EBRSR

HEART & STROKE FOUNDATION
Canadian Partnership for Stroke Recovery

Chapter 16: Nutritional rehabilitation

Abstract

Nutritional status following stroke can have a negative impact on functional recovery and mortality. Complications associated with malnutrition include a greater incidence of infections and pressure sores, and longer lengths of hospital stays. Clinical nutritional management requires effective methods of assessment, an understanding of the underlying causes of nutritional deficiencies, and effective methods of administering nutrients via feeding techniques and supplementation. In this review, the prevalence of malnutrition post stroke is evaluated, and markers used to identify deficiencies are discussed. A summarization of potential causes of nutritional deficiencies is provided, including metabolic rate, nutrient intake, and gastrointestinal impairments. Interventions of enteral feeding and oral supplementation, as well as treatments for dysphagia, are discussed.

Marcus Saikaley, BSc
Jerome Iruthayarajah, MSc
Norine Foley, MSc
Marina Richardson, MSc
Hillel Finestone, MD
Robert Teasell, MD

Chapter 16: Nutritional rehabilitation Table of contents

Key Points **3**

Modified Sackett Scale **4**

New to the 19th edition of the Evidence-based Review of Stroke Rehabilitation **5**

Outcome Measure Definitions **7**

Lipid Consumption 7
Protein Consumption 8
Carbohydrate Consumption 8
Calorie Consumption 8
Vitamins and Mineral Consumption 9
Body Composition 10
Blood Glucose Management 11
Plasma Proteins 11
Blood Pressure 12
Lymphocyte Count 12
Activities of Daily Living 13
Stroke Severity 13

Assessment of Nutritional Status Following Stroke **14**

Prevalence of Malnutrition Following Stroke **16**

Factors Associated With the Development of Malnutrition **22**

Metabolic Rate Following Stroke 22
Gastrointestinal Impairments Following Stroke 23
Nutrient Intake Following Stroke 24

Nutritional rehabilitation interventions **26**

Glucose Regulation 26
Lipid Regulation 30
Vitamin D Supplementation 32
Oral Nutritional Supplementation 35

References **41**

Key Points

Blood glucose management may be beneficial for improving blood glucose, but not other aspects of nutrition.

Atorvastatin may be beneficial for lipid consumption and regulation.

Vitamin D supplements may be beneficial for improving vitamin and mineral consumption, but not lipid consumption, blood pressure, plasma proteins or stroke severity.

Protein and calorie supplements may not be beneficial for improving body composition but may be beneficial for improving stroke severity.

ALAnerv supplements may improve blood glucose management, plasma proteins and activities of daily living.

Modified Sackett Scale

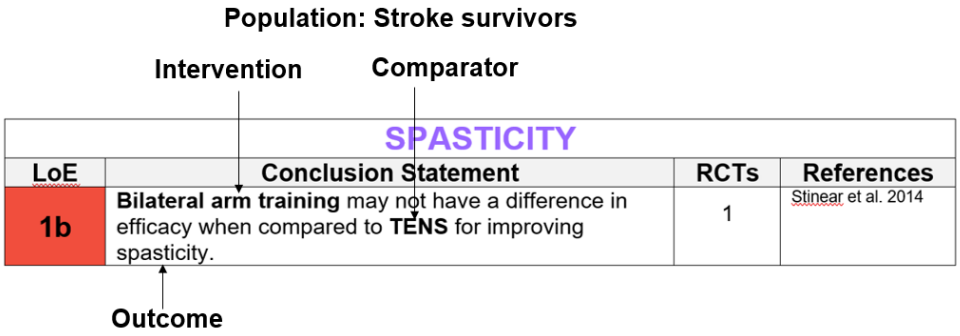
Level of evidence	Study design	Description
Level 1a	Randomized controlled trial (RCT)	More than 1 higher quality RCT (PEDro score ≥6).
Level 1b	RCT	1 higher quality RCT (PEDro score ≥6).
Level 2	RCT	Lower quality RCT (PEDro score <6).
	Prospective controlled trial (PCT)	PCT (not randomized).
	Cohort	Prospective longitudinal study using at least 2 similar groups with one exposed to a particular condition.
Level 3	Case Control	A retrospective study comparing conditions, including historical cohorts.
Level 4	Pre-Post	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects.
	Post-test	A prospective post-test with two or more groups (intervention followed by post-test and no re-test or baseline measurement) using a single group of subjects
	Case Series	A retrospective study usually collecting variables from a chart review.
Level 5	Observational	Study using cross-sectional analysis to interpret relations. Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or "first principles".
	Case Report	Pre-post or case series involving one subject.

New to the 19th edition of the Evidence-based Review of Stroke Rehabilitation

1) PICO conclusion statements

This edition of Chapter 16: Nutritional rehabilitation synthesizes study results from only randomized controlled trials (RCTs), all levels of evidence (LoE) and conclusion statements are now presented in the Population Intervention Comparator Outcome (PICO) format.

For example:

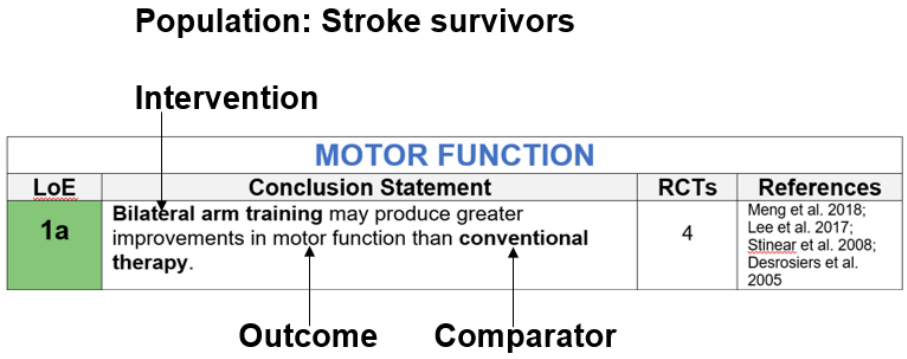


New to these statements is also the use of colours where the levels of evidence are written.

Red statements like above, indicate that the majority of study results when grouped together show no significant differences between intervention and comparator groups.

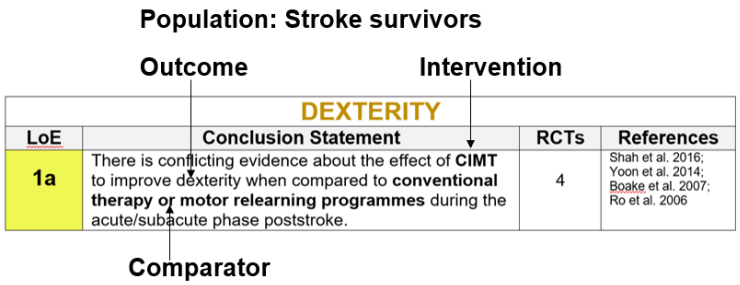
Green statements indicate that the majority of study results when grouped together show a significant between group difference in favour of the intervention group.

For example:



Yellow statements indicate that the study results when grouped together are mixed or conflicting, some studies show benefit in favour of the intervention group, while others show no difference between groups.

For example:



DEXTERITY				
LoE		Conclusion Statement	RCTs	References
1a		There is conflicting evidence about the effect of **CIMT** to improve dexterity when compared to **conventional therapy or motor relearning programmes** during the acute/subacute phase poststroke.	4	Shah et al. 2016; Yoon et al. 2014; Boake et al. 2007; Ro et al. 2006

2) Dysphagia rehabilitation outcome measures

Outcome measures were classified into the following broad categories:

Lipid consumption: Outcome measure related to triglyceride body composition.

Calorie consumption: Assessed caloric intake and fluid intake.

Vitamin and mineral consumption: Assessed the consumption of vitamin or minerals.

Body composition: Different anthropometric measurements.

Plasma proteins: Outcomes that deal with circulating protein levels in a participant's blood.

Blood pressure: Measures of blood pressure.

Lymphocyte count: Is a measure of neutrophil to lymphocyte concentrations.

Activities of daily living: These outcome measures assessed performance and level of independence in various everyday tasks.

Stroke severity: These outcome measures assessed the severity of one's stroke through a global assessment of a multitude of deficits a stroke survivor may experience.

Outcome measures that fit these categories are described in the next few pages.

Outcome Measure Definitions

Lipid Consumption

Cholesterol Levels: Is a measure of the amount of cholesterol present in the body. Cholesterol is a sterol (which is a subset of the lipid family), and is an essential structural component of animal cell membranes. These levels include both low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Normal cholesterol levels are <200mg/dL (Barter et al. 2007).

High Density Liproprotein (HDL): Is a lipoprotein which along with low-density lipoprotein (LDL), forms a substance known as cholesterol. The purpose of HDL is to carry the overall cholesterol molecule from other parts of the body back to the liver. Normal HDL levels for men are 40-50mg/dL and for women normal levels are 50-55mg/dL (Khera et al. 2011).

Daily Lipid Intake: Is a measure of how many grams of fat a patient consumes per day. An average person consumes 44-77 grams of fats per day (Nichols et al. 1976).

Lipid Hydroperoxides: Is a lipid that when oxidized can become n-hexanal. This oxidized form has an important role in regulating the varying signaling processes of the nervous system (Girotti 1998).

Low Density Lipoprotein (LDL): Is a lipoprotein which along with high-density lipoprotein (HDL), forms a substance known as cholesterol. LDL is typically seen as the detrimental form of cholesterol and elevated levels of LDL can lead to artherosclerosis and increased chance of coronary heart disease. Normal levels of LDL in men are 100mg/dL or less and normal levels of LDL in women are 150mg/dL or less (Nissen et al. 2005).

Total Cholesterol Level: Is a measure of the total amount of cholesterol in a patient's body. This measure is calculated by combining the amount of LDL and HDL cholesterol present in a patient's blood. The ideal range for this level is <200mg/dL, while a reading of 200-239mg/dL is borderline high. Finally, a result of 240mg/dL or above is a high reading (Johnson et al. 1993).

Protein Consumption

Protein Intake: Is the amount of protein that a patient should be consuming within a given time frame (usually over the course of a day). Average protein intake should be 0.8 grams per kilogram of body weight. This results in the average man needing approximately 56 grams of protein per day and the average woman needing approximately 46 grams of protein per day (Martin et al. 2005).

Total Protein Level: Is the measure of the amount of protein present in a patient's body. The normal range for this measure is between 6 and 8.3 g/dL in adults (18+). Any number higher or lower than these values could indicate a medical condition (Sudsuang et al. 1991).

Carbohydrate Consumption

Daily Carbohydrate Intake: is the amount of carbohydrates (often in grams or milligrams) that an individual consumes on average per day. The Dietary Reccomendations for Americans suggests between 225g – 325g per day (U.S Department of Health and Human Services & U.S Department of Agriculture, 2015).

Carbohydrate-Protein Ratio: Is the amount of carbohydrates a patient consumes relative to the amount of protein he/she consumes. Dieticians typically recommend a patient eat 40% carbohydrates and 30% protein (with the remaining 30% of a patient's diet coming from fats) (Abete et al. 2009).

Calorie Consumption

Caloric Intake: Is a measure of how many calories a person consumes per day. Although caloric intake/need may vary from individual to individual, the average male consumes 2500 calories per day, while the average female consumes 2000 calories per day (Luchsinger et al. 2002).

Proportion of Prescribed Feed Delivered: Is the amount of food a patient actually consumes. This is significant because patients with dysphagia tend to have a reduced appetite compared to patients without dysphagia (Johnson & Fischer 2004).

Total Fluid Intake: Is a measure of how many fluids a patient consumes in a given time period. Intake is usually measured daily, but measurement can vary across institutions. Additionally, intake can be measured in either millilitres (mL) or litres (L). It includes both prescribed fluid feed and water (Perrier et al. 2013).

Vitamins and Mineral Consumption

25-Hydroxyvitamin D Levels (Calcifediol/Calcidiol): Is a chemical that is naturally produced by the body in the liver, whenever Vitamin D from outside the body enters the bloodstream. This conversion allows for the body to better use Vitamin D to support bone, muscle and teeth health. Normal Vitamin D levels are 50nmol/L (20ng/mL) - 125nmol/L (50ng/mL) (Melamed et al. 2008).

Calorie-Nitrogen Deficit: Is a measure of how much nitrogen a patient has in their body. Nitrogen is typically obtained from meat (both white and red), nuts, leafy greens, pomegranate and more. A deficit in nitrogen could be indicative of other nutritional deficits as well as suboptimal body functioning. Normal nitrogen levels for adults (18+) are between 7 to 20mg/dL (Pikosky et al. 2008).

Iron Intake: Is a measure of the amount of iron a patient consumes over the course of one day. The body needs iron because it is an integral part of hemoglobin. Hemoglobin, in turn is a part of red blood cells that helps transport oxygen throughout the body. The average iron intake for men is 19.3-20.5mg/d and the average iron intake for women is 17.0-18.9mg/d (Ascherio et al. 1994).

Body Composition

Biceps Skinfold Thickness: Is fast way to roughly measure a patient's body fat percentage. This measure is a subsection of anthropometric measures (subscapular skinfold thickness, suprailiac skinfold thickness and bicep skinfold thickness. This assessment is done by a trained clinician using calipers. This assessment has good reliability and validity (Deurenberg, Pieters & Hautvast 1990).

Body Mass Index (BMI): Is a weight-to-height ratio that is calculated by dividing one's weight in kilograms by the square of one's height in meters. Is used to determine if a patient is underweight, normal weight, overweight or obese. The normal weight range is 18.5-24.9 kg/m^2. However, recent work has cast doubt on how accurate BMI testing truly is (Bhurosy & Jeewon 2013; Calle et al. 1999).

Mid-Arm Muscle Circumference (MUAC): Is a measure that can help a clinician determine the nutritional status of a patient. A clinician measures the circumference of the right or left upper arm between the tip of the shoulder and the tip of the elbow. Lower measures are indicative of muscle wasting, which in turn can be indicative of lowered nutritional status and/or malnutrition (Landi et al. 2010).

Percentage of Body Fat: Is the amount of fat a patient has on their body. An acceptable amount of body fat for men is 18-24%, while 25% and above could be a sign of overweight/obesity. In contrast, being below 5% body fat could lead to suboptimal bodily functions. An acceptable amount of body fat for women is 35-31%, while 32% and above could be a sign of overweight/obesity. In contrast, being below 10% body fat could lead to suboptimal bodily functions (Davidson et al. 2002).

