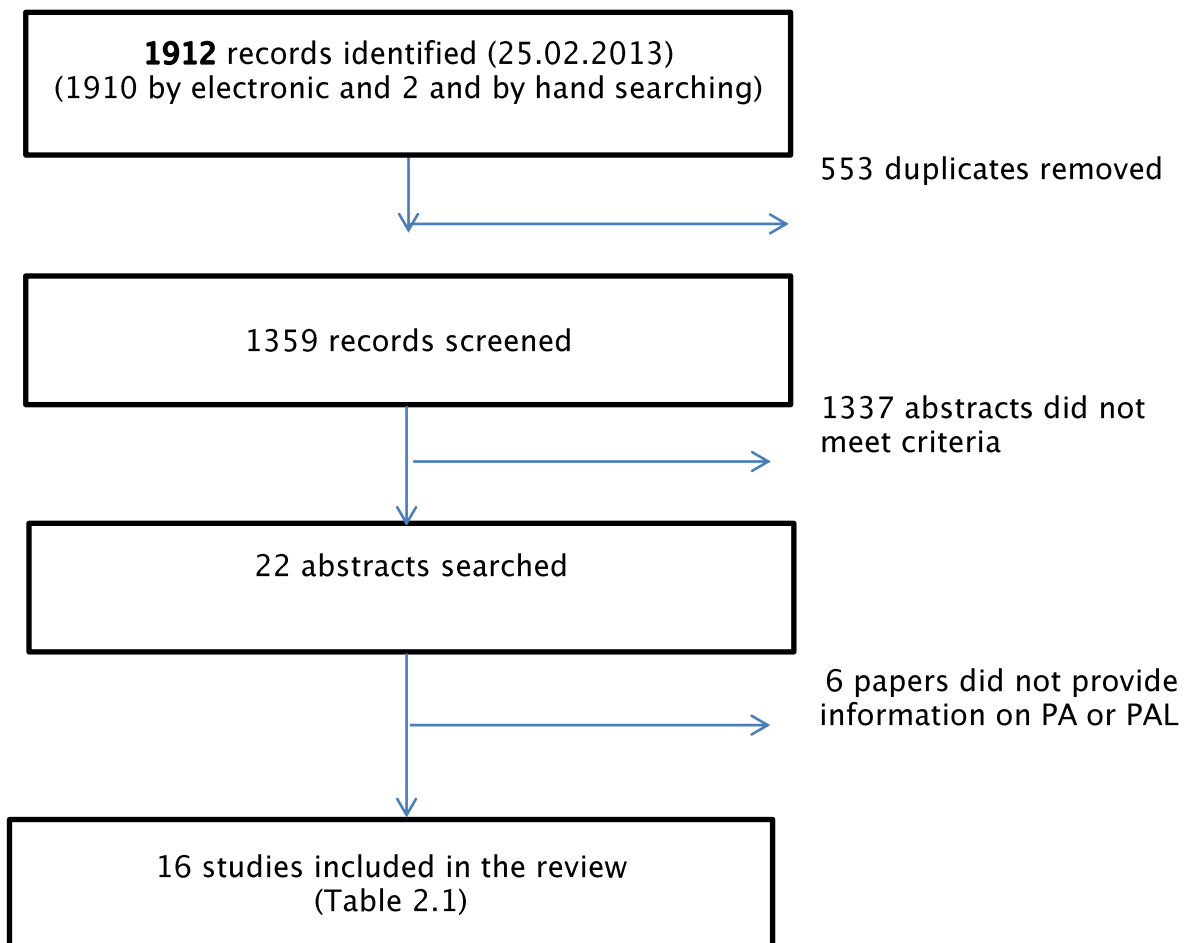


Figure 2–2 Flow diagram of the literature search.

Table 2–1 Studies included in the literature review

	Number of studies	Number of children CKD / Control
Basal metabolic rate	0	0
Resting metabolic rate	3*	49 / 35
Physical activity	0	0
Total energy expenditure	0	0
Energy requirements	0	0
Energy intake	13	496/158

CKD= chronic kidney disease

No studies were found that examined energy requirements of children with CKD. Although one paper included energy requirements in its title, it only attempted to establish REE rather than total energy requirements. Studies identified in table 2.1 above will then be discussed in the subsequent sections in relation to energy expenditure (section 2.2) and energy intake (section 2.3).

2.1.5 Relevance to this thesis and clinical practice

Current UK clinical practice to estimate EE and ultimately energy requirements for children with CKD, has been to use EAR for energy, ⁴² or the Schofield predictive equation and an activity factor. Caution, needs to be taken when applying predictive equations and EAR to today's children who, over the years, have changed in body composition, lifestyle and growth velocity. Ignoring these changes can result in an over or underestimation of requirements and ultimately, obesity, or malnutrition. The fact also remains that both the EAR and predictive equations were intended for groups of healthy children and not individual children suffering from disease. Despite these facts they have been used as a basis for estimating energy expenditure and requirements of individual children with chronic disease such as CKD.

2.1.6 Summary of overall energy requirements of children with CKD

No studies were identified that examined total energy requirements in children with CKD. Before attempting to establish such requirements, it is, therefore, necessary to briefly review the two main approaches, namely EE (section immediately below) and EI (Section 2.3).

2.2 Estimation of energy requirements by measuring EE

Energy requirements can be estimated by measuring EE using two methods: the individual components of EE, namely; metabolic rate (MR) (basal or resting), PA and the TEF, or by measuring TEE. Both methods however, need to include the energy deposition required for growth when estimating the energy requirements for children. This approach has been illustrated in Figure 2.1.

2.2.1 Definitions

BMR has been defined as the rate at which the body expends energy at complete rest⁴². More specifically, this requires the body to be rested both physically and mentally, in thermo neutrality and in the fasted state⁴⁶. BMR is affected by body mass, body composition, age and gender¹³. Body mass is, in turn, affected by ethnicity and pubertal status. In addition, BMR can be influenced by a number of factors including: nutritional state, physiological factors (including recent activity, food and fluid consumption and being awake or asleep), psychological factors, hormonal effects, disease state, medication and ambient temperature⁴²⁴⁶. All of which needs to be considered when measuring and estimating BMR or interpreting BMR study findings.

Resting metabolic rate (RMR) and REE are terms that often are used interchangeably with BMR, although differences between the terms exist. For example, measurements of RMR/REE can be made in the fed or unfed state and at different times of the day, whereas formal measurements of BMR in older children are undertaken in the fasted state after an overnight fast. Thus RMR/REE can be equated to BMR under some circumstances but not others. MR is said to account for 40–70% of energy needs¹³.

PA can be defined as any type of body movement resulting in energy expenditure produced by the contraction of skeletal muscles¹³. Subsets of PA can be divided into spontaneous physical activity (SPA) and exercise¹³. SPA can be defined as all body movements associated with activities of daily living, changes in posture and include fidgeting (which can be considerable in some people), whilst exercise has been described as planned, structured and repetitive activity, and has the goal of improving or maintaining physical fitness and/or health¹³.

In an attempt to quantify the contribution PA makes to TEE, the terms physical activity energy expenditure (PAEE), PAL and physical activity ratio (PAR) have been developed. Their definitions and typical ranges are discussed below.

PAEE can be defined as “the component of energy expenditure related to physical activity”¹³. It can be expressed as kcal per day or as a percentage of TEE. Typically PAEE accounts for 25–50% of TEE and is quantitatively the most variable component.

PAL describes TEE as a multiple of BMR. It is calculated as a ratio to BMR by dividing the total energy needed for a twenty-four hour period by the BMR over the same twenty-four hour period (TEE/BMR)^{13 42}. Typical PAL values in healthy adults range from 1.38–2.5, representing a sedentary lifestyle through to the most active lifestyles¹³. In children, this ranges from 1.4 to 1.85 depending on age and intensity of usual activity¹³. Previous PAL's (current at the time of data collection and analysis) ranged from 1.4–1.99 for sedentary to moderately active adults, and was assumed to be 1.57/1.65 (girls/boys) for children aged 10–18 years⁴².

PAR has been used to describe the duration (per unit of time) and the energy cost of physical activities expressed again as multiples of BMR. Typical PAR values for different activities are: PAR 1.0–1.4 sitting / standing; PAR 2.3–3.3 walking at a normal pace; and PAR 6.0–9.0 jogging, skiing or playing tennis⁴². The 1991 DRV's⁴² suggested a typical PAR for boys and girls as follows: bed 1.0; school 1.6 / 1.5; light 1.6 / 1.5; moderate 2.5 / 2.2; high activity 5.0 (respectively).

TEE is the term given to the sum of energy expended by an individual over twenty four hours and includes: BMR, TEF and PA¹³. This represents the average amount of energy used in a single day¹³. In order to make comparisons between individuals with different age, sex, weight and height, TEE is often expressed as multiples of BMR.

The TEF is the term given to the metabolic cost of food from ingestion through to digestion, absorption and metabolism¹³. The thermic effect of individual macronutrients varies corresponding to the energy content of fat, carbohydrate and protein. Generally, it is assumed to be about 10% of the energy content of ingested mixed diets¹³, although the importance of portion size and composition remain “poorly understood”.^{13 46}

Physical growth can be defined as the increase in size and complexity of the body structure, which requires endocrine and genetic regulation and adequate nutrition¹³. Organ and tissue growth is different at different ages and stages of development, being greatest in the first three months of infancy (35% energy requirements), and then continuing to contribute about 3% of energy needs until mid-adolescence, when there is a slight increase to accommodate the growth spurt^{13 58}. On average, growth accounts for about 1% of energy requirements from 1–16 years of age¹³. In the new SACN requirements, growth has been incorporated in adjusted PAL values for each age group and in the EAR values¹³.

2.2.2 Methods used and their application

A variety of methods both direct and indirect can be used to measure the individual components of EE, and some measure more than one. To simplify this section, a summary of methods used to measure each component will first be given. This will be subsequently followed by a single explanation for each method.

Metabolic rate (MR) can be measured by direct or indirect calorimetry under controlled conditions or estimated by predictive equation. TEE can also be measured by calorimetry (whole body or indirect), DLW or estimated by combining the components of TEE (BMR and PA) each of which can be individually measured or estimated. PA can be estimated by subjective measures, using self-reports and questionnaires (activity diaries (AD)) or objective measures based on physiologic responses (heart rate monitoring (HRM), body movement (accelerometry, pedometers) or from the measurement of TEE by doubly labelled water (DLW).

2.2.2.1 Calorimetry

Calorimetry measures EE (heat) (basal metabolic rate) using either direct or indirect calorimetry under controlled conditions. Direct calorimetry measures heat loss from a subject's body from within a sealed chamber⁵⁹. Subjects are required to remain inside the chamber for a chosen period of time, and heat loss is then measured⁵⁹. Indirect calorimetry is more commonly used, and estimates the heat generated in the body from food or fuel oxidation by measuring oxygen (O₂) consumption (difference between inspired and expired O₂) and carbon dioxide (CO₂) production (difference between expired and

inspired CO_2) under controlled conditions. The amount of energy expended (heat) per litre of oxygen used varies according to the type of nutrient (fuel) consumed (1g of CHO, protein, fat). By measuring the volume of O_2 (VO_2) and CO_2 (VCO_2) exchanged every minute for thirty minutes, an estimation can be made of energy expenditure and the type of fuel contributing to the energy expenditure.^{59 60}.

TEE can then be estimated by further equation involving PA and growth ($\text{BMR} \times \text{PAL} = \text{TEE}$).

A variety of equipment can be used to measure EE but one the most simple systems are the Douglas bag (closed circuit) or ventilated hood techniques (open circuit). In the Douglas bag, inspired and expired air are separated by a valve that directs all the expired air to a non-permeable (air tight) bag to be measured by a gas exchange analyser, (EE is then calculated assuming inspired air is a constant 20.95% (O_2) and 0.03% (CO_2) in well ventilated surroundings). In the ventilated hood system one-directional air (indoor) flows into an enclosed area (ventilate the hood) and is adjusted to keep CO_2 levels under a set threshold. Air is then sampled and analysed^{59 60}.

Calorimetry is based on the principle that it measures net and not actual substrate oxidation, and that O_2 and CO_2 are produced in proportion to heat generated by the body. Calorimetry also has four key assumptions. These are:

1. oxygen consumed is used in oxidative metabolism;
2. all carbon dioxide expired is derived from complete oxidation of fuels;
3. all nitrogen resulting from protein oxidation is collected and measured accurately in urine; and
4. fuel oxidation in the body produces equivalent amounts of energy as complete combustion in a bomb calorimeter.

However, these assumptions require the subject to be in a steady state, unaffected by recent changes in diet, physical activity, temperature, disease or emotional state. Sources of error in calorimetry can be related to deviation from the protocol, or the fact that EE measured under controlled conditions does not represent free-living conditions, which could cause under or over estimation of requirements, and ultimately obesity and malnutrition. Strict adherence to SOP and the use of the same SOP internationally can help improve both accuracy of findings and enable comparison between study findings.

Calorimetry has been used as a reference standard to measure MR in research; however, remains impractical for daily clinical use, and is further limited by cost and the required expertise needed to estimate energy requirements.

2.2.2.2 Predictive equation

Predictive equations estimate EE by factorial calculation using a number of different factors. Typically, weight, age, sex and/or, height are used to estimate BMR. Some disease specific equations have been developed over time; however, none of these have been validated for use in children. Predictive equations are often used in place of calorimetry where calorimetry is not possible or for comparison to calorimetry findings, and can vary internationally making comparison difficult. These equations can be used then in the factorial estimation of TEE.

Predictive equations for BMR use the key assumption that, equations employed to estimate metabolic rate remain representative today of the same groups they were originally intended for and validated against. This makes the validity of these equations difficult when, over the years, today's children have changed in body composition, lifestyle and growth velocity.

Sources of error can occur if these changes are ignored and can result in an over or under estimation of requirements, and ultimately, obesity or malnutrition. Predictive equations are often used to estimate energy expenditure but these require consideration of the aforementioned concerns in order to avoid misinterpretation.

2.2.2.3 Doubly labelled water

DLW measures TEE directly in free-living individuals over several days (typically 10–20 days), using a non-harmful stable radioactive isotopes dose of oxygen (^{18}O) and deuterium (^2H) enriched water. PA is then indirectly estimated using TEE and measured or predicted BMR ($\text{PAL} = \text{TEE}/\text{BMR}$).

The subject consumes a pre-determined dose of ^{18}O and ^2H . These isotopes equilibrate with the oxygen and hydrogen moieties of the body within a few hours of dosing. Energy expended by the body produces CO_2 and water.

Labelled ^2H is lost from the body only as water ($^2\text{H}_2\text{O}$), whereas labelled ^{18}O is lost from the body not only as water (H_2^{18}O), but also carbon dioxide (CO_2). This is because the oxygen in water equilibrates with CO_2 under the catalytic activity of carbonic anhydrase which is found in red blood cells and also in many other tissues. This means that the enrichment of H_2^{18}O declines more rapidly from the body pool than $^2\text{H}_2\text{O}$. The difference in the rate of decline between the two isotopes reflects CO_2 production and is collected by either saliva or urine. To convert CO_2 production to EE, it is necessary to assign an energy equivalent to each litre of CO_2 produced. This value depends to some extent on composition and amount of diet consumed, and whether the subject is in energy balance. PAL can then be estimated by dividing TEE by BMR that has been either measured or predicted (TEE/BMR)^{59 60}.

DLW has five key assumptions:

1. the human body has a constant water content of 73%;
2. the tracer is distributed only in the body water;
3. the tracer is equally distributed in all water compartments;
4. the equilibrium time is rapid and the same regardless of age, gender and disease state; and
5. the tracer and body water are not metabolised during equilibrium.

However, body water can vary with age, and also with obesity, pregnancy and malnutrition. Equilibrium times may also vary according to hydration status and disease state^{61 62}. Sources of error can be attributed to calculation of dose, standard operating procedure (SOP), subject factors such as disease state and treatment mode, collection and storage of samples, choice of equation and technical expertise.

DLW is thought to be most suitable for assessment of PAL for free-living conditions; however, DLW does not give day-to-day information on type, frequency and intensity of activity^{13 63} and is very expensive. There is also no direct measure of PAEE.

2.2.2.4 Factorial method

The factorial method estimates TEE using BMR (measured or predicted) and PAL (measured or estimated). To complete the estimation of energy requirements for children using this method, the cost of energy deposition for growth also needs consideration ($\text{TEE} \times \text{PAL} + \text{Growth}$).

Factorial estimation of TEE assumes that TEE represents energy requirements when the body is in energy balance, but is limited by the lack of information on energy repletion for growth, and whether the body is in an appropriate balance to represent health and wellbeing. For example, an individual can be in energy balance but have an increased EI and EE or decreased EI or EE. Factorial estimations are thought to be the most practical method to assess EE, but this requires all components to be accurately represented.

2.2.2.5 Activity questionnaires

Activity questionnaires \ diaries estimate PA by the use of factorial calculations made up of the daily activities of an individual; each activity is quantified first by time and, later, by its energy cost during specified time periods. Several values for the energy costs of activities have been suggested, but amongst the most frequently used have been those produced by the Department of Health (DoH) in the UK ⁴².

Activity questionnaires \ diaries assume that all activities are representative of daily living (including non-exercise PA), and are accurately collected and interpreted. These diaries are, however, limited by their inability to measure different intensities of activity. Sources of error can be related to the ability of an individual to report information accurately or by a change in habits during the study period. These errors could result in an under or over estimation of PA, leading to misinterpretation of PA and ultimately obesity or malnutrition.

Concerns over accuracy of questionnaires and diaries have been reinforced by SACN (2011),¹³ who suggested that these now have limited precision especially for non-exercise PA, and should be regarded as relatively imprecise measures of PAEE. Objective measures such as HRM and accelerometry are now thought to be more accurate^{13 64}.

2.2.2.6 Heart rate monitoring

HRM measure daily TEE and PA in free-living conditions using the relationship between heart rate and oxygen consumption in free-living individuals⁴⁶. Electrodes which are attached to the chest and a monitor attached typically to

the wrist detects the electrical impulses generated every minute. This allows an estimate of TEE to be determined by using the assumption that heart rate is proportional to the rate to oxygen (O_2) consumption, which is varied by altering the amount of work undertaken (physical activity). Individual standardization is required before measurements can be made ⁴⁶. Information regarding TEE can then be used to estimate PAL using measured or predicted BMR.

HRM assumes all increases in heart rate are due to activity changes and that that heart rate is proportional to the rate to O_2 consumption, which is varied by altering the amount of work undertaken (increases in EE during exercise are linked to increases in work done by the heart due to increased oxygen demand by the body). HRM is, therefore, limited by the inability to distinguish between modest increases in heart rate above resting heart rate that represent activity, and increases in heart rate due to stress or illness. Sources of error can occur if issues such as illness and stress are not taken into account during the study period, and could again lead to an under or over estimation of activity and, ultimately, obesity or malnutrition.

HRM has been thought to be useful as a free-living estimate of EE; however, it does not give day-to-day information on type, frequency and intensity of activity.

2.2.2.7 Accelerometry

Accelerometers measure PA by movement, using single (vertical) or multiple planes (vertical, lateral and anterior) and, subsequently, estimates TEE in free-living individuals over several days using computer software. Sensors are attached to the body either directly or contained inside an armband or leg band.

Several different instruments have been developed over the years to measure PA by accelerometry (such as Sensorware, Actigraph, Actiwatch); one such novel instrument that measures activity on multiple sites is known as the IDEEA⁶⁴. The IDEEA measures the time taken in different physical activities over minutes and hours or days, and estimates physical activity behaviour by providing information on type, duration, frequency and intensity of PA, as well as body movements and postures. Sensors are attached to the chest, thighs and soles of feet by hypoallergenic tape. The device is adjusted to the individual's body

posture by means of the software's own calibration at the start of the measurement to ensure accuracy of measurement. The same software then estimates TEE using the individual's own weight, height, age, sex and estimated fitness level. BMR can also be added to the software to improve the accuracy of the information provided. The IDEEA is validated for use in adults and children aged 13 years and older⁶⁴.

Accelerometry has three key assumptions:

1. all activities are adequately detected;
2. the appropriate energy costs are assigned; and
3. the algorithm used in the software is sufficiently accurate and precise to estimate EE to meet practical needs, as it measures movement not EE.

IDEEA is, essentially, based on two criteria: it adequately captures the type of movement or activity undertaken in free living conditions, and that the conversion of this activity into energy expenditure is accurate. There is some uncertainty with both of these assumptions, which are considered in some detail in this thesis. Sources of error can be related to calibration of equipment, estimation of fitness level, dislodgment of sensors during the test period, change in normal habit, software algorithms, and the inability to measure activities such as swimming and cycling. These sources of error could again lead to an under or over estimation of PA and requirements, and, ultimately, obesity or malnutrition.

IDEEA could be useful in the future clinical management for estimation of PA and TEE; however, the uncertainties above need further exploration.

2.2.2.8 Pedometers

Pedometers measure activity in free-living conditions by recording the number of counts produced by an individual each day when walking, using the stairs and dancing. Stride length is individually assessed and adjusted in the machine before pedometers are attached to the waistband of an individual. A daily count is then estimated. The National Health Service for England (NHS) recommends ten thousand steps per day⁶⁵.

Pedometers assume that all counts recorded are due to body movement that can be related to activity. Sources of error could be related to the misinterpretation

of body movement, calibration of stride length and quality of equipment. Pedometers are limited by their inability to provide any information on type, intensity and duration of activity, their inability to distinguish between movement due to activity or fidgeting, and the ability of the cut off 10000 steps per day being representative of activity required for optimal health and fitness of all individuals.

Pedometers should, perhaps, now be regarded as relatively imprecise measures of PAEE.

2.2.3 Literature review

The search of the literature to investigate the energy requirements of children with CKD using the components of EE has already been discussed in Section 2.1.

Each component of energy requirements will be reviewed separately, together with the effect of disease stage/treatment and body composition/size when included in the literature.

2.2.3.1 BMR

Three full text studies have been published on metabolic rate and children with CKD^{1 3 66}; one after completion of the practical work of this thesis^{1 3 66}. These three studies suggest that metabolic rate in children with CKD is reduced, unchanged or increased compared to healthy controls or predictive equations. The discrepancy in the findings probably relates to methodological differences, including various ways of expressing results. Each study is appraised separately below and will use the corresponding MR terminology (BMR, RMR, REE) chosen by the authors.

The first study by Shapiro et al¹ studied 16 American children with CKD (mean age 9.4 ± 4.6 years) and reported that measured RMR did not differ significantly from values obtained by three predictive equations: Mayo (weight, height and sex), Passmore (weight, height and sex) and FAO/WHO/UNU (weight and age). This study is limited by the absence of a control group. This raises the possibility of a difference in the procedures used in this study and those used to establish the predictive equations. It also raises the possibility of differences in the study population; for example, there are known differences in the weight of

today's children and those used to establish predictive equations many decades ago.

The second study by Tounian et al² studied 18 French children and showed no difference in measured REE (kcal/day) between children undergoing haemodialysis (n=8) and controls (n=10). However, these children were shorter and lighter (significantly for weight), and when the authors expressed REE in kcal/kg/d the values for children with CKD were higher than the control group. This method of comparing results is inappropriate, since individuals who are lighter tend to have higher REE/kg than those who are heavier, even when they have the same proportion of fat and fat free mass/body. The same applies when REE is expressed in kcal/kg/FFM/day. The authors did not attempt to make more appropriate statistical adjustments to overcome these problems.

An insight into the problems involved can be obtained by examining Figures 2.3, it shows Schofield predictive equation values (aged 10–18 year and weight) in kcal/day and kcal/kg/day for children weighing 30–70kg, which is within the range of weight reported in our study population. Although BMR shows the expected increase, as children become heavier there is an associated decrease in BMR/kg/day.

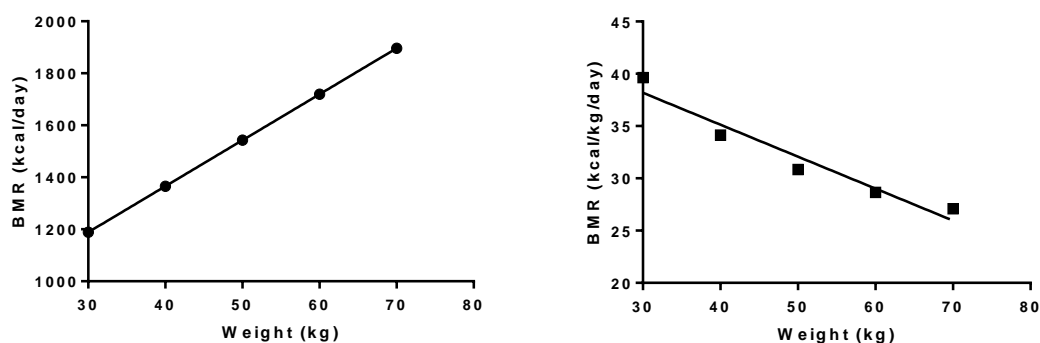


Figure 2–3 BMR (kcal/day and kcal/kg/day) estimated by the Schofield predictive equation for 10–18 year old boys against body weight for children weighing 30–70kg.

BMR kcal/day increases as children get heavier, whilst conversely BMR/kg/day decreases, as children get heavier.

The third study by Marques de Aquino et al³, studied 50 Brazilian children. This study was published after the practical work of this thesis was completed and found that measured REE (kcal/day) was significantly lower in children on haemodialysis (n=25) compared to controls (n=25). However, the children with

CKD were significantly lighter (and had lower BMI, height and Z scores for height for age, arm muscle area and arm fat area). These anthropometric differences could explain the differences in REE kcal/day. The authors did not adjust their results to take into account the differences in weight (or height) but they did adjust for FFM (estimated using tricep skinfold (TSF) thickness and arm muscle circumference). BMR adjusted for FFM was found to be slightly lower in the group with CKD, but it did not differ significantly from healthy controls.

All three studies seemed to be consistent in three respects:

1. children with CKD were more likely to be lighter and shorter and had a tendency towards a lower MR;
2. adjustment for size (weight or FFM) in the first and third studies found no significant difference in MR between the groups;
3. no significant difference in MR (kcal/d) was found when children with CKD were compared to hypothetical children with the same weight, height, sex and age (predictive equations).

However, two studies (Tounian et al⁶⁶ and Marques de Aquino et al³) involved children who were on haemodialysis, and the other study by Shapiro et al¹ involved children who were not yet requiring dialysis. Furthermore, the studies also differed in the age of the children and their sex ratio. Table 2.2 summarises these studies. Finally, the small numbers recruited in all three studies (8–25 children with CKD, 0–25 controls) and the wide range of estimated glomerular filtration rate (eGFR) (0 : >50) might mask a lack of significant difference that could otherwise be found.

2.2.3.2 PAEE

There were no studies published that examine PAEE for children with CKD. One study has published information on pedometer counts in children with CKD at different CKD stages and when transplanted. However, the age range was 7–20 years and the authors did not distinguish between ages, so this study was excluded from the review.

2.2.3.3 TEE

No studies were found that examine TEE for children with CKD.

2.2.4 Relevance to thesis and clinical practice

At the time of study, current UK clinical practice to estimate energy requirements by the components of EE involved the use of the Schofield equation^{42 47}, using weight, \pm height, age and sex, together with the UK 1991⁴² PAL value for children, which will continue to be used here together, with the PAL values for different types of activity. A particular problem that needs to be considered is the need to replete tissues in children suffering from malnutrition and growth failure, an issue that does not apply to healthy children and which is considered inadequately in routine clinical practice.

2.2.5 Summary of energy requirements estimated by the components of EE

This section has reviewed the estimation of energy requirements of children with CKD using the energy expenditure approach.

It shows that individual components can be measured or estimated, but can be subject to misinterpretation leading to an under or over estimation of energy requirements and ultimately obesity or malnutrition.

Furthermore, the evidence base is insecure for two reasons:-

1. Although no significant difference was found between the MR of children with CKD and healthy controls or predictive equations there was uncertainty in these findings due to differing methodologies and the small numbers involved in each study.
2. The lack of literature on PAEE and TEE, combined with the concerns over measuring PAEE and TEE with any degree of accuracy, highlights a huge gap in knowledge. Whilst TEE can also be measured using DLW, this is cost prohibitive. New technologies could prove useful in the estimation of PAEE and TEE but require further validation.

Table 2–2 Comparison of resting metabolic rate in children with chronic kidney disease

Characteristics	Author				
	Tounian ⁶⁶ (n=18)		Marques de Aquino ³ (n=50)		Shapiro ¹ (n=16)
	CKD	Control	CKD	Control	CKD
Number in group	8	10	25	25	16
Treatment	Haemodialysis		Haemodialysis		Conservative
Time on dialysis (months) (range)	15 (1–78)		5 (2.5–3.5)		
GFR (ml/min/1.73m ²)	0		0		>50
Age (years) (mean±sd)	14.6±4.3	14.1±1.3	1.3±3.1 [†]	12.4±3.1	9.4
Gender ratio (m:f)	5:3		15:10	15:10	9:7
Weight (kg)	36.2±9.9	46.0±8.0	29.2±10.3**	43.9±12.8	31.5(–0.8)
Height (m)	1.45±0.18	1.58±0.09	135.9±15.5*	154.2±15.1	1.2(–1.6)
BMI			15.3±2.2*	18.0±2.5	
FFM (kg)	31.3±9.4	35.1±6.7			
LMB fat (kg)					
Girl			22.9±4.4	33.6±8.2*	
Boy			22.4±9.2	37.8±14.5*	
Body fat (kg) Girl			4.9±4.1 [†]	9.6±5.0	
Boy			4.2±2.7	4.6±2.2	
Z scores weight (wt)					–0.85
Z score height (ht)					–1.16
Z score BMI			–1.00±1.30*	10.30±0.60	
Z score (wt/ht)			2.50±1.30*	0.10±0.90	
% weight/height	100.9±10.8	98.7±3.7			
% height/age	92.1±7.1***	99.7±3.7			
REE (kcal/day)	1386±262 [†]	1524±170	1067±191	1372±290*	1147±278
REE (kcal/kg)	40±6*	34±4			
REE (kcal/kg/FFM)	47±9	44±6			
Equations (kcal/d)					
Mayo					1336±299
Passmore					1116±309
FAO/WHO/UNU					1125±329

*p=<0.001; **p=<0.1; ***p=0.009; †p=0.19; *p=0.3; ††p=0.4

2.3 Estimation of energy requirements by measuring EI

Since energy requirements can be estimated by measuring EI (Figure 2.1), it is necessary to define EI and its relative merits to methods relating to EE.

2.3.1 Definition

Energy intake can be defined in the context of this thesis as the energy content of food and fluid consumed. Total energy intake from food and fluid can be determined as the product of energy density (kcal/100g or ml) and the mass of food consumed. Since the energy density of fat, protein and carbohydrate (CHO) varies (4, 4, and 9 kcal/g respectively)^{59 67}, the total energy intake of a meal will depend on its macronutrient composition. Alcohol also contributes to energy intake (7kcal/g), but this is minimal in most children. EI is usually assessed alongside all other nutrients as part of a dietary assessment.

Dietary assessment can be defined in the context of this thesis as the process of estimating and, or measuring the amount, type and frequency of food and fluid consumed over a given period of time⁵⁹.

In UK clinical practice, the units used to express EI are currently based on the older, metric system of calories^{59 67}, often multiplied up to kilocalorie (kcal) (10^3) per day (kcal/day) or kcal per kilogram (kg) (kcal/kg). Many other countries have adopted the joule as the unit of energy; this is known as the international system of units (the modern form of the metric system) and is often multiplied up to a kilojoule (kJ) (10^3) or a mega joule (MJ) (10^6) for ease of use in human nutrition^{59 67}. Kilojoules and kilocalories can be interconverted as follows: 1kcal = 4.184kJ or 1 kJ = 0.239kcal⁴⁶, and are often quoted on nutritional labelling. The contribution of different macronutrients to total dietary intake is also considered in national guidelines for long-term health in the UK ⁴².

2.3.2 Methods used to measure EI

EI can be assessed by a number of different methods that can be divided into two main methods of assessment: prospective or retrospective methods^{59 67}. Prospective methods look at the current intake by direct observation. In children and adolescents, the most commonly used methods are weighed dietary record and household dietary record. Retrospective methods look at current or past intake, and the most commonly used methods for children and adolescents in clinical practice are: the twenty-four hour recall, diet history, or food frequency questionnaire. This review will focus on the more traditional methods currently used.

Weighed dietary records (WDR) detail all food and fluid consumed at the time of recording, using hand held scales and recording weights of each item. WDRs are usually written; however tape-recorder, bar-coding or electronic scales can also be used. The number of days can vary, and does not necessarily have to be sequential. Typically, WDRs can be three to seven days in length, and use both weekdays and weekends, plus or minus school holidays. WDR require a skilled interviewer to verify data and interpret food and fluid for coding and subsequent analysis^{59 61 67-71}.

Estimated dietary records (EDR) detail all food and fluid consumed at the time of recording by use of household measures or portions size, with or without estimation aides (food photographs and or models). Recording of intake and time periods are the same as for weighed records above. The investigator then interprets information into weights that can be used to estimate dietary intake. EDRs also require a skilled interviewer for interpretation and analysis^{59 67-71}.

Twenty-four hour recalls (24HR) record all food and fluid consumed in the recent past, usually during the previous twenty-four hours, and use household measures to record the information. Several days can be used over a given time frame to enable a more representative dietary intake. Several days are needed for meaningful analysis and interpretation^{59 61 67-71}.

A diet history (DH) records all food and fluid consumed over the recent past. DH involves the interviewer asking detailed information on type, frequency, and amount of each food and fluid consumed, as well as where it was bought and, if known, the method of preparation. DH will also ascertain changes due to weekdays or weekends, holidays, or school and seasonal variation^{59 61 67-69 71}.

Food frequency questionnaires (FFQ) are a pre-printed list of commonly consumed foods and fluids to be recorded over a given period of time. Space is provided to indicate typical frequency and/or household measures and additional items not listed^{59 61 67-71}.

2.3.3 Application of methods

Methods used to estimate EI share five key assumptions^{59 61 69 70}:-

1. all food and fluid consumed is recorded;
2. the type of food and fluid consumed is representative of typical intake;
3. the person recording the information is able to conceptualise a food portion and can also read and write;
4. the analysis package being used is up to date;
5. the method chosen is the most appropriate for the children and the nutrient under investigation.

These methods also share some common problems which relate to^{59 61 67-70 72}:-

1. potential bias, as stopping and measuring something potentially changes the character itself;
2. alteration in reporting of food and fluid actually consumed (not all items may be reported, or intake may be simplified to aid reporting, or intake may be altered), leading to an under or over reporting of usual dietary intake. This then leads to the distortion of usual diet and subsequent nutrients within the diet;
3. different databases and food comparison tables having different or limited nutrient information;
4. reporting and analysing errors, and validity and measurement errors leading to incorrect conclusions that may lead to inappropriate decisions by policy makers or stakeholders.

The main advantages, disadvantages and sources of error for each method are summarised in Table 2.3. The key issues relating to children and validity shall be discussed in more detail below.

In children many attempts have been made to address or explain the problems of how to assess dietary intake appropriately. Unfortunately, there appears to be paucity of data from which to draw conclusive advice or recommendations⁷⁰; nevertheless, four issues emerge. Firstly, infants and young children are unable

to complete the diet record. Young children (under nine years) need assistance to complete diet records, and parents often need to consult other carers (e.g. nurseries, child minders) who provide food and drinks which all lead to the potential for less accurate information⁷³. Secondly, dietary patterns change frequently throughout the years. Pre-school children eat small amounts frequently and change food habits often, whilst, older children and adolescents may have irregular meal patterns, can snack often or can skip meals altogether. They also eat away from home more and thus have less parenteral and more peer influence over food choices⁷³. Thirdly, different ages have different cognitive abilities in which to be able to conceptualise food portions and amounts. Various attempts have been made to suggest age appropriate dietary assessment methods, although these are not conclusive. The age of ten years and less has been suggested as the cut off for help with completion of dietary records. In addition, school age children have lower literacy skills, limited attention spans, limited memory and less knowledge of food preparation when compared to adolescents who have full cognitive ability and extensive food knowledge. However, age can often be an arbitrary number as some children (either younger or older) have more or less ability and understanding⁷³. Finally, body weight and age can further compound reporting problems. Older children, adolescents and those who are overweight tend to underreport or give more biased dietary intakes⁷¹.

In more recent years, the validity (measurement error) of dietary intake results regardless of method has come into question^{59 61 67 68 71 73}. The concerns here relate to the incorrect positioning of an individual in relation to the reference (DRV) and the incorrect ranking when comparing with others. If information obtained either under or overestimates energy intake, inappropriate investigations or actions may be taken to alter the excess or deficit when it does not really exist. The incorrect assessment of the relationship between diet and health could also be made which could lead to incorrect / unnecessary actions. In an attempt to address these concerns, reference methods have been undertaken alongside the chosen dietary assessment method. These reference methods are either the gold standard of a seven day weighed intake record and/or newer biomarkers^{59 61 67 68 71 73}. Examples of the latter are: DLW to compare to energy intakes, and ratios of energy intake to BMR to assess under and over reporting in weight stable (or near weight stable) subjects, in whom it is assumed that EI is equal or close to EE. It is noteworthy, however, that biomarkers may add to the problem by

reflecting absorption and metabolism and not just dietary intake and in doing so, are additionally subject to the effects of nutritional status.

Table 2–3 Comparison of methods used to estimate dietary intake

Method	Advantages	Disadvantages	Requirements
Prospective			
WDR	Accurate portion size	Subject to bias (habit change, under-reporting)	Up to date food composition tables
	Vary length of time Widely used so easy to compare	Participant burden high Expensive	Skilled interviewer
EDR	Simplified recording	Reduced precision in portion size unless aides are used	Up to date food composition tables
	Less participant burden Widely used		Skilled interviewer
Retrospective			
24HR	Lower burden	Subject bias (misinterpretation or under reporting)	Good memory
			Able to estimate portion size
	Phone or face to face interview	Estimation of portion size	Skilled interviewer
DH	Information of quality and quantity of eating habits	Subject bias (change in habits / document different intake) Can take up to 2 hours	Able to estimate portion size
FFQ	Vary length of time to suit nutrient studied Low participant burden	Time to develop Need validation pre use	Good memory Skilled interviewer Numeracy and literacy skills
	Self-administered Posted	May not post back	Able to estimate portion size
Overall			
Prospective	Vary duration	Labour intensive	Up to date food composition tables Skilled interviewer Numeracy and literacy skills
Retrospective	Quicker Cheaper	Observer may influence	Good memory Good perception and conceptualisation skills Numeracy and literacy skills
	Easier to complete		

WDR weight diet record; EDR estimated diet record; 24HR 24 hour recall; DH diet history; FFQ food frequency questionnaire

59 61 67–71

2.3.4 Literature review

The search of the literature to investigate the energy requirements of children with CKD has already been discussed in Section 2.1.

Thirteen studies reported dietary energy intakes (DEI) in children with CKD, but EI was the focus for only three.

The first study by Ratsch et al³⁴ reported DEI of 76–88% of recommended dietary allowance (RDA) for 50 Italian children with CKD compared to 90–93% for 93 controls, using four day weighed intake records and three age group categories. The EI in children with CKD was 10% lower than controls. These children were aged between 3–17 years and were on a low protein diet. They were placed in three groups: Group I had a height (ht) sds of -0.5 ± 1.2 (age 3.2 ± 6.9), group II has a sds of -0.6 ± 1.3 (age 7.3 ± 9.9), and group III had a sds of -0.7 ± 1.1 (age 10.5 ± 17.2). This study was limited by the lack of information on nutritional supplementation weight and stability (whether the reported DEI resulted in weight maintenance or loss). In addition, no distinction was made regarding stages of disease or whether the groups were misreporting dietary intake.

The second study by Canepa et al⁷⁴ reported that DEI was $75 \pm 25\%$ of RDA in 19 Italian children on chronic peritoneal dialysis, assessed by the double weighed method, but were limited by the absence of a control group. The mean age of these children was 8.7 ± 3.8 years. Findings on EI included glucose energy from dialysate in the comparisons with RDA. This study was limited by the absence of data on growth, nutritional status, and the lack of information regarding the use of nutritional supplements or weight stability (again no comment was made regarding whether reported DEI led to weight maintenance or loss).

The third study by Zadik et al²³ reported significantly lower DEI ($74.7 \pm 2.9\%$ RDA) for 16 children on peritoneal dialysis (PD) and 15 children on haemodialysis (HD) compared to 44 age matched, short, healthy controls ($98.5 \pm 4.5\%$ RDA ($p < 0.01$)) before growth hormone (GH) therapy, using 3 day diet records in Israel. DEI remained significantly lower even after one year of GH therapy (83.3 ± 3.7 and 105 ± 5.0 respectively) ($p = < 0.01$). These children had a mean age of 8.7 ± 0.5 years, height sds of -3.2 ± 0.2 to -2.8 ± 0.2 ($p = < 0.01$) (CKD: Control). This study was limited by the lack of information on whether DEI included glucose from dialysate or nutritional supplements. In addition, the study did not distinguish between age group, type of dialysis and did not comment on weight stability.

All three studies seemed to be consistent in two respects:

1. children with CKD had lower DEI compared to their national recommendations; and
2. children with CKD had lower DEI than healthy controls.

However, with reported DEI being substantially below EAR, a considerable weight loss would be expected and since weight changes were not documented in these studies findings can be questioned. In addition, DEI may be inaccurate due to underreporting, especially in the two studies using WDR method. In the study by Ratsch et al (where most children had stage three disease), a weight increase would often be expected. Furthermore none of these studies examined the statistical significance of % DEI compared to 100% EAR, and the reliability of the dietary information provided was not explored. Finally the small numbers recruited to all studies might mask significant differences that could otherwise be found. Table 2.4 summarises these studies.

The remaining ten studies that included DEI results (Table 2.4) in older children with CKD^{19 75 76 21 35 77 78 10 24 3} are discussed below, Three of these were undertaken in the UK^{19 10 24}. All the studies differed in CKD stage (eGFR range 6–75), dietary assessment method and presentation of DEI results, and only one compared to healthy controls³. However, there was a general tendency for dietary intake to be reduced even in groups with better kidney function, in which weight increase would be expected. This again raises concerns about misinterpreting reported findings of EI, and the validation of the methodologies. Table 2.5 summaries these study findings.

The lack of DEI validation for most studies, and the concerns raised regarding the use of DEI to estimate energy requirements¹³ further supports the suggestion that literature on DEI should not be used to form the evidence regarding the estimation of energy requirements for older children with CKD. The reasons for these concerns relate to three points:

1. energy intake is not a physiological measure of energy requirements;
2. there is no independent check that EI=EE (except for breast feeding), and
3. EI measurements often under report.

To help overcome these concerns in the future, SACN has recommended the use of DLW to validate DEI assessments¹³.

2.3.5 Relevance to clinical practice and this thesis

In clinical practice, EI has been assessed by 24HR or diet diary (retrospective methods), varying in length and including weekend days or holiday days where possible. In research for children with CKD, both prospective and retrospective methods have been used and in particular, WDR (prospective method), despite being shown to underestimate dietary intake. Each method, however, is subject to the aforementioned problems such as alteration in habitual intake, inaccuracy of assessment and interpretation of methods leading to an under or over reporting of intake and subsequent misinterpretation in findings. This could lead to inappropriate dietary advice and nutritional treatment plans and, ultimately, obesity or malnutrition. In order to address these issues, where appropriate, concurrent validity needs to be undertaken (taking into account the financial and participant burden that may incur), together with consideration of age and cognitive ability and close monitoring of growth status and weight changes.

To further improve dietary estimation of EI, different approaches may need to be considered for younger and older children, and, ideally individualised to suit the child's needs. Consideration, needs to be given to the ability to: estimate portion size; understand, search, evaluate and recall the required information; represent habitual patterns; and detect misreporting^{79 80}. The use of different methods according to age has been suggested⁸¹, but this needs to take into account the aforementioned issues. Until misreporting can be better characterised, and understood all dietary information needs to be interpreted with caution^{79 81}. In addition, the increasing use and potential value of mobile phones and tablets (e.g. iphone and ipads) as a major form of communication, learning and storage for children (and especially teenagers), needs further investigation. In particular, the use of photographic dietary records and storage of dietary advice (a recent observed practice amongst the local paediatric kidney population).

On a practical note, for children with CKD estimation of EI needs to include any nutritional treatment that may contribute to EI. For example, nutritional supplementation and dialysis fluid should be included. Peritoneal dialysis fluid can account for up to 10kcal/kg⁸² of body weight which can be considerable in some children. Failure to consider this information could lead to the

recommendation of a higher EI prescription and consequently the child becoming overweight.

The fact remains, however, that concerns have been raised regarding the ability of EI to adequately represent energy requirements, both with the desired level of accuracy and for the physiological inability of EI to match energy balance. This is because EI is not adequately regulated by appetite to match TEE, and because there is no independent check that EI equals TEE¹³. It is for these reasons that SACN has recommended that EI should no longer be used to guide energy requirements¹³.

2.3.6 Summary of estimating energy requirements by EI

This section has reviewed the estimation of energy requirements of children with CKD using the EI approach.

It demonstrates that, although EI can be measured, there are issues regarding underreporting that render any potential findings suspicious. This was further supported by the literature which suggests that there is a general tendency for dietary EI to be reduced even in groups with better kidney function in which weight increase would be the expected outcome. This highlights the need to validate any methodology to avoid misinterpretation of reported findings.

Furthermore, regardless of which approach is used to estimate the energy requirements, energy for growth and nutritional repletion needs to be included. This is important for children with CKD in order to enable the magnitude of growth failure to be identified, which then facilitates treatment to be adjusted to achieve optimal repletion and thus clinical outcome.

Table 2-4 Energy intake studies in children with CKD

Author & year & Country	Group, number & treatment	Age Years & months	Kidney function ml/min/m ²	Dietary energy intake (DEI)	DEI % of requirement	Height sds	Comment Diet, food diary, medication	Guide for energy
Ratsch et al 1992 Italy	CKD = 50	3-17	15-65*	kcal/kg/d			Low protein diet	RDA
	Group I(3.2±6.9)	4.7±1.1	44.6±18.5*	88±15	88±21	-	4 day weighed	
	Group II (7.3±9.9)	8.5±1.2	40.7±13.8*	65±15	82±8	0.5±1.2		
	Group III (10.5±17.2)	12.7±1.9	36.9±14*	48±14	76±24	-		
						0.6±1.3		
						-		
						0.7±1.1		
	Control = 93			Kcal/day				
	Group I	4.6±0.7		81±15	90±17	0.4±1.3		
	Group II	8.5±1.2		67±13	93±15	0.5±1.3		
	Group III	9.7±0.8		51±12	93±12	0.9±1.4		
Canepa et al 1996 Italy	PD = 19	8.7±3.8			75±26		Double weighed	
Zadik et al 1998 Israel	CKD = 31	8.7±0.5	15.7±1.2**		74.7±2.9	-	3 day	RDA
	HD =16					3.2±0.2	Growth	
	PD = 15						Hormone	
	Pre pubertal Controls = 40	8.4±0.6			98.5±4.5			

Results are presented as mean±sd

* Creatinine clearance ** eGFR = estimated glomerular filtration rate

CKD= chronic kidneys disease; HD=haemodialysis; PD=peritoneal dialysis; RDA=recommended daily allowance

Table 2–5 Energy intake information provided by other studies

Author & year	Group, number 7 treatment	Age years (range)	Kidney function ml/min/m ² eGFR	Dietary energy intake (DEI)	DEI % of requirement	Weight z score	Height z score	Comment Diet, food diary	Guide for energy
Betts & McGrath 1974*	CKD = 33	0.5–16.3	<70		82% 79%			7day recall 3day weighed Prospective	EAR
Grupe et al 1983	HD = 15	11.9±6.3 (0.8–18.7)		kcal/cm/d 10.6±3.6					
Salusky et al 1993	PD = 24 <10 >10	9.68±4.31 (2.25–17.5)		kcal/kg/d 69(25) 47(12)		-1.7±1.1 -1.2±0.7	- 3.0±1.81 -2.9±1.1	3day recall 3day weighed	
Orejas et al 1995	CKD = 15 Group 1 eGFR <50 Group 2 eGFR ≥50	8.9±5.1 (1–18)	11–75		87±14	- 0.46±1.1 -	- 1.17±1.7 -	3day prospective	
Foreman et al 1996	CKD = 120 Group 1 1–3yr Group 2 4–6yr				86 82			4day	
Coleman et al 1998*	CKD = 22 HD = 4 PD = 18	0.6±0.7 (0.1–2.1)		kcal/kg/d 99±21 105±17.8	122±22 115±10.3		-2.22	4day	EAR
Normal et al 1998*	CKD = 2 pre PD PD	Infants		kcal/kg/d 147 137		-1.48 -1.4	-0.44 -0.43		
Ledermann et al 1999*	ESRD = 35 (PD = 6) Group 1 0–2yrs Group 2 2–5yrs	1.6 (0–4.9)	<12.1 (6–26)		6/12 pre EN 93.7±23.2 81.4±21.6 Start EN 104.2±26.2 96.4±14.9	-3.3±1.0 -2.3±1.2 -3.1±1.3 -2.0±1.1	-2.9±0.7 -2.8±0.6 -2.9±1.2 -2.3±0.7	3day	

Results are presented as mean±sd

eGFR = estimated glomerular filtration rate; CKD= chronic kidneys disease; HD=haemodialysis; PD=peritoneal dialysis; RDA=recommended daily allowance; EAR=estimated average requirement. * = UK studies.

Table 2–6 Energy intake information provided by other studies continued

Author & year	Group, number & treatment	Age years (range)	Kidney function (eGFR) ml/min/m ²	Dietary energy intake (DEI)	DEI % of requirement	Weight Z score	Height Z score	BMI z score	Comment Diet, food diary medication	Guide for energy
Norman et al 2000*	Normal eGFR =35	8.2 (2–16.2)	>75		103±17**				3day semi-weighted prospective	
	Group 1 =23	8.2(2–16.9)	50–75		99±10					
	Group 2 =19	8.5(2–16.1)	25–50		92±19					
	Group 3 =18	10.2(2–16.0)	<25		85±27					
	Normal eGFR=35	8.2 (2–16.2)	>75		103±17***					
	Group 1 =23	8.2(2–16.9)	50–75		99±10					
	Group 2 =19	8.5(2–16.1)	25–50		96±18					
	Group 3 =18	10.2(2–16.0)	<25		96±22					
Pereria et al 2000	CKD = 30				90% were <100%RDA				3day	
Edefonti et al 2001	HD = 7, PD = 23				84.82±25.54				3day	
Edefonti et al 2002	PD = 29	10.54±6.28 (2.8–15.24)		kcal/kg/d					3day	RDA
	Group1 <10.33	9.28±6.6		54.56±21.38	70.58±20.47	2.57±1.46	2.78±1.55	-1.05±0.88		
	Group2 ≥10.33	8.09±5.52		56.12±28.68		0.70±1.46	1.46±1.13	0.22±0.88		
				54.01±18.23						
Norman et al 2004*	Group 1 =19	8.2(2–16.9)	50–75			-0.14	-0.29	0	3day semi-weighted prospective	EAR
	Group 2 =19	8.5(2–16.1)	25–50			-0.48	-0.58	-0.1		
	Group 3 =13	10.2(2–16.0)	<25			-1.32	-1.58	-0.4		
Marques de Aquino 2008	HD = 25				98.7±42.1		-2.5±1.3	-1.0±1.3	3day	
	Control = 25						0.1±0.9	-0.3±0.6*		

Results are presented as mean±sd *p = <0.01

** no supplementation; *** with supplements

eGFR = estimated glomerular filtration rate; CKD= chronic kidneys disease; HD=haemodialysis; PD=peritoneal dialysis; RDA=recommended daily allowance; EAR=estimated average requirement. * = UK studies. NS = nutritional supplement.

2.4 Assessment of growth status

Energy requirements include those requirements necessary for growth and nutritional repletion. Whilst Figure 2.1 indicates that the energy cost of normal growth is very small in older children (and for practical purposes can be ignored), the energy deficit in growth retarded children can be substantial, which means that considerable energy may be required (with a range nutrients) for catch up growth, provided this is possible in the midst of the metabolic disturbances associated with kidney disease.

2.4.1 Definition

Growth can be defined as an increase in specific defined parameters, such as weight and height over time, and is interpreted using national reference charts (see Chapter 5) and percentiles or Z scores.

A percentile can be defined as a value given to series of numbers that is out of 100. In clinical terms, the 50th percentile on growth charts relates to the mean value from which values above or below is either 50% more or less than the average of that given population.

Z scores can be defined as a value that has been adjusted for the mean and standard deviation of the distribution from which the value originated⁸³. These can also be referred to as standard deviation scores. In clinical terms, these are values for a given variable, such as weight or height, so that values can be compared independent of age and gender.

2.4.2 Methods used to assess growth status

Growth status can be estimated in children by the use of indices derived from weight (wt.) and height (ht.); measurements such as WFH, HFA, weight for age (WFA) and, more recently, body mass index (BMI) to assess weight deficiency, stunting, wasting and obesity^{84 85}. Z scores can also be used. Details on how these indices are calculated are found in Chapter 4.

2.4.3 Application of methods

There are nine assumptions that are made when using weight and height measurements to assess growth status in clinical practice:–

1. the child is of normal hydration, and not dehydrated or fluid overloaded;
2. the child can stand properly, and has the ability to weight bear and stretch limbs to enable an accurate height measurement;
3. the equipment is regularly calibrated and thus accurate;
4. the same standard operating procedures are used to ensure measurements are standardized and therefore comparable between any clinical area;
5. the same equipment is used for sequential clinic or other comparison measurements;
6. the reference data is representative of the child being measured;
7. measurements are plotted correctly;
8. the same growth charts are being used by all health care professionals involved in the child's care;
9. puberty is normal.

Sources of error can be attributed to lack of equipment maintenance (regular calibration), failure to follow or have comparable standard operating procedures (SOP) across a local clinical setting, the use of different growth charts in different clinical areas (local audit), and failure to check hydration and pubertal status. In reality these assumptions and errors can be overcome by the use of the same SOP and growth charts used by all health professionals involved. However, in practice, different departments and teams may use different SOPs, equipment and charts (local experience), which will reduce the validity and the ability to compare data.

Another important consideration is the reference population used for the development of the growth charts. The current UK 1990 growth charts⁸⁶ for 5–18 year olds are descriptive charts. These charts used a cross-sectional and surveillance approach in their development in an attempt to obtain a representative sample and signify how children did grow. However, the data was from several different sources and ethnicities, which may not be nationally representative of the UK population today. Statistical adjustments were made to minimise the effects of methodological differences. The newer WHO 2005 growth charts⁵³ for 0–4 year olds, on the other hand, are prescriptive charts.

These used cross-sectional and longitudinal data for 7 different geographic sites. In addition, only well-nourished healthy infants and young children who followed established feeding and health recommendations were used to generate a desirable growth standard regarding how children should grow. Caution needs to be exercised when monitoring growth in children who move from the prescriptive charts to the descriptive charts as they get older.

When using these tools in children with a chronic disease, additional care needs to be taken during assessment and monitoring. In chronic disease, growth can be altered, height may be stunted, puberty might be delayed, and weight might reflect fluid shifts rather than fat or lean mass gain or loss. It is also important to check the SOP, pay particular attention when plotting these measurements accurately, and ensure that the same growth charts are kept with each new volume of medical notes that are created. The development of on-line multidisciplinary health care notes and electronically linked equipment may help overcome some of these issues in the future, providing the correct procedures are undertaken and questions are asked to improve interpretation of findings.

Furthermore, sequential measurements taken in clinical practice and plotted on a growth chart, can only monitor the progress of the individual to any given treatment plan, but do not enable comparison to other groups who may use different reference data (i.e. international or national standards of care). The use of Z scores can help overcome this, both in terms of providing a better informed assessment of under and over nutrition that is independent of age, gender and nationality.

Nevertheless, current assessments of growth status do not provide information regarding whether any weight gain or loss is due to fat or lean tissue or fluid. In order to obtain an insight into fat and lean mass or fluid changes, more detailed assessments on body composition are needed.

2.4.3.1 Relevance to clinical practice and this thesis

In clinical practice serial weight and height measurements are plotted on growth charts and converted to percentiles to assess and monitor growth of an individual child in response to clinical treatment. Percentages of indices such as WFH and HFA, and z scores are used occasionally in clinical practice to assess wasting and stunting, and, more recently, childhood BMI charts have become available to assess obesity.

The limited use of Z scores in clinical practice has largely been due to access to software and time restraints. During periods of data collection and analysis, Z scores were only used as a research tool. The inclusion of Z scores in clinical practice could improve the assessment of growth status by allowing international comparison to reference standards that are independent of age and gender.

2.4.3.2 Summary of assessment of growth status

Apart from the first year of life, growth in healthy children is very small.

However, a substantial energy deficit exists in growth retarded children which needs to be taken into consideration during potential catch up growth. More rapid catch up growth requires more energy provision than slower catch up growth.

The standard method of assessing growth failure (which involves measurements of weight, height or BMI) provides little information about body composition, which can give insight into the energy content of the body. This next section (2.5) and Chapter 4 considers body composition in relation to CKD.

