BDA The Association of UK Dietitians

THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION

Editor: **Simon Langley-Evans**

Journal of Human Nutrition and Dietetics

VOLUME 30 • ISSUE 1 • FEBRUARY 2017

- OLDER PEOPLE
- CHILDREN
- CLINICAL NUTRITION
- DIETARY GUIDELINES

WILEY

Journal of Human Nutrition and Dietetics

The Official Journal of the British Dietetic Association

Aims and editorial policy

Journal of Human Nutrition and Dietetics is an international peer reviewed journal publishing papers in applied nutrition and dietetics. Papers are therefore welcomed on:

- Clinical nutrition and the practice of therapeutic dietetics
- Public health nutrition and nutritional epidemiology
- Health promotion and intervention studies and their effectiveness
- Food choice and the psychology of eating behaviour
- Food intake and nutritional status
- Sociology of food intake

Further information on this journal can be accessed at wileyonlinelibrary.com/journal/jhn

The *Journal of Human Nutrition and Dietetics* is published by Blackwell Publishing Ltd: 9600 Garsington Road, Oxford OX4 2DQ, UK. Tel: +44 1865 776868; Fax: +44 (0)1865 714591. Blackwell Publishing was acquired by John Wiley & Sons in February 2007. Blackwell's programme has been merged with Wiley's global Scientific, Technical and Medical business to form Wiley Blackwell.

Production Editor: Patricia Joyce Tulayan (email: jhn@wiley.com)

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

OLDER PEOPLE

Vitamin D supplementation and its influence on muscle strength and mobility in community-dwelling older persons: a systematic review and meta-analysis

H. Rosendahl-Riise,[1] U. Spielau,[2,3] A. H. Ranhoff,[1,4] O. A. Gudbrandsen[3] & J. Dierkes[3]

[1]Department of Clinical Science, University of Bergen, Bergen, Norway
[2]Institute of Agricultural and Nutritional Sciences, Martin-Luther University Halle-Wittenberg, Halle, Germany
[3]Department of Clinical Medicine, University of Bergen, Bergen, Norway
[4]Kavli Research Center for Geriatrics and Dementia, Haraldsplass Deacon Hospital, Bergen, Norway

Keywords
ageing, gait, hand strength, muscle strength, vitamin D.

Correspondence
H. Rosendahl-Riise, Department of Clinical Science, University of Bergen, PO Box 7804, N-5020 Bergen, Norway.
Tel.: +4790158487
E-mail: hanne.gjessing@uib.no

How to cite this article
Rosendahl-Riise H., Spielau U., Ranhoff A.H., Gudbrandsen O.A., Dierkes J. (2017) Vitamin D supplementation and its influence on muscle strength and mobility in community-dwelling older persons: a systematic review and meta-analysis. *J Hum Nutr Diet*. **30**, 3–15 10.1111/jhn.12394

Abstract

Background: It has been suggested that vitamin D status or supplementation is important for maintaining or improving muscle strength and mobility in older adults. The study results, however, do not provide consistent results. We therefore aimed to summarise the available evidence systematically, including only studies conducted in community-dwelling older persons.

Methods: A systematic search of the literature was performed in April of 2016. The systematic review includes studies that used vitamin D with or without calcium supplementation as the exposure variable and various measurements of muscle strength and mobility. The meta-analysis was limited to studies using hand grip strength (HGS) and timed-up-and-go test as the outcome variables.

Results: A total of 15 studies out of 2408 articles from the literature search were included in the systematic review, providing 2866 participants above the age of 65 years. In the majority of studies, no improvement in muscle strength and mobility was observed after administration of vitamin D with or without calcium supplements. In the meta-analysis, we observed a non-significant change in HGS [+0.2 kg (95% confidence interval = −0.25 to 0.7 kg; seven studies)] and a small, significant increase in the timed-up-and-go test [0.3 s (95% confidence interval = 0.1 to 0.5 s; five studies)] after vitamin D supplementation. The meta-analyses showed a high degree of heterogeneity between the studies.

