COPYRIGHT AND USE OF THIS THESIS

This thesis must be used in accordance with the provisions of the Copyright Act 1968.

Reproduction of material protected by copyright may be an infringement of copyright and copyright owners may be entitled to take legal action against persons who infringe their copyright.

Section 51 (2) of the Copyright Act permits an authorized officer of a university library or archives to provide a copy (by communication or otherwise) of an unpublished thesis kept in the library or archives, to a person who satisfies the authorized officer that he or she requires the reproduction for the purposes of research or study.

The Copyright Act grants the creator of a work a number of moral rights, specifically the right of attribution, the right against false attribution and the right of integrity.

You may infringe the author’s moral rights if you:

- fail to acknowledge the author of this thesis if you quote sections from the work
- attribute this thesis to another author
- subject this thesis to derogatory treatment which may prejudice the author’s reputation

For further information contact the University’s Copyright Service.

sydney.edu.au/copyright
NUTRITIONAL ASSESSMENT AND REHABILITATION
OF CHILDREN WITH QUADRIPLEGIC CEREBRAL PALSY

Fiona E Arrowsmith

A thesis submitted in fulfilment
of the requirements for the degree of
Doctor of Philosophy

Discipline of Paediatrics & Child Health
Faculty of Medicine
The University of Sydney
June 2006
Declaration

I declare that the work described in this thesis is entirely my own work except where specifically stated in the text. This work has not been previously submitted for any degree at any institution.

Signature........................................................................................................................................

Fiona E Arrowsmith (author)

Dated.........................................................................................................................................
Ethics Clearance

All studies described in this thesis were approved by the Ethics Committee of The Children’s Hospital at Westmead. Written, informed consent was obtained from the parent or carer of each study participant.
**Abstract**

**Background**: There have been numerous studies describing the body composition of children with quadriplegic cerebral palsy (CP). Most of these studies have focused on measurements of body fatness and the validation of various methods to predict fat stores. There have been no studies directly measuring total body protein (TBP) in children with quadriplegic CP. Furthermore, sophisticated technology used to measure body composition, such as neutron activation analysis (NAA), and dual-energy x-ray absorptiometry (DXA), is not always readily accessible, particularly in the clinic or community setting. No studies have determined whether alternate simpler measures of body composition, such as skinfold anthropometry, can accurately predict body composition (particularly TBP and body fat) in children with quadriplegic CP. Additionally, despite the many studies reporting a high incidence of malnutrition in children with severe CP there have been limited studies investigating the effects of nutritional intervention on body composition parameters. The few studies that have been done have investigated changes in growth parameters (weight and height) and body fat only, with no exploration into the effects of weight gain on TBP, bone mineral content (BMC) and resting energy expenditure (REE).

**Aims**: The aims of this thesis were (i) to measure body composition parameters in children with quadriplegic CP, specifically TBP, fat mass and BMC; (ii) to compare methods for measuring body composition in children with quadriplegic CP, specifically, (a) to determine whether simple indirect measures of body composition can accurately predict TBP; and (b) to compare methods for measuring percent body fat (PBF); (iii) to measure REE and energy and nutrient intake in children with quadriplegic CP, and to relate these measures to their body composition; and (iv) to conduct a randomised controlled trial (RCT) to (a) compare gastrostomy tube feeding
with oral feeding using oral nutrition supplementation and speech therapy, and to (b) determine if nutritional rehabilitation, i.e. weight gain, results in an increase in TBP, fat mass, BMC, and REE in children with quadriplegic CP.

**Methods:** A cross-sectional study was conducted of children with quadriplegic CP between the ages of four and 19 years. All participants were recruited through the Dysphagia Clinic at the Children’s Hospital at Westmead. During an outpatient visit to the hospital the children underwent measurements of anthropometry, TBP by NAA (TBP\textsubscript{NAA}); BMC, lean tissue mass (LTM), and percent body fat (PBF) by DXA; and REE by indirect calorimetry. The parents/carers were asked to complete a three-day weighed food record at home for dietary analysis. In addition, TBP and PBF were estimated from both skinfold anthropometry (TBP\textsubscript{SKIN} and PBF\textsubscript{SKIN}, respectively) and DXA (TBP\textsubscript{DXA} and PBF\textsubscript{DXA}, respectively). The agreement between methods for estimating TBP and PBF were tested using Bland and Altman plot analysis. Finally, an RCT of gastrostomy tube feeding versus oral feeding combined with speech therapy was attempted.

**Results:** The cross-sectional study revealed that the children with CP were significantly stunted and wasted with markedly reduced body fat, TBP, and BMC. Evaluation of methods to measure body composition, by Bland & Altman plot analyses, found that despite TBP\textsubscript{SKIN} and TBP\textsubscript{DXA} both being highly correlated with TBP\textsubscript{NAA}, and PBF\textsubscript{SKIN} being highly correlated with PBF\textsubscript{DXA}, there was poor agreement between methods, and wide individual variation. Furthermore, the measured REE of the children with CP was significantly reduced and widely variable in comparison with that predicted from control data based on fat-free mass (FFM). Comparison of energy intake with measured REE found that on average the three-day food records grossly overestimated energy intake. No parents/carers consented to their child
participating in an RCT; therefore this was abandoned and replaced with a longitudinal cohort study of gastrostomy tube feeding. The nutritional rehabilitation study revealed that significant weight gain in gastrostomy tube-fed children with CP produced significant gains in height, fat mass, measures of muscle mass (FFM and LTM), TBP NAA and BMC. In addition, these children demonstrated significant improvements in their standard deviation (SD) score for weight and for TBP NAA when expressed as a percentage of predicted for height from control data. However, there were no significant improvements seen in height SD score, TBP NAA expressed as a percentage of predicted for age, or for BMC when expressed as an SD score for age or height.

**Conclusions & significance:** Children with quadriplegic CP in this study had greatly reduced TBP, fat mass, and BMC. Both skinfold anthropometry and DXA showed wide individual variability in the estimation of TBP and PBF in this group of children. Further studies using a four-compartment model of body composition are required in order to validate skinfold anthropometry and DXA before they can be accepted as reliable measures of body composition in children with CP. The REE of the children with CP was significantly reduced and widely variable making it difficult to predict from the existing predictive equations. Current recommendations are to either measure REE using indirect calorimetry, or to roughly estimate energy requirements using the available predictive equations and then adjust energy intake according to weight gain. Food records grossly overestimated the energy intake of these children and appear to be of little value in this population. Gastrostomy tube feeding of children with CP resulted in significant improvements in weight, TBP and fat mass, but not height or BMC. Further studies including larger numbers of participants with longer term and more structured follow-up are required to confirm these findings.
Acknowledgements

Firstly and foremost I wish to gratefully acknowledge and thank the parents / carers and children with cerebral palsy who generously volunteered their time to participate in this study. It was a pleasure meeting, and getting to know, each of you. Without your assistance this study would not have been possible.

Next I would like to thank my supervisors Professor Kevin Gaskin, Dr Jane Allen, and Dr Ted O’Loughlin for their advice, guidance and feedback throughout my candidature.

I am also grateful to Professor Louise Baur, Associate Professor Cheryl Jones and Sandra Harris from the Discipline of Paediatrics & Child Health at the University of Sydney, for their ongoing support and encouragement, particularly in the final stages of my PhD.

I would also like to acknowledge the contributions from the following people:

• The members of the Dysphagia Clinic at CHW: Dr Ted O’Loughlin, Dr Helen Somerville, Christine Hill, Gloria Tzannes, Anne Slater, and Jenny Wood. I have thoroughly enjoyed working with each of you in the clinic for the past few years and I look forward to continuing to work with you in the coming years.

• The staff in the Department of Gastroenterology at CHW: Dr Jane Allen, Patricia Bell, Susan Budd, Dr Shoma Dutt, Cheryl Frazer, Professor Kevin Gaskin, Margie Gruca, Vicki Jermyn, Dr Annabel Magoffin, Janice O’Connor, Dr Ted O’Loughlin, and Dr Michael Stormon. Thank you particularly to Margie and Jane for performing the body protein measurements and for analysing the body protein data.
• Julie Briody, Madeleine Thompson and Dr Robert Howman-Giles from the Department of Nuclear Medicine at CHW. Thank you firstly for allowing me to use the DXA machine for my study, and secondly for your expert skills in performing the measurements on this challenging group of children. Thank you particularly to Julie for the many hours spent analysing the DXA data.

• Thank you to Samantha Clarke for getting this project off the ground.

• Special thanks to fellow PhD students Dr Angie Morrow, Dr Jeff Fletcher, and Dr Julie Ward for always lending me your ear and providing endless support, advice and encouragement. You put things in perspective and managed to put a smile on my face during the tough times.

Finally, huge thanks must go to my husband Luke, my family and friends for their love and for always expressing interest in my work. Thank you for the invitations to the many social occasions over the years which provided very welcome distractions and relief from this PhD.
Sources of financial support

This project was supported by a National Health & Medical Research Council Dora Lush Postgraduate Research Scholarship, and was partly supported by Nutricia Pty Ltd.
# Table of Contents

Declaration ........................................................................................................................................ ii  
Ethics Clearance .............................................................................................................................. iii  
Abstract ........................................................................................................................................ iv  
Acknowledgements ......................................................................................................................... vii  
Sources of financial support ........................................................................................................... ix  
Table of Contents .............................................................................................................................. x  
List of Tables ................................................................................................................................... xvii  
List of Figures .................................................................................................................................. xviii  
List of Figures .................................................................................................................................. xviii  
List of Abbreviations ......................................................................................................................... xix  
Publications Arising from Thesis ............................................................................................... xxiii  
Conference Presentations ........................................................................................................... xxiv  
Invited Speaker ............................................................................................................................... xxiv  
Oral presentations ........................................................................................................................... xxiv  
Poster presentations ....................................................................................................................... xxv  
1       Aims and Hypotheses ............................................................................................................. 2  
1.1 Aims ......................................................................................................................................... 2  
1.2 Hypotheses to be tested ............................................................................................................ 2  
2       Literature Review ................................................................................................................ 5  
2.1 Epidemiology of cerebral palsy ................................................................................................. 5  
2.1.1 Definition ............................................................................................................................... 5  
2.1.2 History of cerebral palsy ......................................................................................................... 5  
2.1.3 Causes of cerebral palsy ......................................................................................................... 6  
2.1.4 Identification and classification of cerebral palsy ................................................................. 6  
2.1.5 Incidence and prevalence of cerebral palsy ........................................................................... 7  
2.1.6 Life expectancy ....................................................................................................................... 9  
2.1.7 Causes of death ....................................................................................................................... 10  
2.2 Complications associated with cerebral palsy ......................................................................... 12  
2.2.1 Gastrointestinal complications ............................................................................................ 13  
2.2.1.1 Gastro-oesophageal reflux ............................................................................................... 13  
2.2.1.1.1 Causes of gastro-oesophageal reflux .......................................................................... 14  
2.2.1.1.2 Treatment of gastro-oesophageal reflux ................................................................. 15  
2.2.1.2 Other gastrointestinal complications ................................................................................. 16  
2.2.2 Oral-motor dysfunction .......................................................................................................... 16  
2.2.2.1 Dysphagia ......................................................................................................................... 17  
2.2.2.2 Prevalence of dysphagia in cerebral palsy ................................................................. 17
2.2.2.3 Dysphagia and respiratory problems.................................................................18
2.2.2.4 Effect of dysphagia on food intake .................................................................20
2.2.2.5 Effect of dysphagia on growth ......................................................................21
2.2.3 Energy and micronutrient intakes of children with cerebral palsy...............24
2.3 Growth and cerebral palsy ...................................................................................27
2.3.1 Early studies on growth .....................................................................................27
2.3.2 Assessing growth in children with cerebral palsy ...........................................28
2.3.2.1 Validation of alternate measures for standing height...............................29
2.3.3 Development of growth standards for use in cerebral palsy .........................30
2.3.4 Nutritional and non-nutritional causes of growth failure .................................32
2.3.5 Hormones and growth in children with cerebral palsy ...................................35
2.4 Body composition in children ............................................................................39
2.4.1 Body composition components ......................................................................40
2.4.2 Techniques to measure body composition .......................................................41
2.4.2.1 Densitometry .................................................................................................41
2.4.2.2 Air displacement plethysmography ...............................................................43
2.4.2.3 Anthropometry .............................................................................................46
2.4.2.4 Dual-energy x-ray absorptiometry ...............................................................47
2.4.2.5 Neutron activation analysis ...........................................................................48
2.4.2.6 Total body water ..........................................................................................50
2.4.2.6.1 Intracellular and extracellular water ........................................................51
2.4.2.7 Total body potassium .................................................................................52
2.4.2.8 Electrical conductance ...............................................................................53
2.4.2.8.1 Bioelectrical impedance analysis ..............................................................53
2.4.2.8.2 Total body electrical conductivity .............................................................54
2.4.2.9 Imaging techniques ......................................................................................56
2.4.3 Methods suitable for measuring body composition in children with cerebral palsy .....58
2.4.4 Studies of body composition in children with cerebral palsy .........................61
2.4.4.1 Body water in children with cerebral palsy ...................................................62
2.4.4.2 Bone mineralisation in children with cerebral palsy ....................................68
2.4.4.3 Causes of poor bone mineralisation..............................................................68
2.4.4.3.1 Studies investigating causes of poor bone mineralisation .......................69
2.4.4.3.2 Bone mineralisation and intervention studies ........................................72
2.4.4.3.3 Treatment with bisphosphonates .............................................................73
2.5 Energy expenditure in children with cerebral palsy ...........................................74
2.6 Nutritional therapies in children with cerebral palsy ..........................................78
2.6.1 Oral nutritional supplementation ....................................................................79
2.6.2 Speech therapy ..................................................................................................80
2.6.3 Gastrostomy tube feeding ...............................................................................83
2.6.3.1 Nutritional rehabilitation studies .................................................................84
2.7 Aims of thesis .......................................................................................................85
3 Methods ....................................................................................................................88
3.1 Participants ............................................................................................................88
3.1.1 Children with cerebral palsy ...........................................................................88
3.1.2 Control population ..........................................................................................88
3.2 Study Protocol ......................................................................................................89
3.2.1 Cross-sectional study ......................................................................................89
3.2.2 Nutritional rehabilitation study ......................................................................89
4 Study 1 - Cross-sectional study ................................................................. 105

4.1 Introduction................................................................................. 105
4.2 Aim ....................................................................................... 105
4.3 Participants.......................................................................... 105
  4.3.1 Participant recruitment.................................................. 105
    4.3.1.1 Children with cerebral palsy ......................... 105
    4.3.1.2 Control children ........................................ 106
  4.3.2 Participant description .................................................. 106
    4.3.2.1 Type of cerebral palsy ................................ 107
    4.3.2.2 Cause of cerebral palsy ............................. 107
    4.3.2.3 Method of feeding .................................... 107
    4.3.2.4 Medications ............................................. 107
  4.4 Study protocol........................................................................ 107
  4.5 Data analysis ........................................................................ 108
  4.6 Results.................................................................................. 108
    4.6.1 Anthropometry...................................................... 108
      4.6.1.1 Anthropometric characteristics ............... 108
4.6.1.2 Correlations..................................................................................................109
4.6.1.3 Tube-fed versus oral-fed children with cerebral palsy.................................110
4.6.2 Total body protein by neutron activation analysis......................................................113
4.6.2.1 Total body protein adjusted for age, height, and weight........................................113
4.6.2.2 Correlations..................................................................................................113
4.6.2.3 Tube-fed versus oral-fed children with cerebral palsy........................................114
4.6.3 Body composition by dual-energy x-ray absorptiometry..............................................118
4.6.3.1 Bone mineral content adjusted for age, height, weight, and lean tissue mass........118
4.6.3.2 Lean tissue mass adjusted for height......................................................................118
4.6.3.3 Correlations..................................................................................................119
4.6.3.4 Bone mineral content and anti-epileptic medication use..........................................119
4.6.3.5 Tube-fed versus oral-fed children with cerebral palsy........................................119
4.7 Summary..................................................................................................................124
4.8 Discussion..................................................................................................................124
4.8.1 Anthropometry........................................................................................................124
4.8.1.1 Height and weight deficits ...............................................................................124
4.8.1.2 Normal weight-for-height ..............................................................................125
4.8.1.3 Irregular fat distribution..................................................................................126
4.8.1.4 Reduced fat-free mass.....................................................................................126
4.8.2 Total body protein...................................................................................................127
4.8.3 Body composition by dual-energy x-ray absorptiometry..............................................128
4.8.3.1 Bone mineral content......................................................................................128
4.8.3.2 Lean tissue mass and body fat...........................................................................129
4.8.3.3 Comparisons with other studies......................................................................129
4.8.3.3.1 Nutritional influences on bone mineralisation.............................................131
4.8.3.3.2 Neurological influences on bone mineralisation.........................................133
4.8.3.3.2.1 Anticonvulsant medication use.................................................................133
4.8.3.3.2.2 Lack of weight bearing activity.................................................................134
4.8.3.3.2.3 Relation between bone mineral content and lean tissue mass..................135
4.8.4 Tube-fed versus oral-fed children with cerebral palsy...........................................135

5 Study 2 - Comparison of methods..................................................................................138
5.1 Introduction...............................................................................................................138
5.2 Aim..........................................................................................................................138
5.3 Participants................................................................................................................138
5.3.1 Children with cerebral palsy...............................................................................138
5.3.2 Control children..................................................................................................138
5.3.2.1 Total body protein.........................................................................................138
5.3.2.2 Percent body fat............................................................................................139
5.4 Study protocol..........................................................................................................139
5.4.1 Total body protein..............................................................................................139
5.4.2 Percent body fat..................................................................................................139
5.5 Results......................................................................................................................140
5.5.1 Comparison of methods for measuring total body protein.....................................140
5.5.1.1 Comparison of total body protein derived from neutron activation analysis and dual-energy x-ray absorptiometry..............................140
5.5.1.2 Comparison of total body protein derived from neutron activation analysis and skinfold anthropometry ...........................................................145
5.5.1.3 Correlation between total body protein and basic skinfold anthropometry..............................................................................................146
5.5.2 Comparison of methods for measuring percent body fat..............................................149
  5.5.2.1 Percent fat from dual-energy x-ray absorptiometry and skinfold anthropometry (PBF\textsubscript{SKIN-A}) ..........................................................................149
  5.5.2.2 Percent body fat derived from dual-energy x-ray absorptiometry and skinfold anthropometry (PBF\textsubscript{SKIN-B}) .............................................................154
  5.5.2.3 Correlations between percent body fat and skinfold anthropometry............154
5.6 Summary ..................................................................................................................................158
5.7 Discussion ................................................................................................................................158
  5.7.1 Comparison of methods to measure body protein.........................................................158
    5.7.1.1 Significance of findings...............................................................................158
    5.7.1.2 Comparisons with other studies...................................................................159
  5.7.2 Comparison of methods to measure percent body fat...................................................160
    5.7.2.1 Significance of findings...............................................................................160
    5.7.2.2 Comparisons with other studies...................................................................161

6 Study 3 - Resting energy expenditure and dietary intake .............................................. 164
6.1 Introduction..............................................................................................................................1 64
6.2 Aims.........................................................................................................................................164
6.3 Resting energy expenditure by indirect calorimetry .............................................................164
  6.3.1 Participants ...................................................................................................................164
    6.3.1.1 Children with cerebral palsy ........................................................................164
    6.3.1.2 Control children ...........................................................................................165
  6.3.2 Study protocol...............................................................................................................165
  6.3.3 Data analysis.................................................................................................................165
  6.3.4 Results .....................................................................................................................165
    6.3.4.1 Measured versus predicted resting energy expenditure from Schofield equations......................................................................................................166
    6.3.4.2 Regression analysis of control data..................................................................169
    6.3.4.3 Regression analysis of cerebral palsy data....................................................169
    6.3.4.4 Predictive equations derived from control data .............................................169
    6.3.4.5 Measured resting energy expenditure adjusted for fat-free mass...............170
    6.3.4.6 Influence of nutritional status and anti-epileptic medication use on resting energy expenditure..........................................................174
6.4 Dietary intake...........................................................................................................................175
  6.4.1 Participants ...................................................................................................................175
    6.4.1.1 Children with cerebral palsy ........................................................................175
    6.4.1.2 Reference data..............................................................................................175
  6.4.2 Study protocol...............................................................................................................175
  6.4.3 Data analysis.................................................................................................................175
  6.4.4 Results .....................................................................................................................176
    6.4.4.1 Tube-fed .......................................................................................................176
    6.4.4.2 Oral-fed ........................................................................................................176
    6.4.4.3 Enteral formulas and supplements ................................................................176
    6.4.4.4 Energy and micro-nutrient intakes of children with cerebral palsy .............177
    6.4.4.5 Tube-fed versus oral-fed children with cerebral palsy....................................177
      6.4.4.5.1 Energy and protein intakes ....................................................................177

xiv
7 Study 4 - Nutritional rehabilitation ........................................................................................................... 188
  7.1 Introduction........................................................................................................................................... 188
  7.2 Aim ....................................................................................................................................................... 188
  7.3 Participants........................................................................................................................................... 188
    7.3.1 Recruitment of children with cerebral palsy .................................................................................. 188
    7.3.2 Study protocol............................................................................................................................... 189
      7.3.2.1 Nutritional intervention ........................................................................................................ 190
    7.3.3 Control group and reference data.............................................................................................. 190
    7.3.4 Statistics ........................................................................................................................................ 191
  7.4 Results.................................................................................................................................................. 192
    7.4.1 Participation of children with cerebral palsy .............................................................................. 192
      7.4.1.1 Gastrostomy tube-fed children ........................................................................................ 192
      7.4.1.2 Oral-fed children ............................................................................................................. 192
    7.4.2 Baseline and repeat body composition results ............................................................................ 194
    7.4.3 Anthropometry........................................................................................................................... 194
      7.4.3.1 Comparison with reference data ....................................................................................... 195
    7.4.4 Body composition by dual-energy x-ray absorptiometry........................................................... 195
      7.4.4.1 Comparison with control data ..................................................................................... 196
    7.4.5 Total body protein by neutron activation analysis ...................................................................... 196
      7.4.5.1 Comparison with control data ....................................................................................... 196
    7.4.6 Annualised changes in body composition ................................................................................. 201
    7.4.7 Resting energy expenditure and energy intake ........................................................................... 203
  7.5 Summary of results ............................................................................................................................. 206
  7.6 Discussion.............................................................................................................................................. 206
    7.6.1 Anthropometric changes ............................................................................................................. 206
    7.6.2 Longitudinal studies of bone mineralisation ............................................................................. 211
    7.6.3 Longitudinal studies of total body protein ................................................................................. 213
    7.6.4 Resting energy expenditure and food records ............................................................................ 214
    7.6.5 Significance of findings ............................................................................................................... 215

8 Discussion ............................................................................................................................................... 218
  8.1 Overall conclusions ............................................................................................................................. 218
  8.2 Study 1 - Cross-sectional study ........................................................................................................ 219
    8.2.1 Limitations of using anthropometry in children with cerebral palsy ...................................... 219
      8.2.1.1 Difficulties with measuring height .................................................................................... 219
      8.2.1.2 Skinfold anthropometry ............................................................................................... 220
    8.2.2 Limitations of neutron activation analysis to measure total body protein ............................ 221
    8.2.3 Methodological limitations of dual-energy x-ray absorptiometry to assess soft tissue .......... 222
8.3 Study 2 - Comparison of methods to measure protein and fat .................................................223
  8.3.1 Limitations of DXA and skinfold anthropometry to measure body protein ..............223
  8.3.2 Percent body fat derived from dual-energy x-ray absorptiometry versus skinfold  
      anthropometry.................................................................................................................224
8.4 Study 3 - Resting energy expenditure and dietary intake .........................................................224
  8.4.1 Limitations of estimating energy requirements .............................................................224
  8.4.2 Limitations of estimating energy and nutrient intake ....................................................225
8.5 Study 4 - Nutritional rehabilitation .......................................................................................227
  8.5.1 Inability to conduct a randomised controlled trial .........................................................227
    8.5.1.1 Unstructured follow-up ....................................................................................228
    8.5.1.2 Slow and lack of weight gain .........................................................................229
    8.5.1.3 Small numbers of participants .....................................................................229
  8.5.2 Quality of life ................................................................................................................233
8.6 Future directions ....................................................................................................................233

Reference List ............................................................................................................................... 236

Appendix A - Parent Information Sheet & Consent Form ............................................................ 266
Appendix B - Anthropometric equations ..................................................................................... 271
Appendix C - Total body protein predictive equations ............................................................... 273
Appendix D - Hydration constants .............................................................................................. 274
Appendix E - Medications ............................................................................................................. 275
Appendix F - Equations used for predicting resting energy expenditure .................................... 277
Appendix G – Nutritional rehabilitation study information sheet ............................................... 278
Appendix H - Baseline and repeat measures of oral-fed children ............................................... 282
List of Tables

Table 2.1 Studies of survival rates in children and adults with cerebral palsy ................................................ 11
Table 2.2 Studies of nutritional adequacy in children with cerebral palsy ...................................................... 26
Table 2.3 Summary of advantages and disadvantages of body composition techniques ........................................ 59
Table 2.4 Studies of growth and body composition in children with cerebral palsy in chronological order ........................................................................................................................................................ 66
Table 4.1 Anthropometric characteristics of children with cerebral palsy and controls ....................................... 111
Table 4.2 Physical characteristics and body protein of children with cerebral palsy and controls ............... 115
Table 4.3 Body composition by dual-energy x-ray absorptiometry in children with cerebral palsy and controls ................................................................................................................................................. 121
Table 5.1 Comparison of methods for measuring total body protein ............................................................ 142
Table 5.2 Percent body fat derived from dual energy x-ray absorptiometry and skinfold anthropometry .... 151
Table 6.1 Characteristics of children with cerebral palsy and controls ................................................................. 167
Table 6.2 Measured versus Schofield predicted resting energy expenditure ..................................................... 168
Table 6.3 Regression analysis of resting energy expenditure data .................................................................. 171
Table 6.4 Measured versus control predicted resting energy expenditure ....................................................... 172
Table 6.5 Protein and micro-nutrient intakes of children with cerebral palsy ................................................... 179
Table 7.1 Baseline and repeat anthropometric characteristics of gastrostomy tube-fed and baseline anthropometric characteristics of oral-fed children with cerebral palsy ................................................................. 198
Table 7.2 Baseline and repeat body composition measures by dual-energy x-ray absorptiometry ............... 199
Table 7.3 Baseline and repeat measures of total body protein .............................................................................. 200
Table 7.4 Annualised change in body composition parameters ........................................................................ 202
Table 7.5 Baseline and repeat measures of resting energy expenditure and energy intake ..................... 204
Table 7.6 Baseline and repeat measures of resting energy expenditure and energy intake excluding REE >140% ................................................................................................................................................. 205
List of Figures

Figure 2.1 Feedback control of growth hormone secretion ................................................................. 38
Figure 2.2 Body composition model .................................................................................................. 44
Figure 3.1 Total body nitrogen by neutron activation analysis......................................................... 96
Figure 3.2 Dual energy x-ray absorptiometry .................................................................................. 96
Figure 4.1 Fat-free mass versus age in children with cerebral palsy and controls............................ 112
Figure 4.2 Total body protein versus age ......................................................................................... 116
Figure 4.3 Total body protein as a percent of predicted from controls versus age in children with cerebral palsy .......................................................... 117
Figure 4.4 Bone mineral content versus age .................................................................................. 122
Figure 4.5 Bone mineral content for age versus age in children with cerebral palsy ..................... 123
Figure 5.1 Correlation between total body protein derived from neutron activation analysis and dual-energy x-ray absorptiometry ......................................................... 143
Figure 5.2 Bland & Altman plot analysis for total body protein derived from neutron activation analysis and dual-energy x-ray absorptiometry ......................................................... 144
Figure 5.3 Correlation of total body protein derived from neutron activation analysis and skinfold anthropometry ........................................................................................................... 147
Figure 5.4 Bland and Altman plots for total body protein derived from neutron activation analysis and skinfold anthropometry ........................................................................................................... 148
Figure 5.5 Correlation between percent body fat derived from dual-energy x-ray absorptiometry and skinfold anthropometry (PBF_{SKIN,A}) .......................................................................................... 152
Figure 5.6 Bland and Altman plots for percent body fat derived from dual-energy x-ray absorptiometry and skinfold anthropometry (PBF_{SKIN,A}) .......................................................................................... 153
Figure 5.7 Correlation between percent body fat derived from dual-energy x-ray absorptiometry and skinfold anthropometry (PBF_{SKIN,B}) .......................................................................................... 156
Figure 5.8 Bland and Altman plots for percent body fat derived from dual-energy x-ray absorptiometry and skinfold anthropometry (PBF_{SKIN,B}) .......................................................................................... 157
Figure 6.1 Fat-free mass versus measured resting energy expenditure ............................................... 173
Figure 7.1 Flow chart of subject participation .................................................................................. 193
# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$O</td>
<td>Oxygen-18</td>
</tr>
<tr>
<td>2C</td>
<td>Two compartment</td>
</tr>
<tr>
<td>3C</td>
<td>Three compartment</td>
</tr>
<tr>
<td>4C</td>
<td>Four compartment</td>
</tr>
<tr>
<td>ADP</td>
<td>Air displacement plethysmography</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>BIA</td>
<td>Bioelectrical impedance analysis</td>
</tr>
<tr>
<td>BMC</td>
<td>Bone mineral content</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CHW</td>
<td>Children’s Hospital at Westmead</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CP</td>
<td>Cerebral palsy</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>D$_2$O</td>
<td>Deuterium oxide</td>
</tr>
<tr>
<td>D$_b$</td>
<td>Body density</td>
</tr>
<tr>
<td>d$_F$</td>
<td>Density of fat</td>
</tr>
<tr>
<td>d$_{FFM}$</td>
<td>Density of fat-free mass</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>ECW</td>
<td>Extracellular water</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>F</td>
<td>Female</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat-free mass</td>
</tr>
<tr>
<td>FFM_SKIN</td>
<td>Fat-free mass by skinfold anthropometry</td>
</tr>
<tr>
<td>FFST</td>
<td>Fat-free soft tissue</td>
</tr>
<tr>
<td>FM</td>
<td>Fat mass</td>
</tr>
<tr>
<td>FM_DXA</td>
<td>Fat mass by dual energy x-ray absorptiometry</td>
</tr>
<tr>
<td>FM_SKIN</td>
<td>Fat mass by skinfold anthropometry</td>
</tr>
<tr>
<td>GH</td>
<td>Growth hormone</td>
</tr>
<tr>
<td>GHRH</td>
<td>Growth hormone releasing hormone</td>
</tr>
<tr>
<td>GMFCS</td>
<td>Gross motor function classification system</td>
</tr>
<tr>
<td>GOR</td>
<td>Gastro-oesophageal reflux</td>
</tr>
<tr>
<td>HC_FFM</td>
<td>Hydration constant of fat-free mass</td>
</tr>
<tr>
<td>ICW</td>
<td>Intracellular water</td>
</tr>
<tr>
<td>ID</td>
<td>Intellectual disability</td>
</tr>
<tr>
<td>IGF</td>
<td>Insulin-like growth factor</td>
</tr>
<tr>
<td>IQR</td>
<td>Inter-quartile range</td>
</tr>
<tr>
<td>KH</td>
<td>Knee height</td>
</tr>
<tr>
<td>LBW</td>
<td>Low birth weight</td>
</tr>
<tr>
<td>LLL</td>
<td>Lower leg length</td>
</tr>
<tr>
<td>LTM</td>
<td>Lean tissue mass</td>
</tr>
<tr>
<td>LTM_DXA</td>
<td>Lean tissue mass by dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>M</td>
<td>Male</td>
</tr>
<tr>
<td>MA</td>
<td>Mass</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>MREE</td>
<td>Measured resting energy expenditure</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MUAC</td>
<td>Mid upper arm circumference</td>
</tr>
<tr>
<td>NAA</td>
<td>Neutron activation analysis</td>
</tr>
<tr>
<td>NG</td>
<td>Naso-gastric</td>
</tr>
<tr>
<td>PBF</td>
<td>Percent body fat</td>
</tr>
<tr>
<td>PBF&lt;sub&gt;DXA&lt;/sub&gt;</td>
<td>Percent body fat by dual energy x-ray absorptiometry</td>
</tr>
<tr>
<td>PBF&lt;sub&gt;Skin&lt;/sub&gt;</td>
<td>Percent body fat by skinfold anthropometry</td>
</tr>
<tr>
<td>PREE</td>
<td>Predicted resting energy expenditure</td>
</tr>
<tr>
<td>R</td>
<td>Ratio</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RDI</td>
<td>Recommended dietary intake</td>
</tr>
<tr>
<td>REE</td>
<td>Resting energy expenditure</td>
</tr>
<tr>
<td>RF</td>
<td>Radio frequency</td>
</tr>
<tr>
<td>RTI</td>
<td>Respiratory tract infection</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SDS</td>
<td>Standard deviation score</td>
</tr>
<tr>
<td>SM</td>
<td>Somatomedin</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical package for the social sciences</td>
</tr>
<tr>
<td>SRIF</td>
<td>Somatotropin release inhibiting factor</td>
</tr>
<tr>
<td>TBK</td>
<td>Total body potassium</td>
</tr>
<tr>
<td>TBN</td>
<td>Total body nitrogen</td>
</tr>
<tr>
<td>TBP</td>
<td>Total body protein</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>TBP&lt;sub&gt;DXA&lt;/sub&gt;</td>
<td>Total body protein by dual energy x-ray absorptiometry</td>
</tr>
<tr>
<td>TBP&lt;sub&gt;NAA&lt;/sub&gt;</td>
<td>Total body protein by neutron activation analysis</td>
</tr>
<tr>
<td>TBP&lt;sub&gt;SKIN&lt;/sub&gt;</td>
<td>Total body protein by skinfold anthropometry</td>
</tr>
<tr>
<td>TBW</td>
<td>Total body water</td>
</tr>
<tr>
<td>TEE</td>
<td>Total energy expenditure</td>
</tr>
<tr>
<td>TOBEC</td>
<td>Total body electrical conductivity</td>
</tr>
<tr>
<td>UAFA</td>
<td>Upper arm fat area</td>
</tr>
<tr>
<td>UAL</td>
<td>Upper arm length</td>
</tr>
<tr>
<td>UAMA</td>
<td>Upper arm muscle area</td>
</tr>
<tr>
<td>V</td>
<td>Volume</td>
</tr>
<tr>
<td>WHC</td>
<td>Weight-for-height centile</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
Publications Arising from Thesis


Conference Presentations

Invited Speaker


Oral presentations

Title of presentation: *Weight gain and body composition in malnourished children with cerebral palsy.*


**Poster presentations**

11. Westmead Hospital Annual Hospital Week, August 2004. Title of poster: 
*Reduced body protein and bone mineralisation in children with cerebral palsy.*
Authors: Fiona E Arrowsmith, Jane R Allen, Edward V O’Loughlin, Kevin J Gaskin. Poster presented by Fiona Arrowsmith
CHAPTER 1
AIMS & HYPOTHESES
1 Aims and Hypotheses

1.1 Aims

A. To measure a three-compartment model of body composition in children with quadriplegic cerebral palsy, specifically total body protein, fat mass and bone mineral content.

B. To compare methods for measuring body composition in children with quadriplegic cerebral palsy, specifically,
   (a) to determine whether indirect measures of body composition can accurately predict body protein; and
   (b) to compare methods for measuring percent body fat.

C. To measure resting energy expenditure and energy and nutrient intake in children with quadriplegic cerebral palsy, and to relate these measures to their body composition.

D. To conduct a randomised-controlled trial of nutritional rehabilitation
   (a) to compare gastrostomy tube feeding versus oral feeding using oral nutritional supplementation and speech therapy, and
   (b) to determine if nutritional rehabilitation, i.e. weight gain, results in an increase in total body protein, fat mass, bone mineral content, and resting energy expenditure in children with quadriplegic cerebral palsy.

1.2 Hypotheses to be tested

A. That children with quadriplegic cerebral palsy have a reduced total body protein, fat mass, and bone mineral content, in comparison to healthy control children.
Chapter 1

AIMS & HYPOTHESES

B. That indirect measures of body composition do not accurately predict body protein in children with quadriplegic cerebral palsy; and that different methods used to measure body fat in children with quadriplegic cerebral palsy show poor agreement.

C. That children with quadriplegic cerebral palsy have a reduced resting energy expenditure in comparison with control children; a reduced energy intake compared with measured resting energy expenditure; and a reduced nutrient intake compared with recommended nutrient intakes for age.

D. That gastrostomy tube feeding is more effective than oral nutritional supplementation with speech therapy for nutritional rehabilitation; and that nutritional rehabilitation results in improvements in nutritional status, including an increase in fat mass, total body protein, bone mineral content, and resting energy expenditure in children with quadriplegic cerebral palsy.
CHAPTER 2

LITERATURE REVIEW
2 Literature Review

2.1 Epidemiology of cerebral palsy

2.1.1 Definition

The term cerebral palsy (CP) is used to describe a range of permanent, non-progressive syndromes of posture and motor impairment that result from an insult to the developing central nervous system (CNS) (Koman L.A. et al. 2004). CP is manifested early in life, generally in the first two to three years (Davis 1997), and is the most common serious physical disability affecting children (Colver et al. 2000; Maudsley et al. 1999). The prevalence of CP in Australia is approximately two to three per 1000 live births (Stanley and Watson 1988).

CP is a complex of symptoms rather than a specific disease (Kuban and Leviton 1994). There have been numerous attempts over the past century to define and classify CP, however the most recent consensus definition is that of Bax et al; “CP describes a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behaviour, and/or by a seizure disorder” (Bax et al. 2005).

2.1.2 History of cerebral palsy

CP was first described in 1862 by William John Little, an orthopaedic surgeon from London, UK (Eicher and Batshaw 1993). He presented his observations of a group of children with tonal and developmental abnormalities, which he described as “spastic rigidity”. Many of these children had a history of prolonged labour or preterm or breech delivery. Because of the frequency of these perinatal problems, Little postulated that the motor defects resulted directly from difficulties in the birth
process. Consequently, for over 100 years, most cases of CP were thought to be caused by asphyxia during either labour or the perinatal period (Blair et al. 2001; Paneth 1984). However, recent research has demonstrated that perinatal asphyxia is causative in only 6 – 8 % of CP cases (Reddihough and Collins 2003).

2.1.3 Causes of cerebral palsy

Known causes of CP can be divided into four categories:

(i) antenatal causes - congenital brain malformations, vascular events (e.g. middle cerebral artery occlusion) and maternal infections during the first and second trimesters of pregnancy (e.g. rubella, cytomegalovirus, toxoplasmosis) (Gibson et al. 2006);

(ii) perinatal causes - problems during labour and delivery;

(iii) neonatal problems - neonatal encephalopathy due to severe hypoglycaemia, untreated jaundice, metabolic diseases and severe neonatal infection;

(iv) post-neonatal problems – infection (e.g. meningitis, encephalitis) and head injuries (Reddihough and Collins 2003).

The most commonly reported causes of CP are antenatal and perinatal insults, however, a large number of patients do not have a readily identifiable aetiology of the CP (Fishman and Bousvaros 1999). In addition, the pathophysiologic mechanisms that underlie most of the CP syndromes remain poorly understood (Kuban and Leviton 1994). There is currently neither an objective test that can be used to ‘screen’ for CP, nor a diagnostic test that can be used as a 'gold standard' (Mutch et al. 1992).

2.1.4 Identification and classification of cerebral palsy

Identification and classification of CP are often difficult. CP is a heterogeneous condition with various types and degrees of motor impairment. The clinical
manifestations often differ according to the gestational age at birth, the chronological age, the distributions of the lesions, and the underlying disease (Kuban and Leviton 1994). Furthermore, the expression of CP can change throughout the first few years giving the impression of a progressive neurological disorder (Davis 1997). In addition, children may have a combination of two or more types of CP. However, in general, CP is classified by the Swedish system according to the extremity involved: monoplegia (one limb), hemiplegia (one side of the body), diplegia (legs predominantly affected), and quadriplegia (all four limbs affected); and the characteristics of the neurological dysfunction: spastic, hypotonic, dystonic, athetotic, or a combination thereof (Kuban and Leviton 1994).

Palisano et al (Palisano et al. 1997) recently developed the Gross Motor Function Classification System (GMFCS) to standardise the classification system of children with CP. The GMFCS consists of five levels: level I children have a very mild motor disorder, whilst level V children have the most severe motor disabilities. The GMFCS has been widely adopted in Australia and elsewhere.

Regardless of the classification system used, spastic CP (including hemiplegic, diplegic and quadriplegic) is the most common type, occurring in 70 to 80 % of the CP population (Davis 1997). Spastic quadriplegic CP alone lies at the severe end of the spectrum of CP (GMFCS level IV and V), and is found in approximately one-third of all cases (Stanley and Watson 1988).

2.1.5 Incidence and prevalence of cerebral palsy

Several researchers from various developed countries have studied the incidence and prevalence rates of CP from the 1960s to 1980s (Colver et al. 2000; Pharoah et al. 1987; Pharoah et al. 1996; Pharoah et al. 1998; Stanley and Watson 1988). Most studies agree on the current incidence of CP at around two to three per 1000 live
births (Winter et al. 2002). These studies also report recent rises in the prevalence among live births of the condition and its severity, particularly among preterm infants.

Stanley & Watson analysed the trends in stillbirths, neonatal deaths and CP in all infants born in Western Australia from 1967 – 1985 (Stanley and Watson 1992). During this period death rates fell particularly in low birth weight (LBW) infants (< 2500 g), and CP rates remained steady at 2 - 2.5 per 1000 live births. In contrast, CP rates in infants weighing under 1500 g rose significantly as evidenced by an increase of 53 % in those weighing < 1000 g, and by 77 % in those weighing 1000 – 1499 g. However, this was balanced by a fall of 36 % in the 1500 – 1999 g birth weight group.

The main types contributing to the rise in LBW CP were spastic hemiplegia and quadriplegia. Over the total cohort studied there was a 22 % increase per period (grouped years) in the rate of quadriplegic CP. The most significant increases with time in quadriplegic CP were in the < 1000 g birth weight group (70 % increase) and in the 1000 – 1499 g birth weight group (150 % increase), with a non-significant fall in the other categories.

In several developed countries there is a reported negative correlation between birth weight and rates of CP, i.e. as birth weight falls, rates of CP increase. Also reported in these countries in the LBW populations is a trend to higher rates of CP as mortality falls (Mutch et al. 1992; Stanley and Watson 1992). The LBW populations reported include preterm infants and those infants born small for gestational age.

The reported rise in the prevalence of CP seems to be accounted for largely by improvements in the survival rate of LBW babies, i.e. the incidence has not changed but improved survival rates, particularly among LBW infants, have increased prevalence (Mutch et al. 1992; Pharoah et al. 1987). Survival rates of LBW infants has improved over the last two decades due to dramatic changes in obstetric and
perinatal care, including the increasing availability of foetal heart monitoring and foetal ultrasonography, an increase in caesarean sections (4% in 1970 to 18% in 1985), the establishment of neonatal intensive care units, and the use of surfactant and antenatal steroids to reduce mortality and morbidity associated with hyaline membrane disease (Kuban and Leviton 1994; Pharoah et al. 1998; Stanley and Watson 1992). It appears that many babies < 2500 g who would previously have died in the perinatal period now survive with severe CP (Colver et al. 2000). Stanley & Watson reported that the percentage of CP cases contributed by newborns weighing < 2500 g increased from 33.5% in 1975-1978 to 44% in 1983-1985 (Stanley and Watson 1992). However, Blair et al reported that they did not find any evidence for increased duration of survival since the 1950s despite advances in medical care (Blair et al. 2001). Therefore, it is unknown whether modern therapy makes any difference to survival of LBW infants and increased cases of CP.

2.1.6 Life expectancy

The life expectancy of children with CP has been studied extensively by several groups of researchers in Australia and other developed countries (Blair et al. 2001; Crichton et al. 1995; Evans et al. 1990; Hutton et al. 1994; Hutton et al. 2000; Strauss et al. 1998). The findings of these studies has been summarised in Table 2.1 (pg 11). Although the studies report varying survival rates, they all agree that survival is inversely correlated with the severity of disability, either intellectual or physical (Blair et al. 2001). In addition, several of the studies found that children with CP, who were of higher birth weights, or those born after 32 weeks gestation, had lower survival rates. It has been long recognised that heavier infants tend to have more severe cognitive and motor disabilities than those of LBW; this is thought to be a result of severely damaged premature infants being less likely to survive until diagnosis than
full term infants (Hutton et al. 2000; Pharoah et al. 1998). However this theory has been difficult to prove because CP is not usually diagnosed until several months of age.

In general, the studies reported in Table 2.1 have found that more than half of even the most severely disabled individuals with CP live to adulthood; therefore CP must be regarded as a disability of which people live with rather than a disability of which they die from. It is therefore appropriate to plan for their survival and continue to research to improve the health and well-being of individuals with CP.

2.1.7 Causes of death
Blair et al described the trends, predictors, and causes of mortality in people with CP in Western Australia who were born between 1956 and 1994 (Blair et al. 2001). They obtained the cause of death from death certificates, hospital medical records, and post-mortem reports. Death by respiratory causes accounted for 59 % of all deaths; with aspiration pneumonia and pneumonia accounting for 16.6 % and 37.1 % of all deaths respectively, and other respiratory causes 5.3 %. Further analysis of the data revealed that aspiration pneumonia was strongly associated with profound intellectual deficit and the proportion attributed to this cause was found to be increasing with time. Epilepsy was reported to be the second most common cause of death.

In a similar study to that of Blair et al, Reddihough and colleagues extensively reviewed the medical records of children with CP who had died over a 25-year period (1970 - 1995) in Victoria, Australia in order to establish the cause of death (Reddihough et al. 2001). The average age at death was 6.8 years (range 2 months to 21.8 years), and the majority of the deceased children had severe spastic quadriplegic CP, intellectual disability and epilepsy. The predominant cause of death was
<table>
<thead>
<tr>
<th>Author</th>
<th>Country &amp; Region</th>
<th>Time period</th>
<th>Survival rate</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Evans et al. 1990)</td>
<td>UK SE Thames region</td>
<td>1970 - 1979</td>
<td>90% to 10 years</td>
<td>• 67% of those that died had more severe CP</td>
</tr>
</tbody>
</table>
| (Hutton et al. 1994)    | UK Mersey region         | 1966 - 1984   | 89.3% for females 86.9% for males to 20 years | • For severely disabled children survival rate was 50%  
  • BW >2500g survival 86.4%; BW <2500g survival rate 91.6%  
  • Level of ambulation found to be most predictive of survival |
| (Crichton et al. 1995)  | Canada British Columbia | 1952 - 1989   | 90% to 30 years | • Those with severe ID and epilepsy, survival rate was 66.6%                          |
| (Strauss et al. 1998)   | USA California           | 1980 - 1995   | N/A\(^1\) to 15 years | • Study preferentially included more severe CP, therefore results may not be representative of general CP population  
  • Those with fair motor and eating skills had a 90% survival rate to 15y  
  • Children unable to lift their heads and those who were tube fed, or fed by others, had poorer survival rates (7 to 14 years).  
  • LBW infants had better survival rates |
| (Hutton et al. 2000)    | UK North England         | 1960 - 1990   | 82.8% for females 83.5% for males to 35 years | • LBW infants had better survival rates than those weighing >3000g; 84.2% versus 76% respectively.  
  • Those with severe manual or ambulatory disability had a survival rate of 55 - 59%. |
| (Blair et al. 2001)     | Australia Western Australia | 1956 - 1994 | 85%\(^2\) to 40 years | • 6% died before age of 5 years, and a further 11% between 5 and 40 years  
  • Strongest single predictor of mortality was ID; of those with profound ID, 22% died by 5y, and 50% by 18y.  
  • Those infants born >32 weeks gestation were at higher risk of mortality |
| (Hutton and Pharoah 2006) | UK Mersey region       | Not stated    | 25% to 30 years | • Data are only for children classified as severe CP in terms of ambulation, cognitive ability, manual dexterity, and visual disability. |

\(^1\) Survival rate for whole group was not reported; \(^2\) data are an approximation, author’s state that data were insufficient to predict survival accurately.

BW, birth weight; CP, cerebral palsy; ID, intellectual disability; LBW, low birth weight
pneumonia (39 %), sometimes described as aspiration pneumonia or severe chest infection. However, 41 % of the deceased children died at home and the cause of death was unknown.

Two studies from the UK of causes of death in people with CP report similar findings to the two aforementioned Australian studies (Evans et al. 1990; Maudsley et al. 1999). The UK studies reported the most common cause of death was respiratory failure due to pneumonia and other causes, followed by epilepsy and intellectual disability. However, the authors of these two studies point out that if death certificates alone are studied, many cases may not be identified because the terminal illness may only be recorded rather than the pre-existing condition. CP was not mentioned on a large percentage of the death certificates, which therefore questions the accuracy of studying death certificates alone for causes of death in CP.

