Proceedings of the Nutrition Society (2002), **61**, 321–327 DOI:10.1079/PNS2002164

The Annual Meeting of the Clinical Nutrition and Metabolism Group of the Nutrition Society with the British Association for Parenteral and Enteral Nutrition was held at Harrogate International Centre, Harrogate on 13–15 November 2002

Sir David Cuthbertson Medal Lecture

Understanding chronic malnutrition in childhood and old age: role of energy balance research

John J. Reilly
University of Glasgow Department of Human Nutrition, Royal Hospital for Sick Children, Dalnair Street, Glasgow G3 8SJ, UK

Undernutrition is commonly associated with chronic disease in children and the elderly. Overnutrition is also, but less commonly, associated with chronic illness. In most diseases malnutrition arises because energy intake does not match energy output. Traditionally, the focus of research has been on abnormalities in energy expenditure, in the belief that these factors were the main determinants of energy imbalance. Recent studies using the doubly-labelled-water method to measure total energy expenditure, combined with more complex study design, have suggested an alternative conclusion. In many chronic diseases patient behaviour, and particularly energy intake, is responsible for energy imbalance and malnutrition. Energy balance studies have therefore provided a useful foundation for the design of strategies aimed at preventing or managing chronic malnutrition. However, modifying patient behaviour is an ambitious undertaking which may not be within the scope of existing clinical nutrition services. A number of non-traditional models of managing chronic malnutrition in children and the elderly are promising. Increasing recognition of the value of systematic review will also provide improved strategies for prevention and management of chronic malnutrition.

Chronic illness: Critical illness: Energy requirements: Energy expenditure: Nutritional support: Doubly-labelled-water method

Background: undernutrition and overnutrition in chronic disease

It has long been recognised that chronic disease is associated with, and indeed causes, undernutrition. Undernutrition, in turn, increases susceptibility to disease. The elderly are at particular risk of undernutrition, largely because disease is common in older adults, and compromises maintenance of energy balance. Sick infants, and to a lesser extent children, are also particularly susceptible to negative energy balance and undernutrition. Infants and children are also especially vulnerable to the functional effects of undernutrition, because of the sensitivity of many developing biological systems. In a few chronic diseases overnutrition is a greater risk than undernutrition and, like undernutrition, adverse functional consequences are to be expected. In summary, undernutrition and overnutrition usually result from chronic negative or positive energy balance secondary to disease. Both forms of malnutrition should be of concern because of their functional and clinical consequences. The principal aim of the present review is to consider the contribution which research on energy balance can make to improving the management of chronic malnutrition in children and the elderly.

Measurement of energy balance in disease states: rationale and applications

In essence, energy balance is both very simple and extremely important clinically. By definition, energy balance refers to the difference between energy (food) intake and the sum of the energy outputs (principally total energy expenditure; TEE). Positive balance means that the excess energy must be stored, negative balance means that the energy deficit must be made good by oxidation of body tissues, reduction in TEE and/or compromised growth (in

Abbreviations: ALL, acute lymphoblastic leukaemia; CF, cystic fibrosis; DLW, doubly-labelled water; REE, resting energy expenditure; TEE, total energy expenditure.

Corresponding author: Dr John J. Reilly, fax +44 141 201 9275, email jjr2y@clinmed.gla.ac.uk

Table 1. Studies of total energy expenditure (TEE) using the doubly-labelled-water method in chronic diseases of childhood