Conclusions: In conclusion, we observed no improvement in muscle strength after the administration of vitamin D with or without calcium supplements. We did find a small but significant improvement of mobility. However, this is based on a limited number of studies and participants.

Introduction

Among other changes in body composition and functions, ageing involves a decrease in skeletal muscle mass and strength, and consequently also in mobility [(1)]. This loss of muscle mass and strength is called sarcopenia and is associated with falls, fractures, immobilisation and mortality. Sarcopenia has an estimated prevalence of 5–13% in 60–70 year olds and 11–50% in persons older than 80 years [(2)]. These numbers demonstrate that declining muscle mass and strength are significant and age-dependent problems in older persons. Early and continuous interventions may be key to limiting this decline

[Correction added on 04 October 2018 after first online publication: Some wordings on pages 3, 10, 11 and 12 have been amended for clarity. Please refer to the Corrigendum of this article, JHN 12605, for more details.]

and preserving both muscle mass and strength. A number of dietary measures (supplementation with protein, energy, or *n*-3 polyunsaturated fatty acids, micronutrient supplementations) [3–8] and exercise interventions [9,10] or their combinations have been tested [11–14]. Among these interventions, supplementation with vitamin D has been promoted as having positive effects in older persons with respect to the risk of falls and fractures [15,16]. Usually, meta-analyses investigating the effect of vitamin D on the risk of falling include studies using vitamin D either with or without calcium supplements. Therefore, it is impossible to conclude whether vitamin D supplementation would be effective on its own or not. This can be regarded as a serious limitation of previous randomised controlled trials (RCTs) and meta-analyses and can also lead to inconsistent conclusions [17]. In a newer meta-analysis investigating primarily the effect of vitamin D on hip fractures in older adults [18], however, it was concluded that vitamin D with calcium was effective in preventing fractures, although the effect of vitamin D without calcium was not significant. An increased risk of falls can be seen as a consequence of low muscle strength and mass [19]. It has been estimated that the risk of falls increases with age and the presence of frailty and falls are a common cause of fractures in old adults [20]. The incidence of falls is difficult to measure, and falls may also have many other causes. Direct measurements of muscle strength and mobility are therefore required to study the effect of vitamin D.

Vitamin D deficiency is widespread in adult and older populations [21], even in populations without other overt nutrient deficiencies [22]. Vitamin D supplementation is usually combined with calcium supplementation, aiming to ensure sufficient calcium from the diet during vitamin D supplementation [23,24]. Vitamin D may exert its influence on skeletal muscle cells by the presence of the vitamin D receptor, and may also be needed for optimal muscle function [21] and adequate protein synthesis. In observational studies, an adequate 25(OH)D concentration was associated with better musculoskeletal function and muscle strength [25,26]. However, the optimal level of 25(OH)D in older persons is still unknown, although it is suggested to be ≥65 nmol L^{-1} [27].

Older people represent a very heterogeneous group. In general, community-dwelling older persons are younger and in better health and a better functional state compared to institutionalised individuals, although a high prevalence of comorbidities of chronic diseases may be present. In particular, institutionalised older persons show higher degrees of frailty, are more dependent in activities of daily living, and have a higher prevalence of cognitive decline. It is therefore justified to distinguish between these two groups when analysing dietary measures aimed at reducing the decline in muscle strength and mobility, although a number of studies did not make this distinction [28–33]. However, vitamin D supplementation for the prevention of loss of muscle strength and mobility has not been established in either group. In addition, studies vary in their design, the type and length of the intervention, and the outcomes because different measurements of muscle strength and mobility have been used, and there is no common protocol for these assessments.

The objective of this systematic review and meta-analysis was to investigate the effects of vitamin D supplementation (with or without calcium) in community-dwelling older subjects on muscle strength and mobility, based on the results from RCTs.