Triceps Skinfold Thickness: Is fast way to roughly measure a patient's body fat percentage. This measure is a subsection of anthropometric measures (subscapular skinfold thickness, suprailiac skinfold thickness and bicep skinfold thickness. This assessment is done by a trained clinician using calipers. A normal skinfold thickness for adult men (18+) is 2.5mm and for adult women (18+) is 18.0mm. This assessment has good reliability and validity (Rolland-Cachera et al. 1997).

Waist Circumference: Is used to help calculate a patient's body fat percentage. This assessment is used to calculate the amount of fat held by both men and women on their waist. Having a waist size of over 102cm (40 in) for men and 88cm (35 in) for women can increase a patient's risk of heart disease and diabetes. This assessment has good reliability and validity (Ness-Abramof & Apovian 2008).

Weight Gain: Is the amount of weight a patient with dysphagia gains by the end of an intervention. It is significant because patients with dysphagia have a decreased appetite compared to those patients without dysphagia, which leads to significant weight loss (Korner et al. 2013).

Blood Glucose Management

2hr Post-Load Glucose Levels/Glucose Tolerance Test (Non-Pregnant): Is a test used to measure how well a person's body moves sugar from the blood into tissues like muscle and fat. Patients drink a liquid containing approximately 75 grams of glucose (on an empty stomach). Their blood sugar levels are then taken every 30 to 60 minutes and the ends at the 2hr mark. Normal blood glucose levels at this point are <140mg/dL. On the other hand, prediabetes levels are 140mg/dL-200mg/dL, while diabetic levels are >200mg/dL (Stumvoll et al. 2000).

Plasma Glucagon Like Peptide-1 Levels (GLP-1) Levels Pre-Feed: Is a measure of GLP-1 (a hormone that signals insulin secretion) levels present in a patient's plasma before eating. Average levels are between 0 and 15pmol/L but can increase 2-3x as soon as glucose is consumed (Suzuki et al. 2007).

Fasting Glucose Level: is a measure of the blood glucose concentration taken before any meal has been eaten (usually in the morning). This is a good indicator of insulin sensitivity in the body, and whether or not an individual is diabetic or at risk of developing diabetes. Normal levels have been reported to be less than 100mg/dL (Tirosh et al., 2005).

Fasting Insulin Level: is a measure of the blood insulin concentration taken before any meal has been eaten (usually in the morning). This can be used as an indicator of insulin resistance and/or sensitivity. Greater fasting levels of insulin would indicate a greater resistance.

Plasma Proteins

Albumin Levels: Is a protein that is manufactured naturally in the liver. Its purpose is to help keep fluid in a person's bloodstream so it does not leak into the surrounding tissues. Albumin can also help transport hormones vitamins and enzymes throughout the body. Normal albumin levels are typically 3.4-5.4g/dL, levels lower or higher than these numbers could be indicative of inflammation and/or infection (Gunduz et al. 2008).

Pre-Albumin: Is a protein that is mainly made by the liver and is mainly a building block to make other proteins. For adults (18+) of both sexes normal pre-albumin levels are 15 to 36mg/dL. Levels higher than these could be indicative of kidney disease, Hodgkins disease, iron deficiency, and other ailments (Beck & Rosenthal 2002).

Transferrin: is the principle protein in blood plasma that is responsible for binding iron, and transporting through the circulatory system. Transferrin levels in the blood can be decreased or increased as a result of many different conditions (Bartnikas, 2012).

Hemoglobin: is the protein within red blood cells that bind to and carry oxygen within the blood. Vitamin or nutrients deficiencies can lead to decreased hemoglobin levels.

Blood Pressure

Diastolic Blood Pressure: Is the measure of the pressure in the arteries when the heart rests between beats. During this time the heart fills with blood and receives oxygen, which then allows the heart to effectively pump oxygenated throughout the body. Normal diastolic blood pressure is 80mmHg or lower (Mancia & Grassi 2002).

Flow Mediated Dilation (FMD): Is a term that refers to the dilation (widening) of an artery when blood flow increases in said artery. This widening occurs when nitric oxide is released from the endothelial cells. Patients with stroke typically have arteries that do not dilate as quickly or as much as age and sex-matched patients without stroke (Thijssen et al. 2010).

Systolic Blood Pressure: Is the measure of the pressure in the arteries when the heart contracts. During this time the heart ejects oxygenated blood and sends it throughout the body, which then allows body tissues/muscles to be effectively oxygenated. Normal systolic blood pressure is 120mmHg or lower (Izzo, Levy & Black).

Lymphocyte Count

Neutrophil/Lymphocyte Ratio: Is a measure that can help determine the level of internal stress/inflammation a patient is experiencing. Neutrophils are a type of white blood cell whose primary function is to help heal damaged tissues and resolve infections. Lymphocytes are cells whose primary job is to combat infection. During times of stress a patient's neutrophil count increases while their lymphocyte count decreases. The normal ratio is 1-3, with values of 6 and above signaling increased stress (Forget et al. 2017; Halazun et al. 2008).

Activities of Daily Living

Barthel Index (BI): Is a measure of how well a stroke survivor can function independently and how well they can perform activities of daily living (ADL). The measure consists of a 10-item scale (e.g. feeding, grooming, dressing, bowel control). Possible total scores range from 0 to 100. (Park et al. 2018).

Functional Independence Measure (FIM): Is an 18-item outcome measure composed of both cognitive (5-items) and motor (13-items) subscales. Each item assesses the level of assistance required to complete an activity of daily living on a 7-point scale. The summation of all the item scores ranges from 18 to 126, with higher scores being indicative of greater functional independence. This measure has been shown to have excellent reliability and concurrent validity in its full form (Stineman et al. 1996).

Stroke Severity

Canadian Neurological Scale (CNS): Is a scale that is used to assess overall stroke severity. It is an 11-point scale (out of 10) with the lower end denoting severe stroke and the higher end denoting relatively mild stroke (0=coma, 1-4=severe stroke, 5-7=moderate stroke, >7=mild stroke). The CNS requires less extensive neurological evaluation and can be quickly administered (Bushnell et al. 2001).

Modified Rankin Scale (mRS): Is a measure of functional independence for stroke survivors. The measure contains 1 item. This item is an interview that lasts approximately 30-45 minutes and is done by a trained clinician. The clinician asks the patient questions about their overall health, their ease in carrying out ADLs (cooking, eating, dressing) and other factors about their life. At the end of the interview the patient is assessed on a 6-point scale (0=bedridden, needs assistance with basic ADLs, 5=functioning at the same level as prior to stroke). This measure has been shown to have good reliability and validity (Quinn et al. 2009; Wilson et al. 2002).

National Institutes of Health Stroke Scale (NIHSS): Is a measure of somatosensory function in stroke survivors during the acute phase of stroke. This measure contains 11 items and 2 of the 11 items are passive range of motion (PROM) assessments delivered by a clinician to the upper and lower extremity of the patient. The other 9 items are visual exams conducted by the clinician (e.g. gaze, facial palsy dysarthria, level of consciousness). Each item is then scored on a 3-point scale (0=normal, 2=minimal function/awareness). This measure has been shown to have good reliability and validity (Heldner et al. 2013; Weimar et al. 2004).

European Stroke Scale (ESS): Is a clinician-administered scale that evaluates a patient's physical state post stroke. It consists of 14 distinct evaluations: level of consciousness (0-10), speech comprehension (0,4,8), speech (0-8), visual field (0,8), gaze (0-8), facial movement (0,4,8), arm (maintain outstretch) (0-4), arm (movement) (0-4), wrist extension (0-8), finger strength (0,4,8), leg (maintain position) (0-4), leg (flexion) (0-4),dorsiflexion of the foot (0-8), and gait (0-10) . The higher the score, the stronger the patient (s) physical state. This assessment has been shown to have good reliability and concurrent validity (Hantson et al. 1994).

Assessment of Nutritional Status Following Stroke

Decline in nutritional status following stroke is important given its potential negative impact on functional recovery and mortality in multiple medical and surgical populations. Preliminary results from the international FOOD Trial reported that poor nutritional status was associated with an increase in the odds of death and dependency at 6 months after adjusting for a number of confounders (OR 1.82, 95%CI 1.34-2.47) (FOOD Trial Collaboration, 2003).

Poor nutrition has been found to predict lower functional status following stroke. In a study focusing on the functional consequences of malnutrition in stroke rehabilitation, patients' serum albumin used as an marker of nutritional status was associated with poorer functional mobility, increased complications, and lower self-care scores (Aptaker et al., 1994). Gariballa et al. (1998a) investigated the associations between a variety of anthropometric and biochemical parameters assessed on admission to hospital and outcome following stroke among 201 patients. After adjusting for age, sex, medications, stroke severity, and comorbid conditions, serum albumin was related to an increase in death at 3 months. Each decline of 1 g/L in serum albumin was associated with a 1.13-fold increase in death at follow-up.

Davalos et al. (1996) reported that malnutrition after the first week of stroke among 104 patients was associated with an increased risk of poor outcome (death or dependency) at one month, a greater incidence of infections and pressure sores, and longer lengths of hospital stays. Patients who were considered malnourished had an elevated risk of death or poor outcome at 30 day follow-up (OR 3.5, 95%CI 1.2-10.2). Types of food consumed may also influence mortality risk, as Sharma et al. (2013) revealed that a higher level of meat consumption was associated with an elevated risk of stroke mortality among female participants. Diet has also been used to assess for risk of developing a stroke, such as a study that found a higher Mediterranean Diet Score (MeDi) score was significantly associated with a lower risk of stroke among males (Chan et al., 2013).

Currently, there is no universally accepted gold standard for the assessment of nutritional status. The identification of malnutrition is typically based on the evaluation of a combination of biochemical and anthropometric markers and is inferred from a single or multiple values falling outside of specific population reference ranges or below a certain percentile within these ranges. Since the combination of markers used and the cut-off values are chosen arbitrarily, reports of malnutrition are widely varied. As a result, the true incidence of malnutrition following stroke is likely unknown. Table 1 presents some the more commonly used biochemical indicators used as well as their limitations.

Table 1. Biochemical Markers of Nutritional Status (American Dietetic Association, 2000)

Measure	Limitations
Serum Albumin	Large body pool Poor specificity to nutritional changes Not specific to nutritional status ↓ with acute illness
Serum Transferrin	Not specific to nutritional status ↓ with acute illness
Thyroxin Binding Prealbumin	Not specific to nutritional status ↓ with acute illness
Retinol Binding Protein	Not specific to nutritional status
Total Lymphocyte Count	Poor sensitivity and specificity

Unfortunately, many of these nutrition-sensitive markers are affected independently by factors associated with stroke (or any other acute illness), complicating the process of evaluating the response to nutritional interventions. Although both albumin and prealbumin are used extensively in nutritional assessment, the hepatic production of these two proteins is known to be down-regulated during periods of acute illness, independent of nutritional status (Fleck, 1989; Gabay & Kushner, 1999). Hypoalbuminemia has been repeatedly shown to be associated with morbidity and mortality, but the causal mechanism is not clear. For example, Akner and Cederholm (2001) did not demonstrate a relationship between protein and caloric intake and serum albumin in their institutionalized elderly population. Further difficulties arise due to the fact that biochemical markers of nutrition can change rapidly, whereas a change in nutritional status is considered more latent and takes longer to manifest. In addition, the presence of concurrent infection or elevations in temperature can affect serum markers, mimicking signs of malnutrition.

Measures of nutrition assessment also include indicators of skeletal muscle mass and subcutaneous fat stores including weight, mid-arm muscle circumference, and skinfold thickness. While a decline of these indicators may be associated with the development of malnutrition, factors secondary to stroke may also affect the sensitivity of these measures. Skeletal muscle losses may occur over prolonged periods of time as a result of atrophy, secondary to immobility (Deitrick et al., 1948; Schonheyder et al., 1954). It may be difficult to differentiate between these losses and those that are associated with inadequate food intake, adding to the difficulties of evaluating nutritional status. Malnutrition is considered to be a state that develops over time in response to inadequate intake relative to need, and results in gradual weight loss with associated losses of skeletal muscle mass and subcutaneous fat stores. Since the identification of malnutrition among the majority of studies was made on the basis of both anthropometric and biochemical markers, it is possible that studies reporting a higher percentage of malnourished patients conducted measurements at a later point in the hospitalization period and reflected non-nutritional changes in body composition.

Prevalence of Malnutrition Following Stroke

The prevalence of malnutrition following stroke has been reported to be between 6% and 62%. If widened to include secondary criteria from two studies, the range of estimates broadened to 1.3% and 73%. Some of this variability can be attributed to differences in patient characteristics and the timing of assessments among studies. However, a substantial proportion of the variation in estimates may also be explained by the heterogeneity of nutritional assessment. Among the 22 trials reviewed below, 18 different assessment methods were used. Only 5 trials used previously validated assessment methods: an “informal assessment”, the Subjective Global Assessment (SGA), and the Mini Nutritional Assessment (MNA). The assessment methods used in the remaining studies used had not been previously validated.

The aforementioned valid assessment tools were created for different purposes. The informal assessment was developed to classify patients into groups based on nutritional state within the context of the large, multi-centred FOOD Trials. The SGA was designed for use in the prediction of risk for complications following general surgery based on pre-operative nutritional state. The MNA was developed as a screening and assessment tool to identify geriatric patients at risk for malnutrition. Both the SGA and MNA have been validated subsequently for use in other disease or injury states, but further validation of these tools for the assessment of individuals with stroke is lacking. In a study by Kim et al. (2013), a group of 35 patients with stroke aged 60 to 89 years were assessed for nutritional status using laboratory measures, as well as the SGA and MNA. There was strong correlation between SGA and objective measures when patient nutrition status was classified (normal, mildly malnourished, moderately malnourished, or severely malnourished, r=0. 449), and between MNA and objective measures when patient nutrition status was dichotomized (well-nourished vs. malnourished or at risk of malnutrition, r=0.520). The criteria used to detect malnutrition in studies of patients post stroke, and the prevalence of malnutrition detected within those studies, are presented in Table 2.