Nonetheless, all studies agreed that the predominant cause of death in people with CP was pneumonia and other respiratory causes. However, Reddihough et al commented that while pneumonia was the most frequent terminal event, there were often other contributing factors, such as malnutrition, scoliosis, immobility, poor cough reflex and aspiration both from impaired swallowing mechanisms and gastro-oesophageal reflux (GOR) (Reddihough et al. 2001).

### 2.2 Complications associated with cerebral palsy

Although CP is defined in terms of a motor system impairment, many children with CP also have other handicaps such as impaired cognition, sensory deficits, seizure disorders, feeding problems, behavioural dysfunction, and emotional problems. In general, the more limbs involved, the greater the degree of disability and the higher the likelihood of associated deficits and cognitive impairment (Eicher and Batshaw 1993).
Intellectual disability has been reported in 50 to 66% of children with CP (Davis 1997; Eicher and Batshaw 1993). Approximately one-third to a half of children with CP are reported to have a seizure disorder. Sensory deficits in the form of hearing loss and vision problems (strabismus, refractive errors, retinopathy of prematurity, field deficits, nystagmus, and amblyopia) are also common (Davis 1997; Eicher and Batshaw 1993). Communication disorders in children with CP include speech motor deficits and central processing problems. Feeding problems may result from various motor problems including hypotonia, weak suck, poor coordination of the swallow mechanism, tonic bite reflex, hyperactive gag reflex, and exaggerated tongue thrust. There may be drooling or aspiration resulting from the oral motor problems. GOR may also be present and, together with aspiration, can cause recurrent chest infections. In addition, due to poor communication skills and the inability to independently access food, children with CP are unable to express hunger. These problems are contributors to failure to thrive and poor growth. In fact, one of the first signs that a child might have CP is poor feeding skills, and subsequent failure to thrive (Davis 1997). Each of these problems will be discussed in more detail in the following sections.

2.2.1 Gastrointestinal complications

2.2.1.1 Gastro-oesophageal reflux

GOR is defined as a dysfunction of the lower oesophageal sphincter mechanism with regurgitation of gastric contents into the oesophagus (Hebra and Hoffman 1993). The prevalence of GOR is reportedly higher in neurologically impaired children, including those with CP, than in the general population. Using barium studies, Abrahams & Burkitt reported a high prevalence (12 / 16) of GOR occurring in a group of children and adolescents with severe spastic CP who were experiencing symptoms of reflux,
yet in a similarly disabled group without symptoms, the prevalence of GOR was significantly lower (17 / 63) (Abrahams and Burkitt 1970). Halpern et al conducted a retrospective review of 613 consecutive children who underwent an evaluation for GOR by 18 to 24 hour oesophageal pH monitoring (Halpern et al. 1991). Of the 613 children studied, 132 had documented CNS disease, including CP, prior to the evaluation. The authors reported that in patients older than one year there was an increased incidence of GOR in those with CNS disease (31 / 45) compared with those without CNS disease (38 / 81). In the most recent study, Reyes et al used 24-hour ambulatory oesophageal pH monitoring to study a small group (n = 23) of children with CP, all of whom had one or more symptoms suggestive of reflux (Reyes et al. 1993). The average age of the children was 2.3 years, and approximately half had severe spastic CP. Significant GOR was detected in 16 of 23 patients. However, the latter two studies do not represent all infants and children with GOR and CP, but rather those children with suspected GOR who did not respond to conventional antireflux therapy or who manifested significant complications associated with GOR. Therefore, the reported prevalence of GOR may be higher than in the general CP population.

2.2.1.1.1 Causes of gastro-oesophageal reflux

GOR in neurologically impaired children is thought to be primarily related to abnormal CNS control mechanisms. In addition contributing factors of GOR in children with CP include prolonged supine positioning, liquid feeds, gastrostomy tube placement, slow gastric emptying, impaired oesophageal motility, and increased abdominal pressure due to spasticity or seizures (Fishman and Bousvaros 1999; Hebra and Hoffman 1993). Reflux in this group of patients can cause vomiting, oesophagitis leading to bleeding and iron deficiency, haematemesis, protein-losing enteropathy,
irritability, pain, poor growth and failure to thrive (Fishman and Bousvaros 1999; Hebra and Hoffman 1993). Failure to thrive can result from GOR because of loss of ingested calories (Hebra and Hoffman 1993). Local complications within the oesophagus, in addition to ulceration and bleeding, include strictures and development of Barrett’s oesophagus and Sandifer’s syndrome (Hebra and Hoffman 1993). Extragastrointestinal symptoms of GOR are most commonly respiratory in nature and include pulmonary aspiration, cough, cyanosis, apnoea, reactive airway disease, pneumonitis, and bronchiectasis. Respiratory tract infections (RTIs) have been shown to be a major cause of death in children with CP, as discussed in section 2.1.7 (pg 10). RTIs in children with severe neurodisability are usually caused by aspiration of stomach contents from GOR or direct aspiration of solids or liquids from the mouth and pharynx due to oral and pharyngeal motor problems (Morton et al. 1999).

2.2.1.1.2 Treatment of gastro-oesophageal reflux

Treatment for GOR can begin with conservative measures such as formula changes, thickening of feeds, giving smaller more frequent feeds, avoidance of overfeeding, refeeding after emesis, and burping techniques (Fishman and Bousvaros 1999; Hebra and Hoffman 1993). If the conservative measures fail, the next step is pharmacologic therapy which consists of acid suppressing agents and prokinetic agents. Surgical treatment is available for children who fail pharmacological management, or who have serious complications such as oesophagitis or an oesophageal stricture, that warrant surgical correction of the reflux. Nissen fundoplication, which involves a complete wrap of the gastric fundus around the intra-abdominal oesophagus, is the most widely used procedure for the surgical treatment of GOR (Fishman and Bousvaros 1999; Hebra and Hoffman 1993).
2.2.1.2 Other gastrointestinal complications

Other gastrointestinal complications of CP include gastritis and constipation. Gastritis can be caused by Helicobacter pylori infection. Up to 80% of institutionalised people with a disability are reported to be infected with Helicobacter pylori (Fishman and Bousvaros 1999). Gastritis can lead to abdominal pain and vomiting which in turn can lead to a decreased food intake. Constipation may be caused by diminished colonic motility, but contributing factors include immobility, low fibre intake, low fluid intake, and the effects of medications. Constipation may cause early satiety, poor feeding, gassiness, abdominal pain, and vomiting, again leading to a decreased oral intake and possibly malnutrition (Fishman and Bousvaros 1999). In a survey of 271 children with CP and neurological impairment, Sullivan et al found that gastrointestinal complications were prevalent with 59% suffering from constipation, and 22% with significant vomiting (Sullivan et al. 2000).

2.2.2 Oral-motor dysfunction

The development of oral-motor skills parallel and are closely tied to overall physical development (Ottenbacher et al. 1983a). Abnormal oral patterns and reflexes occur in conjunction with many disabilities, including intellectual disability and CP. Although wide individual differences exist among children, predictable deficits are commonly associated with abnormal oral-motor development. These are poorly co-ordinated breathing, difficulties with sucking and swallowing, persistence of the bite reflex or tonic biting, jaw instability or thrusting, tongue thrusting, decreased tongue movements, decreased lip closure, drooling, and hypo- or hypersensitive gag response. Each of these deficits is frequently associated with, and may be triggered by, other sensory or motor dysfunctions, particularly abnormal muscle tone and tactile hypersensitivity. These abnormal reactions make food intake extremely difficult, and
increase the risk of choking. In addition, duration of meal times is often lengthened, and both the children and the carers become frustrated and anxious.

### 2.2.2.1 Dysphagia

Dysphagia, defined as difficulty with swallowing and associated with feeding difficulties, is common in children with CP, and in many cases, may be the first sign of a developmental problem. Dysphagia is often the result of abnormal neuromuscular control. Swallowing is a complex process involving both autonomic and voluntary musculature. The oral phase of the swallow depends heavily on voluntary movement and, in CP, oral phase abnormalities are most common. Several nerves control the sensory and motor components of swallowing. In CP, neurological control of oral-motor functions by these nerves is impaired, resulting in poorly coordinated mandible and tongue movements, tongue weakness, delay in swallow initiation, and prominent reflexes including jaw jerk, tonic bite and suckle. There are several consequences of these impaired oral-motor functions: (1) slow oral transit time, which causes slow feeding and poor nutrition; (2) poor bolus formation, with food escaping into the pharynx before the swallow reflex and larynx closure; this causes aspiration and gagging; (3) slow pharyngeal transit with pharyngeal residue, allowing aspiration and causing discomfort and irritation (Jones 1989). Symptoms of dysphagia include food spillage, coughing, choking, regurgitation and spitting (Jones 1989).

### 2.2.2.2 Prevalence of dysphagia in cerebral palsy

Sullivan et al conducted a questionnaire to estimate the prevalence and severity of feeding and nutritional problems in children with neurological impairment (n = 271), 93 % of who had CP (Sullivan et al. 2000). Feeding problems were prevalent: 89 % needed help with feeding, and 56 % choked with food. In addition, 38 % of carers...
considered their child to be underweight; yet, despite these concerns, 64% had never
had their feeding and nutrition assessed. In a smaller (n = 35) but similar study, Dahl
et al interviewed the parents of children with moderate to severe CP regarding feeding
practices and problems and found that 21 of 35 children were reported as having daily
feeding problems (Dahl et al. 1996). The most common problems reported were
protracted meal times and difficulty in chewing and swallowing. Reilly et al conducted a similar survey in 49 children aged between 12 to 72 months with varying
degrees of CP. They found that 45 children had clinically significant oral-motor
dysfunction, 27 had sucking and 18 swallowing problems in the first 12 months of
life, and 39 of 49 children had been fed non-ormally on at least one occasion (Reilly et
al. 1996).

The feeding problems reported in these studies were not directly observed or
examined by the researchers, but reported by the parents which might be a reflection
of parental stress and anxiety. In addition, the latter two studies preferentially
included children with more severe CP. Therefore the prevalence of feeding problems
reported may be higher than in the general CP population. Nevertheless, these studies
demonstrate that feeding problems in children with CP are common, under-
recognised, and a cause of significant distress to affected children and their carers.

2.2.2.3 Dysphagia and respiratory problems

Children with dysphagia often cannot adequately protect their airway while feeding
and direct aspiration of food and liquid into the lungs may result in recurrent
pneumonia, chronic lung disease, chronic obstructive pulmonary disease, adult
respiratory distress syndrome, lung abscess formation and pulmonary fibrosis
(Fishman and Bousvaros 1999). Furthermore, aspiration can aggravate GOR, which,
as discussed in section 2.2.1.1 (pg 13), causes discomfort and may itself result in aspiration of stomach contents and further lung damage (Jones 1989).

The principal test to evaluate dysphagia and aspiration is the videofluoroscopic evaluation of swallowing, also known as the modified barium swallow (Griggs et al. 1989; Morton et al. 1993). Using videofluoroscopy, Griggs et al investigated 10 children with multiple handicaps aged between nine months and 24 years, all but one of whom had spastic quadriplegic CP (Griggs et al. 1989). Seven of the 10 children were found to aspirate food or liquid. However, most of these children were referred due to concerns with coughing, choking, and gagging during feeding and therefore the sample was biased. In a similar study using videofluoroscopy, Morton et al found that 11 out of 14 children aspirated and often it was silent, i.e. aspiration occurred without coughing or choking. All except one child had spastic quadriplegic CP, and all had severe feeding difficulty and most had frequent RTIs (Morton et al. 1993). Similar findings were reported by Rogers et al who conducted a retrospective review of 90 patients with CP who had undergone videofluoroscopy for investigation of dysphagia; aspiration was found in 87 of the patients, and often it was silent (Rogers et al. 1994). However, in all three aforementioned studies, most of the children were severely disabled and referred for concerns regarding airway protection during oral feeding; therefore the cohorts were highly selective and the prevalence of aspiration reported is likely to be higher than in the general CP population.

Using videofluoroscopy as well as 24-hour oesophageal pH analysis, Morton et al investigated both GOR and aspiration in 34 children with severe neurodisability due to various causes (Morton et al. 1999). The majority of children studied had spastic quadriplegic CP and all children had some degree of feeding problems. The children were divided into three groups for analysis depending on their history of RTIs (none,
Almost half of the children were found to have GOR, and more than half aspiration. Of the children with severe recurrent RTIs, half had GOR and almost all had aspiration, whereas in the group with no history of RTIs, half had GOR and none had aspiration. The results suggest that dysphagia is a major cause of RTIs in children with severe neurodisability.

2.2.2.4 Effect of dysphagia on food intake

In addition to aspiration and recurrent RTIs, dysphagia can result in malnutrition because of inefficiency of food intake and spillage. Gisel & Patrick compared the eating efficiency of seven children with severe CP and growth failure with healthy children of the same weight (Gisel and Patrick 1988). They found that the children with CP took two to 12 times longer to chew and swallow a standard amount of pureed food and one to 15 times longer for solid food than healthy children. In a similar study, Reilly & Skuse observed and video-recorded children with CP and age and sex matched healthy controls feeding in their own homes (Reilly and Skuse 1992). The authors found that there was no significant difference in the duration of the meal times for the CP and control children. The children with CP were both offered less and consumed less food than the control children during the observed mealtime. In addition, they were reported to consume significantly less food over a 24-hour period than the control group; 804 kcal versus 1283 kcal, respectively. Furthermore, only two out of the 12 children with CP were fed family foods, the rest being fed powdered baby foods, which are low in taste, texture and calories. Considering these findings, it is not surprising that failure to thrive was common in the CP group.

These two studies show that despite most of the children having significant oral motor dysfunction, their mealtimes were relatively brief usually because they were just offered less and consumed less food. The authors state that long meal times do not
compensate for the severity of these children's feeding impairment and, to compensate for inefficiencies of the order reported in these studies, feeding time would need to be in excess of normal waking hours. A study of length of meal times found that mothers of disabled children spend on average 3.5 hours, and some up to 7.7 hours, a day feeding their child compared to 0.8 hours for mothers of non-disabled children (Johnson and Deitz 1985). In a similar study, Reilly et al surveyed the parents of children with CP on how long they spent feeding their child at each meal time and then video recorded a meal time in the home (Reilly et al. 1996). There was a substantial discrepancy between the lengthy duration of mealtimes reported by mothers and those actually observed in the home: 27 minutes versus 18 minutes, respectively. Interestingly, children with the most severe oral-motor dysfunction tended to have shorter mealtimes than those with no or mild oral-motor dysfunction (19 versus 24 minutes respectively), possibly indicating that with the children with more severe oral-motor dysfunction, both child and parent quickly tired and gave up.

2.2.2.5 Effect of dysphagia on growth

Several researchers have found that children with CP who have significant oral-motor dysfunction tend to grow poorly, and that the prevalence is higher in children with more severe CP. These studies are discussed in more detail below. Most researchers agree that the poor growth seems to be predominantly due to the reduced food intake as discussed in the previous section (2.2.2.4, pg 20). In addition, aside from oral-motor dysfunction, further reasons why children with CP have difficulty in achieving an adequate nutritional intake include communication difficulties; impaired expression of hunger or food preferences; lack of self-feeding skills; and the inability to forage for food (Horton 1990).
Krick & Van Duyn conducted a retrospective pilot study comparing the growth of children with CP and oral-motor dysfunction to controls with CP and no oral-motor dysfunction (Krick and Van Duyn 1984). They found that children with oral-motor dysfunction had a significantly decreased weight and height for age in comparison with the control group. The results suggest a relationship between oral-motor dysfunction and growth retardation. However, the study had small numbers of participants (n = 12) and the age range of the participants (eight to 34 months) is younger than the usual age of clinical diagnosis of CP (often 24 to 36 months); therefore the results may not be representative of the CP population. In addition, in order to assess linear growth, this study used anthropometric techniques that were designed for healthy children and consequently subject to error in children with significant contractures and skeletal deformities.

In another retrospective study, Thommessen et al collected cross-sectional data on growth (height and weight) and energy intake from four-day food records in children with CP, half of whom were classed as severely disabled (Thommessen et al. 1991). Overall, half of the children had feeding problems and half had growth retardation, with many regarded as undernourished. In addition, low height for age and feeding problems were significantly more frequent in the most severely disabled children than in the mildly disabled. The children were then split into two groups for further analysis depending on the presence or absence of feeding problems. Children with feeding problems had a significantly lower height for age, weight-for-height, triceps skinfold thickness, and mid-upper arm circumference (MUAC) than children without feeding problems. These findings were substantiated by Troughton & Hill who also found that undernourished children with CP had poorer feeding skills compared to adequately nourished children with CP, and that feeding skills were inversely
correlated with the severity of CP, i.e. children with quadriplegic CP had significantly poorer feeding skills compared to children with milder CP (Troughton and Hill 2001). Thommessen et al reported that children with feeding problems also tended to have a lower energy intake, but the differences were not statistically significant (Thommessen et al. 1991). The authors concluded that the presence of feeding problems was a predictor of poor growth in children with CP. However, as with the study by Krick & Van Duyn this study used anthropometric techniques that may not be accurate in children with CP (Krick and Van Duyn 1984).

Motion et al also reported that feeding problems might be a predictor of poor growth in children with CP (Motion et al. 2002). The authors prospectively studied the prevalence of feeding difficulties at four weeks and six months of age in children subsequently diagnosed with CP in order to determine whether early feeding difficulties could be predictive of functional and growth outcomes at eight years of age. They found that feeding difficulties at four weeks of age were associated with being underweight and having speech and swallowing difficulties at eight years of age. The authors concluded that early, persistent and severe feeding difficulties are a marker for subsequent poor growth, feeding and developmental outcomes.

In addition to nutritional status, Fung et al described parent-reported feeding dysfunction and its association with health in a large group of children with moderate to severe CP (Fung et al. 2002). In agreement with previous studies they reported that feeding dysfunction was associated with poor nutritional status: lower weight, height, upper arm muscle area, and skinfold thicknesses in comparison to reference data. However, they also found that severity of feeding dysfunction was strongly associated with indicators of poor health and nutritional status. Those children with more severe feeding dysfunction spent more days in bed due to illness, were more likely to miss
their regular day program due to illness and experienced more respiratory illness than those with no feeding problems.

In summary, oral-motor dysfunction is present in a significant proportion of children with CP. Oral-motor dysfunction can result in an inadequate nutritional intake, which in turn leads to poor growth and malnutrition. Malnutrition increases the risk of infection, poor wound healing and osteopenia (which is discussed in more detail in section 2.4.4.2, pg 68). Furthermore, children with oral-motor dysfunction often cannot adequately protect their airway while feeding and aspiration may result in recurrent pneumonia or chronic lung disease. Poor feeding also results in long meal times, depriving the children of time for other activities and causing stress for the parents or carers. As demonstrated in the study by the Fung et al all of these factors combined can greatly detract from the child’s quality of life (Fung et al. 2002).

2.2.3 Energy and micronutrient intakes of children with cerebral palsy

There have been many studies investigating the energy and nutrient intakes of oral-fed children with CP. Most of these studies are summarised in Table 2.2 (pg 26). In general, the studies agreed that the energy and micronutrient intakes of most children with CP were below that recommended for age, and that energy intakes tended to decrease with increasing severity of CP. However, the studies used various methodologies, some of which are invalid for measuring dietary intake accurately. Furthermore, accurately estimating energy and nutrient intakes in oral-fed children with CP is difficult due to losses from spillage, vomiting and regurgitation. Alternatively, gastrostomy tube feeding allows a more accurate estimate of dietary intake because there are no, or minimal, losses from spillage, and the exact energy and nutrient composition of the formula are known. Fried & Pencharz retrospectively examined the energy and nutrient intakes of exclusively gastrostomy tube-fed children
with CP and found that the average energy intake of the group was 61% of the recommended dietary intake (RDI) for age (range 43 – 98%) (Fried and Pencharz 1991). Their dietary intake was adequate for protein, and for vitamins A, E, and C, B₁₂, folate, zinc, and iron but below the RDI for vitamin D (62% of RDI), calcium (74% of RDI), and phosphorus (64% of RDI). In addition, although the children appeared to have insufficient intakes of micronutrients in comparison to recommended values, the blood levels of most micronutrients were within normal ranges, suggesting that their intakes were in fact biochemically adequate. However, the authors did not state the methodology used to measure the serum levels of the micronutrients, and it is therefore unknown if valid methods were used.

Gisel & Patrick, on the basis of their experience with feeding neurologically impaired children, suggested that nutritional problems are caused primarily by energy deficits rather than by deficits of protein, vitamins or minerals (Gisel and Patrick 1988). They maintain that it is because the diet given to people with disabilities is qualitatively good but deficient in volume that malnutrition found in individuals with disabilities is rarely associated with either skin changes or hair or mucosal changes; and is also very different from the clinical picture of malnutrition seen in the developing world. The qualitative (micronutrient) adequacy but quantitative (energy) deficiency of the diets provided for children with disabilities might also be one of the reasons that such individuals can survive in a moderately malnourished state for many years. This raises the issue of using recommendations based on healthy children. Is the nutrient intake of children with CP appropriate for their size as distinct from their chronological age?
<table>
<thead>
<tr>
<th>Author</th>
<th>Participants</th>
<th>Methods</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Peeks and Lamb 1951)</td>
<td>N = 29</td>
<td>One-week estimated food record</td>
<td>Up to a half of the children were consuming less than 90% of the American RDI for energy, protein, vitamin C, iron, and calcium, possibly due to low intakes of milk and citrus fruits.</td>
</tr>
<tr>
<td>(Leamy 1953)</td>
<td>N = 21</td>
<td>48-hour weighed and estimated food records</td>
<td>The majority of children were consuming inadequate energy, iron, vitamin C, and niacin, and approximately half were consuming inadequate protein, calcium and thiamine. When comparing energy intake based on skeletal age rather than actual age, they found that energy intake was closer to that recommended based on skeletal age, but two-thirds were still below recommended. The authors also noted that the athetoid children had a higher energy intake than the spastic children.</td>
</tr>
<tr>
<td>(Karle et al. 1961)</td>
<td>N = 12</td>
<td>Estimated 2-3 day food records</td>
<td>All children had energy intakes below recommended, but only two children had protein intakes which were less than recommended. All except one child had low iron intake, yet their haemoglobin values were within the normal range. Blood levels of vitamin A, carotene, and vitamin C were also within the normal range; however, all of the children routinely received a multivitamin and mineral supplement.</td>
</tr>
<tr>
<td>(Hammond et al. 1966)</td>
<td>N = 31</td>
<td>Combination of 24-hour recall and 6-day estimated food record.</td>
<td>In over half of the children, intakes of energy, calcium, iron, and thiamine failed to reach 100% of recommended, however, most nutrient intakes were higher than two-thirds of recommended. Serum levels of haemoglobin, vitamin A, carotene, protein and albumin were all within the normal range. They also observed that energy intakes of children with athetoid CP were higher than those with spastic CP. Energy intakes were inversely correlated with the severity of CP.</td>
</tr>
<tr>
<td>(Berg and Isaksson 1970)</td>
<td>N = 23</td>
<td>Estimated by observation</td>
<td>Energy and nutrient intakes were lower than recommended, however protein intakes were adequate.</td>
</tr>
<tr>
<td>(Sullivan et al. 2002)</td>
<td>N = 94</td>
<td>Combination of diet history, 24-hour recall and 3-day estimated food record</td>
<td>Only 20% of children had energy intakes above recommended for their age, and more than half of the group with severe disabilities consumed less than 80% of recommended. All except four of the children achieved the recommended protein intake. All children met the recommended intake for sodium, potassium, magnesium, phosphorus, and B vitamins. Iron intake was below recommended for almost half of the children. Those children with more severe disability had lower energy and nutrient intakes and poorer growth than those with milder disability, suggesting that inadequate dietary intakes may contribute to their stunted growth.</td>
</tr>
</tbody>
</table>

CP, cerebral palsy; RDI, recommended dietary intake
2.3 Growth and cerebral palsy

Human growth follows a predictable pattern. Normal growth is a marker for health, while growth retardation suggests a psychosocial problem, malnutrition or a medical illness. Aside from feeding difficulties, growth deviation may be the first, or only, signal of a more serious underlying health problem that requires investigation (Krick et al. 1996).

2.3.1 Early studies on growth

The growth failure of children with CP was first recognised and studied in the 1950s and 1960s. Several groups of researchers observed that many children with CP were shorter and lighter than their age-matched peers (Hammond et al. 1966; Pryor and Thelander 1967; Ruby and Matheny 1962; Sterling 1960; Tobis 1961). In addition, they found that the degree of severity of CP correlated with the degree of stunting and wasting. One group also noted that the incidence of fevers and infection tended to be greater in children with CP than in the normal population (Sterling 1960).

Different theories were postulated as to the cause of the poor growth. One group believed that the growth failure might be explained by an increase in metabolic demands whereas another believed that children with athetoid type CP had greater energy expenditure than children with spastic type CP (Ruby and Matheny 1962; Sterling 1960). Others questioned whether the lack of physical activity was the major factor in impairing linear growth, or whether the CNS impairment somehow affects growth with no relation to mobility (Tobis 1961). A summary of these studies in chronological order is presented in Table 2.4 on page 66.
2.3.2 Assessing growth in children with cerebral palsy

All of the early studies on growth in CP used standard measures of height to assess linear growth. While an index of linear growth is essential in the assessment of nutrition and growth of children, it is difficult to obtain in children with CP, mainly because of fixed joint contractures, involuntary muscle spasms and scoliosis (Spender et al. 1989; Stevenson et al. 1994; Stevenson 1995a). Alternate measures to standing height or length are available and include the measurement of arm span and segmental measurements of upper arm length (UAL), lower leg length (LLL) and knee height (KH). The measurement of arm span requires the subject to outstretch their arms in the horizontal position and to hold this position while the distance from fingertip to fingertip on opposing hands is measured. Due to joint contractures and involuntary muscle spasms in children with severe CP, arm span would be difficult to measure and has therefore not been investigated as an alternative to standing height in this population. Segmental lengths of UAL, LLL, and KH require minimal subject cooperation, involve the measurement of only one segment of the limb, thereby minimising the effects of contracted joints, and have been investigated for use in children with CP (Chumlea et al. 1994; Johnson and Ferrara 1991; Spender et al. 1989; Stevenson 1995b).

Stevenson et al developed a set of equations to convert UAL, LLL, and KH to standing height in children with CP aged less than 12 years (Stevenson 1995b). The equations were derived from measurements performed on a group of children with varying degrees of CP. A different set of equations, based on KH only, for use in children aged 12 to 18 years were developed and validated in a group of healthy children by Chumlea et al from the 1960-1970 National Health Examination Surveys of Healthy Individuals (Chumlea et al. 1994). Both sets of equations (i.e. those of
Stevenson and Chumlea), were developed by regression analysis using standing height as the dependent variable and either KH, UAL or LLL as the independent variable. Therefore, in order to develop and validate the equations each individual in the test populations had to have both the segmental length and standing height measured, or in the case of the Stevenson population, recumbent length if the individual was unable to stand. In fact of the 211 sets of measurements from the 172 individuals of the CP population of Stevenson, only 27 were able to stand for a height measurement, the remaining 184 sets of measurements used recumbent length. Recumbent length is known to be greater than stature by up to 2 cm (Moore and Roche 1986). In addition, the database of Stevenson included only seven (4 %) individuals with quadriplegic CP. Furthermore, although they showed that the measurements of segmental length were highly correlated with standing height or recumbent length, they did not compare height estimated by conversion of KH, UAL, or LLL with actual standing height or recumbent length, nor did they cross-validate their equations.

2.3.2.1 Validation of alternate measures for standing height

Johnson et al attempted to validate the equations developed by Chumlea in a population of 31 children with varying degrees of CP (Chumlea et al. 1994; Johnson and Ferrara 1991). The authors measured standing height in all of the study participants, yet approximately one-third of the population had involvement of the lower extremities, and therefore the measurements of standing height are of questionable validity. Although the authors found that KH alone was highly correlated with standing height, they found that the difference between actual measured height and estimated height using KH was too great to make the equations useful in a clinic setting. However, there were only 31 participants in the study with one-third having
lower extremity involvement, which can make standing height difficult to measure and most likely unreliable.

Spender et al also attempted to validate UAL and LLL as a proxy for standing height in 98 children with varying severities of CP and in a control population (Spender et al. 1989). The authors found that they were unable to evaluate the validity of using UAL and LLL to estimate height in children with CP because of the lack of reliable measures of height or length in this group. In the control population, they found that UAL and LLL correlated reasonably well with standing height with correlation coefficients between 0.60 and 0.85. However, the measures of UAL and LLL were not converted to height for comparison and therefore it is difficult to determine from this study if segmental measures are in fact valid proxies for standing height. There are reference charts available for UAL and LLL and the authors recommend using these charts to assess linear growth when it is not possible to measure height or length (Cole 1998).

Therefore, due to the inability to validate the equations to estimate height in populations with severe CP, the equations are of questionable utility. Nonetheless, even with an estimate of standing height, the interpretation of growth in children with CP is unclear. This is mostly because the available reference growth charts are based on healthy physically active children with normal muscle and bone mass which may not be appropriate to compare to children with CP.

2.3.3 Development of growth standards for use in cerebral palsy

In order to overcome the problem and uncertainty of comparing the growth of children with CP with normal standards, Krick et al developed growth charts specifically for children with quadriplegic CP (Krick et al. 1996). On comparing the CP and normal reference growth charts, it was found that the 50th centile of the CP
growth chart was below the 10th centile for normal standards for weight for age and length for age, and was roughly equal to the 10th centile for weight for length. As the children aged, the differences between the CP population and the reference population increased. The authors concluded that the 10th centile for weight (on the normal growth charts) would be an appropriate healthy weight for children with CP. Unfortunately, these growth charts are not recommended for use because the methodology used was flawed in several areas: the authors used measures of weight and length that were collected both prospectively and retrospectively from medical records; in some of the study participants who were unable to stand, part body lengths were measured and summed to give total length which is of unknown reliability; and the data included single observations of some children, but multiple observations of others. Moreover, malnourished children were not excluded from the sample and thus the results were skewed by stunted, chronically undernourished children. Finally, the development of these growth charts suggest that children with CP cannot be expected to grow at normal rates, and that growth failure is an accepted and irremediable consequence of the disease. Currently, evidence for either of these concepts is not available. However, considering that a large proportion of children with CP who can eat normally maintain normal growth, one could question their validity.

As an alternate method to using height growth charts, Samson-Fang & Stevenson evaluated the use of standard reference weight-for-height centile (WHC) charts to screen 276 children with CP for depleted body fat, defined as a mid-upper arm fat area (UAFA) less than the 5th centile (Samson-Fang and Stevenson 2000). A cut-off of WHC <10th centile failed to identify 45 % of children with severely depleted fat stores (UAFA <5th centile). The authors claimed that this was because WHC is a better indicator of acute rather than chronic malnutrition. Furthermore, WHC may
have performed poorly as an indicator of fat stores because of excess “artificial”
weight from clothing, braces, and faecal mass due to constipation. In addition, the
authors claimed that using LLL to estimate height could result in false elevation of
WHC if a child has undergrowth of the lower extremities in association with motor
impairment. MUAC, body mass index (BMI), and subscapular skinfold thickness also
performed poorly as screening tools. The authors found that the best indicator of
suboptimal fat stores and malnutrition was using triceps skinfold cut-off value of
<10th centile for age and sex.

Due to the poor performance of weight-for-height in identifying malnutrition in
children with CP, Lark et al sought to find reliable biochemical indicators of
malnutrition (Lark et al. 2005). They evaluated serum prealbumin and albumin as
markers of undernutrition in 107 children with moderate to severe CP. They found
that prealbumin and albumin were rarely below normal reference ranges and showed
little to no correlation with anthropometric measures, growth, severity of CP or
general health, and therefore these biochemical tests appear to be of little value in the
clinical setting in identifying children with CP and malnutrition.

2.3.4 Nutritional and non-nutritional causes of growth failure
Following the studies from the 1960s which identified significant growth failure in
children with CP, several researchers have sought to determine the cause/s of the
growth failure. Most researchers agree that the cause is multifactorial and is a
combination of both nutritional and neurological, or non-nutritional, factors.
Nutritional factors are primarily protein-energy malnutrition due to inadequate intake,
excess losses from vomiting and spillage, and possibly altered energy requirements
(Stevenson et al. 1994). Neurological or non-nutritional factors that have been
postulated to affect growth include (i) that the CNS injury somehow inhibits growth;
(ii) that a trophic influence from the brain is disrupted causing poor growth; (iii) that the abnormal muscle tone and activity created by damage to the CNS, and the consequent disuse and decreased blood flow to the affected limbs, causes dwarfing of the limbs; and (iv) that parietal lobe defects associated with sensory deficits somehow inhibit growth (Stevenson et al. 1995) (Rempel et al. 1988; Shapiro et al. 1986).

Stallings et al studied the growth patterns of a large group (n = 142) of children with spastic quadriplegic CP to test the hypothesis that poor nutritional status, as indicated by depleted subcutaneous fat stores and muscle stores, is an identifiable cause of growth failure in children with spastic quadriplegic CP (Stallings et al. 1993a). They confirmed the findings of previous researchers that height and weight were significantly reduced, and these measures dropped further below the median as the children aged. In addition, they found that on average the triceps and subscapular skinfold thicknesses, and to a lesser extent upper arm muscle area (UAMA), were significantly reduced. Using regression analysis, the authors sought to determine the relative contribution of various non-disease (age, sex, race, pubertal status) and disease (type of CP, cognitive status, ambulatory status, oromotor status) factors to nutritional status (UAMA and percent body fat) and linear growth failure of the children with CP. The non-disease and disease severity variables explained about 70 to 75 % of the variation in linear growth. After controlling for the non-disease and disease severity factors, nutritional status explained 10 to 15 % of the remaining variation in linear growth. The authors concluded that both nutritional and non-nutritional factors influence the growth of children with CP.

Stevenson et al conducted a similar study to that of Stallings et al in order to investigate the causes and mechanisms of growth failure in children with various severities of CP (Stevenson et al. 1994). They also found greatly reduced height,
weight, and triceps skinfold thickness, and that height standard deviation (SD) score was negatively correlated with age. In addition, their results indicated that children with seizures, spastic quadriplegic CP and those who were non-ambulatory had significantly lower height and weight SD scores. The authors attempted to explore the associations between nutritional (weight, triceps skinfold thickness) and non-nutritional factors (age, type of CP, seizures, non-ambulation) and growth (height), and the contribution which each makes towards growth. Only weight (nutritional) and age (non-nutritional) contributed significantly to height SD score. Therefore, these results support the hypothesis, and the findings of Stallings et al, that both nutritional and non-nutritional factors influence linear growth in children with CP.

However, the two aforementioned studies involved patient populations with a high prevalence of malnutrition, which may have confounded the effects of non-nutritional factors on growth (Stallings et al. 1993a; Stevenson et al. 1994). Therefore, Stevenson et al attempted to further determine the contributions of the various factors by studying children with hemiplegic CP (Stevenson et al. 1995). The authors claimed that children with hemiplegic CP offer a natural model for the study of non-nutritional factors on growth without the confounding effects of malnutrition or endocrinopathy. Furthermore, each child can be used as its own control. They measured breadth, circumference, length and skinfold thicknesses on the limbs of both the affected and unaffected side in a small group of children with spastic hemiplegic CP and normal stature. They found that all measures were significantly shorter or lower on the affected side compared with the unaffected side and, on average, the skinfold measures tended to be larger on the affected side. This study suggests that CP affects growth negatively, even in the absence of malnutrition. The authors claim that a significant portion of the growth failure observed in children with CP is unrelated to
malnutrition, and therefore would be unaffected by nutritional treatments. There have been some studies of the effects of nutritional rehabilitation on growth in children with CP. These studies are summarised and discussed in section 2.6.3.1 (pg 84).

Samson-Fang & Stevenson argued that the previous studies investigating influences on growth in children with CP were cross-sectional only and therefore were unable to accurately identify the factors associated with suboptimal linear growth (Samson-Fang and Stevenson 1998). Therefore, they retrospectively studied linear growth velocity and the factors associated with poor linear growth in a large group (n = 81) of children with varying degrees of CP. Lower growth velocity was seen in children aged less than two years, males, non-ambulatory children, malnourished children (triceps <5th centile), and those with cognitive impairment. However, the authors acknowledged that the use of linear growth velocity to study growth patterns in children with CP was hampered by the difficulty in obtaining accurate measurements of height in this population. Therefore, the authors were only able to study children in whom an accurate measure of height could be obtained, and therefore preferentially excluded those children with more severe CP. A summary of the studies in this section are presented in chronological order in Table 2.4 (pg 66).

2.3.5 Hormones and growth in children with cerebral palsy

Growth is controlled by, and dependent upon, many factors including prenatal growth and development, genetic factors, nutrition and hormones. This sub-section focuses on the hormones that influence and control growth.

Growth hormone (GH, or somatotropin) is necessary for normal linear growth. GH deficiency causes short stature while GH excess leads to gigantism (Jameson and Weetman 1998). In the total absence of GH, linear growth occurs at about half to a third of the normal rate. However, GH does not appear to be the principal direct
stimulator of growth but rather acts indirectly by stimulating the formation of other hormones or factors. These factors, known as somatomedins (SMs, or somatotropin-mediating hormones) or insulin-like growth factors (IGFs), are GH-dependent and are responsible for growth stimulation. IGF-I (formerly SM-C), the most important SM for post-natal growth, is produced mainly in the liver, with other sources including chondrocytes, kidney, muscle, pituitary, and gastrointestinal tract.

GH is controlled by a dual hypothalamic regulation (Figure 2.1, pg 38). Secretion is stimulated by GH-releasing hormone (GHRH) and inhibited by somatostatin (GH-release inhibiting hormone or somatotropin release-inhibiting factor, SRIF). GH deficiency is often a consequence of hypothalamic GHRH deficiency. In addition, the levels of GH and IGF-I depend on nutritional status; IGF-I levels decline, while GH levels increase in states of malnutrition (Jameson and Weetman 1998)(Robinson and Picou 1977) (Hintz et al. 1978; Soliman et al. 1986). It has been hypothesised that the reduced levels of IGF-I found in malnourished children could be due to a general impairment of protein synthesis by the liver, which as mentioned previously is the main source of IGF-I production (Hintz et al. 1978). Thus without the inhibitory effects of IGF-I on GHRH, GH levels increase. Furthermore, it is suggested that high GH and possibly low IGF-I levels mediate lipolysis which is an important adaptive mechanism to assure fuel (fatty acids) supply for metabolism of brain and peripheral tissues during nutritional deprivation (Soliman et al. 1986).

Thyroid hormones also influence growth; however, unlike the pattern of growth with GH deficiency, the total absence of thyroid hormone causes an almost complete cessation of linear growth. Thus adequate thyroid hormone appears to be an absolute prerequisite for normal growth. Thyroid hormones exert direct effects on cell
metabolism, and thyroid deficiency also results in diminished GH secretion in response to stimulation.

Other hormones that influence growth include the gonadal steroids (androgen and oestrogens) during puberty, insulin, and other factors such as nerve growth factor, epidermal growth factor, and platelet-derived growth factor.

Despite the high incidence of growth failure and malnutrition in children with CP, there have been only two small studies and three case reports of GH levels in this population. Hayashi et al reported subnormal GH responses following clonidine (a stimulator of GHRH and GH) administration in four boys with athetoid CP and following GHRH administration in seven boys with spastic CP (Hayashi et al. 1989). The authors suggested that athetoid CP was associated with hypothalamic GHRH deficiency and spastic CP with reduced pituitary reserve of GH.

Another study of children with severe CP reported that six of the 10 children studied had subnormal GH secretion, four of whom also had low IGF-I levels (Coniglio et al. 1996). A further three children in the study who had normal GH levels had low IGF-I levels. In addition it was found that normal growth velocity was strongly predictive of adequate GH secretion; only one of five children with normal growth velocity had subnormal GH secretion, whereas all five children with subnormal growth velocity had subnormal GH secretion. All children in the study had normal thyroid function tests. However, the authors used recumbent lengths as a measure of height which may not have provided an accurate estimate of growth velocity, and the study involved only a small number of participants with varying degrees of malnutrition. Furthermore, their findings are in contradiction with a number of other studies on severely malnourished infants and children that have found significantly elevated basal levels of GH and reduced levels of IGF-I (Soliman et al. 1986).
Figure 2.1 Feedback control of growth hormone secretion

Figure adapted from (Jameson and Weetman 1998). GH, growth hormone; GHRH, growth hormone-releasing hormone; SM, somatomedins (insulin-like growth factors). Stimulating influences are shown by solid lines. Inhibitory influences are shown by dotted lines.
The three case reports found the following:

- Case 1 – a child with moderate CP, short stature and mild malnutrition, found to have low GH levels, low IGF-I levels, normal thyroid functions, showed increased growth velocity with daily GH injections (Coniglio and Stevenson 1995);

- Case 2 – a child with moderate CP, short stature and mild malnutrition, found to have subnormal GH levels, however refused treatment with GH (Coniglio and Stevenson 1995);

- Case 3 – a child with hemiplegic CP, short stature, found to have normal GH levels, however exhibited increased growth during treatment with GH (Shim et al. 2004).

In summary, the studies that have been done involved only small numbers of participants and reported conflicting results. However, they do provide some evidence to suggest that endocrinological factors may play a role in causing growth failure in children with CP. The reasons for the GH abnormalities found in these studies are unclear, but may include anatomic defects of the hypothalamus or pituitary gland or an interaction between malnutrition and a damaged CNS. Further studies are needed to investigate the possible interactions between CNS damage, malnutrition and GH in children with CP, and whether GH therapy might be beneficial in this population.

### 2.4 Body composition in children

Weight and height are often used as a screening tool to assess nutritional status in children. Abnormal growth can be an indicator that the child has an underlying illness or disease that requires further investigation. Waterlow devised a classification system for malnutrition based on weight and height, where the terms wasting and stunting
were used to describe acute and chronic malnutrition, respectively. Acute malnutrition, or wasting, was defined as having a normal height, but a weight that was less than 80% of expected for age (Waterlow 1972). Chronic malnutrition, or stunting, was defined as having a reduced weight-for-age as well as a reduced height-for-age (Waterlow 1972). Chronic malnutrition was further categorised into mild (80 to 90% of expected weight-for-height), moderate (70 to 79% of expected weight-for-height) and severe (less than 70% of expected weight-for-height).

However, weight and height measurements do not describe the composition of the body, i.e. fat, muscle mass, water, or bone; or which of these components are abnormal. Precise and accurate measurement of body composition is important to the understanding of the disease process so that deficits or excesses can be defined and corrected. Body composition is also important to measure in healthy children so that it can be used as reference data.

### 2.4.1 Body composition components

The body consists of essentially six “compartments” – fat, water, protein, glycogen, bone mineral and non-bone mineral (Figure 2.2, pg 44). Often, for simplification, some of the compartments are combined to give either a two compartment (2C) model, where body weight is divided into fat mass (FM) and fat-free mass (FFM), or a four compartment (4C) model, which may consist of fat, water, protein and bone, for example. There are also three, five and six compartment models, however the 2C and 4C are the most commonly used. Several methods exist to measure each compartment or to measure a combination of compartments. Some of these methods are outlined in section 2.4.2. At present there are no methods available for quantifying total body glycogen in vivo. Glycogen constitutes about only 1% of body weight, and depending
Chapter 2  
LITERATURE REVIEW

on the technique used and the compartment measured, glycogen is incorporated into one of the other compartments (Heymsfield et al. 1993).

Critical to the use of most indirect methods utilised to estimate body composition is the assumption that the content of the FFM is relatively constant. Studies based on animals suggested that many species reach a relatively constant FFM composition (chemical maturity) by 4.5 % of the lifespan (Boileau et al. 1984; Moulton 1923). When these observations were extended to humans it was suggested that chemical maturity was achieved by three to four years of age (Moulton 1923). However, the data used were limited to foetuses, infant and adults (Boileau et al. 1984). More recent studies have shown that the proportion of water, protein and minerals in FFM change during maturation, and that chemical maturity is reached after puberty, or around 16 years in girls and 18 years in boys (Boileau et al. 1984; Lohman 1986). Protein and mineral contents of FFM increase with chemical maturity, as water content decreases. The changes are similar for both sexes, but females have a slightly higher water content than males (Boileau et al. 1984). Unfortunately all indirect methods to assess body composition have been developed with the assumption of chemical maturity. This and other assumptions are discussed in more detail in the following section, 2.4.2.

2.4.2 Techniques to measure body composition

2.4.2.1 Densitometry

The term “densitometry” refers to the general procedure of estimating body composition from body density. This method assumes that the body is composed of two distinct components (FM and FFM) and that it is possible to determine each of these components from the measured whole body density (Lukaski 1987). Although
several methods can be used to estimate body density, densitometry has become virtually synonymous with underwater weighing (also known as hydrodensitometry) (Going 1996). Underwater weighing has long been considered the gold standard and has been often used as the criterion method in validation studies of new body composition assessment methods. Underwater weighing essentially measures the volume of the body – when a subject is submerged in water, body volume is equal to the weight of displaced water. Like any material, the density of the human body ($D_{b}$) is equivalent to the ratio of its mass ($M_A$) and volume ($V$):

$$D_b = \frac{M_A}{V}$$

Furthermore, the density of any material is a function of the proportions and densities of its components. In the 2C model, body weight is divided into FM and FFM, thus:

$$\frac{1}{D_b} = \frac{FM}{d_f} + \frac{FFM}{d_{FFM}}$$

where $1/D_b$ equals body mass divided by body density, and $FM/d_f$ and $FFM/d_{FFM}$ are the proportion of fat and fat-free mass divided by their respective densities.

Densitometry is based on several assumptions (Going 1996):

1. that the density of fat is 0.9007 g/ml and that of FFM is 1.100 g/ml,
2. that the separate densities of the body components are additive,
3. the densities of the constituents of the body are relatively constant from person to person,
4. that the proportions of the constituents other than fat are relatively constant from person to person, i.e. the water content of FFM is constant at 73.2 %, and the proportion of bone mineral to muscle in the FFM is constant,
5. that the person being measured differs from a standard reference body only in
the amount of body fat.

However, a number of studies based on chemical and anatomical models have
demonstrated considerable variation in FFM composition and density due to growth
and maturation, specialised training, aging, and sex, which challenge the assumption
of FFM constancy. Furthermore, the technique of underwater weighing requires
complete submersion of the subject in water, and for several reasons is technically
difficult, and is therefore not appropriate for all subject groups, particularly children.

2.4.2.2 Air displacement plethysmography

An alternative approach to underwater weighing is air displacement plethysmography
(ADP). ADP uses pressure-volume relationships to estimate the volume and density
of the body (Going 2005). Although ADP avoids many of the challenges of
underwater weighing, past applications in humans have been limited due to the
technical difficulties in adjusting for irregularities in temperature and humidity of the
air next to the skin and hair (Going 2005). A new system, the Bod Pod (Life
Measurement, Inc, Concord, CA), has improved precision and accuracy compared
with past techniques. The device consists of a single structure with two
complementary chambers: a test chamber of approximately 450 L where the subject is
seated and a reference chamber of approximately 300 L. A moulded fibreglass seat
forms a common wall separating the chambers. A diaphragm oscillates between the
chambers, producing sinusoidal volume perturbations that are equal in magnitude but
opposite in sign. The perturbations result in very small pressure changes within the
chambers, which are monitored by transducers and analysed for pressure at the
frequency of oscillation. The ratio of the pressures is a measure of the test chamber
volume (Fields et al. 2002), which is determined by the application of Poisson’s law:
Figure 2.2 Body composition model
Adapted from Pietrobelli et al (Pietrobelli et al. 1996)
\[
\frac{P_1}{P_2} = \left(\frac{V_2}{V_1}\right)^\gamma
\]

where \(P_1\) and \(V_1\) represent one paired condition of pressure and volume, \(P_2\) and \(V_2\) represent a second condition, and \(\gamma\) is the ratio of the specific heat of the gas at constant pressure to that at constant volume (Going 2005).

When a subject is placed inside the test chamber air is displaced from the test chamber and is added to the reference chamber. The volume of air displaced is equal to the volume of the body inside the test chamber (Fields et al. 2002). Body volume is calculated indirectly by subtracting the volume of air remaining inside the test chamber when the subject is inside from the volume of air inside the test chamber when it is empty (Fields et al. 2002). The body volume measured by the Bod Pod is then corrected for isothermal properties of the air contained in the lungs, near the skin or hair, and in clothing (Ellis 2001). Body density is then calculated from body volume using the same method as for underwater weighing and then converted to percent body fat using the Siri, or other similar, equation (Fields et al. 2002; Siri 1993).

Because the Bod Pod technique uses the same equations as underwater weighing for translating body volume into body density and subsequently body composition, the technique is limited by the validity of the assumptions of these equations described in the previous section.