Materials and methods

Data sources and search strategy

Relevant studies were identified by a systematic search of current literature using PubMed, Embase, Medline, Web of Science and the Cochrane Library, followed by a manual search of the extracted articles and existing reviews. The clinical trial registry 'ClinicalTrials.gov' was searched for unpublished trials. The search covered the period up to 13 April 2016. The search terms are presented in the Supporting information (Appendix S1).

The inclusion criteria are stated in Table 1. Differences in dosage, frequency, mode of delivery or the form of the vitamin D supplementation were not a cause for exclusion. It became apparent that only the outcomes comprising hand grip strength (HGS) and timed-up-and-go (TUG) were investigated in a sufficient number of studies to perform a quantitative meta-analysis, whereas other outcomes of muscle strength and mobility were only included in the systematic review. Two of the authors (HRR, JD) screened the article titles and abstracts to identify studies that were suitable for inclusion. Ninety-four articles were read as full

Table 1 Overview of the inclusion criteria for the present systematic review and meta-analysis

Design	Randomised controlled trials
Participants	Older persons >65 years of age Humans Community-dwelling
Intervention	Vitamin D supplementation – all forms and all doses, with or without calcium supplements or dietary advice
Comparator	Low dose of vitamin D or vitamin D metabolites or placebo, with or without calcium supplement
Outcome measures	
Systematic review	Measures of muscle strength and mobility
Meta-analysis	Hand grip strength (HGS) Timed-up-and-go test (TUG)

papers, and 15 studies were selected for systematic review (Fig. 1). These 15 studies also included one identified by searching clincialtrials.gov [34]. The 15 articles were evaluated by all authors. Three other studies identified from clinicaltrials.gov were either still ongoing or a study protocol, and were therefore not included.

The various outcomes used in these studies are described in the Supporting information (Appendix S2). The overall quality of the full articles was assessed using the CONSORT statement checklist for assessing quality of randomised clinical trials [35]. The CONSORT statements are summarised in the Supporting information (Appendix S3).

Data collection

All relevant information was extracted from eligible studies and is available in Table 2. Any other information necessary for the review, such as potential covariates to the RCT (e.g. the season in which the RCT took place and any ultraviolet-B exposure), the dropout rate and compliance, was also noted when reported.