Table 2. Summary of Studies Examining Malnutrition Prevalence Post Stroke

Author (Year) **Study Type (PEDro Score)** **Sample Size**	**Criteria**	**Prevalence**
Axelsson et al. (1988) Observational $N_{Initial}$=100	≥2 variables below reference limit: • Serum albumin <38g/L (male), <37g/L (female) • Serum prealbumin <0.18g/L • Serum transferrin <1.7g/L (male), <1.5g/L (female) • Body weight <80% of reference population • Tricep skinfold thickness: 4 levels based on age • Arm muscle circumference: 4 levels based on age	• 16% within 4d of symptom onset • 22% at hospital discharge (n=78)
DePippo et al. (1994) RCT (5) $N_{Initial}$=115	≥1 variable below reference limit: • Serum albumin < 25g/L • Sustained ketonuria without glycosuria >2wk	• 6.1% at any point between hospital admission and discharge (TPS_{median}=4.6wk)
Unossen et al. (1994a) Observational $N_{Initial}$=50	≥3 variables below reference limit (1 from each of biochemical, anthropometric, and skin measures): • Serum albumin <36g/L • Serum prealbumin <0.20g/L (male), <0.18g/L (female) • Body weight <80% of reference population • Arm muscle circumference: 4 levels based on age and gender • Tricep skinfold <6mm (male), <12mm (female)	• 8% within 2d of symptom onset

	• Delayed hypersensitivity skin testing <10mm	
Finestone et al. (1995) Observational $N_{Initial}$=49	≥2 variables below reference limit: • Serum albumin <35g/L • Serum transferrin <2.0g/L • Total lymphocyte count <1800n/mm^3 • Body weight <90% of reference population or <95% of usual weight • Body mass index <20 • Sum of 4 skinfolds <5th percentile of reference population • Midarm muscle circumference <5th percentile of reference population	• 49% at hospital admission (TPS_{mean}=22d) • 34% at 1mo (n=32) • 22% at 2mo (n=9) • 19% at 2-4mo (n=42)
Davalos et al. (1996) Observational $N_{Initial}$=104	≥1 variable below reference limit: • Serum albumin <35g/L • Midarm muscle circumference <5th percentile of reference population • Tricep skinfold <10th percentile of reference population	• 16.3% within 24hr of hospital admission • 26.4% at 1wk (n=91) • 35% at 2wk (n=43)
Choi-Kwon et al. (1998) Observational $N_{Initial}$=88	≥3 variables below reference limit (1 from each of biochemical, anthropometric, and skin measures): • Serum albumin <35g/L • Total lymphocyte count <1500/mm^3 • Lean body mass, abdominal skinfold, subscapular skinfold, triceps skinfold <80% of reference population • Body mass index <20	• 87% at acute period (<3mo)
Aquilani et al. (1999) Cohort N=150	≥2 variables below reference limit (including 1 weight measure): • Serum albumin <35g/L • Total lymphocyte count <1800n/mm^3 • Body weight <90% of reference population or <95% of usual weight • Arm muscle area <5th percentile of reference population	• 30% at hospital admission (TPS_{mean}=30d)
Westergren et al. (2001a) Observational N=24	≥2 variables below reference limit (including 1 weight measure): • Serum albumin <36g/L • Body mass index <20 • Body weight <80% of reference population or <95% of usual weight • Subnormal triceps skinfold or mid-upper arm muscle circumference	• 8% within 24hr of symptom onset • 29% at 1mo • 33% at 3mo
Westergren et al. (2001a) Observational N=162	Subjective Global Assessment (Modified Version): A: Well nourished B: Well nourished but at risk of malnourishment C: Suspected malnourishment D: Severely malnourished (C, D = Malnourished)	• 32% within 6d of hospital admission
Davis et al. (2004) Observational N=185	Subjective Global Assessment: A: Well nourished B: Moderately malnourished or suspected malnourishment C: Severely malnourished (B, C = Malnourished)	• 16% within 24hr of symptom onset
Dennis et al. (2005a) RCT (7) N=859	Clinical judgement: Malnourished, normal, or overweight	• 8.6% at hospital admission
Dennis et al. (2005b) RCT (7)	Clinical judgement: Malnourished, normal, or overweight	• 7.8% within 7d of symptom onset

N=4023		
Martineau et al. (2005) Case Series N=73	Subjective Global Assessment (Patient-Generated): A: Well nourished B: Moderately malnourished or suspected malnourishment C: Severely malnourished (B, C = Malnourished)	• 19.2% within 2d of symptom onset
Hama et al. (2005) Cohort N=51	• Serum albumin <40g/L • Body mass index (BMI) <19	• 1d of hospital admission (TPS_{mean}=44d) • 22% based on albumin • 57% based on BMI
Crary et al. (2006) Observational N=76	• Mini Nutritional Assessment score <23.5	• 26.3% at hospital admission
Brynningsen et al. (2007) Cohort $N_{Initial}$=100	≥2 variables below reference limit: • Serum albumin <550micromol/L • Serum transferrin <49micromol/L • Arm muscle circumference <10th percentile of reference population • Tricep skinfold <10th percentile of reference population	• 35% within 1wk of symptom onset • 33% at 5wk • 20% at 3mo • 22% at 6mo (n=89)
Poels et al. (2006) Cohort $N_{Initial}$=69	Primary criteria • ≥1 variable below reference limit: • Body weight <95% at 1mo, <90% at 6mo • BMI <18 for <65yr, <22 for ≥65yr Secondary criteria • ≥1 variable below reference limit: • Serum albumin <35g/L • Fat free mass ≤6kg/m^2 (male), 15 kg/m2 (female) • Tricep skinfold <90% of 12.5mm (male), 16.5 mm (female) • Mid arm muscle circumference <90% of 25.3cm (male), 23.3 cm (female)	Primary • 35% at hospital admission (TPS_{mean}=34d) • 3% at 4wk (n=60) Secondary • 73% at hospital admission • 54% at 4wk
Yoo et al. (2008) Cohort N=131	≥1 variable below reference limit: • Serum albumin <30g/L • Serum prealbumin <0.10g/L • Serum transferrin <1.5g/L • Body weight <95% at 1wk, <90% at 3mo • Body weight <80% of reference population	• 12.2% within 24 hr of symptom onset • 19.8% at 1wk
Chai et al. (2008) Observational $N_{Initial}$=61	• Serum albumin <35g/L • Body mass index <18.5	• 8.2% at chronic period (>6mo)
Lim & Choue (2010) Cohort $N_{Initial}$=73	Subjective Global Assessment (Patient-Generated): A: Well nourished B: Moderately malnourished or suspected malnourishment C: Severely malnourished (B, C = Malnourished)	• 74% at hospital admission (TPS_{mean}=60d)
Crary et al. (2013) Cohort $N_{Initial}$=67	• Serum prealbumin <0.05g/L	• 32% at hospital admission • 33% at 7d
Mosselman et al. (2013)	• Mini Nutritional Assessment score <17	• 5% at 2-5d after hospital admission • 26% between 9-12d (n=23)

Cohort $N_{Initial}$=73		
Paquerau et al. (2014) Observational $N_{Initial}$=71	• Mini Nutritional Assessment (Short Form) • Body mass index • Weight	• 47.9% at acute period (<3mo)

Dysphagia

Eleven studies recruited patients both with and without dysphagia. Greater proportions of patients with dysphagia were classified as malnourished compared to patients with normal swallowing function in four trials: 19/59 vs 10/14, p=0.007 (Martineau et al. 2005); 16/24 vs 15/67, p<0.001 (Davalos et al., 1996); 15/23 vs 9/26, p=0.032 (Finestone et al. 1995); 4/5 vs 17/56, p=0.044 (Chai et al., 2008). Poels et al. (2006) also reported that a greater proportion of subjects with dysphagia was malnourished, although the result was not statistically significant (4/20 vs 4/40, p= 0.233). Crary et al. (2006) did not demonstrate a significant association between the dysphagia and malnutrition assessed within several days of stroke (OR 1.0, 95%CI 0.4-2.8). In a subsequent study by Crary et al. (2013), this finding was repeated, and a significant relationship between dysphagia and dehydration was reported.

In a systematic review of 8 studies, Foley et al. (2009a) reported that the odds of being malnourished were increased given the presence of dysphagia following stroke. However, they also suggested that the relationship may not be causal. While stroke size and location are the greatest determinants of swallowing function, the presence of dysphagia is itself an indicator of greater stroke severity. As well, the type of treatment for dysphagia (e.g. feeding tube) may affect study results concerning its role in the development of malnutrition.

Type and Severity of Stroke

The relationship between stroke severity and malnutrition was examined in three studies (Davis et al., 2004; Dennis et al., 2005a; Yoo et al., 2008). In all of these studies, severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and was examined during the first several days following acute stroke. Increasing stroke severity was associated with baseline malnutrition in one of these studies (Yoo et al., 2008). Only one study examined the relationship between stroke type and malnutrition (Choi-Kwon et al., 1998). The prevalence of malnutrition reported in this study was much higher among patients suffering from intracerebral hemorrhagic than ischemic stroke, though the authors suggested that the result was likely attributable to differences in pre-existing malnutrition between groups. Diet may also play a role in stroke, as Tuttolomundo et al. (2015) reported a negative correlation between NIHSS score and Mediterranean Diet Score (MeDi) score, with greater severity found to be associated with a lower-standard dietary score. Compared with lacunar and cardioembolic infarcts, atherosclerotic stroke was associated with a lower MeDi score. However, Mangat et al. (2013) did not find any significant relationship between dietary patterns and stroke characteristics (type, severity, and prognosis).

Variability of Assessment Criteria

With the single exception of the two related FOOD trials, no two studies used the same criteria. Serum albumin and measures of weight were common to almost all of the studies. However, the

cut-off points used to distinguish well-nourished from malnourished patients were chosen arbitrarily, as were the choice of reference populations, which can affect the degree and proportion of patients who are considered to be malnourished. For instance, most studies used a cut-off point for serum albumin level of 3.5 g/L, while Hama et al. (2005) used a higher point of 4.0 g/L and DePippo et al. (1994)used a much lower point of 2.5 g/L.

There was variability in the percentiles chosen for anthropometric cut-off points, if they were identified. Choi-Kwon et al. (1998) used an undefined reference population, while Unosson et al. (1994b) chose specific, age-dependent cut-off points that did not appear to be based on population norms. Three studies used population-based national survey results as their reference standards (Axelsson et al., 1988; Davalos et al., 1996; Finestone et al., 1995). However, the cut-off values chosen were inconsistent: one used the 5th percentile (Finestone et al., 1995) and another used the 10th percentile (Davalos et al., 1996). Axelsson et al. (1988) and Choi-Kwon et al. (1998) simply made reference to “low values” when they defined their cut-off threshold. Implicit in the assessment of malnutrition is that thin people, relative to the rest of the reference population, are malnourished. The anthropometric and biochemical markers used in the previously summarized studies are presented in Table 3.

Table 3. Individual Nutrition Markers Used in Reviewed Studies

Biochemical Markers					
Study	Albumin	Transferrin	TLC	Prealbumin	Ketonuria
Axelsson et al. (1988)	X	X		X	
DePippo et al. (1994)	X				X
Unosson et al. (1994a)	X	X		X	
Finestone et al. (1995)	X	X	X		
Davalos et al. (1996)	X				
Choi-Kwon et al. (1998)	X		X		
Aquilani et al. (1999)	X		X		
Westergren et al. (2001a)	X				
Hama et al. (2005)	X				
Poels et al. (2006)	X				
Brynningsen et al. (2007)	X	X			
Yoo et al. (2008)	X	X		X	
Chai et al. (2008)	X				
Crary et al. (2013)				X	

Anthropometric Markers			
Study	Weight	Fat (TSF, SS)	Muscle (AMC, MAMC)
Axelsson et al. (1988)	X	X	X
DePippo et al. (1994)			

Unosson et al. (1994a)	X	X	X
Finestone et al. (1995)	X	X	X
Davalos et al. (1996)		X	X
Choi-Kwon et al. (1998)	X	X	X
Aquilani et al. (1999)	X		X
Westergren et al. (2001a)	X	X	X
Hama et al. (2005)	X		
Poels et al. (2006)	X	X	X
Brynningsen et al. (2007)		X	X
Yoo et al. (2008)	X		
Chai et al. (2008)	X		
Paquerau et al. (2014)	X		
Composite Clinical Assessments			
Westergren et al. (2001b), Davis et al. (2004), Dennis et al. (2005a, 2005b), Martineau et al. (2005), Crary et al. (2006), Lim & Choue (2010), Mosselman et al. (2013), Paquerau et al. (2014)			

TLC=Total Lymphocyte Count

SS=Skinfold Sum

MAMC=Midarm Muscle Circumference

TSF=Triceps Skinfold

AMC=Arm Muscle Circumference

In a systematic review of eighteen studies, Foley et al. (2009b) reported that the prevalence of malnutrition following stroke ranged from 6.1% to 62%. Seventeen different methods of nutritional assessment were used, but only four trials used previously validated assessment methods: the informal assessment, SGA, and MNA. The nutritional assessment methods used in the remaining studies used had not been previously validated. The authors suggested that the wide array of nutritional assessment tools contributed to the wide range of malnutrition estimates.

Timing of Assessment

The timing of the assessments may also explain the variability in the reported prevalence of malnutrition. Among the studies that assessed nutritional status within 1 week of stroke, the frequency of malnutrition was <20% in 10 of the studies (Axelsson et al., 1988; Davalos et al., 1996; Davis et al., 2004; Dennis et al., 2005a, 2005b; Martineau et al., 2005; Unosson et al., 1994b; Westergren et al., 2001a; Westergren et al., 2001b; Yoo et al., 2008). Frequency of malnutrition was 26% at 10 days after admission to hospital in 1 study (Mosselman et al., 2013). Among the trials that assessed nutritional state between 22 and 44 days following stroke, the frequency of malnutrition ranged from 30% to 49% in 4 trials (Aquilani et al., 1999; Finestone et al., 1995; Hama et al., 2005; Poels et al., 2006).

Foley et al. (2009a) noted that the pre-stroke nutritional status of patients may be a potential confounding issue. In their systematic review, none of the studies were able to determine

nutritional status prior to stroke, although five studies used anthropometric measures shortly after onset that may be comparable to pre-stroke measurements. Moreover, it remains unclear as to whether malnutrition was pre-existing at the time of assessment or if malnutrition was the consequence of stroke.

Conclusions Regarding the Incidence of Malnutrition

- **The prevalence of malnutrition varies from 6 - 62% post stroke, depending on timing of assessment and criteria used to define malnutrition.**
- **There is currently no "gold standard" for the assessment of nutritional status, and various methods of detection may be used.**

Factors Associated With the Development of Malnutrition

Malnutrition in any disease state develops over a period of time as a result of either increased metabolism or inadequate nutritional intake. There may be occasions when these two factors are superimposed. The development of malnutrition may also be hastened if the gastrointestinal tract is compromised and nutrient absorption is impaired. The evidence with respect to the potential contributions of these mechanisms is reviewed.