Study	Disease	Design	Conclusions
Barden *et al.* (2000)	Sickle cell disease (SCD)	Patients (*n* 36) *v.* healthy controls (*n* 30)	Elevated REE, but not TEE, in SCD
Stallings *et al.* (1996)	Spastic quadriplegic cerebral palsy (SQCP)	Patients (*n* 32) *v.* healthy controls (*n* 32)	Reduced TEE in SQCP
Motil *et al.* (1998)	Rett syndrome (RS)	Patients (*n* 14) *v.* healthy controls (*n* 11)	Elevated REE, but not TEE, in RS
Reilly *et al.* (1998)	Acute lymphoblastic leukaemia (ALL)	Patients (*n* 20) *v.* pair-matched healthy controls (*n* 20) and *v.* estimated average requirements (EAR)	Reduced TEE in ALL, below EAR
Bland *et al.* (2001)	Obstructive sleep apnoea syndrome (OSAS)	Patients (*n* 11) before *v.* after surgery, and compared with pair-matched controls (*n* 22) and with EAR	Elevated REE, but not TEE, in childhood OSAS
Reilly *et al.* (1999*a*)	Cystic fibrosis (CF)	Fourteen children during acute exacerbation *v.* when stable and *v.* EAR	No elevation of TEE
Bronstein *et al.* (1995)	CF	Presymptomatic infants (*n* 18) *v.* retrospective controls (no. of controls not given)	No elevation of TEE
Shepherd *et al.* (1988)	CF	Clinically-stable infants (*n* 9) *v.* healthy retrospective controls (*n* 16)	Increase in TEE in CF, inconclusive
Tomeszko *et al.* (1994)	CF	Stable patients (*n* 25) *v.* healthy controls (*n* 25)	Elevated TEE in CF (?), dependent on genotype

infancy and childhood). Chronic energy imbalance is not an epiphenomenon, but must ultimately have adverse clinical consequences.

Historically, identifying the precise causes of energy imbalance in many diseases has been difficult. This difficulty arose in part because of the complex origins of energy imbalance in many diseases, i.e. a combination of disease effects on patient behaviour, energy intake, digestion or absorption and intermediary metabolism. A further serious difficulty was the inability to accurately measure TEE, the principal determinant of energy requirement. This situation led to a dependence on measurement of resting energy expenditure (REE) in disease states. Measures of REE alone are not very informative when trying to identify causes of energy imbalance, and many studies based exclusively on measurement of REE have produced misleading conclusions (Reilly *et al.* 1997).

The advent of the doubly-labelled-water (DLW) method has revolutionised our understanding of human energy balance. It has high accuracy, with a mean error of <2 % (Speakman, 1998), is relatively straightforward for the subjects being measured, and measures TEE in free-living conditions. The fact that DLW measures TEE, rather than its individual components, makes it an extremely useful approach for assessment of energy needs; it is much more informative than the more traditional experimental approach of only measuring REE. While REE measurements are relatively easy to make, they are difficult to interpret, since any increase or decrease in REE as a result of disease need not be associated with an increase or decrease in TEE (Jebb, 1997; Gibney, 2000). The best-known clinical example of this problem is in adults with HIV infection, where it was assumed that increased REE caused undernutrition. In fact, TEE was low, not high, during periods of weight loss, indicating that undernutrition was the result of compromised energy (food) intake (Macallan *et al.* 1995). Similar conclusions have been reached in a number of chronic diseases of childhood which are characterised by abnormal REE and energy imbalance (Table 1). In old age there is also a good deal of evidence that TEE is low in disease, not high (Prentice *et al.* 1989; Reilly *et al.* 1995). Even in diseases of old age where increased REE has been observed TEE is consistently low (Toth *et al.* 1997; Toth & Poehlman, 2000).

Methodology available for measuring energy balance, and particularly measurement of TEE by DLW, has a number of other important clinical applications. The methodology has been used by our research group to: test hypotheses in relation to causes of energy imbalance (Reilly *et al.* 1996, 1998, 1999*a*; Bland *et al.* 2001); validate clinical methods, such as methods of dietary intake assessment (Reilly *et al.* 2001*c*); assess clinical algorithms for estimating energy needs (Reilly *et al.* 1999*c*).

Energy balance studies in the elderly

Chronically- and acutely-sick elderly patients show a high prevalence of undernutrition, which increases with increasing dependency and disease (Morgan *et al.* 1986). Occasional studies of energy intake had suggested that in some diseases of old age energy intake was adequate, but assessments of energy intake alone (in the absence of measures of TEE) tend to be both inaccurate and imprecise. Use of the DLW method in the healthy elderly (Reilly *et al.* 1993) and chronically- and acutely-sick elderly (Reilly *et al.* 1992, 1995) revealed that energy requirements were exceptionally low in the sick-patient groups. Individuals with low levels of energy expenditure should, in principle, be prone to overnutrition not undernutrition. The apparently paradoxical association between low energy requirements and undernutrition is explained by the observation that it is inadequate energy intake which is usually the main cause of undernutrition in the elderly (Toth & Poehlman, 2000). The elderly may be particularly susceptible to negative energy balance. Some evidence suggests that elderly subjects have diminished capacity to adaptively 'respond' to a period of inadequate food intake, by failing to increase energy intake appropriately (Roberts *et al.* 1994).