Studies in adults and children have revealed good precision (< 0.11 L) for the measurement of body volume by the Bod Pod (Fields et al. 2002). However, there have been only a limited number of studies validating the accuracy of the Bod Pod against 4C models of body composition, and therefore further studies are required to determine the accuracy of this technique (Fields et al. 2002).
In summary, ADP offers several advantages over established reference methods, including a quick, comfortable, automated, non-invasive, and safe measurement process, and accommodation of various subject types (e.g. children, obese, elderly and disabled persons) (Fields et al. 2002). However, both underwater weighing and ADP are limited by the validity of the assumptions that underlie conversion of body density to composition, and thus both methods are best used in combination with other methods in 3C or 4C models (Fields et al. 2002; Going 2005).

2.4.2.3 Anthropometry

Anthropometry, the measurement of body size, weight, and proportions, is one of the most commonly used methods available to assess nutrition. Anthropometry has the advantages of being simple to use, inexpensive, non-invasive and portable. However, the precision of the technique is variable and dependent upon the skill of the anthropometrist. Values derived from the measurement of skinfold thicknesses at two or more sites on the body as well as limb circumferences can be used in various multiple regression equations to predict body density and to calculate FM. FFM is then calculated by subtracting FM from body weight, thereby providing a 2C model of body composition Because FM estimated from skinfold anthropometry is derived using body density, it also relies on the same assumptions as for measuring body density. In addition, skinfold anthropometry itself is based on two main assumptions: that the thickness of the subcutaneous adipose tissue reflects a constant proportion of the total body fat and the sites selected for measurement represent the average thickness of the subcutaneous adipose tissue. Neither of these assumptions has been proven to be true, and therefore the validity of using skinfold equations to predict body composition is restricted to populations from whom the equations were derived (Lukaski 1987; Roche 1996).
2.4.2.4 Dual-energy x-ray absorptiometry

Dual energy x-ray absorptiometry (DXA) was originally designed to measure only bone mineral content (BMC) and bone mineral density (BMD), and is considered a gold standard technique for this purpose (Lohman 1996). However due to the increasing popularity, availability and advantages of this technique, DXA was further developed and can now also measure other compartments of the body, namely lean tissue mass (LTM) and body fat. This method uses a whole-body rectilinear scanner and a high activity gadolinium-153 source that emits energy (photons) at two distinct peaks (44 and 100 keV). The source is mounted beneath a table and is opposite to a scintillation detector above the table. The source and detector are passed across the body at a traverse speed of 1 cm/s with data collected at 0.5 cm intervals (Lukaski 1987). As the photons traverse the subject’s tissues, physical interactions take place that reduce the beam intensity. This process is generally referred to as attenuation (Pietrobelli et al. 1996). When photons at two different energies are passed through the subject, attenuation at the lower energy can be expressed as a ratio (R) to attenuation observed at the higher energy. This process produces an image of the body made up of thousands of pixels which is then analysed by a computer.

The DXA body composition approach assumes that the body consists of three components that are distinguishable by their x-ray attenuation properties: fat, bone mineral, and residual or lean soft tissue (see Figure 2.2 pg 44). However, in practice, DXA can only resolve the fractional masses of a two-component mixture, bone mineral and soft tissue (Pietrobelli et al. 1996). The DXA method for estimating three components is to separate pixels into those with soft tissue only (fat plus lean) and those with soft tissue plus bone mineral. Because the R value for bone mineral is much higher than for soft tissue, bone-containing pixels will be those with the higher
composite R values. The composition of bone mineral is essentially invariable and is therefore accurate in its estimation; however, soft tissue is composed of varying amounts of fat and lean tissue. Variations in fat and lean tissue composition produce differences in R values. Therefore, the fat and lean components of each soft tissue pixel can be established from the measured and assumed R values for the two respective components, using the following equations:

\[
f_1 = \frac{(R_1 - R_2)}{(R - R_1)} \text{ and } f_2 = \frac{(R - R_1)}{(R_2 - R)}
\]

Where \( f_1 \) and \( f_2 \) represent fat and lean tissue, respectively; \( R \) is the measured ratio of attenuation at the two different energy levels; and \( R_1 \) and \( R_2 \) are the assumed or theoretical R values established by measuring “pure” fat (\( R_1 \)) and lean soft tissue (\( R_2 \)) samples. The theoretical R value for lean tissue is based on the assumption that the hydration of lean tissue is constant at 73.2 % (Pietrobelli et al. 1996).

DXA has the advantages of being quick and precise with a low radiation dose (~ 0.2 μSv), and is therefore ideal for use in paediatric populations. However, the cost and availability of the instrumentation may be a limiting factor for its use. Furthermore, the accuracy of the estimation of the soft tissue components by DXA has been questioned, mainly because, like the methods already discussed, it also relies on the assumption that the hydration of LTM is constant at 73.2 %. The hydration of LTM or FFM may vary in some disease states and also during growth and maturation, and the degree to which DXA measurements are sensitive to variation in hydration levels is unknown.

### 2.4.2.5 Neutron activation analysis

The development of in-vivo total body neutron activation analysis (NAA) has provided the only technique currently available for the direct measurement of several
compartments of the body. Absolute content of calcium, sodium, chlorine, hydrogen, phosphorus, and nitrogen can be determined using this technique (Ellis 1996). Of particular value, is the measurement of total body nitrogen (TBN). By measuring TBN, total body protein (TBP) can then be calculated using the following assumed relationship: mass of protein = 6.25 x mass of nitrogen (Baur et al. 1991a).

The basis of this technique is that the subject is bilaterally irradiated with neutrons produced from the decay of two $^{252}$Cf sources, which results in the conversion of $^{14}\text{N}$ to $^{15}\text{N}$ with the emission of a 10.83 MeV gamma ray which is specific for nitrogen (Baur et al. 1991a). The absolute mass of nitrogen ($M_{\text{AN}}$) can be determined by using hydrogen (2.23 MeV gamma ray emission) as an internal standard and the following equation:

$$M_{\text{AN}} = \left(\frac{Y_{\text{N}}}{Y_{\text{H}}}\right) K M_{\text{AH}} C(W)$$

Where $Y_{\text{N}}$ and $Y_{\text{H}}$ are the net nitrogen and hydrogen yields, respectively, $K$ is the calibration factor determined from a phantom with known hydrogen and nitrogen masses, $C(W)$ is the nitrogen-to-hydrogen gamma ray attenuation correction factor which is dependent on subject width, and $M_{\text{AH}}$ is the mass of hydrogen determined from fat mass, as per the following equation, where fat mass ($M_{\text{A}}$) is estimated from skinfold anthropometry using the equations of Brook (Brook 1971), or Durnin & Rahaman (Durnin and Rahaman 1967), and body mass (MA) using the following equation of Vartsky et al (Baur et al. 2001; Vartsky et al. 1979):

$$M_{\text{AH}} = 0.097MA + 0.0219M_{\text{A}}$$

The main advantage of this technique over others is that it directly measures the component of interest while avoiding assumptions. Other advantages include its high precision and accuracy. However, the radiation dose that the subject receives from the
measurement can vary between machines, with most adult units delivering a dose of up to 0.8 mSv. The Children’s Hospital at Westmead (CHW) is fortunate to have its own machine which was purpose built for use in children and delivers a much lower radiation dose than the adult machines (< 0.15 mSv) (Baur et al. 1991a). Nonetheless, the equipment is expensive and requires highly skilled operators to use it, and therefore NAA is of only limited availability.

2.4.2.6 Total body water

Water is by far the most abundant of the components of the body. Body water is almost exclusively associated with FFM, of which it is the largest single component (Boileau et al. 1984). Approximately 57 % of body water is intracellular and 43 % extracellular (Schoeller 1996). The total volume of water in the body can readily be measured by isotope dilution using tritium, deuterium, or $^{18}\text{O}$-labelled water. The typical procedure for this technique is that the subject ingests, or is administered intravenously, a specified quantity of the labelled isotope. After an equilibration period, samples of serum, saliva or urine are collected and analysed for amounts of the labelled isotope.

There are four assumptions in the measurement of total body water (TBW) by dilution (Schoeller 1996):

1. that the labelled isotope is distributed only in body water,

2. that the labelled isotope is equally distributed in all anatomical water compartments,

3. that the rate of equilibrium of the labelled isotope is rapid, and

4. that neither the labelled isotope nor body water is metabolised during the time of tracer equilibrium, nor lost in the urine.
The precision of the technique is dependent on the analytical method as well as the dose of the labelled isotope administered to the subject. Nonetheless, studies have shown that the accuracy and precision of the isotope dilution method for the measurement of TBW is very good (Schoeller 1996). However, due to the laborious procedures and specialised equipment required for this technique, direct measurement of TBW is limited to those units with the appropriate facilities.

By measuring TBW, a 2C model of body composition can also be estimated, i.e. FM and FFM. This model is based on the fact that fat is hydrophobic and thus free of water, which is therefore restricted to the fat-free component. However, the calculation of FFM from TBW depends on the assumption of constant hydration of FFM, i.e. 73.2 %, which as discussed previously may not hold true in all subjects.

2.4.2.6.1 Intracellular and extracellular water

TBW can be divided into intracellular and extracellular water. Although intracellular water (ICW) is quite difficult to measure directly, extracellular water (ECW) can be measured by dilution and ICW calculated as the difference from TBW. The volume of ECW can be measured in vivo using the dilution principle, a method similar to the measurement of TBW (Schoeller 1996). The assumptions underlying the measurement of TBW by dilution are the same assumptions underlying the measurement of ECW (please refer to the previous page). A number of tracers exist that can be used for the measurement of ECW including bromide, chloride, thiocyanate, thiosulphate, sulphate, inulin-sucrose, and mannitol (Schoeller 1996). Each of these behaves differently with respect to the four assumptions, however bromide and isotopic chloride dilution come closest to approximating ECW, with bromide being the most commonly used tracer due to the advent of improved analytical techniques (Schoeller 1996). The relative precision of measuring ECW by
dilution is not as well characterised as that of TBW (Schoeller 1996). As with TBW, the precision of bromide dilution depends on the dose of the tracer and the analytical methods, however it has been reported that a relative precision of 1 % should be attainable if the doses are carefully chosen for the particular analytical method (Schoeller 1996). The precision for the determination of ICW, when calculated by the difference between TBW and ECW, is worse because errors in both variables propagate through the calculation (Schoeller 1996). The accuracy of the determination of ECW and ICW is unknown because direct chemical methods are not available to determine criterion values for these components of the body, but is thought to be probably accurate to 1 % in healthy subjects and around 2 – 5 % in subjects with an atypical ECW space (Schoeller 1996).

2.4.2.7 Total body potassium

The measurement of total body potassium (TBK) can be used to derive a 2C model of body composition, i.e. FFM and FM. The measurement of TBK is based on two facts, firstly, that 90 % of the body’s potassium is located intracellularly and is not present in body fat and secondly, that potassium-40 ($^{40}$K), which emits a characteristic gamma ray at 1.46 MeV, exists in the body at a known natural abundance (0.012 % of total potassium) (Lukaski 1987). These facts have allowed investigators to estimate FFM in humans by external counting of $^{40}$K (Lukaski 1987). The measurement technique involves placing the subject in a specially constructed shielded room (to reduce background radiation sources) with counters that consist of a gamma ray detection system connected to a suitable recording device (Lukaski 1987). The precision and accuracy of TBK measurements has been reported to be within ± 3 % in healthy adults (Lukaski 1987). Once an accurate measurement of TBK is obtained, the data can be translated into an estimate of body composition by assuming that potassium is
Chapter 2

LITERATURE REVIEW

contained only in FFM, at a known and constant concentration (Lukaski 1996). The potassium content of FFM has been reported to be quite consistent, with chemical analyses of human cadavers yielding values of 2.66 and 2.50 g potassium / kg FFM in men and women, respectively (Lukaski 1987; Lukaski 1996). However, the assumption that potassium is at a constant concentration in FFM does not apply to children and adolescents due to their chemical immaturity (Fomon et al. 1982; Lohman 1986), and hence the measurement of TBK in children is less precise than in adults. Finally, the cost of the equipment and the need for specially trained technicians prevents the wider use of this technique.

2.4.2.8 Electrical conductance

In recent times, the use of techniques based on the electrical conductivity of the body’s tissues for the determination of body composition has rapidly grown (Baumgartner 1996). Two of these techniques, bioelectrical impedance analysis (BIA) and total body electrical conductivity (TOBEC) are described below.

2.4.2.8.1 Bioelectrical impedance analysis

BIA is another method that can be used to measure a 2C model of body composition. BIA provides an estimate of TBW, which is then transformed into FFM and subsequently FM (Pietrobelli and Tato 2005). Like skinfold anthropometry, this technique is quick, non-invasive, portable and relatively inexpensive. This technique is based on the principle that in living organisms electrical conductance is related to the water and electrolyte distribution in the biological conductor. Because FFM contains virtually all of the water and conducting electrolytes in the body, conductivity is far greater in the FFM than in the FM of the body. BIA gives a measure of the body’s resistance and reactance to an applied current. The current
(usually 50 kHz) is applied to the body through one pair of electrodes placed distally on the dorsal surfaces of the hand and foot on one side of the body, while a second pair located proximally on the same hand and foot measures the electrical potential providing a measure of resistance and reactance. These values are then placed into one of several available multiple regression equations that convert measurements of bioelectrical impedance to FFM and FM. In fact the main limitation to this technique is the choice or availability of appropriately calibrated, cross-validated predictive equations. It is essential to make a careful selection of equations that were developed from a sample that is similar in age, sex, ethnicity, and health status to the subjects being studied (Baumgartner 1996). There are no validated equations for use in children with CP. A second limitation is that, as with other indirect measurements of body composition discussed in this section, the estimation of FFM from BIA relies on the assumption that the hydration of FFM is known. While the precision of measurements of impedance, resistance, and reactance by BIA is reported to be very good (< 0.5 %), the accuracy is dependent upon the appropriateness of the equation selected for the study population and is therefore variable (Baumgartner 1996). Furthermore, several studies have examined the accuracy of estimated changes in body composition from BIA and found that BIA was best suited for quantifying group changes and could only detect relatively large changes in individuals (Baumgartner 1996).

2.4.2.8.2 Total body electrical conductivity

As with the BIA method, this technique relies upon the differences in electrical conductivity properties of FFM and FM to estimate body composition (Lukaski 1987). The TOBEC instrument consists of a long, uniform, solenoidal coil driven by a 5 MHz oscillating radiofrequency current. The oscillating field will induce an
electrical current in any conductive material placed within the coil (Lukaski 1987). When a body is placed within the coil an electric current is induced in the conductive portion of the FFM, that is, energy is absorbed and more current is put into the coil to maintain the electromagnetic field. The energy absorbed is proportional to the current and the length and conductivity of the conductor, and hence the volume of FFM (Baumgartner 1996). The actual measurement consists of the difference between the coil impedance when empty and that when the subject is inside, which is proportional to the FFM of the subject (Baumgartner 1996). TOBEC measurements are highly precise (< 2 %); however multiple factors affect the accuracy of TOBEC predictions of body compositions (Baumgartner 1996). One of the greatest sources of error is the method of calibration of predictive equations used to convert the TOBEC measurement into body composition. Most TOBEC equations for predicting percent body fat or FFM have been calibrated against estimates of body density by underwater weighing. The technical error of measurement of body density by underwater weighing can result in an error of about ± 2.5 % body fat or about ± 1 kg FFM in healthy young adults, and is likely to be greater in children, the elderly and sick patients (Baumgartner 1996). Therefore, for these groups it is best to use predictive equations that have been calibrated against estimates from multi-compartment models (Baumgartner 1996). Currently, few such equations are available for either BIA or TOBEC. In conclusion, TOBEC is precise, safe, easy to perform, quick, and well-tolerated by most subjects, however its use is limited due to its lack of appropriate predictive equations in certain groups, including children, as well as its high cost and cumbersome equipment.
2.4.2.9 Imaging techniques

Computed tomography (CT) is a modern radiographic method that can be used to determine regional body composition. This approach relates small differences in x-ray attenuation to differences in the physical density of tissues to construct a two-dimensional image of the underlying anatomy in the scanned area, which allows separate recognition of bone, fat tissue, and lean tissue (Despres et al. 1996; Lukaski 1987). Using sophisticated software programs, the cross-sectional area of fat, bone, muscle or organ can then be determined for each image. However, because of the exposure to relatively high levels of ionizing radiation (dose equivalent of 1.5 to 3.0 mSv), routine whole-body scans, particularly in children, are not recommended (Lukaski 1987). Furthermore, the high cost of the scanners prohibits its use for this purpose.

Magnetic resonance imaging (MRI) is a relatively new method with great potential for safe, radiation-free, non-invasive, direct assessment of human body composition. This approach is based on the fact that atomic nuclei can behave like magnets (Despres et al. 1996). When an external magnetic field is applied across a part of the body, each nucleus attempts to align with the external magnetic field. Having aligned the protons in a known direction, a pulsed radio frequency (RF) field is applied to the body tissues causing many protons to flip, or absorb energy (Despres et al. 1996). When the RF field is turned off, the protons gradually return to their original positions, and they release the energy they absorbed in the form of an RF signal. This signal is used to generate the MRI images by computer. Like CT, the MRI produces a cross-sectional image that allows distinction between bone, muscle and fat. This technique is in its early stages of development and validation to assess body composition. Several studies have shown wide variability of precision in measuring fat tissue, particularly
in the abdominal region (Despres et al. 1996). There is little evidence regarding the precision of MRI measures of lean tissue. However, because multiple images can be obtained without any known health risks to the subject, MRI, unlike CT, is suitable for assessment of whole body composition analysis. Yet its high cost, limited availability and lack of validation studies limits its use for this purpose at this stage.

In summary, the technique of choice depends on many factors:

- The test population - if it is to be used with children, the technique needs to be suitable for children, for example minimal or no exposure to radiation, minimal co-operation required from the child, and preferably non-invasive and painless. In addition, the technique must have been validated on children or have reference data available for children.

- The compartment of interest - the technique of choice will depend upon which compartment or compartment model is to be tested.

- The precision and accuracy - precision and accuracy vary with the different techniques. The level of precision and accuracy required will depend upon what the aim of the study is. For longitudinal studies, where change is being measured, precise techniques are required. If the technique is being used for a validation study, both precision and accuracy are important.

- The cost - the cost of many of the sophisticated techniques inhibits their use.

- The availability and practicability - some of the sophisticated techniques, such as those used to measure TBW and TBN, may not be widely available, and/or are limited to a laboratory setting, and are therefore not practical for use in a clinic or community setting.
• Assumptions - nearly all techniques include some assumptions. These assumptions need to be considered and whether they hold true in the test population.

All of these factors need to be taken into account when choosing a method, or methods, to measure body composition, particularly in children. Many of the simpler methods, such as skinfold anthropometry and BIA, are cheaper, portable, safe, and require minimal co-operation from the subject, but include many assumptions, and therefore may lack in precision and/or accuracy. Whereas the more sophisticated methods, such as DXA, dilution techniques to measure TBW, imaging techniques, and NAA, may be more precise and accurate, but are expensive, not widely available or portable, require highly trained personnel, and may involve exposure to radiation. The investigator must therefore weigh up the advantages and disadvantages of each method.

2.4.3 Methods suitable for measuring body composition in children with cerebral palsy

Measuring the body composition of children with CP can be difficult due to their limited ability to co-operate because of involuntary muscle spasms and musculoskeletal deformities. Furthermore, none of the techniques available have been properly validated in children with CP, and hence rely on the assumption that the proportions of the components of FFM do not differ significantly to that of healthy children. These factors were taken into consideration when choosing appropriate methods for the studies in this thesis. Other factors that were taken into account included the suitability of the technique for children, availability of reference data,
<table>
<thead>
<tr>
<th>Technique</th>
<th>Compartment Measured</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air displacement plethysmography</td>
<td>Body density FM &amp; FFM</td>
<td>Quick, comfortable, non-invasive</td>
<td>Contains several assumptions in the conversion of body density to body composition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Precise</td>
<td>Questionable accuracy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suitable for children</td>
<td>Expensive, limited availability, requires skilled operators</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not validated in children with CP</td>
</tr>
<tr>
<td>Bio-electrical impedance analysis &amp; Total body electrical conductivity</td>
<td>TBW FM &amp; FFM</td>
<td>Quick &amp; non-invasive</td>
<td>Indirect measure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BIA is portable &amp; inexpensive</td>
<td>Accuracy dependent on choice of equation to convert measures to body composition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Precise</td>
<td>TOBEC is expensive &amp; non-portable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimal subject co-operation required</td>
<td>Not validated in children with CP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suitable for children</td>
<td></td>
</tr>
<tr>
<td>Computed tomography</td>
<td>Bone FM &amp; LTM</td>
<td>Non-invasive</td>
<td>Involves high level of radiation, therefore not suitable for children</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Direct assessment</td>
<td>Expensive, non-portable, requires skilled operators</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Limited availability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Measures cross-sectional, not whole body, body composition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Requires further validation studies to determine accuracy &amp; precision</td>
</tr>
<tr>
<td>Densitometry</td>
<td>Body density FM &amp; FFM</td>
<td>Gold standard technique for measuring body density</td>
<td>Requires high level of subject co-operation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Accurate &amp; precise in healthy adults</td>
<td>Contains several assumptions in the conversion of body density to body composition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not suitable for children</td>
</tr>
<tr>
<td>Dual-energy x-ray absorptiometry</td>
<td>BMC &amp; BMD PBF &amp; LTM</td>
<td>Gold standard technique for measuring BMC &amp; BMD</td>
<td>Requires a certain level of subject co-operation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quick, low radiation dose</td>
<td>Expensive, limited availability, requires skilled operators</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Precise</td>
<td>Contains assumptions in the measurement of PBF &amp; LTM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suitable for children</td>
<td>Not validated to measure PBF &amp; LTM in children with CP</td>
</tr>
</tbody>
</table>

*Table continued on next page*
<table>
<thead>
<tr>
<th>Technique</th>
<th>Compartment Measured</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Isotope dilution     | TBW                  | • Gold standard technique for measuring TBW  
• Good accuracy & precision  
• Suitable for children who have good oral skills  
• Minimal subject co-operation required | • Expensive & time consuming  
• Requires specialised laboratory equipment & skilled technicians  
• Limited to a laboratory setting  
• Conversion of TBW to FFM assumes normal hydration  
• Not validated to measure FM & FFM in children with CP |
|                      | FM & FFM             |                                                                                                                                            |                                                                                                                                                                                                             |
| Magnetic resonance   | Bone                 | • Safe, radiation-free  
• Non-invasive  
• Direct assessment | • Expensive, non-portable equipment & limited availability  
• Requires highly trained operators  
• Measures cross-sectional, not whole, body composition  
• Requires further validation studies to determine accuracy & precision |
| imaging              | FM & LTM             |                                                                                                                                            |                                                                                                                                                                                                             |
| Neutron activation   | TBP                  | • Directly measures TBP  
• High precision & accuracy  
• Machines with low radiation dose are suitable for children  
• Minimal subject co-operation required | • Variable radiation dose with different machines  
• Expensive, non-portable, limited availability  
• Requires skilled operators |
| analysis             |                      |                                                                                                                                            |                                                                                                                                                                                                             |
| Skinfold anthropometry| Skinfolds thicknesses| • Simple to use, inexpensive, non-invasive, portable  
• Suitable for children  
• Minimal subject co-operation required | • Variable precision & questionable accuracy  
• Contains several assumptions in the measurement of skinfolds & in the conversion of body density to body composition  
• Not validated in children with CP |
|                      | Body density         |                                                                                                                                            |                                                                                                                                                                                                             |
|                      | FM & FFM             |                                                                                                                                            |                                                                                                                                                                                                             |
| Total body potassium | FM & FFM             | • Good precision & accuracy | • Requires expensive equipment & highly trained operators  
• Limited availability  
• Assumes potassium is in constant concentration in FFM – invalid assumption in children due to chemical immaturity  
• Not validated in children with CP |

BIA, bioelectrical impedance analysis; BMC, bone mineral content; BMD, bone mineral density; CP, cerebral palsy; FFM, fat-free mass; FM, fat mass; LTM, lean tissue mass; PBF, percent body fat; TBW, total body water; TOBEC, total body electrical conductivity
exposure to radiation, invasiveness, accessibility of the equipment and trained operators, precision and accuracy, and the compartment of interest. The methods used in the studies described in this thesis included anthropometry to measure FM and FFM, NAA to measure TBP, and DXA to measure BMC, thereby providing a three-compartment (3C) model of body composition, with TBW being the only component missing. Each of the methods is discussed in more detail in Chapter 3.

2.4.4 Studies of body composition in children with cerebral palsy
There have been limited studies of body composition in children with CP. Most of these studies have focused on measures of growth (height and weight) and fat stores, with very little or no investigation of the other compartments of the body, e.g. water, bone, and protein. However the studies that have been done in children with CP suggest that their body composition is significantly different from that of physically active children (see Table 2.4, pg 66). This presents a problem when using many of the simpler techniques, such as skinfold anthropometry, to assess body composition. Most techniques are derived, or validated, from studies of healthy physically active children and/or are based on the assumption that the different compartments of the body are in the same proportion to that of the population from which the technique was validated, e.g. that the hydration of FFM is 73.2 %, and/or that the ratio of protein to bone is fixed. If these assumptions do not hold true in the test population, e.g. children with CP, then the method may not provide an accurate assessment of body composition.

Body composition is particularly important to measure in children with CP, not only because of the above-mentioned problems but also, because of the difficulties in assessing and interpreting growth parameters (weight and height) in this population. Studies have shown that many children with CP are stunted and wasted, yet there has
been little investigation into which compartments of the body are altered (Ruby and Matheny 1962; Samson-Fang and Stevenson 2000; Stallings et al. 1993a; Stallings et al. 1995; Sterling 1960; Tobis 1961). There have been limited studies on body water and bone mineral in children with CP, which are described below, but none measuring body protein.

2.4.4.1 Body water in children with cerebral palsy

Berg & Isaksson conducted the first study of body water in children with CP using tritiated water in 23 children with mild CP (Berg and Isaksson 1970). The authors used the measurement of TBW to estimate FM and FFM, using an assumed hydration factor of FFM of 78%. In agreement with earlier studies, the growth data showed that the children were shorter and lighter for age; however, they had a normal or increased weight-for-height. In addition, the children had a lower FFM than predicted for height; a mean of 86% of predicted. The authors stated that in normal subjects muscle mass comprises 70% of FFM, therefore the reduced FFM found in these subjects was hypothesised to be due to a reduced muscle mass from low physical activity and malnutrition. Interestingly, the mean measured TBW was higher than predicted (115.9%) from reference data based on measurements of healthy children. Furthermore, when expressed per kilogram of FFM, the measured TBW was also higher than predicted (1.85 kg versus 1.34 kg respectively). The authors reported that the increased TBW appeared to be due to an increase in the extracellular water which was estimated from total exchangeable potassium measurements. Body fat was increased in only seven of the participants, reduced in five, with no difference in 11, compared with predicted values. Therefore, the authors concluded that the apparent overweight seen in this population was due to the increased extracellular water, not body fat. Low serum albumin levels have been associated with malnutrition and increased
extracellular water; however, serum albumin levels were not measured in this study. Although the authors did report that the amount of protein consumed was lower than recommended in four of the 19 participants in whom dietary intake was observed.

The next detailed study of body composition was not conducted until around 20 years later (Bandini et al. 1991). The authors used deuterium oxide (D₂O) to measure TBW, and to derive FFM, and FM in 13 adolescents with mild to severe CP, as well as a control group. Again in agreement with previous studies, all of the participants with CP had a low height, and most had a low weight, for age. In the children with CP, the ratio of ECW (measured by bromide) to TBW (49.5 %) was slightly higher than reported in the literature, indicating an increase in ECW (Shizgal 1987). In contrast to the findings of Berg & Isaksson, TBW as a percentage of body weight was not increased, although the values were not reported. Total FFM in the children with CP was significantly lower than in the control group, but the children with CP were shorter and lighter than the control group, and no adjustments were made for body size. In contrast, in most of the children with CP body fat exceeded the 90th centile for age, and on average was higher than the control group, suggesting that this group of children were not representative of the general CP population. In this study, the authors used an assumed hydration constant of FFM of 73.2 %, an assumption which has not been proven to hold true in children with CP. It has been suggested that the hydration of FFM may in fact be higher in children with CP, as increases in body water have been found in association with malnutrition (Shizgal 1987). The reduced height and weight found in this group is suggestive of chronic malnutrition. An increased hydration of FFM would diminish calculated FFM resulting in an increased body fat. Therefore, the high percentage of body fat, and reduced FFM, found in the CP group could be due to an error from using an assumed hydration constant of FFM.
In a similar study, Azcue et al. measured TBW using D\textsubscript{2}O in 13 children with spastic quadriplegic CP and four control children (Azcue et al. 1996). Body FM and FFM were determined by both skinfold anthropometry and by TBW measurements using 73.2 % as the assumed hydration factor of FFM. The authors did not report the values obtained for FM and FFM by TBW, but stated that they were similar to those obtained by skinfold anthropometry, which were lower than the control group. Furthermore, the results for TBW were not expressed as a percentage of body weight, or compared with control children, so the results are difficult to compare with previous studies. However, they did report that the ICW space as a percentage of body weight was significantly decreased in the children with CP (27 %) compared with control children (47 %). It was not elucidated whether this was due to a decrease in TBW or an increase in ECW as was found in the two previous studies. In the study by Azcue et al. ICW was calculated by subtracting the measured ECW from the measured TBW.

Van den Berg-Emons et al. hypothesized that the available skinfold equations derived for healthy children to predict FM might overestimate FM in children with CP as the density of FFM may be lower in children with CP (van den Berg-Emons et al. 1998). They used anthropometry and D\textsubscript{2}O dilution to compare measures of FM and FFM in 22 children with moderate to severe CP and 10 control children. They chose two equations that are commonly used to derive FM from skinfold thicknesses; that of Durnin & Rahaman, which uses the triceps, biceps, suprailiac and subscapular skinfold thicknesses, and that of Slaughter which uses the triceps and subscapular skinfold thicknesses only (Durnin and Rahaman 1967; Slaughter et al. 1988). In the children with CP, the average percentage body fat (PBF) determined by TBW was 28.6 %, by Durnin & Rahaman was 22.5 %, and by Slaughter was 20.2 %, which was significantly higher than in the control group, 15.9 %, 17.4 %, and 13.7 %.
respectively. Therefore, in contrast to what was hypothesised, and in contrast to the
findings of Bandini, in the children with CP, PBF predicted from skinfold
anthropometry was considerably lower than that determined by the TBW method.
Stallings et al found the same result using similar methodology in their study of
children with spastic quadriplegic CP (Stallings et al. 1995). The authors hypothesised
that this may be explained by a proportionally large internal fat deposit, possibly due
to higher levels of body fat, which would not be measured using skinfold
anthropometry. Furthermore, in the study by van den Berg-Emons, TBW as a
percentage of body weight was significantly lower in the children with CP than in the
controls (54 % versus 64 % respectively), which contrasts with the studies by Berg &
Isaksson and Bandini et al. The authors suggest that this discrepancy of a lower
amount of water per kg of body weight might be explained by the increased body fat
in the children with CP compared with the control group. As with the previous TBW
studies, the authors also used assumed hydration factors for the estimation of FFM,
but in contrast to the other studies the authors used hydration factors specifically for
children, which are higher than 73.2 % used for adults; 76 % and 77 % for healthy
boys and girls respectively, and 75 % and 77 % for boys and girls with CP,
respectively.

In summary, these studies concentrated on estimating FM more accurately in children
with CP, rather than studying FFM or body protein. In addition, their method of
estimating FM and FFM from TBW is of questionable validity due to the use of
various assumed hydration factors, and therefore it is not possible to draw any
conclusions from these studies. One way to determine the hydration of FFM is to
measure both TBW and TBP. However, the direct measurement of body protein has
never been performed in children with CP.
<table>
<thead>
<tr>
<th>Author/s</th>
<th>Participants</th>
<th>Methods</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Leamy 1953)</td>
<td>N = 21; 4 – 20y All types of CP</td>
<td>Bone age</td>
<td>The average skeletal age of the group was 107 months compared with 119 months of chronological age</td>
</tr>
<tr>
<td>(Sterling 1960)</td>
<td>N = 100; 6mo – 19y All types of CP</td>
<td>Height &amp; weight</td>
<td>Average shorter &amp; lighter than similar aged children without CP</td>
</tr>
<tr>
<td>(Tobis 1961)</td>
<td>N = 86; 5 – 18y All types of CP</td>
<td>Height &amp; weight</td>
<td>Average significantly shorter and lighter compared with American school children</td>
</tr>
<tr>
<td>(Ruby and Matheny 1962)</td>
<td>N = 137; 2 – 18y Moderate-severe CP</td>
<td>Height &amp; weight</td>
<td>For height &amp; weight, males were approximately 12-15 months below, and females 18 months below 16th percentile with athetotic children smaller than spastic children</td>
</tr>
<tr>
<td>(Hammond et al. 1966)</td>
<td>N = 31; 7 – 16y All types of CP</td>
<td>Height &amp; weight Bone age</td>
<td>Average shorter &amp; lighter than similar aged children without CP</td>
</tr>
<tr>
<td>(McIvor and Samilson 1966)</td>
<td>N = 1232; 0 -&gt;40y All types of CP</td>
<td>Observation</td>
<td>Children with CP have an increased fracture rate</td>
</tr>
<tr>
<td>(Pryor and Thelander 1967)</td>
<td>N = 179; 1 – 15y All types of CP</td>
<td>Height</td>
<td>Height was within the normal range until 10y, then declined perhaps reflecting failure of the adolescent growth spurt</td>
</tr>
<tr>
<td>(Berg and Isaksson 1970)</td>
<td>N = 23; 7 – 20y All types of CP</td>
<td>Height &amp; weight TBK, TBW</td>
<td>Average shorter &amp; lighter for age, but normal or increased weight-for-height</td>
</tr>
<tr>
<td>(Bandini et al. 1991)</td>
<td>N = 13; 15 – 20y All types of CP</td>
<td>Height &amp; weight TBW</td>
<td>Average low weight and height for age</td>
</tr>
<tr>
<td>(Stallings et al. 1993b)</td>
<td>N = 154; 2 – 18y Diplegic- &amp; hemiplegic CP</td>
<td>Weight UAL, LLL, SA</td>
<td>On average reduced weight, LLL, UAL &amp; triceps skinfold, normal subscapular skinfold, increased UAMA</td>
</tr>
<tr>
<td>(Stallings et al. 1993a)</td>
<td>N = 142; 2 – 18y Quadriplegic CP</td>
<td>Weight UAL, LLL SA</td>
<td>Greater reduction in LLL than UAL, average weight &amp; triceps skinfold reduced to 60%, subscapular 80%, and UAMA 90% of normal</td>
</tr>
<tr>
<td>(Stevenson et al. 1994)</td>
<td>N = 171; 10mo – 16y Mostly severe CP</td>
<td>Weight UAL, LLL, SA Height/length</td>
<td>Greater reduction in LLL than UAL, average weight &amp; triceps skinfold reduced to 60%, subscapular 80%, and UAMA 90% of normal</td>
</tr>
</tbody>
</table>

Both disease & nutrition contribute to linear growth

On average, significantly reduced height & weight, & triceps skinfold

Height declined with advancing age

Conclusion – both nutrition & disease contribute to linear growth
<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Methods</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Lingam and Joester 1994)</td>
<td>N = 5; 10 – 19y All types of CP</td>
<td>Observation</td>
<td>Children with CP have a tendency to sustain spontaneous fractures due to poor muscle support of the long bones</td>
</tr>
<tr>
<td>(Henderson et al. 1995)</td>
<td>N = 139; 3 – 15y Moderate-severe CP</td>
<td>SA, DXA</td>
<td>BMD severely diminished in distal femur, and to a lesser extent in lumbar spine Fractures had occurred in ¼ of children &gt;10y</td>
</tr>
<tr>
<td>(Stallings et al. 1995)</td>
<td>N = 136; 2 – 12y Quadriplegic CP</td>
<td>Height &amp; weight SA, TBW</td>
<td>Significantly reduced height &amp; weight, average triceps skinfold 61% and subscapular skinfold 88% of normal; reduced rate of accretion of FFM, lower PBF by SA than by TBW</td>
</tr>
<tr>
<td>(Stevenson et al. 1995)</td>
<td>N = 20; 3 – 18y Spastic hemiplegia</td>
<td>Height &amp; weight SA, bone age</td>
<td>All measures of breadth, circumference &amp; length were significantly smaller, except for skinfold thicknesses, on the affected side of the body concluding that CP impacts on growth independently of nutrition</td>
</tr>
<tr>
<td>(Stevenson 1995b)</td>
<td>N = 172; &lt; 12y All types of CP</td>
<td>Height UAL, LLL, KH</td>
<td>Developed set of equations to convert UAL, LLL &amp; KH to standing height</td>
</tr>
<tr>
<td>(Krick et al. 1996)</td>
<td>N = 360; 1mo – 10y Quadriplegic CP</td>
<td>Weight &amp; length</td>
<td>Sought to develop growth charts for children with CP Due to flawed methodology these charts are not recommended for use</td>
</tr>
<tr>
<td>(Azcue et al. 1996)</td>
<td>N = 13; 2 – 16y Quadriplegic CP</td>
<td>Height &amp; weight SA, TBW</td>
<td>Reduced height &amp; weight compared with control group, but normal weight-for-height Reduced FM, FFM &amp; ICW</td>
</tr>
<tr>
<td>(Henderson 1997)</td>
<td>N = 43; 2 – 5y Quadriplegic CP</td>
<td>Weight SA, TBW</td>
<td>BMD fell further below normal with increasing age Vitamin D levels &amp; weight were not predictive of fracture</td>
</tr>
<tr>
<td>(van den Berg-Emons et al. 1998)</td>
<td>N = 22; 7 – 13y Moderate-severe CP</td>
<td>Height &amp; Weight SA, TBW</td>
<td>Higher PBF than control group TBW produced higher PBF than SA</td>
</tr>
<tr>
<td>(Samson-Fang and Stevenson 1998)</td>
<td>N = 81; 1 – 12y All types of CP</td>
<td>Growth velocity</td>
<td>Lower growth velocity was seen in children &lt;2y, males, non-ambulatory children, malnourished children &amp; those with cognitive impairment</td>
</tr>
<tr>
<td>(Samson-Fang and Stevenson 2000)</td>
<td>N = 276; 3 – 12y All types of CP</td>
<td>Height &amp; weight SA</td>
<td>Weight-for-height was not a good indicator of malnutrition in children with CP Best indicator of suboptimal fat stores was triceps skinfold thickness</td>
</tr>
<tr>
<td>(Henderson et al. 2005)</td>
<td>N = 69; 2 – 18y Moderate-severe CP</td>
<td>DXA</td>
<td>First longitudinal study of BMD; overall BMD increased, but at a slower rate than normal children Children with a higher triceps skinfold experienced greater increases in BMD</td>
</tr>
</tbody>
</table>

BMD, bone mineral density; CP, cerebral palsy; DXA, dual-energy x-ray absorptiometry; ECW, extracellular water; FFM, fat-free mass; FM, fat mass; ICW, intracellular water; KH, knee height; LLL, lower leg length; PBF, percent body fat; pQCT, peripheral quantitative computed tomography; SA, skinfold anthropometry; TBW, total body water; UAL, upper arm length; UAMA, upper arm muscle area
2.4.4.2 Bone mineralisation in children with cerebral palsy

Although delayed bone age in children with CP has been recognised since the early 1950s, the first hint that bone mineralisation was decreased came with the report by McIvor et al in 1966 who found an increased fracture rate in children with CP (Hammond et al. 1966; Leamy 1953; McIvor and Samilson 1966). They reported that of the 134 fractures (in 92 children) over a 10-year period, the majority of the children had spastic quadriplegic CP, and in 70 of the fractures, the mechanism of injury was unknown. Almost 30 years later, Lingam & Joester reported that children and adolescents with CP have a tendency to sustain spontaneous fractures (Lingam and Joester 1994). They hypothesised that spontaneous fractures are due to poor muscle support to the long bones. Henderson found that most fractures in children with CP involved the femur, and agreed with Lingam & Joester that most resulted from minimal trauma or without any specific traumatic event recognised (Henderson 1997). They also found that the occurrence of fractures correlated with history of long periods of immobilisation after surgery.

A small study (n = 13) of children with severe CP showed that one reason this population has an increased fracture rate is because they have smaller and thinner bones thereby compromising bone strength (Binkley et al. 2005). Further reasons for increased fracture rates and poor bone mineralisation in children with CP are discussed in the following section.

2.4.4.3 Causes of poor bone mineralisation

Hypotheses for the poor bone mineralisation found in children with CP can again be divided in to nutritional and non-nutritional factors. Non-nutritional contributing factors are lack of weight bearing activity; periods of immobilisation after multiple
operative procedures; anticonvulsant medication interfering with vitamin D metabolism; lack of exposure to sunlight; and metabolic bone disease associated with prematurity. Nutritional factors include oral motor dysfunction resulting in poor nutrition and low calcium intake (Henderson et al. 1995).

2.4.4.3.1 Studies investigating causes of poor bone mineralisation

Roberts et al and Lin & Henderson attempted to investigate whether the poor bone mineralisation found in children with CP was related to the underlying brain injury or to concomitant malnutrition (Lin and Henderson 1996; Roberts et al. 1994). The authors chose to study children with spastic hemiplegic CP in order to use their unaffected side as the control. All of the children chosen for the study had normal growth, that is, height and weight for age between the 5th and 95th, and “normal” triceps skinfold thickness. These criteria were chosen in order to better characterise the influence of non-nutritional factors on skeletal maturation. The results showed that the skeletal age, BMC, BMD, bone size, and LTM of the affected side was less than that of the unaffected side in all patients, however there was no difference in fat content. The authors found a significant correlation between the skeletal age and the severity of disability which supports an association between functional use of the extremity and bone maturation. However, the authors commented that relative disuse and lack of purposeful activity may have contributed to the diminished muscle mass and BMC in the affected limb. These findings support the hypothesis that at least some of the poor bone mineralisation seen in children with CP is unrelated to malnutrition.

Henderson et al also sought to analyse the effects of a variety of factors on lumbar and femoral BMD in a large group of children with various severities of spastic CP (Henderson et al. 1995). The authors found that current functional level of walking
and nutritional status correlated highly with both femoral and lumbar BMD measured by DXA. In addition, those children with low calcium intakes (< 500 mg/day) had a significantly lower BMD than those children with high calcium intakes (> 500 mg/day). Multiple regression analysis showed that the best predictor of BMD was ambulatory status followed by nutritional status; again supporting the hypothesis that bone mineralisation in children with CP is influenced by several factors.

A more recent study by Henderson et al found that BMD measured by DXA was severely diminished in the distal femur, and to a lesser extent in the lumbar spine in a large group (n = 117) of children with moderate to severe CP (Henderson et al. 2002a). Fractures had occurred in one-quarter of the children older than 10 years of age, and were more common in non-ambulatory children. There was a relation between advancing age and declining BMD SD scores in the distal femur, but not the lumbar spine. Osteopenia, defined as a BMD SD score of less than -2, was found in 97% of all study participants who were unable to stand and were older than 9 years. In addition, there was a negative correlation between severity of disability and BMD SD score of the distal femur. Height, weight and triceps skinfold thickness SD scores correlated with BMD SD scores of the distal femur, suggesting that an improved nutritional status could improve bone mineralisation. However, in contrast with their earlier study, calcium intake did not correlate with BMD SD scores (Henderson et al. 1995). Overall they found that the severity of CP, increasing difficulty in feeding, use of anti-epileptic medications and lower triceps skinfold thickness (in decreasing order of importance) all independently contributed to lower BMD SD scores in the distal femur.

All of the previous studies compared the bone mineralisation of children with CP with healthy age-matched controls, and therefore the presence of growth stunting may have
influenced the interpretation of the results. So it may be plausible that the children with CP had a lower bone mineralisation than healthy age-matched peers. Therefore, Chad et al compared the BMC and BMD, measured by DXA, of children with CP with healthy controls of similar development (measured by pubertal status) rather than chronological age (Chad et al. 2000). The mean BMC and BMD of children with CP was -0.5 SD score compared with developmental age-matched controls, in comparison to -1.8 SD score compared with chronological age-matched controls. King et al reported similar results when correcting lumbar BMD for bone age (King et al. 2003). However, this raises several questions. How should one interpret the bone mineralisation of stunted children with CP? Which interpretation is more correct? Is it acceptable for stunted children with CP to have a lower bone mineralisation than children of the same age, yet the same bone mineralisation of a younger child of the same developmental age or size, i.e. height? Are these children still at risk of fractures in later life? Only a longitudinal study measuring bone mineralisation could answer these questions.

There has been only one longitudinal study of bone mineralisation in children with CP (Henderson et al. 2005). The authors studied the BMD of 69 children with moderate to severe spastic CP (44 children with quadriplegic CP). There were a total of 164 follow-up evaluations. The time interval between the initial and second evaluations ranged from 1.5 to 49.7 months (median 21.5 months). Forty-six participants had a third evaluation, 25 a fourth, and 10 had five to nine evaluations. The authors reported that BMD increased by a median of 2 to 5 % per year, with a wide range of + 42 % per year to -31 % per year. Yet, despite the finding of an overall increase in BMD, BMD SD scores actually decreased which reflects that the BMD of the children with CP in the study did not increase at the same rate as normal children. The change in
BMD per year was found to be correlated with nutritional status: those children with a higher triceps skinfold SD score experienced the greatest change in BMD per year. The change in BMD per year was not statistically related to age, gender, pubertal stage, use of anti-epileptic medications, GMFCS level, difficulty in feeding, height, weight, or general health as assessed by the Child Health Questionnaire (Landgraf et al. 1996).

2.4.4.3.2 Bone mineralisation and intervention studies

It is well known that immobilisation predisposes to bone resorption and decrease in formation, which can reduce BMD leading to an increased risk of fractures (Shaw et al. 1994). However it is difficult to change the ambulation status of children with CP. Chad et al attempted to improve the bone density of non-ambulatory and ambulatory children with CP using an eight-month load-bearing physical activity intervention trial (Chad et al. 1999). Compared with a similarly disabled control group, statistically significant increases in femoral neck BMC (9.6 %), volumetric BMD (5.6 %), and total proximal femur BMC (11.5 %) were observed in the intervention group. Even though these results were statistically significant, it is questionable as to whether they were clinically significant. In addition, the authors did not comment if there was a difference in bone mineral gain between the ambulatory and non-ambulatory children.

Of the nutritional and non-nutritional factors contributing to poor bone mineralisation of children with CP, theoretically it should be easier to change nutrition rather than ambulatory status. The only study reporting a nutritional intervention is that of Jekovec-Vrhovsek et al (Jekovec-Vrhovsek et al. 2000). They conducted a longitudinal cohort study to determine the effect of vitamin D (0.25 ug/day) and calcium supplementation (500 mg/day) on lumbar BMD in a group of non-ambulatory children with CP. After the nine-month supplementation period, they found that
lumbar BMD greatly increased in the treated group (n = 13) (0.383 vs. 0.476 g/cm²),
while in the observed group (n = 7) lumbar BMD significantly decreased (0.393 vs.
0.315 g/cm²). There was no significant change in body weight over the study period in
either group. However, total dietary calcium intake was not assessed in either group,
and the level of supplementation of calcium was relatively low; therefore, it is
unknown whether the intervention group did in fact have a significantly higher
calcium intake than the control group. In addition, as Henderson et al reported, most
fractures in children with CP occur in the femur, and lumbar BMD correlates only
weakly with distal femur BMD, and thus studying lumbar BMD is less clinically
relevant in this population (Henderson et al. 2002a).

2.4.4.3.3 Treatment with bisphosphonates

Until recently there was limited medical treatment for children with CP with reduced
bone mineralisation. Bisphosphonate is an analogue of pyrophosphate and acts by
inhibiting osteoclastic mediated bone resorption (Shaw et al. 1994). However, it is not
licensed for use in children. Two recent studies have assessed the safety and efficacy
of bisphosphonates to treat osteopenia in children with spastic quadriplegic CP.
Henderson et al conducted an 18-month randomised, placebo-controlled, double-
blinded trial of 12 non-ambulatory children with spastic quadriplegic CP (Henderson
et al. 2002b). To ensure adequate calcium intakes each child was given 1000 mg/day
of calcium, as well as a multivitamin supplement containing vitamin D. They
measured BMD by DXA in the distal femur and lumbar spine at three-monthly
intervals. BMD increased by 89 % over 18 months in the study group compared with
9 % in the placebo group, and by 33 vs. 15 % in the lumbar spine. BMD age SD
scores increased from -4.0 to -1.8 in the distal femur in the study group, but did not
change in the placebo group.
Shaw et al found similar results after treating three non-ambulatory children with severe CP with bisphosphonates over 12 to 18 months (Shaw et al. 1994). The three children treated had a 20 to 40% increase in lumbar BMD SDS for age, femur BMD was not measured. There was no significant change in lumbar BMD SD scores for two untreated children over the same period.