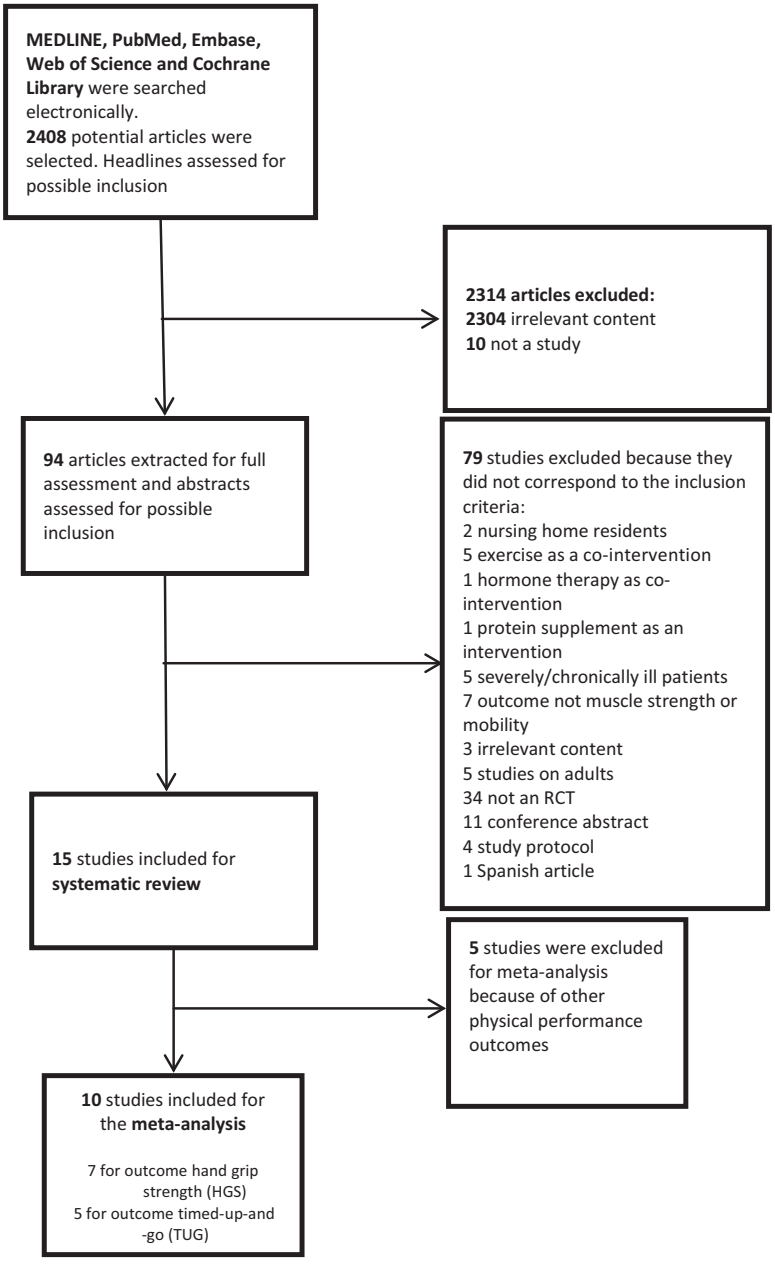

Figure 1 Flow chart of the selection of studies on the effect of vitamin D supplementation with or without calcium supplements on muscle strength and mobility in the present systematic review and meta-analysis. RCT, randomised controlled trial.

Table 2 An overview of the studies included in the systematic review and meta-analysis

Study	Sample size (sex), *n*	Age (years)	Serum 25(OH)D status at baseline (nmol L^{-1}) [mean (SD)]	Method used for analysing 25(OH)D	Study duration	Study design	Comparator	Form and dosage of vitamin D	Calcium supplement (mg)	Physical performance measure
Bischoff-Ferrari (2012) [42]	20 (females)	C: 63.45 (7.78) I: 59.48 (6.27)	C: 35.45 (9.03)‡ I: 30.7 (10.2)‡	HPLC-MS/MS	4 months	Randomised, double-blinded trial	C: 800 IU D_3 day^{-1} C: 5600 IU D_3 $week^{-1}$	I: 20 μg HyD day^{-1} I: 140 μg HyD $week^{-1}$	Non	TUG (3 m) Knee extension Knee flexion strength Repeated sit-to-stand
Ceglia (2013) [34]	21 (females)	C: 80 (5) I: 76 (4)	C: 48.3 (8.8) I: 43.6 (10.3)	RIA (DiaSorin Inc., Stillwater, MN, USA)	4 months	Randomised, double-blind, placebo-controlled Single centre	Placebo	4000 IU (D_3) day^{-1}, oral	Non (dietary intake was assessed)	Knee extension SPPB (incl. 4 m TUG)
Dhesi (2004) [48]	139	C: 76.6 (6.1) I: 77.0 (6.3)	C: 25.0† (23.8–26.3) I: 26.8†(25.5–28.0)	IDS Gamma-B 25-OH immunoassay (IDS, Tyne & Wear, UK)	6 months	Randomised, double-blind, placebo-controlled	Placebo	600 000 IU (D_2) × 1 bolus inj.	Non	Quadriceps strength AFPT
Glendenning 2012 [49]*	686 (females)	C: 76.5 (4) I: 76.9 (4)	C: 66.5 (27.1) I: 65.0 (17.8)	Liaison method (DiaSorin Inc.)	3, 6 and 9 months	Randomised, double-blind, placebo-controlled	Placebo	150 000 IU (D_3) every 3 months, oral	Advice: 1300 (supp./diet)	Grip strength (kg) TUG (3 m)
Grady (1991) [51]*	98	C: 78.9 (5.4) I: 79.4 (5.4)	C: 65.7 (51.4) I: 60.4 (35.3)	Microassay by Reinhart *et al.*, 1984	1, 2, 4, 8, 12, 18 and 24 weeks	Randomised, double-blind, placebo-controlled	Placebo	0.5 μg (1,25-dihydroxyvitamin D_3) day^{-1}, oral	Non (dietary intake was assessed)	Grip strength (kg) Leg muscle strength
Janssen (2010) [53]*	70 (females)	C: 79.2 (6.7) I: 82.4 (4.9)	C: 34.3 (11.5) I: 32.6 (11.6)	NA	6 months	Randomised, double-blind, placebo-controlled	Placebo	400 IU (D_3) day^{-1}, oral	500	Knee extension Hand grip strength (kg) LEP TUG (4 m) Modified Cooper test
Kenny (2003) [52]*	65 (men)	76 (4)	C: 60 (18)‡ I: 65 (18)‡	Competitive protein binding (Endocrine Science Inc., Calabasas Hills, CA, USA)	6 months	Randomised, double-blind, placebo-controlled	Placebo	1000 IU (D_3) day^{-1}, oral	500	Leg extension strength Grip strength (kg) SPPB (incl. 3 m TUG)
Lagari (2013) [44]*	86	73.4 (6.4)	82.5 (25.0)‡	LC/MS/MS	6 months	Randomised, double-blinded trial	400 IU D_3 day^{-1}, oral	2000 IU (D_3) day^{-1}, oral	Calcium supplements was assessed	Grip strength (kg) Gait speed