Metabolic Rate Following Stroke

Increased metabolic has been attributed to the effects of the acute phase response, mediated largely through the effects of cytokines and counter-regulatory hormones, following injury or disease (Staal-van den Brekel et al., 1995; Young et al., 1985). Elevations of peripheral plasma catecholamines, cortisol, glucagons, IL-6, IL-1RA and acute phase proteins have been well described following stroke (Beamer et al., 1995; Fassbender et al., 1994a; Fassbender et al., 1994b; Ferrarese et al., 1999; Muir et al., 1999; Murros et al., 1993; Syrjanen et al., 1989). Prolonged elevations of these compounds may lead to the depletion of muscle and fat, which may contribute to the development of malnutrition. Szczudlik et al. (2004) found that morning IL-6 levels independently predicted evening/night cortisol levels, and both were found to be higher in stroke patients than healthy controls. The authors postulated that ischemic stroke may stimulate the release of IL-6 and may be responsible for regulation of the hypothalamic-pituitary-adrenal axis. Ormstad et al. (2013) suggested that significant reductions in tryptophan and tyrosine may be indicative of a reduced capacity for 5-hydroxytryptamine (5HT) and catecholamines within the brain. Furthermore, IL-10 was found to be positively correlated with tryptophan levels therefore suggesting that higher levels of IL-10 facilitate higher tryptophan availability for 5HT synthesis, suggesting that anti-inflammatory cytokines may prevent a reduction in 5HT synthesis (Ormstad et al., 2013). The levels of various acute phase reactants following stroke are summarized in Table 4.

Table 4. Summary of Studies Examining Acute Phase Reactants Post Stroke

Author (Year)	Sample Size	Time Post Stroke	Indicator (Response)
Syrjanen et al. (1989)	50	Within 72hr	• CRP (↑) • SAA (↑) • ACT (↑)
Murros et al. (1993)	105	Up to 1wk	• Cortisol (↑)
Fassbender et al. (1994a)	23	Up to 7d	• ACTH (-) • Cortisol (↑ until 5d)
Fassbender et al. (1994b)	19	Up to 3d	• IL-1ß (↑) • IL-6 (↑) • TNF (↑)
Beamer et al. (1995)	50	Up to 6d	• IL-1RA (↑) • IL-6 (↑) • CRP (-) • Fibrinogen (↑)
Ferrarese et al. (1999)	40	Up to 90d	• IL-6 (↑ 1-30d) • TNF (↑ 1-90d)
Muir et al. (1999)	228	Within 72hr	• CRP (↑)
Selakovic et al. (2002)	53	Within 48hr	• Cortisol (↑)
Szczudlik et al. (2004)	22	Within 24hr	• IL-6 (↑) • Cortisol (↑)
Ben-Assayag et al. (2007)	219	Up to 6mo	• CRP (↑)
Camerlingo et al. (2011)	387	Within 3hr	• CRP (↑)
Hasani et al. (2011)	120	Within 24hr	• CRP (↑)
Ormstad et al. (2013)	45	Within 72hr	• IL-6 (↑) • IL-10 (↑) • Tryptophan (↓) • Tyrosine (↓)
Shaafi et al. (2014)	45	Up to 90d	• IL-6 (↑)

(-) indicates no change
CRP (C-reactive protein)
SAA (serum amyloid A protein)
ACT (α-antichymotrypsin)
ACTH (adrenocorticotropic hormone)
TNF (tumour necrosis factor)
IL-1ß (Interleukin-1ß)
IL-6 (Interleukin-6)
IL-1RA (Interleukin-1 receptor antagonist)

Conclusions Regarding Metabolism Following Stroke

- **There is insufficient evidence regarding malnutrition during the acute phase of stroke.**

Gastrointestinal Impairments Following Stroke

The major effect on the gastrointestinal tract following stroke is impairment of oral, pharyngeal, and esophageal functions, which is manifested as dysphagia (see Chapter 15 Dysphagia and Aspiration). Dysphagia may resolve spontaneously in the days following stroke or persist for much longer periods. For a minority of patients, severe dysphagia precludes safe oral feeding

and so alternative strategies are required. In 3 studies, the odds of developing malnutrition increased significantly following acute hospital admission at both 1 week post stroke and upon admission to an inpatient rehabilitation unit at approximately 3 weeks post stroke (Davalos et al., 1996; Finestone et al., 1995; FOOD Trial Collaboration, 2003). Although the mechanism was not explored, decreased intake or delayed enteral feeding may have contributed to a decline in nutritional status. At admission to hospital shortly after stroke, nutritional status was unrelated to dysphagia in 2 other studies (Crary et al., 2006; Crary et al., 2013). The latter study reported a relationship between dysphagia and dehydration at both hospital admission and at 7 days post stroke (Crary et al., 2013).

Stroke patients do not appear to be at increased risk for stress ulcer formation or gastric bleeding (Ullman & Reding, 1996). Ogata et al. (2014) reported that gastrointestinal bleeding is a rare occurrence, with a rate of 1.4% in their multicentre study. The authors highlighted significant risk factors for gastrointestinal bleeding including absence of dyslipidemia, history of peptic ulcer, and severity of neurological deficit; no association was found with non-steroidal anti-inflammatory, anticoagulant, and antiplatelet pharmacology. In their systematic review, Schaller et al. (2006) suggested that gastric hemorrhage, small/large intestine dysfunction, gastric motility, and dysphagia may occur post stroke, as they are all modulated through the central nervous system. However, the authors argued that improvements in cerebral and molecular scanning, particularly regarding changes in pharmacodynamics, may elucidate the mechanisms behind these complications. Camara-Lemarroy et al. (2014) speculated that intestinal infection may be the result of post-stroke immunodepression, which could affect barrier function as well as increase septicemia and bacterial translocation. Further research is required into intestinal infections following stroke.

Although constipation is a frequently cited complaint following stroke, this may be due to a variety of factors arising secondary to stroke, including reduced mobility, decreased fluid intake, and medication usage. Stroke is not known to cause constipation (Johanson et al., 1992; Sonnenberg et al., 1994), but Lim et al. (2015) reported that 33% of stroke patients developed new-onset constipation, with 39% of these patients presenting within two days of admission. The authors found that patients who experienced dysphagia, used antacids, had a greater length of stay, and required the use of a bedpan were at greater risk of developing constipation. Scivolotto et al. (1997) reported that 48% of stroke patients developed heartburn, 30% developed constipation, 27% experienced abdominal pain, 15.6% developed dysphagia, and 10% reported faecal incontinence with constipation found to be secondary to stroke. However, constipation can be difficult to characterise due to the subjectivity of symptoms (Schaller et al., 2006).

Conclusions Regarding Gastrointestinal Impairments Following Stroke

- **There is insufficient evidence regarding the development of significant gastrointestinal impairments post stroke.**
- **There is limited evidence suggesting that constipation can develop post stroke.**

Nutrient Intake Following Stroke

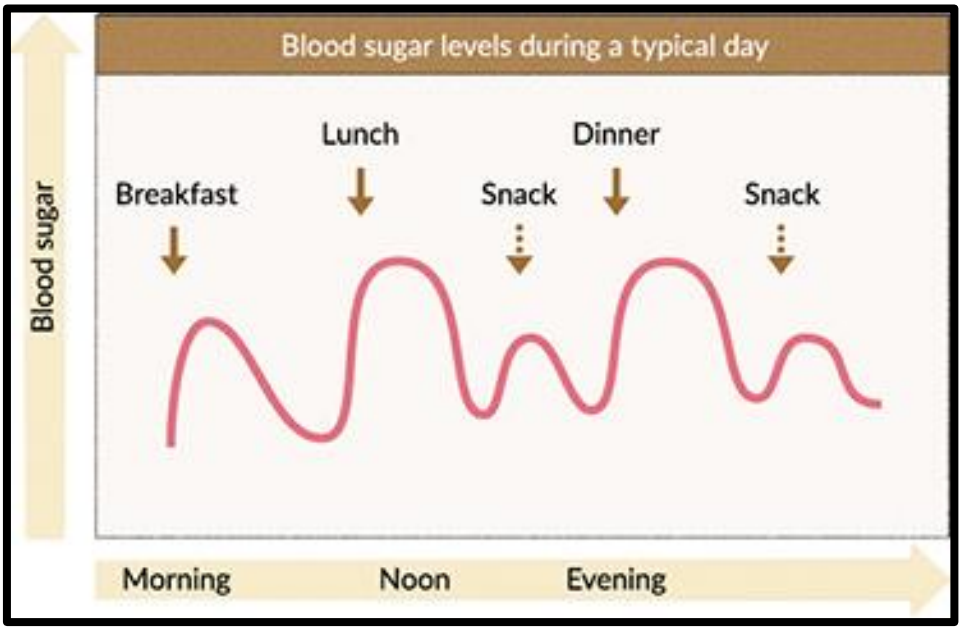
Individuals with stroke may be particularly vulnerable to calorie-protein malnutrition due to a variety of factors that affect their ability or willingness to self-feed. In a review, Finestone et al.

(2003) noted that cognitive changes to attention, concentration, and memory may affect eating behaviours post stroke. Self-feeding ability may be attenuated by upper extremity paresis/paralysis, visuospatial-perceptual deficits, left-right disorientation, hemispatial neglect, apraxia, and agnosia. Sensory disturbances and mood disorders, such as depression, may affect desire to self-feed.

However, there are few studies that describe the protein and calorie intakes of hospitalized individuals with stroke. Gariballa (2001) reported that the average two-week calorie intake of post-stroke patients consuming a regular hospital diet and without dysphagia was 1338 kilocalories (Kcals), which represented 74% of their predicted requirement. However, this level of intake was not significantly different from matched controls who consumed 1317 Kcals, or 73% of requirement, suggesting that the intakes of patients with stroke were similar to those of other hospitalized patients. In another study, Foley et al. (2006) reported that hospitalized patients consumed an average of 85% of calorie requirements and 86% of protein requirements during the first 21 days post stroke, regardless of diet type (oral or non-oral) and texture (regular or texture-modified). A recent study by Murray et al. (2015) reported that patients without dysphagia post stroke consumed 67% of their daily recommended intake and 44% exhibited dehydration based on their blood urea nitrogen/creatine ratio (>20:1) at 7 days post stroke. Moreover, 16% of patients demonstrated one or more of the following: constipation, dehydration, hypernatremia, and urinary tract infection.

Nutritional rehabilitation interventions

Glucose Regulation



Adapted from: https://www.otsuka.co.jp/en/health-and-illness/glycemic-index/glucose-level/

Impaired glucose regulation is the result of impairments to glucose tolerance and fasting glucose, characterized by insulin resistance and elevated glucose levels (hyperglycaemia) (Engberg et al., 2009). Hyperglycaemia following stroke may be the result of previous unrecognised diabetes or glucose metabolism disorders, or as a stress reaction mechanism (Dziedzic et al., 2010; Lindsberg et al., 2011). The hazards of hyperglycaemia post stroke include poor functional outcome, increased risk of cardiovascular disease, future occurrence of parenchymal hematoma, and mortality (Lindsberg et al., 2011). Laird et al. (2014) recommended that monitoring be conducted every 4 hours for the first 72 hours after admission, irrespective of a prior history of diabetes. Blood glucose levels can increase within the first 12 hours of a stroke, with a reported increase of 5.8-6.1mmol/L in mild-moderate stroke and 6.2-6.7mmol/L in severe stroke (Christensen & Boysen, 2002). Correlation between fasting blood glucose (FBG) levels and stroke severity revealed greater severity with elevated FBG level. In addition to insulin, other treatments for blood glucose regulation post stroke may include exercise, dietary changes, and diabetic pharmacology such as metformin.

Three RCTs were found that evaluated glucose regulation for nutritional management. One RCT compared metformin to no medication (Den Hertog et al., 2015). One RCT compared insulin to a placebo (Gray et al., 2007). One RCT compared aerobic exercise to standard physiotherapy (Ivey et al., 2007).

The methodological details and results of all three RCTs are presented in Table 5.

Table 5. Antidiabetics and exercise.

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Metformin vs No medication		
Den Hertog et al. (2015) RCT (7) N_{Start}=40 N_{End}=39 TPS=Acute	E: Metformin (2g/d) C: No medication Duration: 2g/d, 7d/wk for 12wk	• 2hr post-load glucose levels (-) • Fasting glucose levels (-) • Waist circumference (-) • Body Mass Index (-) • Blood pressure (-) • Triglycerides (-) • Cholesterol (-)
Insulin vs a placebo		
Gray et al. (2007) RCT (7) N_{Start}=933 N_{End}=754 TPS=Acute	E: Glucose-Potassium insulin infusions C: Saline infusions Duration: 500mL GKI Regimen + 20mmol KCl for 24hr OR 154mmol/L sodium at 100mL/h for 24hr	• Mean plasma glucose levels (+exp) • Systolic blood pressure (+exp) • Diastolic blood pressure (-) • Modified Rankin Scale (-) • Barthel Index (-) • European Stroke Scale (-)
Aerobic exercise vs conventional physiotherapy		
Ivey et al. (2007) RCT (5) N_{Start}=69 N_{End}=46 TPS=Chronic	E: Aerobic treadmill training C: Conventional physiotherapy Duration: 40min/d, 3d/wk for 24wk	• Fasting insulin levels (+exp) • Total 3hr insulin area (+exp) • Incremental 3hr insulin area (+exp) • Fasting glucose levels (-) • Body weight (-) • Percentage of body fat (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about glucose regulation

LIPID CONSUMPTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Metformin** may not have a difference in efficacy compared to **no medication** for improving lipid consumption.	1	Den Hertog et al., 2015

BODY COMPOSITION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Metformin** may not have a difference in efficacy compared to **no medication** for improving body composition.	1	Den Hertog et al., 2015
2	**Aerobic exercise** may not have a difference in efficacy compared to **conventional physiotherapy** for improving body composition.	1	Ivey et al., 2007

BLOOD GLUCOSE MANAGEMNET			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Metformin** may not have a difference in efficacy compared to **no medication** for improving blood glucose management.	1	Den Hertog et al., 2015
1b	**Insulin** may produce greater improvements in blood glucose management than **a placebo.**	1	Gray et al., 2007
2	**Aerobic exercise** may produce greater improvements in blood glucose management than **conventional physiotherapy.**	1	Ivey et al., 2007

BLOOD PRESSURE			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Metformin** may not have a difference in efficacy compared to **conventional physiotherapy** for improving blood pressure.	1	Den Hertog et al., 2015
1b	There is conflicting evidence about the effect of **insulin** to improve blood pressure when compared to **a placebo.**	1	Gray et al., 2007

ACTIVITIES OF DAILY LIVING			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Insulin** may not have a difference in efficacy compared to **a placebo** for improving activities of daily living.	1	Gray et al., 2007

STROKE SEVERITY			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Insulin** may not have a difference in efficacy compared to **a placebo** for improving stroke severity.	1	Ivey et al., 2007

Key Points

Blood glucose management may be beneficial for improving blood glucose, but not other aspects of nutrition.