2.5 Assessment of body composition

Energy expenditure can be affected by LBM. In addition, in children with CKD, changes in LBM or FM can be masked by abnormal hydration. Failure to identify the type of weight change and thus potential growth deficit could result in incorrect energy prescriptions which could lead to under or over nutrition and ultimately malnutrition or obesity.

2.5.1 Definition

Body composition is a term used to describe what the body consists of and has been defined as a ratio of fat to fat free mass that is often expressed as percentage of body fat⁷¹.

Body composition has been used to estimate the proportions of fat, muscle, bone, water and mineral in the body. Traditionally the body has been divided into two chemical groups: fat and fat free mass (FFM), which form the basis of many body composition techniques. Fat can be defined as all extractable lipids including adipose tissue and other tissues in the body. FFM can be defined as muscle, bone, water and other tissues (connective tissues and other organs). In addition, the term LBM has often been used interchangeably with FFM; however LBM is defined differently as FFM and essential lipids. Over time, the body has been further divided onto three or four component models^{61 71}.

Three-component models consist of either lean soft tissue, bone and fat or water, solids and fat, whilst the four-component models consist of water, protein, bone and fat. The advantages of the multicomponent models are that assumptions that were made by other models can be addressed directly by measuring all body compartments. For example, the four component model measures hydration, density and mineralisation of FFM directly, which previously have only been estimated in the two component model⁸⁷⁻⁸⁹. These models underpin the tools used for body composition and the corresponding equations that have been developed to interpret findings into meaningful estimates of fat and lean mass^{61 71}.

2.5.2 Methods used and their application

Body composition can be measured using a number of different tools and types of equipment. Indirect methods are the most commonly used and are generally limited to research. Indirect methods include skinfold thickness (SKF) to estimate fat, bioelectrical impedance (BIA) to estimate LBM and body water, air displacement plethysmography (ADP) to estimate fat and LBM, dual-energy X-ray absorptiometry (DEXA) to estimate bone mineral content, and dilution techniques to estimate total body water (TBW). Combinations of these methods can also be used to develop the multicomponent models discussed above. Measurements are then interpreted using predictive equations and reference data sets (if they exist,) to provide estimates of fat and lean mass and body water. Raw values can also be used to provide estimates of fatness or body water.

Direct methods such as carcass analysis and *in vivo* neutron activation analysis (INVAA) have also been used previously, but these are rarely used in clinical research today. This section will focus on indirect methods that are commonly used in contemporary clinical research.

2.5.2.1 Skinfold thickness

SKF is the simplest of these measurements, and uses skinfold callipers to estimate the amount of subcutaneous fat (see Chapter 4 for methodology). A number of different sites can be used to estimate total body fat. Most commonly, tricep and bicep thickness are used, although additional sites can also be included, the most popular being the subscapular and suprailiac sites. Reference data and predictive equations have been developed to estimate body fat mass, although raw values can also be used to estimate regional fatness^{61 71 88}.

SKF has two key assumptions and two underlying principles. The assumptions are that

1. SKF is a good measure of subcutaneous fat, subcutaneous fat is distributed evenly throughout the body and is the same regardless of gender, ethnicity and age; and
2. that the sum of subcutaneous fat and total body fat is equal to the sum of several SKF sites.

The principles are:

1. that the sum of SKF (often log Sum of SFT) is linearly related to body density; and
2. that age is an independent predictor of body density.

However, these assumptions are not true. Subcutaneous fat is not evenly distributed throughout the body, and differences occur for gender, ethnicity and age. Body density also changes with age and gender. Predictive equations have been developed for some groups of individuals to help overcome these problems, but are based on the two component model assumptions.

Sources of error for SKF can be classified as, technical skill, calliper type and subject factor. Correct training, evidence based SOP's and regular calibration of equipment can help reduce these errors. Using predictive equations that encompasses as many of the subject factors as possible (for example age, gender and ethnicity) could also help reduce errors. Unfortunately, the validity of these equations in children is limited and further compounded by disease^{61 71}.

The suitability of SKF to estimate body fatness often relates to choice of SKF sites and choice and availability of an equation. Raw values and Z scores can also be used, and when raw values are converted into z scores for comparison with reference data they can be a relatively reliable indicator of regional fatness⁸⁸. However, UK Z score data originates from 1975⁹⁰ which may not be representative of contemporary children and requires caution if used. Nevertheless, on an individual basis, comparison to a reference standard may be useful⁸⁸. In diseased states where hydration is altered, additional care is needed as fluid overload can lead to overestimation of subcutaneous fat.

2.5.2.2 Bioelectrical impedance

BIA uses small electrical currents to detect impedance / resistance (of flow) produced by a change in voltage within the body between two fixed points. Traditionally, these fixed points were electrodes on the hand and foot to produce whole body BIA using a single frequency (typically 50khz); however, segmental methods designed to measure different body parts and multiple frequency ranges designed to measure different fluid compartments (ICF, ECF) have been developed also. The impedance value is measured using the voltage drop across the body between the electrodes on the hand and foot. The volume

of a hypothetical cylinder (used to represent the body) is then estimated using height as a proxy for cylinder length and regression equations (based on factors such as age, gender, height and disease) to predict TBW using resistance indices ($\text{height}^2/\text{resistance}$), that can be converted to fat and LBM (using alternative reference techniques as reference standards). Raw values (resistance or reactance) can be used to give an indication of body composition, and although predictive equations have been developed, these are empirical and depend on the reference method used to establish them.

BIA has one key assumption and two principles. BIA assumes that the human body is made up of five perfect connected cylinders with uniform lengths and cross-sectional areas, and has a fixed frequency. The principles are:

- 1) biological tissues act as conductors / insulators and the flow of a current will follow the path of least resistance. To that extent, FFM which contains about 73% water will be a better conductor of an electrical current compared to fat; and
- 2) impedance is a function of resistance and reactance, which relate to the opposition of current flow and the capacity of cell membranes.

However, the body is not a cylindrical conductor of uniform length or cross-sectional area, and the different frequencies penetrate cells differently. Oedema, ascites and dehydration also alter resistance and invalidate single frequency BIA^{61 62}. In an attempt to overcome the assumptions bioelectrical vector analysis (BIVA) has been developed more recently⁹¹. BIVA utilises the resistance (R) and reactance (Xc) values of BIA, together with height and plots vectors and tolerance ellipses to ascertain and monitor changes in body hydration, which are independent of body weight. These can then be used to identify and monitor changes in hydration and lean mass using a reference graph^{61 71 91}.

Sources of error can be related to calibration of equipment and subject factors, such as body movement, hydration status, medication and nutrition. SOP's can help minimise these subject factors and can improve the accuracy of estimation. This can be further improved by the use of the most appropriate frequency and equation that include resistance and reactance^{61 71}.

Although BIA may be unsuitable for the estimation of body fatness,⁸⁸ (because it measures the properties of LBM) it can be used to estimate changes in body

water (TBW and ECW). Estimation of body water can be undertaken by use of impedance indices (derived from raw values and ratios of impedance) with some level of confidence. However, the more recent development of BIVA developed to improve the assessment LBM and hydration status requires further exploration to determine its validity and use in children. The lack of suitable reference data for children further limits its use and measurements were obtained using stand on equipment which is not comparable to that used with other BIA equipment which place electrodes at the wrist and ankle^{61 71} In disease states where hydration is altered, additional care is needed as fluid overload can lead to underestimation of fat.

2.5.2.3 Air displacement plethysmography

ADP uses pressure changes in a sealed chamber to measure the volume of air displaced by the subject, to determine body volume and density using the same principles as whole body under water weighting (hydro densitometry). ADP uses two chambers, one to measure the subject's volume and a second empty 'reference chamber' that detects the pressure changes of the first chamber via an oscillating diaphragm. The pressure changes are then converted to provide an estimate of body volume. Raw values are then corrected for lung volume and surface area using predictive equations. Body density is then estimated using body volume and body weight (mass). Body mass is measured directly using a weight scale linked to the ADP machine. Further predictive equations are then used to determine lean body mass and body fat^{61 71}.

ADP has five key assumptions. These are:

1. the volume of air displaced is equal to that of the child sitting inside and excludes air trapped in hair and clothing;
2. the child is breathing normally, relaxed and has no altered metabolic rate;
3. there is no additional moisture from hair, body or clothing;
4. the densities of compartments are parallel and constant between individuals; and
5. the two-component model assumptions are all met.

However, body density is not constant between individuals, and can vary with age, gender and ethnicity. LBM density can also vary with disease state and can also be affected by hydration status⁶².

Sources of error relate to software information on body surface area, density and lung volume, and calibration procedures. The use of SOP's and appropriate predictive equations that consider age, gender, body size, body density, lung volume and surface area can all help minimise error in the estimation of fat and FFM^{61 71}.

However, ADP cannot provide regional data and may be sensitive to density changes of LBM in diseases that affect hydration and mineralisation, leading to an overestimation of fatness⁸⁸. ADP may be best used to measure body volume as per the 4 component model, or for obese subjects where density errors are smaller⁸⁸. The lack of suitable reference data for children further limits its use.

2.5.2.4 Dual-energy X-ray absorptiometry

DEXA uses a low intensity neutron beam to detect gamma rays emitted from the body to measure bone mineral content by calculating the different absorption of x rays of two different energies⁸⁸. Algorithms are then used to determine lean and FM. Limited reference data is available for comparison to norms,⁸⁸ which, unfortunately, are not representative.

DEXA has four key assumptions, these are:

1. the child is normally hydrated;
2. there is a constant attenuation in fat and bone-free lean tissue;
3. measurements are not affected by the thickness of the anterior posterior body; and
4. the area analysed is representative of the whole body.

However, hydration of LBM can vary in some subjects who may have altered hydration. Only 40–45% of the body is measured and the remaining body areas may have different fat and fat-free lean tissue proportions that are not measured by DEXA. In addition, obesity may severely increase the thickness of the anterior posterior body and may reduce the penetration of the gamma rays and underestimate bone mineral content⁶².

Sources of error may relate to subject thickness, subject size, hydration status, calibration procedures, software versions, the amount of estimation required by a region of the body to predict LBM, and the instrument, company and model factors^{61 71}.

The suitability of DEXA to measure body composition often relates to accessibility and the model of equipment (modern machines have much less ionising radiation), cost, disease state and area of the body. DEXA may be useful to assess fat and LBM for individual limbs rather than the trunk⁸⁷. However, the lack of normal reference data during childhood further reduces its use. DEXA may best be used for the measurement of bone mineral mass, (which has been shown to be both precise and accurate) and as part of the four component model.

2.5.2.5 Isotope dilution

Dilution techniques measure TBW indirectly, using an isotope tracer. Tritium ($^3\text{H}_2\text{O}$), Deuterium ($^2\text{H}_2\text{O}$) or an isotope of Oxygen (H_2^{18}O) can all be used, but Deuterium is most common. A trace dose is calculated and given orally. Time is allowed for equilibrium of the trace within body water, and samples are taken in saliva or blood for subsequent analysis by gas chromatography or mass spectrometry. TBW is then calculated using equations that estimate difference in volumes and concentrations of the trace pre and post dosage^{61 71}.

Deuterium can be subject to the similar assumptions and errors as DLW as discussed in Section 2.2 above. Essentially, these relate to the distribution of body water, the constancy of FFM water content, equilibrium times, and that the tracer and body water are not metabolised during equilibrium. Sources of error can be attributed to calculation of dose, SOP, subject factors (such as disease state and treatment mode), collection and storage of samples, and technical expertise available⁷¹.

The suitability of deuterium for the estimation of TBW relates to cost and accessibility, resource and expertise. However, hydration issues in disease result in this method being more suited to healthy children or those children who have normal hydration. It is also essential for the certain multicomponent models⁸⁸.

2.5.2.6 Two component model

There are key assumptions that relate to component models which underpin many body composition techniques. These also need to be addressed when appraising each of the aforementioned methods.

The original two component model has four key assumptions. These are:

1. there is one standard body fat density for all ages and genders;
2. there is one density for FFM;
3. body fat and FFM are the same for all ages and genders; and
4. the density of FFM remains constant within an individual and that only fat differs over time.

However, most of these assumptions are not true. This is because age and sex specific density values have become available for children, and fat and FFM have also been shown to change over time, varying with gender and ethnicity. Failure to take into account these differences can result in under or over estimation of fat or FFM^{61 71}.

In addition, the predictive equations used to estimate fat and FFM have been produced using above assumptions, and so can only be accurate when these basic assumptions are met. Any subgroup population that may use these equations would be liable to systematic errors when the above assumptions cannot be met. This is especially important in children who experience changes in the proportions of the constituents of LBM (water, protein and minerals) due to chemical maturation with age and pubertal status. Chronic disease needs additional consideration in regard to potential changes in hydration and deranged body composition.

Therefore, caution needs to be applied to any body composition technique whose development was based on the two component model, which is in addition to any specific assumptions and principles that relate to the individual technique.

2.5.3 Special considerations for children with CKD

In regard to children with CKD, several factors need to be considered when using any of the above techniques, these include: hydration status (both fluid overload and dehydration) relevant to 2 component models of body composition, and those that depend on them e.g. SKF; alteration in fat distribution (relevant to SKF); alteration in growth and pubertal status; treatment mode (e.g. dialysis); and diagnosis (e.g. nephrotic syndrome, cystinosis).

In particular, fluid overload can cause: an increase subcutaneous fat with SKF, leading to overestimation of fatness; an abnormal fluid distribution in BIA, leading to unpredictable estimations of FFM from TBW; an alteration in volume and density of LBM in ADP, leading to an overestimation of LBM and underestimation of fatness; and inadequate equilibration in isotope dilution, leading to overestimation of fluid volume and, hence, underestimation of fat mass and protein mass in the 3 and 4 compartment models. Furthermore, altered distribution of fat can lead to over or underestimation of fat in SKF, whilst alterations in growth and pubertal status can lead to over or underestimation of fat or lean mass if the predictive equation does not account for both age and stage of development. Finally, dialysis and conditions that alter fluid status (e.g. nephrotic syndrome) are subject to the same fluid misinterpretations. Dialysis will also wash out the isotope tracer, which will then render the tracer useless for further assessment.

In summary, failure to take these into consideration can lead to overestimation or underestimation of fat, FFM or fluid volume⁹²; the difference in error relating to the technique used and clinical presentation of the child.

2.5.4 Relevance to clinical practice

In clinical practice, these methods are rarely used despite the need for more information regarding fat and lean mass and hydration status to better guide clinical practice. For example, without this information, a change in weight following nutritional intervention could be due either to fat or lean mass, or fluid. Suboptimal nutritional status could lead to inappropriate alterations in treatment plans, ultimately leading to obesity or malnutrition and adverse clinical outcome.

In addition, in the literature the effects of malnutrition on energy requirements for children with CKD remain unknown.

In research, the choice of method largely relates to access, technical expertise and finance available. SKF and BIA instruments may be preferable because they are portable, cheaper and are quicker to use and produce results. Although they may not be the most accurate and are subject to the special considerations required when assessing children with CKD. Additional methods may be useful when both cost and expertise can be met.

2.5.5 Summary of body composition

In this section, the assessment of body composition has been reviewed. The accuracy of any estimation of body fat, LBM and TBW relies on certain assumptions of the technique being met and the accuracy of any predictive equation used.

It suggests that most techniques need to be used with caution for clinical practice, not only because of problems associated with accuracy, but also cost, the need for technical expertise and the lack of availability of some of the sophisticated techniques. Furthermore, equations and reference standards for children with chronic diseases such as CKD simply do not exist, which makes meaningful interpretation of data into fat and lean mass or hydration status extremely difficult. Nevertheless, the raw measurements obtained by some techniques, such as BIA, or water by water dilution techniques, can be used with more confidence.

2.6 Summary of methods used to estimate energy requirements

No studies were identified that examined total energy requirements in children with CKD. In other chronic diseases, energy requirements are often normal or decreased on account of reduced PA, especially with more severe disease.

In children with CKD, the current evidence base and approach for estimating energy requirements is insecure. EE (BMR, PAEE and TEE), the need for catch up growth (or weight reduction) and body composition needs to be explored.

Of the two major approaches for estimating requirements, measurements of EE are considered preferable to EI. This is because EI methods tend to under-report, lack the desirable level of accuracy and physiologically cannot match energy balance.

The development of new technology such as the IDEEA offers possibilities for establishing a more sound evidence base to inform clinical practice but requires further validation in children.

2.7 Thesis aim and hypothesis

This thesis aims to examine the hypothesis that TEE and requirements in children with CKD are reduced compared to healthy children, and that the extent of this reduction is related to the severity of CKD.

To address this hypothesis, it was deemed necessary to not only establish baseline information on kidney function, growth status and body composition, but to validate also the accuracy and reliability of IDEEA for measuring PA and TEE.

2.8 Overview of experimental studies and structure of thesis

This thesis seeks to explore the energy requirements for children with CKD, using the individual components (namely BMR, PAEE and TEE) and utilising both clinical and research methods. In doing so, some of the gaps outlined will be addressed. The aim of this exploration is to ascertain if current clinical practice should continue and/or could be improved. To achieve this, the thesis starts with reviewing the evidence base and ends with the study findings and recommendations for the translation into clinical practice. A brief description of each chapter is provided below.

Chapter 1 and 2 have provided the background to the thesis development. Chapter 3 presents an overview of the study design and general methodology for the experimental studies. Methodology specific to each chapter shall be described in each subsequent chapter.

Chapter 4 presents the baseline information of the study population, including kidney function, growth status and body composition. The remaining chapters examine whether there are differences in BMR (Chapter 5), PAEE and TEE (Chapter 7) and EI (Chapter 8), using healthy controls for comparison. In addressing TEE, Chapter 6 validates the novel IDEEA for PA under controlled conditions before the application in free-living conditions. The validity of TEE and EI are also explored in free-living conditions in relation to reference standards (Chapter 7 (TEE) and Chapter 8 (EI)).

In Chapters 5, 7 and 8 (BMR, EI, TEE), adjustments were made for confounding variables such as age, gender, weight and height. Potential relationships to kidney function were also established.

Chapter 9 discusses the findings of chapters 5–8 in relation to the estimation of energy requirements for children with CKD in clinical practice. This chapter also provides suggestions to further research.

3. Study design and general methodology

This chapter provides details of the study design and an overview of the clinical methods and procedures. It also refers to sections of the thesis that provide the details of specific methods and associated standard operating procedures connected with the experimental studies.

3.1 Study design

This was a cross-sectional study to estimate the TEE and requirements for children with CKD. A range of prospective measurements were made both on children with CKD and healthy age and gender matched controls. Figure 3.1 shows an overview of the study design. Measurements were made on REE (indirect calorimetry), PA (activity diary, and IDEEA) and TEE (IDEEA and DLW (sub set of controls only)). Dietary intake (food diary) and body composition (BIA, ADP, SKF, DLW (sub set of controls only)) were also measured. Specific details on each measurement (including time periods) can be found in the relevant chapters that follow. To address the relationship between energy expenditure and kidney function, GFR was estimated using plasma creatinine and height⁵ (Chapter 4 for details).

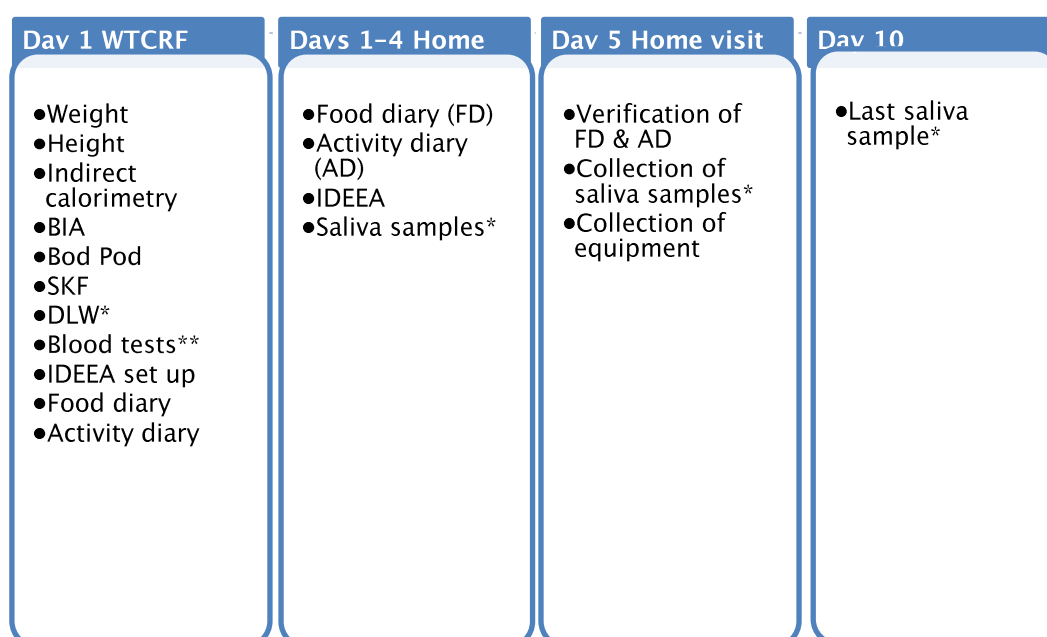


Figure 3-1 Flow diagram of study

BIA = bioelectrical impedance, DLW = doubly labelled water

*DLW & saliva = subset of control group only; ** Blood tests = routine clinic bloods, CKD group only

3.1.1 Sample size calculations

The sample size for this study was limited by the availability of children under the care of Paediatric Nephrology Team at Southampton's University Hospital NHS Foundation Trust during the period of study. Using SamplePower2 (SPSS),⁹³ a sample size of 20 children with CKD and 20 healthy children was sufficient to detect a difference in TEE of 0.18 (expressed as multiples of REE sd 0.2), with a power of 80% and a significance of $p=0.05$.

A sample size of twenty was sufficiently large to establish a relationship with kidney function ($r=0.55$ with a power calculation of 80% and a significance of $p<0.05$).

3.1.1.1 Justification and explanation of a power calculation

A power calculation helps determine the number of subjects needed to ensure a study is adequately powered to reject the null hypothesis if it were false. In the case of this study a significant difference will be produced at any given level between the two independent groups⁸³ and is likely to exist in the whole population. To estimate this for the current study four factors are required: effect size (difference between 2 means); variability (pooled / larger standard deviation (sd)); level of significance and power⁹⁴.

- The effect size is the magnitude of the difference (clinical/minimum value worth detecting). This can be determined from previous research or by a median effect size if no evidence exists.
- The variability represents the spread of distribution and can again be estimated from literature using the largest/pooled sd or estimated using 3sd representing 99.7% of observations.
- The level of significance explores the plausibility of a hypothesis (probability / p value). A 'p-value' calculates the probability of the statistical result having no difference or relationship between the groups / measurements under investigation. A value of 5% (0.05) is traditionally used to minimize the chances of type I and type II errors. A value lower than 0.05 suggests a significant difference and a value greater than 0.05 suggests no significant difference in the results. (the effect size then investigates the strength of the relationship between the two variables).
- The power helps detect if there is a genuine effect in a population. A value of 0–1 (0–100%) is used to translate the meaning of power. A value

of 0 suggests there is no chance of detecting a genuine effect, whilst a value of 1 suggests an effect in the population will definitely be found. A value of 0.8 (80%) has been suggested as the most appropriate value to use to find an effect if one actually exists⁸³.

- The level of significance and power relate to type I (significance/p value) and type II errors (power).
- A type I error rejects the null hypothesis where it is true (i.e. reports a difference between groups when there is actually no difference), whilst type II errors fail to reject the null hypothesis when it is false (i.e. reports no difference between groups when there is actually a difference).
- The null hypothesis suggests that there will be no difference / no effect in the population under investigation. A research hypothesis examines whether the null hypothesis is true or not⁸³.

In addition, the 'r' value measures the effect (correlation) of the relationship between two variables. A value of 0 suggesting no relationship, whilst a positive or negative value of 1 suggesting a relationship and the direction of the relationship⁸³

It is for these reasons that a power of 80% and a p-value of <0.05 were used in combination with a PAL of 0.18 for the desired effect size difference. A value of $r=0.55$ was also used to suggest a relationship between variables (for example eGFR and weight).

3.1.2 Ethical approval

Ethical approval was obtained from the Southampton & South West Hampshire LREC (B) (2005). REC 05/Q1704/128 approval was also obtained from Southampton University Hospitals NHS Trust R&D Department No RHM NUT 0037 (2005).

3.1.3 Inclusion and exclusion

Children with CKD were enrolled if they met the following inclusion criteria:

- uncomplicated CKD with a glomerular filtration rate (GFR) $<60\text{ml/min/1.73m}^2$ (stage 3–5 CKD);
- aged between 6–17 years;
- under conservative management (diet and medication), or maintenance dialysis (Peritoneal Dialysis, Haemodialysis) greater than three months past diagnosis or starting dialysis.

Children with CKD were excluded if they had:

- Recent significant infection (last three months);
- Other co-morbid conditions that limit PA.

Healthy matched control children were included into the study if they met the following criteria:

- children with no known underlying medical condition
- aged between 6–17 years.

3.1.3.1 Justification for criteria

Stage 3–5 CKD was chosen due to the increased MDT and dietetic input that occurs from stage 3 disease. In addition, it was the experience of the clinical team that from stage 3 disease treatment needs increase, whilst growth and appetite worsen.

Children were selected from age 6 above to help maximize tolerance to the number of measurements being taken and in particular the use of IDEEA and ADP. Children over 17.99 years are considered adults in the UK and so were excluded.

A stabilization period of three months on renal replacement therapy is required to ensure any measurements reflect true differences and not an individual's adjustment of therapy mode.

Infection may further alter energy expenditure, whilst some medical conditions may alter PA and so were excluded to reduce the number of co-founding variables that may require statistical adjustment.

3.1.4 Subject selection and recruitment

Children with CKD from Southampton Hospitals University Trust under the care of the regional paediatric nephrology service were screened to ascertain eligibility for the study, and following this screening, 25 children were eligible for inclusion and so were asked to take part in the study. Those who expressed interest were provided with written information and given at least a month to consider participation. Recruitment was conducted at clinic appointments for the children with CKD, and by advert for siblings and healthy controls.

23 children with CKD were recruited into the study and attended the Wellcome Trust Clinical Research Facility (WTCRF), but in the end only 20 were studied to completion. The reason for drop outs were as follows: one child arrived unwell and could not participate; another did not want to be subject to the Bod Pod (ADP) and withdrew; and the third child (although completing the baseline measurements) was withdrawn from the study due to kidney transplantation. The final sample comprised of 20 children with CKD (45% boys), aged 6–17 years. They were age and sex-matched with 20 controls (45% boys) (10 siblings), who were mainly family members or friends. Figure 3.2 shows the flow diagram of subject recruitment through to study completion.

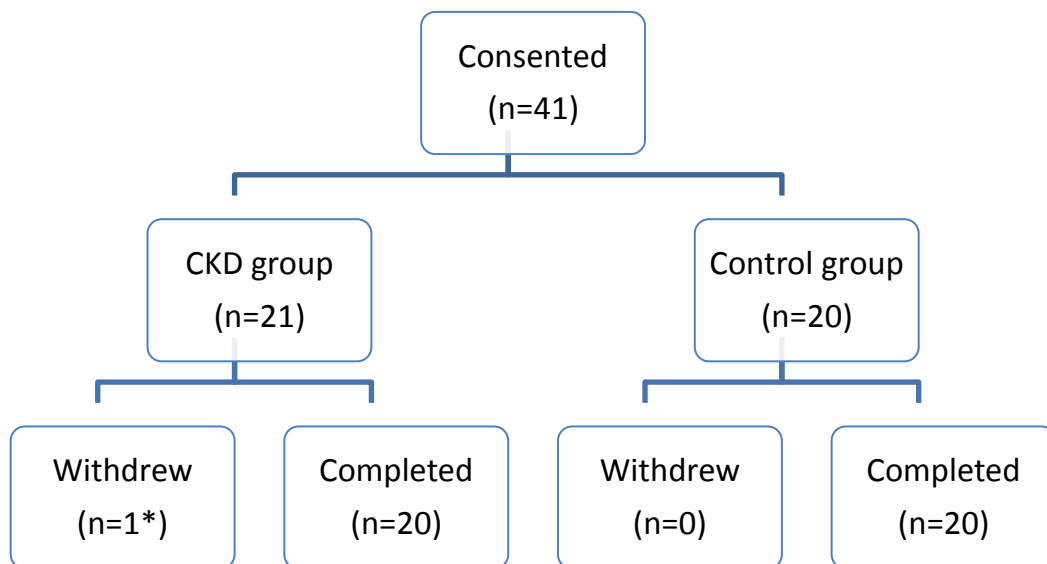


Figure 3–2 Flow diagram of subject recruitment and completion during the study

*1 child in the CKD group withdrew after being called for transplant the night of the study, after completing the Wellcome Trust part of the study.

Healthy controls were recruited by local advertisement in the hospital. Recruitment was random with no attempt at the outset to match each CKD child that was recruited. The advantage of sibling and friend recruitment is their hoped motivation and compliance to the study, as well as the increased inclusion of family members that can sometimes be lost when the focus of care inevitably falls on the child with a chronic disease. The disadvantage is that any eating and activity habits may be familial and not representative of the general population. However, family and friend recruitment was the most successful method found here and on discussion helped the 'healthy' children better understand the needs of the child with CKD.

3.2 Overview of clinical methods and procedures

3.2.1 Clinical methods and procedures

3.2.1.1 Wellcome Trust Clinical Research Facility (WTCRF) visit

Children were given pre-booked appointments to attend the WTCRF at the Southampton University Hospital, where measurements of growth, body composition and EE were undertaken.

Children with CKD had their routine clinical visit and bloods (to determine kidney function) taken during this visit, whilst a subset of the healthy controls were given a dose of DLW. Detailed methodology relevant to each subsequent chapter will follow. A brief description of the study process is described below. Figure 3.3 shows a flow diagram of the measurements taken during the visit to the WTCRF.



Figure 3–3 Flow chart of the clinical methods and procedures undertaken.

Subjects arrived at the WTCRF at 8am on the day of study, following a twelve-hour overnight fast. Subjects were also asked to abstain from exercise (planned activity of greater intensity than day to day activities of living) for twelve hours and maintain their regular medication before attending the research facility.

Written informed consent was obtained from the parents before measurements began. Written information had been given to the child and family/carer at least one month prior to this appointment, and further conversations had been undertaken if clarification was required.

WTCRF standard operating procedures⁹⁵⁻¹⁰³ were followed for each measurement undertaken and details of all methods are found in the subsequent chapters. Subjects were asked to empty their bladder before measurements of weight⁹⁶ and height⁹⁵ were taken. Subjects were then asked to lie down in the supine position and rest for thirty minutes.

REE measurements by indirect calorimetry were then taken for thirty minutes whilst laying at rest, in an ambient temperature^{97 98}. At the end of the thirty minutes, the subjects remained lying for a further ten minutes whilst measurements of BIA^{99 100} were taken. Three repeat measurements were then taken, each lasting less than one minute.

Body composition was then also measured by ADP¹⁰¹. The subjects wore tight fitting swimwear and a swim cap whilst seated in the chamber. Three repeat tests were undertaken, each for three minutes.

Following ADP measurements, the subjects returned to the study room where the children with CKD had bloods for routine clinical investigation taken (Section 3.7) A sub-set of the control group had a saliva sample taken, and drank a test dose of DLW¹⁰².

Once all the fasted measurements were completed, a light meal (cereal, toast and a drink) was consumed. Measurements of SKF was then taken¹⁰³.

On completion of all clinical investigations and measurements, subjects were then fitted with the activity monitor (IDEEA) and shown together with their parents how to use these devices for the free-living part of the study¹⁰⁴. Written instructions were given for home. A food and activity diary was also explained and given for use at home over the same free-living test period.

The sub-set of the control group who took DLW were given saliva sample pots, written instructions for saliva collection and storage at home, and a stamped addressed envelope with which to post samples¹⁰².

Finally, a series of timed activities that included walking and running a set distance, walking up and down stairs, jumping and seating, reclining and lying were undertaken for a set period of time.

On leaving the WTCRF the children were instructed to continue with their usual lives and daily routine. A home visit date was also booked.

Details of each method and procedure will be discussed in detail within each subsequent relevant chapter:

- Chapter 4 provides details on the assessment of growth (weight and height), body composition (BIA, ADP, SKF) and kidney function;
- Chapter 5 provides details on BMR using indirect calorimetry and predictive equations;
- Chapter 6 provides details on PA under controlled conditions;
- Chapter 7 provides details on TEE and PAEE under free-living condition;
- Chapter 8 provides details on EI.

The principles and assumptions regarding each of the above have been discussed in Chapter 2.

3.2.1.2 Free-living measurements at home

The IDEEA was worn for four days at home. Monitors were removed for showering or bathing and then replaced using the instructions provided.

All food and fluid consumed and activity undertaken was recorded in the diary given for the same four day study period.

The subset of children who took DLW also collected saliva samples, which were also either collected at the home visit or posted (Day 10 sample).

Information from the food and activity diary was verified at the home visit, when equipment and saliva samples were collected.

3.2.2 Statistical methods

Data was expressed as mean \pm standard deviation for normally distributed continuous variables.

A number of statistical techniques were employed: The unpaired t-test was used to test the difference between the CKD group and the Control group; Regression analysis was used to assess the relationship within the CKD group; The general linear model (univariate) were used to make adjustments for covariates; A p value of <0.05 (2 tailed) indicated significance; and Bland and Altman plots were used¹⁰⁵ for agreement between different methods for measuring EE and estimating TEE.

All analysis was carried out using software by SPSS (version 20)¹⁰⁶. PRISM (version 6.0) was used to present results graphically¹⁰⁷.

3.3 Clinical, academic and financial support

Clinical and academic support was provided by Dr Rodney Gilbert and Professor Marinos Elia in the design, development, data analysis, and completion of this thesis.

All work including protocol and SOP design, ethical approval, securing funding, data collection and analysis, and thesis writing were conducted by myself, with the support and guidance of Professor Marinos Elia and Dr Rodney Gilbert. Professor Patrick Ritz provided the TEE and TBW values from the DLW saliva samples (see Chapter 4). Equipment preparation/calibration and data collection involving the measurement of body composition, energy expenditure and energy intake was conducted by myself. This included the machine calibrations at the start of each day, and the preparation and administration of DLW, and collection, 'spinning', storage and subsequent posting of DLW saliva samples. Support was provided by the paediatric research nurses if more than one child was being studied (body composition only). The nurses of Dr Gilbert also took the routine clinical blood samples. Training and competencies were provided by the WTCRF.

Research funding was awarded by the Health Foundation, through the 'leadership through clinical practice award' (2005), for clinical research and leadership training. This supported the research study only.

4. Subject characteristics

4.1 Introduction

This chapter provides the general characteristics of the children involved in this study and the methodology used to establish these characteristics. It aims to provide background information to the specific chapters that follow: BMR (Chapter 5), TEE (Chapter 7) and EI (Chapter 8). A summary is provided below of the characteristics of the children, which included age, gender, growth status (percentiles and Z scores (sds) for weight, height and BMI), body composition (based on SKF, BIA, APD) and kidney function. It also examines whether these characteristics differ significantly between children with CKD and healthy controls.

The overall aim of this chapter is to characterise the growth status, body composition and kidney function of the children with CKD who were studied. These characteristics are relevant to all subsequent sections of the thesis which focus on measurement of energy expenditure and intake, and energy balance.

4.2 Methodology

Information on the study design, including recruitment and enrolment, was described in Chapter 3. This section will focus on the methods used to assess the characteristics of children with CKD and their healthy controls, which are used for comparison.

4.2.1 Assessment of growth status

Weight and height and indices of these were used to help assess growth status.

Weight and height were measured at the start of the study with an empty bladder. Weight was measured using Seca floor scales¹⁰⁸ to the nearest 0.1kg and height was measured using a Leicester stadiometer to the nearest 0.1cm¹⁰⁸, according to the procedures outlined in Chapter 3. In those children who were identified as having oedema (n=4), dry weight was estimated by clinical examination by the paediatric nephrologist who was in attendance during the study period. This was based on overall consideration of skin turgor, jugular

venous pressure and blood pressure, together with net fluid balance shifts during dialysis and dialysis tolerance where applicable.

Subjects were asked to wear light clothing with no shoes, and to stand on the measuring equipment over the marked feet. Each measurement was taken in triplicate and the mean calculated.

Weight and height were converted to percentiles and Z scores using the 1990 UK growth chart¹⁰⁹, and the LMS software programme¹⁰⁹.

Z scores (sds) are based on the following equation, which makes use of the reference values of weight and height obtained from children who contributed to the 1990 growth charts ⁸⁴

$$\text{SDS} = \frac{\text{measured value} - \text{value at 50th percentile for standard}}{\text{Standard deviation of the standard}}$$

Z scores were then used to help define under and over nutrition. A Z score of ≤ -2 was used for under nutrition, whilst a z score $> +2$ was used for over nutrition ⁸⁴.

Weight and height were also used to calculate WFH, HFA and WFA and BMI.

WFH, HFA and WFA (often expressed as a percentage of the median), were calculated using measured weight and height by the following equations⁶:

$$\text{Percentage WFH: } \frac{\text{Measured weight}}{\text{Median weight for child's height}} \times 100$$

$$\text{Percentage WFA: } \frac{\text{Measured weight}}{\text{Median weight for age}} \times 100$$

$$\text{Percentage HFA: } \frac{\text{Measured height}}{\text{Median height for age}} \times 100$$

Using these indices, under nutrition (growth failure / malnutrition) was defined as a HFA (stunting) and a WFH (wasting) as $< 90\%$ for mild deficiency, and $< 70\%$ for WFH or $< 80\%$ for HFA for severe deficiency⁸⁴.

BMI was calculated by the following equation:

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height squared (m}^2\text{)}}$$

4.2.2 Assessment of body composition

4.2.2.1 SKF

Percentage body fat (%BF) was calculated according to three commonly used equations: Lohman¹¹³ (model 1)^(a), Johnston¹¹⁴ (model 2)^(b) and Slaughter¹¹⁵ (model 3)^(c).

Model 1 % BF = ((5.3/Db)-4.89*) x 100^(a)

Model 2 % BF = $0.9^{*(d-Db^{*})} \times 100^{(b)}$

$$D_b^* = (d - 0.9)$$

Model 3

(Model 3a) boys

$$\text{pre pubertal} = 1.21 (\text{sum } 2\text{SKF}^*) - 0.008 (\text{sum } 2\text{SKF})^2 - 1.7^{(c)}$$

$$\text{pubertal} = 1.21 (\text{sum 2SKF}^*) - 0.008 (\text{sum 2SKF})^2 - 3.4^{(c)}$$

$$\text{post pubertal} = 1.21 (\text{sum 2SKF}^*) - 0.008 (\text{sum 2SKF})^2 - 5.5^{(c)}$$

$$\text{mean pre and pubertal} = 1.21 (\text{sum 2SKF}^*) - 0.008 (\text{sum 2SKF})^2 - 2.55^{(c)}$$

$$(\text{Model 3a) girls} = 1.33 (\text{sum 2SKF}^*) - 0.013 (\text{sum 2SKF}^*)^2 - 2.5^{(c)}$$

(Model 3b) Tricep and subscapular skinfolds >35mm:

$$(\text{Model 3b) boys} = 0.783 (\text{sum of 2SKF}^*) + 1.6^{(c)}$$

$$(\text{Model 3b) girls} = 0.546 (\text{sum of 2SKF}^*) + 9.7^{(c)}$$

*Where 2SKF = the sum of TSK and SS

In the case of Models 1 and 2, information was also required about body density (Db) which was calculated using the following equations (Johnston^{114(d)}):

$$\text{Db Boys} = 1.166 - (0.007 * (\log 4\text{SKF}^*))^{(d)}$$

$$\text{Db Girl} = 1.144 - (0.0608 (\log 4\text{SKF}^*))^{(d)}$$

Where 4SKF = TSF, BSF, SS, SI.

Body fat (BF) in kilograms (kg) and lean body mass (LBM) (kg & %) were calculated by the following equations using actual body weight for all children, except those with identified oedema (n=4) where estimated dry weight was used:

$$\text{Body fat (kg)}^{61} = \frac{(\%BF * \text{weight (kg)})}{100}$$

$$\text{Lean body mass (\%)} = \frac{(100 - \%fat \text{ mass}) \times \text{weight (kg)}}{100} \quad (\text{Elia M. discussion})$$

$$\text{LBM (kg)}^{59 \ 61} = \text{body weight (kg)} - \text{body fat (kg)}$$

4.2.2.2 ADP

Body density, fat and LBM were measured using ADP,¹¹⁷ according to the procedures outlined in Chapter 3. Calibration was undertaken at the start of each day of measurement, in accordance with the manufacturer's recommendations)¹¹⁷ to ensure volume and pressure in the chambers were at optimal levels.

Children were asked to wear tight fitting swimwear and a swim cap, they were weighed on the ADP scales and asked to sit inside the chamber. The children remained seated in the chamber for three minutes whilst repeat tests were undertaken. Instructions were given as to how to abort the test from inside if needed. Children were asked to relax and breath normally, and were given five minutes inside the chamber to acclimatise before tests were undertaken.

Each measurement was taken in triplicate, and the mean calculated. This provided estimates of fat mass, fat free mass and total body water.

Prior to the commencement of measurements, the Lohman equation designed for children under 19 years of age¹¹⁶ was selected from the software programme to enable estimates of body fat and lean body mass (LBM) because this provides age and gender specific equations for body composition.

4.2.2.3 BIA

Impedance was measured using multi-frequency BIA (model: SFB3 multi frequency BIA monitor (4 to 1000kHz) ImpediMed Ltd., Brisbane, Australia¹¹⁸) in all children with the exception of two (1 CKD and 1 control) due to equipment failure. The procedures are outlined in Chapter 3. Following a fifteen-minute rest in the supine position, electrodes were attached to the hand, wrist, foot and ankle on one side of the body, and BIA measurements were recorded twice.

The BIA measurements were used to establish resistance and reactance values at various frequencies, including 50kHz (R50 and Xc50 respectively), as well as resistance at infinitely high frequency (Rinfinity (RI)), and infinitely low frequency (Rzero (Rz)), using the Cole to Cole plot methodology.

In addition BIVA was undertaken⁹¹. Firstly, z scores for R50/Ht(cm) and Xc50/Ht(cm) were established using a reference population of children by Piccoli et al⁹¹. Secondly, the z scores of R50/Ht(cm) were plotted against Xc50/Ht(cm) so that the confidence ellipses for children with CKD could be compared with that of healthy controls.

4.2.2.4 DLW (healthy control children only)

TBW was estimated using DLW in 13 control children, according to the procedure outlined in Chapter 3. Children consumed a test dose of DLW using a pre-determined mixture of deuterium (2H/D) (99.9%; Aldrich 964) and oxygen-18 (18O) normalised water (10% AT%; ATY Europa Scientific Ltd; batch 109704 10% cortex batch 9759) .

Calculations for DLW solution were based on the following:

1. Calculation of dose needed to make up DLW

$$*0.15\text{g/kg } ^{18}\text{O} \times 50\text{kg (average estimated weight)} = 7.5\text{g} / 75\text{ml of 10\%}$$

$$**0.12\text{g/kg } ^2\text{H} \times 50\text{kg (average estimated weight)} = 6\text{g per child}$$

$$\text{Based on an average estimated child's weight} = 50\text{kg}$$

2. Estimated dose of deuterium needed if 12 children were studied

$$**0.12 \times 50\text{kg} = 6\text{g}$$

$$6 \times 12 \text{ (children)} = 72\text{g deuteriated water}$$

3. DLW solution estimation

$$\text{Weight of bottle} = 60\text{g}$$

$$\text{Weight of bottle} + ^2\text{H } ^{18}\text{O normalised water} = 832\text{g}$$

$$\text{Weight of bottle} + ^2\text{H } ^{18}\text{O} + \text{Deuteriated water} = 964\text{g} (60+832+72^{**})$$

$$\text{Weight of mixture (DLW)} = 964 - 60 = 904\text{g}$$

4. Final DLW Dose

$$904\text{g} / 13 \text{ children (actually studied)} = 71\text{g per dose}$$

$$= 1.4\text{g/kg}^*$$

*We used 1.4 instead of 1.5 to enable the potential study of more children

Each test dose was then calculated using the following equation:

$$1.4\text{g} \times \text{weight of child}$$

Saliva samples were taken immediately prior to the oral dose of DLW, and instructions were given to repeat saliva samples four hours post the dose and on days five and ten at agreed times. Samples were collected on the study home visit (post day 10), and were spun by centrifuge and frozen in the WTCRF laboratory¹⁰².

Total body water (TBW) was calculated from deuterium space by an external collaborator (Professor Patrick Ritz (Pôle de médecine interne et maladies métaboliques, Centre Hospitalier Universitaire d'Angers (CHU) France), who provided estimates of TEE and TBW.

DLW was used to help validate TBW findings using correlations of TBW with BIA (Ht2/R50), TEE findings by IDEEA and AD and EI findings by FD.

4.2.2.5 Assessment of kidney function

Estimated GFR was calculated for each child with CKD by the Schwartz formula⁵, using height and serum creatinine to assess kidney function.

$$\text{eGFR (mL/min/1.73m}^2\text{)} = \frac{\text{Height (cm)} \times 40}{\text{Creatinine (mg/dL),}}$$

eGFR was also ranked according to CKD stage¹¹⁹ using the following guide:

Stage 1: GFR >90;

Stage 2 GFR >60–90;

Stage 3 GFR >30–59;

Stage 4 GFR >15–29;

Stage 5 GFR ≤15 mL/min/1.73m²;

Stage 5b Dialysis.

4.2.2.6 Assessment of weight stability

Weight stability was estimated for the children with CKD, using percentage weight loss from time of study to next clinic follow up, using two steps:

1. calculate weight difference between weight on follow up (1–6months) and expected weight for a sds equivalent to weight sds at the time of study.
2. calculate percentage weight loss was from time of study to the difference found in step 1.

Healthy children were assumed to be weight stable, as they had normal weight status, had not reported any weight loss, and were not suffering from disabilities or disease at the time of study.

4.3 Results

Subject characteristics including age and sex, growth status, body composition and kidney function are provided for children with CKD and healthy controls.

4.3.1 Age and gender

The age and gender of the children in the CKD group and the Control group are shown in Table 4.1. Children in the CKD group were similar in age compared to the Control group (11.9 vs. 11.8 years). Gender was evenly distributed between the groups.

Table 4–1 Age and gender characteristics of the children (boys and girls) by group

Age (years)	Both groups (n=40)	CKD group (n=20)	Control group (n=20)	p*
Boys and girls	12.0 \pm 3.3	11.9 \pm 3.4	11.8 \pm 3.3	0.964
Boys**	11.8 \pm 3.6	11.8 \pm 3.4	11.7 \pm 3.9	0.951
Girls**	12.0 \pm 3.2	12.0 \pm 3.6	12.0 \pm 2.9	1.000

* The P values refer to comparisons between the CKD and control group.

** Boys n=18 (9 CKD: 9 control), Girls = n=22 (11 CKD: 11 controls).

CKD = children with chronic kidney disease.

4.3.2 Characteristics of children with CKD

The characteristics of children with CKD are shown in Table 4.2. 100% of children required medication, 15% required nutritional support, 45% required nutritional supplementation and 75% were following a dietary restriction.

Table 4–2 Characteristics of children with CKD

Characteristic	Number (%)
Number	20
Male	9 (45%)
Diagnosis	
Nephronophthisis	1
FJH Nephropathy	1
ADPKD	2
Drug toxicity	1
Renal artery stenosis	1
Nephrectomy 2° to Wilms' tumour	1
Dysplasia	5
PUV	3
MSG type 1	2
Hypertensive nephropathy	1
Cortical necrosis	1
FSGS	1
Duration of CKD (years, months)	6.2±3.8
Height velocity (cm/year)	4.7±0.9
Number of medications	20 (100%)
1–5	11
6–10	7
>10	1
Nutritional support	3 (15%)
Gastrostomy	2
Nasogastric tube	1
Nutritional supplement	9 (45%)
Glucose polymer	6*
Sip feed	1*
Renal feed	2*
Low phosphate substitute	2*
Vitamin and mineral	1*
Type of diet restriction	15 (75%)
Phosphate	8
Sodium	3
Phosphate and Sodium	1
Combined >2 [†]	3

Diagnosis: FJHN= familial juvenile hypurcaemic nephropathy; ADPKD= autosomal dominant polycystic kidney disease-; PUV= polyurethral values; MGN=membrano-proliferative glomerulonephritis; SGN= segmental glomerulonephritis

* = child on more than one nutritional supplement

[†]Combined diet restriction = phosphate, sodium, potassium and fluid

4.3.3 Assessment of growth status

4.3.3.1 Weight and height

The weight and height of the children in the CKD group and the Control group are shown in Table 4.3. Children in the CKD group had lower values for weight and height. None of the differences were statistically significant (Table 4.3). When boys and girls were considered separately, the findings remained non-significant (Tables 4.3).

Table 4-3 Basic anthropometry characteristics by group and gender

Characteristic	Both groups (n=40)	CKD group (n=20)	Control group (n=20)	p*
Weight (kg)	42.7 \pm 15.7	39.0 \pm 13.9	46.3 \pm 16.8	0.145
Height (m)	1.48 \pm 0.18	1.46 \pm 0.19	1.5 \pm 0.18	0.490
Boys**				
Weight (kg)	41.8 \pm 16.1	39.9 \pm 15.0	43.6 \pm 17.8	0.637
Height (m)	1.47 \pm 0.2	1.46 \pm 0.20	1.49 \pm 0.22	0.796
Girls**				
Weight (kg)	43.4 \pm 15.7	38.4 \pm 13.7	48.5 \pm 16.5	0.132
Height (m)	1.48 \pm 0.2	1.45 \pm 0.2	1.50 \pm 0.2	0.483

*The P values refer to comparisons between the CKD and control group.

**Boys n=18 (9 CKD: 9 control), Girls = n=22 (11 CKD: 11 controls).

Results are expressed as mean \pm SD

Percentiles of weight and height for children in the CKD group and the Control group are shown in Table 4.4. Children in the CKD group were significantly lighter and shorter (Table 4.4).

When boys and girls are considered separately (Tables 4.4), the mean value for each variable remained lower in the CKD group, but significant differences were only observed in the girls for weight (Table 4.4).

Table 4–4 Anthropometric characteristics (percentile) by group and gender

Characteristic	Both groups (n=40)	CKD group (n=20)	Control group (n=20)	p*
Weight	50.7 ± 32.5	38.1 ± 33.1	63.4 ± 27.0	0.012
Height	45.4 ± 32.7	34.6 ± 30.3	56.3 ± 32.1	0.034
Boys**				
Weight	53.8 ± 32.5	47.3 ± 34.7	60.3 ± 29.8	0.404
Height	48.6 ± 33.5	38.9 ± 29.0	58.3 ± 36.6	0.229
Girls**				
Weight	48.2 ± 33.3	30.5 ± 31.4	65.9 ± 25.7	0.009
Height	42.8 ± 32.6	31.0 ± 32.3	54.6 ± 29.6	0.089

*The P values refer to comparisons between the CKD and control group.

** Boys n=18 (9 CKD: 9 control), Girls = n=22 (11 CKD: 11 controls).

Results are expressed as mean ± sd of the percentile

4.3.3.2 BMI

Table 4.5 shows the BMI for children in the CKD group and the Control group. Children in the CKD group had lower BMI values, but not significantly. This trend continued when girls and boys were considered separately (Table 4.5).

Table 4–5 BMI of the children by group and gender

Gender	Both groups (n=40)	CKD group (n=20)	Control group (n=20)	p*
Boys and girls	19.0 ± 3.5	18.0 ± 2.5	20.0 ± 4.1	0.061
Boys**	18.5 ± 2.7	18.1 ± 2.4	19.0 ± 3.1	0.477
Girls**	19.3 ± 4.0	17.9 ± 2.6	20.8 ± 4.7	0.084

Results are expressed as mean ± SD

BMI = body mass index in kg/m²

*The P values refer to comparisons between the CKD and control group.

**Boys n=18 (CKD=9; control=9), girls = 22 (CKD=11; control =11).

When percentiles for BMI were compared to healthy children, children in the CKD group had significantly lower values (Table 4.6). When gender was considered separately, girls had significantly lower values in the CKD group.

Table 4–6 BMI percentile of children by group and gender

Gender	Both groups (n=40)	CKD group (n=20)	Control group (n=20)	p*
Boys and girls	54.9 \pm 30.3	44.2 \pm 29.4	65.5 \pm 27.9	0.024
Boys**	59.5 \pm 27.7	54.5 \pm 30.9	64.4 \pm 25.1	0.463
Girls**	51.1 \pm 32.4	35.7 \pm 26.7	66.4 \pm 31.2	0.022

The P values refer to comparisons between the CKD and control group.

**Boys n=18 (CKD=9; control=9), girls =22 (CKD=11; control=11). Results are expressed as mean \pm SD

4.3.3.3 Z scores

Z scores for weight, height and BMI are shown in Table 4.7. Children in the CKD group had lower Z scores for weight, height and BMI. These differences were only significant for weight and BMI (Table 4.7).

When boys and girls are considered separately (Tables 4.7), the mean value for each variable remained lower in the children in the CKD group but significant differences were only observed in the girls weight and BMI Z scores (Table 4.7).

Table 4–7 Z score anthropometric characteristics by group and gender

Characteristic	Both groups (n=40)	CKD group (n=20)	Control group (n=20)	p*
Weight	0.18 \pm 1.18	-0.31 \pm 1.17	0.66 \pm 0.99	0.008
Height	0.05 \pm 1.30	-0.26 \pm 1.21	0.35 \pm 1.35	0.146
BMI	0.26 \pm 1.11	-0.13 \pm 1.06	0.65 \pm 1.04	0.023
Boys**				
Weight	0.22 \pm 1.22	-0.10 \pm 1.38	0.53 \pm 1.02	0.285
Height	0.03 \pm 1.60	-0.25 \pm 1.37	0.32 \pm 1.84	0.464
BMI	0.37 \pm 1.03	0.15 \pm 1.21	0.58 \pm 0.83	0.393
Girls**				
Weight	0.15 \pm 1.16	-0.47 \pm 1.02	0.76 \pm 0.99	0.009
Height	0.56 \pm 1.03	-0.26 \pm 1.13	0.37 \pm 0.86	0.161
BMI	0.17 \pm 1.19	-0.37 \pm 0.91	0.71 \pm 1.22	0.029

The P values refer to comparisons between the CKD and control group

**Boys n=18 (CKD=9; control=9), girls =22 (CKD=11; control=11)

Results are expressed as mean \pm SD

Figure 4.1 shows the spread of Z scores. Children in the CKD group had lower Z scores for weight, height and BMI compared to healthy controls

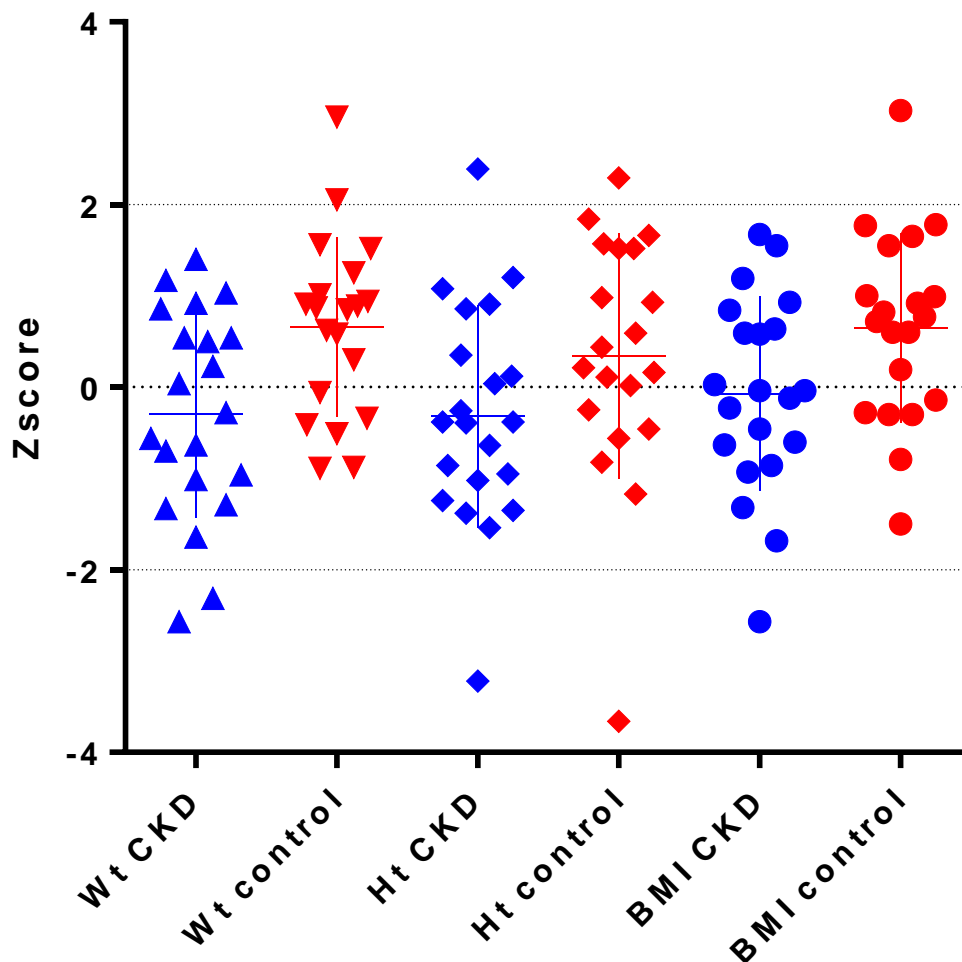


Figure 4-1 Anthropometric variables by group

Weight (Wt), Height (Ht) and BMI z scores, based on Z score (using UK 1990 growth data)¹⁰⁹

The mean zscores \pm sd are as follows: z scores for weight, -0.31 ± 1.17 for CKD and 0.66 ± 0.99 for control ($p=0.008$); z score for height -0.26 ± 1.21 CKD 0.35 ± 1.34 control ($p=0.146$); BMI -0.13 ± 1.06 CKD 0.65 ± 1.04 control ($p=0.023$).