However, some reservations remain about the use of bisphosphonates in growing and maturing bones. At present their use in children remains experimental, and therefore, although bisphosphonates show promising results in children with CP, the treatment is not readily available. Current research and treatment must therefore focus on altering the recognised causes of poor bone mineralisation in children with CP. The level of ambulation is difficult to change; however, nutritional variables can be altered. Yet no-one has studied the impact of nutritional rehabilitation on bone mineralisation.

### 2.5 Energy expenditure in children with cerebral palsy

Researchers from the 1950s and 1960s believed that the energy requirements of children with CP varied depending on the type of CP, with athetoid type CP having a seemingly higher energy expenditure requiring a larger number of calories to maintain an ideal weight, and spastic type CP having a lower energy and calorie requirement (Hammond et al. 1966; Leamy 1953; Phelps 1951; Ruby and Matheny 1962). Phelps was the first to describe the energy requirements of the different types of CP, observing that children with spastic CP “do not move around very much, they do not burn up the food; they store it, and tend to put on weight easily” (Phelps 1951). Therefore, it was recommended that their diet be limited in energy. In contrast, Phelps described children with athetoid type CP as “constantly moving, burning up energy and are usually too thin. It is almost impossible to keep them up to a normal weight on an average diet”, and recommended that the children with athetoid type CP have a
higher energy diet. Similarly, Karle et al noted that "spastics tend to avoid exercise and overweight may become a problem. Thus an intake of calories below the recommendations may be desirable" (Karle et al. 1961).

Similar observations were made in a small pilot study (n = 5) of children with varying degrees of spastic and athetoid type CP: "some athetotic children remain extremely thin and emaciated; other children whose palsy will permit practically no physical activity become obese and grossly overweight" (Eddy et al. 1965). The authors weighed duplicate samples of meals over a six-day study period to determine energy intake. In addition, they attempted to measure basal metabolism by collecting expiratory air in a Douglas bag while the subject was still in bed prior to breakfast, and total daily energy expenditure by measuring heat expenditure during various activities with a Wolff integrating motor pneumotachograph. Overall they found that total energy requirements and energy intakes were less than that of normal children the same age, but comparable to children of the same size. Despite this observation, some researchers and clinicians still believed for many years that the poor growth observed in children with CP was due to increased energy expenditure (Sterling 1960; Stevenson et al. 1994).

More recently Bandini et al studied the resting energy expenditure (REE) and total energy expenditure (TEE) of 13 adolescents with CP using a combination of indirect calorimetry and the doubly-labelled water method (Bandini et al. 1991). They found that the measured REE did not differ significantly from that predicted from the World Health Organisation (WHO) equations (World Health Organisation 1983); however, it was significantly lower when compared with the control group. The ratio TEE/REE is an expression of the amount of energy expended above resting and represents the energy spent on activity and the thermic effect of food. Overall the ratio of TEE/REE
was significantly lower in the non-ambulatory children with CP (n = 6) than the controls (1.23 versus 1.76 respectively), but not in the ambulatory children with CP (n = 3). The results suggested that energy requirements were lower in the non-ambulatory children with CP because their physical activity was limited. However, because of the study’s small sample, the effect of the type of disability and abnormal muscle movements on energy expenditure could not be elucidated.

Stallings et al studied the energy expenditure of 61 non-ambulatory children aged two to 18 years with spastic quadriplegic CP and in a normal control group (Stallings et al. 1996). REE was measured by indirect calorimetry in 61 children with CP and 37 controls, while TEE was measured by doubly-labelled water in a subset of 32 children with CP and in 32 controls. REE expressed as a percentage of that predicted from the WHO equations was significantly lower in the CP group compared to controls (91 % versus 105 %). Furthermore, the TEE of the children with CP was significantly lower than the control group when expressed as kJ/kg/day. The ratio of TEE to REE was similar to that reported by Bandini et al and was significantly lower in the CP group (1.23) than in the control group (1.57) (Bandini et al. 1991). In summary, the measured REE and TEE showed that energy expenditure was not excessive and was far less than that required for healthy children of similar size.

Azcue et al studied the REE by indirect calorimetry of exclusively gastrostomy tube-fed children with spastic quadriplegic CP (Azcue et al. 1996). The mean measured REE as a percent of predicted from the WHO equations, based on age and weight, in the children with spastic quadriplegic CP was 79 ± 21 % (range 50 to 112 %). Energy intakes were assessed by the volume of formula fed in a 24 hour period, and were on average 1.1 times the measured REE.
These studies indicate that the energy requirements of children with spastic quadriplegic CP are reduced. This conclusion was confirmed by a study of the energy intakes of a group of children and adolescents with spastic quadriplegic CP fed exclusively by gastrostomy tube (Fried and Pencharz 1991). These patients exhibited positive growth although their energy intakes were below recommendations for age. All of the children had weights above the 50th centile for age and sex, yet the average energy intake of the group was 61% of the RDI for age (range 43 to 98%). This study was interesting because it showed that even when adequate energy was provided to allow for growth, it was still significantly below that recommended, suggesting that the standard recommendations based on healthy active children are inappropriate for children with CP. This study also suggests that if children with CP have a sufficient energy intake, they can achieve adequate weight gain and growth.

The abovementioned studies demonstrated that the standard WHO equations overestimate the energy requirements of children with CP. Therefore, Krick et al sought to develop a standardised method for estimating energy needs in children with CP (Krick et al. 1992). The energy needs were determined by monitoring the energy intake required to achieve a desired weight gain while the child was in hospital, based on a clinically defined ideal body weight. The formula they developed also took into account muscle tone, activity level, and energy for growth or catch-up growth. Thus the final equation was energy requirements (kcal/day) = basal metabolic rate x tone factor x activity factor + growth factor. The authors used height age rather than chronological age in the calculation. They then attempted to validate the formula by retrospective review of recorded body weight and formula intake from the medical records for 30 tube-fed hospitalised patients. To estimate actual energy needs, they monitored weight gain from admission to discharge. The authors then calculated
energy needs using their own formula and compared it with the WHO recommendation for age. The results showed that mean predicted energy needs from WHO was 90.6 kcal/kg, by the Krick formula 79.4 kcal/kg, and actual estimates while in hospital was 77.9 kcal/kg. However, this equation has not been properly validated for use in children with CP, as there was no comparison with measured energy expenditure by indirect calorimetry or doubly-labelled water; thus, the Krick formula may not be appropriate for estimating the energy requirements in children with CP.

In summary, these studies showed that the recommended age-specific equations to estimate energy requirements based on neurologically intact active children, greatly overestimate the energy requirements of children with CP. However, despite the many years of research in this area, there are still no available equations to accurately estimate the energy requirements of children with CP. Thus the current recommendations are to either roughly estimate requirements using the currently available equations based on healthy children and adjust according to weight change, or to measure REE by indirect calorimetry. However, facilities for measuring REE are not available at all centres.

2.6 Nutritional therapies in children with cerebral palsy

The growth failure and undernutrition described in children with CP have often been accepted as inevitable and irremediable consequences of the disease (Sullivan et al. 2000). Malnourished patients have decreased muscle strength, including respiratory musculature, with resultant impaired cough and predisposition to pneumonia. Malnutrition results in increased circulation times and diminished cardiac work capacity, resulting in cold and mottled peripheries. Malnutrition-related disturbances in immune function predispose to infection, particularly of the lungs and urinary tract (Chandra 1983). Healing of pressure sores is delayed. Cerebral growth, cognitive
development, and motor progress are impaired. Undernourished children show lower levels of exploratory activity and attachment behaviour which may affect social-emotional development. Irritability and decreased activity have been described in undernourished children (Bax 1993; Samson-Fang et al. 2002; Samson-Fang and Stevenson 2000; Stallings et al. 1993a). In addition, undernourished children with CP have differences in body composition compared with normally developing peers. Alterations include increased TBW, severely depleted fat stores, depleted muscle mass, severe short stature and decreased bone density. The numerous untoward consequences of malnutrition are clinically significant, and it is now generally considered that malnutrition in children with CP is unacceptable and should be treated.

The first line of treatment for undernutrition and dysphagia in children with CP is usually oral nutrition supplementation combined with speech therapy. If that fails, or if the dysphagia is so severe that swallowing is not safe, the next step is enteral feeding via a naso-gastric (NG) or gastrostomy tube. The following section describes each of these treatments in more detail.

### 2.6.1 Oral nutritional supplementation

If there is no risk of food aspiration, the first strategy in treating undernutrition is to increase the energy density of ingested food. This can be achieved by offering more energy-dense foods, or by adding fats and glucose polymers to food, as well as including specialised high energy drinks. In addition, an increase in the viscosity of liquids has resulted in a higher intake in some children as aspiration tends to occur more commonly with thin liquids (Nutrition Committee of the Canadian Paediatric Society 1994). In some cases, aspiration occurs with fatigue, and thus can be minimized by small, frequent meals or supplemental forms of nutrition.
Studies of nutritional rehabilitation using oral supplements in children with CP are limited. Hals et al studied 13 severely neurologically impaired institutionalised children, most with CP, to test if a fortified diet improved their nutritional status (Hals et al. 1996). The initial dietary assessment showed that intakes of energy and fat were well below the RDI, while protein was markedly above the RDI for age. They changed the diet based on these findings: they added more fish, meat and whole meal, and supplemented with 5 g of fish oil, 40 g of soya bean oil and 7 g of carbohydrate, yielding a total of 450 kcal energy supplementation, as well as a multi-vitamin and iron supplement. Prior to the intervention weight gain was approximately 200-300 g/month; during the first month of the intervention weight gain increased to 600 g/month; during the second month 500 g; the next seven months weight gain returned to approximately 250-300 g/month. Triceps skinfold thickness also increased significantly over the same time period. However, the authors did not report whether the observed weight gain was greater than would be expected for a child without disability, i.e. it was not elucidated if the children experienced catch-up growth or improved their weight centiles.

2.6.2 Speech therapy
Oral supplementation is usually prescribed in conjunction with speech therapy or oral motor exercises to overcome dysphagia and to help develop chewing and swallowing skills. The aims of speech therapy are to optimise oral intake by proper body positioning, jaw control, oral tactile preparation and proper presentation of food, in order to promote normal oral patterns such as jaw stability, lip closure, tongue movements, and co-ordinated sucking, chewing and swallowing (Ottenbacher et al. 1983a). Children with CP eat more easily when they are well seated. Adaptive seating maintains an upright posture, and may improve head control, retention of food in the
mouth, and eating skills, and can decrease the risk of aspiration (Larnert and Ekberg 1995). Specialised feeding utensils can improve the acceptance of food into the child’s mouth. In addition to these techniques, specific oral-motor programs have been developed; however, there is scanty evidence that oral motor therapy can permanently improve oral motor function and induce weight gain in children with CP (Fischer-Brandies et al. 1987; Ottenbacher et al. 1983a).

The first research to evaluate the effectiveness of oral-motor treatment appeared in the mid 1970s. Since then relatively few studies in this area have been conducted, and these are highly variable, with different purposes, subject populations and independent and dependent variables (Ottenbacher et al. 1983a). Ottenbacher et al treated a group of severely and profoundly disabled children and young adults with oral motor exercises with the purpose of increasing their weight (Ottenbacher et al. 1981). Analysis of the data revealed no statistically significant differences in body weight gain or in development of specific feeding behaviours over the nine-week treatment period. The authors report that two participants appeared to gain a large amount of weight compared to other participants, but this was masked by pooling the data for group analysis. A similar study by the same group of researchers showed that one out of the four children studied evidenced an increase in weight and improved oral motor evaluation as a result of the intervention (Ottenbacher et al. 1983b).

Gisel et al treated several groups of children with moderate to severe CP with an oral sensorimotor programme for 10 to 20 weeks, with one study involving a randomised controlled trial (RCT) (Gisel et al. 1995; Gisel et al. 1996). There was no difference in length of mealtimes or eating duration of different textures; however a significant proportion of the children progressed to eating solids from mashed foods. There was no significant change in weight percentiles over the study period.
Haberfellner et al showed that functional feeding skills, as measured by spoon feeding, biting, chewing, cup drinking, and swallowing improved significantly after one year of intra-oral appliance therapy (Haberfellner et al. 2001). During the course of one year of treatment, children gained weight and height. This weight gain was sufficient for children to maintain their growth trajectory (i.e. there was no improvement in weight percentiles), but the weight gain could not be attributed to the therapy because it occurred during the control period and was the same in magnitude through the treatment phases. Gisel et al followed this group of children for a further year after cessation of the therapy (Gisel et al. 2001). No significant differences were found in functional feeding skills, and no significant differences in weight were found.

Therefore, despite the use of intensive speech therapy programmes for long periods of time, many children with severe CP do not achieve minimal standards of growth with oral feeding alone. These children continue to spill a significant proportion of their food, cannot chew or swallow solids, and many have difficulty drinking or using a straw. As discussed in section 2.2.2.4, children with CP can take two to 18 times longer than controls to chew and swallow a standard amount of pureed food and one to 15 times longer for solid food. As a result some caregivers spend up to seven hours per day feeding their children and, combined with having to conduct daily speech therapy exercises, feeding can be an extremely time consuming process with little apparent gain. Furthermore, as the swallow reflex is a primarily involuntary and reflex activity, it is unlikely there will be much improvement with increasing age in this population (Jones 1989). For these children, tube feeding may become necessary to prevent or to treat malnutrition and to improve the quality of life for their families.
2.6.3 Gastrostomy tube feeding

Because of the difficulty in eating and drinking, many children with CP can achieve an adequate nutritional status only with tube feeding. In a cross-sectional study of both oral-fed and tube-fed children with CP, the presence of a gastrostomy tube was associated with higher fat stores and muscle mass, as assessed by anthropometry (Samson-Fang et al. 2002). Furthermore, each SD decrease in UAFA was associated with a 28% increase in doctor visits, a 31% increase in days missed from school, and a 51% increase in missed activities for the family throughout the preceding four weeks, suggesting that children with a better nutritional status have an improved quality of life. Fung et al. also reported in their cohort study of children with CP, that when the tube-fed children were compared with those of similar disability but who were fed orally, greater height, triceps, and subscapular SD scores and less respiratory illness were observed (Fung et al. 2002). In two other similar cross-sectional studies comparing oral-fed and tube-fed children with severe CP, children with a gastrostomy tube had a greater fat mass than those without; but interestingly, there was no difference in measures of muscle mass (Kong and Wong 2005; Stallings et al. 1995).

However, apart from weight gain and an increase in fat stores, the effects of tube feeding for children with CP have not been clearly described. There is controversy about whether gastrostomy tube feeding may increase the risk of death or GOR (Heine et al. 1995; Lewis et al. 1994; Sleigh and Brocklehurst 2004; Smith et al. 1999; Strauss et al. 1998). Sleigh & Brocklehurst attempted to conduct a review of systematic reviews and/or RCTs to determine the benefits and risks for gastrostomy tube feeding compared with oral feeding for children with CP, however no relevant studies were found (Sleigh and Brocklehurst 2004). They instead reviewed two cohort studies 15 case series, and eight case reports (Fung et al. 2002; Strauss et al. 1998).
One study reported a higher death rate for children fed by a gastrostomy tube but this may have merely reflected the greater disability of these compared with orally fed children (Strauss et al. 1998). No firm conclusions were able to be drawn about whether GOR was increased or decreased with gastrostomy tube feeding. They concluded that the benefits associated with gastrostomy tube feeding are difficult to assess from the available evidence and that a well conducted RCT of sufficient size is needed.

2.6.3.1 Nutritional rehabilitation studies

There have been seven previous longitudinal nutritional rehabilitation studies of children with CP (Isaacs et al. 1994; Naureckas and Christoffel 1994; Patrick et al. 1986; Rempel et al. 1988; Sanders et al. 1990; Shapiro et al. 1986; Sullivan et al. 2005). However, only three of these studies were prospective (Isaacs et al. 1994; Patrick et al. 1986; Sullivan et al. 2005); three were retrospective reviews of the medical records (Naureckas and Christoffel 1994; Rempel et al. 1988; Shapiro et al. 1986); and one did not state how the data was collected (Sanders et al. 1990). Furthermore, all of the studies were based on measures of weight and/or height, with only three including some basic skinfold anthropometry, i.e. triceps skinfold thickness (Isaacs et al. 1994; Patrick et al. 1986; Sullivan et al. 2005). None of the studies included a measure of BMC or body protein.

In general, the studies found that most gastrostomy tube fed children with CP gain significant weight, and that the gains in weight were more dramatic than the gains in length/stature. In the studies that included skinfold anthropometry, significant increases in body fat were observed (Isaacs et al. 1994; Patrick et al. 1986; Sullivan et al. 2005). In addition, some studies reported that the weight gain was associated with healing of persistent pressure sores, the correction of cold and cyanosed extremities,
improvement in the children’s spasticity and affect, and that some children made significant developmental progress post gastrostomy tube feeding (Patrick et al. 1986; Rempel et al. 1988; Sanders et al. 1990). However, these findings were purely anecdotal and not collected in a standardised way.

In conclusion, most children with CP appear to get fatter as a result of tube feeding. Yet, no studies have tested the impact of nutritional rehabilitation on body protein and bone mineralisation in children with quadriplegic CP.

### 2.7 Aims of thesis

There have been numerous studies describing the body composition of children with quadriplegic CP (Henderson et al. 2002a; Ruby and Matheny 1962; Samson-Fang and Stevenson 2000; Stallings et al. 1993a; Stallings et al. 1995; Sterling 1960; Tobis 1961). Most of these studies have focused on measurements of body fatness and the validation of various methods to predict fat stores (Hildreth et al. 1997; Stallings et al. 1995; van den Berg-Emons et al. 1998). There are no studies directly measuring body protein in children with quadriplegic CP, or studies validating indirect methods of assessing body protein. Body protein is important to measure because immune function, response and recovery to disease, as well as skeletal respiratory muscle function, are severely impaired when body protein levels are reduced (Hill 1992).

Thus the first aim of this thesis was to directly measure TBP in children with quadriplegic CP.

Secondly, because the sophisticated technology (NAA and DXA) used in this study to measure body composition is not readily accessible, particularly in the clinic or community setting, a further aim of this thesis was to determine whether alternate simpler measures of body composition, such as skinfold anthropometry, can
accurately predict body composition (particularly TBP and body fat) in children with quadriplegic CP.

Thirdly, information on dietary intake and REE were collected in order to (i) examine energy balance and nutrient intake in this population, and (ii) to investigate any relations between, or influences of, dietary intake and REE and the body composition parameters.

Finally, despite the many studies reporting a high incidence of malnutrition in this population there have been limited studies investigating the effects of nutritional intervention on body composition parameters. The few studies that have been done have investigated changes in growth parameters (weight and height) and body fat only, with no exploration into the effects of weight gain on TBP and bone mineralisation. Therefore, the final aim of this thesis was to (i) conduct an RCT of gastrostomy tube feeding versus oral nutritional supplementation combined with speech therapy, and (ii) to investigate whether nutritional rehabilitation results in significant increases in TBP, bone mineralisation and REE in children with quadriplegic CP.
CHAPTER 3

METHODS
3 Methods

3.1 Participants

3.1.1 Children with cerebral palsy

Fifty-nine children (22F, 37M), between four and 19 years of age, with a diagnosis of quadriplegic CP were recruited through the Dysphagia Clinic at CHW between 2000 and 2005. All children were wheelchair-bound and totally dependent on their parent/carer for their everyday needs.

The Dysphagia Clinic consists of a paediatric gastroenterologist, general paediatrician, nurse, speech therapist, physiotherapist and dietitian. The purpose of the clinic is to assess and treat children with developmental disabilities and complex feeding and nutritional problems.

Children less than four years of age were excluded from this study because of the lack of available control data in this age range.

3.1.2 Control population

The data on the control children were from three separate existing control databases, as outlined below. All control children were healthy with no known medical problems, were of a similar age range to the children with CP (4-19 years), and were recruited through friends and relatives of CHW staff.

1. The control group for the anthropometric and DXA measurements consisted of 172 (84F, 88M) children from an existing DXA control database (Ogle et al. 1995). All children from this database had undergone a DXA measurement. In addition, measurements of height, weight and skinfold anthropometry were recorded at the time of the DXA measurement.
2. The control group for TBP consisted of data from a group of 72 (43F, 29M) children who had undergone TBP measurements at CHW (Baur et al. 1993).

3. The REE measurements of the children with CP were compared with a separate control database consisting of 111 (42F, 69M) children who had undergone REE measurements at CHW (unpublished data). In addition, measurements of height, weight and skinfold anthropometry were recorded at the time of the REE measurement.

3.2 Study Protocol

3.2.1 Cross-sectional study
During an outpatient visit to CHW, the children had measurements of anthropometry, TBP by NAA, body composition by DXA, and REE by indirect calorimetry. Parents/carers were then instructed to complete a weighed food record at home for subsequent dietary analysis.

A Parent Information Sheet detailing the study protocol was provided to all parents/carers prior to them giving written consent for their child to participate in the study (see Appendix A).

3.2.2 Nutritional rehabilitation study
An attempt was made to conduct an RCT of gastrostomy tube feeding versus oral feeding using oral nutritional supplementation and speech therapy. For reasons discussed in Chapter 7 this attempt failed and therefore a longitudinal cohort study of gastrostomy tube-fed versus oral-fed children was conducted.

The measurements that were performed for the cross-sectional study were repeated in a subset of children from the cross-sectional study after weight gain following gastrostomy tube feeding. These children received a gastrostomy tube as part of their
routine care through the Dysphagia Clinic. Some of these children continued to eat orally, therefore, their feeding regimens, which were determined by the Dysphagia Clinic dietitian, were aimed at providing between 75 % and 100 % of their estimated energy requirements through gastrostomy tube feeds using a range of commercially available, micro-nutrient complete, formulas. The energy requirements of the gastrostomy-fed children were initially estimated to be 1.2 times their measured REE, which was measured for the cross-sectional study. Weight gain was monitored at regular intervals through the Dysphagia Clinic, and the feeding regimens adjusted according to weight gain.

In addition, the tests were repeated in a subset of oral-fed children with CP who participated in the cross-sectional study. These children were to be used as a control group for comparison with the gastrostomy tube fed group. The oral-fed children with CP were recruited and monitored through the Dysphagia Clinic. They were provided with standard dietary and speech therapy advice by the Dysphagia Clinic dietitian and speech pathologist, respectively. Advice provided by the dietitian included increasing the energy content of their diets by the addition of energy-dense food and commercially available high-energy oral supplements. Advice provided by the speech pathologist centred on adjusting the texture of food and liquid in order to aid chewing and swallowing.

The same Parent Information Sheet that was given to the parents/carers for the cross-sectional study was re-issued to the parents/carers prior to giving consent for the tests to be repeated.

3.2.3 Ethics approval

The CHW Ethics Committee approved the study and written, informed consent was obtained from each parent/carer (see Appendix A).
3.3 Anthropometry

Two trained observers performed all measurements using standardised techniques (Norton et al. 1996). Please refer to Appendix B for all of the anthropometric equations used in this section.

3.3.1 Height and weight

In the children with CP, standing height was estimated using knee height. Knee height (±0.1 cm) was measured with an anthropometer (Holtain Ltd, Crosswell, Crymmych, Dyfed, Wales) with the knee and ankle each bent to a 90° angle. The distance from the heel to the anterior surface of the thigh over the femoral condyles was measured (Stevenson 1995b). The knee height measurement was then placed into the equations of either Stevenson (for children ≤12 y), or Chumlea et al (for children >12 y) to give an approximate height (see Appendix B) (Chumlea et al. 1994; Stevenson 1995b).

Weight measurements (± 0.1 kg) were made with electronic scales (A&D Mercury Pty Ltd, South Australia) with children wearing minimal clothing. Because the children with CP were unable to stand on the scales, the carer stood on the scales while holding the child, then the carer was weighed on their own and the difference between the two weights was calculated to give the weight of the child.

BMI was calculated as weight (kg) divided by height (m) squared.

Weight and height measurements were converted to SD scores and compared with the United States Centre for Disease Control growth reference data (Kuczmarski et al. 2000). Weight as a percent of ideal weight-for-height was calculated by first estimating the height-age of the child (the age at which the child’s actual height is on the 50th centile), and then dividing the child’s actual weight by the weight that corresponds with the 50th centile for the child’s height-age, and then multiplied by 100.
to give a percentage. Weight-for-height centile charts were not used to determine the
dead weight-for-height because the method described above is the most commonly
used method in the clinic setting at our centre.

3.3.2 **Skinfold anthropometry**

Skinfold thicknesses were measured in duplicate on the right side of the body at four
sites (triceps, biceps, subscapular, and suprailiac) with a Harpenden calliper (British
Indicators Ltd, St Albans, Hertfordshire, UK) and compared with Frisancho reference
data, as well as the control group (Frisancho 1981).

MUAC was measured with a flexible steel tape at the midpoint between the acromion
process and head of the radius on the right arm. An estimate of the UAMA was
derived from the MUAC and triceps skinfold measurement (Frisancho 1981). UAFA
was calculated from the total upper arm area minus the UAMA. The UAMA was
converted to a SD score derived from the Frisancho reference data (Frisancho 1981).
Due to the non-normal distribution of the reference data for the triceps and
subscapular skinfold thicknesses and UAFA, these measures were converted to SD
scores according to the methods of Davies et al (Davies et al. 1993).

3.3.2.1 **Body fat**

An estimate of FM and PBF was calculated from the four skinfold thicknesses
(PBF\textsubscript{SKIN}) using the equations of Brook for prepubertal children, and Durnin &
Rahaman for pubertal children (Brook 1971; Durnin and Rahaman 1967). Please refer
to Appendix B for the equations used in this section.

3.3.2.2 **Fat-free mass**

FFM was derived from skinfold anthropometry (FFM\textsubscript{SKIN}) by subtracting FM from
body weight.
3.3.2.3 Pubertal status

For the purposes of calculating PBF from skinfold anthropometry, the pubertal status of each study participant was determined by asking the parent / carer to select the pubertal status of their child from a pictorial representation of the five Tanner stages of puberty (Tanner and Whitehouse 1976).

3.3.3 Comparisons with control group and reference data

All anthropometric measures were compared with the control group as well as to reference data.

3.4 Total body protein by neutron activation analysis

TBP was calculated from the measurement of TBN by assuming that nitrogen is 16% of protein weight, i.e. mass of protein = 6.25 x mass of nitrogen. The TBN facility is located in the James Fairfax Institute of Paediatric Nutrition at CHW and was designed and built by the Australian Nuclear Science and Technology Organisation (Baur et al. 1991a). TBN was measured by the method of prompt gamma neutron capture analysis, also known as NAA. The TBN measurement involves the child lying supine on a motorised table (see Figure 3.1 pg 96). During the testing, the children with CP were kept in the supine position by carefully wrapping them in a light cotton bed sheet. The child is bilaterally irradiated with neutrons produced from the decay of two $^{252}$Cf sources, which results in the conversion of $^{14}$N to $^{15}$N with the emission of a 10.83 MeV gamma ray which is specific for nitrogen. The absolute mass of nitrogen ($M_N$) can be determined by using hydrogen (2.23 MeV gamma ray emission) as an internal standard and the following equation:

$$M_N = \left( \frac{Y_N}{Y_{H}} \right) K M_{H} C(W)$$
Where $Y_N$ and $Y_H$ are the net nitrogen and hydrogen yields, respectively, $K$ is the calibration factor determined from a phantom with known hydrogen and nitrogen masses, $C(W)$ is the nitrogen-to-hydrogen gamma ray attenuation correction factor which is dependent on subject width, and $MA_H$ is the mass of hydrogen determined from fat mass, as per the following equation, where fat mass ($MA_f$) is estimated from skinfold anthropometry using the equations of Brook, or Durnin & Rahaman, and body mass ($MA$) using the following equation of Vartsky et al (Vartsky et al. 1979):

$$MA_H = 0.097MA + 0.0219MA_f$$

(Baur et al. 2001). The total exposure time is approximately 15 minutes and the effective dose equivalent delivered during a scan is $<0.15$ mSv. The technique has a precision and accuracy of 1.4-5.4 % and 97-101.5 % respectively, in child-sized phantoms (Baur et al. 1991a). All measurements were made relative to a standard phantom, which was measured before and after each group of subjects. In this way corrections were made to account for any drift or change to the equipment or environment (Baur et al. 1991b).

### 3.4.1 Replacement of radioactive sources

Between August 2003 and June 2004, the two $^{252}$Cf sources were replaced and the machine was extensively re-calibrated. The sources were replaced because the previous sources had decayed to the extent that the machine was beginning to read outside the precision allowed for the measurement. The TBP results of six children with CP from the cross-sectional study, and two children from the nutritional rehabilitation study, who were measured between June 2003 and August 2003 were discarded and were not included in the data analysis because of the decay of the sources. No control children were tested during this period. Participant testing recommenced in July 2004.
3.4.2 Comparisons with control data

The TBP measurements of the children with CP were compared with TBP predicted for age, height and weight using equations based on the control data. Please see Appendix C for the predictive equations.

3.5 Body composition by dual-energy x-ray absorptiometry

All DXA measurements were performed and analysed by trained staff in the Department of Medical Imaging at CHW with a commercial x-ray bone densitometer (DPX Lunar Radiation Corp, Madison, WI). Whole body scans were performed on fast scan mode using adult total body software version 4.7 (Lunar Radiation Corp), with the child lying supine (see Figure 3.2 pg 96). The total scan time is approximately 10 minutes with a total radiation dose of around 0.2 μSv. Most of the children with CP were lightly sedated with 0.35 mg/kg of oral midazolam 30 minutes prior to the scan to help reduce involuntary or uncontrollable movements during the test. Some of the children with CP were also carefully wrapped in a light cotton bed sheet to keep them in the supine position during testing.

The DXA measurement provides a three-compartment model of body composition: fat tissue mass (FM_{DXA}), BMC, and lean tissue mass (LTM_{DXA}), where the LTM_{DXA} represents the non-BMC LTM_{DXA}. Percent body fat by DXA (PBF_{DXA}) for the total body was calculated by the following formula:

\[
PBF_{DXA} = \frac{FM_{DXA}}{FM_{DXA} + LTM_{DXA} + BMC}
\]

The precision of the technique in children as assessed at CHW is 1.2 % for BMC, 1.59 % for percentage body fat and 0.82 % for lean tissue mass (Ogle et al. 1995).
Figure 3.1 Total body nitrogen by neutron activation analysis

Picture reproduced with parental consent

Figure 3.2 Dual energy x-ray absorptiometry
3.5.1 **Comparisons with control data**

Measurements for BMC were converted to age, weight, and height SD scores based on data derived from the control group. In addition, following the methods of Högler et al, the BMC measurements of the children with CP were also adjusted for both height and LTM\textsubscript{DXA} and expressed as an SD score for comparison with control data (Hogler et al. 2003). The LTM\textsubscript{DXA} data of the children with CP were converted to a SD score for height for comparison with control data.

3.6 **Comparison of methods to derive body composition**

3.6.1 **Total body protein**

TBP was calculated from the DXA measurement (TBP\textsubscript{DXA}) and also from skinfold anthropometry (TBP\textsubscript{SKIN}) following the method of Fuller et al (Fuller et al. 2001):

\[ TBP = LTM - \text{non-osseous mineral} \times 0.2305 \times BMC + \text{estimated TBW} \times \text{hydration constant of FFM (HC\textsubscript{FFM})}. \]

For TBP\textsubscript{DXA}, the FFM was calculated as the sum of the two non-fat components, LTM\textsubscript{DXA} and BMC. For TBP\textsubscript{SKIN}, the LTM was calculated as FFM\textsubscript{SKIN} minus BMC, where BMC was derived from DXA. Age and sex specific HC\textsubscript{FFM} were used for the estimation of TBW (see Appendix D) (Fomon et al. 1982; Lohman 1986). The TBP\textsubscript{DXA} and TBP\textsubscript{SKIN} were then compared with the TBP derived from the direct assessment method of NAA (TBP\textsubscript{NAA}).

3.6.2 **Body fat**

PBF\textsubscript{DXA} was compared with PBF\textsubscript{SKIN} using two different sets of equations:

(1) With four skinfold thicknesses (biceps, triceps, subcapular, and supra-iliac) using the equations of Brook (for prepubertal children) and Durnin & Rahaman (for pubertal children) (PBF\textsubscript{SKIN-A}, (Brook 1971; Durnin and Rahaman 1967) and
(2) With two skinfold thicknesses (triceps and subscapular) using the equations of Slaughter (PBF\(_{SKIN-B}\)) (Slaughter et al. 1988).

Please refer to Appendix B for the equations used in this section.

### 3.7 Resting energy expenditure by indirect calorimetry

REE was measured in the morning for 20 minutes using an open circuit, flow through, ventilated hood indirect calorimeter (Datex Deltatrac II MBM-200 Metabolic Monitor, Datex-Engstrom Division Instrumentarium Corp., Helsinki, Finland). All children were fasted overnight (from midnight) and were afebrile and in a rested state. REE was calculated from measured gas exchange over 20 minutes and extrapolated to estimate REE (kJ/24h).

The parents/carers of the children with CP were instructed to give their child their regular morning medications prior to the testing. The decision was made not to withhold medications until after testing because many of the children were on anti-epileptic medications and therefore may have been at risk of having a seizure if the medication was delayed. Please see Appendix E for the list of medications taken by the children with CP. Four of the participants with CP who had a measurement of REE reported using bronchodilator medication/s when required for breathing difficulties. However, only one of these four participants reported using the bronchodilator medication the morning of the test.

#### 3.7.1 Comparisons with reference and control data

Measured REE was compared with that predicted from the Schofield equations based on actual weight, as well as that predicted from the control data based on FFM\(_{SKIN}\) (see Appendix F) (Schofield 1985).
3.8 Dietary intake by three-day weighed food records

The dietary intake of the children was estimated from a three-day weighed food record. Parents/carers were provided with portable electronic scales (Salter “Selectronic 2200”, Salter Housewares Ltd, Kent, UK; accuracy ± 2 g) and detailed written instructions as well as given a demonstration on how to use the electronic scales. The parents/carers were instructed to weigh all foods, beverages and supplements consumed by their child over three consecutive days, including two days during the week and one day on the weekend. Parents/carers were asked to record the details of methods of food preparation, description of foods, and brand names (if known). For composite dishes, such as a cake or casserole, the carers were instructed to record the weights of all raw ingredients used in the recipe, as well as the weight of the portion consumed by the child and the final weight of the composite dish. All of the food records were checked on completion and any unweighed foods were quantified. The food records were analysed with a computer program (FoodWorks Version 2, Xyris Software, Brisbane, Australia) based on the Australian food composition database, NUTTAB95, as well as product information supplied by manufacturers (Commonwealth Department of Community Services and Health 1989; National Health and Medical Research Council 1991).

3.8.1 Comparisons with reference and control data

The food records were examined for over- and under-reporting by comparing the energy intake with measured REE. Micro-nutrient (vitamin and mineral) intakes were compared with age-appropriate Australian RDI (National Health and Medical Research Council 1991).
Chapter 3
METHODS

3.9 Statistics

All data were analysed using the programme Statistical Package for the Social Sciences (SPSS) (version 11.5.1, SPSS Inc, Chicago, USA). The significance level was set at $p < 0.05$.

3.9.1 Study 1 - Cross-sectional

3.9.1.1 Anthropometry

A two-factor analysis of variance (ANOVA) test was used to investigate differences in anthropometric characteristics and body composition from skinfold anthropometry between children with CP and control children (from the DXA control database), using sex and group (CP or control) as fixed factors.

A two-tailed one-sample t-test was used to compare mean differences between all participants and reference data (test value = 0) for height and weight SD scores, triceps and subscapular skinfold thickness SD scores, UAMA SD score, and UAFA SD score.

3.9.1.2 Total body protein

A two-factor ANOVA test was used to investigate differences between participant characteristics (age, height, weight, $FFM_{SKIN}$, and $PBF_{SKIN}$) and $TBP_{NAA}$ of the children with CP and that of the TBP control group, using sex and group (CP or control) as fixed factors.

A two-tailed one-sample t-test was used to compare mean differences between $TBP_{NAA}$ as a percentage of that predicted for age, height, and weight based upon control data (test value = 100).
3.9.1.3 Body composition by dual-energy x-ray absorptiometry

A two-factor ANOVA test was used to investigate differences between BMC, \( \text{LTM}_{\text{DXA}}, \text{FM}_{\text{DXA}}, \) and \( \text{PBF}_{\text{DXA}} \) of the children with CP and that of the DXA control group, using sex and group (CP or control) as fixed factors.

A two-tailed one-sample t-test was used to compare mean differences between children with CP and control data (test value = 0) for BMC SD scores for age, height and weight; BMC SD score adjusted for both height and \( \text{LTM}_{\text{DXA}} \); and \( \text{LTM}_{\text{DXA}} \) SD score adjusted for height.

3.9.2 Study 2 – Comparison of methods

A paired t-test was used to test for differences between (i) TBP measured by NAA, DXA, and skinfold anthropometry, and (ii) PBF measured by DXA and skinfold anthropometry. Bland & Altman plots were used to test the agreement between methods to measure TBP (TBP\(_{\text{NAA}}\) versus TBP\(_{\text{DXA}}\), and TBP\(_{\text{NAA}}\) versus TBP\(_{\text{SKIN}}\)) and PBF (PBF\(_{\text{DXA}}\) versus PBF\(_{\text{SKIN-A}}\) and PBF\(_{\text{DXA}}\) versus PBF\(_{\text{SKIN-B}}\)) in both children with CP and controls (Bland and Altman 1986). A univariate analysis of covariance (ANCOVA) was used to statistically analyse and compare the Bland & Altman plots with “difference between methods” as the dependent variable, “average of methods” as the covariate, and group (CP or control) as fixed factors.

3.9.3 Study 3 – Resting energy expenditure and dietary intake

3.9.3.1 Resting energy expenditure

A two-factor ANOVA test was used to investigate differences between participant characteristics (age, height, weight, FFM\(_{\text{SKIN}}\), and PBF\(_{\text{SKIN}}\)) and measured REE of the children with CP and that of the control group, using sex and group (CP or control) as fixed factors.
Linear regression analysis was performed on the REE data of the control group to develop predictive equations to allow for comparisons with the children with CP. Measured REE was used as the dependent variable, with age, weight, height, FFM\textsubscript{SKIN}, and FM\textsubscript{SKIN}, tested separately as independent variables.

Linear regression analysis was also performed on the REE data of the children with CP in order to find predictors of measured REE. Measured REE was used as the dependent variable with age, weight, height, FFM\textsubscript{SKIN}, and FM\textsubscript{SKIN} tested separately as independent variables. In addition, linear regression analysis was performed to investigate any significant associations between anticonvulsant medication use and tube feeding with measured REE and measured REE as a percent of REE predicted from control data (anti-epileptic medications (0 = no, 1 = yes); presence of a gastrostomy or NG tube, 0 = no, 1 = yes)).

A two-tailed one-sample t-test was used to test if measured REE as a percent of that predicted from the Schofield equation (based on weight) was significantly different to 100 % (test value = 100) for both the children with CP and the control group. In addition, in the children with CP only, a two-tailed one-sample t-test was used to test if measured REE as a percent of that predicted from the control data (based on FFM\textsubscript{SKIN}) was significantly different to 100 % (test value = 100).

### 3.9.3.2 Dietary intake

Energy intake was expressed in kilojoules per day as well as a percentage of measured REE. Micronutrient intakes were expressed as a percentage of the RDI. The energy intake of the children with CP was not normally distributed and is presented as median with inter-quartile range (IQR).
A Mann-Whitney U test was used to examine differences in energy intake, expressed as a percentage of measured REE, between oral-fed and tube-fed children with CP. A two-tailed one-sample t-test was used to test if micronutrient intake, expressed as a percentage of RDI, was significantly different to 100 % (test value = 100).

3.9.4 Correlations
Pearson's product-moment correlations (r) were used to investigate relations between anthropometric measures of body composition and TBP\textsubscript{NAA} and DXA and between dietary intake of calcium and protein with BMC and TBP\textsubscript{NAA}, respectively.

3.9.5 Study 4 - Nutritional rehabilitation
The data for the nutritional rehabilitation study were not normally distributed and are presented as medians with IQR.

A Wilcoxon Signed Ranks test was used to compare differences between the baseline and repeat tests of the body composition parameters within each group (gastrostomy tube-fed and oral-fed).

A Mann-Whitney U test was used to compare changes in the body composition parameters between the two groups (gastrostomy tube-fed versus oral-fed).
CHAPTER 4

STUDY 1

CROSS-SECTIONAL STUDY
4 Study 1 - Cross-sectional study

4.1 Introduction

There have been a limited number of studies measuring body composition in children with severe CP. There are no studies that have measured a 3C model of body composition using a direct measure of body protein in this population.

4.2 Aim

To measure a 3C model of body composition in children with quadriplegic CP, specifically TBP, FM and BMC.

4.3 Participants

4.3.1 Participant recruitment

4.3.1.1 Children with cerebral palsy

The parents/carers of 87 children with quadriplegic CP between the ages of four to 19 years were invited to allow their child to participate in the cross-sectional study. Of these, 59 agreed to participate, and 28 declined. The main reason given for declining to participate was parental lack of time. No information was collected on those who declined to participate, so it is unknown if they differed in any way to the study population. However, the purpose of the Dysphagia Clinic is to assess and treat children with developmental disabilities and multiple feeding and nutritional problems, therefore it is likely that those who declined to participate did not differ significantly from those who participated.

Forty-two of the 59 participants were recruited and studied by the candidate, the remaining 17 (8F, 9M) participants had been recruited and studied by Dr Edward O’Loughlin and Ms. Samantha Clarke as an earlier pilot study, but have been included in the total as minimal changes were made to the study design as a result of the pilot
study. Three additional tests were added to the study protocol that were not part of the pilot study:

- Knee height as a proxy for standing height
- REE by indirect calorimetry
- Three-day weighed food records to assess dietary intake

Therefore, data on these three additional tests are not available for the first 17 children with CP who participated in the pilot study.

4.3.1.2 Control children

The control children for the cross-sectional study were from two separate existing control databases, as outlined below. All control children were healthy with no known medical problems, were of a similar age range to the children with CP (4 - 19 y), and were recruited through friends and relatives of CHW staff.

4. The control group for the anthropometric and DXA measurements consisted of 172 (84F, 88M) children from an existing DXA control database (Ogle et al. 1995). All children from this database had undergone a DXA measurement. Measurements of height, weight and skinfold anthropometry were recorded at the time of the DXA measurement.

5. The control group for TBP consisted of data from a group of 72 (43F, 29M) children who had undergone TBP measurements at CHW (Baur et al. 1993).

4.3.2 Participant description

Twelve of the 59 study participants lived in a government-funded or privately-funded group care residential facility, the remainder of study participants lived at home with their biological or adoptive parents.
4.3.2.1 Type of cerebral palsy

For each study participant the type of CP was obtained from the medical records. Twenty-eight of the 59 children had spastic quadriplegic CP, six had athetoid quadriplegic CP; and the remaining 25 did not have a type specified but were described as “severe” quadriplegic CP.

4.3.2.2 Cause of cerebral palsy

The cause of CP was obtained from the medical records of each child and recorded as follows: hypoxic brain injury, 17; unknown, 14; secondary to prematurity, 10; brain abnormalities, 8; infections in-utero, 5; and other causes, 5.

4.3.2.3 Method of feeding

At the time of the study, 20 of the 59 children (5F, 15M) were fed partially or completely by either a gastrostomy (n = 17) or NG tube (n = 3). The remainder of the children were fed orally. Three of the tube-fed children received their gastrostomy tube less than one month prior to being tested. The remainder had their tubes in place for a median of 3.3 years (range 0.4 to 6.5 years).

4.3.2.4 Medications

The majority (n = 56) of children with CP were taking at least one medication (see Appendix E). The most common medications were anti-epileptic medications (n = 40), followed by medications to treat reflux (n = 27), anxiety (n = 16), movement disorders (n = 11), constipation (n = 10), and asthma and allergic rhinitis (n = 8).

4.4 Study protocol

During an outpatient visit to CHW, the children had measurements of anthropometry, TBP by NAA, and body composition by DXA, as outlined in Chapter 3.
A Parent Information Sheet detailing the study protocol was provided to all parents/carers prior to them giving written consent for their child to participate in the study (see Appendix A).

4.5 Data analysis

All data were analysed as outlined in Chapter 3 using the programme SPSS (version 11.5.1, SPSS Inc, Chicago, USA). The significance level was set at $p < 0.05$.

4.6 Results

4.6.1 Anthropometry

4.6.1.1 Anthropometric characteristics

The anthropometric characteristics of the children with CP and control children are shown in Table 4.1 (pg 111). The anthropometric characteristics, except for measures of body fatness in the control group, were not significantly different between the male and female children with CP or controls and therefore the sexes were analysed together.

The children with CP were on average significantly younger (by an average of 1.5 years) than the control children; however, where possible, the data were converted to SD scores to adjust for age differences. The height and weight SD scores for the children with CP were significantly lower than both the control and reference data, however, the mean actual weight as a percent of ideal weight-for-height of the children with CP was $96.3 \pm 14.9\%$ ($n = 42$) which was not significantly different from 100 %. In contrast, measures of body fatness were all significantly reduced. The UAFA and the triceps and subscapular skinfold thicknesses were converted to age and sex specific SD scores to account for differences in sex, and are therefore presented with sexes combined. The mean triceps skinfold thickness was $-1.5 \pm 1.5$ SD score,
the mean subscapular skinfold thickness -1.0 ± 1.5 SD score, and the mean UAFA -1.9 ± 1.7 SD score (n = 58), for children with CP, all of which were significantly (p < 0.01) less than the reference values and the controls. Percent body fat for the female children with CP was significantly lower than the female controls; 12.5 ± 7.3 % (n = 20) versus 22.5 ± 7.3 % (p < 0.001), respectively, and also for male children with CP compared with male controls, 14.2 ± 7.0 % versus 17.6 ± 4.5 % (p < 0.01), respectively. PBF is presented with sexes separated due to the differences between sexes in the control group. In addition, as shown in Table 4.1, the UAMA and FFM\textsubscript{SKIN} of the children with CP were significantly reduced compared with reference data and control data.

Knee height was not measured in the first 17 participants enrolled in the study, and therefore data on height, height SD score and weight as a percent of ideal weight-for-height are unavailable for eight females and nine males. In addition, complete sets of skinfold anthropometry were not obtained on three (1M, 2F) participants with CP due to the inability of the children to cooperate, and therefore the data on UAMA is unavailable for one child (1M), and on FFM\textsubscript{SKIN} and PBF\textsubscript{SKIN} for two children (2F). The control children were not different from the reference data for height and weight as indicated by their SD scores, and are therefore considered to be representative of the normal population.

4.6.1.2 Correlations

Height, weight, UAMA, and FFM\textsubscript{SKIN} were significantly positively correlated with age in the children with CP; r = 0.81, p < 0.001; r = 0.67, p < 0.001; r = 0.54, p < 0.001; r = 0.80, p < 0.001, respectively. Figure 4.1 (pg 112) demonstrates the significant correlation between age and FFM\textsubscript{SKIN} in the children with CP and controls. The figure reveals that the children with CP gain FFM\textsubscript{SKIN} at a reduced rate compared
with the control children, and consequently, in the older children the FFM\textsubscript{SKIN} of the children with CP is further below the control children values.

Height SD score, weight SD score, UAMA SD score, and subscapular skinfold SD score in the children with CP were all significantly negatively correlated with age; \( r = -0.37, p < 0.05; \ r = -0.42, p < 0.01; \ r = -0.38, p < 0.01; \ r = -0.39, p < 0.01, \) respectively.

### 4.6.1.3 Tube-fed versus oral-fed children with cerebral palsy

Twenty of the 59 children with CP who participated in the cross-sectional study were fed via either a naso-gastric or gastrostomy tube. When analysed separately, the tube-fed children (\( n = 16, \) excluding those who received their gastrostomy tubes less than one month prior to being tested) compared with the oral-fed children (\( n = 43 \)) had on average a significantly (\( p < 0.05 \)) higher weight (23.6 vs. 19.4 kg), weight as a percent of ideal weight-for-height (103.9 vs. 91.1 %), UAMA (21.8 vs. 16.5 cm\(^2\)), UAMA SD score (-0.9 vs. -2.7 SDS), UAFA (8.5 vs. 4.4 cm\(^2\)), UAFA SD score (-1.1 vs. -2.7 SDS), BMI (16.2 vs. 14.4 kg/m\(^2\)), BMI SD score (-0.7 vs. -2.0 SDS) and PBF\textsubscript{SKIN} (17.7 vs. 11.7 %), respectively. There was no significant difference between the two groups for weight SD score, height, height SD score, or FFM\textsubscript{SKIN} (data not shown).
Table 4.1 Anthropometric characteristics of children with cerebral palsy and controls

<table>
<thead>
<tr>
<th></th>
<th>CP</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 59</td>
<td>N = 172</td>
<td></td>
</tr>
<tr>
<td>(22F, 37M)</td>
<td>(84F, 88M)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>10.4 ± 4.3</td>
<td>11.9 ± 4.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>20.7 ± 7.1</td>
<td>42.4 ± 17.0</td>
</tr>
<tr>
<td>Weight for age SDS</td>
<td>-4.8 ± 5.3</td>
<td>0.0 ± 0.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>116.7 ± 15.4</td>
<td>147.2 ± 20.6</td>
</tr>
<tr>
<td>Height for age SDS</td>
<td>-3.1 ± 1.6</td>
<td>0.1 ± 0.9</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>15.1 ± 2.4</td>
<td>18.6 ± 3.3</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>-1.5 ± 2.0</td>
<td>0.0 ± 0.8</td>
</tr>
<tr>
<td>UAMA (cm$^2$)</td>
<td>18.1 ± 5.7</td>
<td>32.3 ± 11.6</td>
</tr>
<tr>
<td>UAMA for age SDS</td>
<td>-2.1 ± 2.2</td>
<td>0.4 ± 1.0</td>
</tr>
<tr>
<td>FFM$_{SKIN}$ (kg)</td>
<td>18.0 ± 5.3</td>
<td>33.4 ± 12.7</td>
</tr>
</tbody>
</table>

Data is mean ± SD. BMI, body mass index; CP, cerebral palsy; FFM$_{SKIN}$, fat-free mass measured by skinfold anthropometry; SDS, standard deviation score; UAMA, upper arm muscle area.