Lipid Regulation

Adapted from: https://www.healthline.com/health/atorvastatin-oral-tablet

Lipids can have a detrimental impact on the integrity of small cerebral vessels (Athyros et al., 2010), and thus may play a key role in nutrition following stroke. Larsson et al. (2013) found that women with high dietary cholesterol were at an increased risk of stroke, whereas fat intake was not associated with stroke or any stroke subtype. Compared to healthy participants, patients with stroke showed higher levels of triglycerides, total cholesterol, low-density lipoprotein (LDL), and decreased levels of high-density lipoprotein (HDL) (Bharosay et al., 2014). Compared to patients with transient ischemic attack, patients with stroke only showed higher levels of total cholesterol (Li et al., 2014). In comparing type of stroke, Mahmood et al. (2010) reported significantly abnormal levels of total cholesterol and HDL among patients with ischemic stroke compared to patients with haemorrhagic stroke. The authors noted that previous research found a decrease in HDL at the time of an ischemic stroke, and that low HDL levels may be an acute phase reactant. Statins have been used a form of lipid treatment following stroke, as they decrease total cholesterol and LDL and increase HD (Yaghi & Elkind, 2016), and potentially decrease platelet aggregation thereby reducing the risk of haemorrhage (Athyros et al., 2010). An RCT conducted by Amarenco et al. (2006) revealed that patients treated with Atorvastatin exhibited significantly lower levels of triglycerides, total cholesterol, and LDL, while also demonstrating significantly higher HDL levels and significantly reduced risk of stroke. These results support the hypothesis that the reduction of cholesterols through statin treatment can prevent the recurrence of stroke.

One RCT was found evaluating lipid regulation for nutritional management. It compared atorvastatin to a placebo (Amarenco et al., 2006).

The methodological details and results of the single RCT are presented in Table 6.

Table 6. Lipid Regulation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Amarenco et al. (2006) RCT (7) N_{Start}=4731 N_{End}=4525 TPS=Subacute	E: Atorvastatin (80mg/d) C: Placebo (80mg/d) Duration: 7d/wk, up to 5 years	•High-density lipoprotein (+exp) •Low-density lipoprotein (+exp) •Total cholesterol levels (+exp) •Triglyceride levels (+exp)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

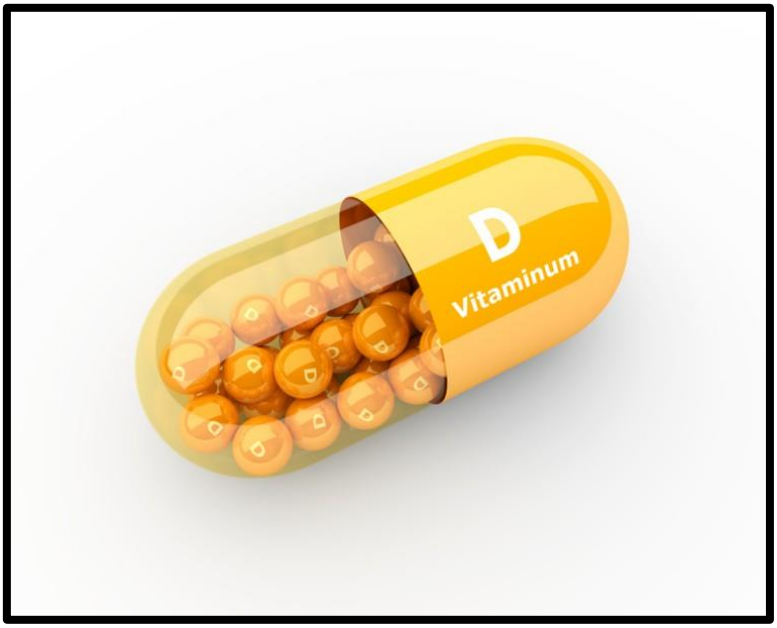
Conclusions about lipid regulation

LIPID CONSUMPTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Atorvastatin** may produce greater improvements in lipid consumption than **a placebo.**	1	Amarenco et al., 2006

Key Points

Atorvastatin may be beneficial for lipid consumption and regulation.

Vitamin D Supplementation



Adapted from: https://www.nutraingredients.com/Article/2016/08/22/Targeted-intervention-boosts-Irish-athletes-vitamin-D-levels

Following stroke, patients may be susceptible to Vitamin D deficiency, which can affect future prognosis and outcomes. Vitamin D has been found to be beneficial for factors linked with stroke such as hypertension, diabetes, and chronic inflammation (Tu et al., 2014). The vascular effects of Vitamin D include modulating smooth muscle cell proliferation, inflammation, and thrombosis, and thus a deficiency can trigger inflammation and vascular remodeling by hyperparathyroidism (Wang et al., 2014). Vitamin D levels may be a prognostic indicator of favourable outcomes, recovery, and survival after discharge (Wang et al., 2014). Tu et al. (2014) reported that patients with stroke demonstrated significantly lower Vitamin D levels than healthy controls at 90-day follow-up, and that decreased Vitamin D levels were associated with increased stroke severity. In addition, patients with favourable outcomes had significantly higher levels of Vitamin D compared to those with unfavourable outcomes, including mortality. In a similar study, Turetsky et al. (2015) revealed that the risk for unfavourable outcome doubled with each 10-ng/mL decrease in Vitamin D at 90 days post stroke. Vitamin D deficiency may also prove to be a risk factor in the development of stroke. Recent studies have found it to be an independent predictor of fatal stroke (Kojima et al., 2012; Pilz et al., 2008), as well as an independent predictor of stroke severity upon admission (Wang et al., 2014). However, Gupta et al. (2014) reported no significant association between Vitamin D deficiency and occurrence of stroke when comparing patients with stroke to healthy controls.

Two RCTs were found evaluating vitamin D supplementation for nutritional management. Both compared vitamin D supplements to a placebo or no medication (Gupta et al., 2016; Witham et al., 2012).

The methodological details and results of all two RCTs are presented in Table 7.

Table 7. Vitamin D Supplementation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Gupta et al. (2016) RCT (5) N_{Start}=53 N_{End}=44 TPS=Acute	E: Vitamin D + Calcium C: No Supplement Duration: 600,000 U of Vitamin D (1x; intramuscular injection) + 60,000 U of Vitamin D (1x/mo; intramuscular) and Calcium 1g/d, 1x/d for 24wk	• 25-Hydroxyvitamin D Levels (+exp) • Modified Rankin Scale (-)
Witham et al. (2012) RCT (7) N_{Start}=58 N_{End}=55 TPS=Acute	E: Single Vitamin D2 dose C: Placebo Duration: 100,000 U of Vitamin D OR 100,000 U of Placebo for 8wks	• Flow mediated dilation change (+exp) • Diastolic blood pressure (-) • Systolic blood pressure (-) • Cholesterol levels (-) • Albumin levels (-) • Vitamin D levels (+exp) • Aldosterone levels (-) • Renin Levels (-) • Parathyroid Hormone (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about vitamin D supplementation

LIPID CONSUMPTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Vitamin D supplements** may not have a difference in efficacy compared to **no supplements** for improving lipid consumption.	1	Witham et al., 2012

VITAMIN AND MINERAL CONSUMPTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Vitamin D supplements** may produce greater improvements in vitamin and mineral consumption than **no supplements or a placebo.**	2	Gupta et al., 2016; Witham et al., 2012

PLASMA PROTEINS			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Vitamin D supplements** may not have a difference in efficacy compared to **no supplements** for improving plasma proteins.	1	Witham et al., 2012

BLOOD PRESSURE			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Vitamin D supplements** may not have a difference in efficacy compared to **no supplements** for improving blood pressure.	1	Witham et al., 2012

STROKE SEVERITY			
LoE	**Conclusion Statement**	**RCTs**	**References**
2	**Vitamin D supplements** may not have a difference in efficacy compared to **a placebo** for improving stroke severity.	1	Gupta et al., 2016

Key Points

Vitamin D supplements may be beneficial for improving vitamin and mineral consumption, but not lipid consumption, blood pressure, plasma proteins or stroke severity.

Oral Nutritional Supplementation

Adapted from: https://www.quickanddirtytips.com/health-fitness/healthy-eating/know-your-nutrients/are-nutritional-supplements-a-waste-of-money

Oral supplementation may be indicated for patients who are safe with oral intake but fail to consume sufficient quantities to meet their nutritional requirements and/or have pre-existing nutritional deficits. Theoretically, oral supplementation can effectively improve nutritional intake, leading to improvements in nutritional parameters and ultimately functional outcomes. In a review of treatments for calorie-protein malnutrition in chronic non-malignant disorders, Akner and Cederholm (2001) identified 3 RCTs treating both dysphagic and non-dysphagic patients post stroke (DePippo et al., 1994; Gariballa et al., 1998b; Norton et al., 1996), as well as 4 "uncontrolled trials" (Davalos et al., 1996; Elmstahl et al., 1999; Nyswonger & Helmchen, 1992; Wanklyn et al., 1995). The authors concluded that the efficacy of calorie-protein malnutrition treatments post stroke could not be measured due to a *"striking lack of published articles".*

Ten RCTs were found evaluating glucose regulation for nutritional management. One RCT compared amino acid supplements to a placebo (Aquilani et al., 2015). Two RCTs compared ALAnerv nutritional supplements to conventional care (Manolescu et al., 2013; Oprea et al., 2013). Three RCTs compared protein and calorie supplementation to a regular diet (Ha et al., 2010a; Ha et al., 2010b; Aquilani et al., 2008a). One RCT compared protein supplementation to a regular diet (Aquilani et al., 2008b). One RCT compared intensive nutritional supplements to standard nutritional supplements (Rabadi et al., 2008). Two RCTs compared a hospital diet with nutritional supplements to a hospital diet alone (Dennis et al., 2005a; Gariballa et al., 1998b).

The methodological details and results of all ten RCTs are presented in Table 8.

Table 8. Oral Nutrition

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Amino Acid supplements vs a placebo		
Aquilani et al. (2015) RCT (6) N_{Start}=42 N_{End}=42 TPS=Subacute	E: Essential amino acids supplement (EAAs) C: Placebo Duration: 4g of EAAs (2x/d), 7d/wk for 35d	•Neutrophil/Lymphocyte Ratio (+exp)
ALAnerv nutritional supplement vs standard care		
Manolescu et al. (2013) RCT (8) N_{Start}=28 N_{End}=28 TPS=Subacute	E: Standard care + ALAnerv nutritional supplement C: Standard care only Duration: 30min/d, 5d/wk for 2wk + 600mg of ALAnerv (2x/d), 7d/wk for 2wk	•Total lipids (+exp) •High-density lipoprotein (+exp) •Low-density lipoprotein (-) •Total cholesterol (-) •Triacylglycerol (-) •Phospholipids (-) •PONA (-) •ARYLA (-) •LACTA (+exp)
Oprea et al. (2013) RCT (6) N_{Start}=28 N_{End}=28 TPS=Subacute	E: Conventional rehabilitation + ALAnerv supplement C: Conventional rehabilitation only Duration: 45min/d, 5d/wk for 2wk + 600mg of ALAnerv (2x/d), 7d/wk for 2wk	•Glucose levels (+exp) •Total Lipids (+exp) •Total cholesterol (-) •Triglyceride (-) •High-density lipoprotein (+exp) •Low-density lipoprotein (-) •Phospholipids (-) •Albumin (-) •Barthel Index (+exp) •Lipid hydroperoxides (-) •Protein carbonyl (-)
Protein and calorie supplementation vs routine care/diet		
Ha et al. (2010a) RCT (5) N_{Start}=170 N_{End}=124 TPS=Acute	E: Individualized Care (calorie and protein supplements) C: Routine care Duration: Individualized Care (3x/d, 7d/wk for 12wk)	•Calorie intake (+exp) •Protein intake (-) •Body weight (-)
Ha et al. (2010b) RCT (5) N_{Start}124 N_{End}= TPS=Acute	E: Individualized care (calorie and protein supplements) C: Routine care Duration: Individualized Care (3x/d, 7d/wk for 24wk)	•Body Mass Index (+exp) •Weight (+exp) •Triceps skinfold thickness (-) •Mid-upper arm circumference (-) •Arm muscle circumference (-)
Aquilani et al. (2008a) RCT (6) N_{Start}=48 N_{End}=48 TPS=Subacute	E: Regular diet + Protein/calorie supplementation C: Regular diet only Duration: Regular Diet 3x/d, 7d/wk for 3wk + 200mL Cubitan 3x/d, 7d/wk for 3wk	•Daily protein intake (+exp) •Daily calorie intake (+exp) •Daily lipid intake (-) •Daily carbohydrate intake (-) •Weight (-) •Body Mass Index (-)
Protein supplementation vs routine diet		
Aquilani et al. (2008b) RCT (6) N_{Start}=42 N_{End}=41 TPS=Acute	E: Regular diet + protein supplementation C: Regular diet only Duration: Regular Diet 3x/d, 7d/wk for 3wk + 200mL Cubitan (with 20g protein) 3x/d, 7d/wk for 3wk	•National Institute of Health Stroke Scale (+exp) •Carbohydrate-protein ratio (+exp) •Nitrogen Balance (+exp) •Daily protein intake (%kcal) (+exp) •Daily energy intake (%kcal) (-) •Daily lipid intake (%kcal) (-) •Daily carbohydrates intake (%kcal) (-)

		•Body Mass Index (-) •Weight (-)
Intensive nutritional supplementation vs standard nutritional supplementation		
Rabadi et al. (2008) RCT (9) N_{Start}=116 N_{End}=102 TPS=Acute	E: Intensive nutritional supplement (720Kcal, 33g protein, 1/d) C: Standard nutritional supplement (381Kcal, 15g protein, 1/d) Duration: 720Kcal (33g protein) 1x/d, 7d/wk until in-patient discharge OR 381Kcal (15g protein) 1x/d, 7d/wk until in-patient discharge	•Weight (-) •Albumin (-) •Pre-albumin (-) •Transferrin (-)
Hospital diet with nutritional supplements vs hospital diet alone		
Dennis et al. (2005b) RCT (8) N_{Start}=4023 N_{End}=4004 TPS=Acute	E: Hospital diet + Nutritional supplement (540Kcal, 62.5g protein, 1/d) C: Hospital diet only Duration: length of stay	•Modified Rankin Scale (-)
Gariballa et al. (1998b) RCT (6) N_{Start}=42 N_{End}=40 TPS=Acute	E: Hospital diet + Nutritional supplement C: Hospital diet only Duration: Hospital Diet 3x/d, 7d/wk for 4wk + approximately 400mL of Fortsip (2x/d) 7d/wk for 4wk	•Albumin (+exp) •Iron (+exp) •Weight (-) •Tricep skin fold (-) •Midarm circumference (-) •Transferrin (-) •Protein intake (+exp) •Calorie intake (+exp) •Barthel Index (-) •Infective complications (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
$+exp_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Conclusions about oral nutritional supplements