Group = CKD ($n=20$) and healthy controls ($n=20$)

Figure 4.2 show the matrix spread of weight against BMI and height against BMI for z scores by group.

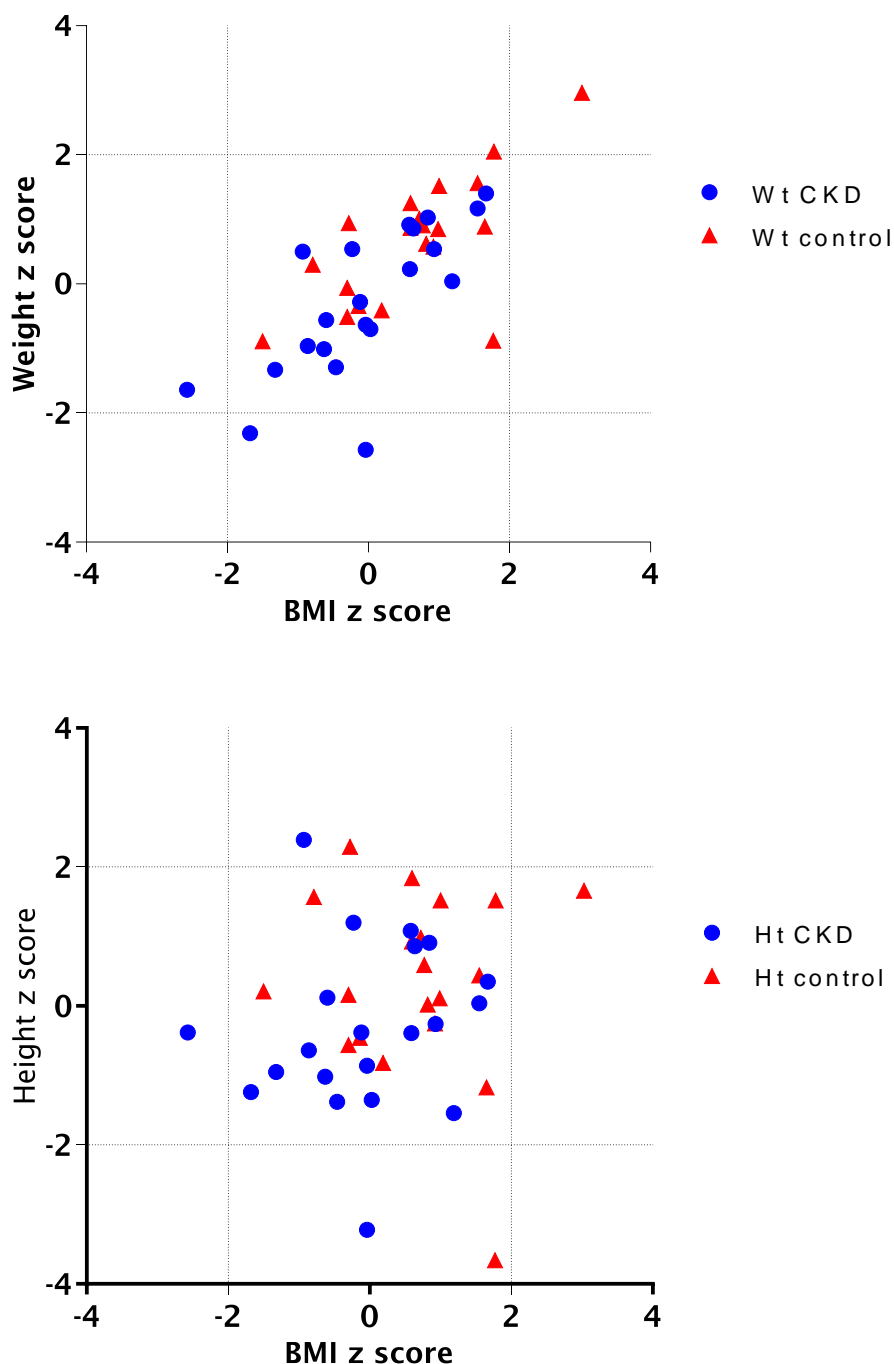


Figure 4-2 Weight and height against BMI z score

Upper = weight against BMI; lower = height against BMI (using z score data using UK 1990 growth data¹⁰⁹). Weight $r^2=0.542$, $p<0.001$ for CKD and $r^2=0.471$, $p<0.001$ for controls; height $r^2=0.019$, $p=0.55$ for CKD and $r^2=0.008$, $p=0.70$. Groups CKD ($n=20$) and healthy controls ($n=20$)

4.3.3.4 Weight and height indices

Table 4.8 shows weight and height as indices against height or age. Children in the CKD group tended to have lower values compared to healthy controls. Significantly lower values were only observed for WFA when boys and girls were combined or when girls were considered alone (Tables 4.8).

Table 4–8 Anthropometric indices (percentage of median) by group and gender

Characteristic	Both groups (n=40)	CKD group (n=20)	Control group (n=20)	p*
WFH	105 ± 17	101 ± 13	110 ± 19	0.075
HFA	100 ± 06	99 ± 06	102 ± 07	0.156
WFA	107 ± 23	98 ± 18	115 ± 24	0.016
Boys**				
WFH	106 ± 15	103 ± 11	108 ± 18	0.569
HFA	100 ± 08	99 ± 06	101 ± 09	0.517
WFA	106 ± 19	102 ± 20	111 ± 19	0.320
Girls**				
WFH	105 ± 19	98 ± 15	112 ± 21	0.084
HFA	100 ± 05	99 ± 05	102 ± 04	0.133
WFA	107 ± 26	95 ± 17	119 ± 28	0.030

*The P values refer to comparisons between the CKD and control group.

**Boys n=18 (CKD=9; control=9), girls =22 (CKD=11; control=11)

Results are expressed as mean ± SD.

WFH = weight-for-height; WFA = weight-for-age; HFA = height-for-age.

Table 4.9 shows WFH and HFA classified into grades of malnutrition and stunting using the WHO standards. Children in the CKD group were found to have more mild to moderate malnutrition and stunting compared to the healthy children (malnutrition: 20 vs. 15%; stunting 10 vs. 5%) (Table 4.9), but this difference did not reach statistical significance.

Table 4–9 Anthropometric indices (percentage) of children by group and classification

Grade [†]	Both groups (n=40)	CKD group (n=20)	Control group (n=20)
WFH [†]			
0	83(33)	80(16)	85(17)
1	15(3)	15(3)	15(3)
2	2(1)	5(1)	0(0)
3	0(0)	0(0)	0(0)
HFA [†]			
0	93(37)	90(18)	95(19)
1	5(2)	5(1)	5(1)
2	2(1)	5(1)	0(0)
3	0(0)	0(0)	0(0)

Results are shown as percentages (number)

WFH = weight-for-height; WFA = weight-for-age; HFA = height-for-age.

[†]Grading: WFH: 0=normal; 1=80–90%; 2=70–80%; 3=<70% (1 mild, 2 moderate, 3 severe malnutrition)

HFA: 0=normal; 1=90–95%; 2=85–90%; 3=<80% (1 mild, 2 moderate, 3 severe stunting)

Using fishers exact 2x2 tables for malnutrition (WFH) (16/4 vs.17/3; no malnutrition vs malnutrition (grades 1–3 combined) respectively) no significant differences were found (p=0.500). Stunting differences (HFA) were not statistically possible because group 2 (grades 1–3 combined) was a constant value (18/1 vs. 19/1).

When boys and girls are considered separately, girls had more malnutrition (27% CKD vs. 18% control), whilst boys were identical to controls (11% CKD vs. 11% Control). The same trends were shown for stunting (girls: 9% vs. 0%; boys 11% vs. 11%). None of these findings were significant (Appendix 3, Table A3.1).

4.3.4 Assessment of body composition

4.3.4.1 Body fat and lean body mass

Body fat (percentage (%) and kg) and LBM (percentage (%) and kg) are shown in Tables 4.10 and 4.11. Children in the CKD group did not significantly differ in body fat and lean body mass, although values for children in the CKD group tended to be lower for body fat (% & kg) and LBM (kg only). There was a significant difference between the three skinfold thickness equations, when each equation was compared by paired t-test to the other two equations. The Lohman equation had the lowest values for body fat, whilst the Slaughter equation the highest (Table 4.10). The opposite observation was shown for lean body mass. These trends continued when children with oedema were removed from the CKD group (Table 4.11).

Table 4–10 Body fat and lean body mass by SKF and ADP by group

Equation	Both groups (n=34)	CKD group (n=16)	Control group (n=18)	p*
<u>Percent body fat⁺</u>				
Lohman	15.3±5.9	14.4±6.7	16.1±5.1	0.406
Johnston	16.9±6.7	16.1±7.4	17.7±6.2	0.501
Slaughter	19.8±7.7	18.6±7.8	20.8±7.8	0.421
ADP	25.6±13.1	23.9±13.4	27.0±13.1	0.505
<u>Body fat (kg)⁺</u>				
Lohman	7.2±4.4	6.1±3.5	8.3±5.0	0.149
Johnston	8.2±5.3	7.0±4.3	9.3±5.9	0.215
Slaughter	9.5±6.4	7.9±4.4	10.9±7.5	0.182
ADP	11.5±7.1	9.7±6.2	13.1±7.7	0.162
<u>LBM (kg)⁺</u>				
Lohman	38.4±12.0	36.3±12.1	40.3±12.0	0.340
Johnston	37.4±11.1	35.3±11.2	39.2±11.1	0.309
Slaughter	36.2±11.1	34.4±11.6	37.7±10.7	0.398
ADP	34.2±12.5	32.3±13.5	35.9±12.5	0.414
<u>Percentage LBM⁺</u>				
Lohman	84.7±5.9	85.6±6.7	83.9±5.1	0.406
Johnston	83.1±6.8	83.9±7.4	82.3±6.2	0.501
Slaughter	80.2±7.7	81.4±7.8	79.2±7.7	0.421
ADP	73.0±13.1	76.1±13.4	73.0±13.1	0.505

*The P values refer to comparisons between the children with CKD and control group.

Results expressed as mean±sd

Equations: Lohman et al 1984; Johnston et al 1988; Slaughter et al 1988

⁺ each equation yields significant different results from the other two equations for % body fat, body fat and lean body mass (LBM).

SKF = skinfold thickness; ADP = air displacement plethysmography.

Figures 4.3–4.5 shows the distribution of FM and LBM by method and group. Children in the CKD group have lower values for both FM and LBM.

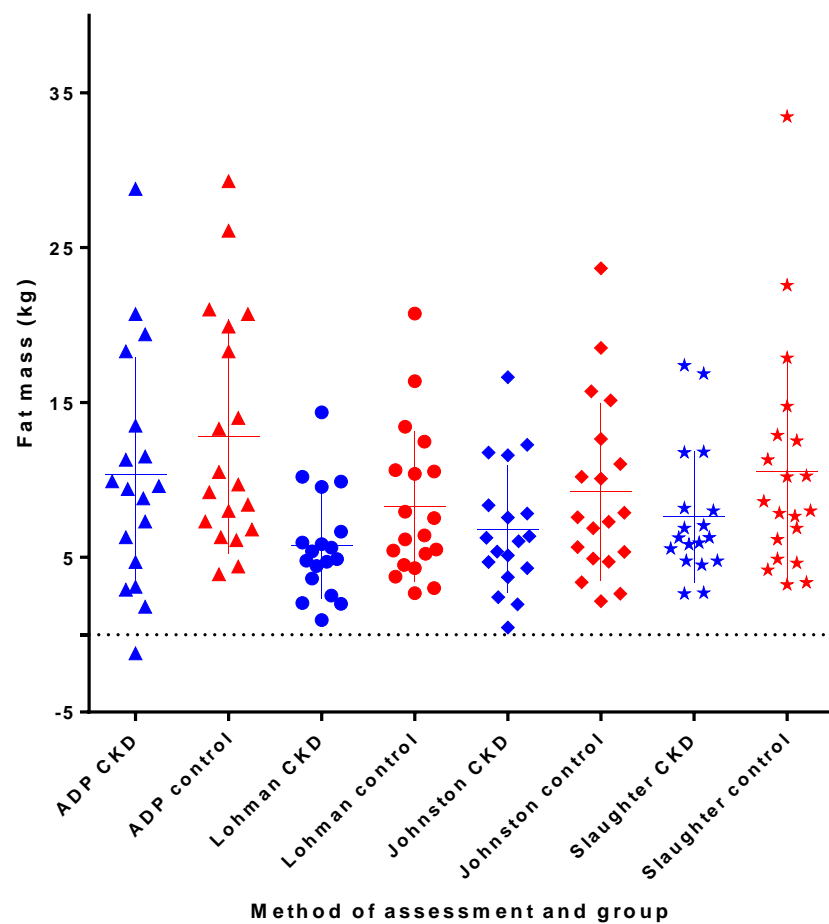


Figure 4–3 Distribution of fat mass (kg) by method and group.

The mean z scores \pm sd are as follows for each method. Skinfold z scores: Lohman 6.1 ± 3.5 for CKD and 8.3 ± 5.0 for controls ($p=0.149$); Johnson 7.0 ± 4.3 for CKD and 9.3 ± 5.9 for controls ($p=0.215$); and Slaughter 7.9 ± 4.4 for CKD and 10.9 ± 7.5 for controls ($p=0.182$). ADP z scores 9.7 ± 6.2 for CKD and 13.1 ± 7.7 for controls ($p=0.162$). Group CKD ($n=16$) and healthy controls ($n=18$)

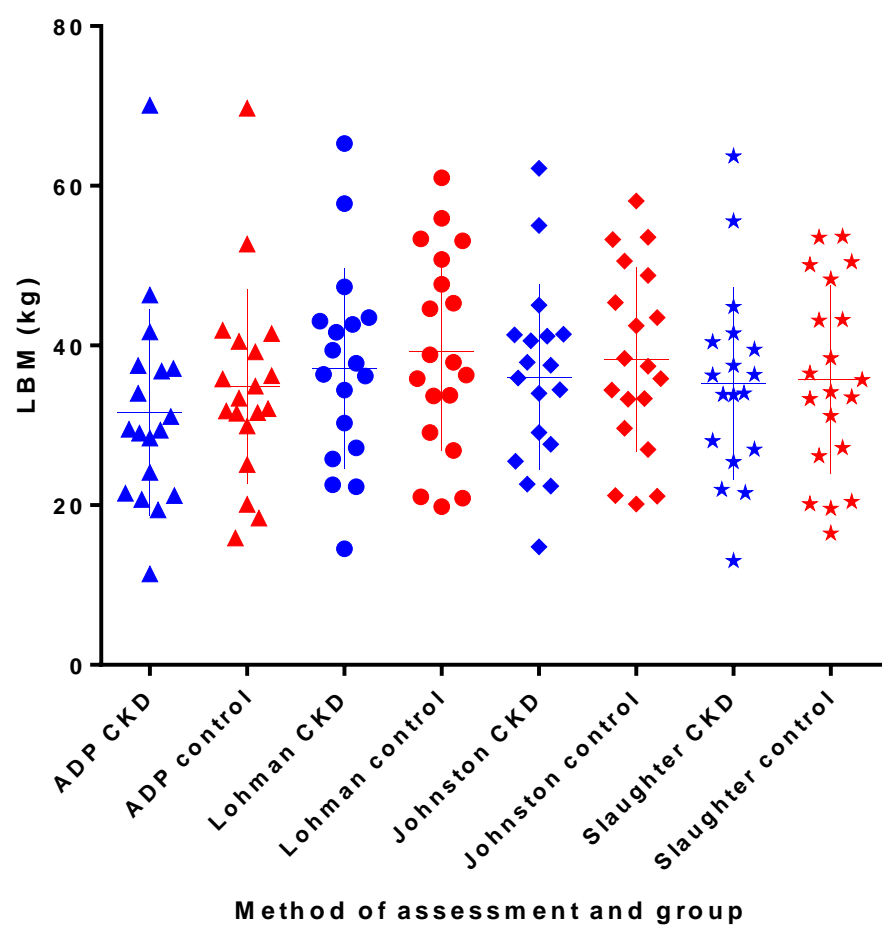


Figure 4–4 Distribution of lean body mass (LBM) (kg) by method and group
The mean z scores \pm sd are as follows for each method. Skinfold z scores: Lohman 36.1 ± 12.1 for CKD and 40.3 ± 12.0 for controls ($p=0.340$); Johnson 35.3 ± 11.2 for CKD and 39.2 ± 11.1 for controls ($p=0.309$); and Slaughter 34.4 ± 11.6 for CKD and 37.7 ± 10.7 for controls ($p=0.398$). ADP z scores 32.3 ± 13.5 for CKD and 35.9 ± 12.5 for controls ($p=0.414$). Group CKD ($n=16$) and healthy controls ($n=18$)

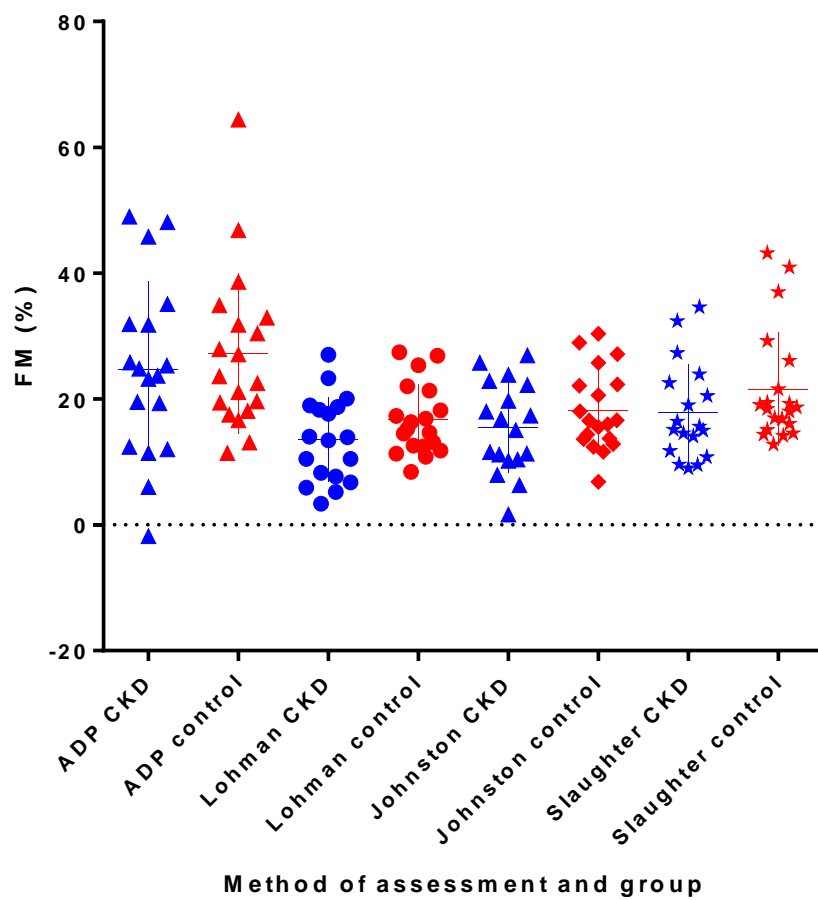


Figure 4-5 Distribution of percentage fat mass (FM %) by method and group

The mean z scores \pm sd are as follows for each method. Skinfold z scores: Lohman 14.4 ± 6.7 for CKD and 16.1 ± 5.1 for controls ($p=0.406$); Johnson 16.1 ± 7.4 for CKD and 17.7 ± 6.2 for controls ($p=0.501$); and Slaughter 18.6 ± 7.8 for CKD and 20.8 ± 7.8 for controls ($p=0.421$). ADP z scores 23.9 ± 13.4 for CKD and 27.0 ± 13.1 for controls ($p=0.505$). Group CKD ($n=16$) and healthy controls ($n=18$)

Table 4–11 Body fat and lean body mass by SKF and ADP excluding oedematous children by group

Equation	Both groups (n=30)	CKD group (n=12)	Control group (n=18)	p
<u>Percent body fat⁺</u>				
Lohman	15.0±5.8	13.3±6.5	16.0±5.1	0.209
Johnston	16.6±6.8	15.1±7.7	17.7±6.2	0.320
Slaughter	19.4±7.7	17.3±7.4	20.8±7.7	0.228
ADP	23.6±12.4	18.4±9.7	27.0±12.4	0.063
<u>Body fat (kg)⁺</u>				
Lohman	7.4±4.6	6.0±3.9	8.3±5.0	0.192
Johnston	8.4±5.4	7.0±4.7	9.3±5.9	0.268
Slaughter	9.6±6.7	7.8±5.0	10.9±7.5	0.233
ADP	10.9±7.3	7.7±5.4	13.1±7.7	0.044
<u>LBM (kg)⁺</u>				
Lohman	39.1±12.0	37.4±12.3	40.3±12.0	0.533
Johnston	38.1±11.1	36.4±11.3	39.2±11.1	0.501
Slaughter	36.8±11.0	35.6±11.7	37.7±10.7	0.613
ADP	35.6±12.3	35.1±13.7	35.9±11.7	0.868
<u>Percentage LBM</u>				
Lohman	85.0±5.8	86.7±6.5	83.9±5.1	0.209
Johnston	83.4±6.8	84.9±7.7	82.3±6.2	0.320
Slaughter	80.6±7.7	82.7±7.4	79.2±7.8	0.228
ADP	76.4±12.4	81.6±9.7	73.0±13.1	0.063

*The P values refer to comparisons between the children with CKD and control group using.

Results expressed as mean±sd CKD group excluded children with oedema.

Equations: Lohman et al 1984; Johnston et al 1988; Slaughter et al 1988.

⁺ each equation yields significant different results from the other two equations for % body fat, body fat and lean body mass (LBM)

SKF = skinfold thickness; ADP = air displacement plethysmography

When boys and girls were considered separately (Appendix 3, Tables A3.2–3.4), the trends were similar, except for LBM in boys who had mixed trend.

4.3.4.2 BIA and BIVA

Table 4.12 shows the raw BIA values for resistance (R), reactance (Xc), R Infinity (Ri), R zero (Rz) and the ratio between Ri and Rz. Children in the CKD group tended to have higher but not significantly different values from healthy controls. When children with oedema were excluded in the CKD group, the same non-significant trends continued with the exception of Ri:Rz which had lower values.

Table 4-12 BIA of children by group

	Both groups (n=36)**	CKD group (n=18)**	Control group (n=18)	p*
All children				
Rz	784±101	798±117	769±84	0.411
Ri	530±84	546±90	514±75	0.267
R ₅₀	658±93	673±100	644±85	0.370
Xc ₅₀	72.3±11.9	74.2±13.3	70.5±10.4	0.365
Ri:Rz	0.68±0.05	0.68±0.05	0.67±0.05	0.358
No oedema				
Rz	776±97	785±113	769±84	0.656
Ri	517±77	522±83	514±75	0.790
Resistance R ₅₀	648±89	652±96	644±85	0.817
Reactance Xc ₅₀	73±11	76±12	71±10	0.151
Ri:Rz	0.67±0.05	0.66±0.04	0.67±0.05	0.870

*The P values refer to comparisons between the children with CKD and control group.

** excluding oedema: both group n=32; CKD group=14; Control group=18.

Results expressed as mean±s; Measurements = ohms

Resistance = R; Reactance = Xc; Rz = Rzero(ECW); Ri = Rinfinity (TBW); R₅₀ = Resistance @50ohms; Xc₅₀ = Reactance @50ohms.

BIA = bioelectrical impedance.

When separated by gender, girls showed the same trends as the group of mixed children, but some raw values were significant. Boys however, showed mixed non-significant trends (Appendix 3, Table A3.5).

Table 4.13 shows impedance indices using impedance values against height. Children in the CKD group tended to have lower values compared to healthy controls, although not significant. These trends continued regardless of when children with oedema were excluded from the CKD group, and when separated by gender (Appendix 3, Table A3.6).

Table 4-13 BIA impedance index of children by group

	Both groups (n=36)**	CKD group (n=18)**	Control group (n=18)	p*
All children				
Ht ² /Rz	29.8±9.6	28.7±9.7	31.0±9.6	0.482
Ht ² /Ri	44.9±17.1	42.4±15.9	47.4±18.4	0.390
Ht ² /R ₅₀	35.9±12.9	34.2±12.4	37.5±13.5	0.450
Ht ² /Xc ₅₀	324±98	313±112	335±84	0.502
No oedema				
Ht ² /Rz	30.5±9.7	29.9±10.3	30.96±9.6	0.763
Ht ² /Ri	46.5±17.4	45.2±16.5	47.4±18.4	0.732
Ht ² /R ₅₀	36.9±13.1	36.2±13.0	37.5±13.5	0.774
Ht ² /Xc ₅₀	324±97	310±113	335±84	0.481

*The P values refer to comparisons between the children with CKD and control group.

** excluding oedema: both group n=32; CKD group=14; Control group=18.

Results are expressed as mean±sd

Measurements: Ht² = cm Rz/Ri = ohm

Resistancce = R; Reactance = Xc; Rz = Rzero(ECW); Ri = Rinfinity (TBW); R₅₀ = Resistance @50ohms; Xc₅₀ = Reactance @50ohms

BIA = bioelectrical impedance

Figure 4.6 shows the correlation in a subset of healthy control children between total body water (TBW) (kg) assessed by Deuterium dilution, and resistance by BIA as a ratio to height squared (Ht²/R₅₀). The mean values were 24.2±13.7 kg TBW by DLW and 32.3±8.9 cm²/ohm by BIA (n=13). A lower TBW by DLW was associated with in a significantly lower impedance index (Ht²/R₅₀) (p=0.019, r²=0.407).

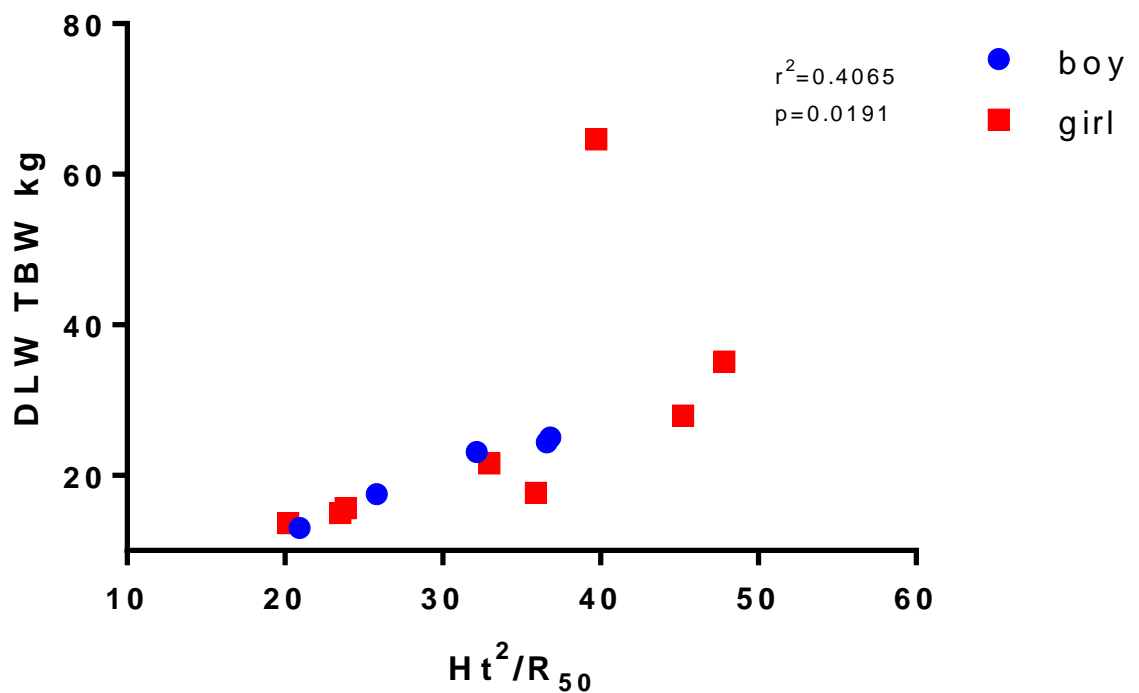


Figure 4–6 Total body water by doubly labelled water and resistance as a ratio to height squared by bioelectrical impedance

DLW = doubly labelled water; TBW = total body water; Resistance = R; 50=frequency in kHz; Ht^2/R_{50} (cm²/ohm)

Table 4.14 shows comparisons between children with CKD and oedema (n=4) compared to children within the CKD group that included or excluded oedema (n=18; n=14 respectively). Children with only oedema (n=4) had a higher ratio of Rinfinity to Rzero (Rl:Rz) and impedance index for reactance (Ht^2/R_{xc}) but lower values for resistance (R), Rz, and Rl when divided by height². Considering further children with oedema alone (n=4, within the CKD group), these children had worse height z scores (sds) and were older when compared to either the CKD group as a whole including or excluding oedema (Table 4.14), and were all girls.

Table 4–14 Characteristics of children by group comparison of children with and without oedema using BIA, age and height

	Oedema (n=4)	CKD+O (n=18)	CKD–O (n=14)
Ri:Rz	0.75±0.04	0.68±0.05	0.66±0.04
Ht ² /Rz	27.4±6.9	28.7±9.7	29.9±10.3
Ht ² /Ri	32.6±9.2	42.4±15.9	45.2±16.5
Ht ² /R ₅₀	27.5±7.7	34.2±12.4	36.2±13.0
Ht ² /Xc ₅₀	321±127	313±112	310±113
Ht sds	-0.61±0.55	-0.32±1.22	-0.04±1.08
Age	12.9±4.9	12.5±3.5	12.1±3.2
Rz	841±136	798±117	785±113
Ri	629±69	546±90	522±83
R ₅₀	744±87	672±100	652±96
Xc ₅₀	67±17	74.2±13.3	76±12
PA ₅₀	16.05±21.4	8.8±9.9	6.7±0.8
R ₅₀ Z score	1.45±1.40	0.34±1.19	0.02±0.96
Xc ₅₀ Z score	0.55±1.52	1.10±1.42	1.26±1.40

Results are expressed as mean±sd

R₅₀ = resistance, Xc₅₀ = reactance PA₅₀ = Phase angle

BIVA was used to explore the hydration status of children in the CKD group compared to healthy controls. Figure 4.7 shows that BIVA using z scores for $R_{50}/Ht_{(cm)}$ and $Xc_{50}/Ht_{(cm)}$, and plotting these against each other enables the 95% ellipses to be compared (separate ellipses with the CKD group in the bottom left quadrant would suggest overhydration). The overlap between children in the CKD group and the healthy controls was almost total. Healthy children were almost completely enclosed within the children with CKD outer ellipse (Figure 4.7 (children with CKD including oedema, and Figure 4.8 children with CKD excluding oedema).

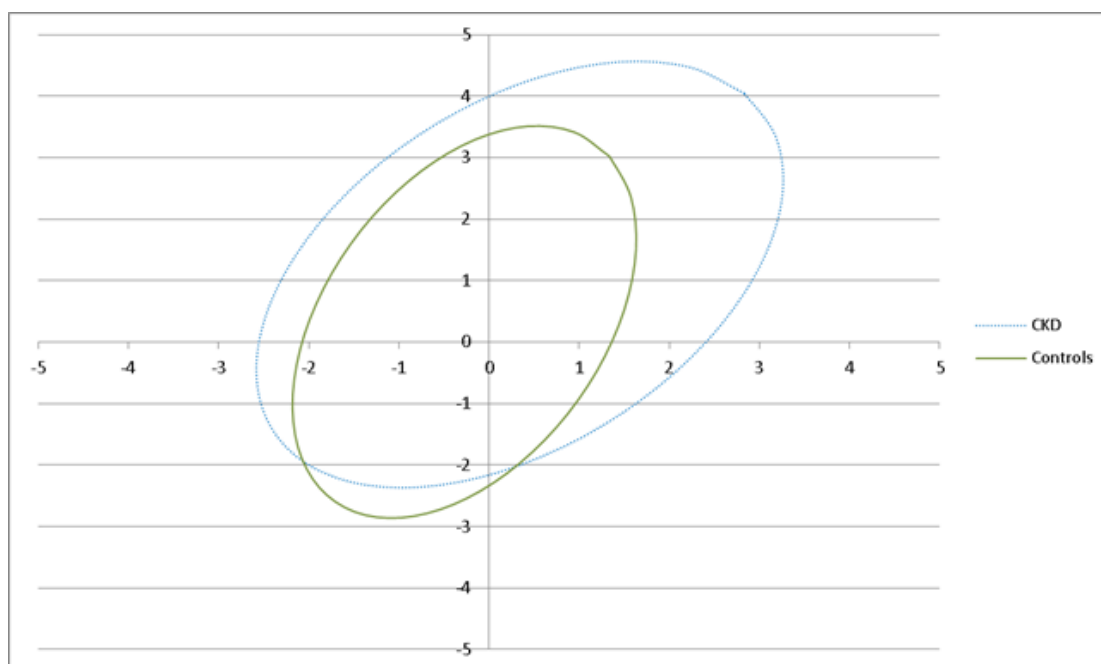


Figure 4-7 BIVA $R_{50}/Ht_{(cm)}$ and $Xc_{50}/Ht_{(cm)}$ Z score for children with CKD and healthy controls

Z scores for $R_{50}/Ht_{(cm)}$ (Horizontal line) and $Xc_{50}/Ht_{(cm)}$ (vertical line) using the Picoli et al data⁹¹

R_{50} = resistance @50kHz; Ht = height in cm; Xc_{50} = reactance @50kHz

Upper left quadrant = dehydrated and lean; lower left = odema and cachectic; upper right = dehydrated and atheltec; lower right = odema and obese.

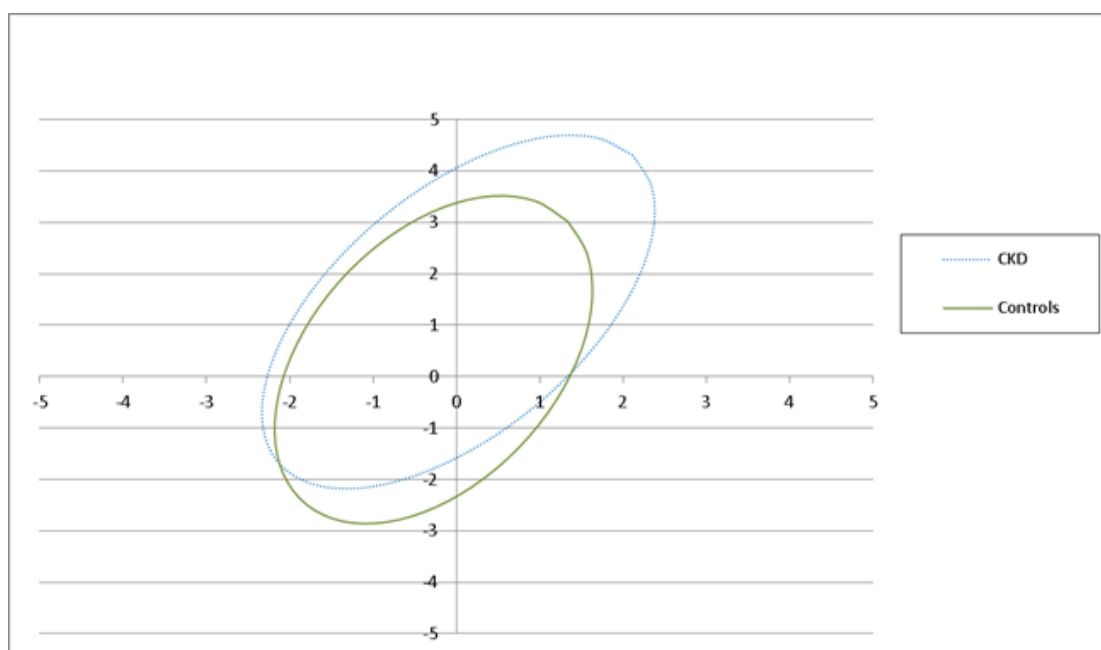


Figure 4-8 BIVA $R_{50}/Ht_{(cm)}$ and $Xc_{50}/Ht_{(cm)}$ Z score for children with CKD and healthy controls, but excludes children who have oedema and CKD

Z scores for $R_{50}/Ht_{(cm)}$ (horizontal line) and $Xc_{50}/Ht_{(cm)}$ (vertical line) using the Picoli et al data⁹¹

R_{50} = resistance @50kHz; Ht = height in cm; Xc_{50} = reactance @50kHz

Upper left quadrant = dehydrated and lean; lower left = odema and cachectic; upper right = dehydrated and atheltec; lower right = odema and obese.

4.3.5 Assessment of Kidney Function

4.3.5.1 Kidney function and CKD stage

Table 4.15 shows kidney function expressed as eGFR. The mean eGFR was 34 ± 21 ml/min/1.73m² (range 0–72.) including children with oedema, and 39 ± 17 excluding oedematous children. No significant difference was found between the girls and boys (Table 4.15).

Table 4–15 Estimated GFR for the children with CKD

	Total (n=20)**	Boys (n=09)**	Girls (n=11)**	p*
CKD (+ oedema)	33.7 ± 20.5	37.7 ± 13.9	30.4 ± 24.8	0.439*
CKD (–oedema)**	39.0 ± 17.1	37.7 ± 13.9	40.4 ± 21.1	0.761

Units = ml/min/1.73m², eGFR = estimated glomerular filtration rate

*P = the values in girls are not significantly different to boys

** excluding oedema: both group n=18 (boys=9; girls=7)

Results are expressed as mean \pm SD

Figure 4.9 shows the distribution of these eGFR values, and Figure 4.10 shows the mean eGFR at each stage of kidney function. No significant differences were found between boys and girls.

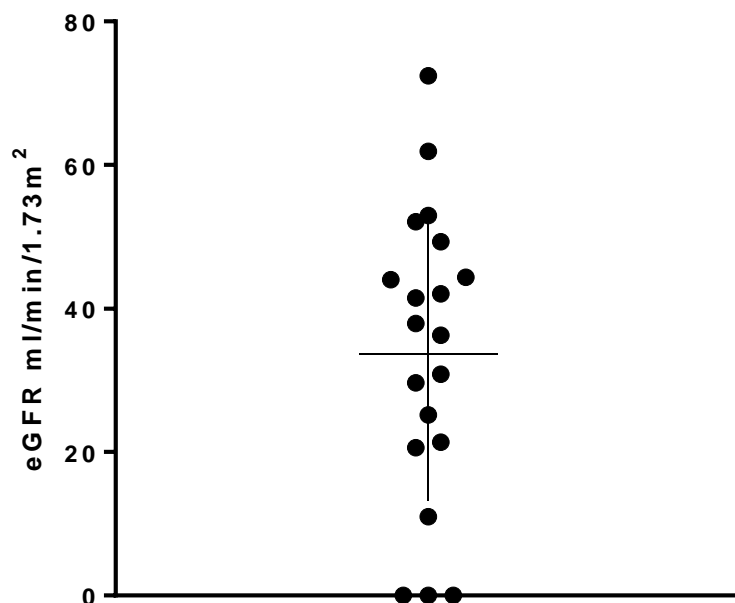


Figure 4-9 Distribution of eGFR values (mean \pm SD).
 eGFR = estimated glomerular filtration rate; Each value is shown as ml/min/m²
 The mean eGFR value \pm sd is 33.7 \pm 20.5

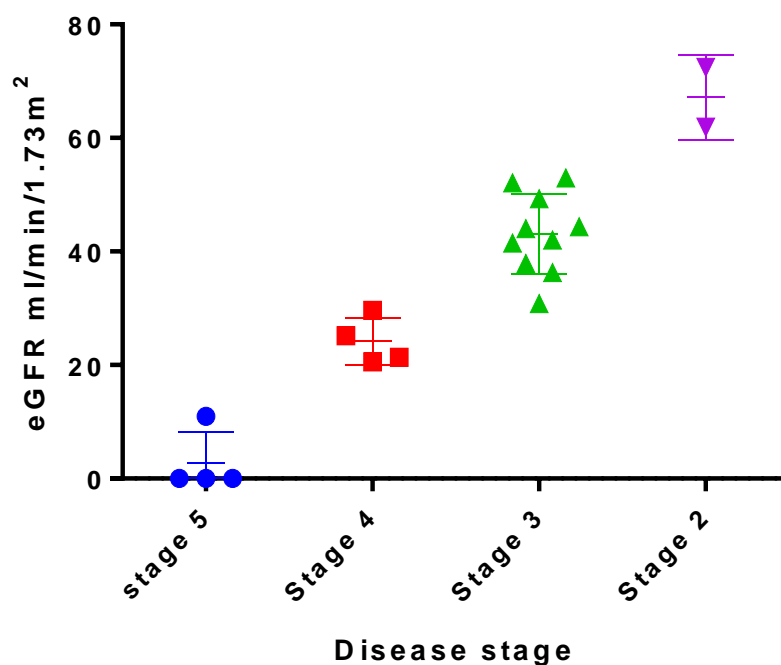


Figure 4-10 eGFR values (mean \pm SD) by CKD stage.
 CKD stages: 1=<90; 2=60/-89; 3=30-59; 4=15-29; 5=<15 or on dialysis.
 eGFR = estimated glomerular filtration rate; Each value is shown as ml/min/m²
 The mean eGFR values \pm sd are as follows: 67.1 \pm 7.4 Stage 2; 43.1 \pm 7.0 stage 3; 24.2 \pm 4.1 stage 2;
 2.7 \pm 5.5 stage 1

4.3.5.2 Relationship between kidney function and growth

Figures 4.11–4.13 shows the relationship between weight and height sds on the one hand and eGFR on the other. There was a slight tendency for weight and height sds to decrease with worsening kidney function. Regression analysis, however, showed that this relationship was not significant.

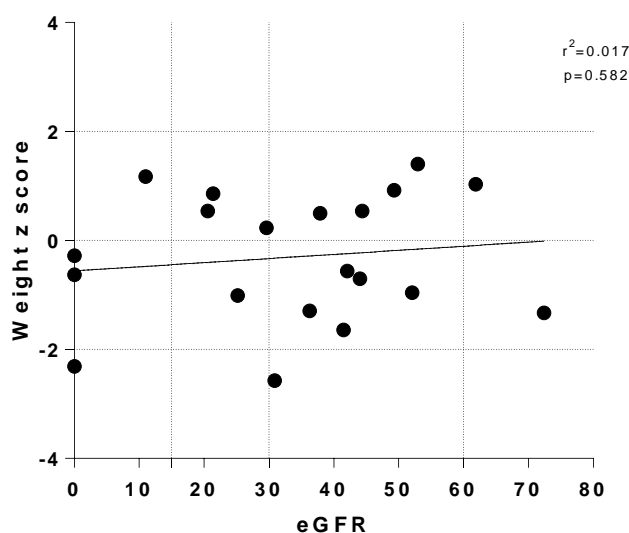


Figure 4–11 Relationship between weight Z score and eGFR

eGFR estimated glomerular filtration rate; units = ml/min/m² (using regression analysis)
Horizontal and vertical line indicate CKD stages of disease

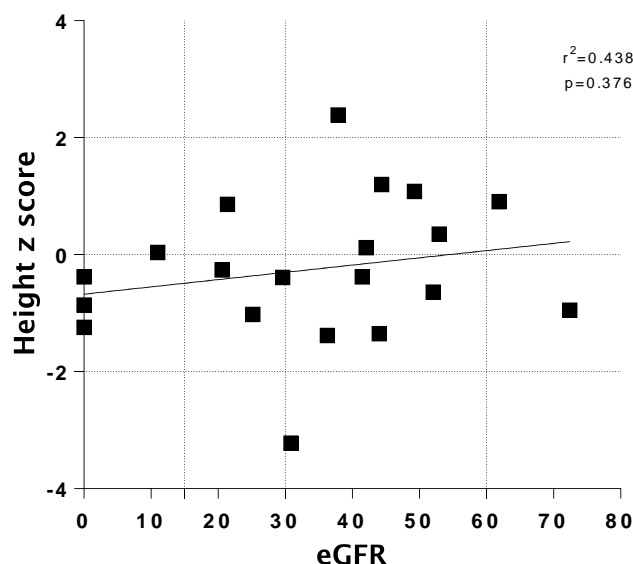


Figure 4–12 Relationship between height Z score and eGFR

eGFR estimated glomerular filtration rate; units = ml/min/m² (using regression analysis)
Horizontal and vertical line indicate CKD stages of disease

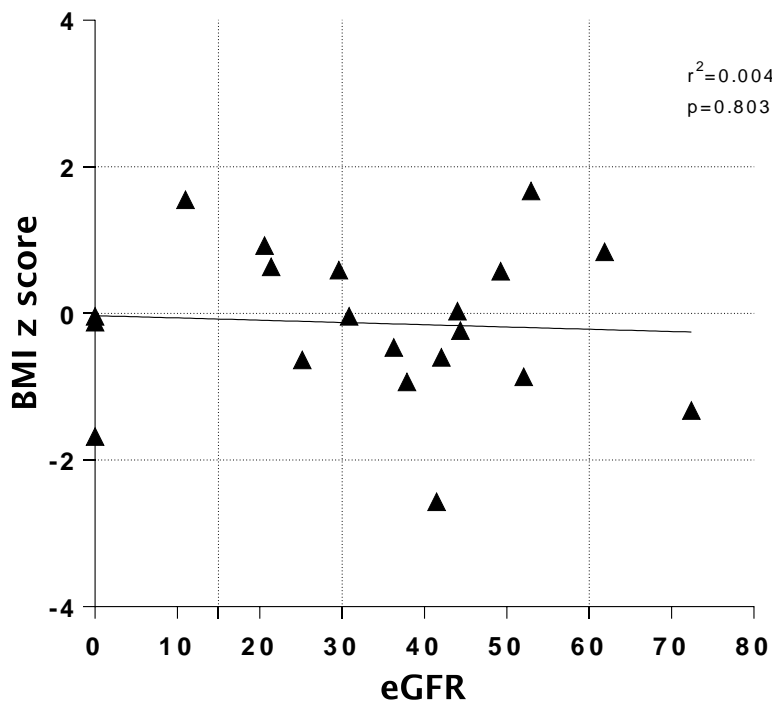


Figure 4–13 Relationship between BMI Z score and eGFR
eGFR estimated glomerular filtration rate; units = ml/min/m² (using regression analysis)
Horizontal and vertical line indicate CKD stages of disease

4.3.5.3 Relationship between kidney function and body composition

Figures 4.14–4.15 show the relationship between body fat (BF (kg and %)) or LBM (kg) and eGFR. The relationship varied with method used and remain unclear.

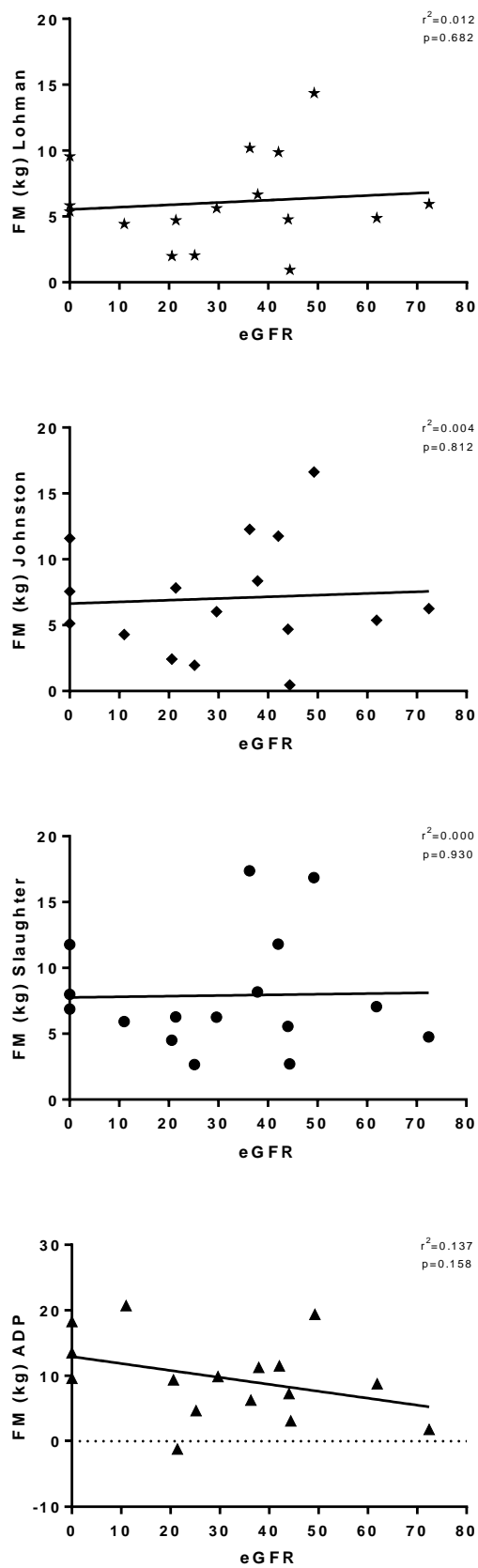


Figure 4-14 Relationship between kidney function (eGFR) and FM (kg)
SKF equations: Lohman; Johnson; Slaughter, (using regression analysis)

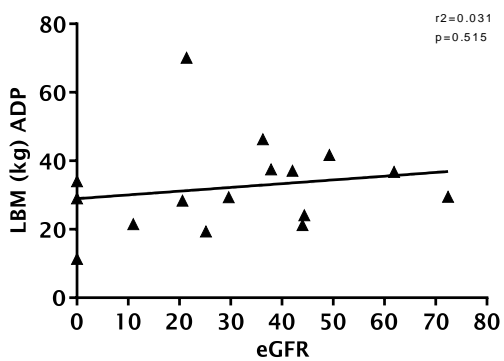
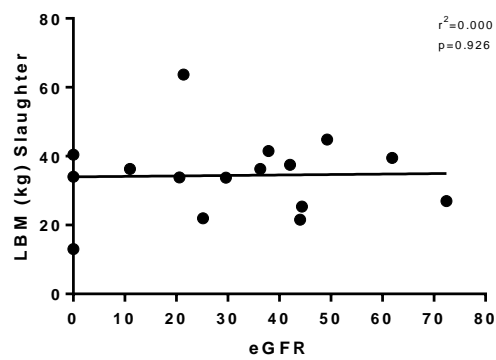
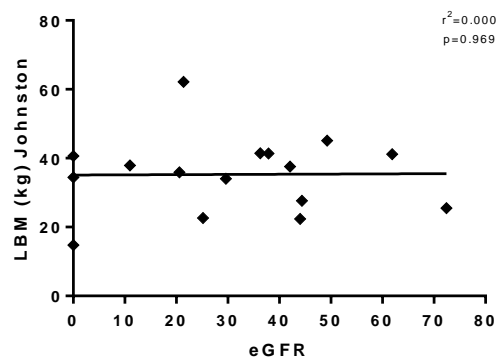
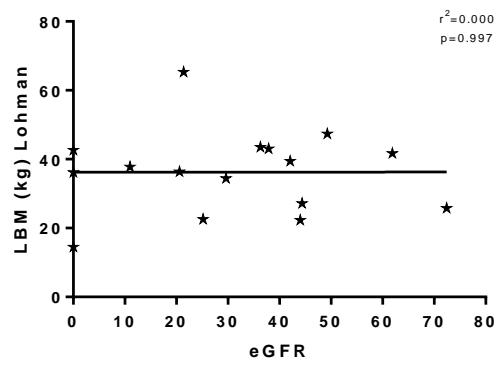


Figure 4-15 Relationship between kidney function (eGFR) and LBM (kg)
SKF equations: Lohman; Johnson; Slaughter, (using regression analysis).

4.3.5.4 Relationship between kidney function and treatment in children with CKD

Figures 4.16–4.18 shows the relationship between eGFR on the one hand and diet restrictions (Figure 4.16), nutritional supplementation (Figure 4.17) or medication (Figure 4.18) on the other. The number of diet restrictions ($r^2=0.635$, $p=0.001$) and number of medications ($r^2=0.648$, $p=0.003$) increased significantly with worsening kidney function. The number of nutritional supplements showed a tendency to increase with more severe disease but was not significant ($r^2=0.122$, $p=0.292$).

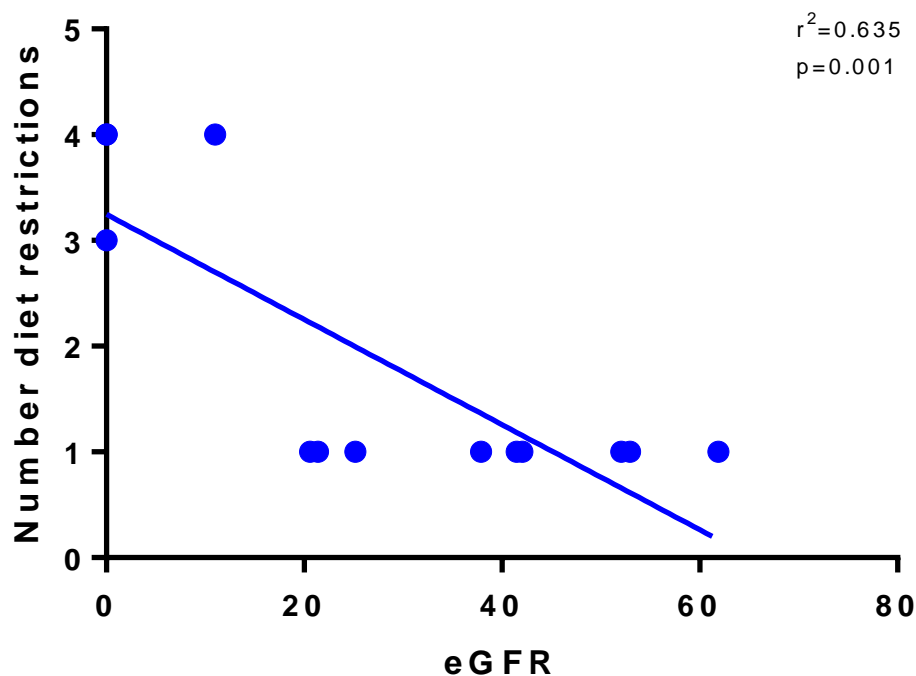


Figure 4–16 Relationship between eGFR and the number of diet restrictions
Using regression analysis

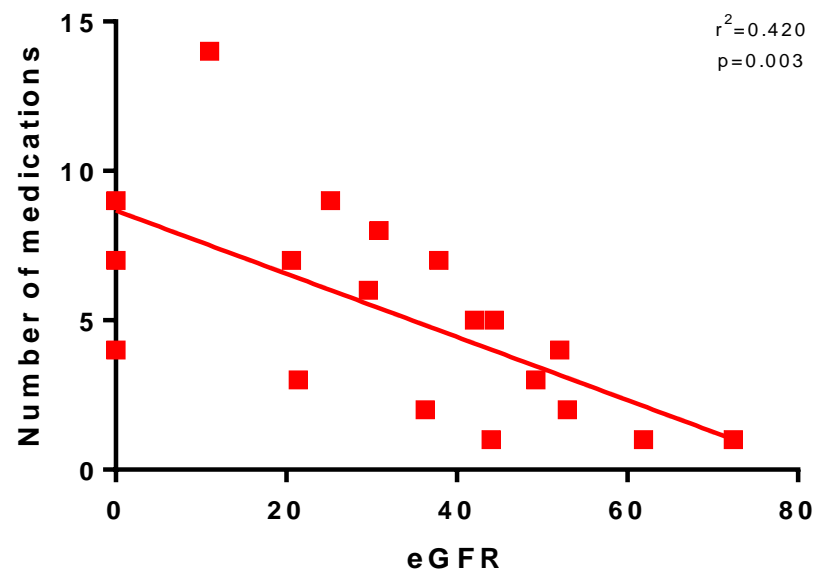


Figure 4–17 Relationship between eGFR and the number of medications
Using regression analysis

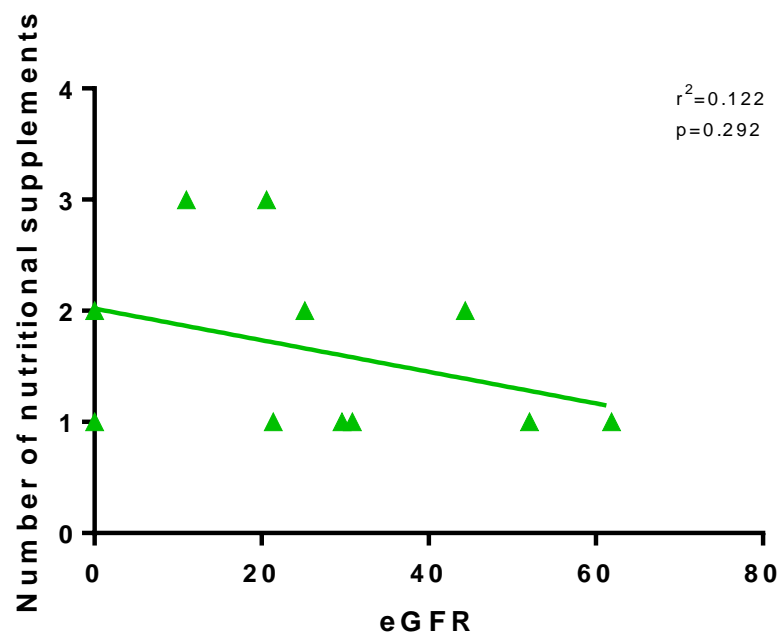


Figure 4–18 Relationship between eGFR and the number of nutritional supplements
Using regression analysis

4.3.6 Assessment of weight stability

Children in the CKD group were weight stable or close to weight stable (table 4.16). The mean weight change was $2.18 \pm 2.14\%$ between weight at time of study and weight on review. Percentage of weight gain expected for growth maintenance accounted for 2% of the weight. Adjusted weight change was $0.1 \pm 2.1\%$. Out of the children in the CKD group, 22% had no weight change, 28% had a weight loss of $<1-4\%$, and 44% had weight gain up to 2.2%.