Table 2. Continued

Study	Sample size (sex), *n*	Age (years)	Serum 25(OH)D status at baseline (nmol L^{-1}) [mean (SD)]	Method used for analysing 25(OH)D	Study duration	Study design	Comparator	Form and dosage of vitamin D	Calcium supplement (mg)	Physical performance measure
Lips (2010) [43]	593	C: 77.6 (6.6) I: 78.5 (6.2)	C: 35.3 (13.8)‡ I: 34.3 (11.0)‡	Reversed phase HPLC by Lensmeyer *et al.*, 2006	16 weeks	Randomised, double-blind, placebo-controlled Multicentre	Placebo	8400 IU (D_3) $week^{-1}$, oral	500 for those with dietary intake <1000 mg	SPPB
Pfeifer (2009) [45]*	242	77 (4)	C: 54 (18) I: 55 (18)	RIA (Immunodiagnostic Systems, Boldon, UK)	12 and 20 months	Randomised, double-blind, placebo-controlled Multicentre	Placebo	800 IU (D_3) day^{-1}, oral	1000	Quadriceps strength (isometric leg extensor strength) TUG (3 m)
Pirotta (2015) [50]*	26	C: 71.5 (5.7) I: 66.1 (4.0)	C: 48.5 (11.1) I: 46.4 (11.4)	Liaison method (DiaSorin)	10 weeks	Randomised, double-blind, placebo-controlled	Placebo	2000 IU (D_3) day^{-1}, oral	Non	Knee extensor Stair climbing power FSST TUG (3 m)
Songpatanasilp (2009) [46]	72 (females)	70.60 (4.30)	69.98 (19.18)‡	RIA (DiaSorin)	12 weeks	Randomised placebo-controlled trial	Placebo	0.5 mg (20 000 IU) (alfacalcidiol) day^{-1}, oral	1500	Quadriceps strength (isokinetic dynamometer)
Wood (2014) [38]*	305 (females)	63.8 (2.2)	Normal: 34. 3 (14.7) Overweight: 33.9 (14.3) Obese: 32.4 (16.3)	LC/MS/MS (Chromsystems, UK)	12 months (bimonthly study visits)	Randomised, double-blind, placebo-controlled	Placebo	I: 400 IU (D_3) day^{-1}, oral I: 1000 IU (D_3) day^{-1}, oral	Non	Grip strength (kg)
Xia (2009) [55]*	142 (females)	C: 70.4 (3.6) I: 70.4 (3.9)	NA	NA	6 and 12 months	Randomised, multicentre, open-label, placebo-controlled	125 IU (Calcitriol) day^{-1}, oral	125 IU + 0.25 μg (Calcitriol) day^{-1}, oral	600/600	Grip strength (kg) FTFFT
Zhu (2010) [47]*	302 (females)	C: 77.0 (4.8) I: 77.6 (4.2)	C: 44.3 (13.0)‡ I: 45.3 (12.5)‡	RIA (DiaSorin)	6 and 12 months	Randomised, double-blind, placebo-controlled	Placebo	1000 IU (D_2) day^{-1}, oral	1000	TUG (3 m) Lower limb muscle strength (ankle, knee, hip)