https://doi.org/10.1079/PNS2002164 Published online by Cambridge University Press

In one of our studies of elderly patients admitted to hospital with acute illness TEE was very low, but simultaneous measurements of energy intake demonstrated that, despite low TEE, patients were in substantial negative energy balance (on average −1·3 MJ/d; Klipstein *et al*. 1995). This factor was of particular concern because these patients were typically undernourished on admission to hospital, and a further marked deterioration in nutritional status was observed during hospitalisation (Potter *et al*. 1995).

From energy balance studies to treatment of undernutrition in the elderly

As noted earlier, the role of energy expenditure in undernutrition is negligible in most patients, and they become undernourished despite low energy needs, not because of high energy needs. Focus on energy intake as the principal determinant of undernutrition in chronic disease is therefore necessary, but this situation has required a paradigm shift. In clinical practice emphasis should be placed on strategies for supporting energy intake. In order to identify successful strategies it is essential to test the evidence base to consider the extent to which current clinical nutrition practices, such as enteral supplementation, are supported by unbiased generalisable empirical evidence. Such questions can be successfully addressed by systematic review, critical evidence appraisal and, where appropriate, meta-analysis.

An important meta-analysis of randomised controlled trials in enteral supplementation of adults was undertaken by Potter *et al*. (1998). This meta-analysis showed that enteral supplementation had positive effects on energy intake and indices of nutritional status such as body-weight change. These conclusions were deemed generalisable across many diverse clinical settings. This study provided a basis for enteral supplementation, but also identified important unanswered questions such as the effect of enteral supplementation on morbidity and mortality. It may seem surprising that questions of such importance in clinical nutrition are unanswered, but systematic review is very effective at highlighting what we do not know. In response to this meta-analysis, and our earlier evidence of undernutrition exacerbated by negative energy balance during hospitalisation, we designed a study to test the hypothesis that sip-feed supplements could improve morbidity and mortality in elderly patients admitted to hospital with acute medical problems. We used a single blind randomised controlled trial design. Emergency medical admissions (*n* 381) from home were randomly allocated to control (standard care) or intervention. The intervention consisted of prescriptions of 3 × 120 ml of a sip-feed, administered on three separate occasions each day at drug rounds, intended to provide 2257 kJ (540 kcal)/d if all were consumed. Administration of supplement in this unorthodox way was intended to maximise compliance with sip-feeding, to provide a means of quantifying compliance, and avoid the non-compliance with supplementation common in sip-feeding (Sridhar *et al*. 1994). The amount of sip-feed prescribed was constant, and intended to eliminate the negative energy balance previously observed in these patients (Klipstein *et al*. 1995; Potter *et al*. 1995). A variety of outcomes were assessed weekly until hospital discharge (mortality, functional ability, length of hospital stay, energy intake, anthropometric indices). We found that supplementation was associated with reduced morbidity and mortality, functional improvements and reduced hospital stay (Potter *et al*. 2001). The benefits were most marked in the most-poorly-nourished patients. This study has provided important evidence to support the use of sip-feed supplementation as a strategy for support of energy intake in elderly hospital patients.

Sip-feeding is of course not the only available clinical option to support energy intake, but it is now firmly evidence-based. In some other diseases characterised by undernutrition research has also progressed from an understanding of the underlying mechanisms (such as the role of the inflammatory response in cachexia) to promising novel treatment strategies (Wigmore *et al*. 1997; Barber *et al*. 1999), and these strategies are now being tested using randomised controlled trials. A general model for improving clinical nutrition strategies is to use systematic review to explicitly identify what is known and what is not known, test for the underlying mechanisms of undernutrition if necessary and design treatments which target the underlying mechanisms. These treatments can then be rigorously tested by randomised controlled trials, the most appropriate means of obtaining unbiased evidence. Obtaining evidence from clinical studies is both difficult and time-consuming, but the examples described earlier show that it is possible.