Table 4-16 Weight stability in children in the CKD group

	CKD group (n=18)
Weight _{zero} (sds)	-0.45 ± 1.12
Weight ₁ (sds)	-0.35 ± 1.09
Difference (wt ₁ -wt _{zero})	0.78 ± 0.93
Percentage loss	2.18 ± 2.14
Difference (wt ₁ -wt ₂)	0.22 ± 1.00
% difference (wt ₂ -wt _{zero})	0.09 ± 2.13
% difference (wt ₂ -wt ₁)	0.58 ± 2.10

Wt_{zero} = weight at time of study; wt₁ = weight at time of review;
wt₂ = weight expected at time of review if they maintained original weight sds.

4.3.7 Summary of characteristics of children

This chapter has described the baseline characteristics of children with CKD, and compared findings to health. The relationship between kidney function and growth deficit and body composition has been explored also.

It showed that children with CKD were found to be significantly shorter and lighter, with a tendency towards more malnutrition and stunting. This growth deficit, however, was small. Furthermore, there were also non-significant trends suggesting that children with CKD had less fat, lean and resistance indices (indicating less TBW and ECW), although there was no indication in a difference in hydration between the groups. In addition, all children were considered weight stable.

When relationships with the severity of disease were explored, children with CKD had significantly more treatment (number of medications and diet restrictions) with worsening disease. The same trends were shown non-significantly for increasing nutritional supplementation and growth deficit. Unfortunately, the relationships with body composition were unclear.

4.4 Discussion

This section of the thesis summarises the general characteristics of children with CKD, including age, gender, growth status, body composition, kidney function and treatment. The characteristics were compared to healthy children who formed the control group of this study. The relationship between kidney function and growth, body composition and treatment were also explored.

Children with CKD were found to be significantly shorter and lighter compared to control children matched for age and gender. There were also non-significant trends, suggesting that children with CKD had a lower WHF (which encompasses wasting) and a lower HFA (which encompasses stunting) but, despite the above differences with the control children, the overall growth deficit was small for children with CKD (z score wt-0.29, ht -0.32, BMI -0.09, WFH 102%, HFA 99% and WFA 99%). In addition, there were also non-significant trends suggesting that children with CKD had less fat, less lean and resistance indices (suggesting less TBW and ECW), but without differences in the ratio of TBW/ECW. However, the overlapping ellipses in BIVA suggested little difference in hydration (over or under hydration) between the groups.

When the findings of this study were compared to the literature, the growth deficits here were much smaller. Both national (UK renal registry (UKRR))¹²⁰ and international (North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS))¹²¹ databases on growth for children with CKD have shown much larger growth deficits for weight and height z scores (sds) (1. Wt sds -0.96 vs. -0.28; and Ht sds -1.8 vs. -0.38 (median) (UKRR vs. this study). 2. Wt sds age 6-12yrs -1.07 ± 0.04 vs. -0.2 ± 0.4 and ≥ 12 yrs -0.81 ± 0.03 vs. -0.4 ± 1.1 ; and Ht sds 6-12yrs -1.62 ± 0.04 vs. -0.6 ± 0.4 and ≥ 12 yrs -1.22 ± 0.03 vs. -0.1 ± 0.3 (mean \pm se) (NAPRTCS vs. this study)). However, z scores for BMI suggested similar values (0.3 vs 0.38 (median) (UKRR vs. this study)). Reasons for these differences could be related to the study populations. This is because both the UKRR and NAPRTCS only presented findings for children on dialysis, which differs from this study which had children with CKD stages 3 to 5 (including children on dialysis). Nevertheless, when only children on dialysis were considered, the same trends were observed, with this present study again having less growth deficit (1. Wt sds -0.96 vs. 0.70; and Ht sds -1.8 vs. 0.23

(both PD & HD) (UKRR this study). 2. PD: Wt sds -1.24 vs. 0.42 ; and Ht sds -1.71 vs. 0.23 . HD Wt sds -0.91 vs. 0.70 ; Ht sds -1.4 vs. 0.30 (NAPRTCS vs. this study). Consideration also needs to be given to study size as both the UKRR and NAPRTCS had considerably larger study numbers, for the databases compared to this study ($n=1452$ (UKRR); $n=5206/5022$ weight/height (NAPRTCS); and $n=21$ (this study)). The same trends were also shown for height and BMI z scores when this study was compared to the only UK study which looked at growth deficit (in relation to growth hormone (GH) use) (Rashid et al¹²²) (Ht sds -1.3 vs. 0.23 ; and BMI sds 0.79 vs. 0.26 (this study vs. Rashid et al pre GH)). The children studied by Rashid et al however, differed by being larger in number ($n=38$ (non GH) vs. 20 respectively), lower in eGFR (27 vs. 34), which represents stage 4 rather than stage 3 studied here, and younger in age (8.9 vs. 12.1 years). It is also noteworthy to consider that a lower eGFR has been shown previously to reduce height in children with CKD^{120 121 123}.

Comparing findings in this study to literature on body composition in terms of fat and lean mass and hydration have been more difficult. This is due to differences in methodology and presentation of results. However, three studies warrant further discussion. Stefandis et al¹²⁴ studied body composition by SKF, and found similar results for body fat (ranging from 13.1 to 15.1 (mean \pm sem) using Brook¹²⁵ and Boileau et al¹²⁶ equations vs. 14.4 to 18.6 using Lohman, Johnston and Slaughter equations for this study), but much lower results for LBM (19.8 to 19.5 vs. 36.3 to 34.4 respectively). However, the different equations were used in each study. Edefonti et al⁷⁷ studied BIA, and found lower impedance values for reactance (X_c) (40.3 vs. 64.6 respectively) between children with CKD pre dialysis and healthy controls, whilst resistance (R) values were similar between groups (700.1 vs. 702.3 respectively). In contrast, this study showed the opposite trends (X_c : 74.2 vs. 70.5 ; 673 vs. 644 CKD vs. control). These children were similar in number ($n=31$) and age (11.3 ± 4.4). Lastly, Bozzetto et al¹²⁷ studied children with different conditions of CKD using BIVA 95% confidence ellipses, and found that values for the CKD stage equivalent to this study were lower for both R and X_c z scores (R sds 0.2 ± 1.9 vs. 0.34 ± 1.19 ; X_c sds -0.5 ± 1.3 vs. 1.1 ± 1.4 stage 3 CKD comparison Bozzetto et al vs. this study). They also found different bivariate 95% confidence ellipses for each pathological CKD condition that detected children accurately who had oedema. This study did not find this, as some children with oedema appeared in the opposite quadrant of

the graph. These children also differed in age (2:14 vs. 6:17 years respectively). In addition, both studies, however, found children with worsening CKD in the dehydrated area of the vector analysis and the reasons for this are unknown. This leads to the suggestion that BIVA requires further validation for use in children with CKD.

When comparing findings in this study to the literature, two additional considerations should be noted. Firstly, children with CKD were less severely impaired in this study (CKD stage 3) than previous studies (often CKD stage 5), which were more likely to have end stage kidney disease. Secondly, it is well documented that worsening kidney function in children (end stage CKD stage ≥ 4) is often associated with a decreased oral nutritional intake, due to decreased appetite, increased taste changes, and increased nausea and vomiting. Subsequently, children with a CKD stage three often have less dietary manipulation (as shown in this study), better appetites, less taste changes, and less nausea and vomiting, so these children should have better growth and nutritional status.

When relationships with kidney function were explored, children with CKD in this study were found to have only a weak relationship between kidney function (eGFR) and height or weight z scores. The lack of significant relationship could be due to the small sample size, and other confounding variables (such as parental anthropometry) which were not taken into account. In addition, nutritional supplements were aggressively prescribed according to local policy, and this may have reduced the growth deficit. Since about half (45%) the children received nutritional supplements, the relationship between eGFR and height z scores (and weight) may have been affected also. Furthermore, as expected, the level of kidney function significantly affected the type of treatment received, including the amount of medication, severity of dietary restriction and use of nutritional supplements.

When weight stability was considered, the findings of this study can be contemplated in relation to be largely weight stable for both children with CKD and health (66% of children with CKD having either no weight change or a 2% change, which is appropriate for growth maintenance). Since the energy deposits for growth in healthy children are considered to be a very small (1%) percentage of TEE¹³, the 2% weight gain found here seems reasonable, especially

in children with chronic disease. This can help in the interpretation of TEE and EI findings, not only in relation to DLW and EAR (both of which assume weight stability), but also in energy balance.

4.4.1 Summary

Children with CKD (mainly stage three disease) were found to be significantly shorter and lighter, with a tendency towards malnutrition and stunting compared to controls children. The growth deficit was, however, small and tended to decrease with worsening disease.

Children with CKD tended to have less fat and lean mass and TBW, although there was no difference in hydration when compared to healthy controls. The relationship with disease severity was unclear.

Children with CKD had significantly more medication and dietary restrictions with worsening disease. The same trends were shown for nutritional supplementation but these were not significant.

These early stages in growth deficit and body composition require optimal treatment and close monitoring to prevent further deteriorations and/or improve deteriorations found. Early correction may help improve clinical outcomes both pre and post transplantation.

Chapters 5–8 will explore the extent to which kidney function affects energy requirements, beginning with the next chapter, which examines whether kidney disease affects BMR.

5. Basal metabolic rate

5.1 Introduction

The previous chapter explored the general characteristics (age, gender, growth, body composition and kidney function) of children with CKD. This now needs to be taken into consideration in the subsequent chapters which explore the components (BMR, TEE and EI) of energy requirements.

This chapter investigates measured BMR (mBMR), which has previously not been studied in UK children with CKD. Predicted BMR (SchBMR) using the Schofield equation ⁴⁷ and percentage mBMR of SchBMR (% mBMR of SchBMR), were also considered.

Findings are compared to healthy controls after adjustments for growth and body composition when required. The relationship between BMR in children with CKD and kidney function was also considered. Percentage and difference from a reference standard were also explored.

5.2 Methodology

The children with CKD (n=20) and control children (n=20), who were recruited according to procedures described in Chapter 3, had their BMR measured by indirect calorimetry and also predicted using the age, weight and height appropriate Schofield equations, as detailed below.

5.2.1 BMR measured by indirect calorimetry

BMR was measured by indirect calorimetry using the ventilated hood system (Chapter 3). More than 75% of the measurements were made using the Deltatrac II (Datex-ohmeda ¹²⁸), which replaced the GEM (Gas Exchange Measurement) analyser (Europa Scientific ¹²⁹) when there were technical problems (22% of measurements). The machine was calibrated at the start of each day according to the manufacturer's recommendations, which involved calibration of the O₂ and CO₂ analysers^{97 98}. Regular alcohol burns were also undertaken to further calibrate the accuracy of the calorimeters.

Subjects were asked to lie down in the supine position and rest for thirty minutes. Twenty minutes into the rest period the clear plastic ventilated hood of the indirect calorimeter was placed over the child's head so that any changes in breathing would have time to stabilise before the start of the measurement period. Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were recorded every minute for thirty minutes under standard conditions, while the child lay resting in the recumbent position at ambient temperature^{97 98}.

Respiratory quotient (RQ) and BMR were calculated and displayed on graphs to ascertain any unusual readings. Any extreme values were investigated and excluded to avoid misleading results. The initial three minutes were automatically discounted, and the mean of the remaining twenty-seven minutes was used to calculate BMR according to the equation of Elia and Livesey¹³⁰:

$$\text{EE (kJ)} = 15.818 \text{ O}_2 + 5.176 \text{ CO}_2.$$

where O_2 and CO_2 are in litres.

5.2.2 BMR predicted using reference equations

BMR was predicted using the following Schofield's equations⁴⁷.

Age 3–10 years

Boys: $19.6 \times \text{weight} + 130.3 \times \text{height} + 414.9 = \text{BMR (kcal/24 hours)}$

Girls: $16.97 \times \text{weight} + 161.8 \times \text{height} + 371.2 = \text{BMR (kcal/24 hours)}$

Age 10–18 years

Boys: $16.25 \times \text{weight} + 137.2 \times \text{height} + 515.5 = \text{BMR (kcal/24 hours)}$

Girls: $8.365 \times \text{weight} + 465 \times \text{height} + 200 = \text{BMR (kcal/24 hours)}$

where weight is in kg and height is in cm.

Measured BMR was expressed in kcal/24 hours and as percentage of Schofield predicted BMR.

$$\text{mBMR (\% of SchBMR)} = \frac{\text{mBMR}}{\text{SchBMR}} \times 100$$

where mBMR = measured BMR; % of SchBMR = percentage of predicted BMR using Schofield equation; and SchBMR = Schofield predicted BMR.

5.2.3 Regression statistics

Regression analysis was used to assess the relationship between BMR and other explanatory variables that effect BMR. Each model builds upon a basic model where BMR is predicted from age and gender. This demonstrates how each variable influences BMR both on an individual level and in combination with other variables. The unstandardized coefficients (B and SE) provide the values required for the regression models for each individual variable. Whilst, the R^2 of the model shows the percentage of the model that can be explained by the other variables under investigation i.e. how much variation in BMR can be accounted for by the individual variables combined. In addition, the corresponding p-values for each variable show any independent effects that may occur on BMR within the models.

Regression was also used to assess the relationship between BMR and eGRF and additional explanatory variables. In addition to B, SE and p above, R was used to show the effect size strength of the relationship between BMR and eGFR.

5.3 Results

5.3.1 BMR in health and CKD

Table 5.1 shows that the measured BMR expressed in kcal/day, and as a percentage of predicted BMR (Schofield equation), did not differ between children with CKD and healthy controls, even when boys and girls were considered separately. The Schofield predicted BMR (kcal/day) (SchBMR) also did not differ significantly between the groups, although the values for children with CKD were lower than healthy controls who were heavier and taller (Chapter 4).

Table 5–1 Measured and predicted BMR in children by group and gender

Characteristics	Both groups (n=40)	CKD group (n=20)	Control group (n=20)	p*
Measured BMR (mBMR) (kcal/day)				
Both boys & girls	1311 ± 255	1296 ± 318	1325 ± 178	0.720
Boys	1397 ± 240	1420 ± 314	1373 ± 150	0.691
Girls	1240 ± 250	1194 ± 297	1286 ± 196	0.402
Schofield predicted BMR (kcal/day)				
Both boys & girls	1314 ± 255	1269 ± 247	1360 ± 261	0.262
Boys	1392 ± 292	1360 ± 273	1425 ± 322	0.651
Girls	1250 ± 206	1194 ± 207	1308 ± 199	0.205
Measured BMR (% mBMR of SchBMR)				
Both boys & girls	100 ± 13	102 ± 12	99 ± 14	0.570
Boys	102 ± 15	104 ± 8	100 ± 20	0.521
Girls	99 ± 12	99 ± 15	99 ± 9	0.912

* The P values refer to comparisons between the CKD and control group.

Results are expressed as mean + SD.

Boys n= 9 (CKD) & 9 (control), girls n= 11 (CKD) & 11 (control).

Chronic kidney disease (CKD); Basal metabolic rate (BMR); measured BMR (mBMR); Schofield predicted BMR (SchBMR).

Figure 5.1 shows that measured BMR was more widely distributed in children with CKD compared to healthy controls. This was not the case with predicted BMR. Figure 5.2 shows that measured BMR as a % of predicted BMR was less widely distributed in children with CKD compared to healthy controls.

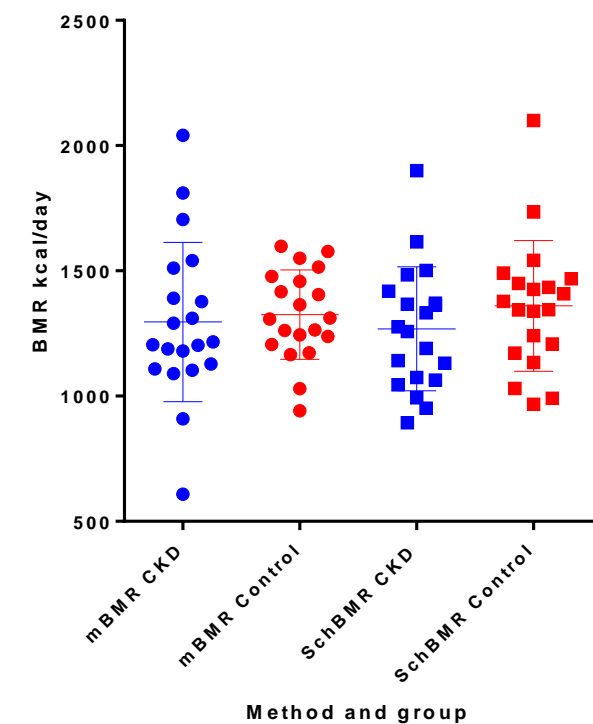


Figure 5-1 BMR (kcal per day) measured (mBMR) and predicted (Schofield equation using weight and height) by group (children with CKD and healthy controls).
The large horizontal lines indicate the mean value and the smaller horizontal lines the upper and lower limits of the 95% confidence interval.
The mean scores are as follows: mBMR 1296±318 (CKD) vs. 1325±178 (control); SchBMR 1269±247 9CKD) vs. 1360±261 (control)

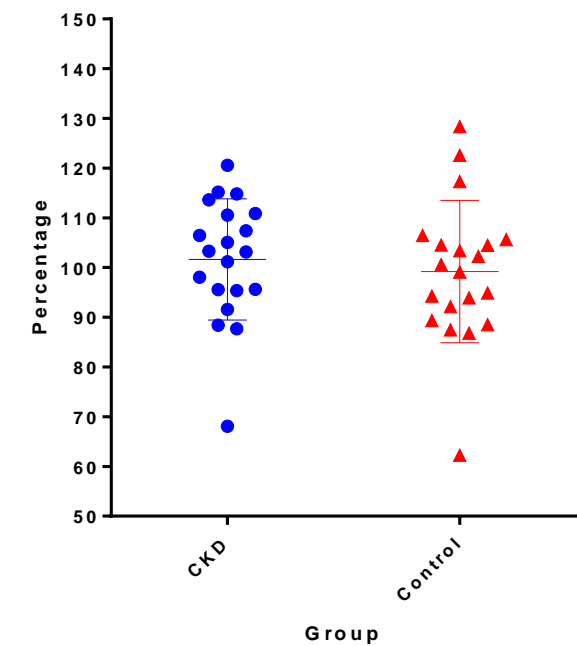


Figure 5-2 Measured BMR as a percentage of predicted (Schofield weight and height) by group (Children with CKD and healthy controls).
The large horizontal lines indicate the mean value and the smaller horizontal lines the upper and lower limits of the 95% confidence interval.
The mean scores are as follows: 102±12 (CKD) vs. 99±14 (control)

A general linear model was used to examine the association between BMR and other explanatory variables (age, sex, anthropometric variables and group) (Table 5.2). Model 1 is a basic model in which BMR is predicted from age and sex. Model 2 is an extension of Model 1, which shows that the sex differences in BMR persist after adjustment for age, weight and height. Height was also found to be close to having an independent effect on BMR ($p=0.057$). Model 3, (a further extension of the previous two models) shows that the sex differences do not persist after additional adjustment for group. (1348 (se 41) CKD vs. 1290 (se 41) control kcal/day, $p=0.809$). This was consistent with the lack of significant difference between groups when measured BMR is expressed as a percentage of predicted BMR (no adjustment of age, sex, weight, height is needed in this comparison because all these variables are used to predict BMR). Table 5.3 is used to illustrate how coefficients from Table 5.2 can be used to calculate BMR for specific values of age, weight and height.

Table 5–2 Regression models of BMR (kcal/day) (n=40) in children with CKD

Regression coefficient				
Model and variable	B	SE	p*	R ² of model*
Model 1				
Intercept	762.467	128.697	0.000	0.364
Age (years)	39.973	10.105	0.000	
Sex	-163.746	66.335	0.018	
Model 2				
Intercept	72.340	378.869	0.850	0.582
Age (years)	-20.396	16.611	0.228	
Weight (kg)	6.074	4.043	0.142	
Height (cm)	777.547	394.597	0.057	
Sex	164.331	55.645	0.006	
Model 3				
Intercept	68.939	382.638	0.858	0.598
Age (years)	-23.752	17.511	0.184	
Weight (cm)	6.971	4.436	0.126	
Height (cm)	773.796	400.340	0.062	
Sex	127.637	80.723	0.123	
Group	75.163	113.816	0.514	

The p* value refers to the between subject effects.

The R² of the model refers to the partial Eta squared of the corrected model

In the models sex is represented as girls 0 and boys 1 and the control group 0 and the CKD group 1. (n=40 in all three models).

Model 1: Measured BMR = age + sex; Model 2: Measured BMR = age + wt + ht + sex; Model 3: Measured BMR = age + wt + ht + sex + group.

Table 5–3 Examples, in which models 1, 2 and 3 (defined in Table 6) are employed to predict BMR for boys and girls

Model	Calculation
Model 1	
Boy BMR (kcal/day)	$= 762.467 + (11.8 \times 39.973) + (1 \times 163.746) = 1398$
Girl BMR (kcal/day)	$= 762.467 + (12.0 \times 39.973) + 0 = 1242$
Model 2	
Boy BMR (kcal/day)	$= 72.340 + (11.8 \times -20.396) + (41.8 \times 6.074) + (1.47 \times 777.547) + (1 \times 164.331) = 1393$
Girl BMR (kcal/day)	$= 72.340 + (12.0 \times -20.396) + (43.4 \times 6.074) + (1.48 \times 777.547) + 0 = 1242$
Model 3	
Boy	
Renal BMR (kcal/day)	$= 68.939 + (11.8 \times -23.752) + (41.8 \times 6.971) + (1.47 \times 773.796) + (1 \times 127.637) + (1 \times 20.227) = 1365$
Control BMR (kcal/day)	$= 68.939 + (11.8 \times -23.752) + (41.8 \times 6.971) + (1.47 \times 773.796) + (1 \times 127.637) + 0 = 1345$
Girls	
Renal BMR (kcal/day)	$= 68.939 + (12.0 \times -23.752) + (43.4 \times 6.971) + (1.48 \times 773.796) + 0 + (1 \times 20.227) = 1252$
Control BMR (kcal/day)	$= 68.939 + (12.0 \times -23.752) + (43.4 \times 6.971) + (1.48 \times 773.796) + 0 + 0 = 1232$

Model 1 = age + sex; Model 2 = age + weight + height + sex; Model 3 = age + weight + height + sex + group.

In the models sex is represented as girls 0 and boys 1 and the control group 0 and the CKD group 1. (n=40 in all three models).

The values for mean age, weight (kg) and height (m) are indicated on bold respectively.

Boys: 11.8yrs, weight 41.8kg, and height 1.47m for boys; Girls: 12.0yrs, 43.4kg, 1.48m.

5.3.2 Effect of renal function (eGFR) on mBMR in children with CKD

5.3.2.1 BMR and kidney function

A separate regression model showed that, within the children with CKD, eGFR is significantly related to mBMR expressed as a percentage of predicted BMR (SchBMR) (Table 5.4).

Table 5–4 Regression model of measured BMR (% of predicted) and kidney function in children with CKD

Model and variable	Regression coefficient			
	Unstandardized coefficients		p*	R
	B	SE		
Intercept	91	4.7	0.000	0.517
eGFR	0.3	0.1	0.019	

The p* value refers to the relationship between eGFR and mBMR effects

N=20

eGFR = estimated glomerular filtration rate

Children with a lower eGFR also had a lower BMR. The regression model indicated that at eGFR of zero (anephric children), BMR was 91% of predicted, and at an eGFR of 70ml/min/1.73m² it was 113% of predicted. The relationship is also shown diagrammatically in Figure 5.3 with all the individual data points plotted.

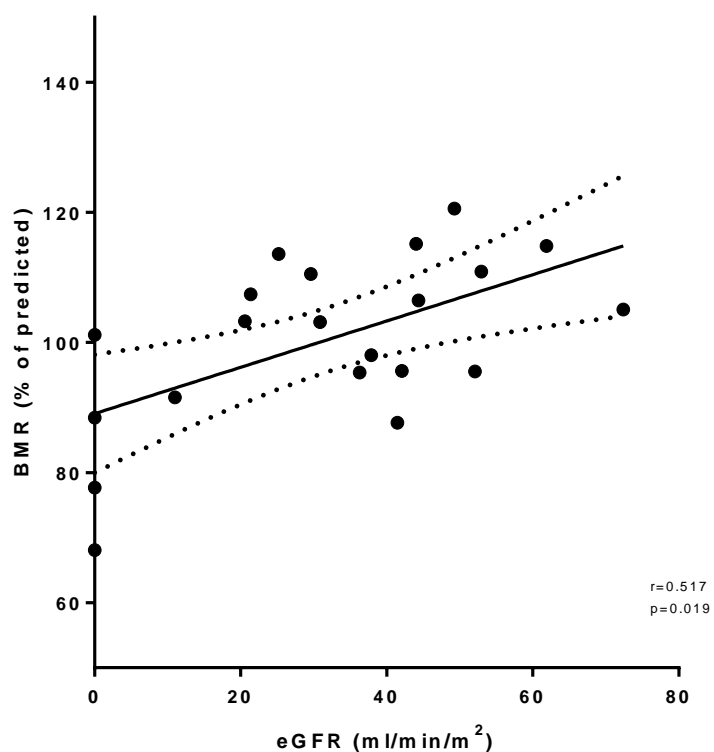


Figure 5–3 Relationship between eGFR (70ml/min/1.73²) and measured BMR (mBMR) expressed as a percentage of predicted by the Schofield equation (% of predicted BMR = 91 + (70 × 0.308)) ($r=0.517$; $p=0.019$).

The curved lines show the 95% confidence interval of the regression line.

mBMR = measured BMR by indirect calorimetry, eGFR = estimated glomerular filtration rate by Schwartz formula (ml/min/m²).

5.3.2.2 BMR, kidney function and nutritional status/ body composition

To examine whether the effect of eGFR on measured BMR (expressed as a percentage of predicted BMR) can be explained by nutritional status (Z scores of weight and height), weight and height Z scores were added to the regression model in Table 5.5. However, eGFR remained an independent significant predictor of BMR ($p=0.024$) (Table 5.5 Model 2), and continued to remain significant when Model 3 was modified further by the addition of BMI Z score, or when BMI Z score was used alone (Table 5.5 Model 4).

Table 5-5 Regression model: measured BMR (%of predicted) on eGFR and weight, height and/or BMI in children with CKD.

Model and variable	B	SE	Regression coefficient p*	R ²	R
Model 1 (n=20)					
Intercept	128.514	±34.118	0.002	0.401	0.633
eGFR	0.361	±0.119	0.008		
Weight (kg)	0.877	±0.504	0.101		
Height (m)	-50.386	±36.140	0.182		
Model 2 (n=20)					
Intercept	91.618	±4.924	0.000	0.343	0.586
eGFR	0.314	±0.123	0.022		
Weight Z score	4.55	±3.380	0.197		
Height Z score	-3.243	±3.322	0.343		
Model 3 (n=20)					
Intercept	89.509	±4.938	0.000	0.430	0.656
eGFR	0.352	±0.121	0.011		
Weight Z score	-12.419	±11.679	0.304		
Height Z score	7.202	±7.607	0.359		
BMI Z score	12.533	±8.283	0.151		
Model 4 (n=20)					
Intercept	91.364	±4.433	0.000	0.384	0.620
eGFR	0.320	±0.113	0.012		
BMI Z score	3.922	±2.191	0.091		

The p* value refers to the relationship between eGFR and mBMR effects

eGFR = estimated glomerular filtration rate

Weight (kg), height (m), eGFR ml/min/m².

Table 5.6 shows that eGFR also remains an independent predictor of BMR (% of predicted), both before and after adjustment for lean body mass (LBM) ($p=0.022$ ADP, $p=0.014$ Lohman, Johnston, Slaughter equation using SKF).

Table 5–6 Regression model: measured BMR (%of predicted) on eGFR and lean body mass† in children with CKD.

Model and variable†	B	Regression coefficient			R
		SE	p*	R ²	
Model 1 (n=16)					
Intercept	86.261	±7.748	0.000	0.391	0.626
eGFR	0.338	±0.131	0.022		
LBM (kg) (ADP)	0.169	±0.210	0.436		
Model 2 (n=16)					
Intercept	82.222	±9.547	0.000	0.414	0.644
eGFR	0.357	±0.126	0.014		
LBM (kg) (Lohman)	0.246	±0.226	0.296		
Model 3 (n=16)					
Intercept	81.446	±9.780	0.000	0.418	0.647
eGFR	0.355	±0.126	0.014		
LMB (kg) (Johnston)	0.276	±0.244	0.279		
Model 4 (n=16)					
Intercept	81.582	±9.236	0.000	0.425	0.652
eGFR	0.353	±0.125	0.014		
LBM (kg) (Slaughter)	0.281	±0.234	0.251		

The p* value refers to the relationship between eGFR and mBMR effects

eGFR = estimated glomerular filtration rate

Weight (kg), height (m), eGFR ml/min/m²

† Lean body mass (LBM) was estimated using four different methods each of which was incorporated into a different regression model (model 1 by Bod Pod; model 2 by SKF and Lohman equation; model 3 by SKF and Johnston equation; model 4 by SKF and Slaughter equation)

Table 5.7 shows that when adjustments were made for weight and height Z scores and LBM together, eGFR continued to be independently related to mBMR (expressed as percentage of predicted BMR), and also independent of nutritional status (assessed by weight and height sds)/ body composition (assessed by lean body mass (kg)).

Table 5-7 Regression model: measured BMR (%of predicted) on eGFR + weight, height and lean body mass† in children with CKD.

Model and variable†	Regression coefficient		p*	R ²	R
	B	SE			
Model 1 (n=16)					
Intercept	84.997	±8.941	0.000	0.418	0.647
eGFR	0.335	±0.143	0.030		
Weight sds	2.800	4.401	0.538		
Height sds	-2.941	4.308	0.509		
LBM (kg) (ADP)	0.198	0.234	0.416		
Model 2 (n=16)					
Intercept	79.394	11.557	0.000	0.445	0.667
eGFR	0.385	0.140	0.019		
Weight Z score	2.205	4.310	0.619		
Height Z score	-3.275	4.223	0.454		
LBM (kg) (Lohman)	0.302	0.267	0.282		
Model 3 (n=16)					
Intercept	78.327	12.096	0.000	0.448	0.670
eGFR	0.384	0.139	0.019		
Weight Z score	1.977	4.316	0.656		
Height Z score	-3.226	4.192	0.458		
LBM (kg) (Johnston)	0.340	0.292	0.268		
Model 4 (n=16)					
Intercept	78.115	11.402	0.000	0.460	0.678
eGFR	0.384	0.138	0.018		
Weight Z score	2.117	4.255	0.629		
Height Z score	-3.499	4.184	0.421		
LBM (kg) (slaughter)	0.355	0.279	0.230		

The p* value refers to the relationship between eGFR and mBMR effects

eGFR = estimated glomerular filtration rate

Weight (kg), height (m), eGFR ml/min/m².

† Lean body mass (LBM) was estimated using four different methods each of which was incorporated into a different regression model (model 1 by Bod Pod; model 2 by SKF and Lohman equation; model 3 by SKF and Johnston equation; model 4 by SKF and Slaughter equation)

The same independent relationship continued to exist if BMI Z score was substituted for weight and height Z scores. The effect of eGFR was also examined in models where BMR in kcal/day was adjusted for age, sex, weight and height ($p=0.035$). EGFR remained significant when weight and height Z score and LMB (kg) were added to the model ($p=0.022$ Lohman and Slaughter, $p=0.024$ Johnston SKF equation) but not quite significant with the ADP ($p=0.078$). The model (which included age, sex, weight and height as covariates) also showed an independent relationship of eGFR with weight ($p=0.033$) and gender ($p=0.023$) (adjustments for age, sex, weight and height).

5.3.3 Summary of results

Compared to children in the control group, those in the CKD group tended to have slightly lower values for mBMR, predicted BMR and mBMR expressed as % of predicted BMR, but these did not reach statistical significance. Within the CKD group, a lower eGFR was significantly associated with a lower BMR (% of predicted) in children with CKD.

This relationship remained independent of nutritional status (assessed by Z score weight, height, BMI) or LBM (kg), when considered either alone or in combination with BMR (% of predicted).

5.4 Discussion

5.4.1 Comparisons between health and CKD

This is the first UK study to report mBMR (kcal/day) in children with CKD. It also adds to the sparse literature available from other countries and helps clarify some conflicting and confusing information. The analysis has shown that there is no difference in measured BMR, predicted BMR and percentage of predicted BMR between children in the CKD group and those in the control group. However, there was tendency towards lower BMR values both for measured BMR and predicted BMR by the Schofield equation.

These results need to be considered in relation to the three other studies in children with CKD^{1 3 66}, which indicated that REE was reduced, unchanged or increased (see Chapter 2 for details about the studies). These discrepancies probably relate to methodological differences and various ways of expressing the results. The study findings of Tounian et al² and Shapiro et al¹ agree with the findings of this study. As the exact conditions for measuring EE in these studies are unknown, the term REE shall be used to distinguish from the present study. Tounian et al showed no difference in measured REE (kcal/day) between children with CKD and controls (1386 ± 262 (CKD) vs. 1524 ± 170 (control) REE kcal/day ($p=0.19$) Tounian study) compared to 1296 ± 318 (CKD) vs. 1325 ± 178 (control) BMR kcal/day ($p=0.74$) in the present study). Like this study, children with CKD were shorter and lighter but, unlike this study, no adjustment was made for this during the analysis. In addition, the Tounian study differed from the present study in various ways; all the CKD population were undergoing haemodialysis (CKD stage 5) which was not the case in the present study (mostly stage 3 with a range 3 to 5 including dialysis ($n=3$)); the population was older (14.6 ± 4.3 (CKD) vs. 14.1 ± 1.3 (control) years) than those involved in the present study (11.9 ± 3.4 (CKD) vs. 11.8 ± 3.3 (control) years), the Tounian study included two adults (both in the CKD group) compared to none in the present study; the sample size was smaller ($n=18$ (8 CKD, 10 control) vs. $n=40$ (20 CKD, 20 control) respectively) and included more boys than girls, (ratio 5:3 in the CKD group) compared to 9:11 in the present study CKD group).

Shapiro et al¹ again showed that REE did not differ significantly but used three predictive equations: Mayo ($1336 + 299 \text{kcal/day}$) (weight, height and gender);

Passmore (1116+309 kcal/day) (weight, height and gender); and FAO/WHO/UNU (1125+kcal/day) (weight and age). This study was, however, limited by the absence of a control group. Like this study, children had a CKD stage ≥ 3 but, unlike this study, contained no children undergoing dialysis. In addition, the Shapiro study differed from the present study in various ways: all the children with CKD had higher height and weight Z scores (sds height 0.16 (Shapiro) vs. -0.26 (this study); sds weight 0.85 vs. -0.31 respectively); the population was younger (9.4 years) than those involved in the present study (11.9 years); the sample size was smaller (16 vs. 20) and indicated more boys than girls (9:7 vs. 9:11 respectively). The applicability of the predictive equations used in the CKD group studied by Shapiro also needs consideration, largely due to the differences in body size and composition of contemporary children.

The most recent study by Marques de Aquino et al ³, which was published after this study was completed, differed from this study's findings by showing a significantly lower measured REE (kcal/day) in children on haemodialysis (HD) compared to controls (1067 \pm 191 (CKD) vs. 1372 \pm 290 (control) (Marques de Aquino): 1296 \pm 318 (CKD (n=20)) vs. 1325 \pm 178 (control) p=0.74 here (HD subgroup in the present study (n=2) 950/483 kcal/day). However, these children were significantly lighter (z score BMI, height, height for age, AMA and AFA), which could explain the differences in REE kcal/day. Again, no adjustment was made for weight, although adjustments were made for FFM. When adjustments were made for FFM, lower values of REE (kcal/kg/FFM) were suggested but these values did not differ significantly from the healthy group. In addition, the Marques de Aquino study differed from the present study in various other ways: all the CKD population was undergoing haemodialysis (CKD stage 5) which was not the case in the present study (mostly stage 3 with a range 3 to 5); the population was older (12.3 \pm 3.1 (CKD HD) vs. 12.4 \pm 3.1 (control) than those involved in the present study (11.9 \pm 3.4 (CKD) vs. 11.8 \pm 3.3 (control) years); BMI Z scores were more negative(-1.0 \pm 1.3 vs. -0.13 \pm 1.1 (respectively)); and the sample size was larger (50 vs. 40) and indicated more boys than girls (15:10 vs. 9:11 respectively).

Despite the differences between studies, all of them seemed to be consistent in three respects: Firstly, children with CKD tended to be shorter and lighter and had a lower BMR. Secondly, when adjustments were made for body size (FFM),

there were no significant differences between the groups. Thirdly, no significant difference was found between children with CKD and hypothetical children with the same weight, height and gender (predictive equations). Looked at in this way, results of this study are consistent with all available literature. However, the sample sizes were all small and the wide range of eGFR might mask any significant differences that might exist. Table 2.2 (Chapter 2) compares study findings.

5.4.2 Effect of kidney function on BMR in children with CKD

This is the first study to explore BMR in the context of kidney function (eGFR) in children with CKD. No studies were found that examined the relationship between eGFR and BMR in children with CKD. In the present study, eGFR was significantly related to BMR: a low eGFR was associated with a low BMR, independently of nutritional status (Z scores for weight & height) and/or LBM (kg).

In contrast to studies in children with CKD, those in adults have examined the relationship between eGFR and BMR but the findings are conflicting and confusing. They indicate that REE can increase, decrease or be unrelated to decreasing kidney function. Discrepancies again relate to methodological differences and methods of expressing the results.

Summarised below are the results of the three studies carried out in adults with CKD and the way they differed from our study.

The first study by Kuhlman et al ¹³¹ reported an increase in measured REE with decreasing creatinine clearance, and (unlike other adult studies) it expressed results as REE/kg/day rather than kcal/day, which makes comparisons difficult. The second study by Panesar and Agarwal ¹³² showed the opposite finding, namely that measured REE (kcal/day) decreases with decreasing eGFR. However, REE was measured in a sitting position a few hours after a light breakfast, which differs from the other REE studies here and the present study. The Panesar and Agarwal study also used adults with CKD and Diabetes, which may affect REE values. The third study by Avesani et al ¹³³ found no relationship between measured REE (kcal/day) and kidney function. This study looked at REE according to different quartiles of creatinine clearance in adults with CKD.

Other differences are summarised in Table A5.8 (Appendix 3, p 252). All studies used adults with CKD with differing kidney function. The studies also differed in age and sex ratio. Looked at it in this way, results of all literature available make it impossible to draw any conclusions from which to compare our findings

5.4.3 Factors affecting BMR/REE in children with CKD

The reasons for the progressively lower BMR findings in the present study in children with more severe CKD are unclear. However, it may be explained in part by the fact that the kidney is known to account for 6% of REE¹³⁴ in healthy children. Since the majority of kidney energy consumption occurs in the kidney tubules and is involved in reabsorbing solutes from the glomerular filtrate, it is likely that, as kidney function decreases, so does kidney EE¹³⁵. To my knowledge, this has not been formally studied in children.

Inflammation^{133 136 137 138 139}, infection¹⁴⁰, and hyperparathyroidism^{137 141} may also affect REE. However, measures to assess inflammation and infection were not studied here, so the effect of these factors on this group of children is unknown. However, all children studied here had parathyroid hormones levels within national recommendations at the time of study, and none had significant infections within the previous 3 months.

5.4.4 Summary of BMR in children with CKD

1. This is the first UK study to compare the mBMR (kcal/day) of children with CKD and age matched control children. Those with CKD (mainly stage 3 disease) were not found to have a significantly different BMR than control children (before and after adjustment for age, sex, weight and height). However, there was a tendency for children with CKD to have lower BMR (measured or predicted) than control children.

2 This is also the first study to examine the relationship between BMR and kidney function (eGFR) in children with CKD. A significant relationship between the two variables was found, so that children with a lower eGFR had a lower BMR both before and after adjustment for weight and height Z scores and LBM.

3. The findings need careful consideration, since BMR alone does not necessarily reflect total energy requirements, which need to take into account PA, probably the most variable component of TEE. In addition, the need for extra energy in

malnourished growth retarded children who need repletion, or less energy in obese individuals who need to lose weight (or not gain it), should also be considered.

Chapters 6 and 7 explore energy requirements further by considering PAEE and TEE. Chapter 9 discusses the overall study findings in relation to children with CKD and considers the implications for clinical management of these children, including the effect of disease. However, before these are considered, the ability of IDEEA to estimate PA with the required level of accuracy for children needs to be explored under controlled conditions.

6. Physical activity under controlled conditions

6.1 Introduction

Previous chapters have considered the general characteristics of children with CKD, (Chapter 4), and the effect of kidney function on BMR (Chapter 5). In order to understand the energy requirements of children with CKD several further steps are required, which take into account the remaining components of energy requirements and balance (EE and EI). Before these components are explored, it is helpful to review the feasibility of the novel tool (IDEEA) that was used to measure PA. This was done by validity tests undertaken under controlled conditions to determine the ability of IDEEA to measure the type and duration of physical activities (see methodology below). The overall aim was to assess the feasibility of IDEEA to measure type and duration of PA, and the associated validity of measurements.

6.2 Methodology

The children with CKD (n=20) and control children (n=20), who were recruited according to procedures described in Chapter 3, wore the IDEEA for standardised activity tests at the start of the four day free-living conditions (i.e. at home) measurements as detailed below.

6.2.1 Measurement of PA by IDEEA

IDEEA was used to obtain quantitative estimates of PAEE. Five sensors were worn, one to the chest, one to each mid-thigh and one to the sole of each foot. Training and written instructions were given to both parents/carers and the child. Specific advice was given to enable replacement of the IDEEA after bathing or showering. The device records all body movement in three planes (vertical, lateral and anterior-posterior). The IDEEA was calibrated before testing under controlled conditions, which was continued during the four-day period of testing under free-living conditions.

6.2.2 Assessment under controlled conditions

The accuracy and reliability of the IDEEA for measuring type and duration of physical activities under controlled conditions was explored using timed activities such as walking, running and climbing stairs. Participants were asked to climb and descend stairs, walk and run a fixed distance and jump twenty times. Activities were recorded by count and stop watch, and compared to those recorded on the IDEEA.

6.3 Results

The agreement between time recorded by IDEEA and stop watch for activities spent in different sedentary positions was good (Table 6.1). These differences did not differ significantly from each other. In addition, the magnitude of the difference was not related to the mean of the two sets of measurements.

Table 6–1 Bland and Altman analysis (observed v. IDEEA recorded) for the time spent in different sedentary positions in children*

Sedentary position	Mean	Difference	p=
	observed & IDEEA (s)	IDEEA – observed (s)	
Sit (n=35)	60.37 ± 6.45	-0.41 ± 1.84	0.200
Quarter recline (n=34)	61.22 ± 5.41	-0.30 ± 2.97	0.564
Half recline (n=35)	61.25 ± 5.42	-0.61 ± 2.06	0.091
Three quarter recline (n=35)	61.26 ± 5.70	-0.60 ± 2.39	0.149
Lie (n=35)	62.40 ± 6.16	-0.56 ± 2.20	0.139

* Results are expressed as mean ± sd for all children (no significant difference between those with CKD and healthy children)***

The P values refer to the difference between IDEEA and observed values (paired t-test)

The agreement between the time and number of steps undertaken recorded by IDEEA and observed values in the under active conditions (specifically those associated with walking up and down stairs and jumping) are shown in Table 6.2. The results were inferior than sedentary activities. The mean sd of the difference related to the mean value, being greater for the former than the latter activities. There was a systematic bias between IDEEA recorded and observed values for time walking downstairs (p=0.042), number of steps walking upstairs (p=0.007) and number of jumps (p=<0.001). In the case of walking upstairs, the difference between the two methods was significantly related to the mean of the two methods (r=0.496, p=0.004). This was not the case for the other activities.

Table 6–2 Bland and Altman analysis (observed v. IDEEA recorded) for the time spent walking upstairs and downstairs and jumping and the associated number of steps and jumps undertaken by children*

Activity	Mean observed & IDEEA	Difference IDEEA – observed	p=
Time taken (s)			
Walking upstairs (n=35)	65.71 ± 11.17	0.72 ± 3.48	0.228
Walking downstairs (n=35)	63.36 ± 11.16	1.45 ± 4.05	0.042
Jumping (n=31)	9.74 ± 1.86	-0.74 ± 0.47	0.384
Number of steps (or IDEEA count)			
Walking upstairs (n=35)	109.66 ± 11.56	-5.90 ± 12.23	0.007
Walking downstairs (n=35)	114.2 ± 9.33	0.97 ± 8.41	0.499
Jumping (n=31)	22.08 ± 4.47	2.64 ± 3.05	<0.001

* Results are expressed as mean ± sd for all children (no significant difference between those with CKD and healthy children)***

The P values refer to the difference between IDEEA and observed values (paired t-test)

A stopwatch recorded the time spent walking up and downstairs, and jumping. The observed number of steps and jumps was also recorded

The agreement between the time spent and number of steps undertaken recorded by IDEEA and observed values in walking and running on flat surfaces is shown in Table 6.3. The results are comparable to those obtained during walking up and down stairs and when jumping. Table 6.3 also shows the distance travelled. There was again a systematic bias between the observed and IDEEA recorded time taken to walk ($p=0.037$) and number of steps ran ($p=0.026$). In the case of number of steps run, the difference between the two methods was related to the mean of the two methods ($r=-0.610$, $p<0.001$).

Table 6-3 Bland and Altman analysis (Observed v. IDEEA recorded) for the time taken, number of steps and distance walked and ran by children*

Activity	Mean observed & IDEEA	Difference IDEEA- observed	P
Time taken (s)			
Walk (n=35)	57.79 ± 9.51	0.89 ± 2.43	0.037
Run (n=35)	30.28 ± 23.95	0.99 ± 4.07	0.393
Number of steps / IDEEA count			
Walk (n=35)	112.09 ± 15.18	-2.99 ± 15.43	0.260
Run (n=33)	74.49 ± 20.35	-2.81 ± 6.92	0.026
Distance travelled (m)			
Walking a fixed distance† (n=35)	78.24 ± 4.55	-1.33 ± 9.09	0.394
Running a fixed distance† (n=33)	78.24 ± 4.55	6.37 ± 6.90	<0.001

* Results are expressed as mean ± sd

The P values refer to the difference between IDEEA and observed values (paired t-test)

A stopwatch recorded the time taken to walk or run.

The observed number of steps and the distance travelled were also recorded

† The distance walked or ran was 78.9m in all cases

In order to compare the extent to which different types of activities reflect the observed measurements (number of jumps or steps or time recorded by a stop watch for the duration of an activity), the results are also presented as percentage of observed values (Table 6.4). Those for jumping and walking upstairs (for number of jumps or steps) were inferior than for other types of activities.

Table 6–4 IDEEA as a percentage of observed values for time taken in different activities and for the number of steps and jumps undertaken for children*

Measurement	IDEA (% of observed) (n=35)	p
Time taken		
Jumping	99.16 ± 5.10 ¹	0.367
Walking upstairs	101.28 ± 5.32	0.166
Walking downstairs	102.34 ± 6.64	0.045
Number		
Jumping	112.86 ± 15.56	<0.001
Walking upstairs	94.79 ± 10.68	0.007
Walking downstairs	101.25 ± 7.73	0.344
Time taken		
Walking	101.53 ± 3.86	0.025
Running	101.98 ± 24.6	0.647
Number		
Walking	98.09 ± 11.88	0.347
Running	97.77 ± 7.82	0.111
Distance travelled †		
Walking	98.32 ± 11.53	0.394
Running	108.07 ± 8.85	<0.001

Results are expressed as mean ± sd.

Differences between IDEEA expressed as percentage of observed (stopwatch time observed number of steps or jumps) and values are indicated (one sample t test).

¹ = results in children were significantly lower than those in adults (IDEA 1 and IDEA 2).

None of the other results in children differed significantly from adults.

6.3.1 Summary of the performance of IDEEA under controlled conditions

The evaluation of IDEEA under controlled conditions suggested good overall performance in children, which could prove valuable for quantifying patterns of PA in free-living conditions, and is considered in the next section.

6.4 Discussion

This study has provided new information on the validity of the IDEEA in children. As far the author is aware, there is a paucity of data in children less than 13 years. A study by Zhang¹⁴² examined the validity of IDEEA by comparison with observations made by an assessor in a mixed population of subjects (age range 13–72 years), but the results of the children and adults were not reported separately. Another recent study examined the performance of the IDEEA in a mixed population of adults and children (age range 8–25 years)¹⁴³, but, again, the results of children and adults were not reported separately.

In this study, the validity of IDEEA was established using a stopwatch to measure the time taken to undertake standardised activities, the observed number of steps and jumps (which were compared with the number of IDEEA counts recorded during some activities), and the measured distance (using a steel tape measure) between two points on a flat surface which could also be compared with that recorded by the IDEEA. The study found that the IDEEA performed well for recording the duration of the activities and less well for the number of steps and jumps and distance travelled.

Since the main purpose of this work was to examine the suitability of the IDEEA for estimating TEE, the findings of this study need to be contextualised in relation to estimates of EE. It is appropriate to consider the accuracy of different activities under controlled conditions in this light. The errors in the time attributed to activities such as walking and running were small (<3%), and would have little effect on the calculation of EE during these activities. Although under controlled conditions the greatest errors were in jumping; under normal free-living conditions this activity is expected to make a tiny contribution to the TEE. However, in calculating EE, it is likely that the overall accuracy depends on propagation of errors, which in the case of walking may involve the number of counts, the distance travelled (i.e. that attributed to walking) and the time taken to travel this distance. However, it is unclear how the IDEEA software calculates energy expenditure (see Chapter 7), and whether it assigns different energy costs to the same activity undertaken at different speeds and/or whether the activity involves a different numbers of steps.

In this study the validity of the IDEEA in children with respect to the number of counts, distance travelled and number of steps or jumps, was not found to be significantly different between children older and younger than 13 and between boys and girls. This is encouraging since it is therefore possible to analyse the results of all the children together.

6.4.1 Related issues

Caution should be taken about extrapolating results obtained by this study under controlled conditions to free living conditions. For example, a potential problem associated with performance of the IDEEA in free-living conditions over longer periods of time is the possibility that electrodes may dislodge from their position as a results of sweating, which could be a particular problem in warm environments, or if the sensors lose their direct contact with skin. Nevertheless, no major problems were encountered that would preclude its use in free-living conditions.

Further work also needs to be undertaken to examine the potential misidentification of activities such as walking, running and jumping.

6.4.2 Summary

The evaluation of the IDEEA under controlled conditions suggests good overall performance in children. The IDEEA could prove to be a valuable tool for quantifying patterns of PA in free-living conditions, but this needs evaluation. The ability to measure TEE and PAEE in clinical practice for children with and without CKD is addressed in the next chapter.

7. Physical activity and energy expenditure under Free-living conditions

7.1 Introduction

Previous chapters have examined the effect of kidney function on BMR (chapter 5), and the feasibility of IDEEA to measure PA under controlled conditions (Chapter 6). To better understand the energy requirements of children with CKD it is necessary to examine the effect of kidney disease on PA and TEE in free-living conditions. In this chapter the validity of IDEEA and activity diaries (AD) in free-living conditions is examined. To be consistent with previous chapters and enable comparison with published information on PAEE and TEE, the situation in children with CKD will be explored by comparison with those healthy controls and also reference standards (EAR) used in routine clinical practice. In children with CKD, the relationship with kidney function will also be explored. The steps taken to achieve this are:

1. Obtain quantitative estimates of PA in free-living conditions.
2. Translate the raw data ascertained by the IDEEA, AD and BMR (measured or predicted) into TEE. In the case of IDEEA, raw data on activity are converted to TEE using an algorithm built into its software, which also relies on imputed information on weight, height and age. In the case of AD, this involves estimating TEE as multiples of BMR, and using measured or reference values for BMR to calculate TEE in kcal/day. In the case of BMR, this involves using reference PALs provided by the UK DRV's 1991⁴² (which was current clinical practice at the time of study).
3. In healthy children the results are validated against DLW. In children with chronic kidney disease, where DLW was not undertaken because of the effect of dialysis on the loss of isotopes in DLW studies, validity is uncertain, but nevertheless the effect of eGFR on TEE, PAEE and TEE measured by alternative methods is examined.

The aim of this chapter is to address each of these issues. In essence it aims to quantify EE in children with CKD, and to assess the validity and plausibility of IDEEA.

7.2 Methodology

The children with CKD (n=20) and control children (n=20), who were recruited according to procedures described in Chapter 3, completed AD and wore the IDDEA for four days in free-living conditions (i.e. at home) as detailed below.

7.2.1 Measurement of PA by AD

AD were used to obtain quantitative estimates of PAEE. They were used to estimate the type and duration of activity, recorded in 15 minute interval blocks of time per 24 hour period for four days, and were based on PAR activities described in the UK 1991 DRV's⁴² (PAR and BMR). Training and written instructions were given to both parents/carers and the child, and the time spend during the study visit was completed with the child and their family to provide practical demonstration. The diaries were collected and inspected for any gaps in information on the home visit, with clarification on type and quantity of activity as required. The information obtained on individual activities was then amalgamated to estimate PAL per 24 hour period. PAL values for each day of the four days were estimated and amalgamated to obtain a mean PAL value over the four day period of study (BMR x PAL).

7.2.2 Measurement of PA and TEE by IDEEA

IDEEA were also used to obtain quantitative estimates of PAEE according to the procedures described in chapter 6. The PA information obtained was then converted to TEE, using an algorithm built into the software, and imputed information on weight, height, age and fitness level. TEE values for each day of the four days were used to obtain a mean TEE value over the four day period of study. BMR (measured or predicted) could also be imputed into the software as needed.

7.2.3 Estimation of TEE

TEE was estimated by IDEEA (by four methods) and by the factorial method (FM), using AD or measured and predicted (Schofield^{42 47}) BMR (by three methods):

IDEAA methods

Method 1 made no alteration to the basic programme of IDEEA, which relies on weight, height, age and fitness level (Method 1_{IDEAA}).

Method 2 incorporated measured BMR (mBMR) in the programme at the IDEEA analysis stage (Method 2_{IDEAA}).

Method 3 incorporated BMR predicted by the Schofield equation⁴² (SchBMR) instead of measured BMR into the IDEEA analysis stage (Method 3_{IDEAA}).

Method 4 used the same information about the type and duration of activities generated by IDEEA and, instead of relying on the IDEEA programme to assign energy values to these activities, DRV PAR values (DRV 1991) were used to estimate TEE and PAL (Method 4_{IDEAA}).

Factorial methods

Method 5 used mBMR and PAR values obtained by AD to obtain calculated PAL and TEE (mBMR x PAL) (Method 5_{AD}).

Method 6 used mBMR and average (median) PAL for children and adolescents⁴² (Method 6_{mBMR}).

Method 7 used SchBMR⁴² and average (median) PAL for children and adolescents⁴² (Method 7_{SchBMR}).

7.2.4 Estimation of PAL and PAEE

To establish PAL and PAEE, both measured and predicted BMR were used. Measured BMR was used for Methods 2, 4, 5 and 6, and predicted BMR (Schofield equation⁴²) was used for Methods 3 and 7. For Method 1, BMR was established indirectly, making use of information provided by IDEEA. When different values of BMR were entered into IDEEA to generate TEE using the same activity results in the same subjects, it was found that there was a linear relationship between BMR and TEE. The BMR corresponding to TEE obtained by Method 1 was then used to calculate PAL by Method 1.

PAEE was calculated by using the following equation:

$$\text{PAEE} = 0.9 \times \text{TEE} - \text{BMR}$$

The value of 0.9TEE excludes the TEF which is generally considered to be about 10% of TEE ($\text{TEF} = 0.1 \times \text{TEE}$). In the above equation, BMR represented either measured (Methods 2_{IDEAA}, 4_{IDEAA}, 5_{AD}, and 6_{mBMR}), Schofield predicted equation (Methods 3_{IDEAA} and 7_{SchBMR}) or obtained from the above equation (Method 1_{IDEAA}).

TEE was also estimated by DLW in a subset of the healthy control children (thirteen) according to the procedures outlined in Chapter 3 and discussed in Chapter 2. DLW was used to validate TEE findings of IDEEA and AD.