LIPID CONSUMPTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Protein and calorie supplements** may not have a difference in efficacy compared to **standard care** for improving carbohydrate consumption.	1	Aquilani et al., 2008a
1b	**Protein supplements** may not have a difference in efficacy compared to **standard care** for improving lipid consumption.	1	Aquilani et al., 2008b

PROTEIN CONSUMPTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	There is conflicting evidence about the effect of **protein and calorie supplements** to improve protein consumption when compared **standard care.**	2	Ha et al., 2010a; Aquilani et al., 2008a
1b	**Protein supplements** may produce greater improvements in protein consumption than **standard care.**	1	Aquilani et al., 2008b
1b	**Hospital diet with supplementation** may produce greater improvements in protein consumption than **hospital diet alone.**	1	Gariballa et al., 1998

CARBOHYDRATE CONSUMPTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Protein and calorie supplements** may not have a difference in efficacy compared to **standard care** for improving carbohydrate consumption.	1	Aquilani et al., 2008a
1b	**Protein supplements** may not have a difference in efficacy compared to **standard care** for improving carbohydrate consumption.	1	Aquilani et al., 2008b

CALORIE CONSUMPTION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Protein and calorie supplements** may produce greater improvements in blood glucose management than **standard care.**	2	Ha et al., 2010a; Aquilani et al., 2008a
1b	**Protein supplements** may not have a difference in efficacy compared to **standard care** for improving calorie consumption.	1	Aquilani et al., 2008b
1b	**Hospital diet with supplementation** may produce greater improvements in calorie consumption than **hospital diet alone.**	1	Gariballa et al., 1998

VITAMIN AND MINERAL CONSUMPTION			
LoE	**Conclusion Statement**	**RCTs**	**References**

1b	**Protein supplements** may produce greater improvements in vitamin and mineral consumption than **standard care.**	1	Aquilani et al., 2008b
1b	**Hospital diet with supplementation** may produce greater improvements in vitamin and mineral consumption than **hospital diet alone.**	1	Gariballa et al., 1998

BODY COMPOSITION			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Protein and calorie supplements** may not have a difference in efficacy compared to **standard care** for improving body composition.	3	Ha et al., 2010a; Ha et al., 2010b; Aquilani et al., 2008a
1b	**Protein supplements** may not have a difference in efficacy compared to **standard care** for improving body composition.	1	Aquilani et al., 2008b
1b	**Intensive nutrient supplements** may not have a difference in efficacy compared to **standard nutrient supplements** for improving body composition.	1	Rabadi et al., 2008
1b	**Hospital diet with supplementation** may not have a difference in efficacy compared to **hospital diet alone** for improving body composition.	1	Gariballa et al., 1998

BLOOD GLUCOSE MANAGEMNET			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**ALAnerv supplements** may produce greater improvements in blood glucose management than **standard care.**	1	Opera et al., 2013

PLASMA PROTEINS			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**ALAnerv supplements** may produce greater improvements in plasma proteins than **standard care.**	1	Opera et al., 2013
1b	**Intensive nutrient supplements** may not have a difference in efficacy compared to **standard nutrient supplements** for improving plasma proteins.	1	Rabadi et al., 2008
1b	There is conflicting evidence about the effect of **hospital diet with supplementation** to improve plasma proteins when compared **hospital diet alone.**	1	Gariballa et al., 1998

LYMPHOCYTE COUNT			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Essential amino acid supplements** may produce greater improvements in lymphocyte count than **a placebo.**	1	Aquilani et al., 2015

ACTIVITIES OF DAILY LIVING			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**ALAnerv** may produce greater improvements in activities of daily living than **standard care.**	1	Opera et al., 2013
1b	**Hospital diet with supplementation** may not have a difference in efficacy compared to **hospital diet alone** for improving activities of daily living.	1	Gariballa et al., 1998

STROKE SEVERITY			
LoE	**Conclusion Statement**	**RCTs**	**References**
1b	**Protein supplements** may produce greater improvements in stroke severity than **standard care.**	1	Aquilani et al., 2008b
1b	**Hospital diet with supplementation** may not have a difference in efficacy compared to **hospital diet alone** for improving stroke severity.	1	Dennis et al., 2005b

Key Points

Protein and calorie supplements may not be beneficial for improving body composition, but may be beneficial for improving stroke severity.

ALAnerv supplements may improve blood glucose management, plasma proteins and activities of daily living.

References

Akner, G., & Cederholm, T. (2001). Treatment of protein-energy malnutrition in chronic nonmalignant disorders. *Am.J.Clin Nutr., 74*(1), 6-24.

Abete, I., Parra, D., De Morentin, B. M., & Alfredo Martinez, J. (2009). Effects of two energy-restricted diets differing in the carbohydrate/protein ratio on weight loss and oxidative changes of obese men. *International journal of food sciences and nutrition*, *60*(sup3), 1-13.

Amarenco, P., Bogousslavsky, J., Callahan, A., 3rd, Goldstein, L. B., Hennerici, M., Rudolph, A. E., . . . Zivin, J. A. (2006). High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med, 355*(6), 549-559. doi:10.1056/NEJMoa061894

American Dietetic Association. (2000). *Manual of clinical dietetics*: American Dietetic Association.

Aptaker, R. L., Roth, E. J., Reichhardt, G., Duerden, M. E., & Levy, C. E. (1994). Serum albumin level as a predictor of geriatric stroke rehabilitation outcome. *Arch.Phys.Med.Rehabil., 75*(1), 80-84. doi:0003-9993(94)90342-5 [pii]

Aquilani, R., Emilio, B., Dossena, M., Baiardi, P., Testa, A., Boschi, F., . . . Verri, M. (2015). Correlation of deglutition in subacute ischemic stroke patients with peripheral blood adaptive immunity: Essential amino acid improvement. *International Journal of Immunopathology and Pharmacology, 28*(4), 576-583. doi:http://dx.doi.org/10.1177/0394632015608249

Aquilani, R., Galli, M., Guarnaschelli, C., Fugazza, G., Lorenzoni, M., Varalda, E., . . . Crespi, M. G. (1999). Prevalence of malnutrition and inadequate food intake in self-feeding rehabilitation patients with stroke. *Europa Medicophysica, 35*, 75-82.

Aquilani, R., Scocchi, M., Boschi, F., Viglio, S., Iadarola, P., Pastoris, O., & Verri, M. (2008a). Effect of calorie-protein supplementation on the cognitive recovery of patients with subacute stroke. *Nutr.Neurosci., 11*(5), 235-240. doi:10.1179/147683008X301586 [doi]

Aquilani, R., Scocchi, M., Iadarola, P., Franciscone, P., Verri, M., Boschi, F., . . . Viglio, S. (2008b). Protein supplementation may enhance the spontaneous recovery of neurological alterations in patients with ischaemic stroke. *Clin Rehabil., 22*(12), 1042-1050. doi:22/12/1042 [pii];10.1177/0269215508094244 [doi]

Ascherio, A., Willett, W. C., Rimm, E. B., Giovannucci, E. L., & Stampfer, M. J. (1994). Dietary iron intake and risk of coronary disease among men. *Circulation*, *89*(3), 969-974.

Athyros, V. G., Tziomalos, K., Karagiannis, A., Wierzbicki, A. S., & Mikhailidis, D. P. (2010). Aggressive statin treatment, very low serum cholesterol levels and haemorrhagic stroke: is there an association? *Curr Opin Cardiol, 25*(4), 406-410. doi:10.1097/HCO.0b013e3283393c1a

Axelsson, K., Asplund, K., Norberg, A., & Alafuzoff, I. (1988). Nutritional status in patients with acute stroke. *Acta Med.Scand., 224*(3), 217-224.

Barter, P., Gotto, A. M., LaRosa, J. C., Maroni, J., Szarek, M., Grundy, S. M., ... & Fruchart, J. C. (2007). HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *New England Journal of Medicine*, *357*(13), 1301-1310.

Bartnikas, T. B. (2012). Known and potential roles of transferrin in iron biology. *Biometals*, *25*(4), 677-686.

Beamer, N. B., Coull, B. M., Clark, W. M., Hazel, J. S., & Silberger, J. R. (1995). Interleukin-6 and interleukin-1 receptor antagonist in acute stroke. *Ann.Neurol., 37*(6), 800-805. doi:10.1002/ana.410370614 [doi]

Beck, F. K., & Rosenthal, T. C. (2002). Prealbumin: a marker for nutritional evaluation. *American family physician*, *65*(8).

Ben-Assayag, E., Shenhar-Tsarfaty, S., Bova, I., Berliner, S., Shopin, L., Peretz, H., . . . Bornstein, N. M. (2007). Triggered C-reactive protein (CRP) concentrations and the CRP gene -717A>G polymorphism in acute stroke or transient ischemic attack. *Eur J Neurol, 14*(3), 315-320. doi:10.1111/j.1468-1331.2006.01661.x

Bharosay, A., Bharosay, V. V., Bandyopadhyay, D., Sodani, A., Varma, M., & Baruah, H. (2014). Effect of lipid profile upon prognosis in ischemic and haemorrhagic cerebrovascular stroke. *Indian Journal of Clinical Biochemistry, 29*(3), 372-376.

Bhurosy, T., & Jeewon, R. (2013). Pitfalls of using body mass index (BMI) in assessment of obesity risk. *Current Research in Nutrition and Food Science Journal*, *1*(1), 71-76.

Brynningsen, P. K., Damsgaard, E. M., & Husted, S. E. (2007). Improved nutritional status in elderly patients 6 months after stroke. *J.Nutr.Health Aging, 11*(1), 75-79.

Bushnell, C. D., Johnston, D. C., & Goldstein, L. B. (2001). Retrospective assessment of initial stroke severity: comparison of the NIH Stroke Scale and the Canadian Neurological Scale. *Stroke*, *32*(3), 656-660.

Calle, E. E., Thun, M. J., Petrelli, J. M., Rodriguez, C., & Heath Jr, C. W. (1999). Body-mass index and mortality in a prospective cohort of US adults. *New England Journal of Medicine*, *341*(15), 1097-1105.

Camara-Lemarroy, C. R., Ibarra-Yruegas, B. E., & Gongora-Rivera, F. (2014). Gastrointestinal complications after ischemic stroke. *J Neurol Sci, 346*(1-2), 20-25. doi:10.1016/j.jns.2014.08.027

Camerlingo, M., Valente, L., Tognozzi, M., Beretta, G. L., Moschini, L., & Cesana, B. M. (2011). C-reactive protein levels in the first three hours after acute cerebral infarction. *Int J Neurosci, 121*(2), 65-68. doi:10.3109/00207454.2010.530005

Chai, J., Chu, F. C., Chow, T. W., & Shum, N. C. (2008). Prevalence of malnutrition and its risk factors in stroke patients residing in an infirmary. *Singapore Med.J., 49*(4), 290-296.

Chan, R., Chan, D., & Woo, J. (2013). The association of a priori and a posterior dietary patterns with the risk of incident stroke in chinese older people in Hong Kong. *Journal of Nutrition, Health and Aging, 17*(10), 866-874.

Choi-Kwon, S., Yang, Y. H., Kim, E. K., Jeon, M. Y., & Kim, J. S. (1998). Nutritional status in acute stroke: undernutrition versus overnutrition in different stroke subtypes. *Acta Neurol Scand, 98*(3), 187-192.

Christensen, H., & Boysen, G. (2002). Blood glucose increases early after stroke onset: a study on serial measurements of blood glucose in acute stroke. *Eur J Neurol, 9*(3), 297-301.

Crary, M. A., Carnaby-Mann, G. D., Miller, L., Antonios, N., & Silliman, S. (2006). Dysphagia and nutritional status at the time of hospital admission for ischemic stroke. *J.Stroke Cerebrovasc.Dis., 15*(4), 164-171. doi:S1052-3057(06)00079-6 [pii];10.1016/j.jstrokecerebrovasdis.2006.05.006 [doi]

Crary, M. A., Humphrey, J. L., Carnaby-Mann, G., Sambandam, R., Miller, L., & Silliman, S. (2013). Dysphagia, nutrition, and hydration in ischemic stroke patients at admission and discharge from acute care. *Dysphagia, 28*(1), 69-76. doi:10.1007/s00455-012-9414-0 [doi]

Davalos, A., Ricart, W., Gonzalez-Huix, F., Soler, S., Marrugat, J., Molins, A., . . . Genis, D. (1996). Effect of malnutrition after acute stroke on clinical outcome. *Stroke, 27*(6), 1028-1032.

Davis, J. P., Wong, A. A., Schluter, P. J., Henderson, R. D., O'Sullivan, J. D., & Read, S. J. (2004). Impact of premorbid undernutrition on outcome in stroke patients. *Stroke, 35*(8), 1930-1934. doi:10.1161/01.STR.0000135227.10451.c9 [doi];01.STR.0000135227.10451.c9 [pii]

Davison, K. K., Ford, E. S., Cogswell, M. E., & Dietz, W. H. (2002). Percentage of body fat and body mass index are associated with mobility limitations in people aged 70 and older from NHANES III. *Journal of the American Geriatrics Society*, *50*(11), 1802-1809.

Deitrick, J. E., Whedon, G. D., & Shorr, E. (1948). Effects of mobilization upon various metabolic and physiological functions. *Am.J.Med., 4*, 3-36.

den Hertog, H. M., Vermeer, S. E., Zandbergen, A. A. M., Achterberg, S., Dippel, D. W. J., Algra, A., . . . Koudstaal, P. J. (2015). Safety and feasibiLIty of Metformin in patients with Impaired glucose Tolerance and a recent TIA or minor ischemic stroke (LIMIT) trial - a multicenter, randomized, open-label phase II trial. *International Journal of Stroke, 10*(1), 105-109.