Energy balance studies in children

Our research group has carried out investigations of overnutrition (obesity) in children with acute lymphoblastic leukaemia (ALL), the most common childhood malignancy. We have also investigated the causes of undernutrition in children with cystic fibrosis (CF), obstructive sleep apnoea syndrome and HIV infection. A detailed description of this work would go beyond the scope of the present review, so the aims here are to briefly summarise the research, to highlight lessons for clinical management of energy imbalance, and to identify research strategies and methods which exist to identify the causes of energy imbalance in chronic disease.

Energy balance and overnutrition in acute lymphoblastic leukaemia

At diagnosis undernutrition is relatively common in children with ALL (Reilly *et al*. 1999*b*), which may have important clinical consequences (Reilly *et al*. 1994; Weir *et al*. 1998). After diagnosis children with ALL gain weight rapidly, in excess of expected rates (Odame *et al*. 1994; Reilly *et al*. 2000). They maintain the excess weight or continue to gain weight excessively even after therapy has ended (typically 2–3 years post diagnosis). An extremely high prevalence of obesity is observed in survivors during childhood, adolescence and adulthood (Didi *et al*. 1995; Ventham & Reilly, 1999; Reilly *et al*. 2000). Children with ALL also have advanced ‘adiposity rebound’, an independent risk factor for adult obesity (Reilly *et al*. 2001*b*). Obesity is of increasing

https://doi.org/10.1079/PNS2002164 Published online by Cambridge University Press

concern in ALL, as it is just one of a number of 'late effects' which are manifest as therapy for childhood cancer improves.

We have systematically tested the underlying mechanisms of weight gain in ALL. Overnutrition in ALL is complex, and could arise from any one or a combination of factors related to treatment (e.g. 'steroid effects' on appetite), lifestyle (changes in habitual physical activity), or reduced REE (Ventham & Reilly, 1999). By systematically testing hypotheses using modern techniques of energy expenditure measurement we have shown that REE is normal in ALL (Reilly *et al*. 1996), but that TEE, measured using DLW, is substantially reduced relative to controls before children become obese. In addition, TEE is predictive of subsequent weight gain (Reilly *et al*. 1998). This reduction in TEE secondary to reduced habitual physical activity in children with ALL confirms an important behavioural or 'lifestyle' component to the development of obesity in ALL. Some treatment effects also contribute. We recently demonstrated that the glucocorticoids used in 'maintenance' chemotherapy for ALL (5 d of steroid treatment with prednisolone or dexamethasone every 28 d) substantially increase energy intake (Reilly *et al*. 2001*a*). This response might not seem unexpected, but a literature review revealed almost no empirical evidence on the effects of corticosteroids on energy intake in clinical studies, and no evidence in children (Reilly *et al*. 2001*a*).

By systematically applying modern techniques of nutritional assessment (e.g. monitoring changes in BMI standard deviation score longitudinally) and energy expenditure (e.g. DLW), we have been able to both describe the natural history of obesity in ALL, and to identify its principal causes. The major remaining challenge is to test whether this knowledge can be used to design effective strategies for prevention of obesity in ALL. Patient behaviour (physical activity and inactivity) is clearly a component of the problem, and to modify the activity level of patients represents the most likely solution, since the scope for modifying drug treatment is limited.

Undernutrition in cystic fibrosis: energy balance studies

Despite a number of improvements in diagnosis and treatment of CF, undernutrition remains common (Morison *et al*. 1997). Undernutrition is widely believed to be due to chronic negative energy balance, but its origins appear to be complex (Reilly *et al*. 1997). CF has a number of features which might predispose patients to negative energy balance: energy intake may be compromised episodically or chronically (Scott *et al*. 1985; Stark *et al*. 1995); faecal energy losses are relatively high as a result of deficits in digestion or absorption (Murphy *et al*. 1991); REE is generally increased, although whether this increase produces an increase in TEE was open to question (Reilly *et al*. 1997). Recent studies by our own group and others suggest that TEE is normal or even low in most patients with CF (Table 1). This observation focuses attention on inadequate energy intake and control of faecal energy losses as more likely causes of undernutrition in CF, and as promising targets for treatment. The most productive means of identifying the causes of undernutrition in CF, and assessing their relative importance, has been to measure all components of energy balance simultaneously (Reilly *et al*. 1997), including TEE by the DLW method, and to study patients during periods of nutritional stress (Reilly *et al*. 1999*a*). The more traditional approach, in CF and other diseases, has been to measure only REE, and to study patients when they are well and clinically stable. The traditional approach has not been particularly informative, and the more complex approach, outlined in Table 2, is essential if mechanisms of negative energy balance and undernutrition are to be understood.