7.2.5 Validity and plausibility

7.2.5.1 IDEEA

To obtain insights into validity and plausibility of IDEEA for accurately estimating TEE in free-living conditions, concurrent validity with DLW (procedures outlined in Chapter 3), a reference method for measuring TEE (a comparison that is justified in weight stable subjects) was undertaken in a subset of healthy controls. Bland and Altman analysis was then used to assess agreement between each IDEEA method and DLW. To obtain further insights into the validity of IDEEA, reality checks were made by using cut-off points to identify unusually high or low values of PAL, which might indicate inaccurate results. Further attempts to identify inaccurate results involved exploration of the relationship between BMR and TEE, PAEE or PAL in both children with CKD and healthy controls.

7.2.5.2 Activity diaries

Attempts to obtain insights into the validity and plausibility of results obtained by food diaries were made by comparing the results of this method to those obtained by a reference technique (DLW) in a subset of the same healthy children.

7.3 Results

7.3.1 TEE

7.3.1.1 Comparison of health and disease

This section first presents the effect of disease on TEE expressed in different ways: in kcal/day, as a proportion of EAR and as multiples of BMR (PAL).

7.3.1.1.1 TEE expressed in kcal/day

Table 7.1 summarizes the mean results of TEE (kcal/day) obtained using IDEEA (Methods 1–4; see footnote to Table) and alternative methods based on factorial methods, which may be used clinically (Methods 5–7). TEE did not differ significantly between children with CKD and healthy controls, except for Method 4 (IDEEA PAR). Children in the CKD group tended to have lower values for TEE (see Table 7.1) but these were not significantly different from the Control group, with the exception of Method 4 (mean difference 788 kcal/day; 788 p=0.003).

Table 7–1 TEE (kcal/day) in children by group

Method†	Both groups (n=36)	CKD group (n=18)	Control group (n=18)	p*
Method _{1IDEEA}	2427±463	2375±541	2478±379	0.513
Method _{2IDEEA}	2232±407	2165±464	2299±341	0.328
Method _{3IDEEA}	2205±441	2112±514	2298±344	0.210
Method _{4IDEEA}	2318±1333	1692±476	2945±1614	0.003
Method _{5AD}	2204±308	2157±265	2252±348	0.360
Method _{6mBMR}	1965±403	1943±501	1988±286	0.743
Method _{7SchBMR}	1993±423	1924±411	2062±435	0.333

* The P values refer to comparisons between the CKD and Control group.

Results are expressed as mean ± SD for unadjusted values and mean and standard error for adjusted values.

Adjustment for weight, height, age, gender and group

† Method_{1IDEEA}: IDEEA machine (no alteration to programme); Method_{2IDEEA}: IDEEA mBMR alteration; Method_{3IDEEA}: IDEEA Schofield BMR alteration; Method_{4IDEEA}: PAR value alteration; Method_{5AD}: activity diary method; Method_{6mBMR}: factorial method using mBMR and DRV PAL; Method_{7SchBMR}: factorial method using Schofield BMR and DRV PAL.

The distribution of TEE by method and health state (children with CKD and healthy controls) is shown in Figure 7.1. The distribution in results established by the IDEEA methods overlapped with each other, as well as those obtained by the factorial methods.

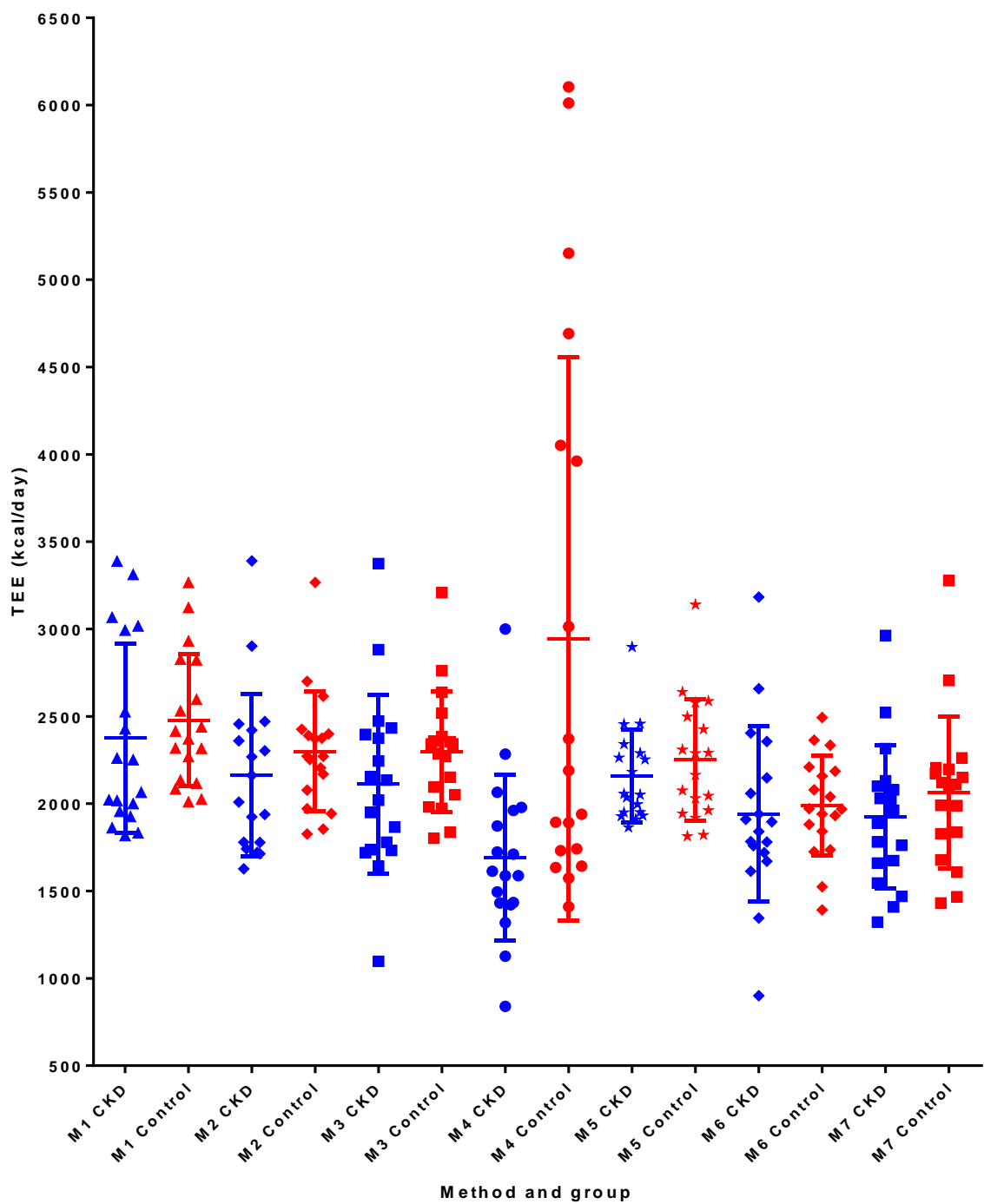


Figure 7-1 TEE distribution by method and subject group (blue= children with CKD ; red = healthy control children).

M1=Method_{1IDEA}; IDEEA machine (no alteration to programme); M2=Method_{2IDEA} IDEEA mBMR alteration; M3=Method_{3IDEA} IDEEA Schofield BMR alteration; M4=Method_{4IDEA} PAR value alteration; M5=Method_{5AD} activity diary method; M6=Method_{6mBMR} factorial method using mBMR and DRV PAL⁴²; M7= Method_{7SchBMR} factorial method using Schofield BMR and DRV PAL⁴².

The large horizontal lines indicate the mean value and the smaller horizontal lines the upper and lower limits of the 95% interval

7.3.1.1.2 TEE as a percentage of the EAR

The mean TEE as a percentage of EAR was consistently lower in the CKD group than the control group (Table 7.2) (by 4% –63%), but the differences were only significant for Method 4 (mean difference 63%; $p=0.003$) and Method 7 (mean difference 6%; $p=0.04$) (Table 7.2).

Table 7–2 TEE (kcal/day) as a percentage of EAR* in children by group

Method†	Both groups (n=36)	CKD group (n=18)	Control group (n=18)	p**
Method _{1IDEA}	120±21	117±25	122±18	0.490
Method _{2IDEA}	110±16	106±17	113±14	0.194
Method _{3IDEA}	107±17	102±19	113±13	0.056
Method _{4IDEA}	114±66	82±16	145±81	0.003
Method _{5AD}	110±24	108±23	113±26	0.563
Method _{6mBMR}	96±15	94±16	98±15	0.494
Method _{7SchBMR}	97±10	94±9	100±10	0.049

*EAR = Estimated average requirement

** The P values refer to comparisons between the CKD and Control group.

Results are expressed as mean ± SD for unadjusted values and mean and standard error for adjusted values. Adjustment for weight, height, age, gender and group

† Method_{1IDEA}: IDEEA machine (no alteration to programme); Method_{2IDEA}: IDEEA mBMR alteration; Method_{3IDEA}: IDEEA Schofield BMR alteration; Method_{4IDEA}: PAR value alteration; Method_{5AD}: activity diary method; Method_{6mBMR}: factorial method using mBMR and DRV PAL; Method_{7SchBMR}: factorial method using Schofield BMR and DRV PAL.

The distribution of TEE expressed as a percentage of EAR for both children with CKD and healthy controls is shown in Figure 7.2. Children with CKD have a wider spread of values for methods using IDEEA and AD compared to healthy controls, with the exception of Method 4. IDEEA (methods 1–4) also has a wider spread of values compared to factorial Methods 6 and 7.

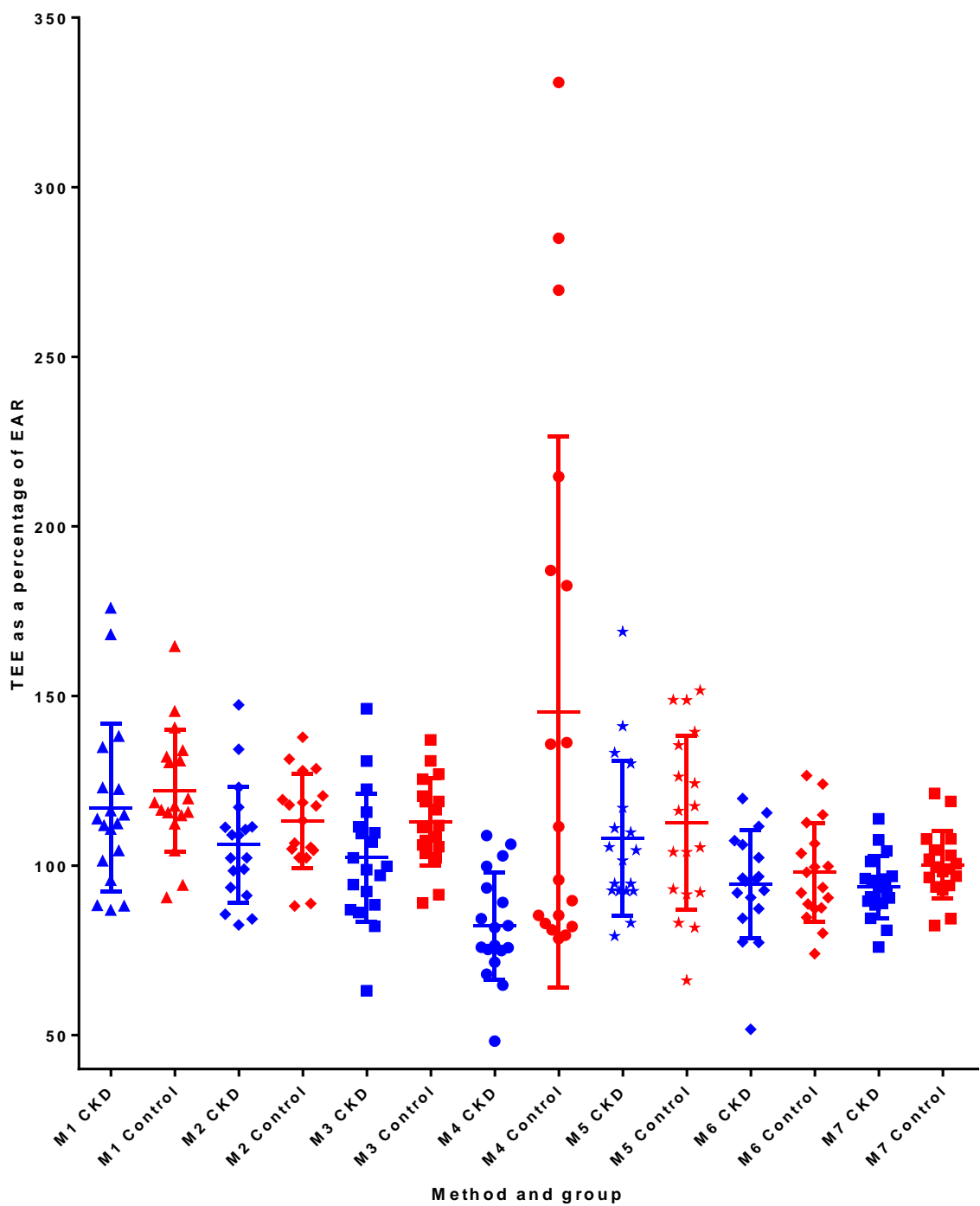


Figure 7-2 TEE distribution as a percentage of EAR by method and subject group (blue= children with CKD ; red = healthy control children).

EAR = estimated average requirement (DRV 1991)⁴²
M1=Method_{1IDEAA}: IDEEA machine (no alteration to programme); M2=Method_{2IDEAA} IDEEA mBMR alteration;
M3=Method_{3IDEAA} IDEEA Schofield BMR alteration; M4=Method_{4IDEAA} PAR value alteration; M5=Method_{5AD} activity diary method; M6=Method_{6mBMR} factorial method using mBMR and DRV PAL⁴²; M7= Method_{7SchBMR} factorial method using Schofield BMR and DRV PAL⁴².
The large horizontal lines indicate the mean value and the smaller horizontal lines the upper and lower limits of the 95% interval.
The vertical dotted lines indicate low and high clinical intervention cut off points (80% and 150% EAR).

7.3.1.1.3 TEE expressed as multiples of BMR (PAL)

PAL (TEE/BMR) values were not significantly different between children with CKD and healthy controls, with the exception of Method 4 (IDEEA PAR) (Table 7.3). Children with CKD tended to have lower values compared to controls for IDEEA methods (by 0.02 – 0.91 PAL). Method 5, however, (using AD) was higher (–0.05 PAL). The mean PAL in children with CKD and healthy controls using the factorial methods (Method 6 and Method 7) were identical because they used the same reference PAL to estimated TEE.

Table 7–3 PAL in children by group

Method†	Both groups (n=36)	CKD group (n=18)	Control group (n=18)	p*
Method _{1IDEEA}	1.38±0.36	1.26±0.35	1.51±0.34	0.038
Method _{2IDEEA}	1.77±0.39	1.76±0.46	1.78±0.30	0.875
Method _{3IDEEA}	1.70±0.28	1.68±0.34	1.72±0.22	0.711
Method _{4IDEEA}	1.77±0.90	1.32±0.10	2.23±1.11	0.001
Method _{5AD}	1.78±0.50	1.80±0.60	1.75±0.40	0.800
Method _{6mBMR}	1.52±0.40	1.52±0.41	1.52±0.41	1.000
Method _{7SchBMR}	1.52±0.40	1.52±0.41	1.52±0.41	1.000

* The P values refer to comparisons between the CKD and Control group.

Results are expressed as mean ± SD for unadjusted values and mean and standard error for adjusted values. Adjustment for weight, height, age, gender and group

† Method_{1IDEEA}: IDEEA machine (no alteration to programme); Method_{2IDEEA}: IDEEA mBMR alteration; Method_{3IDEEA}: IDEEA Schofield BMR alteration; Method_{4IDEEA}: PAR value alteration; Method_{5AD}: activity diary method; Method_{6mBMR}: factorial method using mBMR and DRV PAL; Method_{7SchBMR}: factorial method using Schofield BMR and DRV PAL.

The distribution of PAL between children with CKD and healthy controls is shown in Figure 7.3. Children with CKD had both the highest and lowest values and widest distribution with the exception of Method 4.

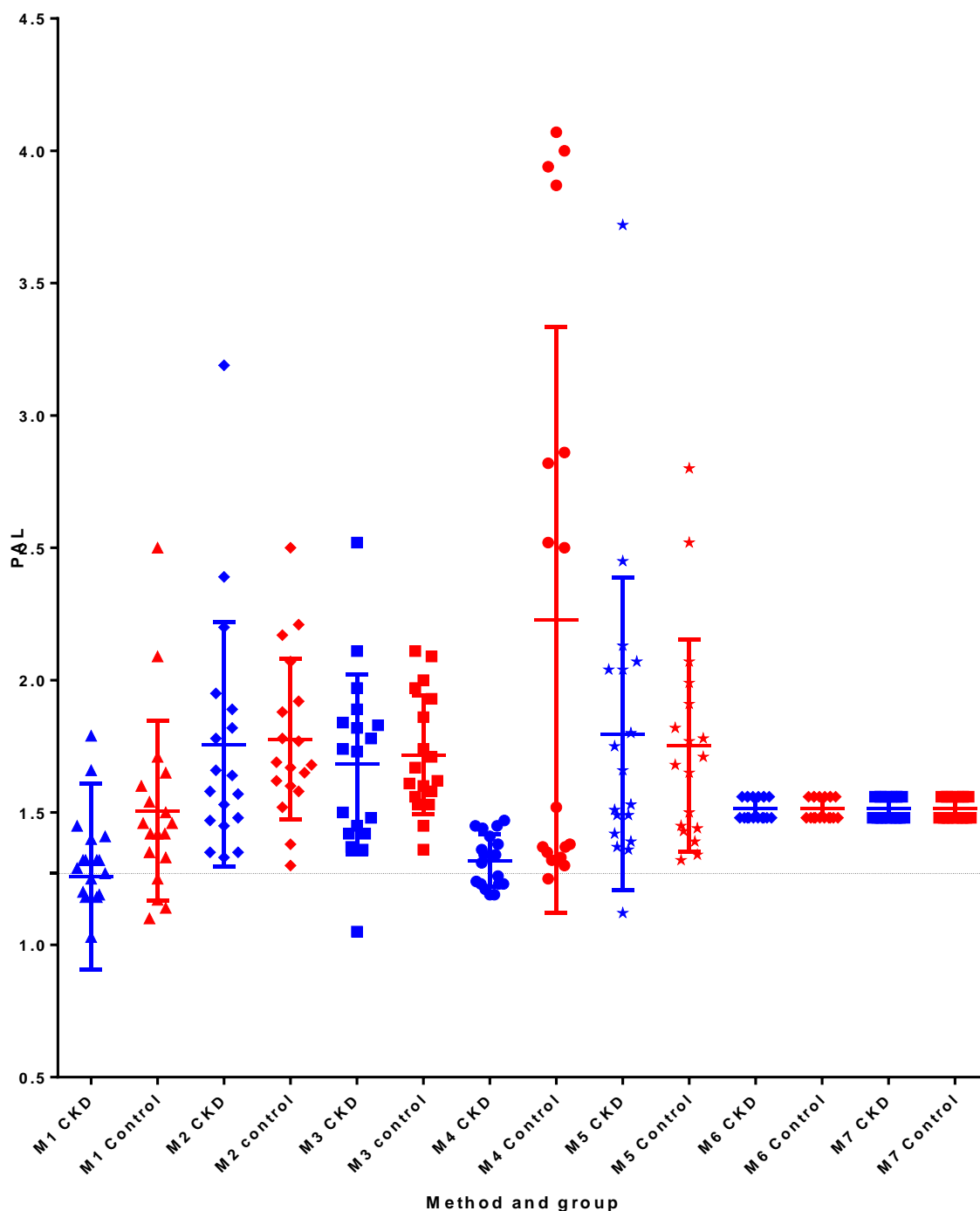


Figure 7-3 PAL distribution by method and subject group (blue= children with CKD ; red = healthy control children).

PAL = physical activity level (TEE expressed as a multiple of BMR (TEE/BMR)).

M1=Method_{1IDEA}: IDEEA machine (no alteration to programme); M2=Method_{2IDEA}: IDEEA mBMR alteration; M3=Method_{3IDEA}: IDEEA Schofield BMR alteration; M4=Method_{4IDEA}: PAR value alteration; M5=Method_{5AD}: activity diary method; M6=Method_{6mBMR}: factorial method using mBMR and DRV PAL⁴²; M7= Method_{7SchBMR}: factorial method using Schofield BMR and DRV PAL⁴².

The large horizontal lines indicate the mean value and the smaller horizontal lines the upper and lower limits of the 95% interval. The vertical dotted lines indicate WHO cut off point for health⁴².

7.3.1.2 The effect of kidney function on TEE

This section presents the effect of kidney function on TEE, expressed in kcal/day and as multiples of BMR (PAL).

Separate regression equations according to the method used to establish TEE show that, within the group of children with CKD, eGFR did not relate significantly to TEE expressed in kcal/day (Figure 7.4). There was a general tendency however, for TEE to decrease as kidney function deteriorated (tendency for TEE to increase with better kidney function).

When the procedure was repeated using TEE expressed as multiples of BMR (PAL), again there was no significant relationship between TEE (PAL) and the kidney function (Figure 7.5)

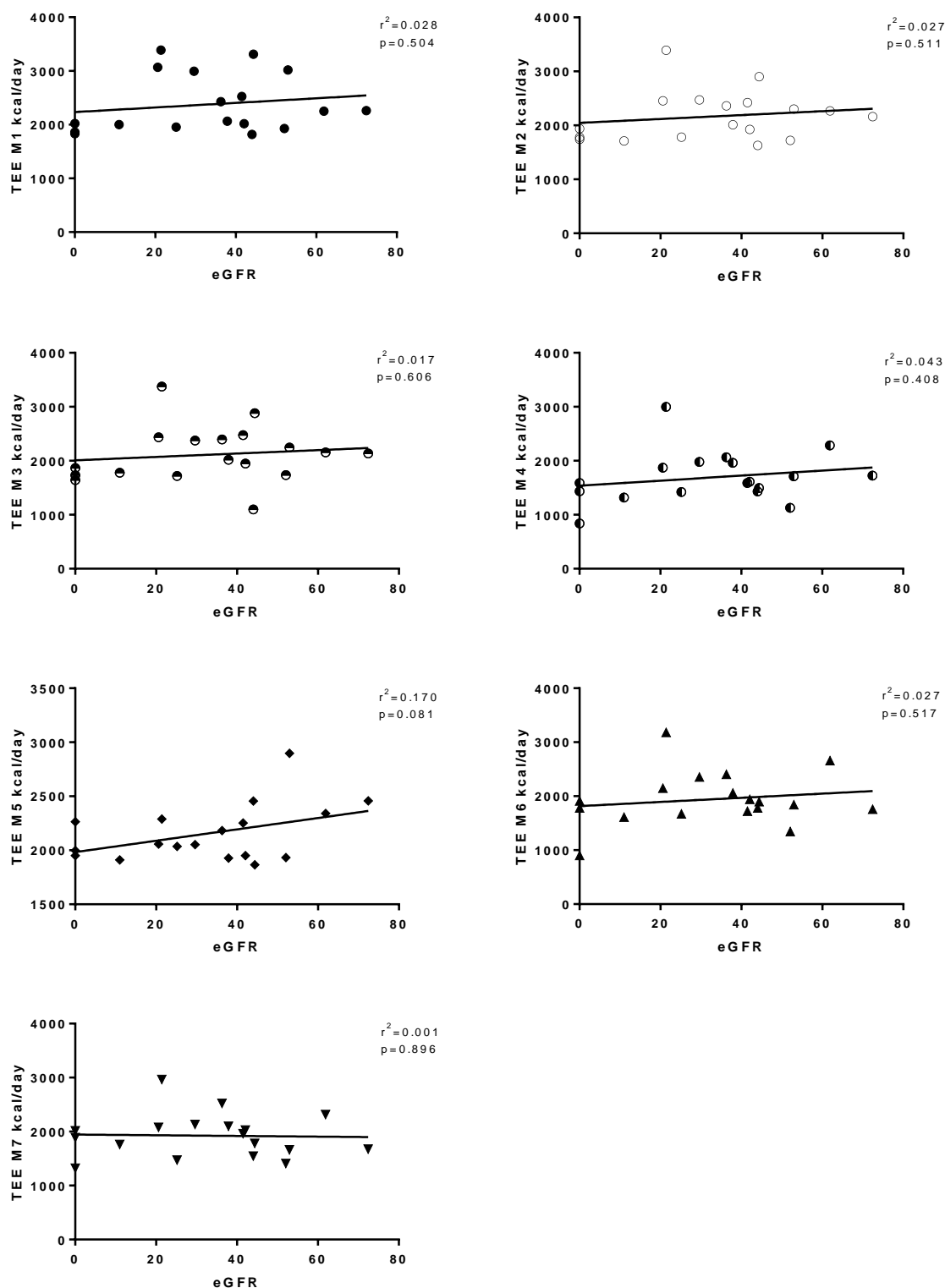


Figure 7-4 Relationship between TEE and eGFR by method.

M1=Method_{1IDEA}: IDEEA machine (no alteration to programme); M2=Method_{2IDEA}: IDEEA mBMR alteration;
 M3=Method_{3IDEA}: IDEEA Schofield BMR alteration; M4=Method_{4IDEA}: PAR value alteration; M5=Method_{5AD}: activity
 diary method; M6=Method_{6mBMR}: factorial method using mBMR and DRV PAL⁴²; M7=Method_{7SchBMR}: factorial method
 using Schofield BMR and DRV PAL⁴².

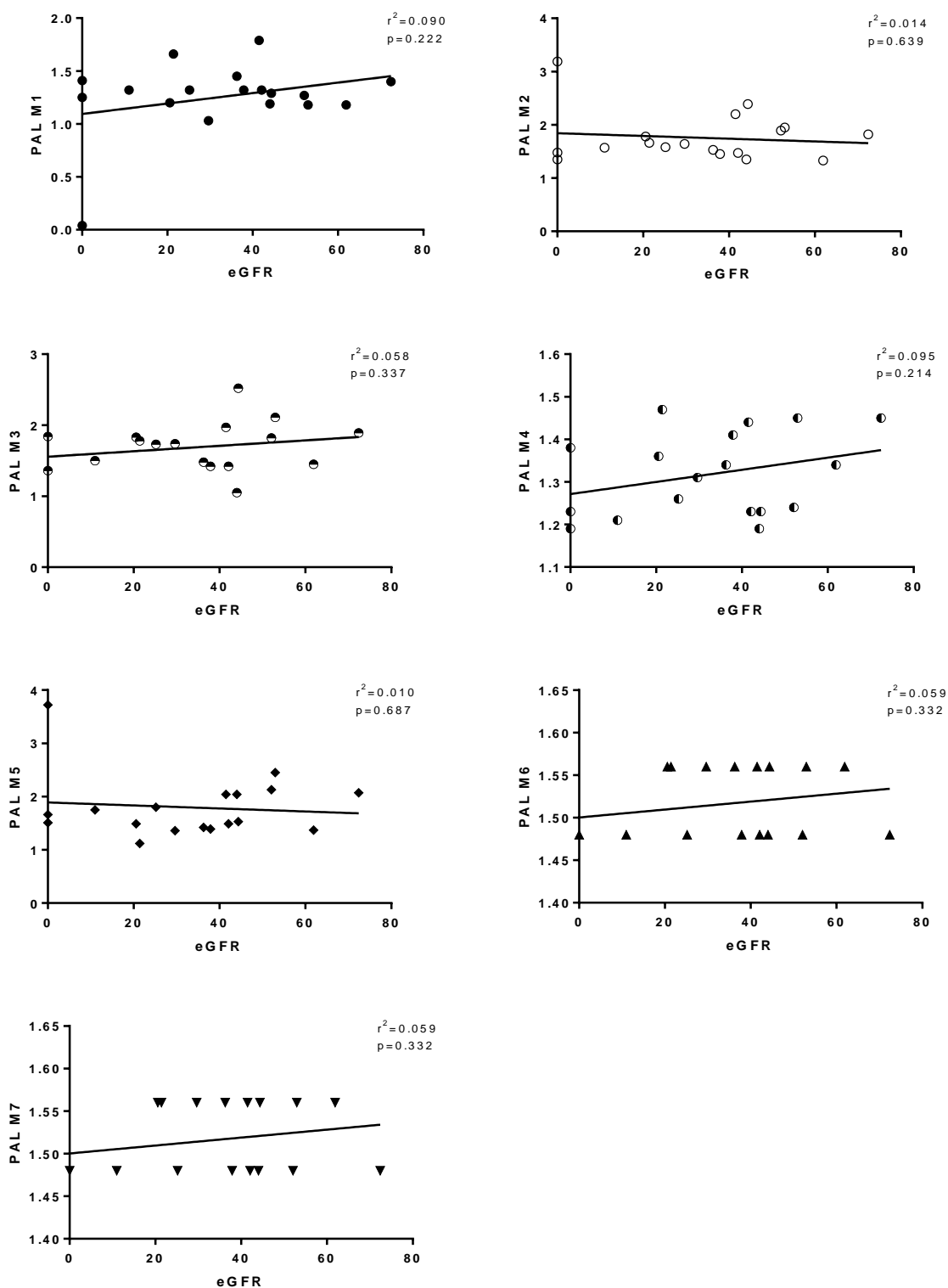


Figure 7-5 Relationship between PAL and eGFR.

M1=Method_{1IDEA}: IDEEA machine (no alteration to programme); M2=Method_{2IDEA}: IDEEA mBMR alteration; M3=Method_{3IDEA}: IDEEA Schofield BMR alteration; M4=Method_{4IDEA}: PAR value alteration; M5=Method_{5AD}: activity diary method; M6=Method_{6mBMR}: factorial method using mBMR and DRV PAL⁴²; M7=Method_{7SchBMR}: factorial method using Schofield BMR and DRV PAL⁴².

7.3.1.2.1 Summary of findings on TEE and PAL

7.3.1.2.1.1 Comparison in health and disease

Children with CKD were found to have lower values of TEE (kcal/day; %EAR; PAL) than healthy controls using all methods, with the exception of the activity diary (Method 5) which yielded higher results for PAL in the CKD group. None of the differences were significant, with the exception of IDEEA Method 4 which yielded lower results for TEE (kcal/day; %EAR; PAL). These findings are considered further in the subsequent section on plausibility.

7.3.1.2.1.2 Effect of kidney function

Within the CKD group, deteriorating kidney function determined by eGFR tended to decrease TEE (kcal/day), but this was not significant with any of the methods. The relationship between TEE expressed as a multiple of BMR (PAL) and eGFR was not significant with any of the methods.

7.3.2 PAEE

7.3.2.1 Comparison of health and disease

The mean results of PAEE obtained using IDEEA (Methods 1–4; see footnote to Table) and alternative methods based on factorial calculations (Methods 5–7), which may be used clinically, are shown below (Table 7.4). Although the mean PAEE was always higher in the control group compared to the CKD group, there was no significant difference between them, except for IDEEA Method 4 (DRV PAR alteration (see methodology for details), which is considered further under the plausibility section below. Children with CKD tended to have lower values compared to controls (mean difference 7–198 kcal/d), except for Method 5, which was higher (–27 kcal/d)

Table 7–4 PAEE (kcal/day) in children by group

Method†	Both groups (n=36)	CKD group (n=18)	Control group (n=18)	p*
Method _{1IDEA}	425±347	323±280	521±383	0.093
Method _{2IDEA}	715±321	671±329	759±316	0.417
Method _{3IDEA}	672±286	634±356	710±199	0.438
Method _{4IDEA}	792±1124	245±151	1340±1395	0.002
Method _{5AD}	716±368	690±369	663±378	0.672
Method _{6mBMR}	475±119	471±146	478±88	0.854
Method _{7SchBMR}	481±125	465±123	498±128	0.444

* The P values refer to comparisons between the CKD and Control group.

Results are expressed as mean ± SD for unadjusted values and mean and standard error for adjusted values.

Adjustment for weight, height, age, gender and group

† Method_{1IDEA}: IDEEA machine (no alteration to programme); Method_{2IDEA}: IDEEA mBMR alteration; Method_{3IDEA}: IDEEA Schofield BMR alteration; Method_{4IDEA}: PAR value alteration; Method_{5AD}: activity diary method; Method_{6mBMR}: factorial method using mBMR and DRV PAL; Method_{7SchBMR}: factorial method using Schofield BMR and DRV PAL.

The distribution of PAEE (kcal/d) by method between children with CKD and healthy controls is shown in Figure 7.6. Methods that used IDEEA (Methods 1–4) and AD (Method 5) had wider distributions compared to the other factorial methods (Methods 6 and 7), which was shown in both children with CKD and healthy controls.

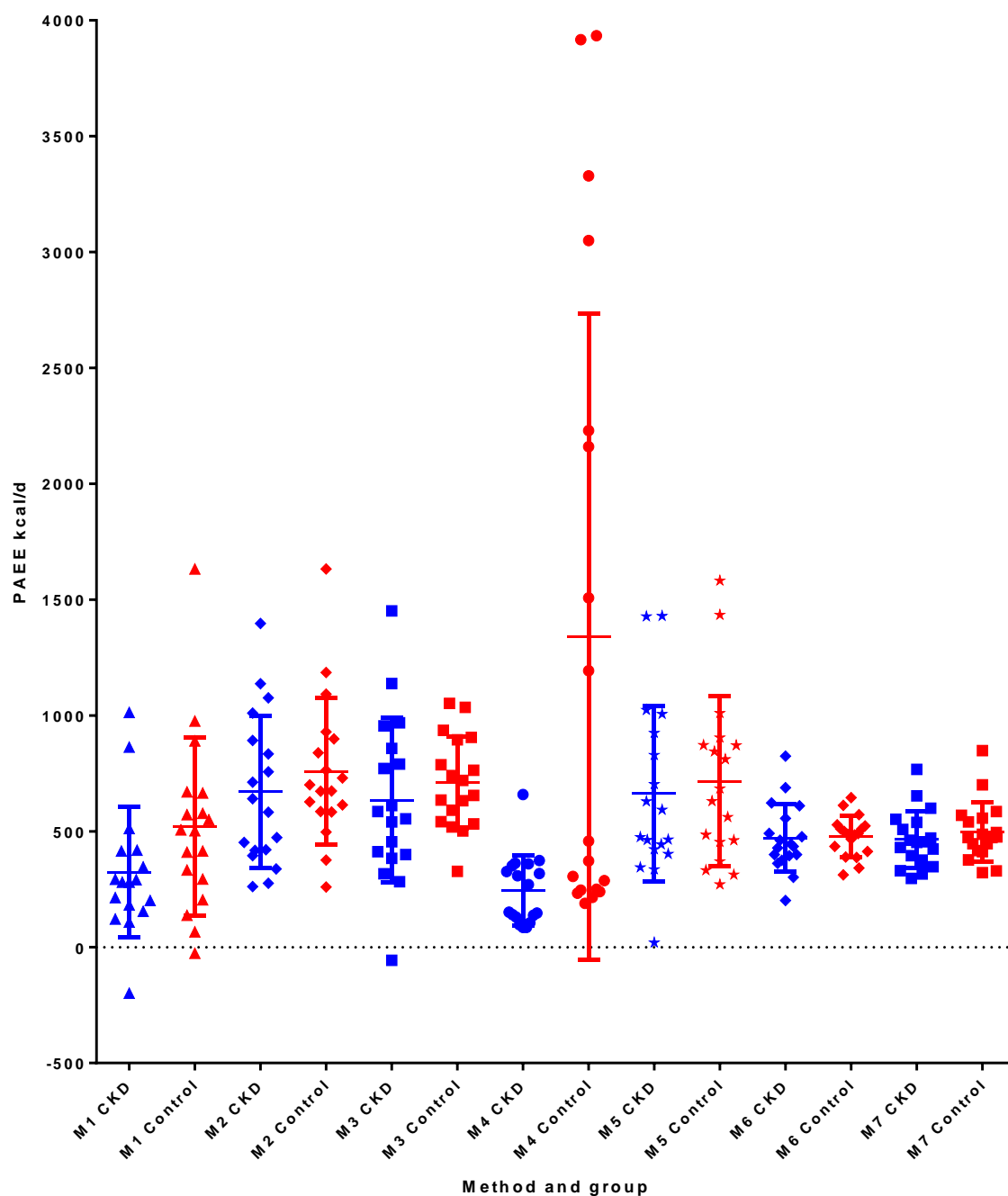


Figure 7-6 PAEE distributions by method and subject group (blue= children with CKD; red = healthy control children).

M1=Method_{1IDEAA}: IDEEA machine (no alteration to programme); M2=Method_{2IDEAA}: IDEEA mBMR alteration; M3=Method_{3IDEAA}: IDEEA Schofield BMR alteration; M4=Method_{4IDEAA}: PAR value alteration; M5=Method_{5AD}: activity diary method; M6=Method_{6mBMR}: factorial method using mBMR and DRV PAL⁴²; M7=Method_{7SchBM}: factorial method using Schofield BMR and DRV PAL⁴².

The large horizontal lines indicate the mean value and the smaller horizontal lines the upper and lower limits of the 95% interval.

PAEE as a percentage of TEE was not significantly different between children with CKD and healthy controls (although children with CKD tended to have lower value), with the exception of Method 4 (21% $p = <0.001$) (Table 7.5), and this is considered further in the plausibility section below. Using Methods 6 and 7, the results of the CKD and control groups were identical, as the same PAL was used to establish the contribution of PAEE to TEE.

Table 7-5 PAEE as a percentage of TEE* in children by group

Method†	Both groups (n=36)	CKD group (n=18)	Control group (n=18)	p**
Method _{1IDEAA}	-58±450	-136±636	21±13	0.576
Method _{2IDEAA}	31±11	30±12	32±9	0.301
Method _{3IDEAA}	30±10	29±12	31±12	0.494
Method _{4IDEAA}	24±19	14±6	35±22	0.000
Method _{5AD}	30±13	30±15	31±12	0.923
Method _{6mBMR}	24±2	24±2	24±2	1.000
Method _{7SchBMR}	24±2	24±2	24±2	1.000

*TEE = total energy expenditure

** The P values refer to comparisons between the CKD and Control group.

Results are expressed as mean ± SD for unadjusted values and mean and standard error for adjusted values. Adjustment for weight, height, age, gender and group

† Method_{1IDEAA}: IDEEA machine (no alteration to programme); Method_{2IDEAA}: IDEEA mBMR alteration; Method_{3IDEAA}: IDEEA Schofield BMR alteration; Method_{4IDEAA}: PAR value alteration; Method_{5AD}: activity diary method; Method_{6mBMR}: factorial method using mBMR and DRV PAL; Method_{7SchBMR}: factorial method using Schofield BMR and DRV PAL.

7.3.2.2 The effect of kidney function on PAEE

Separate regression equations according to method used to establish PAEE show that, within the group of children with CKD, eGFR did not significantly relate to PAEE expressed in kcal/day (Figure 7.7). There was a general tendency however, for PAEE to decrease as kidney function deteriorated (tendency for TEE to increase with better kidney function), with the exception of Method 1 (IDEAA machine) and Method 7 (factorial method using Schofield BMR and PAL).

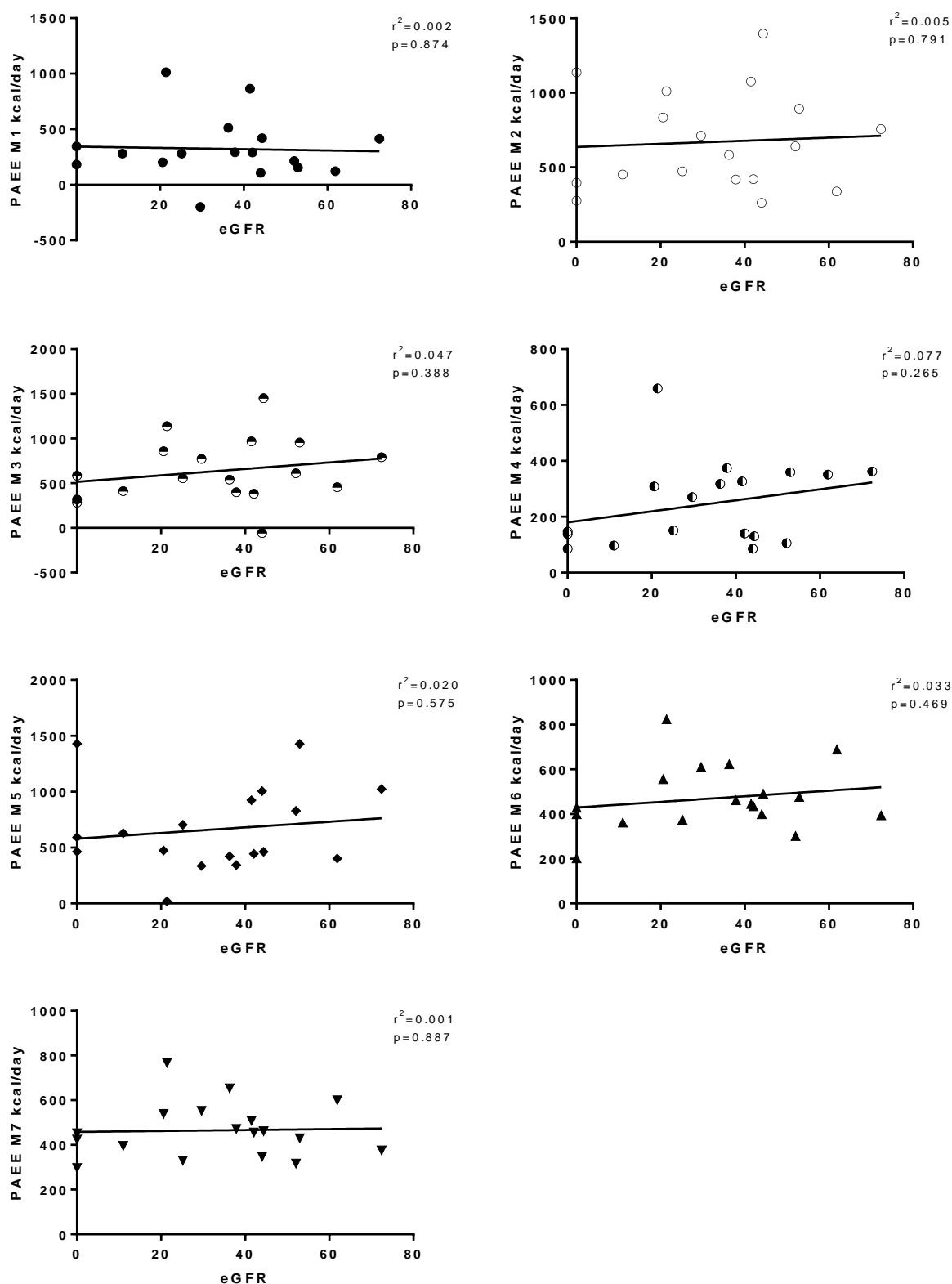


Figure 7-7 Relationship between PAEE and eGFR.

M1=Method_{1IDEA}: IDEEA machine (no alteration to programme); M2=Method_{2IDEA}: IDEEA mBMR alteration;
M3=Method_{3IDEA}: IDEEA Schofield BMR alteration; M4=Method_{4IDEA}: PAR value alteration; M5=Method_{5AD}: activity
diary method; M6=Method_{6mBMR}: factorial method using mBMR and DRV PAL⁴²; M7=Method_{7SchBMR}: factorial method
using Schofield BMR and DRV PAL⁴².

7.3.2.3 Summary of findings on PAEE

7.3.2.3.1 Comparison in health and disease

Children with CKD were found to have lower values of PAEE (kcal/day; and %TEE) using all methods. None of the differences were significant, with the exception of PAEE (kcal/day; and %TEE), using Method 4. These results are considered further in the subsequent section on plausibility.

7.3.2.3.2 Effect of kidney function

Within the CKD group, deteriorating kidney function determined by eGFR tended to decrease PAEE (kcal/day), but this was not significant with any of the methods.

These findings are considered further in the section 'Validity and plausibility of IDEEA for estimating TEE' which follows.

7.3.3 Validity and plausibility of IDEEA for estimating TEE

Comparison of TEE measured by IDEEA and DLW (DLW often regarded as the 'gold' standard) were made to help ascertain the validity of IDEEA to estimate TEE and PAL (Section 7.3.3.1). Comparisons were also made between AD and DLW to compare the merits of each method for use in clinical practice.

7.3.3.1 Concurrent validity between IDEEA and DLW in estimating TEE and PAL

The results of TEE measured by IDEEA and DLW in the same children (n=12) are shown in Table 7.6. TEE expressed in kcal/day, and PAL values were comparable for all methods, with the exception of Method 1 for estimating PAL. This was significantly different using paired t-tests that compared each IDEEA method to DLW ($p < 0.01$).

Table 7-6 TEE (kcal/d) and PAL measured by IDEEA* and DLW*

Method [†]	TEE* kcal/day (n=12)	PAL* (n=12)
Method _{1IDEA}	2405±357	1.47±0.27 ¹
Method _{2IDEA}	2222±289	1.78±0.27
Method _{3IDEA}	2215±299	1.80±0.23
Method _{4IDEA}	2400±144	1.88±0.42
DLW	2253±517	1.78±0.31

*TEE = Total energy expenditure; PAL= physical activity level; DLW = doubly labelled water; IDEEA = intelligent device for estimating energy requirements; mBMR = measured basal metabolic rate

[†]Method_{1IDEA}: IDEEA machine (no alteration to programme); Method_{2IDEA}: IDEEA mBMR alteration; Method_{3IDEA}: IDEEA Schofield BMR alteration; Method_{4IDEA}: PAR value alteration

Results are presented as mean ± sd

Paired t-test shows no significant difference between DLW and IDEEA Methods 1-4 with the exception of PAL and Method 1 ($p < 0.001$)¹

Although the mean values of TEE and PAL obtained by IDEEA and DLW were very close (Table 7.7), the overall agreement was judged to be poor, especially when the comparison involved IDEEA Methods 1 and 4 (Table 7.7). This is because of the wide confidence intervals for the difference (bias). There was a tendency for the difference (bias) to become more negative as TEE (mean of IDEEA and DLW) increased (Figures 7.8 & 7.9 Methods 2-4), but this was significant only for the comparison involving IDEEA Method 4. The bias was not significantly related to

gender, or age of the children, only two of whom were older than 13 years (Figures 7.8 & 7.9). The Bland and Altman plots are shown in Figures 7.8 & 7.9.

Table 7–7 Comparison of daily TEE (kcal per day) and PAL using IDEEA[†] and DLW[‡] in a sub-set of twelve healthy children

	Mean	Difference*	95% CI of the difference	r**	p***
TEE [†]					
Method 1 vs. DLW	2329±303	153±651	-1149 to 1455	-0.355	0.257
Method 2 vs. DLW	2237±339	-31±492	-1015 to 953	-0.552	0.062
Method 3 vs. DLW	2234±343	-38±492	-1022 to 946	-0.526	0.079
Method 4 vs. DLW	2327±623	148±1265	-2382 to 2672	0.661	0.019
PAL [‡]					
Method 1 vs. DLW	1.86±0.20	0.15±0.51	-0.89 to 1.19	0.099	0.758
Method 2 vs. DLW	1.78±0.22	0.00±0.39	-0.78 to 0.78	-0.163	0.613
Method 3 vs. DLW	1.79±0.19	0.01±0.39	-0.79 to 0.77	-0.292	0.356
Method 4 vs. DLW	1.85±0.45	0.13±1.01	-1.89 to 2.15	0.792	0.002

[†]TEE = Total energy expenditure; PAL=physical activity level; DLW = doubly labelled water; IDEEA = intelligent device for estimating energy requirements; mBMR = measured basal metabolic rate; CI=confidence interval
M1=Method_{1IDEA}; IDEEA machine (no alteration to programme); M2=Method_{2IDEA} IDEEA mBMR alteration;
M3=Method_{3IDEA} IDEEA Schofield BMR alteration; M4=Method_{4IDEA} PAR value alteration.

PAL = Method 1 divided by machine estimated BMR; Method 2 divided by measured BMR; Method 3 divided by Schofield BMR; Method 4 divided by measured BMR.

Results are presented as mean ± sd

* The difference (TEE by IDEEA – TEE by DLW) was not significant

** r is the correlation between the difference (IDEA – DLW) and the average of the two methods

*** p is the significance of this relationship (correlation)

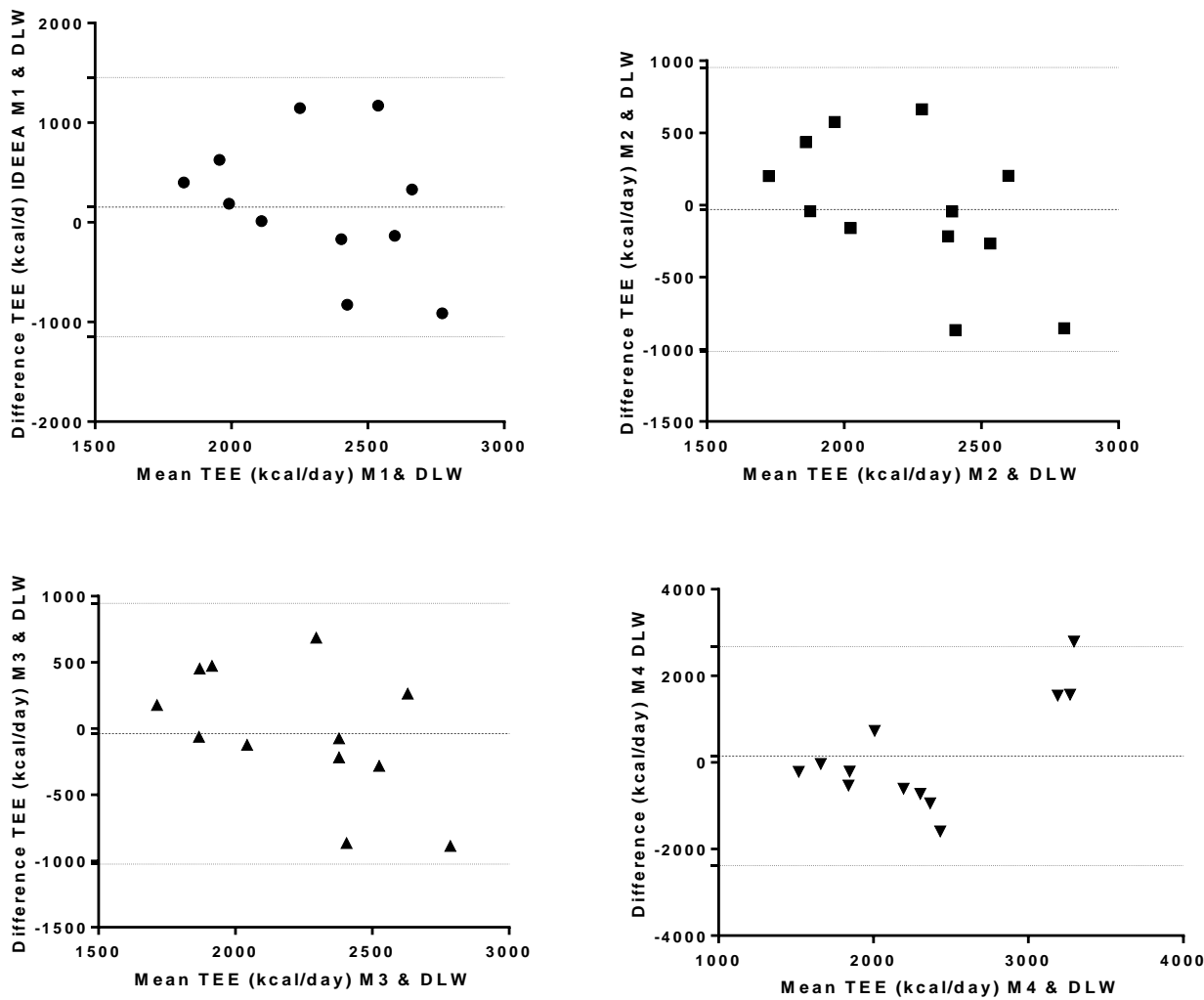


Figure 7–8 Bland and Altman plots for TEE (kcal/day) by IDEEA method and DLW

(upper left_{method1}, upper right_{method2}, lower left_{method3}, lower right_{method4})
TEE = total energy expenditure; DLW = doubly labelled water
M1=Method_{1IDEA}: IDEEA machine (no alteration to programme); M2=Method_{2IDEA} IDEEA mBMR alteration;
M3=Method_{3IDEA} IDEEA Schofield BMR alteration; M4=Method_{4IDEA} PAR value alteration.

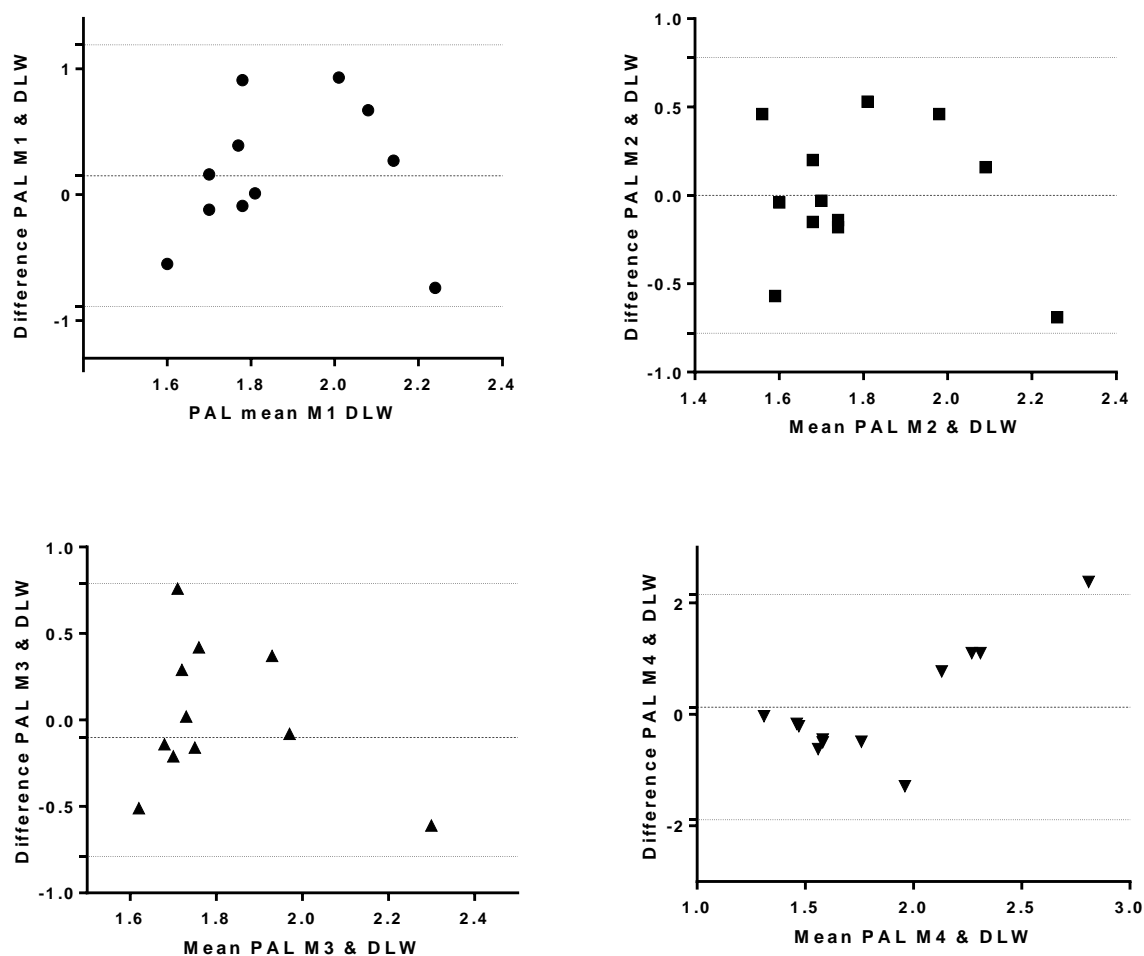


Figure 7–9 Bland and Altman plots for PAL by IDEEA method and DLW

(upper left ^{method1}, upper right ^{method2}, lower left ^{method3}, lower right ^{method4})

PAL=physical activity level (TEE as a multiple of BMR (TEE/BMR)); TEE = total energy expenditure; BMR = basal metabolic rate; DLW = doubly labeled water

M1=Method_{1IDEA}; IDEEA machine (no alteration to programme); M2=Method_{2IDEA} IDEEA mBMR alteration; M3=Method_{3IDEA} IDEEA Schofield BMR alteration; M4=Method_{4IDEA} PAR value alteration

7.3.3.2 Relative merits of IDEEA and AD using DLW as the reference

DLW was also used to establish the relative merits of IDEEA and AD.

The results of TEE measured by AD and DLW in the same children (n=12) are shown in Table 7.8. TEE (expressed in kcal/day) and PAL values were similar for both methods. Paired t-tests comparing AD and DLW showed no significant differences.

Table 7–8 TEE (kcal/d) and PAL* measured by AD and DLW

Method†	TEE* kcal/day (n=12)	PAL* (n=12)
Method _{5AD}	2327±383	1.89±0.42
DLW	2253±517	1.78±0.31

Results are presented as mean ± sd

Paired t-test shows no significant difference between DLW and AD

† Method_{5AD} = activity diary method

*PAL=physical activity level; TEE = Total energy expenditure; DLW = doubly labelled water; AD= activity diary.