Dennis, M. S., Lewis, S. C., & Warlow, C. (2005a). Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial. *Lancet, 365*(9461), 764-772. doi:S0140673605179835 [pii];10.1016/S0140-6736(05)17983-5 [doi]

Dennis, M. S., Lewis, S. C., & Warlow, C. (2005b). Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial. *Lancet, 365*(9461), 755-763. doi:S0140673605179823 [pii];10.1016/S0140-6736(05)17982-3 [doi]

Deurenberg, P., Pieters, J. J., & Hautvast, J. G. (1990). The assessment of the body fat percentage by skinfold thickness measurements in childhood and young adolescence. *British Journal of Nutrition*, *63*(2), 293-303.

DePippo, K. L., Holas, M. A., Reding, M. J., Mandel, F. S., & Lesser, M. L. (1994). Dysphagia therapy following stroke: a controlled trial. *Neurology, 44*(9), 1655-1660.

Dziedzic, T., Pera, J., Trabka-Janik, E., Szczudlik, A., & Slowik, A. (2010). The impact of postadmission glycemia on stroke outcome: glucose normalisation is associated with better survival. *Atherosclerosis, 211*(2), 584-588.

Elmstahl, S., Bulow, M., Ekberg, O., Petersson, M., & Tegner, H. (1999). Treatment of dysphagia improves nutritional conditions in stroke patients. *Dysphagia, 14*(2), 61-66.
Engberg, S., Vistisen, D., Lau, C., Glümer, C., Jørgensen, T., Pedersen, O., & Borch-Johnsen, K. (2009). Progression to impaired glucose regulation and diabetes in the population-based Inter99 study. *Diabetes care, 32*(4), 606-611.
Fassbender, K., Rossol, S., Kammer, T., Daffertshofer, M., Wirth, S., Dollman, M., & Hennerici, M. (1994). Proinflammatory cytokines in serum of patients with acute cerebral ischemia: kinetics of secretion and relation to the extent of brain damage and outcome of disease. *J.Neurol.Sci., 122*(2), 135-139.
Fassbender, K., Schmidt, R., Mossner, R., Daffertshofer, M., & Hennerici, M. (1994). Pattern of activation of the hypothalamic-pituitary-adrenal axis in acute stroke. Relation to acute confusional state, extent of brain damage, and clinical outcome. *Stroke, 25*(6), 1105-1108.
Ferrarese, C., Mascarucci, P., Zoia, C., Cavarretta, R., Frigo, M., Begni, B., . . . De Simoni, M. G. (1999). Increased cytokine release from peripheral blood cells after acute stroke. *J.Cereb.Blood Flow Metab, 19*(9), 1004-1009. doi:10.1097/00004647-199909000-00008 [doi]
Finestone, H. M., Greene-Finestone, L. S., Foley, N. C., & Woodbury, M. G. (2003). Measuring longitudinally the metabolic demands of stroke patients: resting energy expenditure is not elevated. *Stroke, 34*(2), 502-507.
Finestone, H. M., Greene-Finestone, L. S., Wilson, E. S., & Teasell, R. W. (1995). Malnutrition in stroke patients on the rehabilitation service and at follow-up: prevalence and predictors. *Arch.Phys.Med.Rehabil., 76*(4), 310-316. doi:S0003-9993(95)80655-5 [pii]
Fleck, A. (1989). Clinical and nutritional aspects of changes in acute-phase proteins during inflammation. *Proc.Nutr.Soc., 48*(3), 347-354. doi:S0029665189000522 [pii]
Foley, N., Finestone, H., Woodbury, M. G., Teasell, R., & Greene, F. L. (2006). Energy and protein intakes of acute stroke patients. *J.Nutr.Health Aging, 10*(3), 171-175.
Foley, N. C., Martin, R. E., Salter, K. L., & Teasell, R. W. (2009a). A review of the relationship between dysphagia and malnutrition following stroke. *J.Rehabil.Med., 41*(9), 707-713. doi:10.2340/16501977-0415 [doi]
Foley, N. C., Salter, K. L., Robertson, J., Teasell, R. W., & Woodbury, M. G. (2009b). Which reported estimate of the prevalence of malnutrition after stroke is valid? *Stroke, 40*(3), e66-e74. doi:STROKEAHA.108.518910 [pii];10.1161/STROKEAHA.108.518910 [doi]
FOOD Trial Collaboration. (2003). Poor nutritional status on admission predicts poor outcomes after stroke: observational data from the FOOD trial. *Stroke., 34*(6), 1450-1456.
Forget, P., Khalifa, C., Defour, J. P., Latinne, D., Van Pel, M. C., & De Kock, M. (2017). What is the normal value of the neutrophil-to-lymphocyte ratio?. *BMC research notes*, *10*(1), 12.
Gabay, C., & Kushner, I. (1999). Acute-phase proteins and other systemic responses to inflammation. *N.Engl.J.Med., 340*(6), 448-454. doi:10.1056/NEJM199902113400607 [doi]
Gariballa, S. E. (2001). Malnutrition in hospitalized elderly patients: when does it matter? *Clinical nutrition, 20*(6), 487-491.
Gariballa, S. E., Parker, S. G., Taub, N., & Castleden, C. M. (1998a). Influence of nutritional status on clinical outcome after acute stroke. *Am.J.Clin Nutr., 68*(2), 275-281.
Gariballa, S. E., Parker, S. G., Taub, N., & Castleden, C. M. (1998b). A randomized, controlled, a single-blind trial of nutritional supplementation after acute stroke. *JPEN J.Parenter.Enteral Nutr., 22*(5), 315-319.
Girotti, A. W. (1998). Lipid hydroperoxide generation, turnover, and effector action in biological systems. *Journal of lipid research*, *39*(8), 1529-1542.
Gray, C. S., Hildreth, A. J., Sandercock, P. A., O'Connell, J. E., Johnston, D. E., Cartlidge, N. E., . . . Alberti, K. G. (2007). Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol, 6*(5), 397-406. doi:10.1016/s1474-4422(07)70080-7
Gunduz, A., Turedi, S., Mentese, A., Altunayoglu, V., Turan, I., Karahan, S. C., ... & Akcan, B. (2008). Ischemia-modified albumin levels in cerebrovascular accidents. *The American journal of emergency medicine*, *26*(8), 874-878.
Gupta, A., Prabhakar, S., Modi, M., Bhadada, S. K., Kalaivani, M., Lal, V., & Khurana, D. (2016). Effect of Vitamin D and calcium supplementation on ischaemic stroke outcome: a randomised controlled open-label trial. *Int J Clin Pract, 70*(9), 764-770. doi:10.1111/ijcp.12866

Gupta, P., Yadav, S., & Singal, K. K. (2014). Cerebroprotein hydrolysate: Innovation in the treatment of neurodegenerative disorders. *Journal, Indian Academy of Clinical Medicine, 15*(2), 132-133.
Ha, L., Hauge, T., & Iversen, P. O. (2010b). Body composition in older acute stroke patients after treatment with individualized, nutritional supplementation while in hospital. *BMC.Geriatr., 10*, 75. doi:1471-2318-10-75 [pii];10.1186/1471-2318-10-75 [doi]
Ha, L., Hauge, T., Spenning, A. B., & Iversen, P. O. (2010a). Individual, nutritional support prevents undernutrition, increases muscle strength and improves QoL among elderly at nutritional risk hospitalized for acute stroke: a randomized, controlled trial. *Clin Nutr., 29*(5), 567-573. doi:S0261-5614(10)00029-4 [pii];10.1016/j.clnu.2010.01.011 [doi]
Halazun, K. J., Aldoori, A., Malik, H. Z., Al-Mukhtar, A., Prasad, K. R., Toogood, G. J., & Lodge, J. P. A. (2008). Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. *European Journal of Surgical Oncology (EJSO)*, *34*(1), 55-60.
Hama, S., Kitaoka, T., Shigenobu, M., Watanabe, A., Imura, I., Seno, H., . . . Kurisu, K. (2005). Malnutrition and nonthyroidal illness syndrome after stroke. *Metabolism, 54*(6), 699-704. doi:S0026049504004408 [pii];10.1016/j.metabol.2004.11.016 [doi]
Hantson, L., De Weerdt, W., De Keyser, J., Diener, H. C., Franke, C., Palm, R., ... & Herroelen, L. (1994). The European Stroke Scale. *Stroke*, *25*(11), 2215-2219.
Hasani, S. A., Ziai, S. A., Mehrpour, M., Amiri, M., & Motamed, M. R. (2011). Acute phase reactants as a prognostic factor in acute stroke. *Basic and Clinical Neuroscience, 3*(1), 30-34.
Heldner, M. R., Zubler, C., Mattle, H. P., Schroth, G., Weck, A., Mono, M. L., ... & Yan, X. (2013). National Institutes of Health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. *Stroke*, *44*(4), 1153-1157.
Ivey, F. M., Ryan, A. S., Hafer-Macko, C. E., Goldberg, A. P., & Macko, R. F. (2007). Treadmill aerobic training improves glucose tolerance and indices of insulin sensitivity in disabled stroke survivors: a preliminary report. *Stroke, 38*(10), 2752-2758. doi:10.1161/strokeaha.107.490391
Izzo Jr, J. L., Levy, D., & Black, H. R. (2000). Importance of systolic blood pressure in older Americans. *Hypertension*, *35*(5), 1021-1024.
Johanson, J. F., Sonnenberg, A., Koch, T. R., & McCarty, D. J. (1992). Association of constipation with neurologic diseases. *Dig.Dis.Sci., 37*(2), 179-186.
Johnson, C. L., Rifkind, B. M., Sempos, C. T., Carroll, M. D., Bachorik, P. S., Briefel, R. R., ... & Cleeman, J. I. (1993). Declining serum total cholesterol levels among US adults: the National Health and Nutrition Examination Surveys. *Jama*, *269*(23), 3002-3008.
Johnson, M. A., & Fischer, J. (2004). Eating and appetite: Common problems and practical remedies. *Generations*, *28*(3), 11-17.
Khera, A. V., Cuchel, M., De La Llera-Moya, M., Rodrigues, A., Burke, M. F., Jafri, K., ... & Mohler, E. R. (2011). Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *New England Journal of Medicine*, *364*(2), 127-135.
Kim, E. J., Yoon, Y. H., Kim, W. H., Lee, K. L., & Park, J. M. (2013). The clinical significance of the mini-nutritional assessment and the scored patient-generated subjective global assessment in elderly patients with stroke. *Ann Rehabil Med, 37*(1), 66-71. doi:10.5535/arm.2013.37.1.66 [doi]
Kojima, G., Bell, C., Abbott, R. D., Launer, L., Chen, R., Motonaga, H., . . . Masaki, K. (2012). Low dietary vitamin D predicts 34-year incident stroke: the Honolulu Heart Program. *Stroke, 43*(8), 2163-2167. doi:10.1161/strokeaha.112.651752
Körner, S., Hendricks, M., Kollewe, K., Zapf, A., Dengler, R., Silani, V., & Petri, S. (2013). Weight loss, dysphagia and supplement intake in patients with amyotrophic lateral sclerosis (ALS): impact on quality of life and therapeutic options. *BMC neurology*, *13*(1), 84.
Laird, E. A., Coates, V. E., Ryan, A. A., McCarron, M. O., Lyttle, D., & McCrum-Gardner, E. (2014). Hypoglycaemia risk among a hospitalised stroke patient cohort: A case for increased vigilance in glucose monitoring. *Journal of Clinical Neuroscience, 21*(2), 232-235. doi:10.1016/j.jocn.2013.03.031
Landi, F., Russo, A., Liperoti, R., Pahor, M., Tosato, M., Capoluongo, E., ... & Onder, G. (2010). Midarm muscle circumference, physical performance and mortality: results from the aging and longevity study in the Sirente geographic area (ilSIRENTE study). *Clinical Nutrition*, *29*(4), 441-447.
Larsson, S. C. (2013). Dietary fats and other nutrients on stroke. *Current Opinion in Lipidology, 24*(1), 41-48. doi:10.1097/MOL.0b013e3283592eea

Li, X., Song, G., Jin, Y., Liu, H., Li, C., Han, C., & Ren, S. (2014). Higher level of heme oxygenase-1 in patients with stroke than TIA. *Journal of Thoracic Disease, 6*(6), 772-777. doi:10.3978/j.issn.2072-1439.2014.06.28

Lim, H. J., & Choue, R. (2010). Nutritional status assessed by the Patient-Generated Subjective Global Assessment (PG-SGA) is associated with qualities of diet and life in Korean cerebral infarction patients. *Nutrition, 26*(7-8), 766-771. doi:10.1016/j.nut.2009.10.003

Lindsberg, P. J., Tuomi, T., & Kaste, M. (2011). Oral glucose tolerance test should be performed after stroke and transient ischemic attack. *International Journal of Stroke, 6*(4), 317-320.

Luchsinger, J. A., Tang, M. X., Shea, S., & Mayeux, R. (2002). Caloric intake and the risk of Alzheimer disease. *Archives of Neurology*, *59*(8), 1258-1263.

Mahmood, A., Sharif, M. A., Khan, M. N., & Ali, U. Z. (2010). Comparison of serum lipid profile in ischaemic and haemorrhagic stroke. *J Coll Physicians Surg Pak, 20*(5), 317-320. doi:04.2010/jcpsp.317320

Mangat, A., Grewal, D., Kaur, P., Jyotsna, R., Singh, R., & Pandian, J. D. (2013). Dietary patterns in stroke patients in Northwest India. *Nutritional Neuroscience, 16*(6), 288-292. doi:10.1179/1476830513y.0000000058

Manolescu, B. N., Berteanu, M., & Cintezã, D. (2013). Effect of the nutritional supplement ALAnerv® on the serum PON1 activity in post-acute stroke patients. *Pharmacological Reports, 65*(3), 743-750.

Martin, W. F., Armstrong, L. E., & Rodriguez, N. R. (2005). Dietary protein intake and renal function. *Nutrition & metabolism*, *2*(1), 25.

Martineau, J., Bauer, J. D., Isenring, E., & Cohen, S. (2005). Malnutrition determined by the patient-generated subjective global assessment is associated with poor outcomes in acute stroke patients. *Clin Nutr., 24*(6), 1073-1077. doi:S0261-5614(05)00143-3 [pii];10.1016/j.clnu.2005.08.010 [doi]

Melamed, M. L., Michos, E. D., Post, W., & Astor, B. (2008). 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Archives of internal medicine*, *168*(15), 1629-1637.

Mosselman, M. J., Kruitwagen, C., Schuurmans, M. J., & Hafsteinsdottir, T. B. (2013). Malnutrition and Risk of Malnutrition in Patients With Stroke: Prevalence During Hospital Stay. *Journal of Neuroscience Nursing, 45*(4), 194-204. doi:10.1097/JNN.0b013e31829863cb

Muir, K. W., Weir, C. J., Alwan, W., Squire, I. B., & Lees, K. R. (1999). C-reactive protein and outcome after ischemic stroke. *Stroke, 30*(5), 981-985.