Table 1. Recommendations for identifying causes of energy imbalance in complex disease states

Methods
Measure all components of energy balance (REE, TEE, energy intake)
Measure energy balance components simultaneously, in same patient
Measure TEE using DLW where possible
Measure body composition appropriately, taking account of effects of disease on methodology
Setting and design
Study patients during periods of clinical instability or nutritional stress
Use longitudinal studies
Consider multicentre studies to provide sufficient sample size, power and generalisability
Consider using each patient as his (her) own control
Choose appropriate controls or match for main determinants of energy expenditure

REE, resting energy expenditure; TEE, total energy expenditure; DLW, doubly-labelled water

Undernutrition in cystic fibrosis: from energy balance to treatment strategies

The research described earlier suggests an important role for patient lifestyle in the management or prevention of undernutrition in CF. This role includes compliance with the diet prescription and pancreatic enzyme-replacement therapy. Several other lines of evidence support this view. First, our own studies have shown that in some patients the effect of poor compliance with therapy can have large effects in energy balance terms (Reilly *et al*. 1999*a*). Second, in both the UK and USA socio-economic status is a major determinant of clinical outcome (for example, see Schechter & Margolis, 1998), independent of access to medical care. Third, reduced doses of pancreatic enzyme-replacement therapy can actually improve growth and nutritional status, probably as a result of improved compliance with pancreatic enzyme-replacement therapy (Lowdon *et al*. 1998). The most convincing evidence comes from randomised controlled trials in which families of children with CF receive intensive therapy directed at achieving changes in patient behaviour (for example, see Jelalian *et al*. 1998). By teaching strategies which enable children and families to increase food intake and comply with therapy, nutritional status can be substantially improved in children with CF. This approach may be a useful model for improving nutritional status in other chronic diseases of childhood (Mackner *et al*. 2001). This research also implies that the more

https://doi.org/10.1079/PNS2002164 Published online by Cambridge University Press

traditional medical model of prescribing medication and/or supplements, with a little patient education, is insufficient to prevent or manage undernutrition successfully.

Approaching the problem of undernutrition in CF from a cognitive or behavioural viewpoint, therefore, appears to be a successful evidence-based strategy. However, the cognitive or behavioural approach may not be readily generalisable, because it requires an intensive input of resources and access to health professionals not widely available, such as clinical psychologists. Nevertheless, recognising that patient behaviour can be central to managing malnutrition in chronic disease, and setting out to change patient behaviour, appears to be worthwhile, but requires a fundamental change in our approach to the treatment of many diseases. A number of other examples of the success of novel behavioural approaches to nutritional treatment exist in diverse chronic diseases in both children and adults (for example, see Wright *et al*. 1998; Epstein *et al*. 2000; Jeffery *et al*. 2000).

An important systematic review concluded recently that traditional clinical approaches to managing undernutrition in children, such as enteral supplementation, are not evidence-based at present (Poustie *et al*. 2002). This conclusion not only questions our standard clinical methods, but clearly and specifically identifies important research needs, a similar outcome to the systematic review of enteral supplementation in adults (Potter *et al*. 1998). This absence of a sound evidence base to clinical practice is not unique to undernutrition, but also applies to childhood obesity (Reilly *et al*. 2002), and to paediatric practice in general (Smyth, 2001). However, not being uniquely disadvantaged in terms of our evidence base is little consolation; it still represents an important challenge to clinical nutrition research.

Conclusions

The advent of the DLW method has made it possible to definitively identify causes of overnutrition and undernutrition in chronic disease. The method is particularly effective when combined with simultaneous measurements of energy intake, REE and appropriate measures of body composition. Longitudinal studies which include periods of nutritional stress or weight loss are also particularly informative as to causes of weight loss. In many chronic diseases the underlying causes of malnutrition have now been identified as a result of applying modern energy balance methods. Chronic disease is rarely, if ever, associated with increased TEE. In most cases the evidence strongly suggests that patient behaviour in general, and energy intake in particular, is the main determinant of undernutrition or overnutrition. Even when patient behaviour is not the underlying cause of the nutritional problem, modifying behaviour is likely to be part of the solution. This approach is likely to require a major revision of the way in which we manage or prevent chronic malnutrition, with greater emphasis on the need to understand and modify patient behaviour.