A two-factor ANOVA was used to test the difference between CP and control group, using gender and group (CP or control) as fixed factors. A two-tailed, one-sample t-test was used to test the difference between SDS and reference data (test value = 0).

1$^p < 0.05$; 2$^p < 0.001$; significantly different from controls
3$^p < 0.001$; significantly different from reference data
4$n = 42$, 5$n = 58$, 6$n = 57$
Figure 4.1 Fat-free mass versus age in children with cerebral palsy and controls

The above figure illustrates a strong positive correlation between fat-free mass measured by skinfold anthropometry (FFM_{SKIN}) and age in children with cerebral palsy (CP) and controls. Although FFM_{SKIN} in children with CP increases with age, it is below the rate of the control children.

CP: n = 57, r = 0.80, p < 0.001.
Controls: n = 172, r = 0.87, p < 0.001

Statistical analysis (univariate ANCOVA) revealed a significant difference in the slopes of the regression lines between the two groups; p < 0.001.
4.6.2  **Total body protein by neutron activation analysis**

Fifty-three (21F, 32M) children with CP had measurements of TBP$_{\text{NAA}}$. The characteristics of the children with CP and controls are shown in Table 4.2 (pg 115). The mean TBP$_{\text{NAA}}$ of the children with CP was 3.0 ± 1.2 kg, while that of the controls was 6.4 ± 2.9 kg (43F, 29M). There was no significant difference between the females and males with CP or controls and therefore the data are presented and analysed with sexes combined. As detailed in Chapter 3, the TBP$_{\text{NAA}}$ results of six (1F, 5M) children with CP were excluded from the analysis because they were tested immediately prior to the radioactive sources being replaced. There was no control children tested during this period.

4.6.2.1  **Total body protein adjusted for age, height, and weight**

The TBP$_{\text{NAA}}$ results for the children with CP, expressed as a percentage of predicted from control data for age, height and weight were significantly reduced 56.1 ± 17.3 % (p < 0.001, n = 45), 81.5 ± 15.7 % (p < 0.001, n = 34), and 83.9 ± 17.2 % (p < 0.001, n = 45), respectively. Eight (1F, 7M) children with CP were excluded from the analysis of TBP$_{\text{NAA}}$ predicted for age, height and weight because their ages fell outside the range for which the predictive equations were developed from control data (Appendix C).

4.6.2.2  **Correlations**

TBP$_{\text{NAA}}$ (g) was significantly positively correlated with age in both the children with CP ($r = 0.74$, $p < 0.001$) and the control group ($r = 0.89$, $p < 0.001$) (Figure 4.2, pg 116). However, the TBP$_{\text{NAA}}$ percentage of predicted for age was significantly negatively correlated with age ($r = -0.58$, $p < 0.001$, n = 45) in the children with CP (Figure 4.3, pg 117). These two figures demonstrate that as children with CP age they
gain body protein but not at the same rate as control children, and subsequently in the older children body protein is further below the control children. For example, in Figure 4.2, at age 10 years the body protein of the control children is approximately twice that of the children with CP (approximately 6 kg vs. 3 kg, respectively). Whereas at age 16 years, the body protein of the control children is approximately two and a half times that of the children with CP (approximately 10 kg vs. 4 kg, respectively).

In the children with CP, TBP\textsubscript{NAA} was highly correlated (p < 0.001) with FFM\textsubscript{SKIN} (r = 0.86), weight (r = 0.80), height (r = 0.75), UAMA (r = 0.69), and MUAC (r = 0.56). In the control group there was a significant positive correlation between TBP\textsubscript{NAA} and FFM\textsubscript{SKIN} (r = 0.98, p < 0.001), weight (r = 0.97, p < 0.001), and height (r = 0.93, p < 0.001). Data on UAMA was unavailable for the control group. There was also a significant correlation between TBP\textsubscript{NAA} and LTM\textsubscript{DXA} in both children with CP and in a subset of the control group who had both TBP and DXA measurements; r = 0.88, p < 0.001 (n = 49), r = 0.99, p < 0.001 (n = 28), respectively. There were no significant correlations between TBP\textsubscript{NAA} and measures of body fatness (data not shown).

### 4.6.2.3 Tube-fed versus oral-fed children with cerebral palsy

There was no significant difference in TBP\textsubscript{NAA}, when expressed in kilograms or as percentage of that predicted for age or height, between those children with CP fed via a tube or fed orally (data not shown).
Table 4.2 Physical characteristics and body protein of children with cerebral palsy and controls

<table>
<thead>
<tr>
<th></th>
<th>CP</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 53 (21F, 32M)</td>
<td>N = 72 (43F, 29M)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>10.0 ± 4.1</td>
<td>10.7 ± 3.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>114.8 ± 15.0</td>
<td>142.4 ± 19.2</td>
</tr>
<tr>
<td>Height SDS</td>
<td>-3.1 ± 1.6</td>
<td>0.1 ± 0.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>20.0 ± 6.9</td>
<td>39.2 ± 17.6</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>-4.8 ± 5.5</td>
<td>0.1 ± 1.0</td>
</tr>
<tr>
<td>FFM\textsubscript{SKIN} (kg)</td>
<td>17.4 ± 5.1</td>
<td>29.9 ± 11.7</td>
</tr>
<tr>
<td>TBP\textsubscript{NAA} (kg)</td>
<td>3.0 ± 1.2</td>
<td>6.4 ± 2.9</td>
</tr>
<tr>
<td>PBF\textsubscript{SKIN} (%)</td>
<td>12.5 ± 7.6</td>
<td>21.3 ± 8.5</td>
</tr>
</tbody>
</table>

Data is mean ± SD. CP, cerebral palsy; FFM\textsubscript{SKIN}, fat-free mass measured by skinfold anthropometry; PBF\textsubscript{SKIN}, percent body fat by skinfold anthropometry; SDS, standard deviation score; TBP\textsubscript{NAA}, total body protein measured by neutron activation analysis.

A two-factor ANOVA was used to test for differences between CP and control group, using gender and group (CP or control) as fixed factors.

1 \( p < 0.001 \), significantly different from controls
2 \( n = 36 \), 3 \( n = 51 \)
Figure 4.2 Total body protein versus age

This figure demonstrates the correlation between total body protein measured by neutron activation analysis and age in both children with CP and controls. The figure shows that children with CP gain body protein as they age; however, it deviates further from the control children as they age.

CP: \( n = 53, r = 0.74, p < 0.001 \)
Controls: \( n = 72, r = 0.89, p < 0.001 \)

Statistical analysis (univariate ANCOVA) revealed a significant difference in the slopes of the regression lines between the two groups; \( p < 0.001 \).
Figure 4.3 Total body protein as a percent of predicted from controls versus age in children with cerebral palsy

The above figure demonstrates the relation between total body protein measured by neutron activation analysis (TBP_{NAA}) for age as a percentage of predicted from control data and age in children with cerebral palsy (CP). This figure shows that in the older children with CP their body protein deviates further from the control population.

n = 45, r = -0.58, p < 0.001.

---------- represents the control population, or predicted TBP_{NAA} for age (100%).
4.6.3 **Body composition by dual-energy x-ray absorptiometry**

The results for the DXA measurements are shown in Table 4.3 (pg 121). The measures of \( \text{LTM}_{\text{DXA}} \), \( \text{FM}_{\text{DXA}} \), and \( \text{PBF}_{\text{DXA}} \) were significantly different between sexes for the control group only; therefore data for the males and females were analysed separately. The results for BMC were not significantly different between sexes for the children with CP or control children. Three children with CP (1F, 2M) with metallic implants were removed from the analysis. Another child with CP (1M) was unable to remain motionless for the total body DXA scan and therefore their data was not included in the analysis.

4.6.3.1 **Bone mineral content adjusted for age, height, weight, and lean tissue mass**

The BMC results of the children with CP adjusted for age, height, and weight and expressed as SD scores were all significantly reduced: -2.6 ± 1.5 SD score \((p < 0.001, n = 55)\), -0.7 ± 1.1 SD score \((p < 0.001, n = 39)\) and -0.5 ± 1.2 SD score \((p < 0.001)\) respectively. Since LTM is a major predictor of BMC (Ogle et al. 1995), others have recommended adjusting the BMC value for LTM (Hogler et al. 2003). The adjusted BMC for \( \text{LTM}_{\text{DXA}} \) was -1.2 ± 1.5 SD score, which was significantly reduced \((p < 0.001)\). Furthermore, because of the stunted growth of the children with CP, height as well as \( \text{LTM}_{\text{DXA}} \) was taken into account. Hence, following the methods of Hogler et al, the BMC/\( \text{LTM}_{\text{DXA}} \) ratio for height was -1.2 ± 1.7 SD score, which was significantly reduced \((p < 0.001, n = 42)\).

4.6.3.2 **Lean tissue mass adjusted for height**

The \( \text{LTM}_{\text{DXA}} \) of the children with CP adjusted for height was -0.1 ± 1.5 SD score, which was not significantly different from the control data (i.e. SD score of 0).
4.6.3.3 Correlations

BMC was positively correlated with age in both the control group (r = 0.88, p < 0.001) and the children with CP (r = 0.76, p < 0.001) (Figure 4.4, pg 122). However, BMC for age SD score was negatively correlated with age (r = -0.60, p < 0.001) in the children with CP (Figure 4.5, pg 122). The two figures demonstrate that although children with CP gain bone mineral as they age, it is slower than the gain seen in the control population and subsequently in the older children the BMC of the children with CP is further below that of the control children.

In addition, in the children with CP and control group, BMC was highly correlated with LTM\textsubscript{DXA} (r = 0.89, p < 0.001 and r = 0.97, p < 0.001, respectively) and with FFM\textsubscript{SKIN} (r = 0.93, p < 0.001 and r = 0.97, p < 0.001, respectively). BMC was also highly correlated with TBPNAA in the children with CP (r = 0.86, p < 0.001, n = 49), and in a subset of the control group who had both TBP and DXA measurements (r = 0.99, p < 0.001, n = 28).

4.6.3.4 Bone mineral content and anti-epileptic medication use

There was no significant relation between BMC and anti-epileptic medication use in the children with CP (data not shown), i.e. the BMC or BMC SD scores of the children with CP who were taking anti-epileptic medications did not differ significantly from those children with CP who were not taking anti-epileptic medications.

4.6.3.5 Tube-fed versus oral-fed children with cerebral palsy

Those children with CP fed via either a NG or gastrostomy tube, compared with the oral-fed group, had on average a significantly (p < 0.05) higher FM\textsubscript{DXA} (5.5 vs. 2.8 kg), PBF\textsubscript{DXA} (22.4 vs. 14.1 %), and BMC for LTM\textsubscript{DXA} SD score (-0.6 vs. -1.4 SD...
score). There was no significant difference between the two groups for BMC, BMC for age or height SD scores, $LTM_{DXA}$, or BMC adjusted for both $LTM_{DXA}$ and height (data not shown).
### Table 4.3 Body composition by dual-energy x-ray absorptiometry in children with cerebral palsy and controls

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CP</td>
<td>Controls</td>
<td>CP</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>N = 21</td>
<td>N = 84</td>
<td>N = 34</td>
<td>N = 88</td>
</tr>
<tr>
<td>BMC (g)</td>
<td>583 ± 246</td>
<td>1645 ± 666</td>
<td>706 ± 297</td>
<td>1713 ± 908</td>
</tr>
<tr>
<td>LTM&lt;sub&gt;DXA&lt;/sub&gt; (kg)</td>
<td>15.3 ± 4.4</td>
<td>29.4 ± 9.2</td>
<td>18.2 ± 6.5</td>
<td>33.6 ± 15.1</td>
</tr>
<tr>
<td>FM&lt;sub&gt;DXA&lt;/sub&gt; (kg)</td>
<td>3.3 ± 3.1</td>
<td>9.9 ± 6.2</td>
<td>3.9 ± 2.8</td>
<td>6.5 ± 4.3</td>
</tr>
<tr>
<td>PBF&lt;sub&gt;DXA&lt;/sub&gt; (%)</td>
<td>15.9 ± 8.4</td>
<td>23.3 ± 7.7</td>
<td>17.1 ± 10.8</td>
<td>15.8 ± 6.7</td>
</tr>
</tbody>
</table>

Data is mean ± SD. BMC, bone mineral content; CP, cerebral palsy; DXA, dual-energy x-ray absorptiometry; FM, fat mass; LTM, lean tissue mass; PBF<sub>DXA</sub>, percent body fat by DXA.

A two-factor ANOVA was used to test for differences between CP and control group, using gender and group (CP or control) as fixed factors.

<sup>1</sup>p < 0.001, significantly different from control group.
Figure 4.4 Bone mineral content versus age

The above figure shows the correlation between bone mineral content (BMC) and age in children with cerebral palsy (CP) and controls. Although, BMC increases with age in the children with CP, it deviates further from the control group as the children age.

CP: n = 55, r = 0.78, p < 0.001
Controls: n = 172, r = 0.88, p < 0.001

Statistical analysis (univariate ANCOVA) revealed a significant difference in the slopes of the regression lines between the two groups; p < 0.001.
Figure 4.5 Bone mineral content for age versus age in children with cerebral palsy

The above figure demonstrates that the bone mineral content (BMC) of children with cerebral palsy (CP) deviates further from normal values as the children age.

n = 55, r = -0.60, p < 0.001

---------- represents the control population, or predicted BMC SD score for age (i.e. SD score of 0).
4.7 Summary

In summary, this cross-sectional study of body composition in children with quadriplegic CP revealed that they were markedly stunted, with greatly reduced fat stores, TBP and BMC. Furthermore, the height, weight, TBP and BMC of the children with CP deviated further from control values in the older children. In addition, in comparison with the oral-fed children, the tube-fed children with CP had on average a significantly higher weight, weight-for-height, and PBF, but did not differ significantly in their TBP or BMC.

4.8 Discussion

4.8.1 Anthropometry

4.8.1.1 Height and weight deficits

The deficits in height and weight are in agreement with several other studies conducted in similar populations (Fung et al. 2002; Hammond et al. 1966; Krick et al. 1996; Pryor and Thelander 1967; Ruby and Matheny 1962; Samson-Fang et al. 2002; Samson-Fang and Stevenson 2000; Stallings et al. 1993a; Stallings et al. 1995; Sterling 1960; Stevenson et al. 1994; Thommessen et al. 1991; Tobis 1961; Troughton and Hill 2001). In addition, it has been found, in this study as well as others that the deficits in height and weight were greater in the older children. It has been postulated that this is due to the cumulative effects over time of the combination of an inadequate dietary intake and neurological influences on growth. Alternatively, the increasing deviation in height could be an effect of worsening scoliosis with age which is common in this population, but this would not explain the same finding for body weight.
4.8.1.2 Normal weight-for-height

Even though the mean height and weight SD scores of the children with CP were significantly reduced, the mean actual weight as a percent of ideal weight-for-height was not significantly different from 100%, implying that although stunted they were not wasted. In contrast, skinfold anthropometry revealed that the children with CP had reduced skinfold thicknesses (the triceps more so than the subscapular), UAFA, PBF, UAMA, and FFM in comparison with the reference data and a similar-aged control group. Furthermore, these anthropometric measures differed more from the normal values in the older aged children. These findings suggest that, despite their apparently normal weight-for-height, they were in fact wasted.

A normal weight-for-height, despite wasting of body fat and FFM, has also been found in two previous studies of children with CP (Berg and Isaksson 1970; Samson-Fang and Stevenson 2000). These studies are discussed in more detail in Chapter 2, sections 2.3.3 (pg 30) & 2.4.4.1 (pg 62). Samson-Fang et al concluded that the best indicator of suboptimal fat stores and malnutrition was using triceps skinfold cut-off value of <10th centile for age and sex rather than weight-for-height (Samson-Fang and Stevenson 2000).

These findings suggest that the commonly used Waterlow classification system of weight-for-height as an indicator of malnutrition with wasting may be inappropriate for this group of children (Waterlow 1972). One possible explanation for this incongruity is that the use of knee height to estimate height could result in false elevation of weight-for-height because this method has not been cross-validated in children with CP. Another possible explanation is that malnourished children with CP have abnormally high TBW as increased TBW has been reported in malnutrition (Shetty 1995). Increased TBW could result in a falsely elevated body weight and lean
body mass. Others have measured TBW in children with CP using isotope dilution methods and reported varying results which has been discussed in Chapter 2, section 2.4.4.1 (Bandini et al. 1991; Berg and Isaksson 1970; van den Berg-Emons et al. 1998). Therefore, it is plausible that the normal weight-for-height seen in this population could be due to a falsely elevated body weight due to increased body water. A study of TBW in a larger and more representative group of children specifically with quadriplegic CP is needed to verify this hypothesis. The limitations of using anthropometry in this group of children are discussed further in Chapter 8.

4.8.1.3 Irregular fat distribution

In this study it was found that the triceps skinfold thickness was reduced to a greater extent than the subscapular skinfold thickness, suggesting an irregular distribution of fat. Other studies of children with CP that have included skinfold anthropometry have shown similar irregularities in fat distribution (Samson-Fang and Stevenson 2000; Spender et al. 1988; Stallings et al. 1993a). However, as suggested by Spender et al, the apparent depletion of the triceps fat in the children with CP may be related to the arm muscle wasting due to the neurological disease.

4.8.1.4 Reduced fat-free mass

The reduction of FFM in older children compared with control data has been reported previously in a study of children with spastic quadriplegic CP; where the authors used doubly-labelled water and assumed hydration factors to estimate FFM (Stallings et al. 1995). Again this was believed to be caused by the cumulative effect over time of an inadequate dietary intake and muscle wasting from the neurological disease. We attempted to determine the effect of nutrition on growth and body composition by
conducted a nutritional rehabilitation study, the results of which are presented and discussed in Chapter 7.

4.8.2 Total body protein

In this study it was found that TBP for age, height and weight was significantly reduced in children with CP and that the body protein of children with CP differed more from control values in older children.

There have been no other studies that have measured TBP in children with CP. However, there have been a number of other studies conducted by our centre in stunted children with chronic diseases, including idiopathic short stature, chronic renal failure, chronic liver disease, and cystic fibrosis (Allen et al. 1996; Baur et al. 1991b; Baur et al. 1994; Baur et al. 2001). Like the children with CP, all of these populations had a reduced TBP for age as a percentage of that predicted from control data. However, in contrast to the children with CP, the children with idiopathic short stature and chronic renal failure had a TBP for height as a percentage of predicted from control data that was not significantly different to 100 %, i.e. they had appropriate levels of TBP for height. Thus, these children had chronic protein-energy malnutrition causing stunted linear growth. In the remaining groups, the children with CF and chronic liver disease, the mean values for TBP for height, as well as for age, as a percentage of that predicted from control data, were significantly reduced. This is a similar finding to the current study of children with CP. A reduced TBP for height is usually suggestive of acute malnutrition causing wasting (decreased weight-for-height). In fact, all three groups included individuals with acute wasting. Although, the average weight-for-height of children with CP was not significantly different from 100 %, the range was from 70 to 130 %. Therefore, the reduced TBP for height suggests acute protein-energy malnutrition, superimposed on chronic protein
depletion. Alternatively, in the children with CP, it could possibly result from a combination of protein-energy malnutrition and muscle wasting from neurological impairment and/or from lack of use, or from inaccuracies in estimating height from the knee height measurement. We attempted to determine the relative contribution of malnutrition to the low TBP for age and height by conducting a nutritional rehabilitation study, the results of which are presented and discussed in Chapter 7.

Interestingly, in the children with CP the low TBP\textsubscript{NAA} for height is in contrast to the finding of a normal LTM\textsubscript{DXA} for height. One possible explanation for this discrepancy could be that the children with CP have increased hydration, since increases in TBW have been associated with malnutrition (Shetty 1995). Water is included in the LTM\textsubscript{DXA} measurement, but is not part of TBP. Alternatively, the discrepancy found between these two measures could be due to the inaccuracies in estimating height from the knee height measurement. These two possible explanations are expanded on further in Chapter 8 in the limitations to the study.

### 4.8.3 Body composition by dual-energy x-ray absorptiometry

#### 4.8.3.1 Bone mineral content

The BMC of the children with CP was significantly reduced in comparison with similar aged controls. However, this was not surprising considering that the children with CP were significantly reduced in body size (height and weight) in comparison with the controls. However when the BMC was adjusted for both height and LTM, following the methods of Högler et al for stunted children, it remained reduced (Hogler et al. 2003).

In addition, BMC was highly correlated with age as well as measures of muscle mass, i.e. LTM\textsubscript{DXA}, TBP\textsubscript{NAA}, and FFM\textsubscript{SKIN}. However, BMC SD score for age was negatively
correlated with age, demonstrating that in the older children with CP their BMC deviated further from control values than in the younger age groups.

### 4.8.3.2 Lean tissue mass and body fat

\( \text{LTM}_{\text{DXA}} \) and \( \text{FM}_{\text{DXA}} \) were significantly reduced in children with CP compared with controls. \( \text{PBF}_{\text{DXA}} \) was significantly lower in females with CP compared to controls, but was not different to the controls in males with CP. In addition, \( \text{LTM}_{\text{DXA}} \) adjusted for height was within normal ranges, which is in contrast to the reduced \( \text{TBP}_{\text{NAA}} \) for height, as discussed in section 4.8.2.

### 4.8.3.3 Comparisons with other studies

Other studies have assessed bone mineralisation in children with CP. The two largest studies involved children with varying severities of CP, rather than just those with quadriplegic CP (Henderson et al. 1995; Henderson et al. 2002a). Using DXA, the researchers measured areal BMD of the femur and spine, which were both found to be severely diminished in comparison with age-matched controls. The results of the two studies are difficult to compare with the current study as the populations were not as severely affected, they measured areal BMD in two specific sites rather than total body BMC, and there was no adjustment made for height or LTM.

Chad et al measured total body BMC by DXA in a small population of children with varying degrees of spastic CP, the majority of which were wheelchair-bound (Chad et al. 2000). The total body BMC for age SD score was -1.8 as compared to -2.6 SD score in the current study. They then compared the results with developmentally age-matched controls determined by pubertal status. The mean bone mineralisation of children with CP was around -0.5 SD score compared with developmental age-matched controls, but again there was no adjustment made for body size or LTM.
It is important to note that BMD as assessed by DXA is not a true volumetric density, but rather, it is the mass of bone mineral per projection area (g/cm$^2$) and is given the term “areal BMD” (aBMD). Areal BMD is a size-dependent measure. Shorter children, such as those with CP, therefore have a reduced aBMD compared to age-matched controls. Children with chronic illness frequently have short stature resulting from their primary disease or its treatment, and may have a reduction in aBMD, not because there is anything abnormal with the composition or structure of their bones, but simply because the bones are small. It is therefore important to correct for height when interpreting aBMD (Munns and Cowell 2005). In fact in a small study of 13 children with CP, using peripheral quantitated CT, the authors found that children with CP have smaller and thinner bones, leading to an overall reduced bone strength, and not a lower BMD (Binkley et al. 2005).

Nevertheless, the results of the studies support our findings of a decreased bone mineralisation for age which could possibly lead to an increased fracture risk. Hypotheses for the poor bone mineralisation found in children with CP can again be divided into nutritional and non-nutritional, or neurological, factors. Nutritional factors include oral motor dysfunction resulting in poor nutrition including a low calcium intake (Henderson et al. 1995). Non-nutritional contributing factors are lack of weight bearing activity; periods of immobilisation after multiple operative procedures; anticonvulsant medication interfering with vitamin D metabolism; lack of exposure to sunlight and metabolic bone disease associated with prematurity. In the current study a relation between advancing age and declining BMC SD score was found. This finding is supported by Henderson et al who found the same relation in three studies of children with varying severities of CP (Henderson 1997; Henderson et al. 2002a; Henderson et al. 2004). It has been postulated that again this is due to the
cumulative effects over time of a combination of lack of weight bearing activity and poor nutrition. However, in the current study no correlation or relation was found between BMC and nutrition (measures of body fatness, calcium intake, method of feeding - tube or oral), or with anti-epileptic medication use, possibly because the study population was relatively homogeneous.

4.8.3.3.1 Nutritional influences on bone mineralisation

In contrast to our findings, Henderson et al found a positive correlation between nutritional status assessed by a combination of skinfold thicknesses, BMI, and caloric intake, and BMD SD score of the proximal and distal femur and lumbar spine (Henderson et al. 1995; Henderson et al. 2002a). Furthermore, in one of their studies, the use of a feeding tube was associated with lower BMD SD scores in the femur. However, their studies included children with differing severities of CP, and it was found in one of their studies that bone mineralisation was negatively correlated with the severity of CP (Henderson et al. 2002a). Also children with more severe forms of CP are more likely to be non-weight bearing and to have a poorer nutritional status because of increased oral motor dysfunction, and are therefore more likely to be tube-fed. In addition, energy intake was determined by a food frequency questionnaire which is designed to obtain qualitative not quantitative data (Gibson 1990). Therefore, their results are possibly confounded by these factors. In the latter study the authors conducted a multi-factorial analysis to account for the confounders, they found that a lower triceps skinfold thickness SD score independently contributed to lower BMD SD scores in the femur (Henderson et al. 2002a). A further analysis of this data published in 2004 reported that weight SD score was the best single predictor of BMD SD score (Henderson et al. 2004). Their results suggest that a better nutritional status could improve bone mineralisation. Until now, this had not been investigated by a
longitudinal nutritional rehabilitation study. We attempted to study the influence of weight gain and an improved nutritional status on bone mineralisation, the results of which are discussed in section Chapter 7.

4.8.3.3.1 Calcium intake

In a study of children with varying degrees of CP, Henderson et al found that those children with low calcium intakes (<500 mg/day), determined by food frequency questionnaire, had a significantly lower BMD than those children with higher calcium intakes (at least 500 mg/day) (Henderson et al. 1995). However, they found no significant increase in the BMD of those children with calcium intakes of 500 to 1200 mg/day and more than 1200 mg/day. Furthermore, in another similar study by the same group they found no correlation between BMD and calcium intake, also estimated by a food frequency questionnaire (Henderson et al. 2002a). As mentioned in the previous section food frequency questionnaires are designed to obtain qualitative not quantitative data, and this may be the reason that the authors found conflicting results.

Jekovec-Vrhovsek et al conducted a study to determine the effect of vitamin D (0.25 ug/day) and calcium supplementation (500 mg/day) on lumbar BMD in a group of non-ambulatory children with CP (Jekovec-Vrhovsek et al. 2000). After a nine-month supplementation period, they found that lumbar BMD greatly increased in the treated group (n = 13) (0.383 vs. 0.476 g/cm²), while in the observed group (n = 7) lumbar BMD significantly decreased (0.393 vs. 0.315 g/cm²). However, dietary intake of calcium was not assessed for either group, and the level of supplementation of calcium was relatively low, therefore, it is unknown whether the intervention group did have a significantly higher calcium intake than the control group. In addition, as Henderson et al reported, most fractures in children with CP occur in the femur, and
lumbar BMD has been found to correlate weakly with distal femur BMD, therefore studying lumbar BMD may be less clinically relevant in this population (Henderson et al. 2002a).

4.8.3.3.2 Neurological influences on bone mineralisation

In this study it was difficult to determine the influence of the non-nutritional or neurological factors on bone mineralisation because our population was relatively homogeneous. However, our finding of a relation between advancing age and declining BMD SD score is supported by Henderson et al who found the same relation in three studies of children with varying severities of CP. It has been postulated that again this is due to the cumulative effects over time of a combination of neurological and nutritional influences (Henderson 1997; Henderson et al. 2002a; Henderson et al. 2004).

4.8.3.3.2.1 Anticonvulsant medication use

Sixty-eight percent of our population had epilepsy and were taking at least one anti-epileptic medication. We found no difference in BMC between those with epilepsy and those without. This finding is partly supported by Henderson et al who also found no significant difference in the BMD of the proximal femur between those children with and without epilepsy, but did find a significant difference between these children in the lumbar BMD SD score (Henderson et al. 1995). In contrast, in another similar study by the same group of authors, they found that use of anti-epileptic medications was correlated with BMD SD score of the distal femur, but not the lumbar spine (Henderson et al. 2002a). These contradictory findings could be because their study populations included children with varying degrees of CP, and the incidence of epilepsy is higher in those with more severe CP. In turn, the children with more severe
CP such as those with quadriplegic CP are likely to be non-weight bearing and have a poorer nutritional status and therefore the results are likely to be confounded by these factors. In fact, the authors reported that in their earlier study the correlation between BMD SD score and use of anti-epileptic medications ceased to exist when these confounding factors were controlled for.

### 4.8.3.3.2.2 Lack of weight bearing activity

In this study we were not able to determine the impact of a lack of weight bearing activity on BMC because all of our population was non-ambulatory. However, several other studies have shown a relationship between lack of weight bearing activity and poor bone mineralisation (Henderson et al. 1995; Henderson et al. 2002a; Henderson et al. 2004).

Lin & Henderson attempted to investigate whether the poor bone mineralisation found in children with CP was related to the underlying brain injury or to malnutrition (Lin and Henderson 1996). The authors studied children with spastic hemiplegic CP in order to use their unaffected side as the control, and to control for confounding variables such as nutritional factors, vitamin D levels and anti-epileptic medications. The authors found that the total BMC in the involved limb averaged 21% less than in the contralateral unininvolved limb. In addition, the average bone size (area) was reduced by 16.2% and bone density by 5.6%. LTM was also reduced by 14.8%; however there was no difference in fat content. The authors proposed that relative disuse and lack of purposeful activity may have contributed to the diminished muscle mass and BMC. These findings support the hypothesis that at least some of the poor growth and bone mineralisation seen in children with CP is unrelated to malnutrition.
4.8.3.3.2.3 Relation between bone mineral content and lean tissue mass

The relation between BMC and measures of LTM has been shown to exist in normal children, suggesting that peak BMC is determined by the amount of LTM (Ogle et al. 1995). This implies that a poor muscle mass may predispose children with CP to a low bone mineralisation which, in turn, could minimise the attainment of peak bone mass, and therefore increase the risk of fractures in adulthood. However, it is difficult to prove this association and simply because two factors are strongly related it does not necessarily infer causality.

In conclusion, the factors that contribute to a decreased bone mineralisation in children with CP are multi-factorial and include both nutritional and non-nutritional factors.

4.8.4 Tube-fed versus oral-fed children with cerebral palsy

In this cross-sectional study, the tube-fed children with CP, in comparison with the oral-fed children, had on average a significantly higher weight, weight-for-height, and PBF, but did not differ significantly in their TBP or BMC.

There have been only three other cross-sectional studies that have compared the body composition of tube-fed and oral-fed children with quadriplegic CP (Fung et al. 2002; Kong and Wong 2005; Stallings et al. 1995). In one study, the authors derived FM and FFM from measurements of TBW and found that children with a gastrostomy tube had nearly twice as much FM as those without (4.2 vs. 2.4 kg, respectively), but they did not differ significantly in their FFM (Stallings et al. 1995). However, the authors did not report if there were differences in weight or height between the two groups. The second study also reported in their cohort study of children with CP, that when the tube-fed children were compared with those of similar disability but who
were fed orally, greater height, triceps, and subscapular SD scores and less respiratory illness were observed (Fung et al. 2002). In the third study, the authors compared weight-for-height measurements and skinfold thicknesses in tube-fed and oral-fed children with CP and found that the tube-fed children had greater fat stores and weight-for-height (Kong and Wong 2005). However, the latter two studies did not include a measure of muscle mass, nor did any of the studies include a direct measure of body protein or bone mineralisation. The effect of gastrostomy tube feeding on body protein and bone mineralisation was explored further in a longitudinal nutritional rehabilitation study, the results of which are presented in Chapter 7.

These finding of this cross-sectional study as well as recommendations and future directions for study are discussed in more detail in Chapter 8.
CHAPTER 5

STUDY 2

COMPARISON OF METHODS
5 Study 2 - Comparison of methods

5.1 Introduction
The sophisticated technology used in this study to measure body composition, i.e. NAA and DXA, is not always readily accessible, particularly in the clinic or community setting. Therefore we sought to determine whether alternate simpler measures of body composition, such as skinfold anthropometry, can accurately predict body composition (particularly TBP and body fat) in children with quadriplegic CP.

5.2 Aim
To compare methods for measuring body composition in children with quadriplegic CP, specifically, (i) to determine whether indirect measures of body composition can accurately predict TBP; and (ii) to compare methods for measuring PBF.

5.3 Participants

5.3.1 Children with cerebral palsy
The data collected on the 59 (22F, 37M) children with quadriplegic CP who participated in the cross-sectional study (Study 1) were used for this study to compare methods for measuring TBP and PBF.

5.3.2 Control children

5.3.2.1 Total body protein
The control children for comparing methods of measuring TBP consisted of a subset of 28 (17F, 11M) children from the existing DXA and TBP control databases who underwent measurements of both DXA and TBP.
5.3.2.2 Percent body fat

The control children for comparing methods of measuring PBF consisted of 172 (84F, 88M) children from the existing DXA database who underwent measurements of both DXA and skinfold anthropometry.

5.4 Study protocol

The children underwent measurements of skinfold anthropometry, TBP by NAA and DXA as described in detail in Chapter 3.

5.4.1 Total body protein

TBP was calculated from the DXA measurement (TBP\text{DXA}) and also from skinfold anthropometry (TBP\text{SKIN}) following the method of Fuller et al (Fuller et al. 2001) as:

\[
\text{TBP} = \text{LTM} - \text{non-osseous mineral} \times (0.2305 \times \text{BMC}) - \text{estimated TBW} \times (\text{FFM} \times \text{hydration constant of FFM} (\text{HC}_{\text{FFM}})).
\]

For TBP\text{DXA}, the FFM was calculated as the sum of the two non-fat components, LTM\text{DXA} and BMC. For TBP\text{SKIN}, the LTM was calculated as FFM\text{SKIN} minus BMC, where BMC was measured by DXA. Age and sex specific HC\text{FFM} were used for the estimation of TBW (see Appendix D) (Fomon et al. 1982; Lohman 1986). The TBP\text{DXA} and TBP\text{SKIN} were then compared with the TBP derived from the direct assessment method of NAA (TBP\text{NAA}) using Bland & Altman plot analysis.

5.4.2 Percent body fat

PBF\text{DXA} was compared with PBF\text{SKIN} using two different sets of equations (Appendix B):

(1) With four skinfold thicknesses (biceps, triceps, subscapular, and supra-iliac) using the equations of Brook (for prepubertal children) and Durnin & Rahaman (for pubertal children) (PBF\text{SKIN-A}), and
(2) With two skinfold thicknesses (triceps and subscapular) using the equations of Slaughter (PBF_{SKIN-B}).

5.5 Results

5.5.1 Comparison of methods for measuring total body protein

TBP values derived from NAA, DXA and skinfold anthropometry are shown in Table 5.1 (pg 141).

5.5.1.1 Comparison of total body protein derived from neutron activation analysis and dual-energy x-ray absorptiometry

For the children with CP, complete data sets of both DXA and TBP measurements were obtained on 49 (20F, 29M) of the 59 study participants. The TBP_{NAA} measurements of six children were discarded due to the decay and subsequent replacement of the radioactive sources, one child did not have a DXA scan, and a further three children with metallic implants were removed from the DXA data set.

There was a strong positive correlation between TBP_{NAA} and TBP_{DXA} in the children with CP, \( r = 0.91, \ p < 0.001 \), and the control group \( r = 0.99, \ p < 0.001 \) (Figure 5.1, pg 143).

Bland & Altman plots were constructed to test agreement between TBP_{NAA} and TBP_{DXA} (Figure 5.2, pg 144). For the children with CP, there was a mean difference between TBP_{DXA} and TBP_{NAA} of 0.1 ± 0.5 kg. As shown in Figure 5.2 and Table 5.1, the 95 % range of agreement was -0.9 to 1.1 kg (-2 SD to +2 SD). For the average child in this study, this equated to a variation of 1.0 kg, or 33.3 %. Conversely, for the control children, TBP_{DXA} underestimated body protein by a mean of 1.0 ± 0.6 kg with a variation of ± 15.4 %. In addition, in the control group there was a significant negative slope for mean difference versus average in Figure 5.2 (\( r = 0.74, \ p < 0.001 \),
indicating a systematic error when estimating body protein by DXA, i.e. DXA increasingly underestimated TBP as body protein increased.

Statistical analysis (univariate ANCOVA) revealed that the pattern of the Bland & Altman plots was significantly different between the children with CP and the controls (p = 0.02).

Furthermore, as previously reported in Chapter 4, there was a significant positive correlation between $\text{LTM}_{\text{DXA}}$ and $\text{TBP}_{\text{NAA}}$ in both the children with CP and the control group; $r = 0.88, p < 0.001$ (n = 49), $r = 0.99, p < 0.001$ (n = 28), respectively.
Table 5.1 Comparison of methods for measuring total body protein

<table>
<thead>
<tr>
<th></th>
<th>CP</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 49 (20F, 29M)</td>
<td>n = 28 (17F, 11M)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>95% limits of</strong></td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td><strong>Difference</strong></td>
<td><strong>agreement</strong></td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>95% limits of</strong></td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td><strong>Difference</strong></td>
<td><strong>agreement</strong></td>
</tr>
<tr>
<td>TBP&lt;sub&gt;NAA&lt;/sub&gt; (kg)</td>
<td>3.0 ± 1.2</td>
<td>-</td>
</tr>
<tr>
<td>TBP&lt;sub&gt;DXA&lt;/sub&gt; (kg)</td>
<td>3.1 ± 1.2</td>
<td>0.1 ± 0.5</td>
</tr>
<tr>
<td>TBP&lt;sub&gt;SKIN&lt;/sub&gt; (kg)</td>
<td>3.4 ± 1.1&lt;sup&gt;1,4&lt;/sup&gt;</td>
<td>0.3 ± 0.5&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CP, cerebral palsy; TBP<sub>NAA</sub>, total body protein derived from neutron activation analysis; TBP<sub>DXA</sub>, total body protein derived from dual-energy x-ray absorptiometry; TBP<sub>SKIN</sub>, total body protein derived from skinfold anthropometry.

<sup>1</sup> p < 0.001, significantly different from TBP<sub>NAA</sub>, paired t-test; <sup>2</sup> p < 0.001; significantly different from 0, one-sample t-test.

<sup>3</sup> Calculated from Bland and Altman plot analysis (see Figure 5.2 & Figure 5.4).

<sup>4</sup> n = 47 (18F, 29M)
Figure 5.1 Correlation between total body protein derived from neutron activation analysis and dual-energy x-ray absorptiometry

The above figure demonstrates the strong positive correlation between total body protein derived from neutron activation analysis (TBP\textsubscript{NAA}) and dual-energy x-ray absorptiometry (TBP\textsubscript{DXA}) in children with cerebral palsy (CP) and controls.

CP: $n = 49$, $r = 0.88$, $p < 0.001$

Controls: $n = 28$, $r = 0.99$, $p < 0.001$

Statistical analysis revealed a significant difference in the slopes of the regression lines for the above figure; $p < 0.001$
For children with cerebral palsy (CP), the mean difference (MD) between total body protein derived from DXA (TBP_{DXA}) and total body protein derived from neutron activation analysis (TBP_{NAA}) was 0.1 ± 0.5 kg. The 95% limits of agreement (2SD = 1.1 kg, -2SD = -0.9 kg) equate to a variation of 1.0 kg, or 33.3% when expressed as a percentage of the mean of TBP_{NAA}. (------) \( r = 0.06, p = 0.69 \).

For control children, TBP_{DXA} underestimated body protein by a MD of -1.0 ± 0.6 kg. The 95% limits of agreement (2SD = 0.1 kg, -2SD = -2.2 kg), when expressed as a percentage of the mean TBP_{NAA}, equate to a variation of ±15.4%. (------) \( r = -0.74, p < 0.001 \).

Statistical analysis revealed a significant difference in the slopes of the regression lines for the above figures; \( p = 0.02 \).
5.5.1.2 Comparison of total body protein derived from neutron activation analysis and skinfold anthropometry

For the children with CP, there were complete data sets of skinfold anthropometry, DXA (for BMC) and TBP measurements on 47 (18F, 29M) of the 59 study participants, as the TBP_{NAA} measurements of six children were discarded due to technical problems previously described, one child did not have a DXA scan, three children with metallic implants were removed from the DXA data set, and a further two children had only two out of the four skinfold thicknesses measured due to their inability to cooperate.

There was a strong positive correlation between TBP_{NAA} and TBP_{SKIN} in both the children with CP and the control group $r = 0.90, p < 0.001$ and $r = 0.99, p < 0.001$, respectively (Figure 5.3, pg 147). Bland & Altman plots were constructed to test agreement between TBP_{NAA} and TBP_{SKIN} (Figure 5.4, pg 148).

On average, TBP_{SKIN} overestimated body protein in the children with CP by $0.3 \pm 0.5$ kg (see Table 5.1, pg 142; Figure 5.4, pg 148). For the average child in this study, the 95 % limits of agreement equated to a variation of $\pm 1.0$ kg (33.3 %). For the control children, TBP_{SKIN} underestimated body protein by $0.7 \pm 0.6$ kg (see Table 5.1, pg 142; Figure 5.4, pg 148). When expressed as a percentage of the mean TBP_{NAA}, the 95 % limits of agreement equated to a variation of $\pm 16.5$ %.

In addition, in the control group there was a significant negative slope for mean difference versus average in Figure 5.4 ($r = -0.65, p < 0.001$), indicating a systematic error when estimating body protein from skinfold anthropometry, i.e. skinfold anthropometry increasingly overestimated TBP as body protein increased. Statistical analysis (univariate ANCOVA) revealed that the pattern of the Bland & Altman plots
was not significantly different between the children with CP and the controls (p = 0.46). Further analysis revealed that the intercepts of the regression lines on the y-axes were significantly different between the two groups (p < 0.001).

5.5.1.3 Correlation between total body protein and basic skinfold anthropometry

As previously reported in Chapter 4, in the children with CP there was a significant positive correlation between $\text{TBP}_{\text{NAA}}$ and $\text{FFM}_{\text{SKIN}}$ ($r = 0.86$, $p < 0.001$), weight ($r = 0.80$, $p < 0.001$), height ($r = 0.75$, $p < 0.001$), UAMA ($r = 0.69$, $p < 0.001$), and MUAC ($r = 0.56$, $p < 0.001$). In the control group there was a significant positive correlation between $\text{TBP}_{\text{NAA}}$ and $\text{FFM}_{\text{SKIN}}$ ($r = 0.98$, $p < 0.001$), weight ($r = 0.97$, $p < 0.001$), and height ($r = 0.93$, $p < 0.001$). Data on UAMA were unavailable for the control group.
Figure 5.3 Correlation of total body protein derived from neutron activation analysis and skinfold anthropometry

The above figure demonstrates the significant relation between total body protein derived from neutron activation analysis (TBPNAA) and skinfold anthropology (TBPSKIN) in both children with cerebral palsy (CP) and controls.

CP: n = 47, r = 0.90, p < 0.001
Controls: n = 28, r = 0.99, p < 0.001

Statistical analysis revealed a significant difference in the slopes of the regression lines for the above figure; p < 0.001
Figure 5.4 Bland and Altman plots for total body protein derived from neutron activation analysis and skinfold anthropometry

For the children with cerebral palsy (CP), total body protein derived from skinfold anthropometry (TBP<sub>S</sub>) overestimated body protein by a mean difference (MD) of 0.3 ± 0.5 kg. The 95% limits of agreement (2SD = 1.3 kg, -2SD = -0.7 kg), equated to a variation of 1.0 kg, or 33.3%, when expressed as a percentage of the mean of the total body protein derived from neutron activation analysis (TBP<sub>N</sub>). (-----) regression line, r = -0.17, p = 0.24.

For the control children, TBP<sub>S</sub> underestimated body protein by a MD of -0.7 ± 0.6 kg. The 95% limits of agreement (2SD = 0.5 kg, -2SD = -1.9 kg), when expressed as a percentage of the mean TBP<sub>N</sub>, equated to a variation of ± 16.5%. (-------) regression line, r = -0.65, p < 0.001.

Statistical analysis revealed no significant difference in the slopes of the regression lines for the above figures; p = 0.46; however a significant difference was found in the intercepts on the y-axes of the two figures, p < 0.001.
5.5.2 Comparison of methods for measuring percent body fat

Percent body fat values derived from DXA and skinfold anthropometry are shown in Table 5.2, pg 151. For the children with CP complete data sets of both skinfold anthropometry and DXA measurements were obtained on 53 (19F, 34M) of the 59 children, as two children did not have two of the four skinfold thicknesses measured due to their inability to cooperate, one child did not have a DXA scan due to the inability to remain motionless, and a further three children were removed from the DXA data set because they had metallic implants.

5.5.2.1 Percent fat from dual-energy x-ray absorptiometry and skinfold anthropometry (PBF\textsubscript{SKIN-A})

There was a strong positive correlation between PBF\textsubscript{DXA} and PBF\textsubscript{SKIN-A} (refer to definition section 5.4.2, pg 139) in both the children with CP and the control group $r = 0.87$, $p < 0.001$ (n = 53) and $r = 0.91$, $p < 0.001$ (n = 172), respectively (Figure 5.5, pg 152). Bland & Altman plots were constructed to test agreement between PBF\textsubscript{DXA} and PBF\textsubscript{SKIN-A} (Figure 5.6, pg 153).

For the children with CP, the Bland and Altman plots revealed a significant mean difference of $3.7 \pm 5.3\%$ between PBF\textsubscript{DXA} and PBF\textsubscript{SKIN-A}, with DXA producing a higher percent body fat in comparison to skinfold anthropometry. For the average child in this study, the 95 % limits of agreement equated to a variation of $\pm 10.5\%$.

For the control children, the Bland and Altman plots revealed a significant mean difference of $-2.3 \pm 3.4\%$ between PBF\textsubscript{DXA} and PBF\textsubscript{SKIN-A}, with DXA producing a lower percent body fat in comparison to skinfold anthropometry. The 95 % limits of agreement equated to a variation of $\pm 6.7\%$. In addition, in both the children with CP and the control group there was a significant positive slope in Figure 5.6 ($r = 0.58$, $p <$
0.001; \( r = -0.44, \ p < 0.001 \), respectively). Statistical analysis (univariate ANCOVA) revealed that the pattern of the Bland & Altman plots was significantly different between the children with CP and the controls \( (p = 0.02) \).
Table 5.2 Percent body fat derived from dual energy x-ray absorptiometry and skinfold anthropometry

<table>
<thead>
<tr>
<th></th>
<th>CP n = 53 (19F, 34M)</th>
<th>Controls n = 172 (84F, 88M)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Difference$^3$</td>
<td>95% limits of agreement$^3$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBF$^{\text{DXA}}$ (%)</td>
<td>17.5 ± 10.3</td>
<td>17.7 ± 8.0</td>
</tr>
<tr>
<td>PBF$^{\text{SKIN-A}}$ (%)</td>
<td>13.9 ± 7.2$^1$</td>
<td>3.7 ± 5.3$^2$</td>
</tr>
<tr>
<td>PBF$^{\text{SKIN-B}}$ (%)</td>
<td>11.6 ± 6.2$^1$</td>
<td>5.9 ± 5.4$^2$</td>
</tr>
</tbody>
</table>

CP, cerebral palsy; PBF$^{\text{DXA}}$, percent body fat derived from dual-energy x-ray absorptiometry; PBF$^{\text{SKIN-A}}$, percent body fat derived from skinfold anthropometry using the equations of Brook for prepubertal children, and Durnin and Rahaman for pubertal children; PBF$^{\text{SKIN-B}}$, percent body fat derived from skinfold anthropometry using the equations of Slaughter et al.

1 $p < 0.001$, significantly different from PBF$^{\text{DXA}}$, paired t-test.

2 $p < 0.001$, significantly different from 0, one-sample t-test.