7.3.3.2.1 Comparison of AD and IDEEA (with DLW as reference)

Before comparing the relative merits of AD and IDEEA to predict TEE and PAL measured by DLW, it is necessary to report on the extent to which the AD agrees with the measurements obtained by the DLW method. The results for TEE (Table 7.9; Figure 7.10 for Bland and Altman plot) and for PAL (Table 7.9; Figure 7.11 for Bland and Altman plot) indicate a generally poor agreement between the two methods. Although the mean differences between the two methods are not large (74kcal/day for TEE and 0.1 for PAL), the standard deviation of the difference (610 kcal/day and 0.5 respectively) and the 95% CI of the differences are large (–1146 to 1294 kcal/day; and –0.94 to 1.14 respectively).

Table 7–9 Comparison of TEE (kcal per day) and PAL using AD and DLW in subset of twelve healthy children

	Mean	Difference*	95% CI of the difference	r**	p***
<u>TEE</u>					
AD vs. DLW	2290±338	74±610	–1146 to 1294	–0.293	0.356
<u>PAL</u>					
AD vs. DLW	1.83±0.26	0.10±0.52	–0.94 to 1.14	0.288	0.365

Results are presented as mean ± sd. TEE by AD = method_{5AD}; PAL AD = method_{5AD}

* The difference (AD–DLW) was not significantly different from zero (p=0.683)

** r is the correlation between the difference (AD – DLW) and the average of the two methods (see Figure 20)

*** p is the significance of this relationship (correlation)

TEE = Total energy expenditure; DLW = doubly labelled water; AD = activity diary; PAL = physical activity level; DLW = doubly labelled water; IDEEA = intelligent device for estimating energy requirements; mBMR = measured basal metabolic rate; AD = activity diary

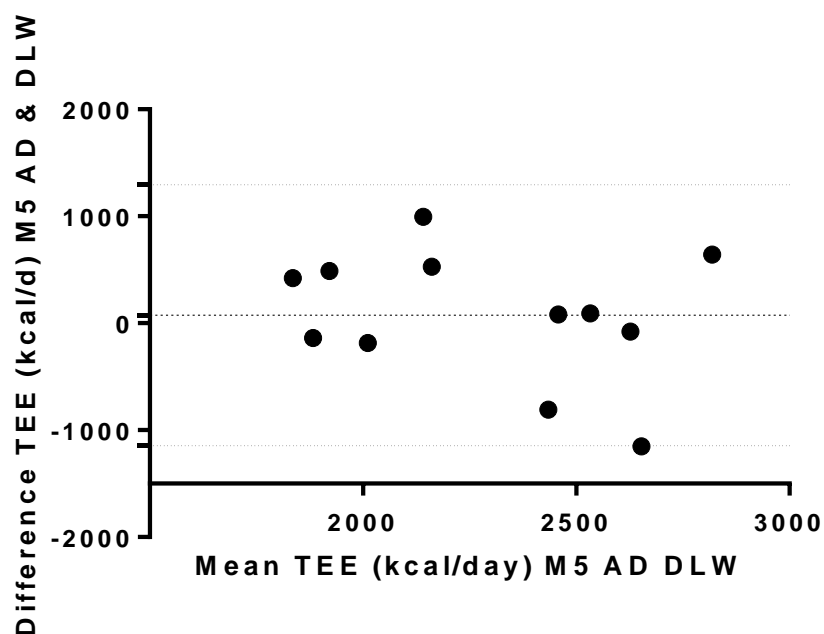


Figure 7-10 Bland and Altman plots of TEE (kcal/day) by AD and DLW

TEE = Total energy expenditure; DLW = doubly labelled water; AD = activity diary;
 TEE by AD = M5=Method_{5AD}

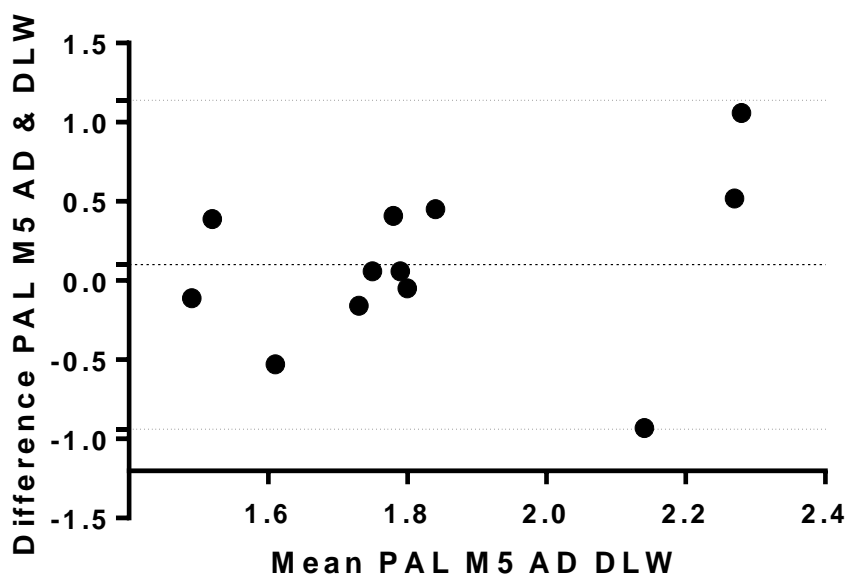


Figure 7-11 Bland and Altman plots of PAL by AD and DLW

PAL = physical activity level (TEE as a multiple of BMR (TEE/BMR));
 TEE = total energy expenditure; BMR = basal metabolic rate; DLW = doubly labelled water;
 AD = activity diary; TEE by AD = M5=Method_{5AD}

7.3.3.2.2 Relative merits of AD and DLW compared to IDEEA and DLW

To compare the relative merits of IDEEA and AD in predicting measurements of TEE and PAL measured by DLW, the difference between AD and DLW (Table 7.10 for TEE and Table 7.11 for PAL) was compared with the corresponding difference between IDEEA (4 methods) and DLW (Table 7.7 for TEE and Table 7.8 for PAL). The following observations can be made:–

1. Both were associated with small mean differences and wide standard deviations (and 95% CI ($\pm 2sd$)) of the differences.
2. For TEE, the mean difference between AD and DLW was within the range of differences obtained by the 4 IDEEA methods–DLW comparisons (it was less than two of the 4 IDEEA – DLW comparisons and greater than the other two). The same was applied to the standard deviation (and 95% CI) of the difference (Tables 7.7 and Table 7.10).
3. For PAL, the mean difference between AD and DLW was within the range of differences obtained by the 4 IDEEA methods and DLW (it was less than two of the 4 methods and greater than the other two methods). The standard deviation of the difference (and 95% CI) was smaller than one of the four IDEEA–DLW comparisons and larger than the other three (Table 7.8 and Table 7.11).

7.3.3.3 Summary of concurrent validity of IDEEA and DLW

In predicting results of TEE and PAL obtained from the DLW, both IDEEA and AD performed poorly. No clear overall advantage of the four IDEEA methods over the AD method could be identified, although Methods 2 and 3 (and also Method 1 in the case of PAL) appear to have performed better than the AD.

7.3.3.4 Plausibility considerations associated with the use of IDEEA in free living conditions

Unexpected and potentially implausible results were identified using four methods:–

- 1) a comparison between different IDEEA methods (Plausibility 1);
- 2) the use of high and low EAR and PAL cut off values (Plausibility 2);
- 3) the relationship between BMR and other indices of EE (TEE, PAEE and PAL) (Plausibility 3);
- 4) two case studies involving IDEEA measurements of EE (Plausibility 4). Each of these is considered in turn below.

7.3.3.4.1 Plausibility Consideration 1: Comparison between IDEEA methods

Bland and Altman comparisons of TEE and PAL obtained by four different IDEEA methods are shown in Table 7.10. Results obtained by Method 1 and Method 2 (using the same activity data) identified three important problems: there was a systematic bias between the methods (Method 1 giving higher results than Method 2 by an average of 194 kcal $P < 0.001$); the bias (difference between Method 1 and 2) became larger as TEE increased (mean of two methods) (Table 7.10 & Figure 7.12), although not significantly $p = 0.101$; and, most importantly, the 95% confidence interval for the difference between methods is substantial (828 kcal). Similar problems were identified when PAL was assessed using the same methods (Table 7.10, Figure 7.13).

Table 7–10 Comparison of TEE and PAL in all thirty–six children using the IDEEA programme

	Mean	Difference*	95% CI	r**	p***
TEE (kcal per day)					
M1 vs. M2	2329±423	194±207	–608 to 220	0.278	0.101
M1 vs. M3	2316±437	222±233	–244 to 688	0.097	0.574
M2 vs. M3	2219±421	27±113	–199 to 253	–0.304	0.071
M1 vs. M4	2373±742	–108±1335	–2778 to 2562	0.789	0.000
PAL					
M1 vs. M2	1.57 ±0.25	–0.39±0.56	0.73 to –1.59	–0.058	0.737
M1 vs. M3	1.54 ±0.23	–0.32±0.46	0.60 to –1.24	0.242	0.155
M2 vs. M3	1.73±0.30	0.07±0.30	0.67 to –0.53	0.372	0.026
M1 vs. M4	1.58±0.54	0.39±0.85	2.09 to –1.31	0.742	0.000

TEE = Total energy expenditure; PAL = physical activity level; IDEEA = intelligent device for estimating energy requirements; mBMR = measured basal metabolic rate.

Results are presented as mean ± sd.

M1=Method_{1IDEA}: IDEEA machine (no alteration to programme); M2=Method_{2IDEA}: IDEEA mBMR alteration; M3=Method_{3IDEA}: IDEEA Schofield BMR alteration; M4=Method_{4IDEA}: PAR value alteration
 PAL Method_{1IDEA} = Method_{1IDEA}/machine estimated BMR; PAL Method_{2IDEA} = Method_{2IDEA}/mBMR; PAL Method_{3IDEA} = Method_{3IDEA}/Schofield BMR; PAL Method_{4IDEA} = Method_{4IDEA}/mBMR.

* The difference (Method_{1IDEA} – Method_{2IDEA}; Method_{1IDEA} – Method_{3IDEA}; Method_{1IDEA} – Method_{3IDEA}; Method_{1IDEA} – Method_{4IDEA}) was significant (p<0.01)

** r is the correlation between the difference (Method_{1IDEA} – Method_{2IDEA}; Method_{1IDEA} – Method_{3IDEA}; Method_{2IDEA} – Method_{3IDEA}) and the average of each of the two methods

*** p is the significance of this relationship (correlation)

Results for Method 3 (Schofield equation entered at the point of analysis instead of measured BMR as in Method 2 and Method 4 (PAR values assigned to the same IDEEA activity data) were then used to further explore the performance of the IDEEA machine (Method 1) in estimating TEE and PAL (Table 7.12). The largest discrepancy was between Method 1 (machine TEE) and Method 4 (–108±1335), which seems implausible. A similar implausibility was noted when TEE (PAL) instead of TEE (kcal/day) was used in the comparisons (Table 7.12 and Figures 7.12 & 7.13).

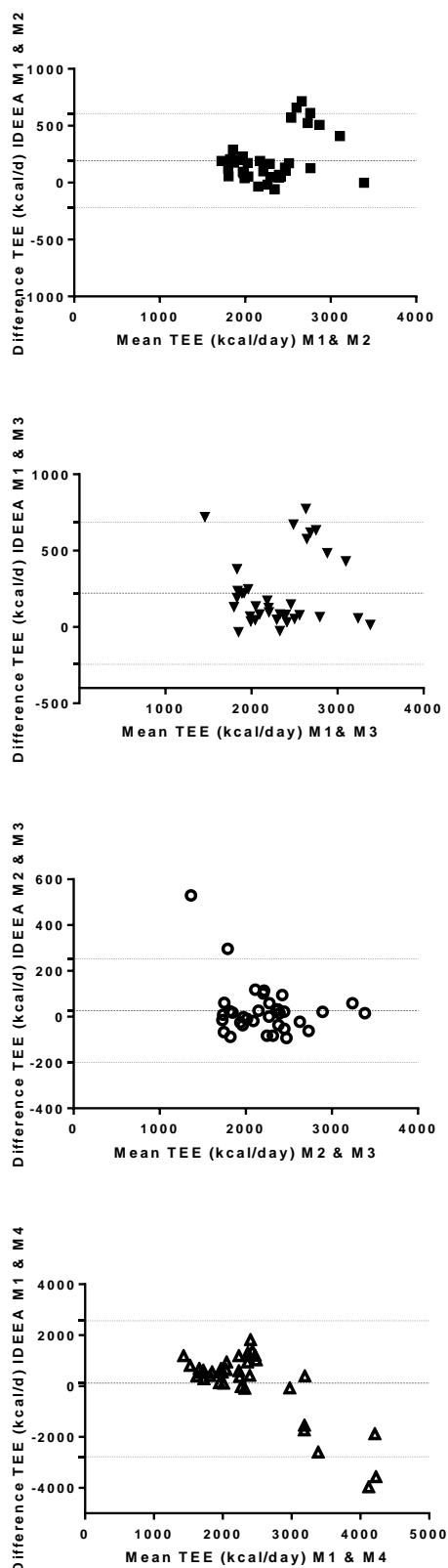
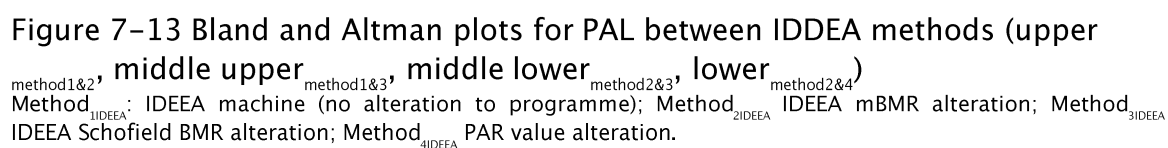


Figure 7-12 Bland and Altman plots for TEE (kcal/d) between IDEEA methods (upper ^{method1&2}, middle top ^{method1&3}, middle lower ^{method2&3}, lower ^{method2&4})

Method ^{1IDEEA}: IDEEA machine (no alteration to programme); Method ^{2IDEEA}: IDEEA mBMR alteration; Method ^{3IDEEA}: IDEEA Schofield BMR alteration; Method ^{4IDEEA}: PAR value alteration



7.3.3.4.2 Plausibility Consideration 2: Use of EAR and PAL cut off values

Close examination of results of TEE when expressed as a percentage of EAR and PAL by IDEEA showed some unusually high and low values (Table 7.14).

PAL values less than 1.27 are considered by the World Health Organisation (WHO)¹⁴⁴ to be incompatible with health. In our study, low values (PAL <1.27) varied according to the method used (Table 7.11). For Method 1, values less than 1.27 applied to 33% (6/18) of children for children with CKD and 22% (4/17) in the control group. In contrast, for Method 2 such unusual results were not encountered. For the other methods variable results were obtained. Unusually high PAL values (>2.0) and very high PAL values (>2.5) were observed with all methods, but the frequency varied with group and the method used. These ranged from 0% with Methods 1 and 4 for children with CKD, to 41% (7/17) with Method 4 for the control children.

In clinical practice, values of TEE that are >150% of EAR are generally considered to be unusually high. Such values were found with Methods 1 (involving CKD and control groups) and 4 (control group only) but not with Methods 2 and 3 (Table 7.11).

Table 7-11 Unusual values for IDEEA TEE and PAL according to different methods

Characteristic	CKD group (n=18)				Control group (n=18)			
	Method				Method			
	1	2	3	4	1	2	3	4
TEE (% EAR)								
<80%	0	0	1	8	0	0	0	2
<90%	3	3	5	14	0	2	1	8
>150%	2	0	0	0	1	0	0	4
PAL (TEE/BMR)								
< 1.0	0	0	0	0	0	0	0	0
<1.27	6	0	1	8	4	0	0	1
>2.0	0	3	2	0	2	4	3	8
>2.5	0	1	1	0	1	1	0	7
>3.0	0	1	0	0	0	0	0	4

Method 1 = IDEEA with no alteration (machine); Method 2 = IDEEA using measured BMR; Method 3 = IDEEA using Schofield BMR; Method 4 = IDEEA and PAR values (1991 DRV). EAR = estimated average requirement (1991 DRV).

Method_{1IDEA}: IDEEA machine (no alteration to programme); Method_{2IDEA}: IDEEA mBMR alteration; Method_{3IDEA}: IDEEA Schofield BMR alteration; Method_{4IDEA}: PAR value alteration; Method_{5AD}: activity diary method; Method_{6FM}: factorial method using mBMR and DRV PAL; Method_{7FM}: factorial method using Schofield BMR and DRV PAL.

7.3.3.4.3 Plausibility Consideration 3: The relationship between BMR and other indices of EE (TEE, PAEE and PAL)

Close examination of the relationship between BMR and other indices of energy expenditure (TEE (Figure 7.14), PAEE (Figure 7.15), or PAL (Figure 7.16)), obtained by different IDEEA methods, showed some unexpected findings. For Methods 1, 2 and 3, an increase in BMR was associated with an increase in TEE (as expected), but PAEE and PAL showed a profound and unexpected decrease (affecting both CKD and control group), which seems implausible. The relationship between BMR and TEE (or PAEE or PAL) in the CKD group did not differ significantly from that obtained in the control group (Fisher's transformation test for comparing two independent r 's).

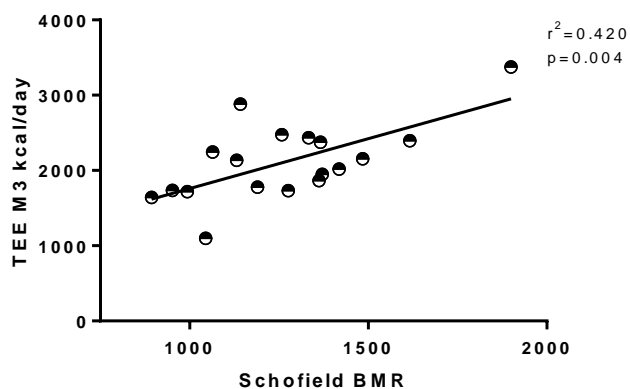
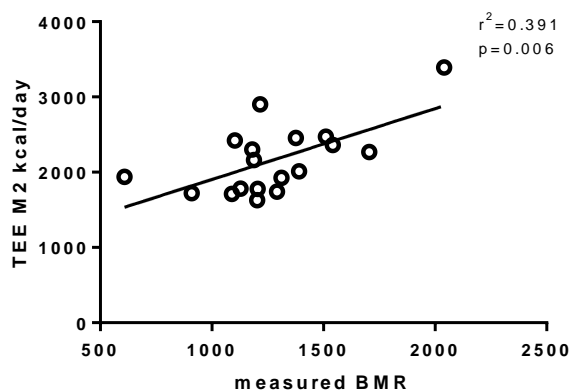
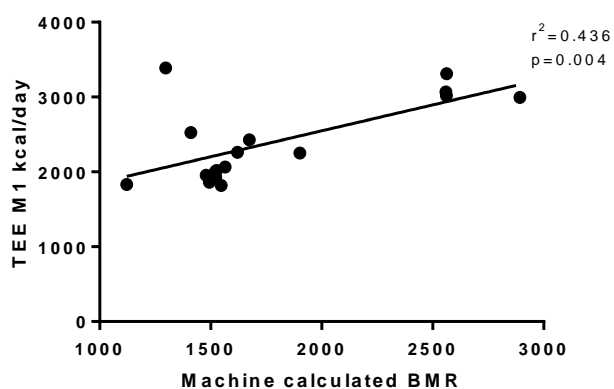


Figure 7-14 Relationship between TEE and BMR by IDEEA method

Using regression analysis.

Method_{1IDEA}: IDEEA machine (no alteration to programme); Method_{2IDEA}: IDEEA mBMR alteration;
Method_{3IDEA}: IDEEA Schofield BMR alteration.

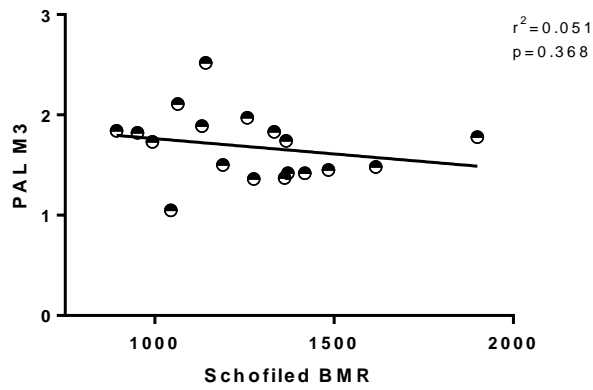
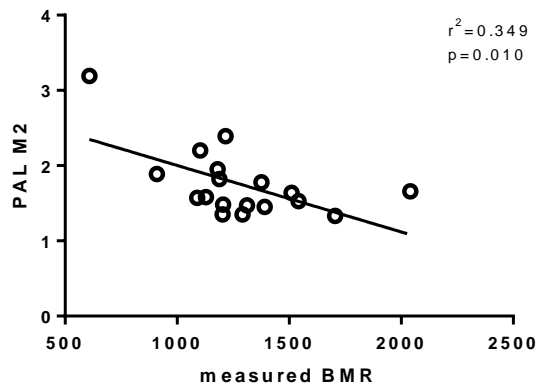
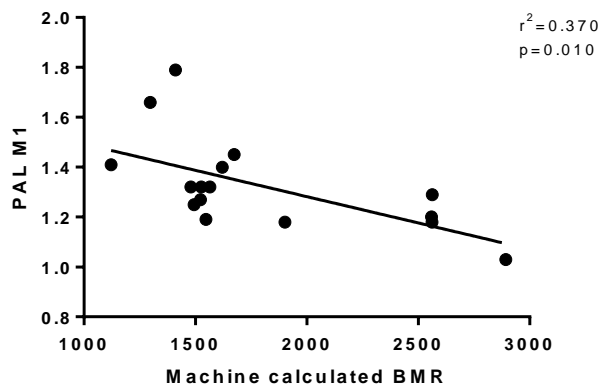


Figure 7-15 Relationship between PAL and BMR

Using regression analysis.

Method_{1IDEAA}: IDEEA machine (no alteration to programme); Method_{2IDEAA}: IDEEA mBMR alteration;
Method_{3IDEAA}: IDEEA Schofield BMR alteration.

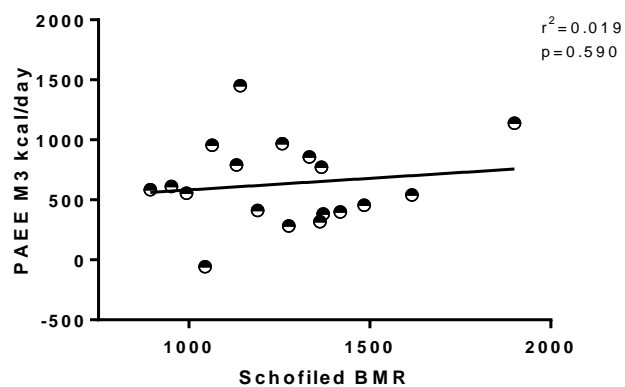
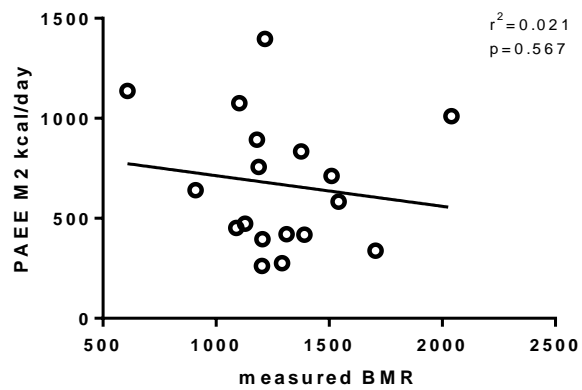
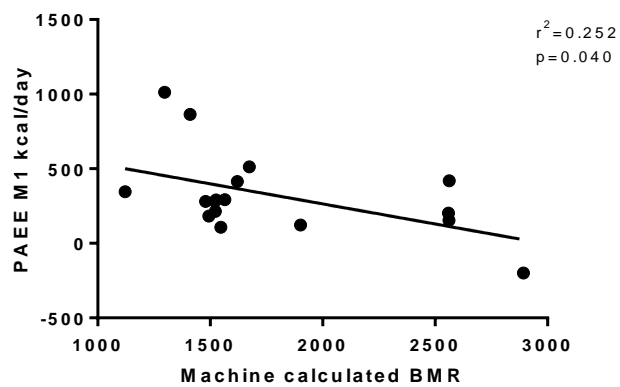


Figure 7-16 Relationship between PAEE and BMR

Using regression analysis.

Method_{1IDEAA}: IDEEA machine (no alteration to programme); Method_{2IDEAA}: IDEEA mBMR alteration;
Method_{3IDEAA}: IDEEA Schofield BMR alteration.

7.3.3.4.4 Plausibility Consideration 4: two case studies involving IDEEA measurements of EE

This relationship between BMR and TEE (or PAL) was further explored using two control case studies, one involving a boy and the other a girl. In the model used, different BMR values ranging from 80% to 120% were entered into the IDEEA machine (at the point of IDEEA analysis) so that different TEE results could be generated (Table 7.14). This BMR range is somewhat greater than would be expected for the subjects of the same age, weight, height and gender as the two case studies (Case 1 (42) = Male, aged 17 years, weight 133lbs (60.5kg), height 170cm, Case 2 (40) = Female, aged 15 years, weight 135lbs (61.4kg), height 155cm, BMI 25.6kg/m²). According to the Schofield database, the 95% confidence interval (mean \pm sd) would have a range of $\pm 15\%$ for the boy (85–115%) and $\pm 12\%$ for the girl (88–112%). In both of these cases, the analysis involved the same activity data. As expected, an increase in BMR was associated with an increase in TEE. However, this was also associated with a decrease in PAL and a decrease in PAEE, which was not expected (Table 7.12 & Figure 7.17). The variation induced in the girl was so large (almost 1 PAL unit, and an absolute value as high as 2.65)) that the plausibility of the results can be questioned.

Table 7–12 TEE and PAEE values obtained from entering multiples of measured BMR into the IDEEA data analysis programme.

Case study	% of measured BMR	BMR*	TEE*	PAL	PAEE*
1, Boy	80.00	1281.60	2196.50	1.71	695.25
	90.00	1438.56	2311.30	1.61	641.61
	100.00*	1598.40*	2426.00	1.52	585.00
	110.00	1758.24	2540.80	1.45	528.48
	120.00	1918.08	2655.60	1.38	471.96
2, Girl	80.00	990.72	2622.80	2.65	1369.80
	90.00	1114.56	2661.20	2.39	1280.52
	100.00*	1238.40*	2699.60	2.18	1191.24
	110.00	1362.24	2737.90	2.01	1101.87
	120.00	1486.08	2776.30	1.87	1012.59

BMR = basal metabolic rate; TEE = total energy expenditure; Wt = weight; Ht = height; *Units kcal per day
 Method 1= IDEEA using measured BMR; Method 2 = IDEEA with no alteration; Method 3 = IDEEA using Schofield BMR.

Case 1 = Boy, aged 17 years, weight 133lbs (60.5kg), height 170cm, BMI 20.9kg/m²

Case 2 = Girl, aged 15 years, weight 135lbs (61.4kg), height 155cm, BMI 25.6kg/m²

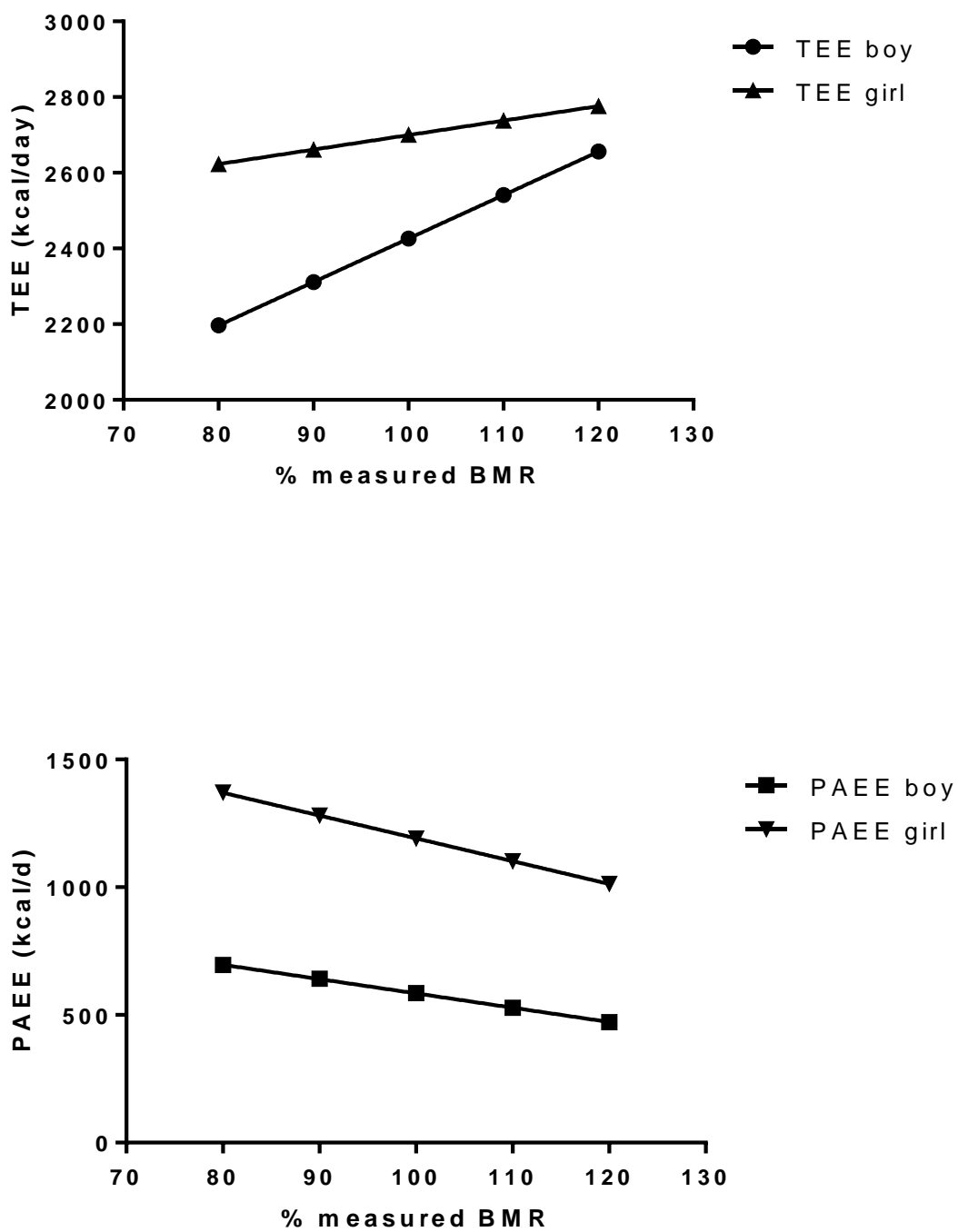


Figure 7-17 Relationship of TEE (left) and PAEE (right) to BMR using the two case studies

Another potential implausibility is suggested by comparing the BMR assigned to the children by the IDEEA during its routine use (Method 1, with no alteration in entries into the software programme) to other methods of BMR estimation. The BMR assigned to the children by the IDEEA was higher than that measured, as well as those predicted by the Schofield and Harris Benedict equations (Table 7.13). In the case of the healthy girl the value was surprisingly high (137% of measured BMR), which again seems rather implausible.

Table 7–13 Comparison of linear regression derived equation to calculated BMR with predictive equations

Case study	Method	BMR	% of mBMR
1 , Boy	Measured BMR	1598	100
	Harris Benedict	1636	102
	Schofield equation (wt)	1731	108
	BMR extracted from IDEEA	1834	113
2, Girl	Measured BMR	1238	100
	Harris Benedict	1459	118
	Schofield (wt)	1435	116
	BMR extracted from IDEEA	1654	137

Linear regression equation using TEE and BMR data above: Boy $(2579-1267)/0.726$; Girl $(2827-2336)/0.292$

7.3.4 Summary of the use of IDEEA in free living conditions

Comparisons of both IDEEA and AD with DLW correlated poorly, which was largely due to the wide confidence intervals. This could translate to a large error in estimation of TEE and PAL if either IDEEA or AD were used to estimate TEE or PAEE. Four different sets of observations indicated that IDEEA calculates unusually high or low values, with some unexpectedly high ranges for TEE and indices of energy expenditure. The plausibility of these results are explored in the discussion. The lack of confidence in IDEEA and AD to accurately estimate TEE was further supported by the number of individual values below cut off ranges of PAL and % EAR.

In view of these findings, the results on TEE, PAEE and PAL by IDEEA and AD cannot be used with any degree of confidence to help estimate the energy requirements of children with CKD.

7.4 Discussion TEE

7.4.1 TEE and PAEE

This is the first study to report measurements of TEE and PAEE in children with CKD. Since the DLW method could not be used to estimate TEE in children with CKD (due to the major water exchanges associated with dialysis that would invalidate the method), more indirect approaches were used. These were based on making use of IDEEA (Methods 1–4_{IDEEA}), which was found to be valid under controlled conditions, activity diaries (Method 5_{AD}), current methods used in clinical practice or research (e.g. the factorial method which involved the estimation of TEE as fixed PAL (1.57 for girls and 1.65 for girls⁴²) and measured BMR (Method 6_{mBMR}) or Schofield predicted BMR (Method 7_{SchBMR}) (see methodology above). However, with the exception of one method (Method 4_{IDEEA} which is suspiciously inaccurate for reasons given below) none of the methods showed significant differences in TEE or PAEE between children with CKD and control children, although all methods yielded results that were lower in children with CKD. Furthermore, no significant relationship was found between TEE and PAEE on the one hand and kidney function (eGFR) on the other hand within the CKD group, although several methods suggested a weak tendency for PAEE and TEE to be reduced as kidney function deteriorated. One interpretation of these findings is that CKD (stages 4–5), like many other chronic diseases, tends to reduce TEE as a result of reduced PAEE, but the effects are small and not significant. It might even be argued that the advice given by the treating physicians to children with CKD to increase their activity (on the basis that it might slow down the progression of kidney disease) could explain the lack of significant differences in TEE and PAEE between the groups. It is tempting to speculate that the results would be more marked in children with stage 5 CKD because they are generally more unwell and that the frequent dialysis sessions restricts the time for PA. However, only three of the studied children were undergoing dialysis, which makes it difficult to draw broad conclusions.

Another interpretation of the results is that they are very tentative, due to the poor validity of the methods used to estimate TEE and PAEE. The limitations of AD are well recognised (see Chapter 2) and therefore if another method such as IDEEA proved to be superior to the AD in both accuracy and precision, it would help establish with greater certainty the energy requirements of children with

CKD and other conditions. However, this was not found to be the case with IDEEA in the present study; therefore the major contribution of this work to the scientific literature relates the evaluation of the suitability of IDEEA for measuring TEE and PAEE in free-living conditions. This issue is considered next.

7.4.2 Validity and plausibility of IDEEA and AD under free-living conditions

IDEEA has been suggested to be an accurate tool to measure TEE and PAEE in adults and children⁶⁴, but supporting evidence in children in both controlled and free-living conditions was lacking. Therefore, this validation study was undertaken to address this issue. The study provided novel information about its validity under free-living conditions, which applied to children both older and younger than 13 years old. Unfortunately, the study has raised major concerns about its use in children for at least four reasons.

Firstly, when comparing IDEEA to the reference standard of DLW, (see Figures 7.8 & 7.9 for Bland and Altman analysis), it was clear that there was poor agreement between methods, suggested by wide confidence intervals for the differences. Secondly, despite the potential of IDEEA to act as a simple tool to accurately measure TEE, it was found to have little advantage over the standard factorial method based on activity diaries. Thirdly, there are concerns that IDEEA gives widely different results depending on whether measured or predicted BMR, (or only weight, height, age and gender) is included in the analysis. Lastly, IDEEA has produced some unusual and implausible results which were explored using a series of scenarios (see plausibility considerations in the results section above). For example, as weight and BMR increase, TEE and PAEE are also expected to increase because more energy is expended in weight bearing activities. In contrast, IDEEA suggests the opposite, and this is a cause of concern. Other implausibilities were: that 4/18 (22%) of children assessed using IDEEA Method 1 had a PAL of <1.27 , which (according to the WHO)⁴⁶ is incompatible with healthy living; there was poor agreement between the IDEEA methods; and that some unexpected results were found in TEE, PAEE and PAL when two case studies were further explored for within machine variability. Taken together, these observations suggest that IDEEA has important limitations which prevent it from being used as a reference standard.

The reasons for the poor agreement between IDEEA and DLW estimates of TEE is perhaps surprising, given that IDEEA was validated for the type and duration of physical activities undertaken under controlled conditions. A possible explanation is that the EE assigned to specific activities is inaccurate, despite taking into account the power and speed associated with these activities. Unfortunately, the manufacturer has not released the relevant information that would allow this issue to be assessed directly. Nevertheless, an attempt was made to examine whether standard energy costs associated with specific activities (those reported in the UK DRV report)⁴² would improve the IDEEA performance, when used in combination with the duration of activities recorded by IDEEA. However, the agreement between this procedure (Method 4_{IDEEA}) and DLW was worse than that between other IDEEA methods (Methods 1–3_{IDEEA}) and DLW.

Another possible explanation for the poor agreement between the standard IDEEA method (Method 1_{IDEEA}) and DLW, is that, despite adequate validation of IDEEA with respect to the type and duration of activities under controlled conditions, this may not reflect the situation under free-living conditions. Three examples are suggested below. Firstly, cycling may not be adequately assessed by IDEEA,¹⁴⁵ as it might be ascribed to other types of activities. Although cycling was not undertaken by most of the children it may have a significant effect on the energy expenditure of children who did cycle (children who cycled n=1). The lack of detection of arm movements is also a possible source of error, especially if strenuous upper body activity is undertaken. In addition, the transition time between different types of activities, such as running and walking, jumping, and the extent to which walking up the slope of a hill or a road might be interpreted as walking upstairs needs to be considered. There is also some uncertainty as to whether the energy cost of these activities differs substantially.

Secondly, during measurements over longer periods of time in free-living conditions there is the possibility that electrodes may dislodge from their position as a result of sweating, which could be a particular problem in warm environments, or if the sensors lose their direct contact with skin. Under these circumstances, energy expenditure could be underestimated, especially if the sensors became detached. This source of error would contribute to the

discrepancies between IDEEA and DLW. However, other factors may also operate which result in overestimation of energy expenditure by IDEEA. An overestimation is suggested by several of our results, especially those using Methods 1 and 4. A recent study in 14 adults who were studied in free-living conditions also suggested that IDEEA overestimated TEE measured by DLW¹⁴⁵.

Thirdly, the number of days IDEEA was worn and DLW was tested were not the same. For practical reasons associated with the difficulties in wearing the IDEEA device for 10 days in children, the measurement period by IDEEA (four days) was shorter than that by DLW (ten days). It was assumed that TEE over four days was representative of TEE over 10 days, but this is probably not correct.

An alternative explanation for the large discrepancies between IDEEA and DLW is that they are not entirely due to the IDEEA, which implies there is a need to consider the validity of DLW technique and its contribution to the discrepancy with the IDEEA measurements. Although DLW is generally regarded as the 'gold standard', a review of studies that compared DLW to indirect calorimetry¹⁴⁶ found a 10–20% difference in children. These studies were also all conducted under laboratory conditions and on not free-living individuals, and so it may be difficult to translate these results into real life situations, especially those associated with clinical practice. DLW also relies on certain assumptions. One of these is that the body's loss of water in breath is proportional to total water turnover (fractionation of samples error), which may not be entirely correct. Another assumption is that the energy equivalent of CO₂ is fixed (when in fact it varies according to the type of substrate being oxidised). Inaccuracies in these assumptions or failure to consider them contribute to the inaccuracies of the DLW method.

Fourthly, there are some other limitations associated with the study design. The overall number of children recruited was small, mainly because of the limited population sample size of children with CKD attending this regional kidney dialysis centre. In addition, the turnover of this population can be slow which made it difficult to recruit a sufficient number of subjects during the period allocated to data collection. Furthermore, DLW was used in a subset of control children only. It was not possible to use DLW in children on dialysis, which was the focus of the research, because the dialysate would have washed the labelled water out of the body. It was hoped that the IDEEA method would be validated

against DLW and then used in both groups of children with confidence; this however, did not prove to be the case.

Yet another possible limitation is that subjects may become self-conscious as a result of wearing the IDEEA equipment, especially the long wires that are attached to the sensors on the legs and feet. This may result in altered activity patterns that would be different from their habitual pattern.

Finally, although activity diaries are known to be problematic in estimating EE, this study demonstrated no advantage of using IDEEA over AD to predict measurements of TEE made by DLW. The use of PAR values as the basis of calculating TEE using AD have long been questioned,¹³ both in terms of a lack of comprehensive activities available and an inability to capture the variation of intensity and duration of any activity that can occur across all ages of children. In addition, reporter error could result in either under or overestimation of PAEE. However, since AD are simpler and less cumbersome to undertake than IDEEA monitoring, there is currently little scope for using IDEEA in children. Even if a wireless system was introduced to make the device more user-friendly, there would still be concerns about the validity of using IDEEA to estimate TEE in free living conditions.

7.4.3 Summary of EE and implications for future clinical practice

Despite the original hopes of using IDEEA to measure PAEE and TEE in free-living children with CKD, this study found that IDEEA has major limitations and cannot be used to adequately address the hypothesis raised in this thesis. Although differences between TEE in children with kidney failure and control children have been reported, the concerns about the accuracy of IDEEA and AD in free-living conditions makes it difficult to draw definitive conclusions from these findings. Under these circumstances, there remains no one simple tool to measure TEE for children with CKD. TEE should therefore continue to be estimated by other simple methods such as the factorial method or EAR.

Given that the TEE, PAEE and PAL using the factorial methods (Methods 6 and 7 based on measured or predicted (Schofield) BMR and fixed PAL values for each sex⁴²) was not significantly different from that of IDEEA and AD, a case can be made for considering the trends of these findings for TEE, PAEE and PAL by the factorial methods when estimating energy requirements in clinical practice. However, the study indicates a major need to develop an evidence base to guide clinical practice. This evidence needs to take into account not only the stage and severity of disease but also the variability associated with lifestyle. Until such time, the continued use of EAR as the basis of energy prescriptions for children with CKD in clinical practice is reasonable. However, it is clear that more accurate estimates of TEE and PAEE are needed to guide practice.

8. Energy intake

8.1 Introduction

Previous chapters have examined the effect of kidney function on BMR (Chapter 5) and EE (Chapters 6 & 7). Another approach is to measure EI over a period of time in weight stable, free-living subjects who are likely to be close to energy balance. Under these conditions, EI approximates to EE. Reflecting the energy requirements of children who do not need extra energy to enable catch up growth, or who have less energy to enable a more appropriate weight status to be established in obese individuals. As in previous chapters, the results in children with CKD will be related to kidney function and compared with healthy controls, and reference standards (EAR) used in routine clinical practice.

Therefore, the overall aim of this chapter is to explore the value of EI as a measure of energy requirements. In healthy children the results are validated against DLW. In children with CKD, where DLW was not undertaken because of the effect of dialysis on the loss of isotopes in dialysates, validity is uncertain (especially since TEE estimated by IDEEA was poorly related to DLW). Nevertheless the effect of eGFR and BMR on EI is examined.

8.2 Methodology

The children with CKD (n=20) and control children (n=20), who were recruited according to procedures described in Chapter 3, completed food diaries in free-living conditions (i.e. at home), as detailed below.

8.2.1 Measurement of EI

Food diaries used in routine clinical practice were used to obtain quantitative estimates of EI. All food and fluid consumed was recorded, and household measures were used to record amounts for four days. Training and written instructions were given to both parents/carers and the child, and the time spent during the study visit was completed together (parent, child and researcher) to further help understanding. The diaries were collected and inspected for any gaps in information on the home visit, with clarification on type, quantity and cooking method as required. The information obtained by food diaries was then used to estimate dietary EI by analysis and synthesis using a computer package (Netwisp, Tuvinel software¹⁴⁷ version 3). Energy intakes for each day were estimated and the mean calculated. EI was classified into two categories: total dietary energy intake (TDEI) and food energy intake (FEI). $TDEI = FEI + \text{nutritional supplements (tube feeds } \pm \text{ oral nutritional supplements)}$ and $FEI = FEI \text{ alone (without supplementation)}$.

8.2.2 Assessment of weight stability

As described in Chapter 4, children with CKD participating in this study had weight checks during the clinical review or the closest one after the study (ideally within three months), to assess weight stability. The healthy controls were assumed to be weight stable as they had normal weight status, had not reported any weight loss, and were not suffering any disabilities or disease at the time of study.

8.3 Results

8.3.1 Comparison of health and disease

Table 8.1 also shows that TDEI in kcal/day did not differ significantly between the children with CKD and healthy controls, even when boys and girls were considered separately. Children with CKD showed a tendency towards greater energy intake values (1784 ± 536 (CKD) vs. 1668 ± 377 (control) kcal/d). Using multivariate analysis, children with CKD showed a tendency towards higher TDEI values compared to healthy children, after controlling for weight (kg), height (m) and age (years) (1768 ± 113 vs. 1709 ± 113 kcal/d respectively), but these were again non-significant .

Table 8–1 TDEI (kcal/day) in children before and after adjustment for weight, height, age, gender and group

Characteristics	Both groups (n=36)	CKD group (n=18)	Control group (n=18)	p*
Unadjusted				
Both boys & girls	1726 ± 461	1784 ± 536	1668 ± 377	0.456
Boys	1864 ± 465	1911 ± 579	1818 ± 350	0.704
Girls	1615 ± 437	1683 ± 507	1547 ± 370	0.503
Adjusted**				
Both boys & girls	1739 ± 77	1768 ± 113	1709 ± 113	0.884
Boys	1853 ± 115	1895 ± 163	1811 ± 163	0.362
Girls	1642 ± 103	1641 ± 154	1607 ± 153	0.365

* The P values refer to comparisons between the CKD and Control group

Results are expressed as mean \pm SD for unadjusted values and mean and standard error for adjusted values.

**Adjustment for weight, height, age, gender and group

Boys n= 8 (CKD) & 8 (control), girls n= 10 (CKD) & 10 (control).

TDEI = total dietary energy intake (without nutritional supplementation).

Table 8.2 shows that FEI in kcal/day did not differ significantly between children with CKD and healthy controls, even when boys and girls were considered separately. Children with CKD tended to have generally lower energy intake values compared to healthy controls (1469 ± 565 vs. 1668 ± 377 kcal/d). When multivariate analysis was used to examine the association between FEI and weight (kg), height (m) and age (years), the opposite non-significant trends to TDEI were shown (1447 ± 115 vs. 1724 ± 115 kcal/d respectively).

Table 8–2 FEI (kcal/day) in children before and after adjustment for weight, height, age, gender and group

Characteristics	Both groups (n=36)	CKD group (n=18)	Control group (n=18)	p*
Unadjusted				
Both boys & girls	1568 ± 484	1469 ± 565	1668 ± 377	0.224
Boys	1748 ± 376	1679 ± 411	1818 ± 350	0.481
Girls	1424 ± 520	1301 ± 633	1547 ± 370	0.303
Adjusted**				
Both boys & girls	1585 ± 78	1447 ± 115	1724 ± 115	0.109
Boys	1738 ± 117	1655 ± 116	1823 ± 166	0.389
Girls	1433 ± 105	1240 ± 157	1625 ± 156	0.389

* The P values refer to comparisons between the CKD and Control group.

Results are expressed as mean ± SD for unadjusted values and mean and standard error for adjusted values.

**Adjustment for weight, height, age, gender and group

Boys n= 8 (CKD) & 8 (control), girls n= 10 (CKD) & 10 (control).

FEI = food energy intake (without nutritional supplementation).

8.3.2 Comparison to UK DRV EAR for energy

Table 8.3 shows that both TDEI and FEI as a percentage of EAR for energy⁴² did not differ between children with CKD and healthy controls, even when boys and girls were considered separately. Children with CKD tended to have higher TDEI values (88±22 vs. 82±20 %EAR respectively) than healthy controls, which is the opposite finding to FEI (72±27 vs. 82±20 %EAR respectively). Values for FEI for children with CKD were also all below the 80% cut off that is used clinically as a general guide for starting nutritional supplementation.

A one-sample t test (two tailed) showed that TDEI differed significantly from 100% of EAR for both the children with CKD (88±22, p=0.002) and control groups (82±20, p=0.002); however, when gender was considered separately, the children in the CKD group did not differ from 100% EAR. FEI showed the same significant differences from 100% EAR for all values. I (72±27%, p=<0.001; 82±20%, p=0.002 respectively), and even when boys and girls were considered separately.

Table 8–3 EI in children expressed as a percentage of EAR according to DRV⁴² by group

Characteristics	Both groups (n=36)	CKD group (n=18)	Control group (n=18)	p*
FEI (%)				
Both boys & girls	77 ± 24 ¹	72 ± 27 ¹	82 ± 20 ²	0.211
Boys	79 ± 20 ²	76 ± 23 ³	82 ± 18 ³	0.610
Girls	76 ± 27 ²	69 ± 31 ³	83 ± 22 ³	0.265
TDEI (%)				
Both boys & girls	85 ± 21 ¹	88 ± 22 ³	82 ± 20 ²	0.468
Boys	84 ± 21 ²	86 ± 25	83 ± 18 ³	0.695
Girls	86 ± 21 ²	89 ± 21	83 ± 22 ³	0.556

* The P values refer to comparisons between the CKD and Control group.

Results are expressed as mean ± SD for unadjusted values and mean and standard error for adjusted values.

Adjustment for weight, height, age, gender and group

One-way student t-test p=<0.001¹; p=<0.01²; p=<0.05³

Boys n= 8 (CKD) & 8 (control), girls n= 10 (CKD) & 10 (control).

FEI = food energy intake (without nutritional supplementation); TDEI – total dietary energy intake (with nutritional supplements); EAR = estimated average requirement for energy⁴²

Figure 8.1 shows the mean and distribution of EI by group expressed as kcal/day (Figure 8.1) and as a percentage of EAR (Figure 8.2). Children with CKD had the highest TDEI and the lowest FEI values compared to the control group. The spread of the difference was not statistically significant; however, these patterns could be clinically useful.

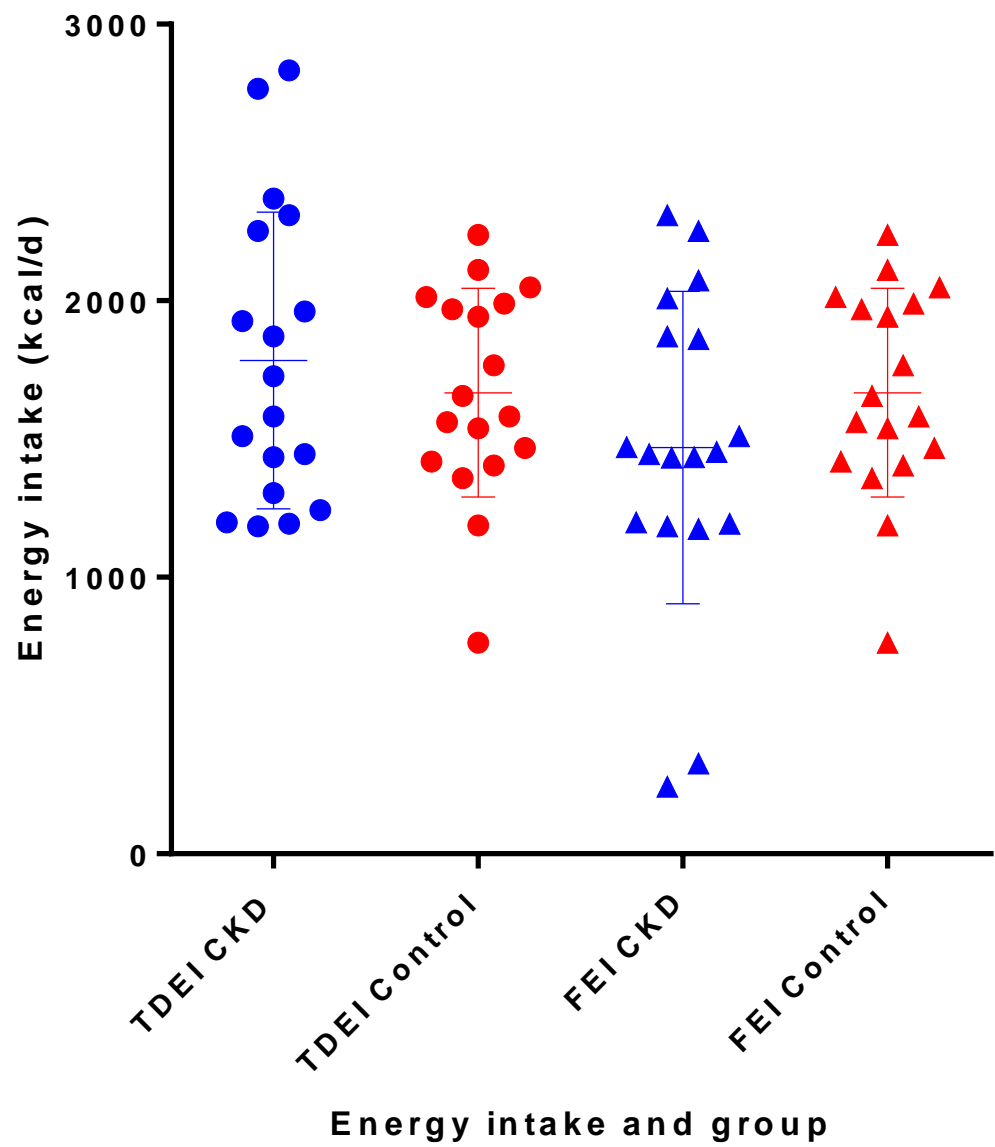


Figure 8-1 Energy intake (kcal/day) with and without nutritional supplementation in children by group
TDEI = total dietary energy intake with nutritional supplementation
DEI = food energy intake without nutritional supplementation.
The large horizontal lines indicate the mean value and the smaller horizontal lines the upper and lower limits of the 95% interval. The mean \pm sd values are as follows: TDEI 1768 \pm 113 (CKD) vs. 1709 \pm 113 (control); FEI 1447 \pm 115 (CKD) vs. 1724 \pm 115 (control).

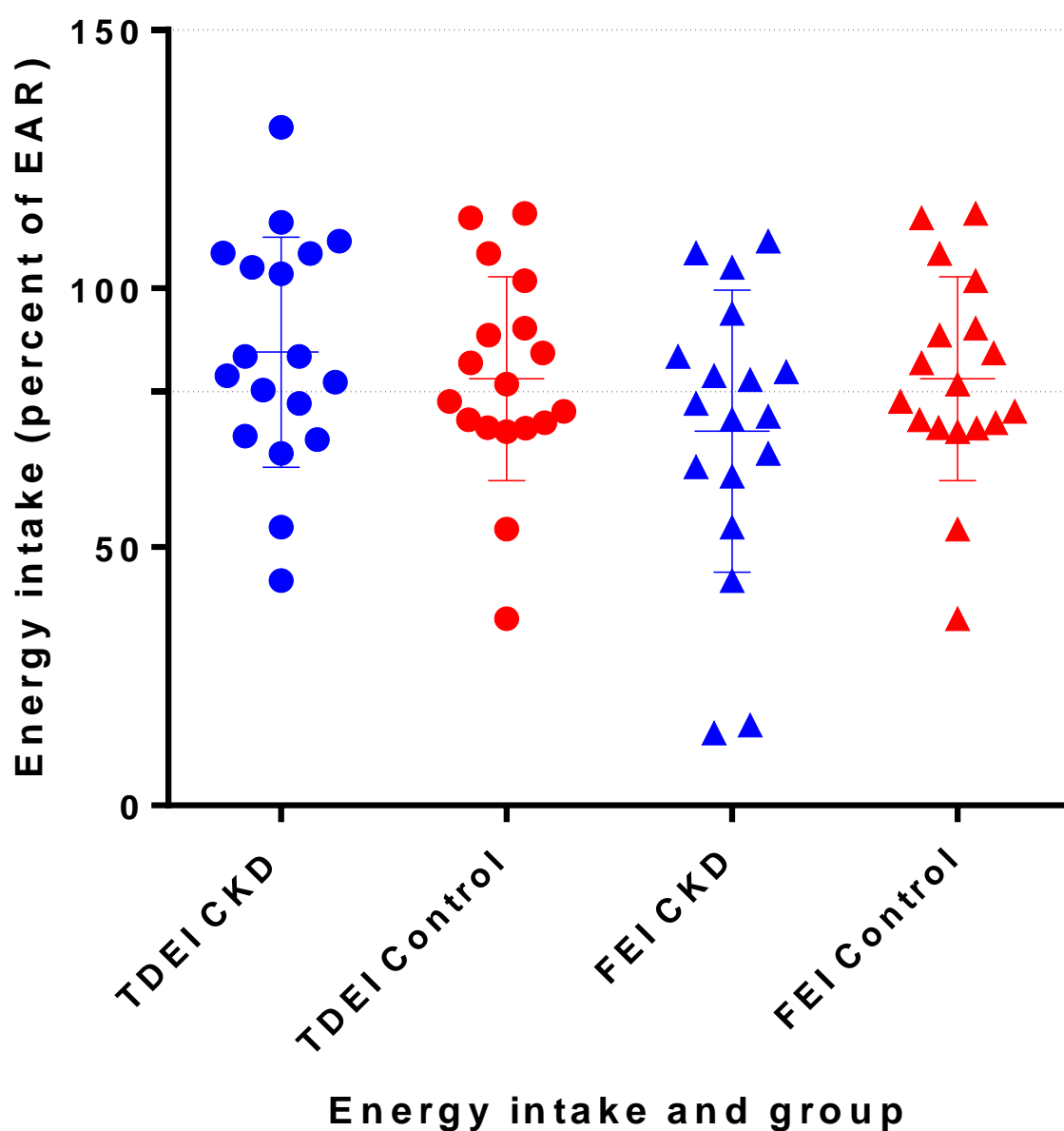


Figure 8–2 Energy intake as a percentage of EAR in children by group

TDEI = total dietary energy intake with nutritional supplementation

DEI = food energy intake without nutritional supplementation.