Systematic review provides a powerful means of identifying the evidence base for clinical nutrition. It can usefully identify research needs and improve treatment strategies. Systematic review can also deal with the problem noted by Mark Twain: ‘It aint the things we know which are the problem, it’s the things we know that aint so’.

Acknowledgements

I am indebted to a great many collaborators and mentors. The work described here refers to a programme of research over 11 years, and so the number of colleagues, and funding bodies, who merit an acknowledgement is too great to list here. I thank them all.

References

Barber MD, Ross JA, Preston T, Shenkin A & Fearon KCH (1999) Fish oil enriched nutritional supplement attenuates progression of the acute phase response in weight losing patients with advanced pancreatic cancer. *Journal of Nutrition* **129**, 1120–1125.

Barden EM, Zemel BS, Kawchack DA, Goran MI, Ohere-Frempony K & Stallings VA (2000) Total and resting energy expenditure in children with sickle cell disease. *Journal of Pediatrics* **136**, 73–79.

Bland RM, Bulgarelli S, Ventham JC, Jackson D, Reilly JJ & Paton JY (2001) Total energy expenditure in children with obstructive sleep apnoea syndrome. *European Respiratory Journal* **18**, 164–169.

Bronstein MN, Davies PSW, Hambridge KM & Accurso FJ (1995) Normal energy expenditure in the infant with presymptomatic cystic fibrosis. *Journal of Pediatrics* **126**, 28–33.

Didi M, Didcock E, Davies HA, Ogilvy-Stuart AL, Wales JKH & Shalet SM (1995) High incidence of obesity in young adults after treatment of acute lymphoblastic leukaemia in childhood. *Journal of Pediatrics* **127**, 163–167.

Epstein LH, Paluch RA, Gordy CC & Dorn J (2000) Decreasing sedentary behaviours in treating pediatric obesity. *Archives of Pediatrics and Adolescent Medicine* **154**, 220–226.

Gibney ER (2000) Energy expenditure in disease: time to revisit? *Proceedings of the Nutrition Society* **59**, 199–247.

Jebb SA (1997) Energy metabolism in cancer and human immunodeficiency virus infection. *Proceedings of the Nutrition Society* **56**, 763–775.

Jeffery RW, Drewnowski A, Epstein LH, Stunkard AJ, Wilson GT, Wing RR & Hill DR (2000) Long term maintenance of weight loss: current status. *Health Psychology* **19**, 5–16.

Jelalian E, Stark LJ, Reynolds L & Seifer R (1998) Nutrition intervention for weight gain in CF: a meta-analysis. *Journal of Pediatrics* **132**, 486–492.

Klipstein K, Reilly JJ, Potter J, Edwards CA & Roberts MA (1995) Energy intake and expenditure in elderly patients admitted to hospital with acute illness. *British Journal of Nutrition* **73**, 323–334.

Lowdon JL, Goodchild MC, Ryley HC & Doull IJM (1998) Maintenance of growth in CF despite reduction in pancreatic enzyme supplementation. *Archives of Disease in Childhood* **78**, 377–378.

Macallan DC, Noble C, Baldwin C, Jebb SA, Prentice AM, Coward WA, Sawyer MB, McManuys TJ & Griffin GE (1995) Energy expenditure and wasting in HIV infection. *New England Journal of Medicine* **333**, 83–88.

Mackner LM, McGrath AM & Stark LJ (2001) Dietary recommendations to prevent and manage chronic pediatric health conditions: adherence, intervention, and future directions. *Journal of Developmental and Behavioural Pediatrics* **22**, 130–143.

https://doi.org/10.1079/PNS2002164 Published online by Cambridge University Press