*Included in the meta-analysis.

†Geometric mean and 95% confidence interval.

‡Calculated to nmol L^{-1}using coefficient of 2.5.

AFPT, aggregate functional performance time; C, control; FSST, the four square step test; FTFFT, Five-times-sit-to-stand-test; HPLC, high-performance liquid chromatography; HyD, 25-hydroxyvitamin D3; I, intervention; LC/MS/MS, liquid chromatography, tandem mass spectrometry; LEP, Leg extension power; NA, not available; RIA, radioimmunoassay; SPPB, Short Physical Performance Battery; TUG, timed-up-and-go.

Statistical analysis

Other outcomes than TUG and HGS were reviewed narratively as a result of the low number of studies evaluating these outcomes. Only for TUG and HGS did we find more than three studies for a quantitative meta-analysis. We used RevMan, version 5.3 (Cochrane collaboration) [36] for the analysis, with the outcome being represented by Forrest plots (Figs 2 and 3). Weighted mean differences for vitamin D versus placebo/control were calculated by subtracting the mean of the outcome of interest at the end of the study from the mean at baseline. Standard deviations (SDs) of the differences were calculated using a formula given in the *Cochrane Handbook* [37], applying correlation coefficients of 1.0 for the HGS and 0.8 for the TUG-test. Because significant heterogeneity was observed between studies with a fixed effect model, we finally applied a random effects model. Studies that included more than one intervention group [38] were treated by dividing the number of subjects in the control group by the number of comparisons at the same time as retaining the mean (SD) of the change according to the *Cochrane Handbook* [37].

Subgroup analysis was conducted with predefined study characteristics: baseline vitamin D status, oral administration of the supplement, daily dose of vitamin D, placebo group, supplementation with vitamin D_2 or D_3, and advice on calcium supplementation to explore possible reasons for the observed heterogeneity [39,40].

Results

Search results

As per the Quality of Reporting of Meta-analyses (QUOROM) [41] flow diagram (Fig. 1), 15 out of 2408 studies were included in the systematic review and 10 of the 15 were eligible for the meta-analysis.

Narrative review

Study characteristics

We included a total of 15 studies, with a total of 2866 participants aged 65 years and older. Two studies were included with an average age of the participants of 63.8 years (range 60–70 years) [38] and 61.5 years (range 50–70 years) [42], whereas the average age in the other studies included was between 70 and 80 years. The ratio of men to women was approximately 1 : 9 (229/2044), not including one study that did not specify the participants' sex (n = 593) [43]. The studies were conducted in