Muò, R., Cancialosi, P., Galimberti, L., Cacciola, B. C., Gilardone, M., & Schindler, A. (2015). Validation of the Italian version of the American Speech-Language and Hearing Association—Functional Assessment of Communication Skills for adults (I-ASHA-FACS). *Aphasiology, 29*(9), 1110-1130. doi:http://dx.doi.org/10.1080/02687038.2015.1010475

Murray, J., Doeltgen, S., Miller, M., & Scholten, I. (2015). A Descriptive Study of the Fluid Intake, Hydration, and Health Status of Rehabilitation Inpatients without Dysphagia Following Stroke. *J Nutr Gerontol Geriatr, 34*(3), 292-304. doi:10.1080/21551197.2015.1054573

Murros, K., Fogelholm, R., Kettunen, S., & Vuorela, A. L. (1993). Serum cortisol and outcome of ischemic brain infarction. *J.Neurol.Sci., 116*(1), 12-17.

Ness-Abramof, R., & Apovian, C. M. (2008). Waist circumference measurement in clinical practice. *Nutrition in Clinical Practice*, *23*(4), 397-404.

Nichols, A. B., Ravenscroft, C., Lamphiear, D. E., & Ostrander Jr, L. D. (1976). Daily nutritional intake and serum lipid levels. The Tecumseh Study. *The American journal of clinical nutrition*, *29*(12), 1384-1392.

Nissen, S. E., Tuzcu, E. M., Schoenhagen, P., Crowe, T., Sasiela, W. J., Tsai, J., ... & Ganz, P. (2005). Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *New England Journal of Medicine*, *352*(1), 29-38.

Norton, B., Homer-Ward, M., Donnelly, M. T., Long, R. G., & Holmes, G. K. (1996). A randomised prospective comparison of percutaneous endoscopic gastrostomy and nasogastric tube feeding after acute dysphagic stroke. *BMJ, 312*(7022), 13-16.

Nyswonger, G. D., & Helmchen, R. H. (1992). Early enteral nutrition and length of stay in stroke patients. *J.Neurosci.Nurs., 24*(4), 220-223.

Ogata, T., Kamouchi, M., Matsuo, R., Hata, J., Kuroda, J., Ago, T., . . . Kitazono, T. (2014). Gastrointestinal bleeding in acute ischemic stroke: recent trends from the fukuoka stroke registry. *Cerebrovasc Dis Extra, 4*(2), 156-164. doi:10.1159/000365245

Oprea, E., Berteanu, M., Cinteza, D., & Manolescu, B. N. (2013). The effect of the ALAnerv nutritional supplement on some oxidative stress markers in postacute stroke patients undergoing rehabilitation. *Applied Physiology Nutrition and Metabolism-Physiologie Appliquee Nutrition Et Metabolisme, 38*(6), 613-620. doi:10.1139/apnm-2012-0436

Ormstad, H., Verkerk, R., Aass, H. C., Amthor, K. F., & Sandvik, L. (2013). Inflammation-induced catabolism of tryptophan and tyrosine in acute ischemic stroke. *J Mol Neurosci, 51*(3), 893-902. doi:10.1007/s12031-013-0097-2

Paquereau, J., Allart, E., Romon, M., & Rousseaux, M. (2014). The long-term nutritional status in stroke patients and its predictive factors. *Journal of Stroke and Cerebrovascular Diseases, 23*(6), 1628-1633. doi:10.1016/j.jstrokecerebrovasdis.2014.01.007

Park, C. S. (2018). The test-retest reliability and minimal detectable change of the short-form Barthel Index (5 items) and its associations with chronic stroke-specific impairments. *Journal of physical therapy science*, *30*(6), 835-839.

Perrier, E., Rondeau, P., Poupin, M., Le Bellego, L., Armstrong, L. E., Lang, F., ... & Klein, A. (2013). Relation between urinary hydration biomarkers and total fluid intake in healthy adults. *European journal of clinical nutrition*, *67*(9), 939

Pikosky, M. A., Smith, T. J., Grediagin, A. N. N., Castaneda-Sceppa, C., Byerley, L., Glickman, E. L., & Young, A. J. (2008). Increased protein maintains nitrogen balance during exercise-induced energy deficit. *Medicine & Science in Sports & Exercise*, *40*(3), 505-512.

Pilz, S., Dobnig, H., Fischer, J. E., Wellnitz, B., Seelhorst, U., Boehm, B. O., & Marz, W. (2008). Low vitamin d levels predict stroke in patients referred to coronary angiography. *Stroke, 39*(9), 2611-2613. doi:10.1161/strokeaha.107.513655

Poels, B. J., Brinkman-Zijlker, H. G., Dijkstra, P. U., & Postema, K. (2006). Malnutrition, eating difficulties and feeding dependence in a stroke rehabilitation centre. *Disabil.Rehabil., 28*(10), 637-643. doi:H0962517U144535W [pii];10.1080/09638280500276612 [doi]

Quinn, T. J., Dawson, J., Walters, M., & Lees, K. R. (2009). Reliability of the modified Rankin Scale: a systematic review. *Stroke*, *40*(10), 3393-3395.

Rabadi, M. H., Coar, P. L., Lukin, M., Lesser, M., & Blass, J. P. (2008). Intensive nutritional supplements can improve outcomes in stroke rehabilitation. *Neurology, 71*(23), 1856-1861. doi:01.wnl.0000327092.39422.3c [pii];10.1212/01.wnl.0000327092.39422.3c [doi]

Rolland-Cachera, M. F., Brambilla, P., Manzoni, P., Akrout, M., Sironi, S., Del Maschio, A., & Chiumello, G. (1997). Body composition assessed on the basis of arm circumference and triceps skinfold thickness: a new index validated in children by magnetic resonance imaging. *The American journal of clinical nutrition*, *65*(6), 1709-1713.

Schaller, B. J., Graf, R., & Jacobs, A. H. (2006). Pathophysiological changes of the gastrointestinal tract in ischemic stroke. *Am J Gastroenterol, 101*(7), 1655-1665. doi:10.1111/j.1572-0241.2006.00540.x

Schonheyder, F., Heilskov, N. C., & Olesen, K. (1954). Isotopic studies on the mechanism of negative nitrogen balance produced by immobilization. *Scand.J.Clin Lab Invest*, 178-188.

Scivoletto, G., Petrelli, A., Lucente, L. D., & Castellano, V. (1997). Psychological investigation of spinal cord injury patients. *Spinal cord, 35*(8), 516-520.

Selakovic, V. M., Jovanovic, M. D., & Jovicic, A. (2002). Changes of cortisol levels and index of lipid peroxidation in cerebrospinal fluid of patients in the acute phase of completed stroke. *Vojnosanit Pregl, 59*(5), 485-491.

Shaafi, S., Sharifipour, E., Rahmanifar, R., Hejazi, S., Andalib, S., Nikanfar, M., . . . Mehdizadeh, R. (2014). Interleukin-6, a reliable prognostic factor for ischemic stroke. *Iran J Neurol, 13*(2), 70-76.

Sharma, S., Cruickshank, J. K., Green, D. M., Vik, S., Tome, A., & Kolonel, L. N. (2013). Impact of Diet on Mortality From Stroke: Results From the US Multiethnic Cohort Study. *Journal of the American College of Nutrition, 32*(3), 151-159. doi:10.1080/07315724.2013.791798

Sonnenberg, A., Tsou, V. T., & Muller, A. D. (1994). The "institutional colon": a frequent colonic dysmotility in psychiatric and neurologic disease. *Am.J.Gastroenterol., 89*(1), 62-66.

Staal-van den Brekel, A., Dentener, M. A., Schols, A. M., Buurman, W. A., & Wouters, E. F. (1995). Increased resting energy expenditure and weight loss are related to a systemic inflammatory response in lung cancer patients. *Journal of clinical oncology, 13*(10), 2600-2605.

Stineman, M. G., Shea, J. A., Jette, A., Tassoni, C. J., Ottenbacher, K. J., Fiedler, R., & Granger, C. V. (1996). The Functional Independence Measure: tests of scaling assumptions, structure, and

reliability across 20 diverse impairment categories. *Archives of physical medicine and rehabilitation*, *77*(11), 1101-1108.
Stumvoll, M., Mitrakou, A., Pimenta, W., Jenssen, T., Yki-Järvinen, H. A. N. N. E. L. E., Van Haeften, T., ... & Gerich, J. (2000). Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. *Diabetes care*, *23*(3), 295-301.
Sudsuang, R., Chentanez, V., & Veluvan, K. (1991). Effect of Buddhist meditation on serum cortisol and total protein levels, blood pressure, pulse rate, lung volume and reaction time. *Physiology & Behavior*, *50*(3), 543-548.
Suzuki, T., Oba, K., Igari, Y., Matsumura, N., Watanabe, K., Futami-Suda, S., ... & Nakano, H. (2007). Colestimide lowers plasma glucose levels and increases plasma glucagon-like PEPTIDE-1 (7-36) levels in patients with type 2 diabetes mellitus complicated by hypercholesterolemia. *Journal of Nippon Medical School*, *74*(5), 338-343.
Syrjanen, J., Teppo, A. M., Valtonen, V. V., Iivanainen, M., & Maury, C. P. (1989). Acute phase response in cerebral infarction. *J.Clin Pathol., 42*(1), 63-68.
Szczudlik, A., Dziedzic, T., Bartus, S., Slowik, A., & Kieltyka, A. (2004). Serum interleukin-6 predicts cortisol release in acute stroke patients. *J Endocrinol Invest, 27*(1), 37-41. doi:10.1007/bf03350908
Thijssen, D. H., Black, M. A., Pyke, K. E., Padilla, J., Atkinson, G., Harris, R. A., ... & Green, D. J. (2010). Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. *American Journal of Physiology-Heart and Circulatory Physiology*, *300*(1), H2-H12.
Tirosh, A., Shai, I., Tekes-Manova, D., Israeli, E., Pereg, D., Shochat, T., ... & Rudich, A. (2005). Normal fasting plasma glucose levels and type 2 diabetes in young men. *New England Journal of Medicine*, *353*(14), 1454-1462.
Tu, W. J., Zhao, S. J., Xu, D. J., & Chen, H. (2014). Serum 25-hydroxyvitamin D predicts the short-term outcomes of Chinese patients with acute ischaemic stroke. *Clinical Science, 126*(5-6), 339-346. doi:10.1042/cs20130284
Turetsky, A., Goddeau, R. P., Jr., & Henninger, N. (2015). Low Serum Vitamin D Is Independently Associated with Larger Lesion Volumes after Ischemic Stroke. *J Stroke Cerebrovasc Dis, 24*(7), 1555-1563. doi:10.1016/j.jstrokecerebrovasdis.2015.03.051
Tuttolomondo, A., Casuccio, A., Butta, C., Pecoraro, R., Di Raimondo, D., Della Corte, V., . . . Pinto, A. (2015). Mediterranean Diet in patients with acute ischemic stroke: Relationships between Mediterranean Diet score, diagnostic subtype, and stroke severity index. *Atherosclerosis, 243*(1), 260-267. doi:10.1016/j.atherosclerosis.2015.09.017
Ullman, T., & Reding, M. (1996). Gastrointestinal dysfunction in stroke. *Semin.Neurol., 16*(3), 269-275. doi:10.1055/s-2008-1040984 [doi]
Unosson, M., Ek, A. C., Bjurulf, P., von Schenck, H., & Larsson, J. (1994). Feeding dependence and nutritional status after acute stroke. *Stroke, 25*(2), 366-371.
Unosson, M., Ek, A. C., Bjurulf, P., von, S. H., & Larsson, J. (1994). Feeding dependence and nutritional status after acute stroke. *Stroke, 25*(2), 366-371.
U.S. Department of Health and Human Services and U.S. Department of Agriculture. *2015 – 2020 Dietary Guidelines for Americans*. 8th Edition. December 2015.
Wang, J., Luo, B., Xie, Y., Hu, H. Y., Feng, L., & Li, Z. N. (2014). Evaluation methods on the nutritional status of stroke patients. *Eur Rev Med Pharmacol Sci, 18*(24), 3902-3907.
Wanklyn, P., Cox, N., & Belfield, P. (1995). Outcome in patients who require a gastrostomy after stroke. *Age Ageing, 24*(6), 510-514.
Weimar, C., Konig, I. R., Kraywinkel, K., Ziegler, A., & Diener, H. C. (2004). Age and National Institutes of Health Stroke Scale Score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: development and external validation of prognostic models. *Stroke*, *35*(1), 158-162.
Westergren, A., Karlsson, S., Andersson, P., Ohlsson, O., & Hallberg, I. R. (2001). Eating difficulties, need for assisted eating, nutritional status and pressure ulcers in patients admitted for stroke rehabilitation. *J.Clin Nurs., 10*(2), 257-269.
Westergren, A., Ohlsson, O., & Rahm, H., I. (2001). Eating difficulties, complications and nursing interventions during a period of three months after a stroke. *J.Adv.Nurs., 35*(3), 416-426. doi:jan1884 [pii]

Wilson, J. L., Hareendran, A., Grant, M., Baird, T., Schulz, U. G., Muir, K. W., & Bone, I. (2002). Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. *Stroke*, *33*(9), 2243-2246.

Witham, M. D., Dove, F. J., Sugden, J. A., Doney, A. S., & Struthers, A. D. (2012). The effect of vitamin D replacement on markers of vascular health in stroke patients - a randomised controlled trial. *Nutr Metab Cardiovasc Dis, 22*(10), 864-870. doi:10.1016/j.numecd.2010.11.001

Yaghi, S., & Elkind, M. S. (2016). Lipid Control and Beyond: Current and Future Indications for Statin Therapy in Stroke. *Curr Treat Options Cardiovasc Med, 18*(4), 27. doi:10.1007/s11936-016-0448-8

Yoo, S. H., Kim, J. S., Kwon, S. U., Yun, S. C., Koh, J. Y., & Kang, D. W. (2008). Undernutrition as a predictor of poor clinical outcomes in acute ischemic stroke patients. *Arch.Neurol., 65*(1), 39-43. doi:65/1/39 [pii];10.1001/archneurol.2007.12 [doi]

Young, B., Ott, L., Norton, J., Tibbs, P., Rapp, R., McClain, C., & Dempsey, R. (1985). Metabolic and nutritional sequelae in the non-steroid treated head injury patient. *Neurosurgery, 17*(5), 784-791.