Morgan DB, Newton HM, Schorah CJ, Jewitt MA, Hancock MR & Hullin RP (1986) Abnormal indices of nutrition in the elderly: a study of different clinical groups. *Age and Ageing* **15**, 65–76.
Morison S, Dodge JA, Cole TJ, Lewis PA, Coles EC, Geddes D, Russell G, Littlewood JM & Scott MT (1997) Height and weight in CF: cross sectional study. *Archives of Disease in Childhood* **77**, 497–500.
Motil KJ, Schultz RJ, Wong WW & Glaze DG (1998) Increased energy expenditure associated with repetitive involuntary movement does not contribute to growth failure in girls with Rett Syndrome. *Journal of Pediatrics* **132**, 228–233.
Murphy JL, Wootton SA, Bond SA & Jackson AA (1991) Energy content of stools in normal healthy controls and patients with CF. *Archives of Disease in Childhood* **66**, 495–500.
Odame I, Reilly JJ, Donaldson M & Gibson BES (1994) Patterns of obesity in boys and girls following therapy for acute lymphoblastic leukaemia. *Archives of Disease in Childhood* **71**, 147–149.
Potter J, Klipstein-Grobusch K, Reilly JJ & Roberts MA (1995) The nutritional status and clinical course of acute admissions to a geriatric unit. *Age and Ageing* **24**, 131–136.
Potter J, Langhorne P & Roberts M (1998) Routine protein energy supplementation in adults: systematic review. *British Medical Journal* **317**, 495–501.
Potter JM, Roberts MA, McColl JH & Reilly JJ (2001) Protein-energy supplements in unwell elderly patients: a randomised controlled trial. *Journal of Parenteral and Enteral Nutrition* **25**, 323–329.
Poustie VJ, Smyth RL & Watling RM (2002) Oral protein calorie supplementation for children with chronic disease. *The Cochrane Library* 1, 2002. Oxford: The Cochrane Library.
Prentice AM, Leavesley K, Murgatroyd PR, Coward WA, Schorah CJ, Bladon PT & Hullin RP (1989) Is severe wasting in elderly mental patients caused by an excessive energy requirement? *Age and Ageing* **18**, 158–167.
Reilly JJ, Blacklock CJ, Dale E, Donaldson M & Gibson BE (1996) Resting metabolic rate and obesity in childhood acute lymphoblastic leukaemia. *International Journal of Obesity* **20**, 1130–1132.
Reilly JJ, Brougham M, Montgomery C, Richardson F & Gibson BES (2001*a*) Effect of glucocorticoid therapy on energy intake in children treated for acute lymphoblastic leukemia. *Journal of Clinical Endocrinology and Metabolism* **86**, 3742–3745.
Reilly JJ, Edwards CA & Weaver LT (1997) Malnutrition in cystic fibrosis: the energy balance equation. *Journal of Pediatric Gastroenterology and Nutrition* **25**, 127–136.
Reilly JJ, Kelly A, Ness P, Dorosty AR, Wallace WHB, Gibson BES & Emmett PM (2001*b*) Premature adiposity rebound in children treated for acute lymphoblastic leukemia. *Journal of Clinical Endocrinology and Metabolism* **86**, 2775–2778.
Reilly JJ, Lord A, Bunker VW, Prentice AM, Coward WA & Briggs RS (1992) Energy balance and physical activity in healthy women and women with chronic illness. *Age and Nutrition* **3**, 121–122.
Reilly JJ, Lord A, Bunker VW, Prentice AM, Thomas A, Briggs RS & Coward WA (1993) Energy balance in healthy elderly women. *British Journal of Nutrition* **69**, 21–27.
Reilly JJ, Lord A, Bunker VW, Prentice AM, Thomas A, Coward WA & Briggs RS (1995) Total energy expenditure as measured by doubly-labelled water in two groups of elderly female inpatients. *Age and Nutrition* **6**, 10–15.
Reilly JJ, Montgomery C, Jackson D, MacRitchie J & Armstrong J (2001*c*) Energy intake by multiple pass 24 hour recall and total energy expenditure: a comparison in a representative sample of 3–4-year-olds. *British Journal of Nutrition* **86**, 601–605.
Reilly JJ, Odame I, McColl J & Gibson BS (1994) Does weight for height have prognostic significance in children with acute lymphoblastic leukemia? *American Journal of Pediatric Hematology and Oncology* **16**, 225–230.
Reilly JJ, Ralston JM, Paton JY, Edwards CA, Weaver LT, Wilkinson J & Evans TJ (1999*a*) Energy balance during acute respiratory exacerbations in children with cystic fibrosis. *European Respiratory Journal* **13**, 804–809.