3 Calculated from Bland and Altman plot analysis (see Figure 5.6 & Figure 5.8).
Figure 5.5 Correlation between percent body fat derived from dual-energy x-ray absorptiometry and skinfold anthropometry (PBF\textsubscript{SKIN-A})

The above figure demonstrates the significant relation between percent body fat derived from dual-energy x-ray absorptiometry (PBF\textsubscript{DXA}) and skinfold anthropometry using the equations of Brook for prepubertal children and Durnin & Rahaman for pubertal children (PBF\textsubscript{SKIN-A}) in both children with cerebral palsy (CP) and controls.

CP: $n = 53$, $r = 0.87$, $p < 0.001$

Controls: $n = 172$, $r = 0.91$, $p < 0.001$

Statistical analysis revealed a significant difference in the slopes of the regression lines for the above figure; $p < 0.001$. 
Figure 5.6 Bland and Altman plots for percent body fat derived from dual-energy x-ray absorptiometry and skinfold anthropometry (PBF_{SKIN-A})

For the children with cerebral palsy (CP), percent body fat derived from dual-energy x-ray absorptiometry (PBF_{DXA}) overestimated body fat by a mean difference (MD) of 3.7 ± 5.3 % in comparison with percent body fat derived from skinfold anthropometry (PBF_{SKIN-A}) using the equations of Brook for prepubertal children and Durnin & Rahaman for pubertal children. The 95 % limits of agreement (2SD = 14.1%, -2SD = -6.8 %), equated to a variation of 10.5%. (----) regression line, \( r = 0.58, p < 0.001 \).

For control children, PBF_{DXA} underestimated body fat in comparison to PBF_{SKIN-A} by a MD of -2.3 ± 3.4 %. The 95 % limits of agreement (2SD = 4.4 %, -2SD = -9.0 %), equated to a variation of ± 6.7 %. (-------) regression line, \( r = 0.44, p < 0.001 \).

Statistical analysis revealed a significant difference in the slopes of the regression lines for the above figures; \( p = 0.02 \).
5.5.2.2 Percent body fat derived from dual-energy x-ray absorptiometry and skinfold anthropometry (PBF\textsubscript{SKIN-B})

There was a strong positive correlation between PBF\textsubscript{DXA} and PBF\textsubscript{SKIN-B} (refer to definition in section 5.4.2, pg 139) in both the children with CP and the control group; $r = 0.89$, $p < 0.001$ (n = 53) and $r = 0.91$, $p < 0.001$ (n = 172), respectively (Figure 5.7, pg 156). Bland & Altman plots were constructed to test agreement between PBF\textsubscript{DXA} and PBF\textsubscript{SKIN-B} (Figure 5.8, pg 157).

For the children with CP, the Bland & Altman plots revealed a mean difference of 5.9 ± 5.4 % between PBF\textsubscript{DXA} and PBF\textsubscript{SKIN-B}, with DXA producing a higher percent body fat in comparison to skinfold anthropometry (see Table 5.2, pg 151). For the average child in this study, the 95 % limits of agreement equated to a variation of ± 10.5 %.

For the control children, the Bland and Altman plots revealed a mean difference of 0.9 ± 3.5 % between PBF\textsubscript{DXA} and PBF\textsubscript{SKIN-B}, with DXA producing a higher percent body fat in comparison to skinfold anthropometry. The 95 % limits of agreement equated to a variation of ± 6.8 %. In addition, in both the children with CP and the control group there was a significant positive slope in Figure 5.8, $r = 0.76$, $p < 0.001$; $r = 0.55$, $p < 0.001$, respectively. Statistical analysis (univariate ANCOVA) revealed that the pattern of the Bland & Altman plots was significantly different between the children with CP and the controls ($p < 0.001$).

5.5.2.3 Correlations between percent body fat and skinfold anthropometry

Correlation analysis revealed that of the four skinfold thicknesses (triceps, biceps, subscapular and suprailiac) and UAFA, the triceps skinfold was most highly correlated with PBF derived from DXA and from skinfold anthropometry, using either equation, in both the children with CP and the control group. The results are as
follows for the triceps skinfold thickness: in the children with CP, for $\text{PBF}_{\text{DXA}}, r = 0.87, p < 0.001$; for $\text{PBF}_{\text{SKIN-A}}, r = 0.85, p < 0.001$; for $\text{PBF}_{\text{SKIN-B}}, r = 0.96, p < 0.001$; in the control children, $\text{PBF}_{\text{DXA}}, r = 0.84, p < 0.001$; for $\text{PBF}_{\text{SKIN-A}}, r = 0.87, p < 0.001$; for $\text{PBF}_{\text{SKIN-B}}, r = 0.95, p < 0.001$. 
Figure 5.7 Correlation between percent body fat derived from dual-energy x-ray absorptiometry and skinfold anthropometry (PBF<sub>SKIN-B</sub>)

The above figure demonstrates the significant relation between percent body fat derived from dual-energy x-ray absorptiometry (PBF<sub>DXA</sub>) and skinfold anthropometry using the equations of Slaughter (PBF<sub>SKIN-B</sub>) in both children with cerebral palsy (CP) and controls.

CP: n = 53, r = 0.89, p < 0.001

Controls: n = 172, r = 0.91, p < 0.001

Statistical analysis revealed a significant difference in the slopes of the regression lines in the above figure, p < 0.001.
Figure 5.8 Bland and Altman plots for percent body fat derived from dual-energy x-ray absorptiometry and skinfold anthropometry ($\text{PBF}_{\text{SKIN-B}}$)

For children with cerebral palsy (CP), percent body fat derived from dual-energy x-ray absorptiometry ($\text{PBF}_{\text{DXA}}$) overestimated body fat by a mean difference (MD) of $5.9 \pm 5.4\%$ in comparison to percent body fat derived from skinfold anthropometry ($\text{PBF}_{\text{SKIN-B}}$) using the equations of Slaughter. The 95% limits of agreement (2SD = 16.5%, -2SD = -4.6%), equated to a variation of 10.5%. ($\cdots\cdots$) regression line, $r = 0.76$, $p < 0.001$.

For control children, $\text{PBF}_{\text{DXA}}$ overestimated body fat in comparison to $\text{PBF}_{\text{SKIN-B}}$ by a MD of $-0.9 \pm 3.5\%$. The 95% limits of agreement (2SD = 7.7%, -2SD = -5.9%), equated to a variation of $\pm 6.8\%$. ($\cdots\cdots\cdots\cdots$) regression line, $r = 0.55$, $p < 0.001$.

Statistical analysis revealed a significant difference in the slopes of the regression lines for the above figures; $p < 0.001$.  

For children with cerebral palsy (CP), percent body fat derived from dual-energy x-ray absorptiometry ($\text{PBF}_{\text{DXA}}$) overestimated body fat by a mean difference (MD) of $5.9 \pm 5.4\%$ in comparison to percent body fat derived from skinfold anthropometry ($\text{PBF}_{\text{SKIN-B}}$) using the equations of Slaughter. The 95% limits of agreement (2SD = 16.5%, -2SD = -4.6%), equated to a variation of 10.5%. ($\cdots\cdots$) regression line, $r = 0.76$, $p < 0.001$.

For control children, $\text{PBF}_{\text{DXA}}$ overestimated body fat in comparison to $\text{PBF}_{\text{SKIN-B}}$ by a MD of $-0.9 \pm 3.5\%$. The 95% limits of agreement (2SD = 7.7%, -2SD = -5.9%), equated to a variation of $\pm 6.8\%$. ($\cdots\cdots\cdots\cdots$) regression line, $r = 0.55$, $p < 0.001$.

Statistical analysis revealed a significant difference in the slopes of the regression lines for the above figures; $p < 0.001$. 

Figure 5.8 Bland and Altman plots for percent body fat derived from dual-energy x-ray absorptiometry and skinfold anthropometry ($\text{PBF}_{\text{SKIN-B}}$)
5.6 Summary

Comparison of methods to measure TBP found significant correlations between skinfold anthropometry and NAA, and between DXA and NAA. Simple anthropometric measures of FFM and UAMA, as well as LTM by DXA, were also found to correlate well with TBP by NAA. Despite these significant correlations, agreement between the methods revealed that both skinfold anthropometry and DXA produced wide and unacceptable individual variation in the estimation of TBP in children with CP and in the control population.

Comparison of methods to measure PBF found a strong positive correlation between PBF derived from DXA and skinfold anthropometry in both the children with CP and controls. Yet method agreement analysis revealed wide variation in both groups, with a larger variation seen in the children with CP. On average, DXA produced a higher PBF than skinfold anthropometry, using either equation, in the children with CP. However, in the control group, DXA on average produced a lower PBF than skinfold anthropometry using the Brook, Durnin & Rahaman equations, but a slightly higher PBF compared to the Slaughter equations. In addition in both groups, DXA appeared to underestimate PBF in the lower ranges of fat, and overestimate PBF in the higher ranges in comparison to skinfold anthropometry.

5.7 Discussion

5.7.1 Comparison of methods to measure body protein

5.7.1.1 Significance of findings

Comparison of methods to measure TBP revealed significant correlations between TBP derived from DXA and skinfold anthropometry with TBP derived from NAA. Furthermore, significant correlations were found between simple anthropometric
measures of FFM and UAMA, as well as LTM by DXA, with TBP by NAA, demonstrating that both of these methods can be used as indicators of body protein. However, method agreement analysis found that for individuals DXA and skinfold anthropometry do not provide accurate estimates of TBP.

5.7.1.2 Comparisons with other studies

There have been no other studies that have measured TBP in children with CP. However, Fuller et al, in healthy children, compared TBP estimated from a 4C model with that from DXA using the same methodology as this study (Fuller et al. 2001). In agreement with the findings from this study of children with CP, they reported that DXA provided an acceptable estimate of TBP for the group, but found considerable individual variation suggesting that the methods are not interchangeable for assessing individuals. However, in contrast to this study, the authors did not measure body protein directly. To derive TBP using the 4C model they combined measurements of body water, BMC and FM and subtracted the total from body weight. This method does not take into account the presence of other body components such as glycogen, free amino acids, nucleic acids, and urea. The authors acknowledge that such components were most likely to be included in the estimate of TBP. However, they point out that such components are also included in the DXA model for estimating body protein because components that are not either measured or predicted (e.g. free glycogen, free amino acids) are included with the estimate of TBP. Interestingly, the study showed that incorporating estimated rather than measured hydration factors for FFM in the DXA model improved its accuracy for predicting TBP and also reduced it variability in predicting TBP for individuals. The authors hypothesise that this may have occurred because when an individual’s hydration deviates further from the assumed population-specific constant, which could be the case in children with CP;
discrepant measurements of fat-free soft tissue (FFST) would be obtained. Under such circumstances, discrepant FFST assessments would lead to erroneous estimates of TBP when measured TBW is then integrated into the DXA model i.e. although TBW is correct, the difference between FFST and TBW is incorrect and it was by difference that TBP was calculated.

Using similar methodology to this study, but in adult patients undergoing peritoneal dialysis, Borovnicar found that on average for the group FFM from DXA was similar to FFM derived from a 4C model of body composition using direct measurement of TBP by NAA (Borovnicar et al. 1996). However, again there was wide individual variation suggesting that DXA may be accurate to derive body protein for groups, but not for individuals. Furthermore, they reported that DXA increasingly overestimated FFM in individuals with increasing levels of over-hydration, and vice versa.

5.7.2 Comparison of methods to measure percent body fat

5.7.2.1 Significance of findings

Comparison of methods to measure PBF revealed poor agreement between PBF derived from DXA and PBF derived from skinfold anthropometry, using either equation. However, correlation analysis revealed strong positive correlations between the triceps skinfold thickness and PBF derived from DXA and skinfold anthropometry, using either equation, indicating that the triceps skinfold thickness can be used in the clinic setting as an indicator of fat stores. Further studies, using a 4C model of body composition, need to be done in order to validate both skinfold anthropometry and DXA as an accurate measure of PBF.
5.7.2.2 Comparisons with other studies

Van den Berg-Emons compared PBF measured by skinfold anthropometry with that derived from the deuterium dilution ($D_2O$) technique in a small group of children with CP ($n = 22$) and healthy controls ($n = 10$) (van den Berg-Emons et al. 1998). Like the current study, they also compared PBF derived from the Durnin and Rahaman equations and with that derived from the Slaughter equations. Overall, they found that PBF predicted from skinfold anthropometry, using either equation, was significantly lower than that determined by the $D_2O$ technique in the children with CP, but not in the controls. Interestingly, they also found a similar correlation to this study, that $D_2O$ (rather than DXA) underestimated PBF in the lower ranges of fat and overestimated PBF in the upper ranges compared with PBF from skinfold anthropometry.

The authors hypothesised that a proportionally large internal fat deposit and a different distribution of subcutaneous fat may be responsible for their finding. On the other hand, the $D_2O$ technique uses assumed hydration factors, and as discussed in the previous Chapter, these may not be applicable to children with CP. The authors do in fact acknowledge this, and state that in the event of a higher proportion of water in FFM the discrepancies found between PBF derived from skinfold anthropometry and $D_2O$ would be even more pronounced because, using the $D_2O$ technique, an increase in the hydration factor would diminish calculated FFM and body fat would appear increased (Bandini et al. 1991). This could account for the difference in findings between the children with CP and controls. Alternatively, the lack of difference in the control group could be due to the small number of children studied.

In a similar study to that of van den Berg-Emons, Stallings et al also found that FM derived from skinfold anthropometry, using the Slaughter equations, was significantly lower than that derived from $D_2O$ in the children with spastic quadriplegic CP ($n = \ldots$)
28), but was not significantly different in the control group (n = 39) (Stallings et al. 1995).

The only study to compare PBF derived from both skinfold anthropometry and DXA with a dilution technique ($^{18}$O) in people with CP was done in adults (Hildreth et al. 1997). The authors reported that they found no significant difference between PBF measured by DXA and $^{18}$O dilution (mean difference 0.06 ± 9.6 %), but found a large discrepancy between PBF derived from skinfold anthropometry and $^{18}$O dilution (mean difference -6.3 ± 12.3 %). However the limits of agreement for DXA versus $^{18}$O dilution were wide 9.67 % to -9.56 %, and, like the current study and that of van den Berg-Emons, they also found a significant positive correlation between the mean versus the difference on the Bland and Altman plot. This suggests a bias with DXA at the low and high ranges of body fatness particularly in people with CP. Yet surprisingly the authors concluded that DXA had good agreement with the $^{18}$O dilution technique and is therefore an accurate measure of body composition, which may have been the case for the total group, but not for individuals.

In conclusion, simple skinfold anthropometry can be used in the clinic setting as indicators of body protein and body fat, but they cannot be used to provide an accurate estimate of these body compartments. Further studies using a 4C model of body composition are required in order to validate the use of DXA and skinfold anthropometry as accurate and precise measures of body composition in children with CP. In the 4C model used for validation, gold standard techniques must be used, i.e. TBW is measured by dilution techniques, TBP by NAA, BMC by DXA, and then body fat is determined by subtracting the sum of TBW, TBP, and BMC from body weight. This recommendation as well as limitations of the study and future directions are discussed further in Chapter 8.
CHAPTER 6

STUDY 3

RESTING ENERGY EXPENDITURE

AND DIETARY INTAKE
6 Study 3 - Resting energy expenditure and dietary intake

6.1 Introduction

There have been a limited number of studies measuring REE in children with CP, and only one study that has related measured REE with dietary intake and body composition parameters. REE and dietary intake is important to assess in this group of children so that dietitians and clinicians can tailor their advice and/or nutritional therapies to suit the specific requirements, and optimise the care, of these children.

6.2 Aims

To measure REE and energy and nutrient intake in children with quadriplegic CP, and to relate these measures to their body composition.

6.3 Resting energy expenditure by indirect calorimetry

6.3.1 Participants

6.3.1.1 Children with cerebral palsy

Forty (12F, 28M) of the 59 children with CP who participated in the cross-sectional study (Study 1) underwent measurements of REE by indirect calorimetry. As previously mentioned, the first 17 (8F, 9M) children with CP enrolled in the cross-sectional study did not have their REE measured because it was not part of the study protocol at that stage. A further two (2F) children with CP declined to have their REE measured. In addition, one female with CP had an REE that was more than two standard deviations above the mean of the group and her data were removed from the analyses.
6.3.1.2 Control children

The control children for this study was from a separate control database consisting of 111 (42F, 69M) healthy children who had undergone REE measurements at CHW on the same machine (unpublished data).

6.3.2 Study protocol

The children with CP and the controls underwent measurements of REE and anthropometry as outlined in Chapter 3.

6.3.3 Data analysis

All data were analysed as outlined in Chapter 3 using the programme SPSS (version 11.5.1, SPSS Inc, Chicago, USA). The significance level was set at $p < 0.05$. The measured REE of the children with CP was compared with:

(i) predicted REE using the Schofield equations based on body weight ($\text{PREE}_{\text{SCHO}}$); and with

(ii) predicted REE using equations developed from the control database based on $\text{FFM}_{\text{SKIN}}$ ($\text{PREE}_{\text{CTRL}}$).

6.3.4 Results

The anthropometric characteristics of the children with CP and controls are shown in Table 6.1 (pg 167). The children with CP were of similar age to the control group, however, they were significantly shorter and lighter, and had less FFM and body fat than the controls.

The body composition parameters and measured REE were significantly different between male and female controls, but not between male and females children with CP; therefore the data for measured REE were analysed with sexes separated.
However, the data for predicted REE and percent of measured versus predicted was analysed with sexes combined because the predictive equations are adjusted for sex.

6.3.4.1 Measured versus predicted resting energy expenditure from Schofield equations

In the male and female children with CP, the measured REE was significantly lower than predicted using the Schofield equations for age and weight (Table 6.2, pg 168). Whereas, in the control group, the measured REE was significantly lower than predicted in the females and significantly higher than predicted in the males. Therefore, new predictive equations were developed using the control database.
<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CP</strong></td>
<td>Controls</td>
<td><strong>CP</strong></td>
</tr>
<tr>
<td>N = 11</td>
<td>N = 42</td>
<td>N = 28</td>
</tr>
<tr>
<td>Age (y)</td>
<td>9.2 ± 2.6</td>
<td>9.4 ± 2.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>120.0 ± 18.5&lt;sup&gt;1&lt;/sup&gt;</td>
<td>137.6 ± 16.6</td>
</tr>
<tr>
<td>Height SDS</td>
<td>-3.3 ± 1.5&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.4 ± 1.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>18.7 ± 7.0&lt;sup&gt;1&lt;/sup&gt;</td>
<td>34.7 ± 12.5</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>-2.6 ± 0.9&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.3 ± 0.9</td>
</tr>
<tr>
<td>FFM&lt;sub&gt;SKIN&lt;/sub&gt; (kg)</td>
<td>16.4 ± 4.2&lt;sup&gt;1, 3&lt;/sup&gt;</td>
<td>27.2 ± 8.3</td>
</tr>
<tr>
<td>PBF&lt;sub&gt;SKIN&lt;/sub&gt; (%)</td>
<td>13.2 ± 8.7&lt;sup&gt;2, 3&lt;/sup&gt;</td>
<td>20.5 ± 6.4</td>
</tr>
</tbody>
</table>

Data is mean ± SD. CP, cerebral palsy; FFM<sub>SKIN</sub>, fat-free mass measured by skinfold anthropometry; PBF<sub>SKIN</sub>, percent body fat measured by skinfold anthropometry; SDS, standard deviation score.

A two-factor ANOVA was used to test for differences between CP and control group, using sex and group (CP or control) as fixed factors. A two-tailed, one-sample t-test was used to test for differences between SD scores and reference data (test value = 0).

<sup>1</sup> p < 0.001; <sup>2</sup> p < 0.05; significantly different from control group.

<sup>3</sup> n = 10
### Table 6.2 Measured versus Schofield predicted resting energy expenditure

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CP</td>
<td>Controls</td>
<td>CP</td>
<td>Controls</td>
</tr>
<tr>
<td>N = 11</td>
<td></td>
<td>N = 42</td>
<td>N = 28</td>
<td>N = 69</td>
</tr>
<tr>
<td>MREE (kJ / 24hr)</td>
<td>2044 ± 628&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4315 ± 1001</td>
<td>2919 ± 1245&lt;sup&gt;1&lt;/sup&gt;</td>
<td>6309 ± 1729</td>
</tr>
<tr>
<td>PREE&lt;sub&gt;SCHO&lt;/sub&gt; (kJ / 24hr)</td>
<td>3670 ± 585</td>
<td>4800 ± 845</td>
<td>4238 ± 650</td>
<td>5887 ± 1583</td>
</tr>
<tr>
<td>MREE / PREE&lt;sub&gt;SCHO&lt;/sub&gt; (%)</td>
<td>57.4 ± 21.0&lt;sup&gt;2&lt;/sup&gt;</td>
<td>89.4 ± 9.6&lt;sup&gt;2&lt;/sup&gt;</td>
<td>67.8 ± 24.2&lt;sup&gt;2&lt;/sup&gt;</td>
<td>107.4 ± 9.5&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data is mean ± SD. CP, cerebral palsy; MREE, measured resting energy expenditure by indirect calorimetry; PREE<sub>SCHO</sub>, predicted resting energy expenditure calculated from the Schofield equation using weight only.

A two-factor ANOVA was used to test for differences between CP and control group, using gender and group (CP or control) as fixed factors. A two-tailed, one-sample t-test was used to test for differences between measured as a percent of predicted REE (test value = 100).

<sup>1</sup> p < 0.001; significantly different from control group.

<sup>2</sup> p < 0.001; significantly different from 100 %.
6.3.4.2 Regression analysis of control data

Linear regression analysis was performed separately on the male and female control groups in order to develop predictive equations for REE. The most significant predictor of REE in both the female and male control groups was found to be FFM\textsubscript{SKIN}, followed by weight, height, age, and then FM\textsubscript{SKIN} (Table 6.3, pg 171). FFM\textsubscript{SKIN} accounted for 80% of the variance in the measured REE for female controls and 90% for male controls.

6.3.4.3 Regression analysis of cerebral palsy data

The REE data of the children with CP were combined for linear regression analysis because of the small number of females and because the body composition parameters did not differ significantly between sexes (Table 6.3, pg 171). In the children with CP the most significant predictor of REE was FFM\textsubscript{SKIN}, followed by weight, age, height, and then FM\textsubscript{SKIN}. FFM\textsubscript{SKIN} accounted for 34% of the variance in the measured REE for the CP group with sexes combined. Figure 6.1 (pg 173) demonstrates the significant relation between FFM\textsubscript{SKIN} and measured REE in both the children with CP and controls.

6.3.4.4 Predictive equations derived from control data

The following predictive equations for REE were developed from linear regression analysis of the measured REE versus FFM\textsubscript{SKIN} in the control group:

Females: $$\text{REE (kJ / 24hr)} = 1370 + 108.2 \times \text{FFM}_{\text{SKIN}} \text{ (kg)}$$

Males: $$\text{REE (kJ / 24hr)} = 2778 + 102.7 \times \text{FFM}_{\text{SKIN}} \text{ (kg)}$$
6.3.4.5 Measured resting energy expenditure adjusted for fat-free mass

The REE data of the children with CP were then re-analysed using the above predictive equations derived from the control data (Table 6.4, pg 172). The children with CP had a significantly reduced REE compared to controls.
### Table 6.3 Regression analysis of resting energy expenditure data

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th></th>
<th></th>
<th>CP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Sexes combined</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 42</td>
<td>N = 69</td>
<td>(11F, 28M)</td>
<td></td>
</tr>
<tr>
<td>FFM&lt;sub&gt;SKIN&lt;/sub&gt; (kg)</td>
<td>0.80&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.90&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.34&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.79&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.88&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.22&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.74&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.83&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.17&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.55&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.70&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.18&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FM&lt;sub&gt;SKIN&lt;/sub&gt; (kg)</td>
<td>0.55&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.49&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data is adjusted r-squared. CP, cerebral palsy; FFM<sub>SKIN</sub>, fat-free mass measured by skinfold anthropometry; FM<sub>SKIN</sub>, fat mass measured by skinfold anthropometry.

Linear regression analysis was performed using measured REE as the dependent factor with FFM<sub>SKIN</sub>, weight, height, age, TBP<sub>NAA</sub> and FM<sub>SKIN</sub> entered as separate independent variables.

<sup>1</sup> p < 0.001; <sup>2</sup> p < 0.01
### Table 6.4 Measured versus control predicted resting energy expenditure

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CP</td>
<td>Controls</td>
</tr>
<tr>
<td>N = 11</td>
<td>2044 ± 628&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4315 ± 1001</td>
</tr>
<tr>
<td>N = 42</td>
<td>3091 ± 464</td>
<td>4315 ± 900</td>
</tr>
<tr>
<td>MREE (kJ/24hr)</td>
<td>2044 ± 628&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4315 ± 1001</td>
</tr>
<tr>
<td>PREE&lt;sub&gt;CTRL&lt;/sub&gt; (kJ/24hr)</td>
<td>3091 ± 464</td>
<td>4315 ± 900</td>
</tr>
<tr>
<td>MREE/ PREE&lt;sub&gt;CTRL&lt;/sub&gt; (%)</td>
<td>68.2 ± 25.3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>100.0 ± 9.4</td>
</tr>
</tbody>
</table>

Data is mean ± SD. CP, cerebral palsy; MREE, measured resting energy expenditure by indirect calorimetry; PREE<sub>CTRL</sub>, predicted resting energy expenditure calculated from control group regression equations based on fat-free mass.

A two-factor ANOVA was used to test for differences between CP and control group, using sex and group (CP or control) as fixed factors. A two-tailed, one-sample t-test was used to test for differences between measured as a percent of predicted REE (test value = 100).

<sup>1</sup> p < 0.001; significantly different from control group.

<sup>2</sup> p < 0.001; significantly different from 100%.
The above figure demonstrates a significant relation between measured resting energy expenditure (REE) and fat-free mass measured by skinfold anthropometry (FFM_{SKIN}) in both children with cerebral palsy (CP) and controls. The figure also demonstrates that after adjustment for FFM_{SKIN}, the measured REE of children with CP is below that of controls.

CP: n = 39, r = 0.60, p < 0.001.

Controls: n = 111, r = 0.90, p < 0.001.

Statistical analysis revealed a significant difference in the slopes of the regression lines in the above figure; p < 0.001.
6.3.4.6 Influence of nutritional status and anti-epileptic medication use on resting energy expenditure

Due to the relatively low contribution of $\text{FFM}_{\text{SKIN}}$ to predict REE in children with CP, nutritional status, tube feeding, and anti-epileptic medication use were investigated as possible influences on the measured REE. Regression analysis was performed in order to investigate any significant associations between the aforementioned factors and measured REE and measured REE as a percent of REE predicted from control data. Fat mass ($\text{FM}_{\text{SKIN}}$) was chosen as an indicator of nutritional status. No significant associations were found with $\text{FM}_{\text{SKIN}}$, or with children who were fed via a tube ($n = 28$) and those fed orally ($n = 11$), with measured REE or with measured REE as a percent of REE predicted from control data (data not shown).

Twenty-seven of the 39 children with CP who had their REE measured were taking one or more anti-epileptic medications. Linear regression analysis was conducted to test if there was an influence of anti-epileptic medications on the measured REE or on the percent of measured REE versus REE predicted from control data. There was no significant association found (data not shown).
6.4 Dietary intake

6.4.1 Participants

6.4.1.1 Children with cerebral palsy
Thirty-eight of the 59 children with CP who participated in the cross-sectional study completed a three-day weighed food record.

The first 17 children enrolled in the study did not complete food records because it was not part of the study protocol at that stage. The parents/carers of a further four children with CP declined to keep food records due to lack of time.

6.4.1.2 Reference data
The energy intake of the children with CP was compared with their measured REE. Protein and micro-nutrient (vitamin and mineral) intakes were compared with Australian RDIs for age.

6.4.2 Study protocol
The study participants completed three-day weighed food records as outlined in Chapter 3.

6.4.3 Data analysis
All data were analysed using the programme SPSS (version 11.5.1, SPSS Inc, Chicago, USA). The significance level was set at p < 0.05.

Energy intake was expressed in kilojoules per day as well as a percentage of measured REE. Micronutrient intakes were expressed as a percentage of the RDI. The energy intake of the children with CP was not normally distributed and is presented as median with IQR.
A Mann-Whitney U test was used to examine differences in energy intake, expressed as a percentage of measured REE, between oral-fed and tube-fed children with CP. A two-tailed one-sample t-test was used to test if micronutrient intake, expressed as a percentage of RDI, was significantly below 100 % (test value = 100).

6.4.4 Results

The results of the three-day weighed food records are shown in Table 6.5 (pg 179).

6.4.4.1 Tube-fed

Eighteen of the 38 children who completed food records were fed either partially or completely by a gastrostomy or naso-gastric tube. Fifteen of these children received 100 % of their energy intake via tube feeds; the remaining three children received 13 %, 27 % and 34 % of their energy intake from oral feeds in addition to tube feeds.

6.4.4.2 Oral-fed

Twenty of the children with CP who completed food records were fed orally. Of this oral-fed group only eight of the food records were entirely weighed. The remaining 12 records included unweighed amounts and metric measures, e.g. “2 biscuits”, “1 slice of bread”, and metric measures, e.g. “1 cup of rice”, “3 tablespoons of mashed potato”.

6.4.4.3 Enteral formulas and supplements

Of the 18 children who were tube-fed, six were fed with PediaSure® (Abbott, Chicago, IL, USA), six with Jevity® (Abbott), two with Ensure® (Abbott), two with TwoCal HN® (Abbott), one with Osmolite (Abbott), and one child was on the ketogenic diet (a combination of MCT oil® (SHS, Liverpool, UK), Calogen® (SHS),
Carbohydrate-Free Mixture® (SHS), Polyjoule® (Nutricia, Zoetermeer, The Netherlands), and Paediatric Seravit® (SHS)).

Three children in the oral-fed group were taking a vitamin and/or mineral supplement at the time of the study. One child had 300 mg/day of calcium, another 100 mg/day of Vitamin C plus 121 mg of calcium, and the third had 1.7 mg/day of thiamine, 1.7 mg/day of iron, plus 33 mg/day of vitamin C. In addition, in the oral-fed group, five children, including one who also took a vitamin and mineral supplement, consumed enteral supplements orally; Ensure® (Abbott) (n = 4), PediaSure® (Abbott) (n = 1), and Nurture Follow-On® (Heinz, London, UK) (n = 1).

6.4.4.4 Energy and micro-nutrient intakes of children with cerebral palsy

The median energy intake of the children with CP was 5222 kJ (IQR 4392 to 6636 kJ). The energy intakes of the children with CP were widely variable and not normally distributed and are therefore presented in the text as medians with IQR. The average micro-nutrient intakes, including supplements, of the children with CP were not below recommended intakes (Table 6.5, pg 179). The energy intakes of the children with CP were compared with their measured REE, the results of which are presented in section 6.4.4.6 (pg 180).

6.4.4.5 Tube-fed versus oral-fed children with cerebral palsy

6.4.4.5.1 Energy and protein intakes

The group was then sub-divided into tube-fed and oral-fed to compare results (Table 6.5, pg 179). The median energy intake of the tube-fed group was 5020 kJ/day (IQR 4055 to 6520 kJ), which was not significantly different to the oral-fed group, 5471 kJ/day (IQR 4432 to 6794 kJ). The average protein intake of the oral-fed group was significantly higher than the tube-fed group.
6.4.4.5.2 Micro-nutrient intakes

Intakes of thiamine, magnesium, iron and zinc were significantly lower in the oral-fed group compared with the tube-fed group, but were all above or close to 100 % of the RDI.
# Table 6.5 Protein and micro-nutrient intakes of children with cerebral palsy

<table>
<thead>
<tr>
<th></th>
<th>Combined Group</th>
<th>Tube-fed</th>
<th>Oral-fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of RDI</td>
<td>% of RDI</td>
<td>% of RDI</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>281 ± 118</td>
<td>222 ± 81</td>
<td>334 ± 123&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thiamine</td>
<td>228 ± 122</td>
<td>297 ± 131</td>
<td>167 ± 72&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>182 ± 64</td>
<td>197 ± 76</td>
<td>169 ± 48</td>
</tr>
<tr>
<td>Niacin</td>
<td>220 ± 96</td>
<td>235 ± 112</td>
<td>206 ± 78</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>531 ± 340</td>
<td>620 ± 322</td>
<td>451 ± 343</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>228 ± 113</td>
<td>241 ± 72</td>
<td>216 ± 142</td>
</tr>
<tr>
<td>Magnesium</td>
<td>152 ± 70</td>
<td>181 ± 74</td>
<td>125 ± 54&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Calcium</td>
<td>103 ± 39</td>
<td>116 ± 45</td>
<td>93 ± 28</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>114 ± 40</td>
<td>105 ± 40</td>
<td>123 ± 39</td>
</tr>
<tr>
<td>Iron</td>
<td>172 ± 80</td>
<td>221 ± 77</td>
<td>128 ± 54&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Zinc</td>
<td>146 ± 80</td>
<td>198 ± 72</td>
<td>99 ± 54&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data is mean ± SD. RDI, recommended dietary intake.

Data for the oral-fed group includes nutritional supplements.

A two-tailed one-sample t-test was used to test if micronutrient intake, expressed as a percentage of RDI, was significantly different to 100 % (test value = 100).

<sup>1</sup>significantly higher than tube fed group; p < 0.01.
<sup>2</sup>significantly lower than tube fed group; p < 0.01.
6.4.4.6 Energy intake versus measured resting energy expenditure

The energy intakes of the children with CP were compared with their measured REE by indirect calorimetry. Two children with CP who completed food records did not have their REE measured. For the whole group (n = 36), the median energy intake expressed as a percentage of measured REE was 204 % (IQR 140 - 304 %); for the tube-fed group (n = 17) it was 149 % (IQR 124 – 264 %) and for the oral-fed group (n = 19) it was 272 % (IQR 190 – 410 %).

Of the children who received 100 % of their energy intake from tube feeds (n = 14), their median energy intake as a percent of measured REE was 154 % (IQR 118 – 262 %), which was not significantly different from that of the children who received some oral food as well as tube feeds (n = 3) (149 %; IQR 128 – 306 %), but was significantly lower than the oral-fed group (p = 0.006, Mann-Whitney U Test).

In the oral-fed group, the median energy intake as a percent of measured REE for the eight records that were completely weighed was 190 % (IQR 139 – 361 %) compared to 279 % (IQR 201 – 406 %; n = 12) for the partially unweighed records. This was not statistically significantly different (p = 0.20; Mann-Whitney U test).

6.4.4.7 Correlations between energy intake and resting energy expenditure

There were no significant correlations between energy intake and measured REE, in the group as a whole or when subdivided into tube-fed and oral-fed (data not shown).

6.4.4.8 Correlations between nutrient intake and body composition

A correlation analysis was not performed to test for associations between nutrient intakes and body composition parameters due to the finding that the food records were overestimated.
6.5 Summary

The REE of the children with CP was significantly reduced in comparison with the Schofield equations, which are based on weight. However, the Schofield equations did not accurately predict the REE of the control children. The equations overestimated REE in female controls and underestimated in male controls. It was found that FFM, rather than body weight, was the most significant predictor of REE in the control group and in the children with CP, accounting for 80% of the variance in female controls and 90% in males, yet accounted for only 34% in the children with CP. The REE data from the children with CP were reanalysed using the control predictive equations based on FFM, however, on average, their REE was still significantly reduced. There was also wide variation in the group, with REEs ranging from 23.5 to 125.1% of predicted from the control data.

Nutritional status, gastrostomy tube feeding, and use of anti-epileptic medications were also investigated as possible influences on the measured REE in the children with CP, but were found to be insignificant.

The dietary intake data presented in this Chapter revealed that the energy intakes of the children with CP were grossly overestimated by the weighed food records. The median reported energy intakes were double the measured REE. Furthermore, the food records of oral-fed children were overestimated to a greater extent than the tube-fed children.

Furthermore, no correlation was found between energy intake and measured REE confirming the inaccuracy of food records in this group of children.
6.6 Discussion

6.6.1 Resting energy expenditure

The measured REE of children in this study was significantly less than that of control children of a similar size and FFM.

6.6.1.1 Comparisons with other studies

In a similar study to the current study, Stallings et al studied the body composition and REE by indirect calorimetry of 61 children with spastic quadriplegic CP and a normal control group (Stallings et al. 1996). The average age, weight and PBF of the group were similar to this study, and one-quarter of the group were tube-fed, compared to approximately one-third for this study. Despite the similarities of the methods and study population to the current study, the measured REE expressed as a percentage of that predicted from the WHO equations was 91 %. While this was significantly lower than 100 %, and significantly lower in comparison to their control group (105 %), it was not reduced to the same extent as this study. The authors did not report the range of results, but the SD of the measurement of the whole group was 20 %, compared to 12 % for the control group, suggesting wide variation. Furthermore, the authors found that FFM, by skinfold anthropometry, was the most significant contributor to measured REE, however they did not report the r-squared value. They adjusted the measured REE for both FFM and fat stores based on the triceps skinfold thickness. They found that in children with low fat stores (n = 47) REE was 88 % of predicted, while for those with adequate fat stores (n = 14), it was 101 %. In this study, no significant correlation was found between REE and FM. The authors suggested that the lower REE found in the group with low fat stores may have been an adaptation to chronically low food intake, a recognised metabolic change in response
to a low energy intake. In the same study, the authors also measured TEE using doubly-labelled water. They reported that the ratio of TEE to REE, an indication of the amount of energy required above REE, was significantly lower for all children with CP (1.23), and for those with low fat stores (1.29) and those with adequate fat stores (1.07) than in the control group (1.57).

In the current study, the finding of a significantly reduced measured REE in comparison to that predicted from the Schofield equations is in contrast to the findings of Bandini et al (Bandini et al. 1991). Bandini et al studied body composition and REE, by indirect calorimetry, of nine adolescents with CP, six of whom had quadriplegic CP, four were non-ambulatory. They found no significant difference between measured REE and that predicted from the WHO equations based on weight and age (range 85 to 110 %). Their methodology was similar to the current study. However, the number of participants in their study was small, and the average age was 18.6 years, compared to 10.4 years in the current study. In addition, most of their participants were above the 95\textsuperscript{th} centile for PBF, averaging 34 %, and not all were as severely disabled as in the current study. Also in contrast to the current study, they found no significant correlation between measured REE and FFM, which may be due to their narrow range of data and small numbers. However, they did find that the measured REE was significantly lower when compared with their control group. Yet their control group was significantly taller and had a higher FFM than the group with CP and no adjustments were made for this. The authors also measured TEE by doubly-labelled water and, in agreement with Stallings et al, they reported a significantly lower TEE to REE ratio in the six non-ambulatory adolescents with CP compared with their control group; 1.23 versus 1.76, respectively.
Interestingly the same group of authors conducted another similar study a few years later, this time in a group of 12 adolescents with severe CNS disorders (Bandini et al. 1995). In contrast to their previous study, all of the participants were exclusively gastrostomy tube-fed, and the measurement of REE was performed while non-fasted. This time they found that the measured REE was only 63.7% of predicted from the WHO equations with a range of 37.8 – 96.8%, which was similar to findings from the current study. In addition, they found that the best predictor of REE was length; however there was no measure of FFM, and length was measured by summing the lengths of five segments of the body, and therefore may be inaccurate.

Azcue et al studied the REE by indirect calorimetry of 13 exclusively gastrostomy tube-fed children with spastic quadriplegic CP (Azcue et al. 1996). The results showed that the mean measured REE as a percent of predicted from the WHO equations, based on age and weight, in the children with CP was 79 ± 21% (range 50 to 112%), and in the control group 104 ± 9% (n = 21). The authors found that the best predictor of REE was ICW measured by dilution techniques (r = 0.35, p = 0.03), and reported that FFM was a poor predictor of REE.

In summary, the current study and the aforementioned studies, indicate that the energy requirements of children with CP are lower than healthy children of the same size, are widely variable and difficult to estimate using the currently available equations. On average, the recommended age-specific equations to estimate energy requirements based on healthy, physically active children, tend to overestimate the energy requirements of children with CP. However, despite the many years of research in this area, there are still no equations available to accurately estimate the energy requirements of children with CP. Thus the current recommendations are to either measure REE by indirect calorimetry, however such sophisticated technology is not
available at all centres; or to roughly estimate energy requirements using the currently available equations and adjust energy intake according to weight change.

6.6.2 Dietary intake

In a similar study of 50 children with spastic quadriplegic CP, Stallings et al also found energy intakes from three-day weighed food records were grossly overestimated in comparison with measured REE by indirect calorimetry (Stallings et al. 1996). They reported that the average energy intake was 170 % when expressed as a percentage of their measured REE. Furthermore, this was not significantly different to their control population of physically active children (160 %). Fifteen of the children in their study were tube-fed, but they did not separate them for analysis. However, they did separate children according to their fat stores based on the triceps skinfold thickness and found that children with low fat stores (n = 38) overestimated their energy intakes to a greater extent than those with adequate fat stores (n = 12), 180 % versus 150 %, respectively. The authors also measured TEE by doubly-labelled water in half of the children with CP and in most of the control group. They found that the ratio of reported energy intake to TEE, indicating the accuracy of the dietary intake data, was 0.98 in the control group, but was significantly higher in the CP children overall (1.51) and within the groups with low (1.54) and adequate (1.44) fat stores. This indicates a 44 to 54 % overestimation of reported energy intake.

The current study, and that of Stallings et al, confirms that estimating energy and nutrient intake from food records in oral-fed children with CP is difficult. The overestimation of energy intake seen in both studies may be due to food losses from spillage, vomiting and regurgitation due to the poor oral skills in this population. If this was the reason, then it would be expected that food records from exclusively
tube-fed children would be more accurate because there are no or minimal losses from spillage. In this study we found that the ratio of energy intake to measured REE of exclusively tube-fed children (1.54) was significantly lower than that of the oral-fed group (2.72), but still appeared to be overestimated compared to reports of TEE discussed in section 6.6.1.1. Similar to the current study, Azcue et al assessed energy intakes of a group of exclusively tube-fed children with CP (n = 13) and found that they were on average 1.1 times their measured REE (Azcue et al. 1996).

The verdict that the food records were overestimated is also supported by the results of the cross-sectional study, Chapter 4, which found that this group of children were severely malnourished. If the food records were an accurate estimate of their energy intakes then these children could not possibly be malnourished.

In conclusion, the results from the current study demonstrated that the REE of children with severe CP is on average greatly reduced and widely variable and does not appear to be strongly influenced by any one body composition parameter. In addition, analysis of food records found that energy intakes in oral-fed children with CP are on average grossly overestimated and are therefore of limited value in this population. Reasons for these findings including limitations of the study, recommendations and future directions are discussed further in Chapter 8.
CHAPTER 7

STUDY 4

NUTRITIONAL REHABILITATION
7 Study 4 - Nutritional rehabilitation

7.1 Introduction

Despite the many studies reporting a high incidence of malnutrition in children with severe CP there have been limited studies investigating the effects of nutritional intervention on body composition parameters. The few studies that have been done have investigated only changes in growth parameters (weight and height) and body fat, with no exploration into the effects of weight gain on TBP, BMC and REE.

7.2 Aim

To conduct a RCT of nutritional rehabilitation

(i) to compare gastrostomy tube feeding versus oral feeding using oral nutritional supplementation and speech therapy, and

(ii) to determine if nutritional rehabilitation, i.e. weight gain, results in an increase in TBP, FM, BMC, and REE in children with quadriplegic CP.

7.3 Participants

7.3.1 Recruitment of children with cerebral palsy

The parents/carers of 19 children with quadriplegic CP were approached regarding participation in a six-month RCT of gastrostomy tube feeding versus oral feeding (see Appendix G for Parent Information Sheet). These were children without gastrostomy tubes who were undergoing investigations for feeding problems and undernutrition through the Dysphagia Clinic at CHW. None of the parents/carers consented to their child participating in a RCT. The parents/carers were then given the option to choose which arm of the study they would like their child to participate in, but none agreed to participate citing lack of time and the inability to commit to a six-month trial.
However, nine agreed to participate in the cross-sectional study only. Therefore, the
decision was made to abandon the RCT. In place of this, the 39 children who took
part in the cross-sectional study, who did not have a gastrostomy tube at the time of
the study, were monitored through the Dysphagia Clinic. Any of these children who
then received a gastrostomy tube (n = 22) as part of their routine care were monitored
for weight gain and invited to undergo repeat measures after significant weight gain
(defined as a 25 % increase in body weight). This included three children who
received their gastrostomy tube less than one month prior to participating in the cross-
sectional study. In addition, a further four children who had a gastrostomy tube for at
least six months prior to the cross-sectional study and had initially failed to gain
weight, but then gained significant weight later, were also invited to have repeat
measures performed. Therefore, a total of 26 children were potentially eligible to
participate in the nutritional rehabilitation study. Please refer to Figure 7.1 (pg 193)
for a flow chart of subject participation.

A further 12 oral-fed children with quadriplegic CP who participated in the cross-
sectional study, who did not have a gastrostomy tube at the time of the study, and who
did not receive a gastrostomy tube as part of their care, were invited to have repeat
measures conducted. These children were to be used as a CP control group to compare
with the gastrostomy tube-fed group.

7.3.2 Study protocol

During an outpatient visit to CHW, the children had measurements of anthropometry,
TBP by NAA, body composition by DXA, and REE by indirect calorimetry. Parents/carers were then asked to complete a three-day weighed food record at home
for subsequent dietary analysis. These tests were conducted for the cross-sectional
study and then repeated for this study. The methods for each test are described in detail in Chapter 3.

A Parent Information Sheet detailing the study protocol was provided to all parents/carers prior to them giving written consent for their child to participate in both the cross-sectional study and the nutritional rehabilitation study (see Appendix A).

### 7.3.2.1 Nutritional intervention

The feeding regimens of the gastrostomy tube-fed children were determined by the Dysphagia Clinic dietitian. Some of the gastrostomy tube-fed children continued to eat orally, therefore their feeding regimens were designed to provide between 75% and 100% of their energy requirements through gastrostomy tube feeds using a range of commercially available, micro-nutrient complete, formulas. The energy requirements of the gastrostomy tube-fed children were initially estimated to be 1.2 times their measured REE, which was measured at the time of the cross-sectional study. Weight gain was monitored at regular intervals through the Dysphagia Clinic, and the feeding regimens adjusted according to weight gain.

The oral-fed children with CP were provided with standard dietary and speech therapy advice by the Dysphagia Clinic dietitian and speech pathologist, respectively. Advice provided by the dietitian included increasing the energy content of their diets by the addition of energy-dense food and commercially available high-energy oral supplements. Advice provided by the speech pathologist centred on modifying the texture and consistency of food and liquid in order to aid chewing and swallowing.

### 7.3.3 Control group and reference data

The data on the control children were from three separate existing control databases, as outlined below. All control children were healthy with no known medical
problems, were of a similar age range to the children with CP (4 - 19 years), and were recruited through friends and relatives of CHW staff.

1. The control group for the anthropometric and dual-energy x-ray absorptiometry (DXA) measurements consisted of 172 (84F, 88M) children from an existing DXA control database (Ogle et al. 1995). All children from this database had undergone a DXA measurement. In addition, measurements of height, weight and skinfold anthropometry were recorded at the time of the DXA measurement.

2. The control group for total body protein (TBP) consisted of data from a group of 72 (43F, 29M) children who had undergone TBP measurements at CHW (Baur et al. 1993).

3. The REE measurements of the children with CP were compared with a separate control database consisting of 111 (42F, 69M) children who had undergone REE measurements at CHW (unpublished data). In addition, measurements of height, weight and skinfold anthropometry were recorded at the time of the REE measurement.

Weight and height measurements were converted to SD scores and compared with the United States Centre for Disease Control growth reference data (Kuczmarski et al. 2000).

7.3.4 Statistics

The data for the nutritional rehabilitation study were not normally distributed and are presented as medians with IQR.

A Wilcoxon Signed Ranks test was used to compare differences between the baseline and repeat tests of the body composition parameters within each group (gastrostomy tube-fed and oral-fed).
A Mann-Whitney U test was used to compare changes in the body composition parameters between the two groups (gastrostomy tube-fed versus oral-fed).

7.4 Results

7.4.1 Participation of children with cerebral palsy

7.4.1.1 Gastrostomy tube-fed children

Of the 26 gastrostomy tube-fed children who were potentially eligible to participate in the nutritional rehabilitation study, the parents of 15 consented to have the tests repeated. The remaining 11 children either were either lost to follow-up (n = 3), failed to gain weight (n = 3), declined to have repeat measures conducted (n = 3), or were over the age of 18 years and had moved on to adult care (n = 2). Please refer to Figure 7.1 (pg 193) for the flow chart of subject participation.

In nine of the children in the gastrostomy tube-fed group, there was a median time delay of 5.0 months (IQR 3.9 to 9.2 months, min-max 0.3 to 13.7 months) between having the baseline measurement and insertion of a gastrostomy tube, therefore the median length of time of actual gastrostomy tube feeding was 10.1 months (IQR 7.1 to 34.8; min-max 3.7 to 80.4 months).