The large horizontal lines indicate the mean value and the smaller horizontal lines the upper and lower limits of the 95% interval. The dotted horizontal lines represent clinical cut off points for nutritional intervention.

The mean \pm sd are as follows: TDEI 88 \pm 22 (CKD) vs. 82 \pm 20 (control); FEI 72 \pm 27 (CKD) vs. 82 \pm 20 (control).

8.3.3 The relationship to BMR

Table 8.4 shows that both TDEI and FEI as a ratio to measured BMR (mBMR) (TDEI/BMR or FEI/BMR) did not differ significantly between children with CKD and controls, even when boys and girls are considered separately. Children with CKD tended to have higher ratios for TDEI overall (1.44 ± 0.43 vs. 1.29 ± 0.33 respectively), but varied when gender was considered separately. The opposite trend was shown for FEI/BMR (1.20 ± 0.53) compared to healthy controls (1.29 ± 0.33), and boys and girls when considered separately.

A one-sample t test (two tailed) showed that the ratio of FEI/BMR did not differ significantly from 1.27 (which has been recommended by WHO as being incompatible with health), even when gender was considered separately. The same findings were shown for TDEI/BMR. Under reporting and the plausibility of these ratios are considered further in Section 8.3.7 below.

Table 8–4 EI in children expressed as a ratio to measured BMR by group

Characteristics	Both groups (n=36)	CKD group (n=18)	Control group (n=18)	p*
FEI				
Both boys & girls	1.25 ± 0.44	1.20 ± 0.53	1.29 ± 0.33	0.526
Boys	1.28 ± 0.34	1.20 ± 0.37	1.36 ± 0.30	0.352
Girls	1.22 ± 0.51	1.20 ± 0.64	1.24 ± 0.36	0.937
TDEI				
Both boys & girls	1.37 ± 0.39	1.44 ± 0.43	1.29 ± 0.33	0.245
Boys	1.35 ± 0.34	1.34 ± 0.40	1.36 ± 0.30	0.871
Girls	1.38 ± 0.43	1.53 ± 0.46	1.24 ± 0.36	0.141

* The P values refer to comparisons between the CKD and Control group.

Results are expressed as mean \pm SD for unadjusted values and mean and standard error for adjusted values.

Adjustment for weight, height, age, gender and group

Boys n= 8 (CKD) & 8 (control), girls n= 10 (CKD) & 10 (control).

FEI = food energy intake (without nutritional supplementation); TDEI – total dietary energy intake (with nutritional supplements); BMR = basal metabolic rate.

8.3.4 The effect of kidney function

Regression analysis shows that in children with CKD eGFR did not significantly relate to TDEI (or FEI) when expressed in kcal per day, or percentage EAR. In contrast, a significant relationship was found when TDEI was expressed as multiples of BMR (TDEI/BMR), and, in addition, it was positive, implying that children with more severe CKD have increased TDEI ratios. So, at an estimated glomerular filtration rate (eGFR) of 0 the, ratio was 1.81 compared to 1.26 at a eGFR of 50 (Figure 8.2). Opposite trends were shown by scatter plots for TDEI and FEI (kcal/day, %EAR, ratio EI/BMR) (figures 8.3).

Table 8–5 Regression model: TDEI/mBMR and eGFR for children with CKD (n=18)

Model and variable	B	Regression coefficient			R ²	R
		SE	p*			
Intercept	1.814	0.166	0.000		0.302	0.549
eGFR	-0.011	0.004	0.018			

The p* value refers to the relationship between eGFR and mBMR effects

eGFR = estimated glomerular filtration rate; ratio (TDEI/BMR) = $1.814 + (-0.011 \cdot \text{eGFR})$.

B & SE = unstandardized coefficients.

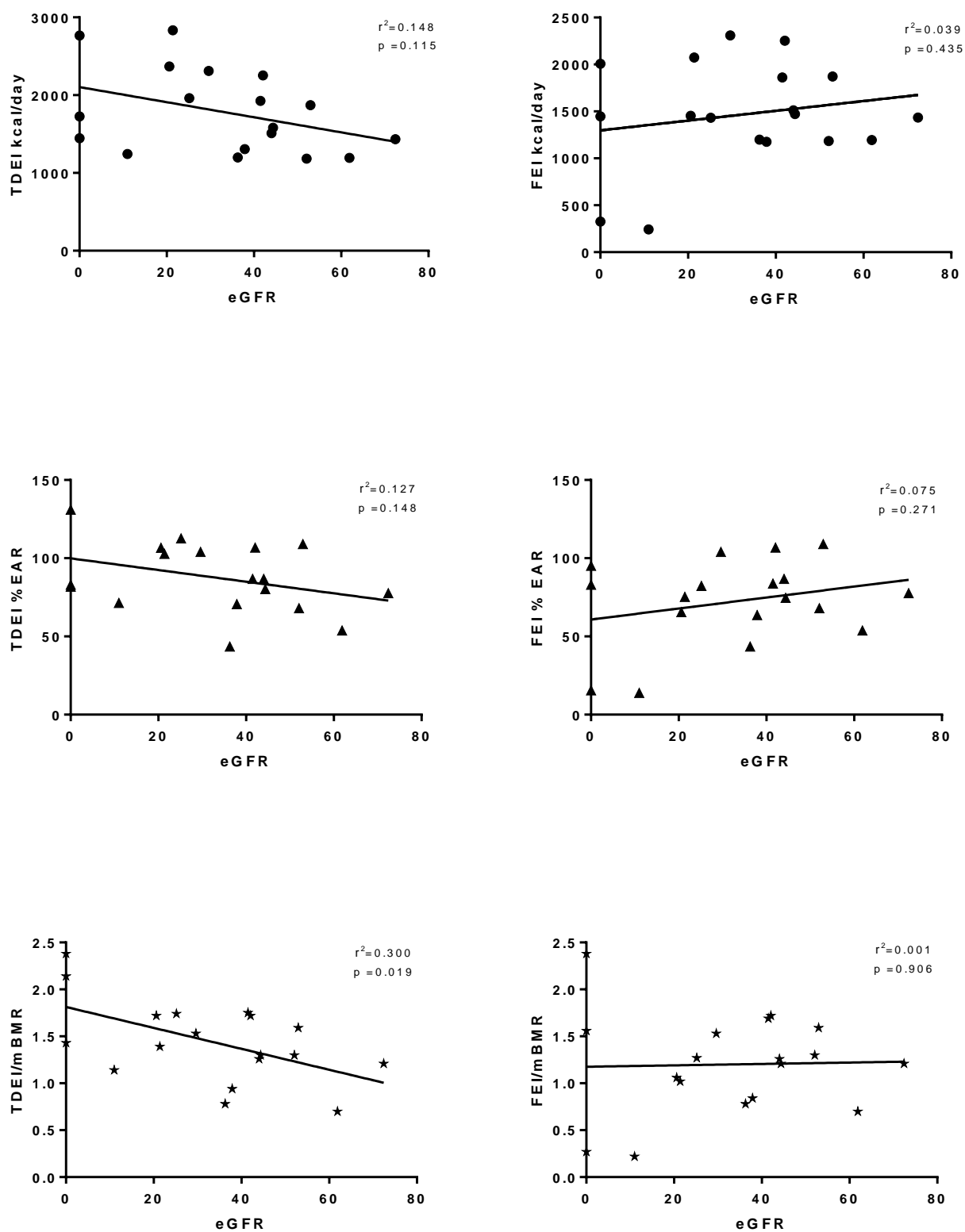


Figure 8-3 Relationship between FEI and TDEI (kcal/day, % EAR, as a ratio to mBMR) and kidney function

Top row = kcal per day; middle row = % EAR; bottom row = as a ratio to mBMR.

TDEI = total dietary energy intake, mBMR = measured basal metabolic rate and kidney function = eGFR (estimated glomerular filtration rate) (ml/min/m²). Using regression analysis.

8.3.5 Validity and plausibility of EI using food diaries

Comparison of EI measured by FD and DLW (DLW often regarded as the 'gold' standard) were made to help compare the merits of IDEEA and FD for use in clinical practice.

8.3.5.1 Validity of food diaries using DLW as a reference

The results of EI by FD and TEE by DLW in a subset of control children (n=12) are shown in Table 8.6. EI expressed in kcal/day were significantly lower ($p=0.006$) using a paired t-test.

Table 8–6 EI (kcal/d) by food diary compared to TEE by DLW in a subset of twelve healthy children *

Method	kcal/day (n=12)
EI* _{FD}	1654±436 [†]
TEE _{DLW*}	2253±517

*EI = energy intake; DLW = doubly labelled water (Schoeller); FD = food diary

Results are presented as mean ± sd

Paired t-test shows a significant difference between DLW and EI ($p<0.006$)[†]

The mean values of EI obtained by FD and TEE by DLW showed a poor overall agreement because of the wide confidence interval (–1823:625) (Table 8.7), and the large significant difference between the techniques (–599±612; $p=0.006$) (Table 8.7). There was also a tendency for the bias to become more negative as EI (mean of EI and DLW) increased (Figure 8.4). The Bland and Altman plots are shown in Figure 8.4.

Table 8–7 Comparison of dietary EI (kcal per day) using food diaries and DLW in a subset of twelve healthy children

EI (kcal per day)	Mean	difference	95% CI	r=	p=
FD vs. DLW	1954±368	–599±612 [†]	–1823:625	–0.171	0.595

TEE = total energy expenditure; FD = food diary; DLW = doubly labelled water

Results are presented as mean±sd

[†]The difference (FD–DLW) was significantly different from zero ($p=0.006$)

*r is the correlation between the difference (FD–DLW) and the average of the two methods (Figure 1)

**p is the significance of this relationship (correlation)

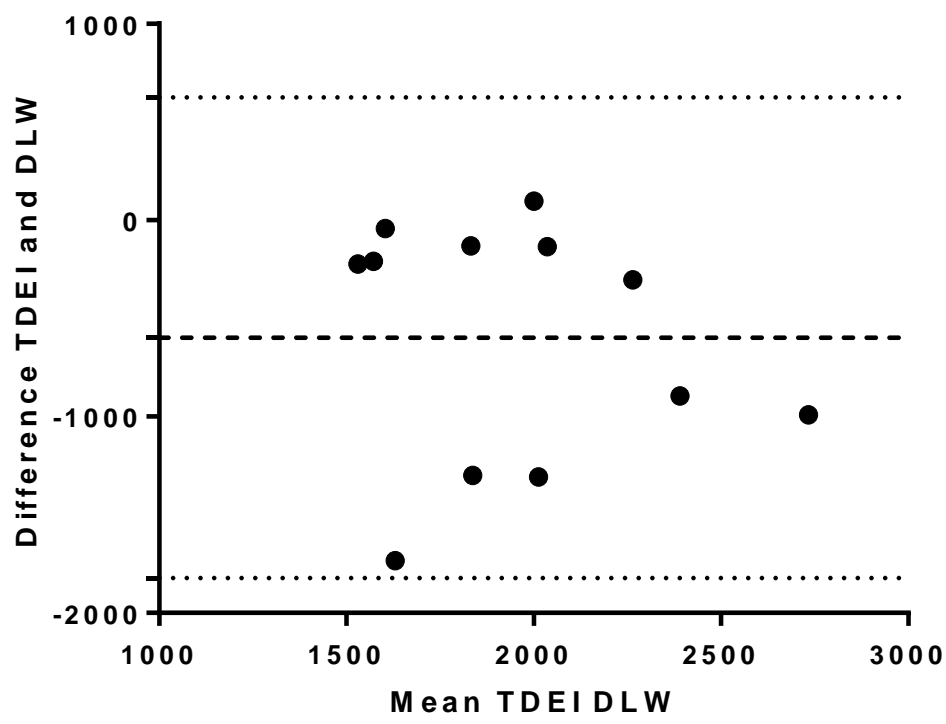


Figure 8–4 Bland and Altman plot of dietary energy intake by food diary and doubly labelled water (DLW) (EI–DLW)
TDEI = total dietary energy intake (including nutritional supplementation)

8.3.5.2 Plausibility considerations associated with food diaries

Unexpected and implausible results (Table 8.8 & 8.9) were identified using three methods:

1. The use of low %EAR (UK DRV⁴²) cut off values
2. The use of low ratio values (EI/BMR) and WHO¹⁴⁴ health guidance
3. The use of Torun et al¹⁴⁸ underreporting cut off values

Examination of EI expressed as a percentage of EAR (UK DRV⁴²) showed some unusually low values (Table 8.8), using the 80% EAR clinical cut off (the point at which nutritional supplementation should be considered). 28% (5/18) of children with CKD had values <80%EAR for TDEI, and 56% (10/18) for FEI, and compared to 50% of children in the control group (Table 8.8). 85% of the children with CKD were also considered weight stable on review after the study period and all children in the control group were considered to be weight stable.

Table 8–8 Percentage of children below cut off recommendations for EAR by group

Characteristics	Both groups (n=36)	CKD group (n=18)	Control group (n=18)
Percentage of EAR			
FEI <80%	49	56	50
TDEI <80%	36	28	50

* The P values refer to comparisons between the CKD and control group using one-way ANOVA.

Results are expressed as a percentage

FEI = food energy intake (without nutritional supplementation); TDEI – dietary energy intake + nutritional supplementation.

Examination using WHO¹⁴⁴ health guidance (PAL (TEE/BMR) values <1.27 are considered to be incompatible with health) and EI/BMR found low values (<1.27) in 28% of children with CKD for TDEI, and 39% for FEI. In the control group, 39% of children also had a PAL of <1.27 (Table 8.9).

Examination using under reporting cut off values suggested by Torun et al¹⁴⁸ (based on ratios of EI:BMR), found low values (<1.39) in 60% of boys for TDEI and 50% for FEI in children with CKD, compared to 63% for controls. In girls, 40% had low values (<1.3) for TDEI and 25% for FEI in children with CKD, compared to 50% for controls (Table 8.9).

Table 8–9 Percentage of children above or below ratio cut off recommendations for energy expenditure expressed as PAL equivalents*.

Characteristics	CKD group (n=18)	Control group (n=18)
<hr/>		
*WHO health guidance ¹⁴⁴		
FEI <1.27	39	39
TDEI <1.27	28	39
*DRV health guidance ¹³		
Age ≥10years		
FEI <1.75	100	93
TDEI <1.75	80	93
Age <10years		
FEI <1.58	85	100
TDEI <1.58	60	100
*Torun underreporting cut offs		
Boys		
FEI <1.39	50	63
TDEI <1.39	60	63
Girls		
FEI <1.3	25	50
TDEI <1.3	40	50

Results are expressed as a percentage

FEI = food energy intake (without nutritional supplementation); TDEI = dietary energy intake + nutritional supplementation.

Ratio = EI/BMR as a proxy for PAL used for examination with PAL (see below)

*WHO health guidance¹⁴⁴ (UK DRV 1991⁴²) (EE/BMR); DRV health guidance (SACN 2011¹³) (EE/BMR); Torun et al¹⁴⁸ (EE/BMR) using UK DRV 1991⁴².

8.3.6 Summary of food diaries in free-living conditions

Compared to healthy children, those with CKD tended to have higher values for TDEI and lower values for FEI expressed as either kcal/day, %EAR and as a ratio to BMR, but this did not reach statistical significance. Within the CKD group, deteriorating kidney function determined by eGFR tended to increase for TDEI and decrease for FEI but again non-significantly.

Exploration of EI findings using the four day food diary method raised concerns over the accuracy, validity and plausibility of food diaries to estimate energy requirements in children with CKD. There was poor agreement between EI by FD and TEE by DLW in control children, with significantly lower EI than TEE. Using recommended cut-off values for EI/BMR, 25–60% of the CKD group and 50–63% of the control group were found to underreport DI. The reasons for these inconsistencies and their implications are discussed next.

8.4 Discussion

Although measurement of TEE is the preferred approach to estimate energy requirements¹³, another approach is to measure EI over a period of time in weight stable, free-living subjects who are likely to be close to energy balance. EI can reflect the energy requirements under these conditions, if neither catch up growth, or weight loss are required. It is for these reasons that EI has been used in the past to estimate energy requirements, and the reason it is discussed here.

This study shows that there was no significant difference in EI (with or without nutritional supplementation) between children with CKD and controls, whether expressed as kcal per day or as a percentage of EAR⁴². There was, however, a tendency for TDEI to be higher in children with CKD (although lower when only FEI was considered). Furthermore, no significant relationship was found between TDEI or FEI and kidney function, although there was a tendency for TDEI to increase with the deterioration of kidney function, and FEI to decrease. One interpretation of these findings is the increased intensity of medical and dietetic reviews' in children with worsening disease, resulting in increased nutritional supplementation. This mirrors the local policy to closely monitor children with CKD stages 3–5, and to promptly prescribe nutritional supplements when FEI is <80% EAR and when there is growth faltering (declining percentiles). In addition, clinical experience suggests that appetite declines as eGFR declines. It is tempting to speculate that nutritional supplementation suppresses food intake, which could explain the paradox between FEI and TDEI when children were compared with healthy controls, but appetite changes over time were unfortunately not considered here. Another interpretation is that children with CKD keep better records of dietary intake than healthy children so that underreporting is less pronounced in the CKD children. It is also possible that children with more severe CKD keep better records than those with less severe disease, which would explain the significant negative relationship between an TDEI (expressed as a ratio of BMR (TDEI:BMR)) and deteriorating kidney function assessed by eGFR. The same significant trends were shown for BMR in Chapter 5.

However, the above conclusions and interpretations should be regarded as tentative because of the problems associated with dietary intake methodology^{59 61 67 71}. This leads to concerns that previous recommendations were made using EI data that may have been invalid, despite being used to establish local and national guidance.

In an attempt to overcome these concerns, the present study took steps to identify problems associated with food diary accuracy after applying four checks in methodology and analysis. Firstly, the food diaries completed by the children and their families were verified and reviewed with the child and their families in their homes at the time of the study, using the same research dietitian. Secondly, food diaries were validated by comparisons to DLW (in a subset of control children), and thirdly, attempts were made to establish implausibility using recommended EAR and PAL cut off values^{13 144} in children with CKD and healthy controls, as well as the cut off ratios of EI/BMR according to Torun et al¹⁴⁸.

In a subset of healthy subjects in the present study, EI was found to be substantially less than TEE using DLW and to poorly agree, suggesting that the food diaries used in clinical practice are likely to be inaccurate and need to be interpreted with care (although some of the inaccuracy may be due to DLW as discussed in Chapter 7). The present study also found EI was less than 80% EAR in a considerable number (28–56%) of children in both groups, which was suggestive of those children needing energy supplementation (<80% EAR), but these findings seem implausible when both children with CKD and healthy controls were weight stable. This implausibility was further supported by the PAL values of less than 1.27 (regarded as incompatible with health according to WHO¹⁴⁴), which were found to occur in more than 30% of children in both groups of children. A note of caution should, however, be exercised when interpreting the DLW agreement, due to the time difference between the two methods (four days for food diary and ten days used for DLW) and the lack of weekends that some food diaries failed to capture. Finally, the present study found that EI was under reported in 25–63% of children (CKD (25–60%) and healthy controls (50–63%)) using the Torun et al¹⁴⁸ criteria, despite the apparent weight stability in both groups. Therefore, under-reporting remains a major potential problem in both research and clinical practice.

The findings of the present study are supported by the literature^{34 149 150} which generally suggests that children with CKD have lower TDEI compared to the national recommendations (EAR or equivalent, and that under reporting occurs in children with CKD¹⁰. However, these studies need closer examination, as each study has some methodological concerns which are detailed below.

Ratsch et al³⁴ reported lower EI ranging from 76–88% ($88\pm 21\%$ group I (age 3.2 ± 6.9), $82\pm 8\%$ group II (age 7.3 ± 9.9), $76\pm 24\%$ group III) (age 10.5 ± 17.2)) of recommended dietary allowance (RDA) for 50 Italian children with CKD compared to 90–93% (90 ± 17 , 93 ± 15 , 93 ± 12 respectively) for 93 controls using four day weighed intake records. The EI in children with CKD was 10% lower than controls and was significant for Groups II and III. The present study also found a 10% lower difference in EI using FEI (and a 4% higher difference if nutritional supplements were included). Unlike the present study, younger children were included in this study (6–17 years (here) vs. 3–17 years (Ratsch et al)); they also had lower height sds for the children with CKD (-0.26 ± 1.21 vs. -0.5 ± 1.2 group I, -0.6 ± 1.3 group II, -0.7 ± 1.1 group III respectively), were larger in number (20:20 CKD: control vs. 40:93 CKD: control respectively) and were all on a low protein diet. None of the children in the present study were on low protein diets. The study by Ratsch et al was limited in four ways: firstly, the authors did not state whether the children with CKD were weight stable; secondly, they did not distinguish between the stages of CKD; thirdly, they did not state whether children were on nutritional supplements and, finally, they did not consider whether the groups were misreporting dietary intake.

Canepa et al¹⁴⁹ reported that EI was $75\pm 25\%$ of RDA in 19 Italian children on chronic peritoneal dialysis assessed by the double weighed method, but was limited by the absence of a control group. Unlike the present study, the children differed in mean age (11.9 ± 3.4) (here) vs. 8.7 ± 3.8 years (Canepa et al), were all on dialysis, and their energy intake included the likely contribution of glucose in the dialysate. The study by Canepa's study was limited by the absence of data on growth, nutritional status and the use of nutritional supplements or weight stability. The authors also did not consider whether the children were misreporting dietary intake.

Zadik et al¹⁵⁰ reported significantly lower EI ($74.7 \pm 2.9\%$ RDA) in 16 children on PD and 15 children on HD, compared to 44 age matched, short, healthy controls ($98.5 \pm 4.5\%$ RDA ($p < 0.01$)) before growth hormone (GH) therapy, using 3 day diet records in Israel. EI remained significantly lower after one year of GH therapy (83.3 ± 3.7 and 105 ± 5.0 respectively) ($p = < 0.01$). The energy difference here was 24 vs. 22% lower in children with CKD than controls, and so much greater than the differences found in the present study between children with CKD and controls. Unlike the present study, the children were again younger (8.7 ± 0.5 years (Zadik et al) vs. 11.9 ± 3.4 (here)) and had lower height sds (-3.2 ± 0.2 : -2.8 ± 0.2 CKD: control ($p = < 0.01$) vs. -0.26 ± 1.21 : 0.35 ± 1.35 ($p = 0.146$) respectively). This study was limited by the lack of information on whether EI included glucose from dialysate or the use of nutritional supplements. In addition, the authors did not distinguish between age group or dialysis type for EI values and did not comment on weight stability or validity of findings. Again no consideration was made as to whether the groups were misreporting dietary intake.

The small sample size of all four studies, and the absence of information on EI according to the type of treatment received and CKD stage, might mask significant differences that could otherwise exist.

Several other studies have reported EI in older children with CKD^{19 3 10 21 24 35 76-78 151} (although EI was not the main focus of these studies). They differed in CKD stage, dietary assessment method and presentation of EI results, and none compared to healthy controls, making comparisons extremely difficult. Nevertheless, overall they are consistent with our study and the studies referred to above in suggesting that EI is typically less than % EAR.

Only one other study has looked at EI under reporting in children with CKD¹⁰. The findings of Norman et al¹⁰ agreed with the present study, showing that children with CKD under report EI (range 14–71%) and deteriorate over time as kidney function worsens. The level of under reporting was greater in this study compared to the present study (25–60% for children with CKD; 50–60% for controls). In addition, the children were younger (2–16 years) than the present study (6–18 years); had less severe disease (stage 2 vs. a mean of stage 3 (range stage 5–2) respectively); and none were on dialysis ($n = 3$ present study).

8.4.1 Severity of CKD

This study found a non-significant tendency for EI (kcal/day or % EAR) to decrease with deteriorating kidney function in children with CKD. Three other studies^{19 21 24}, also explored the relationship between EI and kidney function. .

The first study by Betts and McGrath¹⁹ (n=33) (details Table 2, Chapter 2), like the present study found no significant correlation between % EAR for EI and GFR ($r=0.34$, $p=>0.1$) for children with CKD in the UK aged between 0.5–16.3 years, with an eGFR of $<70\text{ml/min/m}^2$.

In contrast, the second study by Orejas et al²¹ (n=15) (details Table 2, chapter 2) found that EI decreased significantly with worsening kidney function for Spanish children aged 8.9 ± 5.1 with a GFR between $11\text{--}75\text{ml/min/1.73m}^2$ ($p=0.$). The same trend was shown non-significantly in the present study ($p=<0.005$).

The third study by Norman et al²⁴ (n=95) (details Table 2, Chapter 2) also found a positive correlation between EI prior to supplementation and eGFR ($r^2=0.12$; $p=0.001$) for UK children with CKD, aged 2–16 years, with a eGFR range of $<25\text{--}75$. Unlike the other two studies and our study (which had a small sample size) this study involved a much larger sample size, which increased the power of the study.

Taken together, these studies suggest that there is a relationship between EI and kidney function. The present study showed a tendency for such a relationship, but it was not significant, possibly because it was underpowered (small sample size of $n=20$) and associated with type II error. Such conclusions would be consistent with current opinion and day-to-day clinical experience (verbal discussion with members of PRING and BAPN).

8.4.2 Relationship between EI and BMR

This is the first study to examine the relationship between FEI and BMR. It found that EI did not relate significantly to measured BMR when children with CKD were compared to controls, which is counter-intuitive, since larger and older children with higher EE would be expected to eat more. The lack of relationship may be due to the imprecision of the dietary intake methodology coupled with a small sample size.

8.4.3 Justification of method

In the present study, the food diaries used in clinical practice were chosen as the method of choice to assess FEI for three reasons: Firstly, children with CKD were familiar with this method. Secondly, these diaries could be completed over the same four consecutive days period alongside activity diaries and IDEEA and, thirdly, the weighed food record method has been shown previously to underreport^{152 153} (Chapter 2). Although the findings of this study and others have shown FD under report EI by roughly 10%, these methods are used in clinical practice. Therefore, in order to assess the accuracy, measures need to be undertaken to ascertain validity and plausibility alongside FD data collection. These measures should include methods to assess under reporting and weight stability, which could easily be incorporated easily into clinical practice.

8.4.4 Summary of energy intake and implications for future clinical practice

The EI of children with CKD did not meet the EAR, and even remained less than EAR with the addition of nutritional supplements. Children with CKD were also not significantly different from health and tended to have deteriorating EI (FEI) with worsening disease but increasing TDEI.

However, questions arise regarding how much of the findings are genuine and how much could be attributed to methodological issues. There are serious concerns about the validity and plausibility of EI methodology, because healthy (weight stable) children also did not meet EAR. This was further supported by the poor agreement between EI and DLW. These concerns (together with the under reporting found in both weight stable groups) indicates that the FD used in clinical practice need to be interpreted with care. These findings also support the recent suggestion by SACN¹³ that EI may be unsuitable to estimate energy requirements.

There is a need for a more robust methodology for measuring EI in clinical practice, since this is important to routine clinical care. The use of age and cognition specific methods in relation to the nutrient under investigation is required (Chapter 2), together with concurrent assessment of EI accuracy, but these all require further research.

The overall conclusion here is that, whilst children with CKD may have differing values compared to health, the validity of the information is uncertain and so energy intake should not be used in older children to estimate energy requirements for children with CKD. Further research needs to be conducted into how to improve estimation of EI for children with CKD at different ages and stages of CKD, and how to improve the assessment of EI in clinical practice.

The findings of Chapters 4–8 now need to be considered in relation to the thesis, hypothesis and clinical practice when estimating energy requirements for children with CKD. Chapter 9 will discuss the findings of each chapter in relation to clinical practice together with any potential trends that have arisen that may help further enlighten clinical practice and future research.

9. General discussion and implications of findings

9.1 Introduction

The overall aim of this thesis was to provide a better understanding of the factors influencing the EE and EI, and, ultimately, the energy requirements of children with CKD. The thesis arose by asking a simple clinical question, which is ‘Why do we use EAR to estimate the energy requirements of children with CKD?’. To address this issue, it was necessary to evaluate first the evidence base and appraise the methodology, and then explore the components of energy requirements for children with CKD, including any influencing factors. The potential value of new methods for measuring the components of the energy balance equation was also explored. It is now necessary to integrate this information and consider the implications for routine clinical practice. Therefore, the final chapter will review the key findings, consider their implications for routine clinical practice, and suggest the type of research that needs to be undertaken to address unsolved problems.

9.2 Characteristics of children with CKD

This work adds to the very limited information that exists regarding growth, body composition and EE in older children with CKD.

Children with CKD (disease stage ranging from 2–5; mean stage 3; see Chapters 1, 2 & 4 for more details) were found to be shorter and lighter than healthy age and gender matched control children (assessed by Z scores), but were taller and heavier than children with stage 5 disease for which some information is available (see Chapters 2 and 4). In the present study, a relationship was found between growth failure and severity of disease (using eGFR, as a marker of kidney function), but it was not strong enough to reach significance. These observations are not unexpected, because as children progress from milder to more severe stages of disease (stage 4 and 5 children), they experience worsening symptoms, including nausea and vomiting, taste changes and loss of appetite, which contribute to the growth failure. In addition, treatment in more advanced disease often involves more dietary restrictions, which would tend to

exacerbate growth failure even more. However, the quantitative aspects are poorly defined, which suggests that there is a need to document the magnitude of the changes during progression of CKD and the way this is affected by age in order to obtain a better understanding of the requirements for individual treatment. However, the situation is complex because some children refuse supplements, while others do not comply with the dietary restrictions. In the former case, growth failure would ensue, and in the latter situation, uremic symptoms will become more severe, which could detrimentally affect appetite with secondary effects on growth.

In clinical practice, the degree of the growth deficit could alter clinical management; specifically the energy requirements of children with CKD. For example, if the aim of nutritional support is to maintain current weight and growth status, less energy would be required than if the aim was to achieve catch up growth. If the aim also includes the alteration of plasma urea, potassium and/or plasma phosphate, this would further alter energy requirements, as additional energy is required to reduce uremic symptoms and prevent muscle breakdown.

The energy needs of children with CKD can be further informed by the measurement of body composition, since the REE of individuals depends on body composition, being higher in those with a greater proportion of LBM (or smaller proportion of fat mass). However, assessment of body composition in children with CKD can be problematic because fluid disturbances may not be clinically evident (Chapter 2). Fluid disturbances can lead to either underestimation or overestimation of LBM (corresponding to overestimation and underestimation of fat), depending on the method used to assess body composition (see Chapter 2). For example, in overhydrated individuals, standard densitometry by ADP tends to overestimate LBM (underestimate FM), whereas water dilution tends to do the opposite. SFK will tend to underestimate LBM and overestimate FM.

However, there are three reasons that suggest that over hydration was not a major problem in the children who participated in this study. Firstly, they showed a tendency towards both less lean and FM compared to healthy children, irrespective of the body composition method used. Secondly, the analysis of body composition was undertaken without the three subjects who were clinically identified as being fluid overloaded, without change in conclusions. Thirdly, the

ratio of whole body BIA at low and high frequency (reflecting the ratio of extracellular to total body water) in children with CKD (after exclusion of three fluid overloaded children) did not differ significantly from that of healthy children. The relationship between body composition (like that of growth) and severity of disease also did not reach significance (Chapter 4), and was not unexpected for the same reasons described above. Further research is needed to examine the accuracy of body composition methods in children with CKD and whether energy requirements and LBM vary according to type of treatment, age and stage of disease. Such information potentially could lead to improvements in morbidity and mortality (pre and post transplantation) and better resource targeted care. If changes in growth or body composition begin in stage 3 disease or earlier, the question arises as to whether nutritional assessment and intervention by the renal team should be initiated at an early stage in all children with CKD, before the development of clinical abnormalities, such as alterations in phosphate, urea or potassium. Early intervention could potentially attenuate deterioration in growth and reduce its impact in more advanced stages of the disease, but the evidence needs to be gathered.

9.3 BMR and children with CKD

This work adds to the limited information on BMR/REE in children with CKD. Firstly, children with a mean of stage 3 disease were found to have a comparable BMR to healthy children, which means that 'normal' BMR can be used to crudely calculate TEE using factorial methods in this group of children. However, the validity of the factorial method relative to other methods needs to be evaluated, taking into account the potential confounding effects of kidney function.

Secondly, a significant relationship was found between BMR and severity of disease, which could help improve predictions of energy requirements in clinical practice. The reasons for decreasing BMR with worsening disease are unclear but they may involve a combination of factors, including the loss in the mass of the kidneys which contributes to about 6% of BMR (see Chapter 5 for discussion).

Attempts were also made to identify other possible explanatory variables for variability in % predicted BMR (which depends on age, gender, weight and

height), but none were found. However, it is acknowledged that the sample size was small and that larger studies would be useful to explore this potential relationship. Due to lack of measurements on inflammatory markers, it was not possible to explore the effect of inflammation, although this could be a fruitful area for future research. What would be of interest clinically is an accurate bedside method for identifying children at the extreme ends of the distribution of % predicted BMR. Longitudinal studies to establish such information would be preferable to cross-sectional studies. Extension of such studies to assess the effects of interventions, biochemical abnormalities, growth deficits/repletions (including nutritional deficiencies) on individual children would be valuable.

However, BMR is only part of the TEE equation, and the most variable component is physical activity.

9.4 TEE and children with CKD

This study provides information on measurements of PAEE and TEE, neither of which has been reported previously in children with CKD.

Children with a mean of stage 3 CKD studied here did not differ significantly in TEE and PAEE compared to healthy controls. Furthermore, no significant relationship was found between either TEE or PAEE and severity of disease. Although this may be genuine, there is concern about the validity of the methodology to accurately estimate TEE and PAEE (see Chapter 7). However, confounding clinical factors need to be taken into account. For example, in local practice increasing PA is recommended in an attempt to delay disease progression, although this is not standardised for all children. Additionally, in children receiving dialysis ($n=3$ in this study), the time spent on dialysis and automated travel could have reduced the time available for activity. This adds to the variability in PAEE and TEE, making it more difficult to identify differences between groups. Larger studies taking these issues into account may provide a clearer understanding of the energy requirement of different groups of children with CKD. Longitudinal changes to examine factors that affect individual children would also be valuable.

9.5 EI and children with CKD

Although EI has been shown to be inferior to estimating EE regarding the determination of energy requirements (Chapter 2), it is nevertheless considered here for completeness.

The dietary intake of children with CKD stage 3 studied here did not meet the EAR from food alone (77% of EAR). Whilst the inclusion of supplements increased the EI, the total intake still remained below EAR (85%). There are however, serious concerns about the validity of the dietary intake methodology, because the healthy normally growing control children also did not meet EAR. The overall result is that there was no significant difference in total EI between groups, but both fell short of EAR. This is most likely to be due to under-reporting. The only other study that reported EI as multiples of BMR for children with CKD also concluded that there was under-reporting. Therefore, there is some concern that dietary intake is used in clinical practice to guide treatment.

Despite these concerns, an attempt was made to explore the relationship between EI and the severity of disease (eGFR). A significant negative relationship was found between total EI expressed as multiples of BMR and eGFR (more energy intake in children with poorer renal function). This appears paradoxical or counter-intuitive, since children with more advanced disease are expected to have poorer appetites and eat less. One possible explanation for the finding is that children with more severe kidney disease underreport less than those with better kidney function. Another possibility is the local intensive nutritional intervention policy for children with more advanced CKD. It may be possible to obtain greater insights into these issues with more labour intensive observations, using different dietary intake methodologies for measuring dietary intake in children with CKD differing in age and cognitive abilities. There is a need to establish a more robust methodology for measuring dietary intake in clinical practice, since this is important to routine dietetic practice.

9.6 Future implications for clinical practice

Whilst this work has not been able to address specifically the hypothesis raised in this thesis (mainly because of inadequacies in methodology), it has helped identify at least four areas that could help improve the estimation of energy requirements in children with CKD in current clinical practice.

Firstly, since the energy cost of growth is negligible in children aged 6 years and over (such as those participating in this study), methods for calculating energy requirements typically depend on the estimation of EE. However, children who are depleted require extra energy, protein and other nutrients for repletion. A simple way of assessing the extent of depletion is by measuring z scores for weight, height and BMI. A better method might be to measure body composition. In overweight and obese individuals, a small reduction in EI may be necessary to achieve a better body composition. However, in clinical practice, z scores are only sometimes used, and body composition measurements are rarely used. Taking these into account in an attempt to establish a better understanding of growth or body composition could improve the nutritional care of patients. A strategy to incorporate such simple concepts into clinical practice could be valuable. However, this may require the introduction of a programme of education and training which takes into account the principles of energy requirements and growth, as well as practical methods for calculating z scores. It may also require equipment for measuring weight and height to be accessible, accurate, and regularly calibrated to defined national standards. The overall nutritional management of children with CKD could be further enhanced by using a combination of information on growth provided by z scores and body composition. For example, as indicated above, if the aim is for energy requirements to achieve catch up growth, their energy needs will be different from those who require maintenance growth; and if symptoms of disease such as uraemia also need to be addressed, energy needs could be altered further.

Secondly, current practice for calculating EAR has been based on a single value for PAL (1.65 for boys and 1.57 for girls⁴²). BMR can be estimated from Schofield or the more recent Henry equations, and used in conjunction with PAL to estimate energy requirements. However, there is wide variation in physical activity between individuals. For example, in children aged 3–10 years the SACN

report (DRV for energy) indicate that the median PAL is 1.57 and ranges from 1.35 (10th centile) to 1.77 (90th centile) corresponding to 86% to 113% (range 27%), which is substantial. Using SACN¹³ data for this age group it, should be possible to establish three reference points for PAL (25th 50th and 75th centiles; 1.42, 1.57, and 1.69 respectively), which could be assigned to high, medium and low activity levels. Simple methods such as asking children how they compare to their peers (less active more active, or about the same) or a simple report of their activity including, playing sport, cycling or walking to and from school, could help improve current practice, but there is still a need to validate such simple and practical methods.

Thirdly, in those receiving peritoneal dialysis it is necessary to take into account the amount of glucose that is likely to be absorbed through the peritoneum into the systemic circulation, since this is thought to contribute to about 8–10 kcal/kg per day, and sometimes more, which can be substantial and predispose to obesity. However, the amount varies according to the frequency of dialysis, state of the peritoneum and the type of dialysis solution. With the availability in recent years of certain types of dialysis solutions that do not contain glucose, much less energy is absorbed through the peritoneum. It is, therefore, necessary to take into account the type of solution used for dialysis.

Finally, the risk of developing obesity might also be reduced by a better understanding of the growth deficit and PAL of an individual child. For example, in children with end stage CKD, a balance needs to be reached between providing sufficient energy and medication to control blood biochemistry (high potassium, urea and phosphate) and the start of dialysis. In some cases, delaying dialysis by continued increases in EI can make children obese, which is undesirable. Earlier treatment with dialysis would be preferable in such children.

9.7 Further research

This thesis has led to many more questions being raised, which was not unexpected, considering the lack of research in paediatric CKD. Potential ideas have been broken down into three themes: understanding the effect of disease; the need for improvements in methodology; and the need for improvements in the evidence base.

9.7.1 The effect of disease

The effect of CKD on EE requirements, growth, and body composition can be studied by cross-sectional and longitudinal studies. The advantage of the cross sectional studies are that answers can be obtained more quickly, often with a larger number of subjects. The advantage of longitudinal studies are that they provide information on changes within subjects, which eliminates some of the 'noise' associated with between subject variability. However, compliance over long periods of time may be difficult. Both types of studies should include information on nutrition (growth & body composition), kidney function and treatment stage, to help determine any associations that may alter clinical treatment and improve clinical outcome.

9.7.2 Improvements in methodology

The accuracy of methodology to assess body composition, PAEE, TEE and EI for children with CKD, requires further refinement to provide more reliable information on fat and lean mass, and energy requirements. For example, the four component model is generally considered one of the most accurate methods for assessing body composition because it relies on a few assumptions. It measures water directly so that disturbances in fluid and balance should not confound interpretation. The effect of bone on the overall density of the body is also taken into account because it is measured by DXA. The density of the body is also estimated to provide more realistic measures of fat and fat free mass than many other methods, especially during fluid disturbances and growth failure. More contemporary UK reference data for children using different methodologies is also needed to enable comparisons to health.

9.7.3 Evidence base

This thesis has identified three areas in which the evidence base needs to be improved:– measurement of EE, interactions between body composition and EE, and clinical outcomes.

9.7.3.1 Measurement of energy expenditure

The failure of this work to provide better estimates of energy requirements was due to inadequate methodology for measuring TEE and PAEE. Whilst IDEEA provided adequate measurements of physical activity in controlled conditions, it did not do so under free-living conditions. A close investigation of the factors that lead to the breakdown in methodology from controlled to free living conditions could help resolve the problem. The lack of information about the algorithms used to estimate PAEE and TEE is a real impediment to progress. Basic, ground root research is required to address this issue. Such research could also help address some of the implausible results produced by IDEEA. Only when such issues are adequately addressed will there be a more realistic chance of obtaining more accurate estimates of energy requirements in individual children. The practicalities of undertaking the measurements also need to be addressed, and the development of a wireless Wi-Fi system could help facilitate the research. Other methodology for estimating energy expenditure (e.g. heart rate monitoring in conjunction with pedometers) and EI (development of reliable biochemical indicators of nutritional intake) should also continue to be explored. In children with CKD who are not on dialysis, use could be made of DLW, but for those on dialysis in whom the information is most needed, such a method is inappropriate due to loss of DLW in the dialysate.

9.7.3.2 Interactions between body composition and energy expenditure

Only when the above issues on EE and body composition are addressed, will it be possible to examine more sophisticated issues, such as the interaction between lean body mass and TEE as the disease progresses from the early to the late management of disease.

9.7.3.3 Clinical outcomes

The role of the dietitian in clinical outcomes (CO) is a complex area of much debate. Clarity is needed first regarding the definition of clinical outcome for use in dietetic practice. Once this has been more clearly defined, links that establish the relationship between specific markers for CO and indicators of CO needs to be strengthened. Figure 44 demonstrates some of the clinical outcome considerations for children with CKD.

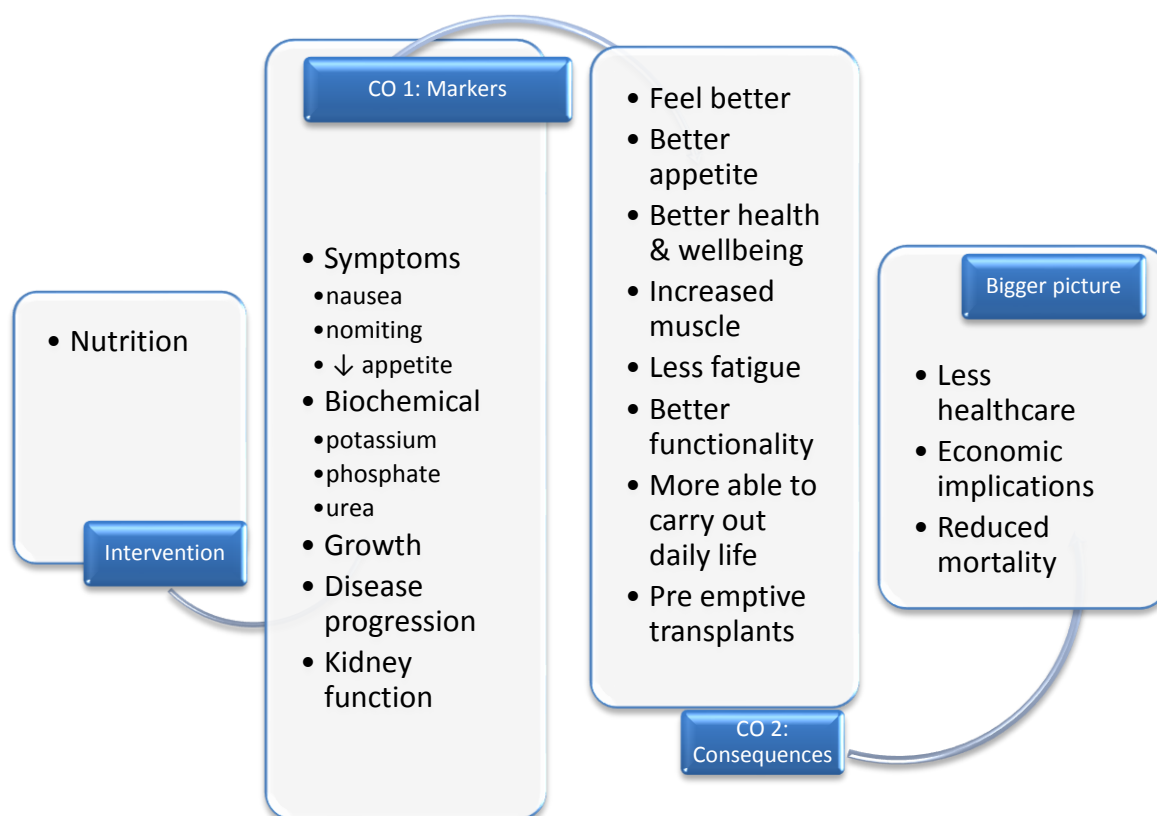


Figure 9–1 Clinical outcome considerations for children with CKD.

CO=clinical outcome

An example of clinical outcomes in the dietetic management of childhood CKD will now be discussed, together with other considerations to demonstrate some of the challenges. Improvement in appetite following dietary manipulation of energy and protein to reduce high plasma urea could be regarded as a dietetic clinical outcome. Reductions in plasma urea can reduce symptoms of nausea and vomiting and improve kidney function, which, in turn, could improve appetite, nutritional intake and growth. However, alterations in medication and

dialysis could also change plasma urea and appetite, and so the process cannot be simply attributed to dietary changes.

The above discussion highlights that nutrition is not just the responsibility of the dietitian but many members of the MDT. Accordingly, management requires a MDT approach to establish both a clinical management plan and agreed goals. The development of links between clinical and academic professionals (such as those that have evolved here) can help develop a structure and process to bridge the gap between clinical practice and clinical outcomes. The evidence base that is often lacking can be developed and connections can be established between the understanding of specific clinical markers and the indicators of clinical outcomes. Studies that integrate growth, body composition and energy requirements (discussed above) for children with CKD (when combined with data on quality of life and functional capacity), can help strengthen the use of clinical outcomes in clinical practice.

9.8 Conclusion

The optimal energy requirements of children with CKD remain uncertain. They represent a complex issue that encompasses many aspects of clinical care that can affect and be affected by many other clinical needs.

In undertaking this thesis, an important outcome emerged that was perhaps inadequately considered at the outset. This is that the local clinical and academic communities have been brought together to enable collaborative research to enhance clinical practice. A framework has been developed to explore the energy needs of children with CKD, and this collaboration could be extended to cover other aspects of dietetic practice.

Despite the uncertainties about energy requirements in CKD, an approximate estimate is still needed in current clinical practice, and until a better approach is identified, it seems reasonable to continue to use EAR as the basis of energy prescriptions. In the quest to establish better methodology, a more systematic approach to the assessment of nutritional management for children with CKD is required. This needs to be supported by appropriate tools that can measure what they are intended to measure and with the level of accuracy and reliability that is required.

In undertaking this thesis, several aspects of routine dietetic practices have been challenged, such as the accuracy of dietary intake assessed by food diary, the assessment of nutritional status and growth, and methods for calculating energy requirements. Whilst this is difficult for some practicing clinical professionals to take such findings on board, critically reviewing practice with an open scientific mind would help improve clinical advice, and potentially clinical outcomes.

A continued integrated approach to both clinical practice and research to explore the issues raised in this thesis on an on-going basis would require appropriate funding, infrastructure and professional support. This in itself is a challenge in both the clinical setting and in academia, where financial constraints often take precedence.

Appendices

Appendix 1 Patient information sheets

Appendix 2 Paper work

Appendix 3 Additional tables

Appendix 4 Abstracts and posters

Appendix 1 Patient information sheets

Parents

Children

GP letter

Parent CKD letter

Caroline Anderson
Paediatric Dietitian

Clinical Support Services
Department of Nutrition and Dietetics
D Level, Mail point 32
Southampton General Hospital
Tremona Road
Southampton SO16 6YD
Tel: 023 8079 6072

Parent/Guardian Information Sheet

Study Title: Children's Energy Expenditure and Requirements in Kidney Failure

Investigators: Caroline Anderson (Renal Dietitian), Dr Rodney Gilbert (Renal Consultant), and Professor Elia (Professor of Clinical Nutrition and Metabolism & Honorary Consultant)

Your child has been invited to take part in a research study. Before you decide whether you would like your child to participate or not, it is important that you understand why the research is being undertaken and what it will involve.

Please take the time to read the following information very carefully and discuss this with others if you so wish. Please do not hesitate to contact us if you need clarification on any of the details or if you require additional information. We feel that it is important that you understand why we wish your child to take part in this research study and therefore would like you to browse through this information at your leisure.

Thank you for reading this.

What is the purpose of the study?

Children need lots of energy for growth, development and physical activity. Children with kidney failure can require extra energy to help their kidney function. They can also have problems growing, as there are many difficulties in getting enough energy sources into their diets.

The amount of energy your child takes each day (energy intake) is decided by how much they eat and drink. The amount of energy they need and use up (energy expended) depends on your child's nutritional status and the amount of activity they undertake each day.

Children with kidney problems can have different energy needs from other children of the same age and sex, and from each other. This could be affected by the degree of kidney failure and the type of treatment they receive, for example, dialysis and/or dietary restriction.

We don't know exactly how much energy is needed or used for children with kidney problems. Our study is to try to investigate these needs. The study also aims to establish how energy needs change with decreasing kidney function, and how the energy needs of children with kidney failure differs from healthy children.

To achieve this, we need to measure resting energy expenditure and physical activity.

Resting energy expenditure (REE) can be measured by breathing into a ventilated plastic hood, after an overnight fast.

Physical activity can be recorded by measuring the amount and type of activity your child does each day.

Why has your child been chosen?

The research study involves children aged six to eighteen years old either with kidney failure under the care of the Children's Renal Team at Southampton General Hospital, or healthy volunteers. Your child has been chosen because he/she meets these requirements.

We require a total of twenty children with kidney problems and twenty healthy children without kidney problems to complete the study.

Does my child have to take part in the study?

It is for you to decide whether or not you wish your child to participate. If you decide to assist the research team, you will be given this information sheet to keep and also asked to sign a consent form. If you decide to allow your child to participate, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your child receives.

What will happen to my child if I take part?

Your child will be invited to attend an extended hospital out-patient appointment on the same day as a routine appointment. You will need to record some additional information alongside your child's usual food diary at home. Your child will only need to take part in the study once. This does not involve any treatment changes.

The research study will take up to two hours, in addition to your child's routine clinic review in hospital and collection of information on diet and activity for up to four days at home.

The study will require the following:

- 1) You and your child will be invited to attend the Wellcome Trust Clinical Research Facility on the morning of a routine appointment with the Children's Renal Team at Southampton General Hospital NHS Trust.
- 2) We will first ask your child to empty their bladder, and then measure your child's weight and height.
- 3) In the morning we will measure your child's resting energy expenditure. This involves him/her lying under a transparent ventilated hood. The amount of oxygen used by your child is then measured. This procedure, which is not unpleasant, takes about half

an hour. In order for the test to be accurate, it requires that ***your child does not eat from midnight the night before*** until after the test has been completed. Your child can however drink some water and will be given breakfast shortly after this measurement.

- 4) We would also like to assess the amount of fat, muscle, bone and water that makes up your child's body. This will be measured by three methods:
 - The first is a special machine that measures the resistance of the body (bioelectrical impedance). This runs a harmless small electrical current through the body for a few seconds. It cannot be sensed (like the electrical current of a heart beat) and is totally painless.
 - The second is a special machine (Bod Pod) that measures the volume of your child, which together with body weight provides information about body composition. Your child will need to sit in a spaceship-like chamber, with a clear perspex front. It will take a few minutes to measure the air in the chamber and in your child's body. Your child will need to wear a swimsuit or tight fitting swim shirts and a swimming cap (which we will provide). They will also need to sit still while the measurements are being taken.
 - The third is a skin fold calliper that measures the fat on different parts of the body. A pinch of fat will be measured three times on four different sites on your child's body. This will take a couple of minutes and feels like someone is gently pinching the skin. It does not hurt.
- 5) We would then like to measure your child's physical activity levels, including the amount, type and length of activity carried out each day. To measure activity, we will ask your child to wear a lightweight instrument (MiniSun) the size of a small packet of cigarettes, which records movement and heart rate. This is worn all day and involves your child wearing a small portable battery operated belt recorder and four sensors, attached to the tummy and legs. A pedometer and heart rate monitor will also be worn.
We will also ask you and your child to record their daily activity on the combined food and activity diary.
- 6) We will also need to assess your child's energy intake. This will be measured by recording everything your child eats and drinks at home for four days.
- 7) Caroline Anderson (your child's Renal Dietitian) and Dr Gilbert (your child's Renal Consultant) will then carry out your child's routine clinic appointment. Routine measurements of weight, height, food intake and blood tests will be recorded as part of your child's routine clinical review. Medical details will remain confidential.
- 8) A date will then be made to collect the equipment and the food and activity diary.

Travel expenses over and above those involved in routine clinic reviews will be reimbursed.

What do I, the parent/guardian, have to do?

Your child does not need any changes to medication or diet for this study. This is an observational study of normal behaviour.

In order to allow some of the measurements to be carried out properly, ***your child must not eat after midnight the night before***. This includes breakfast. Your child can however drink some water. Breakfast will be provided shortly after the energy measurements.

Your child will need to bring a swimming costume or tight swim shorts for the Bod Pod measurement. Swimming caps will be provided on the day.

Your child will be asked to wear some small, light equipment for four days following the hospital visit and record activity as discussed above. The activity needs to be recorded alongside their routine food and drink intake for four days. You may need to help your child record the food and activity in the diary.

Clear instructions will be provided for you to take home and contact details provided to help you during this four-day period.

What are the possible disadvantages and risks of taking part?

We cannot think of any possible disadvantages or risks to taking part in the study.

There is a possibility that your child may feel unfamiliar in the study environment, and some may experience difficulties in keeping still during the study period. One test involves placing a transparent, perspex, ventilated hood over the child's head, whilst he/she is lying still for a period of about 30 minutes.

To help overcome this, we are using The Wellcome Trust Clinical Research Facility. This facility has child friendly facilities and staff who are experienced in taking these measurements and working with children.

What are the possible benefits of taking part?

The information we gather from the study will help us better understand and meet the energy needs of children with kidney failure.

You and your child will be provided with information on their pattern of physical activity and body composition. This can be of relevance if your child needs to change their weight status (i.e. if they are underweight or overweight). Your dietitian will advise and support you on this as needed.

This information will help everyone, both for general health and lifestyle issues and also enable parents/guardians to have an informed choice in regard to diet and exercise.

What if new information becomes available?

Sometimes during the course of a research project, new information relevant to clinical management becomes available. If this happens, your Research Dietitian and Consultant will be able to advise you about it and then discuss with you whether you wish to continue in the study. If you decide to withdraw, your Dietitian will make arrangements for your child's routine care to continue. If you decide to continue in the study, you will be required to sign an updated consent form.

On receiving new information, your Research Dietitian and Consultant might consider it to be in your best interests to withdraw your child from the study. They will explain their reasons and arrange for your child's routine care to continue as before.

What if something goes wrong?

If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect on the way you have been approached or treated during the course of this study, the normal National Health Service mechanisms should be available to you.

Will my child taking part in this study be kept confidential?

All information which is collected about your child during the course of the research will be kept strictly confidential. Any information about your child which leaves the hospital will have their name and address removed so that they cannot be recognised from it.

Your GP and shared care local consultants will be informed of your child's participation in the study, as will the Renal Team. This will be in the form of a letter to other hospital consultants or GP surgeries, and a copy of the consent form will be placed in your child's medical notes at Southampton University Hospital NHS Trust.

What will happen to the results of the research study?

We will analyse the results and publish them in medical journals and present our findings at conferences to inform other health care professionals. We will not reveal the names and any personal details of the participants.

Written information will also be available for you and your child should you wish to be informed of the results of the study.

Who is organising and funding the research?

The study is being organised by Southampton General University Hospitals NHS Trust. The Health Foundation is funding the study.

Who has reviewed the study?