Reilly JJ, Ventham JC, Newell J, Aitchison T, Wallace WHB & Gibson BES (2000) Risk factors for excess weight gain in children treated for acute lymphoblastic leukaemia. *International Journal of Obesity* **24**, 1537–1541.
Reilly JJ, Ventham J, Ralston JM, Donaldson M & Gibson BES (1998) Reduced energy expenditure in pre-obese children treated for acute lymphoblastic leukemia. *Pediatric Research* **44**, 557–562.
Reilly JJ, Weir J, McColl JH & Gibson BES (1999*b*) Prevalence of protein-energy malnutrition at diagnosis in children treated for acute lymphoblastic leukemia. *Journal of Pediatric Gastroenterology and Nutrition* **29**, 194–197.
Reilly JJ, Wilkinson J, Evans TJ & Paton JY (1999*c*) Adequacy of clinical formulae for estimation of energy requirements in children with cystic fibrosis. *Archives of Disease in Childhood* **81**, 120–124.
Reilly JJ, Wilson M, Summerbell CD & Wilson D (2002) Childhood obesity: evidence based answers to common clinical questions. *Archives of Disease in Childhood* (In the Press).
Roberts SB, Fuss P, Heyman MB, Evans WJ, Tsay R, Rasmussen H, Fiatarone M, Cortella J, Dallal GE & Young VR (1994) Control of food intake in older men. *Journal of the American Medical Association* **272**, 1601–1606.
Schechter MS & Margolis PA (1998) Relationship between socio-economic status and disease severity in CF. *Journal of Pediatrics* **132**, 260–264.
Scott RB, O'Laughlin EV & Gall DG (1985) Gastro-oesophageal reflux in CF. *Journal of Pediatrics* **108**, 223–227.
Shepherd RW, Vasques-Velasquez L, Prentice AM, Holt TL, Coward WA & Lucas A (1988) Increased energy expenditure in young children with CF. *Lancet* **i**, 1300–1303.
Smyth RL (2001) Research with children: paediatric practice needs better evidence – gained in collaboration with parents and children. *British Medical Journal* **322**, 1377–1378.
Speakman JR (1998) The history and theory of the doubly labelled water technique. *American Journal of Clinical Nutrition* **68**, 932s–938s.
Sridhar MK, Galloway A, Lean MEJ & Barham SW (1994) Study of an outpatient nutritional supplementation programme in malnourished patients with emphysematous chronic obstructive pulmonary disease. *European Respiratory Journal* **7**, 720–724.
Stallings VA, Zemel BS, Davies JC, Cronk CE & Charney EB (1996) Energy expenditure of children and adolescents with severe disabilities: a cerebral palsy model. *American Journal of Clinical Nutrition* **64**, 627–634.
Stark LJ, Jelalian E, Maluihill MM, Powers SW, Bowmen AM & Speith LE (1995) Eating in pre-school children with CF and healthy controls: a behavioural analysis. *Pediatrics* **95**, 210–216.
Tomeszko JL, Stallings VA, Kawchak DA, Going JE, Diamond G & Scanlin TF (1994) Energy expenditure and genotype of children with CF. *Pediatric Research* **35**, 451–460.
Toth MJ, Fishman PS & Poehlman ET (1997) Free living daily energy expenditure in patients with Parkinsons Disease. *Neurology* **48**, 88–91.
Toth MJ & Poehlman ET (2000) Energetic adaptation to chronic disease in the elderly. *Nutrition Reviews* **58**, 61–66.
Ventham JC & Reilly JJ (1999) Childhood leukaemia: a model of pre-obesity. *Proceedings of the Nutrition Society* **58**, 277–281.
Weir J, Reilly JJ, McColl J & Gibson BES (1998) No evidence for an effect of nutritional status on clinical outcome in childhood

acute lymphoblastic leukemia. *Journal of Pediatric Hematology and Oncology* **20**, 534–538.
Wigmore SJ, Fearon KCH, Maingay JP & Ross JA (1997) Down-regulation of the acute phase response in patients with pancreatic cancer cachexia receiving oral eicosapentanoic acid is mediated via suppression of interleukin-6. *Clinical Science* **92**, 215–222.
Wright CM, Callum J, Birks E & Jarvis S (1998) Effect of community based management of failure to thrive: a randomised controlled trial. *British Medical Journal* **317**, 571–574.

https://doi.org/10.1079/PNS2002164 Published online by Cambridge University Press