7.4.1.2 Oral-fed children

The parents/carers of nine of the 12 oral-fed children agreed for their child to have repeat measures conducted; one declined, and two were on the waiting list to have a gastrostomy tube inserted and requested to delay repeat testing until after weight gain. Of the nine who agreed to participate, only eight children had the tests repeated because one (1M) failed to attend his appointment and was unable to reschedule in time for his data to be included in the analysis.
Figure 7.1 Flow chart of subject participation

CP, cerebral palsy; REE, resting energy expenditure
7.4.2 Baseline and repeat body composition results

The baseline anthropometric characteristics of the 15 (8F, 7M) gastrostomy tube-fed children and eight (4F, 4M) oral-fed children with CP are shown in Table 7.1 (pg 198). Although there was no significant difference in age between the two groups, there was a significant difference between weight, height, LTM_{DXA}, and TBP_{NAA} at baseline testing, with the oral-fed group being significantly higher in all of the aforementioned parameters than the gastrostomy tube-fed group. This was likely to be due to the oral-fed group having less severe disease compared with the gastrostomy tube-fed group. Although all of the children in this study were defined as having severe quadriplegic CP there was still some variation in the severity of disease and therefore it is possible that the oral-fed group were less severely disabled compared with the gastrostomy tube-fed group. Furthermore, there was a significant difference between the two groups in the length of time between the baseline and repeat measurements. In the gastrostomy tube-fed group, the median time difference between baseline and repeat testing was 15.8 months (IQR 9.3 to 25.1 months; min-max 7.3 to 48.2 months), whereas in the oral-fed group the median time difference was 36.4 months (IQR 14.5 to 40.2 months; min-max 12.6 to 42.6 months). Therefore, due to the abovementioned factors, it was decided that it would be inappropriate to compare the two groups. Consequently, all data on the oral-fed group, apart from the baseline characteristics, were removed from this Chapter and are presented in Appendix H. Thus this Chapter presents the comparison of baseline and repeat measures in the gastrostomy tube-fed group only.

7.4.3 Anthropometry

The baseline and repeat anthropometric measures of the gastrostomy tube-fed group, as well as the baseline characteristics only of the oral-fed group, are shown in Table
7.1 (pg 198). In the gastrostomy tube-fed group, there was a significant increase in all body composition parameters measured by anthropometry between baseline and repeat testing.

Baseline measures of height, height SD score, and weight as a percent of ideal weight-for-height were unavailable for seven (4F, 3M) of the gastrostomy tube-fed children because the measurement of knee height was not part of the study protocol at the time of their participation in the cross-sectional study. In addition, one female did not have a complete set of skinfold thicknesses collected at baseline due to her inability to cooperate, and therefore there is no baseline data for this participant for FFM_{SKIN}, FM_{SKIN}, and PBF_{SKIN}. Furthermore, the carer of one male declined for him to have skinfold anthropometry collected at the repeat measure, and therefore there was no data for this participant for UAMA, UAFA, FFM_{SKIN}, FM_{SKIN}, and PBF_{SKIN} at repeat testing. For each parameter in Table 7.1, only those participants with both a baseline and repeat measure were included.

### 7.4.3.1 Comparison with reference data

Where possible the anthropometric measures were converted to SD scores to allow for comparison with reference data. The gastrostomy tube-fed group showed significant increases in their SD scores for weight, UAMA, and UAFA, but not height.

### 7.4.4 Body composition by dual-energy x-ray absorptiometry

The baseline and repeat body composition measures by DXA are shown in Table 7.2 (pg 199). The gastrostomy tube-fed children showed significant increases in BMC, PBF_{DXA}, FM_{DXA} and LTM_{DXA} between baseline and repeat testing.
7.4.4.1 Comparison with control data
The gastrostomy tube-fed children demonstrated no significant changes in their LTM\textsubscript{DXA} for height SD score, or their BMC SD scores for age or height, or BMC adjusted for both LTM\textsubscript{DXA} and height.

As previously mentioned, a baseline measurement of height was unavailable for seven (4F, 3M) of the gastrostomy tube-fed children, therefore, for these participants baseline data was unavailable for BMC for height SD score, BMC for LTM & height SD score, and LTM for height SD score. For each parameter in Table 7.2, only those participants with both a baseline and repeat measure were included.

7.4.5 Total body protein by neutron activation analysis
The baseline and repeat measures of TBP\textsubscript{NAA} for the gastrostomy tube-fed children are shown in Table 7.3 (pg 200). There was a significant increase in TBP\textsubscript{NAA} between baseline and repeat testing.

7.4.5.1 Comparison with control data
The gastrostomy tube-fed children demonstrated a significant increase in TBP\textsubscript{NAA} as a percentage of predicted from control data for height between baseline and repeat testing. However, there was no significant change in TBP\textsubscript{NAA} expressed as percentage of predicted from control data for age.

As previously mentioned, a baseline measurement of height was unavailable for seven (4F, 3M) of the gastrostomy tube-fed children, therefore, for these participants baseline data was unavailable for TBP\textsubscript{NAA} expressed as a percentage of predicted for height. In addition, the carer of one male declined for him to have a repeat measure of TBP\textsubscript{NAA}, and therefore there is no data available for this child at repeat testing. Furthermore, the repeat measurement of TBP\textsubscript{NAA} for two males had to be discarded.
because it was conducted immediately prior to the radioactive sources being replaced as discussed in Chapter 3. For each parameter in Table 7.3, only those participants with both a baseline and repeat measure were included, and therefore data on 12 participants is presented.
**Table 7.1** Baseline and repeat anthropometric characteristics of gastrostomy tube-fed and baseline anthropometric characteristics of oral-fed children with cerebral palsy

<table>
<thead>
<tr>
<th></th>
<th>Gastrostomy tube-fed</th>
<th>Oral-fed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(8F, 7M)</td>
<td>(4F, 4M)</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>7.6 (4, 9, 11.4)</td>
<td>8.6 (7.4, 12.3)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>14.0 (11.6, 19.2)</td>
<td>21.0 (16.6, 24.7)</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>-5.1 (-7.0, -3.1)</td>
<td>-3.1 (-4.0, -2.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>105.0 (95.3, 111.8)</td>
<td>120.3 (105.0, 128.2)</td>
</tr>
<tr>
<td>Height SDS</td>
<td>-4.1 (-5.4, -2.4)</td>
<td>-3.0 (-4.3, -1.8)</td>
</tr>
<tr>
<td>Ideal weight-for-height (%)</td>
<td>91.0 (82.3, 99.9)</td>
<td>100.0 (93.0, 108.3)</td>
</tr>
<tr>
<td>UAMA (cm²)</td>
<td>13.9 (11.0, 17.1)</td>
<td>19.7 (15.5, 21.7)</td>
</tr>
<tr>
<td>UAMA SDS</td>
<td>-2.1 (-3.2, -1.1)</td>
<td>-1.4 (-2.2, -0.9)</td>
</tr>
<tr>
<td>UAFA (cm²)</td>
<td>3.4 (2.6, 6.6)</td>
<td>5.3 (3.0, 6.0)</td>
</tr>
<tr>
<td>UAFA SDS</td>
<td>-2.5 (-3.9, -0.9)</td>
<td>-1.9 (-2.9, -0.8)</td>
</tr>
<tr>
<td>FFMskin (kg)</td>
<td>12.5 (10.9, 17.5)</td>
<td>18.5 (15.2, 20.2)</td>
</tr>
<tr>
<td>FMskin (kg)</td>
<td>1.4 (0.7, 2.6)</td>
<td>2.5 (0.9, 4.3)</td>
</tr>
<tr>
<td>PBFskin (%)</td>
<td>10.2 (6.1, 17.1)</td>
<td>10.7 (5.8, 17.7)</td>
</tr>
<tr>
<td><strong>Repeat</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>10.1 (7.5, 13.1)³</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>20.6 (16.1, 25.2)⁴</td>
<td></td>
</tr>
<tr>
<td>Weight SDS</td>
<td>-3.0 (-5.1, -1.4)⁵</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>115.2 (111.4, 119.7)¹⁵</td>
<td></td>
</tr>
<tr>
<td>Height SDS</td>
<td>-3.4 (-4.4, -2.0)⁵</td>
<td></td>
</tr>
<tr>
<td>Ideal weight-for-height (%)</td>
<td></td>
<td>85.9 (75.7, 102.5)</td>
</tr>
<tr>
<td>UAMA (cm²)</td>
<td>19.6 (14.9, 23.3)²⁴</td>
<td></td>
</tr>
<tr>
<td>UAMA SDS</td>
<td>-0.4 (-2.3, 0.0)²⁴</td>
<td></td>
</tr>
<tr>
<td>UAFA (cm²)</td>
<td>7.4 (3.8, 10.6)²⁵</td>
<td></td>
</tr>
<tr>
<td>UAFA SDS</td>
<td>0.1 (-2.2, 0.7)²⁵</td>
<td></td>
</tr>
<tr>
<td>FFMskin (kg)</td>
<td>17.1 (14.4, 29.5)³⁴</td>
<td></td>
</tr>
<tr>
<td>FMskin (kg)</td>
<td>3.6 (2.0, 5.6)³⁵</td>
<td></td>
</tr>
<tr>
<td>PBFskin (%)</td>
<td>17.2 (9.9, 25.1)³⁵</td>
<td></td>
</tr>
</tbody>
</table>

Data is median (inter-quartile range). FFMskin, fat-free mass by skinfold anthropometry; FMskin, fat mass by skinfold anthropometry; PBFskin, percent body fat by skinfold anthropometry; SDS, standard deviation score; UAFA, upper arm fat area; UAMA, upper arm muscle area.

¹ n = 8, ² n = 14, ³ n = 13; ⁴ p <0.001, ⁵ p <0.05; significantly different between baseline and repeat test; Wilcoxon Signed Ranks test.
Table 7.2 Baseline and repeat body composition measures by dual-energy x-ray absorptiometry

<table>
<thead>
<tr>
<th>Gastrostomy tube-fed (8F, 7M)</th>
<th>Baseline</th>
<th>Repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMC (g)</strong></td>
<td>434 (365, 626)</td>
<td>597 (444, 698)²</td>
</tr>
<tr>
<td><strong>BMC for age SDS</strong></td>
<td>-2.6 (-3.7, -1.5)</td>
<td>-2.7 (-3.8, -1.4)</td>
</tr>
<tr>
<td><strong>BMC for height SDS</strong></td>
<td>-0.2 (-0.6, 0.0)¹</td>
<td>-0.4 (-1.2, 0.1)¹</td>
</tr>
<tr>
<td><strong>BMC for LTM &amp; ht SDS</strong></td>
<td>-1.3 (-2.0, 0.4)¹</td>
<td>-1.2 (-1.7, -0.5)¹</td>
</tr>
<tr>
<td><strong>LTM_{DXA} (kg)</strong></td>
<td>12.2 (10.1, 15.1)</td>
<td>15.6 (13.5, 17.3)²</td>
</tr>
<tr>
<td><strong>LTM_{DXA} for height SDS</strong></td>
<td>-0.2 (-0.6, 0.5)¹</td>
<td>0.0 (-1.2, 0.3)¹</td>
</tr>
<tr>
<td><strong>FM_{DXA} (kg)</strong></td>
<td>1.5 (1.1, 2.4)</td>
<td>3.9 (1.8, 7.1)²</td>
</tr>
<tr>
<td><strong>PBF_{DXA} (%)</strong></td>
<td>12.5 (7.5, 22.3)</td>
<td>21.8 (10.0, 31.3)²</td>
</tr>
</tbody>
</table>

Data is median (inter-quartile range). BMC, bone mineral content; DXA, dual-energy x-ray absorptiometry; FM_{DXA}, fat mass by DXA; LTM_{DXA}, lean tissue mass by DXA; PBF_{DXA}, percent body fat by DXA; SDS, standard deviation score.

¹ n = 8
² p < 0.01; significantly different between baseline and repeat testing; Wilcoxon Signed Ranks test.
### Table 7.3 Baseline and repeat measures of total body protein

<table>
<thead>
<tr>
<th>Gastrostomy tube-fed</th>
<th>Baseline</th>
<th>Repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td>(8F, 4M)</td>
<td>2.1 (1.5, 2.8)</td>
<td>3.4 (2.1, 3.9)</td>
</tr>
<tr>
<td>TBP$_{\text{NAA}}$ (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBP$_{\text{NAA}}$ for age (%)</td>
<td>51.3 (44.4, 56.4)</td>
<td>58.8 (38.0, 76.5)</td>
</tr>
<tr>
<td>TBP$_{\text{NAA}}$ for height (%)</td>
<td>75.6 (67.8, 87.7)</td>
<td>101.9 (96.7, 117.9)</td>
</tr>
<tr>
<td>TBP$_{\text{NAA}}$ for weight (%)</td>
<td>77.0 (70.0, 83.9)</td>
<td>87.0 (70.8, 101.3)</td>
</tr>
</tbody>
</table>

Data is median (inter-quartile range). FFM$_{\text{SKIN}}$, fat-free mass measured by skinfold anthropometry; NAA, neutron activation analysis; TBP$_{\text{NAA}}$, total body protein.

1 $n = 6$

2 $p < 0.05$, significantly different between baseline and repeat testing; Wilcoxon Signed Ranks test.
### 7.4.6 Annualised changes in body composition

Table 7.4 (pg 202) shows the annualised change in the body composition parameters for the gastrostomy tube-fed children. The annualised change was calculated as the difference between the baseline and repeat measure divided by the actual time of gastrostomy feeding (in years), not the time difference between the dates of the two measurements. This was done because, as previously mentioned, in nine of the children in the gastrostomy tube-fed group, there was a median time delay of 5.0 months (IQR 3.9 to 9.2 months) between having the baseline measurement and insertion of a gastrostomy tube, therefore the median length of time of actual gastrostomy tube feeding was 10.1 months (IQR 7.1 to 34.8; min-max 3.7 to 80.4 months). Upon review of the medical records for each gastrostomy tube-fed child it was found that there was no significant difference in weight between when the child participated in the cross-sectional study and when the gastrostomy tube was inserted.

In addition, due to the variation in length of time that the gastrostomy tube-fed children were followed-up, an attempt was made to determine if these children gained significantly more in any of the body composition parameters in the acute phase of re-feeding (i.e. <12 months). In the gastrostomy tube-fed children there were nine children who were underwent their repeat testing within 12 months of receiving a gastrostomy tube (median of 7.1 months). The data on these nine children are represented in Table 7.4 in the column labelled “<12 months”, and the data on the remaining six gastrostomy tube-fed children are represented in the column labelled “>12 months” (median of 35.9 months of gastrostomy tube feeding). Comparison of these two groups revealed that the children who were tube-fed for <12 months gained significantly more per year in weight, height, UAMA, UAFA, FM_{SKIN}, FFMSKIN, PBF_{SKIN}, and LTM_{DXA}, than those children who were tube-fed >12 months.
### Table 7.4 Annualised change in body composition parameters

<table>
<thead>
<tr>
<th></th>
<th>Gastrostomy tube-fed (8F, 7M)</th>
<th>Gastrostomy tube-fed (N = 9) &lt; 12 months</th>
<th>Gastrostomy tube-fed (N = 6) &gt; 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight (kg) / y</strong></td>
<td>3.9 (2.1, 7.9)</td>
<td>6.7 (4.9, 9.6)</td>
<td>1.7 (1.0, 3.2)</td>
</tr>
<tr>
<td><strong>Height (cm) / y</strong></td>
<td>9.7 (3.5, 14.2)¹</td>
<td>9.0 (5.8, 15.4)⁵</td>
<td>2.9 (1.6, 5.4)⁷⁻⁸</td>
</tr>
<tr>
<td><strong>UAMA (cm²) / y</strong></td>
<td>3.6 (2.5, 6.2)²</td>
<td>5.9 (4.0, 9.3)¹</td>
<td>2.3 (1.0, 3.0)⁸</td>
</tr>
<tr>
<td><strong>UAFA (cm²) / y</strong></td>
<td>2.2 (0.4, 3.7)²</td>
<td>3.4 (2.0, 6.0)¹</td>
<td>0.7 (-0.2, 1.9)⁹</td>
</tr>
<tr>
<td><strong>FM_{SKIN} (kg) / y</strong></td>
<td>1.4 (0.3, 3.3)³</td>
<td>2.6 (1.4, 4.0)¹</td>
<td>0.3 (0.0, 1.0)⁵⁻⁸</td>
</tr>
<tr>
<td><strong>FFM_{SKIN} (kg) / y</strong></td>
<td>2.8 (1.4, 3.9)⁵</td>
<td>3.8 (3.0, 5.0)¹</td>
<td>1.2 (1.0, 2.0)⁵⁻⁸</td>
</tr>
<tr>
<td><strong>PBF_{SKIN} (%) / y</strong></td>
<td>3.9 (0.6, 10.7)³</td>
<td>8.1 (3.7, 17.7)¹</td>
<td>0.8 (-0.6, 3.2)⁵⁻⁸</td>
</tr>
<tr>
<td><strong>BMC (g) / y</strong></td>
<td>63.9 (39.6, 111.9)</td>
<td>105.3 (33.0, 190.6)</td>
<td>46.5 (30.0, 58.1)</td>
</tr>
<tr>
<td><strong>LTM_{DXA} (kg) / y</strong></td>
<td>2.4 (1.1, 4.8)</td>
<td>4.7 (2.7, 6.4)</td>
<td>1.1 (0.6, 1.5)⁸</td>
</tr>
<tr>
<td><strong>FM_{DXA} (kg) / y</strong></td>
<td>1.4 (0.7, 3.0)</td>
<td>2.2 (1.1, 4.6)</td>
<td>1.1 (0.3, 1.4)</td>
</tr>
<tr>
<td><strong>PBF_{DXA} (%) / y</strong></td>
<td>5.0 (1.7, 10.0)</td>
<td>9.3 (2.7, 13.2)</td>
<td>2.8 (0.6, 5.9)</td>
</tr>
<tr>
<td><strong>TBP_{NAA} (g) / y</strong></td>
<td>382 (105, 509)⁴</td>
<td>325 (-28.6, 2242)⁶</td>
<td>382 (261, 416)</td>
</tr>
</tbody>
</table>

Data is median (inter-quartile range). DXA, dual-energy x-ray absorptiometry; UAMA, upper arm muscle area; UAFA, upper arm fat area; FM_{SKIN}, fat mass by skinfold anthropometry; FFM_{SKIN}, fat-free mass by skinfold anthropometry; PBF_{SKIN}, percent body fat by skinfold anthropometry; BMC, bone mineral content; LTM_{DXA}, lean tissue mass by DXA; FM_{DXA}, fat mass by DXA; LTM_{DXA}, lean tissue mass by DXA; PBF_{DXA}, percent body fat by DXA; TBP_{NAA}, total body protein by neutron activation analysis; y, year.

¹ n = 8; ² n = 14; ³ n = 13; ⁴ n = 12; ⁵ n = 5; ⁶ n = 6; ⁷ n = 3

² p < 0.05; significantly different between <12 months and >12 months, Wilcoxon Signed Ranks Test.
7.4.7 Resting energy expenditure and energy intake

Table 7.5 (pg 204) shows the REE and energy intake of the gastrostomy tube-fed children at baseline and repeat testing. Eight (4F, 4M) children underwent both baseline and repeat testing of REE by indirect calorimetry and completed three-day weighed food records. There was a significant increase in their measured REE (kJ/24h) and their measured REE as a percent of predicted REE between baseline and repeat testing. Interestingly there was no significant change in their reported energy intake, and a significant decrease in their reported energy intake as a percentage of their measured REE between baseline and repeat testing.

There were two children who had unusually high measured REEs at repeat testing (1F, 1M; 171 % and 141 % of predicted, respectively). The parents / carers of only one of these children (1F) agreed for their child to have the test repeated – it was equally as high when repeated. Clinic physicians were concerned that these patients may have unrecognised metabolic disorders causing a CP phenotype and abnormally high REE and thus these two children were removed from the data set and the data were re-analysed, the results of which are presented in Table 7.6 (pg 205). The results did not change significantly from when these children were included in the data set, i.e. there remained a significant increase in their measured REE (kJ/24h) and their measured REE as a percent of predicted REE, no significant change in their reported energy intake, and a significant decrease in their reported energy intake as a percentage of their measured REE between baseline and repeat testing.
### Table 7.5 Baseline and repeat measures of resting energy expenditure and energy intake

<table>
<thead>
<tr>
<th>Gastrostomy tube-fed (4F, 4M)</th>
<th>Baseline</th>
<th>Repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td>MREE (kJ / 24hr)</td>
<td>2040 (1792, 3342)</td>
<td>4245 (3540, 5950) (^1)</td>
</tr>
<tr>
<td>MREE / PREE (%)</td>
<td>67.6 (59.0, 76.4)</td>
<td>115.6 (90.7, 139.6) (^1)</td>
</tr>
<tr>
<td>Energy Intake (kJ / 24hr)</td>
<td>4897 (4625, 6254)</td>
<td>5782 (4428, 6694)</td>
</tr>
<tr>
<td>Energy Intake / MREE (%)</td>
<td>244 (154, 297)</td>
<td>113 (106, 152) (^1)</td>
</tr>
</tbody>
</table>

Data is median (inter-quartile range). MREE, measured resting energy expenditure by indirect calorimetry; PREE, predicted resting energy expenditure adjusted for fat-free mass using equations developed from control database.

\(^1\) p < 0.05, significantly different between baseline and repeat measurements, Wilcoxon Signed Ranks test.
Table 7.6 Baseline and repeat measures of resting energy expenditure and energy intake excluding REE >140%

<table>
<thead>
<tr>
<th></th>
<th>Gastrostomy tube-fed</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(3F, 3M)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Repeat</td>
<td></td>
</tr>
<tr>
<td>MREE (kJ / 24hr)</td>
<td>1879 (1775, 2837)</td>
<td>3997 (3367, 4399)(^1)</td>
</tr>
<tr>
<td>MREE / PREE (%)</td>
<td>64.9 (55.7, 73.8)</td>
<td>103.9 (85.0, 129.0)(^1)</td>
</tr>
<tr>
<td>Energy Intake (kJ / 24hr)</td>
<td>4745 (4462, 5862)</td>
<td>4783 (4463, 6295)</td>
</tr>
<tr>
<td>Energy Intake / MREE (%)</td>
<td>244 (181, 305)</td>
<td>123 (109, 169)(^1)</td>
</tr>
</tbody>
</table>

Data is median (inter-quartile range). MREE, measured resting energy expenditure by indirect calorimetry; PREE, predicted resting energy expenditure adjusted for fat-free mass using equations developed from control database.

\(^1\) p < 0.05, significantly different between baseline and repeat measurements, Wilcoxon Signed Ranks test.
Chapter 7

STUDY 4 – Nutritional rehabilitation

7.5 Summary of results

The nutritional rehabilitation study revealed that significant weight gain in gastrostomy tube-fed children with CP produced significant increases in height, measures of fat mass, FFM_{SKIN}, LTM_{DXA}, TBP_{NAA}, BMC and REE. The gastrostomy tube-fed children demonstrated significant improvements in their SD scores for weight, UAMA, and UAFA, and for TBP_{NAA} expressed as a percentage of predicted for height from control data as well as their REE expressed as a percentage of predicted from control data. There were no significant improvements seen in height SD score, TBP_{NAA} expressed as a percentage of predicted for age, or for BMC when expressed as an SD score for age or height.

7.6 Discussion

7.6.1 Anthropometric changes

There have been seven previous longitudinal nutritional rehabilitation studies of children with CP (Isaacs et al. 1994; Naureckas and Christoffel 1994; Patrick et al. 1986; Rempel et al. 1988; Sanders et al. 1990; Shapiro et al. 1986; Sullivan et al. 2005). However, only three of these studies were prospective (Isaacs et al. 1994; Patrick et al. 1986; Sullivan et al. 2005); three were retrospective reviews of the medical records (Naureckas and Christoffel 1994; Rempel et al. 1988; Shapiro et al. 1986); and one did not state how the data was collected (Sanders et al. 1990). Furthermore, all of the studies were based on measures of weight and/or height, with only three including some basic skinfold anthropometry, i.e. triceps skinfold thickness (Isaacs et al. 1994; Patrick et al. 1986; Sullivan et al. 2005). None of the studies included a measure of BMC or body protein.
Naureckas & Christoffel retrospectively collected data from the medical records on weight and height of 26 NG (n = 13) and gastrostomy tube-fed (n = 13) children with neurological disability (CP or degenerative neurological disorder) who had tube feeds for a mean of 23 months (Naureckas and Christoffel 1994). For all children, tube feeds resulted in significant improvements in their weight as a percent of ideal weight-for-height (73.2 to 94.2 %). No significant change in height percentile for age was observed, although the authors did not state their method used to measure height.

Shapiro et al conducted a retrospective review of weight and height from the medical records of 19 gastrostomy tube-fed children with quadriplegic CP and other severe neurological disorders (Shapiro et al. 1986). On average the children had been receiving gastrostomy tube feeds for 23 months. Prior to gastrostomy tube feeding the average weight-for-length of the group was -2.7 SDS. Post gastrostomy tube feeding this improved to -1.2 SDS. The authors reported that the gains in weight were more dramatic than the gains in length/stature and improvements in weight-for-length did not correlate with duration of follow-up. The authors reported that comments by parents and carers suggested that gastrostomy tube feeding decreased irritability and improved the quality of life for the child and family.

Patrick et al attempted to conduct a prospective RCT of NG tube feeding versus oral feeding of 10 children with wasting and severe CP (Patrick et al. 1986). However, the children who were in the oral feeding arm of the study were studied for less than five weeks before switching to the NG tube feeding arm because of lack of weight gain. The authors reported that in all of the children weight gain ceased four to five weeks after it started. The children gained an average of 23 % body weight over this time, as well as increased their triceps skinfold thickness by an average of 83 % and UAMA by 14 %, which the authors reported was most likely a reflection of increased fat
stores rather than increased muscle mass. Furthermore, the weight gain was associated with healing of persistent pressure sores and the correction of cold and cyanosed extremities. There was also anecdotal evidence to suggest improvement in the children’s spasticity and affect.

Rempel et al also reported anecdotal evidence of an improvement in the children’s disposition in a retrospective review of 35 gastrostomy tube-fed children with spastic quadriplegic CP (Rempel et al. 1988). The average length of time for gastrostomy tube feeding was 3.4 years. Even though weight gain was achieved in the majority of study participants, a large percentage of the children remained below the 5th centile for both height and weight. However, only a few remained below the 5th centile of weight-for-height, with most children reaching what the authors define as their “appropriate” weight-for-height (between the 25th and 75th centile). Only one quarter of the group showed an improvement in their height curve. Children who had received a gastrostomy tube prior to two years of age, and those with a gastrostomy tube for more than two years, showed the highest percentages in achieving appropriate weight-for-height. This is in contrast to the finding of Shapiro et al who found no correlation with weight gain and duration of follow-up.

Sanders et al conducted a relatively large study of 51 tube fed patients with severe CP (Sanders et al. 1990). The average length of follow-up was 2.4 years (range six months to 5.5 years). They found that after six months of feeding, children who received tube feeding soon after their CNS insult, and those who were around four years of age or younger, had better outcomes in terms of weight and length gain, than those who were older and received tube feeds more than 12 years after their CNS insult. The authors commented that this finding may be because the older children were reaching sexual maturation and therefore probably had little chance for
significant change in length. Overall, in agreement with Shapiro and Patrick, the gains in weight were more marked than the gains in length. Furthermore, parents reported that the children appeared more alert, less irritable and made significant developmental progress with weight gain.

Isaacs et al studied 22 gastrostomy tube-fed children with neurological impairment (15 with CP), and followed their progress for 10 months to four years (Isaacs et al. 1994). They found that after at least 12 months of tube feeding most children gained significant weight, but less than half gained length, although the authors used recumbent length to measure stature which does not provide an accurate measure of stature (Moore and Roche 1986). In addition, half of the group improved their weight-for-age centile, with children who were initially less than the 5th centile for weight, showing greater improvement than those who were at the 50th centile weight for age. Furthermore, nearly half of the children showed an increase in their triceps skinfold thickness.

Sullivan and colleagues conducted a large longitudinal, prospective, multi-centre study on the outcomes of gastrostomy tube feeding in 46 children with CP, the majority with spastic quadriplegic CP (Sullivan et al. 2005). They measured weight, LLL, UAL (as proxies for linear growth) and triceps and subscapular skinfold thicknesses, in the children at baseline, and then at six and 12 months post gastrostomy tube feeding. They found that on average the children increased their weight SD scores from -3.0 to -1.6 after 12 months. In addition, the children achieved some linear growth, with LLL SD scores increasing from -1.3 to -0.4, and UAL SD scores increasing from -0.14 to 0.58. However, the triceps SD scores increased only in the first six months from -0.9 to -0.5, and then dropped back to -0.7 SD score after 12 months. Interestingly, overall the greatest rate of change, or gains, in all parameters
was in the first six months with a decreased rate of change between six and 12 months.

Generally all of the above studies support the findings from the current study. Most studies found that the gains in weight were greater than the gains in height and in those studies that measured skinfold anthropometry, significant gains in body fat were also observed. However two studies reported that not all children gained weight with gastrostomy tube feeding (Isaacs et al. 1994; Rempel et al. 1988). In the current study, in the gastrostomy tube-fed group, only those children who gained weight were remeasured, as the aim of the study was to examine what changes occur in body composition with weight gain. Though, as mentioned in the participant description of this Chapter, three children were not remeasured because they failed to gain weight. This suggests that not all children with CP will benefit from the insertion of a gastrostomy tube. This is discussed further in the limitations of the study in Chapter 8.

The lack of improvement in height SD scores observed in the current study and other nutritional rehabilitation studies of children with CP is most likely due to the lack of weight bearing activity in these children. Immobilisation, or disuse, during growth results in reduced growth in bone length and subsequently a lack of growth in height (Bass et al. 2005). Therefore, despite the provision of adequate nutrition in the gastrostomy tube-fed group, no improvement in height SD scores were observed. This is discussed further in section 7.6.2.

The study by Sullivan and colleagues found that the greatest gains in weight, height and body fat were observed in the first six months of nutritional rehabilitation with a plateau in change between six and 12 months (Sullivan et al. 2005). In the current study it was found that those children who were re-measured after < 12 months of gastrostomy tube feeding gained significantly more in all of the anthropometric
parameters than those re-measured after > 12 months of gastrostomy tube feeding. This suggests, in agreement with the findings of Sullivan et al, that there may have been short term rapid gains which then plateau with time. In future studies a more structured study with set follow-up appointments every six months, for example, would assist in characterising the pattern of change in growth and body composition with refeeding in children with CP.

7.6.2 Longitudinal studies of bone mineralisation

Aside from the current study, there has been only one other longitudinal study of bone mineralisation in children with CP (Henderson et al. 2005). Although the authors were not conducting a nutritional rehabilitation study, they did find that a better nutritional status, as assessed by the triceps SD score, was associated with greater change in BMD per year in 69 children with moderate to severe spastic CP. The study by Henderson et al also reported that BMD SD scores decreased over time in spite of overall increases in BMD, whereas in the current study it was found that there was no significant change in BMC SD scores for age or height in the gastrostomy tube-fed group. However, the results are difficult to compare with the current study because the authors measured rate of change in areal BMD in the distal femur and lumbar spine, compared with total body BMC in this study, they had larger numbers of participants, they studied the children over a longer period of time (40 out of the 69 were studied over 3 years), no adjustments were made for body size, and they conducted an observational rather than an interventional study.

In the current study, despite overall increases in BMC, no improvements in BMC SD scores for age or height were observed. Similar to the lack of improvement in height SD scores discussed in the previous section, this may be because both physical activity and nutrition are responsible for the growth and development of bone (Bass et
Immobilisation during growth results in reduced growth in bone length and a loss of bone strength due to large losses in bone mass. Studies have shown that under adequate nutrition, physical activity has the potential to increase the muscle forces acting on bone and thus can lead to a proportional increase in bone strength. In contrast, nutrition alone, without physical activity, does not influence muscle or bone development (Bass et al. 2005). The intrinsic relationship between muscle and bone is summed up by the “mechanostat” theory, which postulates that increasing maximal muscle force during growth or in response to increased loading will affect bone mass, size and strength predictably and correspondingly. Similarly, unloading (disuse or immobilisation) will lead to reduced muscle development (and muscle force) and invariably have a negative effect on the mass, size, and strength of bone (Bass et al. 2005). Studies of patients with a spinal cord injury have shown that adequate nutrition alone, without the influences of physical activity, are not enough to maintain bone density and strength (Bass et al. 2005). Nutrition has its most profound effect on the muscle and bone unit when in a state of deficiency. Energy and protein restriction appear to act by retarding growth in length and size, resulting in a proportionately smaller skeleton and reduced cortical mass. Reduced stature as a result of energy deficiency has been characteristic of the evolution of the human species. Energy and, more so, protein deficiency also reduces body weight and muscle mass, which diminishes the mechanical demands on bone for adaptation in bone strength. Therefore, both exercise and nutrition are important for the development of muscle and bone during growth. Adequate nutrition in the absence of physical activity will not maintain bone strength and vice versa. Consequently, in children with CP, it is unlikely that any significant improvements in BMC SD scores will be seen with adequate nutrition alone. In a study of both ambulant and non-ambulant children with
CP, weight-bearing activity was shown to significantly improve femoral neck BMC compared to controls although the ambulant and non-ambulant children were not separated for analysis (Chad et al. 1999). In another study of non-ambulant children only with CP, a standing frame to facilitate an upright position was shown to improve BMD, with the gains in BMD being proportional to the duration of standing (Caulton et al. 2004). Possibly future nutritional intervention studies will also need to include a weight-bearing activity program. However, it is important to note that in the current study although no significant improvements in BMC SD scores were observed, no significant decreases in BMC SD scores were observed either. It could be postulated that adequate nutrition alone, while not enabling a significant increase in BMC SD scores, may be enough to maintain BMC SD scores and prevent further decline. A nutritional intervention study including larger numbers of participants with longer term follow up is needed before coming to any firm conclusions on the effects of gastrostomy tube feeding on bone mineralisation.

7.6.3 Longitudinal studies of total body protein

The current study is the only study to report longitudinal data on TBP in children with CP; therefore there are no other studies in children with CP for comparison. However, our centre has measured longitudinal changes in TBP in healthy control children. Allen et al (Allen et al. 1996) reported that the average annual accretion of TBP of prepubertal healthy control children (n = 17) was 481 g/y. Compared with the healthy controls, the gastrostomy tube-fed children with CP gained less TBP per year, yet they showed significant improvements in their TBP as a percent of predicted for height, but not for age, although there was wide variation. Nonetheless, this study demonstrated that significant increases in body protein can be achieved in children with severe CP with gastrostomy tube feeding.
7.6.4 Resting energy expenditure and food records

In the current study it was found that the measured REE of the gastrostomy tube-fed children with CP increased from 65% of predicted at baseline testing to 104% of predicted after significant weight gain. However the number of participants in this part of the study was small (n = 6).

There have not been any other studies in children with CP that have explored the effects of nutritional rehabilitation on REE. However, there have been a number of other studies in patients with anorexia nervosa which have also demonstrated a significantly decreased REE which subsequently increases with refeeding (de Zwaan et al. 2002b; de Zwaan et al. 2002a; Krahn et al. 1993; Russell et al. 1998; Salisbury et al. 1995; Schebendach et al. 1997; Van Wymelbeke et al. 2004). One of the theories postulated for this is that during semi-starvation the body adapts by a reduction in REE. With refeeding there is a reversal of this adaptive function (Schebendach et al. 1997; Vaisman et al. 1991). This is possibly what occurred in the gastrostomy tube-fed patients with CP, however a larger number of children will need to be studied before and after nutritional rehabilitation before coming to any firm conclusions on this.

Analysis of the food records revealed that at baseline testing, when the children with CP were fed orally, energy intake was grossly overestimated in comparison to measured REE. This was also demonstrated in the cross-sectional study and is discussed in more detail in Chapters 6 and 8. At repeat testing, the food records of the gastrostomy tube-fed children with CP appeared to be more accurate. This was most likely because the children were fed almost entirely through the gastrostomy tube with specialised formulas which are a known volume and composition and are therefore easy to record.
These findings demonstrate that nutritional rehabilitation of children with CP possibly results in a reversal of the adaptive response to semi-starvation, and that these children can gain significant weight with an energy intake that is approximately 1.1 times their measured REE. In a cross-sectional study of 61 children with quadriplegic CP, Stallings et al reported that on average the children required an energy intake of 1.23 times their measured REE, or 1.29 for those with reduced fat stores and 1.07 for those with higher fat stores, compared with 1.57 in a healthy control group (Stallings et al. 1996). In another similar, but smaller (n = 6) cross-sectional study, the authors reported that the children with CP, compared with a healthy control group, required on average an energy intake that was 1.23 versus 1.76 respectively, times their measured REE (Bandini et al. 1991). The finding from the current study supports the two aforementioned studies and provides further evidence that children with CP can achieve adequate weight gain on energy intakes that are only slightly higher than their measured REE. Finally, in agreement with the findings from the cross-sectional study, food records in oral-fed children with CP appear to be of limited value.

7.6.5 Significance of findings

The data from this nutritional rehabilitation study suggest that gastrostomy tube feeding in children with severe CP can induce large gains in weight in most, but not all, children, with significant increases in height, PBF, BMC and TBP. In addition, it was found that nutritional rehabilitation possibly may reverse the adaptive response of a reduction in REE to semi-starvation, however larger numbers of children need to be studied to confirm this finding.

This longitudinal nutritional rehabilitation study needs to be continued in order to collect data on a larger number of children. In addition, it is suggested that future children included in the study have two to three repeat measures both pre- and post-
gastrostomy tube feeding so that each child can be used as its own control. Furthermore, it is recommended that the repeat measurements follow a set structure with testing every six months, for example, in order to better compare and characterise the patterns of change in body composition.

Further limitations, recommendations and future directions are discussed in the overall discussion of this thesis in Chapter 8.
CHAPTER 8

DISCUSSION
8 Discussion

8.1 Overall conclusions

Children with quadriplegic CP in this study were stunted and wasted with greatly reduced body protein, fat mass, and bone mineralisation. The measurement of weight and height alone did not identify those children with malnutrition. A more detailed assessment of body composition in the clinic setting using skinfold anthropometry is recommended to help identify those children at risk of malnutrition. Simple anthropometric measures such as the triceps skinfold thickness, UAMA and FFM showed good correlation with more sophisticated techniques to measures body fat and body protein. However, as an accurate and precise measure of body protein in individuals, both skinfold anthropometry and DXA showed wide variability and are therefore not recommended in this population. Furthermore, as a measure of percent body fat, DXA and skinfold anthropometry showed poor agreement indicating that one, or both, of these techniques is inaccurate for the measurement of percent body fat in children with CP. Further studies using a 4C model of body composition are required in order to validate skinfold anthropometry and DXA before they can be accepted as precise measures of body composition in children with CP.

The REE of the children with CP was significantly reduced, widely variable and poorly correlated with body composition parameters making it difficult to predict from the existing predictive equations. Thus, it is recommended to either measure REE by indirect calorimetry, however such sophisticated technology is not available at all centres; or to roughly estimate energy requirements using the currently available Schofield equations and adjust energy intake according to weight change (Schofield 1985). Food records were found to grossly overestimate the energy intake of these
children; particularly those fed orally, and appear to be of limited value in this population.

Gastrostomy tube feeding of children with CP resulted in significant increases in weight, height, FM, measures of muscle mass (FFM and LTM), TBP, BMC and REE. In addition, these children demonstrated significant improvements in their weight SD score and for TBP_{NAA} when expressed as a percentage of predicted for height from control data. However, there were no significant improvements seen in height SD score, TBP_{NAA} expressed as a percentage of predicted for age, or for BMC when expressed as an SD score for age or height.

Further studies including larger numbers of participants with longer term, more structured follow-up pre- and post-gastrostomy tube feeding are required to confirm these findings and recommendations.

These conclusions as well as limitations of the study are discussed in more detail in this Chapter.

8.2 Study 1 - Cross-sectional study

8.2.1 Limitations of using anthropometry in children with cerebral palsy

8.2.1.1 Difficulties with measuring height

Two different sets of equations were used in this study to convert knee height to an estimate of standing height. As discussed in Chapter 2 (section 2.3.2.1, pg 29) these equations have not been properly validated in children with quadriplegic CP, and are therefore of questionable accuracy in this population. However, a measure of height is useful to have in this population in order to adjust measures of body composition, such as TBP and BMC, according to body size to allow for comparisons with
reference data. Estimated measures of height must be used and interpreted cautiously with an understanding of their limitations.

8.2.1.2 Skinfold anthropometry

As reported in Chapter 2, skinfold anthropometry is a popular method for assessing body composition in the clinic setting because the instruments are portable and relatively cheap and minimal training is required. However, estimating body fat and FFM by skinfold anthropometry is based on several assumptions, none of which have been proven to be true in the normal population, let alone in children with CP. Furthermore, the precision of the measurement of a skinfold thickness is dependent upon the skill of the anthropometrist and the site measured. In general, the error of precision can increase if the skinfold thickness gets very large (>15 mm) or small (<5 mm) (Roche 1996). Skinfold thicknesses less than 5 mm were common in this study. Also, the bony landmarks that are required to determine the site of measurement are difficult to locate in children with quadriplegic CP because of joint contractures and scoliosis, and the inability of the participant to cooperate. Finally, the skinfold thickness should be taken while the participant is standing and with their muscles relaxed. Children with severe CP are usually unable to stand and suffer from involuntary muscle contractions making the measurement of skinfold thicknesses possibly unreliable.

Furthermore, apart from assuming a normal hydration of FFM, skinfold anthropometry is also based on the assumptions that

- the participant has a normal bone size and density (Roche 1996). As this study and others have shown, children with severe CP have a reduced bone mineralisation.
for the calculation of the UAFA and UAMA include: the mid-arm is circular; the triceps skinfold is twice the average fat rim diameter; the mid-arm muscle compartment is circular; and bone, which is included in the anthropometric UAMA, atrophies in proportion to muscle protein-energy malnutrition, none of these assumptions have been proven to hold true in children with CP (Lukaski 1987).

Further work, using a 4C model of body composition, needs to be done to validate this potentially useful technique in patients with CP. This is discussed further at the end of this Chapter.

8.2.2 Limitations of neutron activation analysis to measure total body protein
The advantage of this technique over the conventional method of analysis is that errors in counting resulting from differences in irradiation and detection conditions from differences in size and shape of subjects are reduced considerably. This reduction in error makes sequential nitrogen measurements more reliable, particularly when subject weight has changed significantly, which was the case in the nutritional rehabilitation study of this thesis (Lukaski 1987). However, some may argue that one potential source of error in the equation used to calculate TBP is in the estimation of FM by skinfold anthropometry. Calculations have shown that an uncertainty of ± 30 % in the FM will produce an acceptable uncertainty in the hydrogen content of up to 2.5 %, for fat masses ranging from 5 to 40 % of body mass (Baur et al. 1991a), and therefore NAA is considered to be the most accurate and precise method available to measure TBP. In addition, compared with skinfold anthropometry and DXA, minimal subject cooperation is required. The main disadvantages that limit the wide use of this method is its high cost, the need for highly skilled operators, lack of mobility, and the use of ionizing radiation. However, the current study found that basic skinfold
anthropometry can be used in the clinic setting to provide an indicator of TBP, but further work needs to be done to validate skinfold anthropometry as an accurate and precise measure of TBP in individuals.

8.2.3 Methodological limitations of dual-energy x-ray absorptiometry to assess soft tissue

DXA was originally designed to measure bone mineralisation and has been well validated for this purpose. However, using DXA to measure the soft tissue components of the body, i.e. LTM and FM, is less well validated; it incorporates several assumptions as discussed in Chapter 2 (section 2.4.2.4, pg 47) and is therefore of questionable accuracy (Lohman 1996; Pietrobelli et al. 1998).

The estimation of FM and LTM by DXA is derived from assumed attenuation coefficients which are based on a hydration of LTM of 73.2 %. As discussed previously, the hydration of the LTM in children with CP is unknown, and could in fact be greater than 73.2 %. The degree to which DXA measurements are sensitive to variation in hydration levels is unknown (Roubenoff et al. 1993).

Another assumption of DXA is related to the area of the body analysed to obtain body composition data. DXA does not include any soft tissue that is directly above or below bone, therefore DXA makes assumptions about the associations between the soft tissue content of the area analysed with the soft tissue content of the area that is not analysed. It has been estimated that 40 to 45 % of the 21,000 pixels in a typical whole body scan contain bone in addition to soft tissue, and these pixels are therefore excluded from the calculation of values for soft tissue (Lohman 1996). Thus, the extent to which the composition in the excluded area differs from the considered area in a given population is a source of systematic error for that population (Lohman 1996). Furthermore, the influence of the arm and thorax on the total body composition
estimates may be under-represented because of the relatively large areas of bone in these regions. As a result, proportionately fewer pixels are used to estimate soft tissue composition in these regions than in the lower extremities and the abdomen. In the current study, the anthropometric measures showed that the children with CP had an irregular distribution of fat, with more fat on the thorax than on the extremities. As mentioned previously the thorax contains large areas of bones and consequently proportionately fewer pixels are included in the estimate of soft tissue composition in this region. It is unknown what impact this has on the estimation of body composition of the children in this study, but it can be speculated that DXA may therefore underestimate fat in this group. This will be discussed further in the next section. Comparison with a 4C model of body composition in children with CP is required to validate the accuracy of the soft tissue estimates by DXA.

8.3 Study 2 - Comparison of methods to measure protein and fat

8.3.1 Limitations of DXA and skinfold anthropometry to measure body protein

In addition to the limitations and assumptions involved in using skinfold anthropometry and DXA to derive body composition of soft tissue discussed in previous sections of this Chapter, the method used in this study to estimate body protein from these two measures was based on two assumptions. Firstly, that the hydration of the LTM was estimated; and secondly, that the non-osseous mineral to bone mineral ratio was 0.18:0.82 such that the mass of non-osseous mineral was 0.23 x BMC. The applicability of these assumptions to the current study population is questionable because it is unknown if malnourished children with severe CP have a normal hydration and furthermore the children in this study were found to have a significantly reduced BMC.
8.3.2 Percent body fat derived from dual-energy x-ray absorptiometry versus skinfold anthropometry

The major limitation of comparing PBF derived from DXA and skinfold anthropometry is that neither technique is considered to be a gold standard. Furthermore, both techniques incorporate several assumptions as discussed in previous sections of this Chapter. However, these two techniques are commonly used to assess body composition in children with CP, so which one is more accurate, and which one should clinicians use to assess body composition?

In conclusion, before skinfold anthropometry and DXA can be widely accepted as accurate measures of nutritional status in children with CP, both techniques need to be validated against a 4C model of body composition. A 4C model of body composition, which divides body weight into fat, water, protein and bone, is more robust to interindividual variability in the composition of FFM, and allows evaluation of several assumed constant relations that are central to the 2C model (Wells et al. 1999).

8.4 Study 3 - Resting energy expenditure and dietary intake

8.4.1 Limitations of estimating energy requirements

The Schofield equations are the most commonly used equations to estimate the energy requirements of children, including those with CP. These equations are based on data collected from several studies over many decades. In addition, 75 % percent of the studies used as source data for these equations were conducted before 1939, and predominantly in the USA. At that time most of the measurements were made with a respirometer. It has been found that REE determined by the ventilated hood technique is lower than REE measured with a respirometer (Clark and Hoffer 1991).

In the current study, and others, it was shown that these equations do not provide an accurate estimate of the energy requirements of children with CP. Thus the logical
conclusion would be to develop predictive equations based on data collected in children with CP. Unfortunately, CP populations tend to be quite heterogeneous with differing degrees of severity. Even in the current study of children with an apparently similar severity of CP, wide variation was found in their measured REE. Furthermore, regression analysis showed that there was no single variable that could adequately account for a significant proportion of the variation making it quite problematic to develop an equation that could accurately predict energy requirements in this group. Thus the current recommendations are to either measure REE by indirect calorimetry, however such sophisticated technology is not available at all centres; or to roughly estimate energy requirements using the currently available equations and adjust energy intake according to weight change.

8.4.2 Limitations of estimating energy and nutrient intake
Accurately estimating an individual’s dietary intake is particularly difficult. There are several methods that can be used to estimate dietary intake, namely 24-hour recall, food frequency questionnaires, diet history, and estimated or weighed food records. A weighed food record was chosen for this study because it is considered to be the most precise method available for estimating food and nutrient intake of individuals (Gibson 1990). Weighed food records minimise errors resulting from memory lapses and inadequate estimation of portion size that can occur with other methods (Gibson 1990). However, weighed food records have several limitations. Firstly, they are laborious and time consuming. It is possible that in this study the food records were inaccurate simply because the parents or carers did not have enough time to complete them accurately. Secondly, it has been reported in other studies that people change their diet for the days that the food intake is being recorded either to simplify the weighing process, or alternatively, to impress the investigator (Gibson 1990). It is
possible that parents or carers were reporting what they believe their child should eat rather than what they were actually eating. Related to this, it has been shown in other studies of the general population that low dietary intakes tend to be overestimated and high dietary intakes underestimated (Gibson 1990). This is known as the “flat slope syndrome” or is sometimes referred to as “talking a good diet”. In this study, it may have been that the parents or carers wanted the study investigators to believe that their child had an adequate energy intake, despite their child being markedly underweight. The parents or carers may have been afraid that if it was shown that their child had an inadequate dietary intake, an intervention such as a gastrostomy tube may have been recommended. However, that would not explain the overestimation of energy intake also found in the tube-fed group.