The Southampton & South West Hampshire Research Ethics Committee B, The Directorate of Clinical Services at Southampton General University Hospitals NHS, and The Health Foundation have all independently reviewed and approved the study.

Contact for Further Information

Thank you for taking the time to read this information and considering taking part in this study.

If you have any questions that have not been answered in this information sheet, or would like to discuss anything in more detail, please don't hesitate to contact Caroline Anderson on extension 6072 (02380796072) or bleep 2087 (02380777222 2087).

Parent Control letter

Caroline Anderson
Paediatric Dietitian

Clinical Support Services
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D Level, Mail point 32
Southampton General Hospital
Tremona Road
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Parent/Guardian Information Sheet

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Investigators: Caroline Anderson (Renal Dietitian), Dr Rodney Gilbert (Renal Consultant), and Professor Elia (Professor of Clinical Nutrition and Metabolism & Honorary Consultant)

Your child has been invited to take part in a research study. Before you decide whether you would like your child to participate or not, it is important that you understand why the research is being undertaken and what it will involve.

Please take the time to read the following information very carefully and discuss this with others if you so wish. Please do not hesitate to contact us if you need clarification on any of the details or if you require additional information. We feel that it is important that you understand why we wish your child to take part in this research study and therefore would like you to browse through this information at your leisure.

Thank you for reading this.

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Children need lots of energy for growth, development and physical activity. Children with kidney failure can require extra energy to help their kidney function. They can also have problems growing, as there are many difficulties in getting enough energy sources into their diets.

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Children with kidney problems can have different energy needs from other children of the same age and sex, and from each other. This could be affected by the degree of kidney failure and the type of treatment they receive, for example, dialysis and/or dietary restriction.

We don't know exactly how much energy is needed or used for children with kidney problems. Our study is to try to investigate these needs. This study also aims to establish how energy needs change with decreasing kidney function and how the energy needs of children with kidney failure differs from healthy children.

To achieve this, we need to measure resting energy expenditure and physical activity.

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We require a total of twenty children with kidney problems and twenty healthy children without kidney problems to complete the study.

Does my child have to take part in the study?

It is for you to decide whether or not you wish your child to participate. If you decide to assist the research team, you will be given this information sheet to keep and also asked to sign a consent form. If you decide to allow your child to participate, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your child may receive in the future.

What will happen to my child if I take part?

Your child will be invited to attend an out-patient appointment at the Wellcome Trust Clinical Research Facility at Southampton General Hospital NHS Trust. You will need to record some additional information at home. Your child will only need to take part in the study once.

The research study will take up to two hours in hospital, and for up to four days at home to collect information on diet and activity.

The study will require the following:

- 9) You and your child will be invited to attend the Wellcome Trust Clinical Research Facility.
- 10) We will first ask your child to empty their bladder, and measure your child's weight and height.
- 11) In the morning we will measure your child's resting energy expenditure. This involves him/her lying under a transparent ventilated hood. The amount of oxygen used by your child is then measured. This procedure, which is not unpleasant, takes about half an hour. In order for the test to be accurate, it requires that ***your child does not eat from midnight the night before*** until after the test has been completed. Your child can however drink some water and will be given breakfast shortly after this measurement.

12) We would also like to assess the amount of fat, muscle, bone and water that makes up your child's body. This will be measured by three methods:

- The first is a special machine that measures the resistance of the body (bioelectrical impedance). This runs a harmless small electrical current through the body for a few seconds. It cannot be sensed (like the electrical current of a heart beat) and is totally painless.
- The second is a special machine (BodPod) that measures the volume of your child, which together with body weight provides information about body composition. Your child will need to sit in a spaceship-like chamber, with a clear perspex front. It will take a few minutes to measure the air in the chamber and in your child's body. Your child will need to wear a swimsuit or tight fitting swim shorts and a swimming cap (which we will provide). They will also need to sit still while the measurements are being taken.
- The third is a skin fold calliper that measures the fat on different parts of the body. A pinch of fat will be measured three times on four different sites on your child's body. This will take a couple minutes and feels like someone is gently pinching the skin. It does not hurt.

13) We would like to measure your child's physical activity levels, including the amount, type and length of activity carried out each day. To measure activity, we will ask your child to wear a lightweight instrument (MiniSun) the size of a small packet of cigarettes, which records movement and heart rate. This is worn all day and involves your child wearing a small portable battery operated belt recorder and four sensors, attached to the tummy and legs. A pedometer and heart rate monitor will also be worn.

We will also ask you and your child to record their daily activity on the combined food and activity diary.

14) We will also need to assess your child's energy intake. This will be measured by recording everything your child eats and drinks at home for four days.

15) Lastly we will need your child to drink some special water. This is called Doubly Labelled Water and harmless but more concentrated in dose compared to normal water. We need to collect three samples of their saliva or alternatively of urine. One sample must be collected within 24 hours of the first drink, one after 5 days and one after 10 days. These need to be posted back in the specimen pots and envelope provided.

16) A date will then be arranged to collect the equipment and the food and activity diary.

Travel expenses will be reimbursed.

What do I, the parent/guardian, have to do?

Your child does not need any changes to medication or diet for this study. This is an observational study of normal behaviour.

In order to allow some of the measurements to be carried out properly, ***your child must not eat after midnight the night before***. This includes breakfast. Your child can however drink some water. Breakfast will be provided shortly after the energy measurements.

Your child will need to bring a swimming costume or tight swim shorts for the Bod Pod measurement. Swimming caps will be provided on the day.

Your child will be asked to wear some small, light equipment for four days following the hospital visit and record activity as discussed above. The activity needs to be recorded alongside your child's food and drink intake for four days. You may need to help your child record the food and activity in the diary.

Clear instructions will be provided for you to take home and contact details provided to help you during this four-day period.

What are the possible disadvantages and risks of taking part?

We cannot think of any possible disadvantages or risks to taking part in the study.

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You and your child will be provided with information on their pattern of physical activity and body composition. This can be of relevance if your child needs to change their weight status (i.e. if they are underweight or overweight). The Research Dietitian will liaise with your child's GP should the need arise following the test results.

This information will help everyone, both for general health and lifestyle issues and also enable parents / guardians to have an informed choice in regard to diet and exercise.

What if new information becomes available?

Sometimes during the course of a research project, new information relevant to clinical management becomes available. If this happens, your Research Dietitian will be able to advise you about it and then discuss with you whether

you wish to continue in the study. If you decide to withdraw, your Dietitian will make arrangements for any routine care for your child to continue. If you decide to continue in the study, you will be required to sign an updated consent form.

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Will my child taking part in this study be kept confidential?

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What will happen to the results of the research study?

We will analyse the results and publish them in medical journals and present our findings at conferences to inform other health care professionals. We will not reveal the names and any personal details of the participants.

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Who is organising and funding the research?

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Contact for Further Information

Thank you for taking the time to read this information and considering taking part in this study.

If you have any questions that have not been answered in this information sheet, or would like to discuss anything in more detail, please don't hesitate to contact Caroline Anderson on extension 6072 (02380796072) or bleep 2087 (02380777222 2087).

Check List

Please remember to:

- **Not eat anything from midnight the night before.** You are, however, allowed to drink water.
- Bring a swimming costume or tight swim shorts and a swimming cap (if possible).
- Ask any questions if you are worried about anything. We are here to make your visit as comfortable as possible

Contact Details:

Caroline Anderson
Paediatric Dietitian
Department of Nutrition and Dietetics
D Level, Mail Point 32
Southampton General Hospital NHS Trust
Southampton SO16 6YD
Telephone: 023 8079 6072

Produced by Department of Nutrition and Dietetics and with kind permission from The Wessex Growth Study.
Southampton General Hospital

Children's Energy needs in Kidney Disease



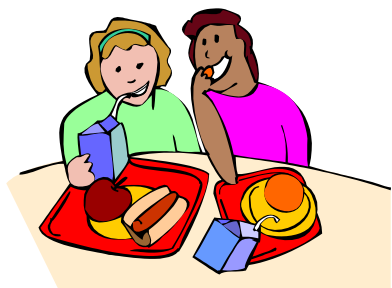
Child Information Sheet

Southampton **NHS**
University Hospitals NHS Trust



We need lots of energy to grow and play. Energy comes from the food we eat and drink each day.

The amount of energy we need depends on how much we eat and drink, how active we are and how much fat, muscle, water and bone our bodies contain.



We are trying to find out the amount of energy that children with kidney problems need. This can be measured with some special equipment at the hospital, and also other equipment that you can wear at home.

Fun Word Search!!!

R O T I N O M E T A R T R A E H
 S S Y M Y I B A H L W S Y F H I
 L T W G N M O N A L G K O V C A
 X I N I R Y N T N I A O Y E Y X
 E X S E M E E H K T D W W R R N
 K U B U M S N I Y S W G A W O C
 N Y V T R E U E O P H I X T Y M
 D O P D O B R I U E D P Z T E N
 D R I N K W A U T E O P I N V R
 H O S P I T A L S K Z V E V M A
 I O D R U T B Y C A I X L S O S
 Y Z Z A N Z W Z G T E J C L O T
 M N F E G M T V C Z O M S C F K
 M X H E J S O A Q A S D U M B Z
 C J H V P X R C L W R U M V Q A
 E P P F K S E T A F X B S U T V

ACTIVITY
 DIARY
 FAT
 HOSPITAL
 MINISUN
 THANKYOU

BODPOD
 DRINK
 FOOD
 KEEPSTILL
 MUSCLE
 WATER

BONE
 ENERGY
 HEARTRATEMONITOR
 MEASUREMENTS
 SWIMSUIT

.....the amount of water in your body

The human body feels solid, but about 65 % of it is water!
 Too much or too little water can affect your health.

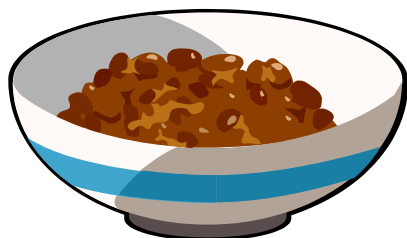


We can not only measure how much water you have in your body, but also how much energy your body is using, by giving you a small drink of water. This differs very slightly from ordinary water (you will not be able to taste the difference) and is called doubly labelled water. We will collect the moisture in your mouth or your urine before the drink, and then collect a specimen again a few hours and days later.

If you agree to help us, we would like you to spend a morning with us at the hospital.

Appendix 1 Patient information sheets

It is important that you **don't eat anything from midnight the night before your visit**. You are allowed to drink some water.



We will give you breakfast before you leave hospital.



At the hospital, you will be met by the researcher and a children's nurse.

This is how we will measure the fat, muscle, and water you have and the energy you use up.

Appendix 1

Height



Weight



Arm

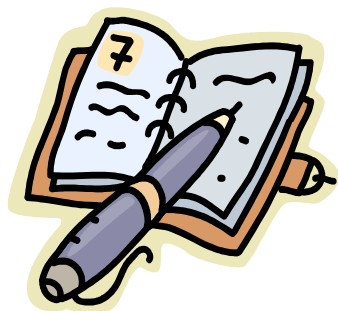
&

Skinfolds

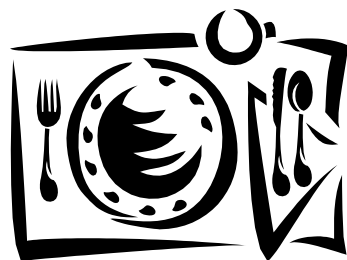


....the amount of energy you eat and drink

To determine this you will need to record how much food and drink you eat over a four day period.



Recording your food and drink will tell us how much energy you eat and drink each day.



Appendix 1 Patient information sheets



....the amount of activity you do

Activity can be measured in many ways. Measuring your heart rate and the number of steps you take gives us an idea of how much activity you do. You will need to wear a pedometer and heart rate monitor.



We will also require you to wear a small battery operated box and four sticky patches placed on your tummy and legs. This will tell us how you move and by how much.

You will also be asked to write down what activity you do alongside your food diary.

The nurse will also measure.....

Appendix 1

..... your body size

This is measured by the Bod Pod, which looks a bit like a spaceship! It works by measuring the amount of air your body takes up and with your weight can tell us how much muscle, fat and water is in your body.

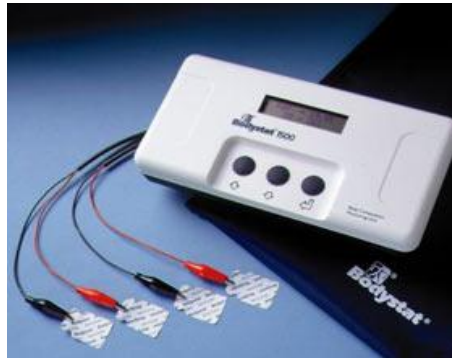


We will need you to sit very still inside the Bod Pod for a few minutes. You need to wear a swimsuit or tight fitting swim shorts and swimming cap during the test because air trapped in your clothing and hair can cause inaccurate measurements.

.....the amount of fat your body contains

Measuring your skin folds (those squidy bits on your arm and back) gives us an idea of how much fat your body hold, but a better way is to use a quick test called Bioimpedance

Appendix 1 Patient information sheets



During the test you will need to lie on a bed and four sticky patches will be placed on your hand, wrist, foot, and ankle. A very weak electrical current will pass through your body and this will tell us how much fat your body contains. This will not hurt you.

.....the amount of energy you use

Appendix 1



This machine uses your breath to measure the amount of energy you use up. You have to lie very still while a clear perspex hood is placed over your head. You can watch TV or listen to radio while we measure your breath.

Although a baby is shown in the picture, a child or adult can be measured using the same technique.

Clinical Support Services
Department of Nutrition and Dietetics
D Level, Mail point 32
Southampton General Hospital
Tremona Road
Southampton SO16 6YD

Tel: 023 8079 6072

Fax: 023 8079 8665

Dear Dr

Re: Patients name
DOB
Address

**Subject: Clinical Research Study:
Children's Energy Expenditure Requirements in Kidney Failure**

I am writing to inform you that.....(patient name) has been consented by their parents/guardians to take part in the above study. This study has been approved by Southampton & South West Hampshire Research Ethics Committee B and has ethical approval.

This study is an observational study that is being conducted to investigate the resting energy expenditure (REE) and total energy expenditure (TEE) of children with chronic renal failure. The outcomes of this study will determine REE adjusted for body composition for children with chronic renal failure. We aim to produce a more accurate assessment for TEE to provide evidence based energy intake figures that will guide clinical practice on a day-to-day basis.

Ensuring adequate energy as well as complete nutrition is well recognised to maximise growth and development, and delay progression of renal dysfunction. Current UK practice uses estimated average requirement (EAR) (DoH 1991) as a basis for energy calculations. There are a number of inaccuracies in using these figures, in particular the use of height, which is known to be affected by renal disease; and the problem that current methodology does not take into account the most variable component of TEE, which is physical activity.

We aim to resolve these issues by investigating total energy expenditure, body composition and relate them to renal function.

This is a case control study and will have two groups. Group 1 will consist of children with chronic renal failure under the care of the paediatric renal service at Southampton General Hospital, and Group 2 will consist of siblings or age and gender matched healthy controls.

Please find enclosed a copy of the Patient Information Sheet for this study, which gives more detail on what is required from your patient. If you have any questions or concerns regarding your patient taking part in this study, please do not hesitate to contact me.

With kind regards,

Yours sincerely

Caroline Anderson
Paediatric Renal Dietitian

Appendix 2 Paper work for the study

Consent form

Food and activity diary

Advice for home

Data collection sheets

Clinical Support Services

Department of Nutrition and Dietetics

D Level, Mail point 32

Southampton General Hospital

Tremona Road

Southampton SO16 6YD

Tel: 023 8079 6072

Fax: 023 8079 8665

Study Number:

Patient Identification Number for this trial:

Title of Project: Children's' Energy Expenditure and Requirements in Kidney Failure

Name of Researcher: Caroline Anderson, Senior Paediatric Dietitian

Please initial box

1. I confirm that I have read and understand the Patient Information Sheet dated.....(version) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my child's participation is voluntary and that he/she is free to withdraw at any time, without giving any reason and without their medical care or legal rights being affected. ☐
3. I understand that the information will be anonymised at all times. I Understand that the information may be looked at by all investigators involved in this study. I give permission for these individuals to have access to my records. ☐
4. I understand that the data will only be used for the purposes it was intended. ☐
5. I agree for my child to take part in the above study. ☐

Name of participant	Date	Signature
---------------------	------	-----------

Name of person taking consent Date (If different from the researcher)	Date	Signature
--	------	-----------

Researcher	Date	Signature
------------	------	-----------

1 for the participant

1 for the researcher

1 to be kept with hospital notes

Advice for Home

MiniSun

Please take off before showering / bathing

Note position of sensors

Replace after showering / bathing using advice sheet provided and secure with tape provided

In hot weather you may need extra tape to secure

Do not wear shoes with a heel higher than 1cm

Do not get the minisun wet

Coil extra wire around knee and secure with tape or tuck into your socks

Food and Activity Diary

Please record all you eat and drink for 4 days starting with the day you visit us

Please record all you do (your activity) for 4 days starting with the day you visit us

Any questions

If you have any questions during the study period please call.....

Caroline Anderson on 02380796072

If Caroline is not at her desk she will return your call as soon as she can

Study ID: Initials: Birth Date:

WELCOME

Parent and Child to be met at Wellcome CRF

Address any questions parent or child may have

Obtain written consent from parent and child

Enter date of visit.....

PRE-TEST PROCEDURE

Establish from parent that child is fasted.....

Establish if the child has swimwear, swim cap and short and trainers.....

Ask child to **empty bladder**.....

Measure **height** and **weight** and record overleaf.....

Ask the child to walk 10 paces and measure distance
inches

Calculate stride length for step-o-meter
ft&inches

Apply Ametop/Emla cream for blood sample as identified

Ask child to lie flat on back on the bed next to the calorimeter in bay.....
and rested and relax for 30 minutes...

Put on DVD or Video of child's choice

Locate blood forms

FASTING BLOOD SAMPLE CKD CHILDREN ONLY

Dr Gilbert to take blood samples, label and send for processing

Take 5ml fasting blood sample from child

Fasting time_____pm

Time sample sent to lab.....am

Record Results

Urea

Sodium

Inorganic Phosphate

Correct Calcium

PTH

Est. GFR

Albumin

Fasting TG

Fasting LDL/LDL chol

Cholesterol

Glucose

Creatinine

Potassium

Calcium

Ionised Calcium

Bicarbonate

Actual GFR

Hb

Ratio Chol:HDL

Fasting HDL/HDL chol

Ferritin

IMPEDENCE MEASUREMENT

Child should be rested flat on back and relaxed

Position electrodes on right hand, wrist, foot and ankle taking care to follow instructions (SOP.....)

Perform test with SFB3 impedance meter, making sure to store results and record values below.

Client number %fat Impedance Phase Angle TBW
 □□ □□.□□ □□□□z □□.□□ □□.□□

LBM FFM Resistance Reactance EBW
 □□.□□ □□.□□ □□□□r □□.□□x_c □□.□□

Repeat test

Client number %fat Impedance Phase Angle TBW
 □□ □□.□□ □□□□z □□.□□ □□.□□

LBM FFM Resistance Reactance EBW
 □□.□□ □□.□□ □□□□r □□.□□x_c □□.□□

INDIRECT CALORIMETRY

Child should be rested flat on back and relaxed

Place hood over child ensure edges are tucked in lightly

Place O2 saturation monitor on child's finger

Follow instructions (SOP.....)

Perform test and record machine total summary results below....

Time Mean VO2 Mean VCO2
 □□.□□ □□□□ml/min □□□□ml/min

Mean EE Mean RQ
 □□□□□kcal/d □.□□□

Sats

□□□□□

Save results and instructed...saved as.....

□□□□□□□□.raw./dat.

Print out results manually feeding sheets into printer

Sample number □□

BODPOD MEASUREMENT

Ask child to empty bladder and change into swimwear

Note Bod Pod Weight.....□□.□ kg

Perform test using **Loman** equations

When % Fat result is displayed, record result below

% Fat	% lean	fat	lean	Total body wt
□□.□	□□.□	□□.□g	□□.□g	□□.□kg

Press F1 to display **Lung volume, Density** and **Area Artifact** and record results below

Lung Volume	Density	Area Artifact
□.□□□L	□.□□□kg/L	□.□□□m ²

Press F1 again to display **Volume** measurements and record results below.

□□.□□□L	□□.□□□L	□□.□□□L
---------	---------	---------

Record RO □.□□□□□□□□

R1 □.□□□□□□□□

Print and attach results sheet

BREAKFAST

Give child breakfast.....

Amount of fluid given	Type of fluid
□□□□ml	-----

AUXOLOGY

Undress & mark measuring points for body circumferences

Measure and record each of the variables below then repeat process

Weight (kg)	1. □□□.□	2. □□□.□
Standing Height (cm)	1. □□□.□	2. □□□.□
Waist circumference	1. □□□.□	2. □□□.□ 3.□□□.□
Hip circumference	1. □□□.□	2. □□□.□ 3.□□□.□
Mid-Arm (cm)	1. □□□.□	2. □□□.□ 3.□□□.□
Mid-Arm muscle circumference	1. □□□.□	2. □□□.□ 3.□□□.□
Biceps skinfold (mm)	1. □□□.□	2. □□□.□ 3.□□□.□
Triceps skinfold (mm)	1. □□□.□	2. □□□.□ 3.□□□.□
Subscapular skinfold (mm)	1. □□□.□	2. □□□.□ 3.□□□.□
Suprailiac skinfold (mm)	1. □□□.□	2. □□□.□ 3.□□□.□

MINISUN

Enter age and gender of child

Age Gender initial Wt (kg) Ht (cm)
years

Child stands to position sensors

Ask child to take socks and trainers off and place MiniSun recorder on belt

Position and secure sensors taking care to follow instructions (SOP.....)

Ask child to put socks and shoes back on

Ask child to sit for calibration of MiniSun

Place wood blocks under child's feet to ensure legs are at a right angle

Perform start up and calibration test following instructions

Record file name, start time, programme ID and day

File name

@_ _ _

Time Programme ID Day
hrsmin ...

Unplug child from computer

Ask child to walk 10 paces

STEP-O-METER

Child can be sitting

Perform set up and check stride length and step count is at zero

Check sensitivity is at the mid-arm setting

Ask the child to wear around their belt

Close front cover

Record start time for today..... Pedometer

No......am

Pedometer No......am

FOOD AND ACTIVITY DIARY

Explain food and activity diary and how to complete

Ask the child to write down their name, the date and day today on the relevant sheets of the diary

Give food and activity diary

Arrange date to collect diary and equipment

Date Time Location
.. .

CLINIC APPOINTMENT CKD CHILDREN ONLY

Use for **children with Chronic Kidney Failure ONLY**

Bleep Dr Gilbert

Take diet history recall

Answer any dietary questions

Dr Gilbert to conduct clinic review

DEUTERIUM DILUTION CONTROLS ONLY

Use for **Healthy children ONLY**

Collect pre-dose saliva sample, demonstrating procedure to parent

Ask child to drink prepared double labelled water solution

Push straw inside bottle and tighten cap

Enter total weight of bottle, cap, straw and remaining solution

(B)..... □□□.□□

Subtract **(B)** from **(A)** to calculate total drunk **(C)** and enter

(C)□□□.□□

Ensure parent has instructions and materials to collect/post the other samples

Saliva tubes labelled and pre dated

Plastic container

Padded, addressed, and stamped envelope

DISCHARGE PROCEDURE

Check all procedures have been completed and data attached

Make sure parent and child have instructions regarding collection of saliva, food and activity and minisun and attaching MiniSun sensors after showers.

Reimburse travelling expenses

Give child copy of output from BODPOD

Give fact sheets 1 & 2

Minisun self validation

Ask the child to jump on the spot for 20 times

Record and repeat

Number of steps	Time taken	Number of steps	Time taken
□□	□□m□□sec	□□	□□m□□sec

Ask the child to walk up and down the stairs in _____block by WTCRF

Record and repeat

Stairs	Number of stairs	Time taken	Pedometer 3	4
Up	□□□	□□.□□	□□□	□□□
Down	□□□	□□.□□	□□□	□□□
Up	□□□	□□.□□	□□□	□□□
Down	□□□	□□.□□	□□□	□□□

Ask the child to walk along G level corridor from one set of lift to the next

Record and repeat

Number of steps	Time taken	Pedometer 3	4
□□□	□□.□□	□□□	□□□
□□□	□□.□□	□□□	□□□
□□□	□□.□□	□□□	□□□
□□□	□□.□□	□□□	□□□

Ask the child to run along G level at a steady pace from one set of lifts to the next

Record and repeat

Number of steps	Time taken	Pedometer 3	4
□□□	□□.□□	□□□	□□□
□□□	□□.□□	□□□	□□□
□□□	□□.□□	□□□	□□□
□□□	□□.□□	□□□	□□□

Ask the child to stand for 30 seconds then sit for one minute

Ask the child to stand for 30 seconds then recline in position 1 for one minute

Ask the child to stand for 30 seconds then recline in position 1 for one minute

Ask the child to stand for 30 seconds then recline in position 1 for one minute

Ask the child to stand for 30 seconds then lie for one minute

Record and repeat

Position	Time taken	Time taken
Sit	□□.□□	□□.□□
Recline 1	□□.□□	□□.□□
Recline 2	□□.□□	□□.□□
Recline 3	□□.□□	□□.□□
Lie	□□.□□	□□.□□

Health Questionnaire**All Children**

Record time of last eating and drinking

Food

Fluid

Record current medication

Record past medical history

Record parental occupation

Mum

Dad

Record activity level in comparison to child's peers

Less / Same / More

CKD Children only

Record current type of dialysis

CCPD / CAPD / HD

Record last dialysis session

Date

Day

Record current dietary restrictions

Fluid

Phosphate

Sodium

Potassium

Other

Record Oedema on scale

1 / 2 / 3 / 4 / 5

....**Doctors to assess**

1 = none 2 = just detectable 3 = mild < knee

4 = moderate > knee 5 = severe up to thigh / pulmonary oedema

Clinic – CKD children only

Appetite

Bowels

Nausea / Vomiting

Illness recently

Diet Recall

On waking

Breakfast

Mid–morning

Lunch

Mid–afternoon

Dinner

Evening

Night

General comments

Next review date & Action

Appendix 3 Additional tables and figures

Table A3.1 Anthropometric indices (percentage) of boys and girls by group and classification

Table A3.2 Body fat and LBM by SKF and ADP in boys

Table A3.3 Body fat and LBM by SKF and ADP in girls, including girls with oedema

Table A3.4 Body fat and LBM by SKF and ADP in girls, excluding girls with oedema

Table A3.5 BIA in boys and girls by group and oedema status

Table A3.6 BIA impedance index in boys and girls by group and oedema status

Table A5.8 Comparison of studies looking at the effect of kidney function on BMR in adults with CKD

Table A3.1 Anthropometric indices (percentage) of boys and girls by group and classification

Grade [†]	Both groups (n=40)	CKD group (n=20)	Control group (n=20)
Boys			
Weight-for-height[†]			
0	89 (36)	89 (36)	89 (36)
1	11 (4)	11 (4)	11 (4)
2	0	0	0
3	0	0	0
Height-for-age[†]			
0	89 (36)	89 (36)	89 (36)
1	0	0	0
2	11 (4)	11 (4)	11 (4)
3	0	0	0
Girls			
Weight-for-height[†]			
0	77 (31)	73 (29)	82 (33)
1	18 (7)	18 (7)	18 (7)
2	5 (2)	9 (4)	0
3	0	0	0
Height-for-age[†]			
0	95 (38)	91 (36)	100 (40)
1	5 (2)	9 (4)	0
2	0	0	0
3	0	0	0

Results are shown as percentages

No significant differences were found between the groups

[†]Grading: Weight-for-height: 0=normal; 1=80-90%; 2=70-80%; 3=<70% (1 mild, 2 moderate, 3 severe malnutrition)

Height-for-age: 0=normal; 1=90-95%; 2=85-90%; 3=<80% (1 mild, 2 moderate, 3 severe stunting)

Table A3.2 Body fat and LBM by SKF and ADP in boys

Equation	Both groups (n=13)	CKD (n=6)	Control (n=7)	p*
<u>Percent body fat⁺</u>				
Lohman	12.2±5.8	9.8±5.9	14.2±5.4	0.187
Johnston	13.9±7.1	11.4±7.3	16.0±6.7	0.267
Slaughter	18.5±8.9	15.6±8.7	21.1±8.9	0.284
ADP	16.7±7.5	15.2±10.2	18.0±4.6	0.517
<u>Body fat (kg)⁺</u>				
Lohman	6.3±5.0	4.7±3.2	7.6±6.0	0.321
Johnston	7.3±5.9	5.7±4.1	8.7±7.1	0.389
Slaughter	9.5±8.0	7.4±5.2	11.4±9.9	0.392
ADP	7.2±3.3	6.1±4.4	8.1±1.8	0.266
<u>LBM (kg)⁺</u>				
Lohman	41.2±11.7	41.4±13.1	41.0±11.5	0.953
Johnston	40.1±10.6	40.4±11.8	39.9±10.4	0.938
Slaughter	37.9±10.5	38.8±13.1	37.2±8.6	0.398
ADP	39.4±15.7	39.2±17.0	39.6±15.8	0.803
<u>Percentage LBM⁺</u>				
Lohman	87.8±5.9	90.2±5.9	85.8±5.4	0.187
Johnston	86.1±7.1	88.6±7.3	84.0±6.7	0.501
Slaughter	81.5±8.9	84.4±8.7	78.9±8.9	0.267
ADP	82.2±7.5	84.8±10.2	82.0±4.6	0.284

*The P values refer to comparisons between the children with CKD and control group using one-way ANOVA. Results expressed as mean±sd

Equations: Lohman et al 1984; Johnston et al 1988; Slaughter et al 1988

⁺ each equation yields significant different results from the other two equations for % body fat, body fat and lean body mass (LBM)

No boys had clinical oedema

Table A3.3 Body fat and LBM by SKF and ADP in girls including girls with oedema

Equation	Both groups (n=21)	CKD (n=10)	Control (n=11)	p*
<u>Percent body fat</u> ⁺				
Lohman	17.2±5.1	17.1±5.7	17.3±4.8	0.947
Johnston	18.8±5.9	18.9±6.3	18.7±5.9	0.962
Slaughter	20.5±7.1	20.4±7.0	20.6±7.4	0.959
ADP	31.0±13.0	29.2±12.6	32.7±13.7	0.549
<u>Body fat (kg)</u> ⁺				
Lohman	7.9±4.1	6.9±3.5	8.7±4.5	0.310
Johnston	8.8±4.9	7.8±4.4	9.7±5.4	0.394
Slaughter	9.4±5.3	8.2±4.2	10.5±6.1	0.336
ADP	14.1±7.6	11.8±6.3	16.3±8.4	0.188
<u>LBM (kg)</u> ⁺				
Lohman	36.6±12.2	33.2±11.0	39.8±12.8	0.221
Johnston	35.7±11.4	32.2±10.1	38.8±12.0	0.191
Slaughter	35.1±11.6	31.8±10.4	38.0±12.2	0.229
ADP	31.0±9.0	28.2±9.6	33.5±8.1	0.185
<u>Percentage LBM</u> ⁺				
Lohman	82.8±5.1	82.9±5.7	82.7±4.8	0.947
Johnston	81.2±5.9	81.1±6.3	81.3±5.9	0.962
Slaughter	79.4±7.1	79.6±7.0	79.4±7.4	0.959
ADP	69.0±13.0	70.8±12.6	67.3±13.7	0.549

*The P values refer to comparisons between the children with CKD and control group using one-way ANOVA. Results expressed as mean±sd

Equations: Lohman et al 1984; Johnston et al 1988; Slaughter et al 1988

⁺ each equation yields significant different results from the other two equations for % body fat, body fat and lean body mass (LBM)

Table A3.4 Body fat and LBM by SKF and ADP in girls without oedema

Equation	Both groups (n=17)	CKD (n=6)	Control (n=11)	p*
<u>Percent body fat</u> ⁺				
Lohman	17.1±4.8	16.9±5.3	17.3±4.8	0.886
Johnston	18.8±6.0	18.8±6.6	18.7±5.9	0.994
Slaughter	20.0±6.8	19.0±6.1	20.6±7.4	0.660
ADP	28.8±13.10	21.7±8.7	32.7±13.7	0.097
<u>Body fat (kg)</u> ⁺				
Lohman	8.2±4.3	7.3±4.3	8.7±4.5	0.528
Johnston	9.2±5.2	8.3±5.3	9.7±5.4	0.606
Slaughter	9.7±5.8	8.3±5.2	10.5±6.1	0.466
ADP	13.8±8.2	9.3±6.2	16.3±8.4	0.097
<u>LBM (kg)</u> ⁺				
Lohman	37.5±12.3	33.4±11.1	39.8±12.8	0.323
Johnston	36.6±11.5	32.4±10.1	38.8±12.0	0.285
Slaughter	36.0±11.6	32.4±10.2	38.0±12.2	0.356
ADP	32.7±8.3	31.1±9.2	33.5±8.1	0.573
<u>Percentage LBM</u> ⁺				
Lohman	82.8±4.8	83.1±5.3	82.7±4.8	0.886
Johnston	81.2±6.0	81.2±6.6	81.3±5.9	0.994
Slaughter	80.0±6.8	81.0±6.1	79.4±7.4	0.660
ADP	71.2±13.1	78.3±8.7	67.3±13.7	0.097

*The P values refer to comparisons between the children with CKD and control group using one-way ANOVA. Results expressed as mean±sd

Equations: Lohman et al 1984; Johnston et al 1988; Slaughter et al 1988

⁺ each equation yields significant different results from the other two equations for % body fat, body fat and lean body mass (LBM)

Table A3.5 BIA of boys and girls by group

	Both groups	CKD group	Control group	p*
Boys				
Rz	749±104	736±123	765±79	0.625
Ri	495±89	495±92	495±94	0.988
R ₅₀	622±100	616±107	631±101	0.788
Xc ₅₀	73.7±11.3	73.2±12.9	74.4±9.9	0.849
Ri:Rz	0.66±0.05	0.67±0.03	0.64±0.07	0.324
Girls (oedema)				
Rz	806±95	847±89	771±90	0.063
Ri	552±73	586±69	524±66	0.046
R ₅₀	681±81	717±71	651±80	0.052
Xc ₅₀	71.5±12.4	75.0±14.2	68.6±10.5	0.240
Ri:Rz	0.69±0.05	0.69±0.07	0.68±0.04	0.539
Girls (no oedema)				
Rz	798±87	850±56	771±90	0.068
Ri	535±64	557±58	524±66	0.314
R ₅₀	667±75	700±59	651±80	0.204
Xc ₅₀	73±12	81±10	69±11	0.034
Ri:Rz	0.67±0.04	0.66±0.05	0.68±0.04	0.266

*The P values refer to comparisons between the children with CKD and control group, using independent t-tests.

Results expressed as mean±s

Measurements = ohms

R = resistance; Xc = reactance; Rz = Rzero(ECW); Ri = Rinfinity (TBW); R₅₀ = Resistance @50ohms; Xc₅₀ = Reactance @50ohms

No boys had clinical oedema: n=14 (CKD =8; Control=6); Girls (including oedema) n=22 (CKD=10; Control=12); Girls (excluding oedema) n=18 (CKD=6; Control=12).

Table A3.6 BIA index of boys and girls by group

	Both groups	CKD group	Control group	p*
Boys				
Ht ² /Rz	32.1±12.2	32.0±11.8	32.4±13.8	0.953
Ht ² /Ri	50.1±23.1	48.1±19.9	52.7±28.6	0.726
Ht ² /R ₅₀	39.4±16.9	38.5±15.2	40.6±16.9	0.826
Ht ² /Xc ₅₀	323±107	322±119	323±99	0.988
Girls (+odema)				
Ht ² /Rz	28.3±7.4	26.0±7.2	30.3±7.2	0.189
Ht ² /Ri	41.7±11.4	37.9±10.8	44.7±11.4	0.166
Ht ² /R ₅₀	33.7±9.3	30.9±9.0	36.0±9.2	0.389
Ht ² /Xc ₅₀	324±95	305±112	341±80	0.988
Girls (no oedema)				
Ht ² /Rz	29.2±7.4	27.1±7.8	30.3±7.2	0.413
Ht ² /Ri	43.6±11.1	41.4±11.1	44.7±11.4	0.562
Ht ² /R50	35.1±9.2	33.1±9.8	36.0±9.2	0.545
Ht ² /Xc50	325±91	293±113	341±80	0.318

*The P values refer to comparisons between the children with CKD and control group, using independent t-tests.

Results expressed as mean±s

Measurements = ohms

R = resisistance; Xc = reactacne; Rz = Rzero(ECW); Ri = Rinfinity (TBW); R₅₀ = Resistance @50ohms; Xc₅₀ = Reactance @50ohms

No boys had clinical oedema: n=14 (CKD =8; Control=6); Girls (including oedema) n=22 (CKD=10; Control=12); Girls (excluding oedema) n=18 (CKD=6; Control=12).

Table A5.8 Comparison of studies looking at the effect of renal function on BMR in adults with CKD

	Kuhlman	Avesani		Panesar & Agrawal	Avesani
	CKD	CKD	Control	CKD	CKD
Number	51	45	45	16	91
GFR (ml/min/1.73 ²)				71	
Creatinine clearance (ml/min /) (range)	(6.9–52)	29.1±14.6 (6–61)			30.8±14.9 (5–65)
Age	53.2±13.9	44.9±11.7	44.6±11.5	53+9	50.7±12.6
Sex	31 men	20 male	20 male	14 male	56 men
BMI		25.3±4.21	25.7±3.62	39±6.2	25.9±4.2
Weight (kg)	68±6.96			119±24	
Height (cm)	168.7±5.93				
MAMC %		96±11.3	94.9±8.51		
TSF %		106.5±50.9	108.1±36.4		
LBM % (BIA)		71.3±11.3	71.8±7.54		
BF % (BIA)		28.6±11.3	28.1±7.54		
REE	kJ/d 6.787±609 (CI 184)	kcal/d 1325±206 (p=0.01)	kcal/d 1448±258	kcal/d 2724±501	kcal/d 1350±227
REE kcal/d male		1447±221 (p=0.07)	1590±240		
REE kcal/d female		1228±130 (p=0.01)	1327±206		
REE kg/kJ/d	100±4.96 (CI 184)				
REE kcal/LBM/kg/d				41.8±6.5	
REE kJ/min/1.73 ²	4.6±0.18 (CI 0.05)				
REE Kcal/min/1.73 ²		0.92±0.11 (=p0.04)	0.97±11		
Predicted BMR		kcal/d 1445±195	kcal/d 1489±241		
REE/BMR		0.91±0.09 (p=0.01)	0.98±0.12		
Result	↑ REE ↓ RF	borderline		REE ↓ RF ↓	NS

Appendix 4 Abstracts and Posters

Abstracts

BMR in children with chronic kidney disease: BAPEN 2008

The effect of kidney function and body composition in children on basal metabolic rate in chronic kidney disease: ESPN 2009

Posters

Total energy expenditure and energy requirements for children with chronic kidney disease: 2008 Health Foundation meeting

Basal metabolic rate in children with chronic kidney disease: BAPEN 2008

The effect of kidney function and body composition on basal metabolic rate: ESPN 2009

BMR in children with chronic kidney disease

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The data on the effect of chronic kidney disease in children on BMR are conflicting, confusing and limited. This causes difficulty in calculating energy requirements. The aim of the present study was to 1) examine the extent to which BMR in children with CKD differs from that of healthy children and 2) to determine whether resting energy expenditure in a group of children with CKD differs from that of healthy children. The present study involved twenty children with chronic renal failure and twenty control children who did not differ in age (years; 12.1 (SD 3.5) v. 11.8 (SD 3.3)), (weight (kg); 40.1 (SD 14.5) v. 46.3 (SD 16.8)) or (height (m); 1.46 (SD 0.2) v. 1.50 (SD 0.18)). Glomerular

filtration rate (GFR) in the renal group was 34 (SD 19.9) ml/min per 1.732. Z scores were significantly different for weight (– 0.29 (SD 1.15) v. 0.66 (SD 0.99); $P = 0.007$), and BMI (– 0.99 (SD 1.1) v. 0.65 (SD 1.0) $P = 0.031$) but not height (– 0.32 (SD 1.22) v. 0.35 (SD 1.35)). BMR was measured by indirect open circuit calorimetry using Deltatrack II (Datex-Ohmeda, Helsinki, Finland). Children were asked to fast overnight for 12 h and then rest for 30 min in a recumbent position prior to measurements of gaseous exchange. Readings were taken for 30 min in a quiet room with an ambient temperature of approximately 23°C. Energy expenditure was calculated using the equation of Elia and Livesey(1). Predicted BMR was calculated using the Schofield equations for age, gender, weight and height(2). The dry weight of children with chronic kidney disease was estimated by clinical examination by a consultant paediatric nephrologist. GFR was calculated using the Schwartz formula(3,4).

The results show (1) GFR was significantly related to BMR ($R^2 = 0.261$, $R = 0.511$, $P = 0.021$) so that at a GFR of 0 BMR was 91% of predicted BMR and at a GFR of 70 BMR was 112% of predicted BMR. This could not be explained by nutritional status. Thus the significance of this relationship was 0.021 before adjustment for Z scores weight and height and 0.024 after adjustment. (2) There was no significant difference in measured BMR (kJ/d) between the renal and healthy groups either before (5431 (SD 1297) v. 5544 (SD 745); $P = 0.736$) or after adjustment for age and gender (5435 (SE 192) v. 5586 (SE 197); $P = 0.588$). BMR, as a percentage of Schofield predicted values, also did not differ between groups (100 (SD 13) v. 99 (SD 13); $P = 0.768$).

In conclusion, although the BMR of this group of children with chronic renal failure did not differ from that of normal children, this was lower in more severe renal disease (lower GFR), and needs consideration when estimating the energy requirements of children with severe chronic renal failure whose growth is of concern. Consideration also needs to be given to the effects of CKD on total energy expenditure, which includes physical activity.

The Health Foundation funded this project.

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THE EFFECT OF KIDNEY FUNCTION AND BODY COMPOSITION ON BASAL METABOLIC RATE

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Little information has been published on basal metabolic rate (BMR) and children with chronic kidney disease and especially the relationship between glomerular filtration rate (GFR) and BMR. The aim of the present study was to examine the extent to which BMR is affected by renal function in children with chronic kidney disease (CKD) and whether this is independent of body composition.

BMR was measured by indirect open circuit calorimetry following a 12 hour fast. Readings were taken for 30 min in a recumbent position in a quiet room at 23°C. Dry weight was estimated by clinical examination and GFR was calculated using the modified Schwartz formula (1,2). Fat and lean body mass (LBM) was estimated by four site skinfold thickness using Harpenden callipers and the equations of slaughter(3).

Nineteen children were studied. Mean age was 12.1yrs (SD 3.5), weight 40.1kg (SD 14.5) height 1.46m (SD 0.2), GFR 34 (SD 19.9) ml/min per 1.732, percent body fat 20.3 (SD 7.5) and LBM 8.7kg (SD 5.7). GFR significantly affected BMR ($p=0.021$) even after adjustment for percentage body fat ($p=0.037$). Trends were also observed when BMR (kcal/day) was related to GFR adjusted for age sex and LMB ($p=0.08$).

BMR is lower in more severe renal disease and appears to be independent of body composition assessed by skinfold thickness. This finding needs consideration when estimating the energy requirements of children with severe chronic renal failure whose growth is of concern. Consideration also needs to be given to the effects of CKD on total energy expenditure, which includes physical activity.

The Health Foundation funded this project through the leadership through practice award.

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Basal metabolic rate in children with chronic kidney disease

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Introduction

The principles for calculating energy requirements for children with chronic kidney disease (CKD) are not robust. The estimated energy requirements for healthy children are often used as an initial goal for energy prescription. These requirements depend on resting energy expenditure (REE) (basal metabolic rate) and physical activity (PA) both of which are known to alter in CKD. The largest component is REE, but there is limited data on children with CKD.

Aims and Objectives

The overall aim was to examine the extent to which REE is related to renal function in children with CKD and whether overall REE of a group of children with CKD differs from healthy children.

Subjects and Methods

21 children with chronic renal failure and 20 healthy children were studied (19 male, 21 female). The average age was 12.28 (sd 3.3) years and the mean estimated glomerular filtration rate (eGFR) in children with chronic kidney disease was 34 (sd 19.9)ml/min/1.73m².

Measurements undertaken were:

- REE by open circuit indirect calorimetry (Deltatrack II (Datex-ohmeda, Inc. Finland) after an overnight fast.
- Renal function tests to estimate GFR (eGFR)¹.

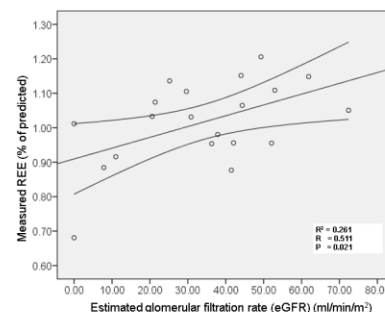
Results

Table 1 Age, anthropometry and estimated GRF (mean \pm sd)

	Renal group (n=21)	Control group (n=20)	P
Age (years)	12.1 \pm 3.5	11.8 \pm 3.3	0.815
Weight (kg)	40.1 \pm 14.4	46.3 \pm 16.8	0.212
Height (m)	1.46 \pm 0.19	1.5 \pm 0.18	0.569
BMI (kg/m ²)	18.1 \pm 2.6	20.0 \pm 4.1	0.077
eGFR (ml/min/m ²)	34 \pm 19.9		
Weight Z score	-0.29 \pm 1.15	0.66 \pm 0.99	0.007
Height Z score	-0.32 \pm 1.22	0.35 \pm 1.35	0.106
BMI Z score	-0.99 \pm 1.1	0.65 \pm 1.0	0.031

No significant difference was found between healthy children and those with disease except for weight and BMI z score (table 1)

Graph 1 REE and estimated GFR



Estimated GFR was significantly related to REE ($p=0.021$) in children with chronic renal Failure (graph 1). At eGFR 0 REE = 91% of predicted by Schofield equation, and at eGFR 70 REE = 112%

Table 2 REE, estimated GFR and nutritional status

	eGFR P value	eGFR by category P value
Before adjustment	0.021	0.026
Adjusted for Z score Wt & Ht	0.024	0.047
Adjusted for Z score BMI	0.013	0.026
Adjusted for Z score Wt, Ht, BMI	0.009	0.024

(Wt = weight, Ht = height) Categories = CKD disease stages 1-5

A significant relationship between estimated GFR and REE remained even after adjustment for nutritional status (table 2)

Table 3 Resting energy expenditure (mean \pm sd)

REE	Renal group (n=21)	Control group (n=20)	P value
Measured (kcal/day)	1298 \pm 310	1325 \pm 178	0.736
Adjusted (kcal/day)	1338 \pm 40	1294 \pm 41	0.471
% of predicted	100 \pm 1.3	99 \pm 1.4	0.768

No significant difference in REE was found between healthy children and those with disease (table 3).

Conclusions

- The study suggests that
 - REE is lower in children with more severe CKD (lower eGFR) & in a group of children with CKD and variable renal function
 - REE did not differ significantly from healthy children.
- Estimated GFR remained an independent explanatory variable after adjustment for weight, height and BMI Z scores.
- Consideration needs to be given to:
 - a) the effect of REE in end stage kidney disease
 - b) the effect of energy requirements on kidney disease on total energy expenditure which includes physical activity.

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The effect of kidney function and body composition on basal metabolic rate

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Objectives and Study

The principles for calculating energy requirements for children with chronic kidney disease (CKD) are not robust. Estimated energy requirements for healthy children is often used as the goal for energy prescription. This depends on resting energy expenditure (REE) / basal metabolic rate (BMR) and physical activity (PA), both of which are known to alter in CKD. The largest component of which is BMR.

Little information had been published on BMR and children with CKD, and the relationship between glomerular filtration rate (GFR) and BMR.

The aim of the present study was to examine the extent to which BMR is affected by kidney function in children with CKD and whether this is independent of body composition (body fat (BF) and lean body mass (LBM)).

Subject and Methods

Nineteen children with CKD were studied (9 male, 10 female). The average age was 12.2yrs (sd 3.5) and the estimated GFR (eGFR) mean was 35ml/min/1.73m² (sd19.6).

Measurements undertaken were: BMR by indirect calorimetry; eGFR calculated using plasma creatinine, height and the modified Schwartz formula (1,2); Body composition by skinfold thickness using harpenden callipers and the equations of Slaughter (3); Estimated dry weight by clinical examination

Results

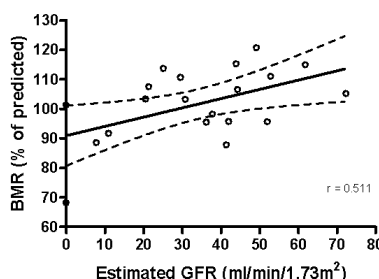
Table shows age, anthropometry and eGFR (mean \pm sd)

	Mean \pm sd
Age (years)	12.19 \pm 3.52
Weight (kg)	40.06 \pm 14.81
Height (kg)	1.47 \pm 0.19
BMI (kg/m ²)	17.92 \pm 2.61
eGFR (ml/min/m ²)	35.27 \pm 19.62
Weight Z score	-0.36 \pm 1.13
Height Z score	-0.33 \pm 1.25
BMI Z score	-0.17 \pm 1.03
BF (%)	20.32 \pm 7.53
LBM (%)	31.37 \pm 10.59

Results

BMR expressed as a percentage of predicted eGFR showed a significant correlation with REE ($p=0.035$; $r=0.485$) even after adjustment for body fat ($p=0.037$; $r=0.494$) or LBM ($p=0.033$; $r=0.492$).

Figure BMR and eGFR



At eGFR 0 REE=91% of predicted, & at eGFR 70 REE = 114%.

A trend was also observed when BMR (kcal/d) was related to eGFR adjusted for age, sex and body fat ($p=0.090$; $r=0.293$).

Conclusions

1. The study suggests that BMR is lower in more severe kidney disease.
2. The relationship between BMR and eGFR seems to be independent of body composition
3. Consideration needs to be given to:
 - a) the effect of BMR in end stage kidney disease in children
 - b) the effects of CKD & the contribution of BMR on total energy expenditure which includes physical activity

Key references

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Total energy expenditure and energy requirements for children with chronic renal failure.

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Introduction

Energy requirements for children with chronic renal failure are currently calculated from estimates of resting energy expenditure (REE) in healthy children. This may be inadequate since disease may not only affect REE but also physical activity (PA) which is the most variable component of total energy expenditure (TEE).

Aims & Objectives

The overall aim of the entire study is to examine whether REE and TEE requirements differ between healthy children and those with chronic renal failure.

This poster addresses the following issues:
Whether REE differs between children with CRF and healthy controls
The extent to which REE is related to renal function, and
The overall status of the project.

Subjects and Methods

21 children with chronic renal failure and 20 healthy control children were studied (19 male, 21 female).
The average age was 12.28 (sd 3.3) years and the Glomerular filtration rate (GRF) mean was 34 (sd 19.9) ml/min/1.73m² for children with renal failure (key stage 3).

Measurements undertaken were:
REE by indirect calorimetry
Renal function tests (blood measurements)
Others (see status of project)

Results

Measure	Renal	Control
Height (m)	1.46 (±0.19)	1.50 (±0.18)
Weight (kg)	40.17 (±14.5)	46.32 (±16.8)
BMR (kcal)	1299 (±313)	1320 (±173)

Presented as mean and standard deviation

No significant difference in BMR was found between healthy children and those with disease (figure 1)

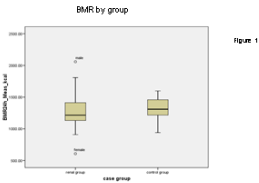
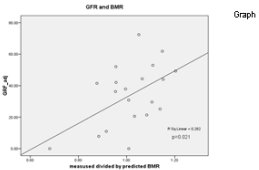


Figure 1

GFR showed a significant correlation with BMR (p=0.021) in children with chronic renal Failure (graph 1)



Graph 1

The similar relationship was found when BMR is adjusted for age, sex, weight and height.

Status of the project

The following measurements have also been made:
Body composition (related to REE) using anthropometry, skinfold thickness, bioelectrical impedance (BIA), & air displacement plethysmography (Bod Pod).
Energy intake using a food diary
PA using the Intelligent Device for Energy Expenditure and Activity (IDEEA), an activity diary and a pedometer
TEE using IDEEA & doubly labelled water (DLW)

Initial analysis of TEE using IDEEA shows a relationship with GFR. DLW analysis (reference for TEE) is still awaited.

Conclusions

BMR is related to the degree of renal function (and TEE measured by IDEEA data not shown).
These results have implications for recommendations for energy requirements for children with chronic renal failure.
Mass spectrometry for DLW analysis is required to complete the study.

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Funding

The health foundation @ health.org.uk

Glossary

Accelerometry	Method of assessing free-living energy expenditure by activity and movement
Activity diary	Method of assessing free-living energy expenditure by activity and duration of time spend per activity in the recent past
Air displacement plethysmography	Method used to measure pressure changes inside a sealed chamber. To measure the volume of air displaced by the subject. Body volume, density, lean and fat mass can then be estimated
Anthropometry	Body measurements made non-invasively to assess body composition, physiological development and nutritional status
Body composition	Proportion of fat, muscle, bone, water and minerals within the body
Basal metabolic rate	Rate at which the body uses energy at complete rest, and requires physical and mental rest, in thermo neutral conditions and fasted.
Bioelectrical impedance	Method used to measure body impedance by passing a small electrical current through two specific points in the body. The impedance is produced by the change in voltage within the body.
Body Mass Index	Index used to assess body fatness
Component models	Framework to help conceptualise body composition
Dietary intake	Process of estimating and/or measuring the amount, type and frequency of food and fluid consumed

Diet history	A method used to record all food and fluid consumed over the recent past
Dietary reference value	Term used to express an estimated need for any nutrient
Doubly labelled water	Method used to determine total body water, fat and lean mass and energy expenditure by the use of isotopes of oxygen and hydrogen
Energy balance	Difference between energy intake and expenditure
Energy expenditure	Term used to describe the energy used/needed by the body
Energy intake	Energy content of food and fluid consumed
Energy requirements	Level of food energy required to maintain a healthy body weight in otherwise healthy people at existing levels of physical activity
Estimated average requirement	Term used to describe of any nutrient at which half a population would require more and half less
Estimated dietary record (EDR)	Records all food and fluid consumed at the time of recording in household measures or portion sizes without the use of estimation aides
Growth	Physical term given to the increase in size and complexity of the body structure, requiring endocrine and genetic regulation
Fat mass	All extractable lipids from adipose tissue and other tissues in the body

Fat free mass	All residual lipid-free chemicals and tissues including water, muscle, bone, connective tissues and internal organs
Food diary	Method of assessing food and fluid consumed in free-living conditions, see 24HR & EDR
Heart rate monitoring	Measures daily TEE in free-living conditions using the relationship between heart rate and oxygen consumption
Indirect calorimetry	Measurement of oxygen and carbon dioxide production using a gaseous exchange analyser
IDEEA	Type of accelerometry used to assess daily physical activity behaviour under controlled or free-living condition. Estimations of TEE can also be made
Kilocalorie / Kilojoule	Term used to describe the energy value of food
Lean body mass	FFM and essential lipids
Physical activity	Any type of body movement resulting in energy expenditure produced by the contraction of skeletal muscles
Physical activity level	Total energy expenditure as a multiple of BMR
Physical activity energy expenditure	Component of energy expenditure related to physical activity
Physical activity ratio	Duration and energy cost of physical activities, expressed as multiples of BMR
Resting energy expenditure	Term used when BMR conditions cannot be met completely

Skinfold thickness	Method used to estimate the amount of subcutaneous fat using a skinfold caliper
Spontaneous physical activity	Body movements associated with activities of daily living, changes in posture and includes fidgeting
Thermic effect of feeding	Metabolic cost of food from ingestion through to digestion, absorption and metabolism
Total energy expenditure	Sum of BMR, TEF, PAEE
Twenty four hour recall (24HR)	Records all food and fluid consumed in the recent past, usually last 24 hours and uses household measures to record information

Glossary of statistical terms

Analysis of variance	Test for the significant difference between one or more things
Bland and Altman analysis	Statistical comparison used to compare to methods/tests
Confidence intervals	Confidence in the interval within which the population parameter will be found
Dependent variable	Measure under observation / Outcome variable
Descriptive statistics	Values that describe the characteristics of a population
Evidence based practice	Treatments and procedures based upon research
Hypothesis	Statement of supposition that related variables to each other
Independent variable	Treatment or predictor variable that could influence the dependent variable
Linear regression	A correlation technique where an average line is drawn between data points on a scatterplot, to give the strength of the association between variables
Mean	Average of values added together and divided by the total number of values
Null hypothesis	Hypothesis that there is a zero effect in the population
Standard deviation	A standardised measure of the deviation of scores in a sample from the mean
One way ANOVA	Analysis of variance for one independent variable
Reliability	Repeatability of values
Statistical power	The ability of the study to detect a whether the difference exists in the test population
Statistical significance	A statistical test P-value calculated for to enable the null hypothesis to be rejected
T-test	A parametric test used to determine the significance of two variables
Validity	Accuracy of values
Z score	Score adjusted for the mean and standard deviation of the distribution of scores

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