In this study, the parents or carers were instructed to record their child’s intake for two days of the week plus one weekend day. However, most of the food records included two weekend days, and some parents reported keeping their child home from school during the week in order to record their food intake. The parent’s explanation for this was that due to the time consuming nature of weighed food records it would have been too difficult for school teachers to do while having to care for and feed several disabled children. Furthermore, anecdotal evidence suggests that children with severe CP eat more when at home because their parent or carer is able to feed them better than anyone else. So it may have been that the food records were in fact accurate for the three days that they were recorded, but because the child normally spends five days per week at school, this high energy intake is not sustained and is therefore not representative of their usual intake.

In conclusion, for whatever reason, in this study it was shown that energy intakes from food records were grossly overestimated and therefore invalid in this study.
population. Food records are time consuming for the parents / carers and appear to be of little value, and are therefore not recommended to assess dietary intake in this population.

### 8.5 Study 4 - Nutritional rehabilitation

As discussed in Chapter 7, this study was limited firstly because of the small numbers of participants and, secondly because the oral-fed CP group appeared to have less severe disease than the gastrostomy tube-fed group and therefore comparisons were unable to be made. These limitations are discussed in more detail below.

#### 8.5.1 Inability to conduct a randomised controlled trial

The original plan for the nutritional rehabilitation study was to conduct an RCT of gastrostomy tube feeding versus oral feeding with speech therapy. However as previously mentioned in Chapter 7, no parents / carers agreed to their child participating in an RCT. Other researchers have attempted to conduct RCTs of feeding in children with severe CP, yet none have been successful. Sleigh & Brocklehurst endeavoured to conduct a systematic review of findings from RCTs to assess the risks and benefits of gastrostomy tube feeding, yet no RCTs were found (Sleigh and Brocklehurst 2004). Furthermore, Sullivan et al suggested that an RCT of gastrostomy tube versus oral feeding, or the use of an oral-fed control group for comparison, may be unethical because it would involve delaying intervention in a situation in which it would be clinically indicated (Sullivan et al. 2005). The authors suggested that in the absence of an RCT the next best thing would be a longitudinal, prospective, uncontrolled cohort study of gastrostomy tube feeding. This type of study was attempted yet it was difficult to recruit a large number of participants. The reasons for this are discussed in section 8.5.1.3 (pg 229).
8.5.1.1 Unstructured follow-up

One limitation of the nutritional rehabilitation study was the lack of structured follow up and the difference in time between baseline and repeat measures in the gastrostomy tube-fed children. As discussed in the previous section the original plan for an RCT with structured follow-up appointments had to be abandoned due to a lack of willing participants. Much time, approximately 10 months, was spent attempting to recruit participants to the RCT. After the RCT was abandoned, it was decided to monitor and conduct repeat testing on any of the 39 oral-fed children who took part in the cross-sectional study, who then received a gastrostomy tube as part of their routine care. Different lengths of time elapsed from when the child participated in the cross-sectional study, to when they then received a gastrostomy tube, and to when they achieved significant weight gain. Because the original aim of the study was to assess what changes occurred in body composition when these children gained weight, the children were not remeasured until they had gained significant weight – this occurred over varying lengths of time in each participant (range of 3.7 to 80.4 months). Therefore, in many of the participants, weight gain was slower than anticipated and three children from the cross-sectional study who received a gastrostomy tube failed to gain weight altogether and were therefore not re-measured. The possible reasons for the lack of weight gain are discussed in the next section. Moreover the TBN machine was unable to be used for a period of 12 months while the radioactive sources were replaced and the machine extensively recalibrated. During this time repeat testing of study participants was delayed, thereby further complicating any structured follow up. Therefore, a study with set follow up times may not have necessarily improved this study.
8.5.1.2 Slow and lack of weight gain

As mentioned in the previous section some of the gastrostomy tube-fed children experienced slow weight gain, and some, lack of weight gain altogether. In most of these children this was due to complications post surgery, including wound dehiscence and infection, leakage around the gastrostomy tube site, intolerance of feeds, development of dumping syndrome, and development of GOR post gastrostomy tube insertion requiring a subsequent fundoplication, all resulting in lack of, or slow, weight gain. Studies have shown that 11 - 26 % of children experience complications post-gastrostomy tube insertion (Davidson et al. 1995; Gauderer et al. 1988; Heine et al. 1995; Sullivan et al. 2005), including one study (Pearl et al. 1990) that reported children with severe neurological disability have more than twice the complication rate, four times the re-operative rate, and three times the mortality rate of neurologically normal children requiring a gastrostomy tube such as those with cystic fibrosis or congenital heart disease. These complications contributed to the reduction in the number of children undergoing repeat testing. Further reasons for the small numbers of participants in the study are discussed in the next section.

8.5.1.3 Small numbers of participants

Despite there being 39 oral-fed children in the original cross-sectional study, only 26 opted to receive a gastrostomy tube, and only 15 of these consented to have the tests repeated. The parents / carers of the remaining 13 oral-fed children from the cross-sectional study declined a gastrostomy tube. Therefore, despite these children being referred to the Dysphagia Clinic because of severe nutritional and feeding problems there was a resistance, or reluctance, for gastrostomy tube feeding. Several groups of researchers, through extensive interviews with parents of disabled children, have examined reasons why parents / carers may be reluctant for their child to receive a
gastrostomy tube and why they take so long to make the decision. The studies revealed that parental decisions to have a gastrostomy tube inserted in their child involved a series of complex and interrelated issues. Some of these issues are summarised in the following points:

- Loss of mother-child interaction - parents felt that gastrostomy tube feeding would have negative impact on the parent-child relationship because it lacked the closeness of oral feeding (Craig et al. 2003; Guerriere et al. 2003; Sleigh 2005; Spalding and McKeever 1998; Thorne et al. 1997).

- Enjoyment of eating – Parents felt that gastrostomy tube feeding would remove one of the few pleasures and basic human abilities that their children appeared to enjoy (Craig et al. 2003; Guerriere et al. 2003; Sleigh 2005; Spalding and McKeever 1998; Thorne et al. 1997).

- Maintaining skills – parents raised concerns that their child might become dependent on the gastrostomy tube for feeding and lose or fail to acquire feeding skills (Craig et al. 2003).

- Maintaining a normal family life - for families with a chronically ill or disabled child any normal activities, such as eating, are highly valued (Brotherson et al. 1995; Sleigh 2005; Thorne et al. 1997).

- The insertion of a gastrostomy tube is a surgical procedure - although the insertion of a gastrostomy tube may be considered a “low tech” procedure by clinicians, the parents regarded it as an invasive procedure with an unjustified risk to their child (Craig et al. 2003; Spalding and McKeever 1998; Thorne et al. 1997).

- Giving up hope - for some parents a gastrostomy tube signalled that their child was never going to feed properly (195), and the suggestion by health professionals that their child needed a gastrostomy tube implied that the professionals had given
up hope for recovery (Craig et al. 2003; Thorne et al. 1997). Parents also believed that the presence of a gastrostomy tube emphasised, and increased the visibility of, their child’s disability (Brotherson et al. 1995; Guerriere et al. 2003; Spalding and McKeever 1998). One study revealed that, although some parents agreed to their child having a gastrostomy tube they did not use it to its full potential, preferring to rely on oral feeding which may partly explain why not all children who receive a gastrostomy tube will gain weight (Craig et al. 2003).

- Impact of gastrostomy tube feeding on social relationships – feeding through a tube was seen as having a negative impact on feeding as a social activity, and parents expressed concern that gastrostomy tube feeding might exclude their child from participating in school and family life. Several studies described families wanting more information about the gastrostomy tube prior to its placement, not only about medical aspects but also about how the gastrostomy tube would affect their everyday life (Craig et al. 2003; Guerriere et al. 2003).

- Perceived benefits and the need for evidence – the issue of whether the child needed the gastrostomy tube and the lack of convincing evidence was a strong theme. Not all parents accepted that their child’s weight was the main priority and different views were expressed about the possibility, or desirability, of weight gain. Concerns that the child might become too heavy to handle and that carer support might be withdrawn because of weight restrictions placed on lifting. Parents also commented on the lack of evidence or good advice about the growth potential of their child (Craig et al. 2003; Sleigh 2005).

- A more challenging source of ambivalence hinted at by some parents was that the renewed health of the child raised some new problems – such as getting too heavy to lift. In addition, in eliminating the terrible episodes in which parents were faced
with thoughts of “What if my child dies?” the gastrostomy tube raised the new and
different spectre of “What if my child lives?” In contrast to the uncertain and
tenuous hold on life that the child may have had in a malnourished state, the
gastrostomy tube-fed child now seemed physically strong enough to live in this
debilitated state indefinitely (Thorne et al. 1997).

The above points help to explain why not all parents / carers will consent to a
gastrostomy tube when it may appear to the health professional to be a straight-
forward and clear-cut decision. Two of the studies reported that it took anywhere from
six months to two years for the parents / carers to give consent for their child to get a
gastrostomy tube from when it was first suggested (Craig et al. 2003; Spalding and
McKeever 1998). Although in the current study there was no information collected on
when a gastrostomy tube was first suggested to parents / carers, in the children who
did receive a gastrostomy tube there was a median time difference of 19 months
(range 12 to 78 months) from when they first visited the Dysphagia Clinic for
assessment to when they received a gastrostomy tube.

In summary, parental decisions about gastrostomy tube insertion are complex,
difficult and emotionally laden. Most often, professionals are convinced of the need
for a gastrostomy tube long before it is acceptable to parents (Spalding and McKeever
1998; Thorne et al. 1997). Health care professionals need to understand the
significance of being unable to be nourished by mouth, and recognise that these
aspects of the decision are important to parents. These studies emphasise the need for
a family advocate when professionals fail to appreciate the family’s feelings and fears
associated with gastrostomy tube feeding (Thorne et al. 1997). A better understanding
and acknowledgement of these issues may help in future nutritional rehabilitation
studies involving gastrostomy tube feeding.
8.5.2 Quality of life

Many people may question the benefit and purpose of weight gain and gastrostomy tube feeding in severely disabled children with CP. Why do we want to make their growth and body composition more “normal”? One of the answers to this question is that we hope it will improve the overall health and quality of life of the child. The nutritional rehabilitation study in this thesis revealed that body protein can be significantly increased with gastrostomy tube feeding; and as mentioned in Chapter 2 (section 2.7, pg 85), adequate body protein is important for immune function, response and recovery to illness, as well as respiratory skeletal muscle function. Therefore, it may be hypothesised that an improvement in body protein may lead to an improvement in quality of life. Unfortunately, an assessment of quality of life was beyond the scope of the current study. However, other studies of children with CP have found positive correlations between nutritional status and quality of life (Chapter 2, section 2.6.3, pg 84). Future studies should endeavour to include a measure of quality of life pre- and post-nutritional rehabilitation.

8.6 Future directions

In summary, this research has provided valuable insights into nutritional assessment and the effects of nutritional rehabilitation on the body composition of children with quadriplegic CP. Despite the limitations of this study, the results indicate that nutritional rehabilitation does improve body fat and protein and therefore it is a worthwhile exercise. Further studies are recommended to build on the work that has been done so far. Future directions for research include:

1. Conduct a 4C model of body composition in order to validate DXA and skinfold anthropometry as accurate measures of body composition in children with CP;
2. Continue collecting data on a larger number of children undergoing nutritional rehabilitation via gastrostomy tube feeding. Include longer term and more structured follow-up pre- and post-gastrostomy tube feeding.

3. Include a measure of quality of life pre- and post-nutritional rehabilitation.

4. Consider the inclusion of a family advocate, or the development of a support group, for families who are making the decision for their child to receive a gastrostomy tube.
REFERENCE LIST
Reference List


Baumgartner, R.N. 1996. "Electrical impedance and total body electrical conductivity." In A.F. Roche, S.B. Heymsfield, and T.G. Lohman, editors,


children and adolescents with moderate to severe cerebral palsy."


Morton, R.E., R. Wheatley, and J. Minford. 1999. "Respiratory tract infections due to
direct and reflux aspiration in children with severe neurodisability."

problems in children with cerebral palsy: weight and neurodevelopmental


Musculoskelet.:262-272.

epidemiology: where are we now and where are we going? [see comments]."

National Health and Medical Research Council. 1991. *Recommended dietary intakes

Naureckas, S.M. and K.K. Christoffel. 1994. "Nasogastric or gastrostomy feedings in


APPENDICES
Appendix A - Parent Information Sheet & Consent Form

PARENT / CAREGIVER INFORMATION

Nutritional Assessment in Children with Cerebral Palsy

STUDY INVESTIGATOR'S DETAILS

Mrs Fiona Arrowsmith
Study Coordinator and Dietitian
Department of Gastroenterology
The Children's Hospital at Westmead,
Ph: (02) 9845-3983

Dr. Ted O'Loughlin
Gastroenterologist, Department of Gastroenterology
The Children's Hospital at Westmead,
Ph: (02) 9845-3999

Dr. Helen Somerville
Paediatrician
The Children's Hospital at Westmead,
Ph: (02) 9845-2146

Professor Kevin Gaskin
Gastroenterologist, Department of Gastroenterology
The Children's Hospital at Westmead,
Ph: (02) 9845-3999

Dear Parent or Carer,

We are undertaking a nutritional study in children with severe Cerebral Palsy and would like you to consider your child participating.

Why are we doing the study?
Usually, the assessment of nutritional status in children is relatively straightforward. Just measuring weight and height provides us with enough information to determine whether there is a problem. However, in Cerebral Palsy, nutritional assessment is often complicated by muscle wasting from brain dysfunction, muscular spasms and scoliosis. These factors make the usual height and weight measures unreliable for determining nutritional status. We are in the process of developing simple measures that accurately predict nutritional status. We expect these measures will be useful in determining whether a child with Cerebral Palsy has a problem with nutrition that requires further assessment. We would like the measures to be used in a community setting where specialist equipment and staff are not always available.

Who can participate in the study?
Any child with a diagnosis of quadriplegic cerebral palsy between the ages of 4 and 18 years.

What does the study involve?
The measurements will be conducted at The Children’s Hospital at Westmead mostly in the Department of Gastroenterology. We will ask you to accompany your child to the hospital for one morning. The testing should take approximately 2.5 hours. This study requires that your child be fasted from midnight. Water only is permitted during this fasting period.

1. We will take simple measurements (also called "anthropometry") of your child’s weight, upper arm circumference (with a tape measure) and measure the thickness of skin folds at several sites on the body. This is not in any way painful or uncomfortable.

2. Your child's metabolic rate (also called resting energy expenditure or REE) will be measured when they are fasted and resting. This procedure is painless and requires your child to lie quietly on a bed with their head under a soft, large and clear plastic headbox. Room air is continually flowing through the headbox, so that your child is able to breathe normally. At the same time, the air that your child breathes out is continually being analysed. In this way, we can determine how much energy is being used (rate of metabolism). The test will take about 20 minutes. After this test has been completed your child may have something to eat or a tube feed.

3. The amount of fat tissue and bone mineral density will be measured by a DXA machine. This test takes approximately 10 minutes and involves a very small radiation dose. (Please read attached "DXA information sheet" for more details). This test requires your child to lie quite still, therefore, we might need to administer a light oral sedation (similar to Valium, it will make your child relaxed, they will not go to sleep). Medical staff will administer the sedation. Nursing staff will be present to monitor your child closely during the testing. The sedation lasts for approximately 1 hour. Please note that the sedation is NOT the same as a general anaesthetic, your child will not go to sleep and they will not require ventilation.

4. The amount of protein (or muscle) in the body will be measured using a total body nitrogen (TBN) machine. The TBN involves your child lying on a table and being scanned much the same as for DXA. This involves a very small radiation dose.

5. At home, after the above tests have been completed, we will ask you to record your child's food and drink intake for 3 days in a row. This will require weighing or measuring of all food and drink consumed during this period. We will provide you with electronic scales and measuring cups. If your child has tube feeds only, there is no need to complete a food record.

Once the measurements are complete, we will compare the very accurate measurements of DXA and TBN with the simple anthropometric measurements to determine which most accurately reflect nutritional status.

**Are there any risks?**
The weight, arm circumference and skin fold measures are risk free. DXA and TBN are safe. They involve extremely low exposure to radiation - the equivalent to 2 months exposure to radiation from the atmosphere. These tests have been approved as completely safe for children and have been used for more than 10 years in our hospital.

**What are the benefits for your child?**
We will obtain very accurate measurements of your child’s nutritional status. The information will be of assistance in any recommendations we make regarding further tests or treatment and you will be provided with a full report of these findings. This information will also be available in your child’s medical record and to the doctors and other staff involved in your child’s care.
What if you don’t want to participate?
Participation in this project is voluntary and if you decide not to take part or decide to withdraw at any time this will not otherwise affect your child’s care at the Hospital.

All data will be stored under lock and key and in computer files protected by passwords. Only investigators involved in the study will have access to these data. We will treat all information provided as strictly confidential and your child will not be identified in the results of the study.

If you have any concerns about the conduct of this study, please do not hesitate to discuss them with any of the investigators listed on this information sheet or with Ms Anne O’Neill (ph: 9845-3013) the secretary of the Ethics Committee which has approved this study.

This Information Sheet is for you to keep. If you decide for your child to participate in this study a copy of the signed Consent Form will be given to you.
DXA (Dual Energy X-Ray Absorptiometry)

Information Sheet

DXA or DEXA is short for “Dual-Energy X-ray Absorptiometry”. DXA is used to measure the amount of bone mineral in the bone and thus give an estimate of bone density. Bone density is a measure of how strong the bones are.

Additionally, DXA is used to determine body composition as the technique can measure the amount of lean tissue and fat tissue in the body.

At the Children's Hospital at Westmead, DXA measurements are made of the total body, lower spine and the top of the femur. The skin entrance dose for the three scans is less than 75 μSv, (effective dose less than 2 uSv) which is less than that normally received daily from natural sources of radiation (effective dose of 6 μSv/day).

DXA is an easy, painless test. There are no needles or injections. The only preparation required is the removal of any pieces of clothing and accessories that contain metal or thick plastics.

All you need to do is lie on a table for approximately 15 minutes. Whilst you lie on the table, an x-ray beam is passed through your body. As the x-ray travels through your body, air, bone and tissue stop some of the x-ray. By knowing how much x-ray your body stops, the machine can work out how much bone and tissue your body contains. (It also uses the information to make a picture like that shown on the left.)
CONSENT FORM FOR PARENTS/CAREGIVERS

Nutritional Assessment in Children with Cerebral Palsy

INVESTIGATORS

Mrs. Fiona Arrowsmith
Dr. Ted O'Loughlin
Dr. Helen Somerville

I have read and understood the Parent/Caregiver Information Sheet, and give consent for my child to participate in this research study, which has been explained to me by ________________

I understand that this project involves the exposure of my child to radiation measuring <0.152 mSv.

I have been advised by ________________ that the total exposure of my child to radiation for research purposes to age 18 years is restricted to a total of 5 mSv. It is also recommended that my child should not be exposed to more than 0.5 mSv in one year, for research purposes.

My child

☐ Is or has not been involved in any other research projects involving the use of ionising radiation.

☐ Is or has participated in other research projects and to date has been exposed to ______mSv
   (For research purposes only)

I understand that I am free to withdraw from the study at any time and this decision will not otherwise affect my child’s treatment at the Hospital.

Name of child (please print): ________________________________ Please print

Name of parent or guardian: ________________________________ Please print

Signature of parent or guardian: ____________________________ Date: ____________

Name of witness: ________________________________ Please print

Signature of witness: ____________________________ Date: ____________

Name of interpreter: ________________________________ Please print

Signature of interpreter: ____________________________ Date: ____________
Appendix B - Anthropometric equations

1  Knee Height (KH)

The following formula was used for estimating stature (S) in children with CP less than or equal to 12 years of age (Stevenson 1995b)

\[ S = (2.69 \times KH) + 24.2 \]

The following formulae were used for estimating stature (S) in children with CP aged 13 years and above (Chumlea et al. 1994).

Boys

6 - 18 years \[ S = (2.22 \times KH) + 40.54 \]

19 - 59 years \[ S = (1.88 \times KH) + 71.85 \]

Girls

6 - 18 years \[ S = (2.15 \times KH) + 43.21 \]

19 - 59 years \[ S = (1.86 \times KH) - (\text{age} \times 0.05) \pm 70.25 \]

2  Body mass index (BMI)

\[ \text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2} \]

3  Upper arm muscle area (UAMA)

\[ \text{UAMA} = \frac{(\text{MUAC} - \pi \times \text{TSK})^2}{4\pi} \]

Where MUAC is mid upper arm circumference; TSK is triceps skinfold thickness.
Percent body fat

(a)

**Brook (for prepubertal children)** (Brook 1971):

Males: \[ D_b (\text{g/ml}) = 1.1690 - 0.0788(\log \Sigma X_4) \]

Females \[ D_b (\text{g/ml}) = 1.2063 - 0.0999(\log \Sigma X_4) \]

**Durnin and Rahaman (for pubertal children)** (Durnin and Rahaman 1967)

Males: \[ D_b (\text{g/ml}) = 1.1533 - 0.0643(\log \Sigma X_4) \]

Females: \[ D_b (\text{g/ml}) = 1.1369 - 0.0598(\log \Sigma X_4) \]

Where \( D_b \) is body density; \( \Sigma X_4 \) is the sum of the four skinfold thicknesses (biceps + triceps + suprailiac + subscapular).

For the above two sets of equations, body density (\( D_b \)) was converted to percent body fat using the following equation (Siri 1993):

\[ \text{PBF} = \{(4.95 / D_b) - 4.50\} \times 100 \]

(b)

**Slaughter equations** (Slaughter et al. 1988)

**Males**

Prepubertal \[ \text{PBF} = 1.21(\Sigma X_2) - 0.008(\Sigma X_2)^2 - 1.7 \]

Pubertal \[ \text{PBF} = 1.21(\Sigma X_2) - 0.008(\Sigma X_2)^2 - 3.4 \]

Postpubertal \[ \text{PBF} = 1.21(\Sigma X_2) - 0.008(\Sigma X_2)^2 - 5.5 \]

**Females**

All \[ \text{PBF} = 1.33(\Sigma X_2) - 0.013(\Sigma X_2)^2 - 2.5 \]

Where \( \Sigma X_2 \) is the sum of the triceps and subscapular skinfold thicknesses.
Appendix C - Total body protein predictive equations

The following equations were developed from the TBP control database (34F, 5 – 14.4y; 27M, 4 - 15.9y) and were used to predict TBP for age, height and weight in the children with CP.

1  Total body protein predicted for age:

   Males  \( \text{TBP} = 2980 + [2.564 \times \text{age(y)}^3] \)

   Females  \( \text{TBP} = 2790 + [2.27 \times \text{age(y)}^3] \)

2  Total body protein predicted for height:

   Males  \( \text{TBP} = 2212 + [(6.444 \times 10^{-8}) \times \text{height(cm)}^5] \)

   Females  \( \text{TBP} = 2157 + [(5.563 \times 10^{-8}) \times \text{height(cm)}^5] \)

3  Total body protein predicted for weight:

   Males  \( \text{TBP} = 293 + [160.7 \times \text{weight(kg)}] \)

   Females  \( \text{TBP} = 759 + [133 \times \text{weight(kg)}] \)
Appendix D - Hydration constants

1 Hydration constants of fat-free mass used for children aged less than or equal to 7 years (Fomon et al. 1982).

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>77.0</td>
<td>77.7</td>
</tr>
<tr>
<td>5</td>
<td>76.6</td>
<td>77.6</td>
</tr>
<tr>
<td>6</td>
<td>76.3</td>
<td>77.5</td>
</tr>
<tr>
<td>7</td>
<td>75.9</td>
<td>77.3</td>
</tr>
</tbody>
</table>

2 Hydration constants of fat-free mass used for children aged 8 years and above (Lohman 1986).

<table>
<thead>
<tr>
<th>Age range (y)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 – 9</td>
<td>76.8</td>
<td>77.6</td>
</tr>
<tr>
<td>10 – 11</td>
<td>76.2</td>
<td>77.0</td>
</tr>
<tr>
<td>12 – 13</td>
<td>75.4</td>
<td>76.6</td>
</tr>
<tr>
<td>14 – 15</td>
<td>74.7</td>
<td>75.5</td>
</tr>
<tr>
<td>16 – 17</td>
<td>74.2</td>
<td>75.0</td>
</tr>
<tr>
<td>18 - 20</td>
<td>74.0</td>
<td>74.8</td>
</tr>
</tbody>
</table>

1 The age of the study participant was rounded to nearest whole number.
## Appendix E - Medications

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Medication Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
</tr>
<tr>
<td>2</td>
<td>a, b</td>
</tr>
<tr>
<td>3</td>
<td>a, d, e, f</td>
</tr>
<tr>
<td>4</td>
<td>a, b</td>
</tr>
<tr>
<td>5</td>
<td>a, b, c, d</td>
</tr>
<tr>
<td>6</td>
<td>a, b, d</td>
</tr>
<tr>
<td>7</td>
<td>c, f</td>
</tr>
<tr>
<td>8</td>
<td>a, d</td>
</tr>
<tr>
<td>9</td>
<td>a, b, f</td>
</tr>
<tr>
<td>10</td>
<td>a, d</td>
</tr>
<tr>
<td>11</td>
<td>a, b</td>
</tr>
<tr>
<td>12</td>
<td>a, b, e, f</td>
</tr>
<tr>
<td>13</td>
<td>e</td>
</tr>
<tr>
<td>14</td>
<td>d, e</td>
</tr>
<tr>
<td>15</td>
<td>a, b</td>
</tr>
<tr>
<td>16</td>
<td>c</td>
</tr>
<tr>
<td>17</td>
<td>a</td>
</tr>
<tr>
<td>18</td>
<td>Nil</td>
</tr>
<tr>
<td>19</td>
<td>a, f</td>
</tr>
<tr>
<td>20</td>
<td>a, e</td>
</tr>
<tr>
<td>21</td>
<td>b, c, d, e</td>
</tr>
<tr>
<td>22</td>
<td>a, c</td>
</tr>
<tr>
<td>23</td>
<td>b, d</td>
</tr>
<tr>
<td>24</td>
<td>a, b, d</td>
</tr>
<tr>
<td>25</td>
<td>a, b</td>
</tr>
<tr>
<td>26</td>
<td>a, b</td>
</tr>
<tr>
<td>27</td>
<td>a, b</td>
</tr>
<tr>
<td>28</td>
<td>b</td>
</tr>
<tr>
<td>29</td>
<td>a, f</td>
</tr>
<tr>
<td>30</td>
<td>a, b, e</td>
</tr>
<tr>
<td>31</td>
<td>a, b, d</td>
</tr>
<tr>
<td>32</td>
<td>a, b, c, d</td>
</tr>
<tr>
<td>33</td>
<td>d, e</td>
</tr>
<tr>
<td>34</td>
<td>a, d, e</td>
</tr>
<tr>
<td>35</td>
<td>a, d, f</td>
</tr>
<tr>
<td>36</td>
<td>a</td>
</tr>
<tr>
<td>37</td>
<td>a, d</td>
</tr>
<tr>
<td>38</td>
<td>b, c</td>
</tr>
<tr>
<td>39</td>
<td>a</td>
</tr>
<tr>
<td>40</td>
<td>c</td>
</tr>
<tr>
<td>41</td>
<td>Nil</td>
</tr>
<tr>
<td>42</td>
<td>a, b</td>
</tr>
<tr>
<td>43</td>
<td>f</td>
</tr>
<tr>
<td>44</td>
<td>Nil</td>
</tr>
<tr>
<td>45</td>
<td>a</td>
</tr>
<tr>
<td>46</td>
<td>a</td>
</tr>
<tr>
<td>47</td>
<td>No subject</td>
</tr>
<tr>
<td>48</td>
<td>b</td>
</tr>
<tr>
<td>49</td>
<td>b, c</td>
</tr>
<tr>
<td>50</td>
<td>a, b</td>
</tr>
<tr>
<td>51</td>
<td>a</td>
</tr>
<tr>
<td>52</td>
<td>a</td>
</tr>
<tr>
<td>53</td>
<td>a</td>
</tr>
<tr>
<td>54</td>
<td>a, d</td>
</tr>
<tr>
<td>55</td>
<td>a, b</td>
</tr>
<tr>
<td>56</td>
<td>a, b</td>
</tr>
<tr>
<td>57</td>
<td>a</td>
</tr>
<tr>
<td>58</td>
<td>b</td>
</tr>
<tr>
<td>59</td>
<td>b, e</td>
</tr>
<tr>
<td>60</td>
<td>a, d</td>
</tr>
<tr>
<td>Medication Group Code</td>
<td>Name of medication</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------</td>
</tr>
</tbody>
</table>
| **Group (a) Anti-epileptic** | Phenobarbitone  
Epilim  
Tegretol  
Lamictal  
Rivotril  
Frisium  
Vigabatrin  
Gabapentin  
Topamax  
Dilantin  
Lamotrigine |
| **Group (b) Anti-reflux** | Losec  
Zantac  
Prepulsid (cisapride)  
Acimax |
| **Group (c) Constipation** | Parachoc  
Coloxyl  
Actilax  
Senokot  
Duphalac |
| **Group (d) Anti-anxiety** | Valium  
Mogadon  
Ativan  
Diazepam |
| **Group (e) Movement disorders** | Baclofen  
Madopar  
Sinemet  
Artane |
| **Group (f) Asthma prophylaxis** | Atrovent  
Ventolin  
Pulmicort  
Seretide |
Appendix F - Equations used for predicting resting energy expenditure

1  Schofield predictive equations based on weight (Schofield 1985):

   Males

   Age range (y)   REE (kJ / 24hr)
   3-10   {[0.095 x weight (kg)] + 2.110} x 1000
   10-18  {[0.074 x weight (kg)] + 2.754} x 1000

   Females

   Age range (y)   REE (kJ / 24hr)
   3-10   {[0.085 x weight (kg)] + 2.033} x 1000
   10-18  {[0.056 x weight (kg)] + 2.898} x 1000

2  Predictive equations developed from control database based on fat-free mass measured by skinfold anthropometry (FFM_{SKIN}):

   Males:  REE (kJ / 24hr) = 2778 + [102.7 x FFM_{SKIN} (kg)]
   Females: REE (kJ / 24hr) = 1370 + [108.2 x FFM_{SKIN} (kg)]
Appendix G - Nutritional rehabilitation study information sheet

PARENT/CAREGIVER INFORMATION

Nutritional Therapy in Children with Cerebral Palsy

INVESTIGATOR’S DETAILS

Ms. Fiona Arrowsmith  
Study Coordinator and Dietitian  
Department of Gastroenterology  
The Children’s Hospital at Westmead, Ph:(02) 9845-3983

Dr. Ted O’Loughlin  
Gastroenterologist, Department of Gastroenterology  
The Children’s Hospital at Westmead, Ph:(02) 9845-3999

Dr. Angie Morrow  
Paediatrician  
The Children’s Hospital at Westmead, Ph:(02) 9845-3039

Dr. Helen Somerville  
Paediatrician  
The Children’s Hospital at Westmead, Ph:(02) 9845-2146

Professor Kevin Gaskin  
Gastroenterologist, Department of Gastroenterology  
The Children’s Hospital at Westmead, Ph:(02) 9845-3999

Dear Parent or Carer,

We would like you to consider your child participating in a nutritional study of children with severe cerebral palsy that will be conducted in the Department of Gastroenterology at the Children’s Hospital at Westmead.

What is the study about?

Many children with Cerebral Palsy suffer from undernutrition because of difficulties in swallowing resulting in the inability to get in enough calories (energy). Swallowing problems can also contribute to chest disease if the food is inhaled into the lungs. There are several therapies used to overcome these problems. We are interested in studying two therapies that are currently used as routine therapies at this hospital, (1) basic speech pathology combined with dietary advice, and (2) tube feeding.
Speech pathology is designed to improve swallowing by means of proper positioning of the child’s body and head during feeding, adaptation of cups or other utensils, a programme of oral exercises, and changing food choices, for example, choosing different textures of food, and increasing the thickness of fluids. The aim of dietary advice is usually to increase the energy and nutrient content of food, for example, by choosing high energy foods, or by adding fats, or with specific high energy nutritional supplements. Speech pathology and dietary advice go hand-in-hand to maximise your child’s oral intake. Whereas tube feeding bypasses the swallowing problem by placing "food" directly into the stomach. Both therapies aim to improve nutritional intake and therefore improve your child’s nutritional status.

We wish to study these therapies to determine if they result in improved nutrition and also to determine the benefits and disadvantages of either approach. It is also important to know if improved nutrition results in improved general health and quality of life.

Who can participate in the study?
Any child with a diagnosis of spastic quadriplegic cerebral palsy, between the ages of 4 and 18 years, who does not currently have a nasogastric or gastrostomy tube.

What does the study involve?
The study will be conducted at The Children's Hospital at Westmead. Ideally, we would like to randomly allocate your child to either group (I) Basic Dietary Advice and Speech Pathology Programme, or (II) Tube Feeding Programme, for a period of 6 months. This means that your child will be placed into either of these groups based on a computer-generated allocation that is random. In other words, yourself or your doctor does not determine this. If you agree for your child to be randomly allocated to either group, this will not prevent the use of speech therapy or tube feeding after the 6-month trial if the initial therapy is unsuccessful. Alternatively, you may have strong feelings about which therapy is suitable for your child and will not agree to this random allocation process. You can discuss this with any of the study investigators listed on the first page of this information sheet.

If you agree to join this study, your child will undergo an initial evaluation which involves some measurements of nutritional status as outlined in the parent information sheet entitled “Nutritional Assessment in Children with Cerebral Palsy”.

The treatment will be slightly different depending on which group your child enters.

**Group 1**
If your child enters the Basic Dietary Advice and Speech Pathology Programme they will undergo an evaluation by a speech pathologist and a dietitian (Fiona Arrowsmith). This entails two consultations (one with the speech pathologist and one with the dietitian); a modified barium swallow to assess your child’s swallow, observation of your child’s eating pattern, and discussion of your child’s usual dietary intake and food choices. The speech pathologist and dietitian will give you recommendations to improve your child’s swallow and nutritional intake. Please see Table 1 on the following page for the timetable of assessments during the 6-month study period.

**Group 2**
If your child enters the Tube Feeding Programme they will have either a tube inserted into the stomach via the nose (nasogastric tube) or through the skin of the stomach (gastrostomy tube). A special tube feeding formula will be administered via the tube to provide nutrition in
addition to oral intake of food. Our study dietitian (Fiona Arrowsmith) will advise you about the type and amount of formula to use. You will also be given instruction in how to do this at home. Please see Table 1 on the following page for the timetable of assessments during the 6-month study period.

During the study period you will be in weekly contact with study co-ordinator (Fiona Arrowsmith). The programmes will continue for 6 months during which time we will monitor growth and nutritional parameters as outlined in Table 1 and in the “Nutritional Assessment in Children with Cerebral Palsy” information sheet. In addition, your child will be regularly examined by one of the doctors involved in the study.

We are also interested to know how the treatment affects the quality of life of your child and importantly whether it affects you and your family. You will be asked to fill out a questionnaire and invited to join a discussion group with other parents and carers to express your views about your child’s treatment.

**TABLE 1** – Timetable for 6-month study period for both programmes

<table>
<thead>
<tr>
<th>Tests</th>
<th>Month 0</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropometry</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>TBN</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>DXA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>REE</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Food Record</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood Sample</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Medical Ass.</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Please read the Parent/Caregiver Information Sheet entitled “Nutritional Assessment in Children with Cerebral Palsy” for details of the tests listed in Table 1.

**Are there any side-effects and risks associated with this study?**

We are not proposing to undertake any investigation or treatment that is not already routinely offered to children with cerebral palsy except for the DEXA, TBN and resting energy expenditure measurements described in the “Nutritional Assessment in Children with Cerebral Palsy” information sheet.

There are no medical risks associated with the Basic Speech Pathology and Dietary Advice Programme unless your child has proven food inhalation with swallowing. This will be investigated prior to your child being included in the study.

Nasogastric or gastrostomy tube feeding can be a medical risk in children with reflux and/or food inhalation. If your child suffers from either reflux or food inhalation with swallowing, they may require anti-reflux surgery to prevent complications from tube feeding. This will be explored by your doctor and explained in detail if anti-reflux surgery is required. Please note that the surgery is routinely offered to children with cerebral palsy if their doctors are concerned about reflux or inhalation.
Are there any benefits for my child participating in the study?

Your child will be under the care of doctors and health professionals who are experts in the field of cerebral palsy. The therapy that your child receives will be examined to determine if it is of benefit to your child in terms of improved nutrition and importantly in terms of quality of life for your child, yourself and your family.

We hope the information we obtain from this study may enable us to design therapies that are of proven benefit in cerebral palsy.

What if I don’t want to participate?

We would be very grateful for the opportunity to undertake these investigations on your child. However, participation in this study is voluntary. If you decide not to participate, or decide to withdraw your child from the study at any time, this will not otherwise affect your child’s care at the Hospital.

All data will be stored under lock and key and in computer files protected by passwords. Only investigators involved in the study will have access to these data. We will treat all information provided as strictly confidential and your child will not be identified in the results of the study.

If you have any concerns about the conduct of this study, please do not hesitate to discuss them with any of the investigators listed on this information sheet or with Ms Anne O’Neill (ph: 9845-3013) the secretary of the Ethics Committee which has approved this study.

This Information Sheet is for you to keep. If you decide for your child to participate in this study a copy of the signed Consent Form will be given to you.
### Appendix H - Baseline and repeat measures of oral-fed children

Table H1: Baseline and repeat anthropometric characteristics of oral-fed children with cerebral palsy

<table>
<thead>
<tr>
<th></th>
<th>Oral-fed (4F, 4M)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Repeat</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>8.6 (7.4, 12.3)</td>
<td>10.9 (10.3, 15.4)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>21.0 (16.6, 24.7)</td>
<td>25.1 (19.4, 31.7)</td>
<td></td>
</tr>
<tr>
<td>Weight SDS</td>
<td>-3.1 (-4.0, -2.1)</td>
<td>-3.9 (-6.5, -2.0)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>120.3 (105.0, 128.2)</td>
<td>133.0 (118.1, 135.6)</td>
<td></td>
</tr>
<tr>
<td>Height SDS</td>
<td>-3.0 (-4.3, -1.8)</td>
<td>-2.7 (-4.7, -1.3)</td>
<td></td>
</tr>
<tr>
<td>Ideal weight for height (%)</td>
<td>85.9 (75.7, 102.5)</td>
<td>86.7 (78.4, 103.8)</td>
<td></td>
</tr>
<tr>
<td>UAMA (cm²)</td>
<td>19.7 (15.5, 21.7)</td>
<td>21.5 (19.0, 25.3)</td>
<td></td>
</tr>
<tr>
<td>UAMA SDS</td>
<td>-1.4 (-2.2, -0.9)</td>
<td>-0.9 (-3.1, -0.5)</td>
<td></td>
</tr>
<tr>
<td>UAFA (cm²)</td>
<td>5.3 (3.0, 6.0)</td>
<td>5.5 (4.1, 7.7)</td>
<td></td>
</tr>
<tr>
<td>UAFA SDS</td>
<td>-1.9 (-2.9, -0.8)</td>
<td>-0.2 (-2.6, 1.0)</td>
<td></td>
</tr>
<tr>
<td>FFM&lt;sub(SKIN)&lt;/sub&gt; (kg)</td>
<td>18.5 (15.2, 20.2)</td>
<td>21.3 (17.0, 26.1)</td>
<td></td>
</tr>
<tr>
<td>FM&lt;sub(SKIN)&lt;/sub&gt; (kg)</td>
<td>2.5 (0.9, 4.3)</td>
<td>2.9 (1.8, 5.0)</td>
<td></td>
</tr>
<tr>
<td>PBF&lt;sub(SKIN)&lt;/sub&gt; (%)</td>
<td>10.7 (5.8, 17.7)</td>
<td>12.0 (8.6, 18.0)</td>
<td></td>
</tr>
</tbody>
</table>

Data is median (inter-quartile range). FFM<sub(SKIN)</sub>, fat-free mass by skinfold anthropometry; FM<sub(SKIN)</sub>, fat mass by skinfold anthropometry; PBF<sub(SKIN)</sub>, percent body fat by skinfold anthropometry; SDS, standard deviation score; UAFA, upper arm fat area; UAMA, upper arm muscle area.

<sup>1</sup> p < 0.05; significantly different between baseline and repeat test; Wilcoxon Signed Ranks test.
Table H2: Baseline and repeat body composition measures by DXA of oral-fed children with cerebral palsy

<table>
<thead>
<tr>
<th>Oral-fed (4F, 4M)</th>
<th>Baseline</th>
<th>Repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMC (g)</strong></td>
<td>564 (515, 717)(^1)</td>
<td>721 (623, 991)(^{1,2})</td>
</tr>
<tr>
<td><strong>BMC for age SDS</strong></td>
<td>-2.0 (-2.2, -1.2)(^1)</td>
<td>-3.0 (-3.4, -1.6)(^1)</td>
</tr>
<tr>
<td><strong>BMC for height SDS</strong></td>
<td>-0.7 (-2.7, 0.1)(^1)</td>
<td>-1.0 (-2.7, 0.2)(^1)</td>
</tr>
<tr>
<td><strong>BMC for LTM &amp; ht SDS</strong></td>
<td>-1.6 (-1.9, -0.8)</td>
<td>-1.4 (-1.5, -0.8)(^1)</td>
</tr>
<tr>
<td><strong>LTM(_{\text{DXA}}) (kg)</strong></td>
<td>16.9 (14.0, 19.3)</td>
<td>21.0 (16.3, 24.2)(^2)</td>
</tr>
<tr>
<td><strong>LTM(_{\text{DXA}}) for height SDS</strong></td>
<td>-0.2 (-2.0, 1.7)(^1)</td>
<td>0.1 (-2.2, 0.7)</td>
</tr>
<tr>
<td><strong>FM(_{\text{DXA}}) (kg)</strong></td>
<td>3.2 (1.3, 4.6)</td>
<td>2.5 (1.9, 6.6)</td>
</tr>
<tr>
<td><strong>PBF(_{\text{DXA}}) (%)</strong></td>
<td>14.2 (7.1, 19.8)</td>
<td>13.2 (8.3, 23.8)</td>
</tr>
</tbody>
</table>

Data is median (inter-quartile range). BMC, bone mineral content; DXA, dual-energy x-ray absorptiometry; FM\(_{\text{DXA}}\), fat mass by DXA; LTM\(_{\text{DXA}}\), lean tissue mass by DXA; PBF\(_{\text{DXA}}\), percent body fat by DXA; SDS, standard deviation score.

\(^1\) n = 7

\(^2\) p < 0.05; significantly different between baseline and repeat testing; Wilcoxon Signed Ranks test.
<table>
<thead>
<tr>
<th>Oral-fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>(4F, 4M)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>TBP&lt;sub&gt;NAA&lt;/sub&gt; (kg)</td>
</tr>
<tr>
<td>TBP&lt;sub&gt;NAA&lt;/sub&gt; for age (%)</td>
</tr>
<tr>
<td>TBP&lt;sub&gt;NAA&lt;/sub&gt; for height (%)</td>
</tr>
<tr>
<td>TBP&lt;sub&gt;NAA&lt;/sub&gt; for weight (%)</td>
</tr>
</tbody>
</table>

Data is median (inter-quartile range). FFM<sub>Skin</sub>, fat-free mass measured by skinfold anthropometry; NAA, neutron activation analysis; TBP<sub>NAA</sub>, total body protein.

<sup>1</sup> p < 0.05, significantly different between baseline and repeat test; Wilcoxon Signed Ranks test.
Table H4: Annualised change in body composition parameters in the oral-fed children with cerebral palsy

<table>
<thead>
<tr>
<th></th>
<th>Oral-fed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(4F, 4M)</td>
</tr>
<tr>
<td>Weight (kg) / y</td>
<td>1.6 (0.8, 4.7)</td>
</tr>
<tr>
<td>Height (cm) / y</td>
<td>4.0 (2.1, 6.6)</td>
</tr>
<tr>
<td>UAMA (cm²) / y</td>
<td>2.3 (0.0, 3.6)</td>
</tr>
<tr>
<td>UAFA (cm²) / y</td>
<td>0.5 (0.1, 1.4)</td>
</tr>
<tr>
<td>FM⁹SKIN (kg) / y</td>
<td>0.4 (0.2, 1.2)</td>
</tr>
<tr>
<td>FFM⁹SKIN (kg) / y</td>
<td>1.3 (0.5, 3.5)</td>
</tr>
<tr>
<td>PBF⁹SKIN (%) / y</td>
<td>1.1 (0.4, 2.0)</td>
</tr>
<tr>
<td>BMC (g) / y</td>
<td>77.1 (43.3, 116.1)</td>
</tr>
<tr>
<td>LTM⁹DXA (kg) / y</td>
<td>1.3 (0.7, 3.2)</td>
</tr>
<tr>
<td>FM⁹DXA (kg) / y</td>
<td>0.4 (1.2, 1.6)</td>
</tr>
<tr>
<td>PBF⁹DXA (%) / y</td>
<td>0.5 (-0.3, 2.5)</td>
</tr>
<tr>
<td>TBP⁹NAA (g) / y</td>
<td>567 (301, 986)</td>
</tr>
</tbody>
</table>

Data is median (inter-quartile range). DXA, dual-energy X-ray absorptiometry; UAMA, upper arm muscle area; UAFA, upper arm fat area; FM⁹SKIN, fat mass by skinfold anthropometry; FFM⁹SKIN, fat-free mass by skinfold anthropometry; PBF⁹SKIN, percent body fat by skinfold anthropometry; BMC, bone mineral content; LTM⁹DXA, lean tissue mass by DXA; FM⁹DXA, fat mass by DXA; LTM⁹DXA, lean tissue mass by DXA; PBF⁹DXA, percent body fat by DXA; TBP⁹NAA, total body protein by neutron activation analysis; y, year.

¹ n = 7
Table H5: Baseline and repeat measures of resting energy expenditure and energy intake

<table>
<thead>
<tr>
<th>Oral-fed</th>
<th>Baseline</th>
<th>Repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td>(4F, 4M)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MREE (kJ / 24hr)</td>
<td>2331 (1749, 3637)</td>
<td>4612 (3699, 5371) (^1,^4)</td>
</tr>
<tr>
<td>MREE / PREE (%)</td>
<td>62.4 (45.0, 81.1)</td>
<td>97.1 (79.9, 157.0) (^1,^4)</td>
</tr>
<tr>
<td>Energy Intake (kJ / 24hr)</td>
<td>4296 (3793, 6800) (^1)</td>
<td>5602 (4223, 5685) (^2)</td>
</tr>
<tr>
<td>Energy Intake / MREE (%)</td>
<td>191 (175, 283) (^3)</td>
<td>123 (79, 255) (^3)</td>
</tr>
</tbody>
</table>

Data is median (inter-quartile range). MREE, measured resting energy expenditure by indirect calorimetry; PREE, predicted resting energy expenditure adjusted for fat-free mass using equations developed from control database.

\(^1\) n = 7, \(^2\) n = 4, \(^3\) n = 3

\(^4\) \text{p} < 0.05, \text{significantly different between baseline and repeat measurements, Wilcoxon Signed Ranks test.}
Table H6: Baseline and repeat measures of resting energy expenditure and energy intake excluding REE >140%

<table>
<thead>
<tr>
<th>Oral-fed (2F, 4M)</th>
<th>Baseline</th>
<th>Repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td>MREE (kJ / 24hr)</td>
<td>2267 (1633, 3947)</td>
<td>4329 (2947, 4991) (^1)</td>
</tr>
<tr>
<td>MREE / PREE (%)</td>
<td>53.5 (42.0, 80.0)</td>
<td>85.5 (70.8, 104.4) (^1)</td>
</tr>
<tr>
<td>Energy Intake (kJ / 24hr)</td>
<td>6778 (4045, 6870) (^1)</td>
<td>5602 (4223, 5685) (^2)</td>
</tr>
<tr>
<td>Energy Intake / MREE (%)</td>
<td>272 (171, 344) (^1)</td>
<td>123 (79, 255) (^3)</td>
</tr>
</tbody>
</table>

Data is median (inter-quartile range). MREE, measured resting energy expenditure by indirect calorimetry; PREE, predicted resting energy expenditure adjusted for fat-free mass using equations developed from control database.

\(^1\) n = 5, \(^2\) n = 4, \(^3\) n = 3

\(^2\) p < 0.05, significantly different between baseline and repeat measurements, Wilcoxon Signed Ranks test.
~ The End ~