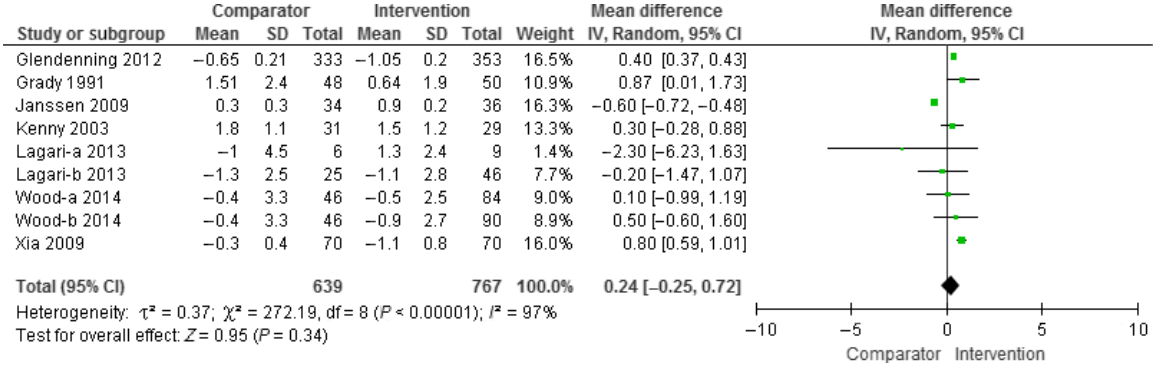

Figure 2 Results of the meta-analysis of the effect of vitamin D supplementation with or without calcium on hand grip strength (kg) (n = 7 studies). The results were obtained using a random effects model. One study reported results for men and women separately (Lagari a – men and Lagari b – women). For one study, we have divided the comparator group in two (Wood-a and Wood-b). CI, confidence interval.

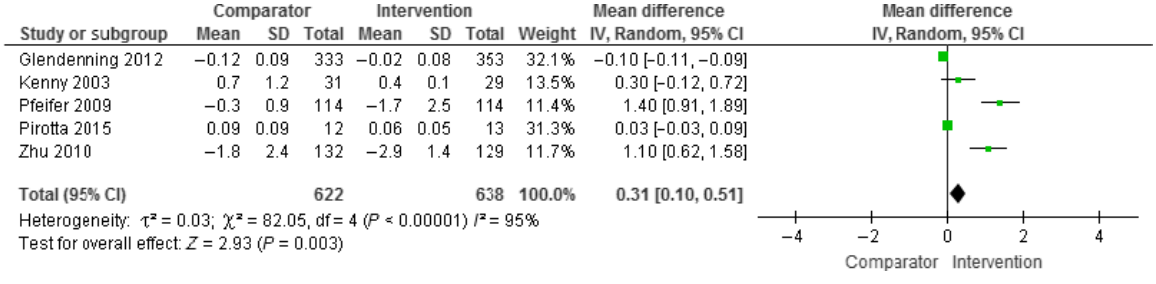

Figure 3 Results of the meta-analysis of the effect of vitamin D supplementation with or without calcium on timed-up-and-go (TUG) (n = 5 studies). The results were obtained using a random effects model. CI, confidence interval.

Australia, China, Thailand, USA, Canada and Europe (Germany, Austria, Netherlands, Switzerland, Scotland and the UK). One study was a multicentre study, with centres in North America, Mexico and Europe [43]. The participants were all community-dwelling older persons, who were generally in age-related good health, and a history of chronic conditions such as cardiovascular disease was usually not treated as an exclusion criterion. All studies excluded patients with acute diseases. In general, underlying diseases serving as exclusion criteria were not sufficiently described.

The vitamin D status was measured as the 25(OH)D concentration in 13 of the 15 studies, with chromatographic methods being used in four of them [38,42–44]. Other studies used radioimmunoassay (DiaSorin Inc., Stillwater, MN, USA) [34,45–47], IDS Gamma-B 25-OH immunoassay (IDS, Tyne & Wear, UK) [48], Liaison method (DiaSorin Inc.) [49,50] microassay as described per Reinhardt *et al.*, 1984 [51], competitive protein binding (Endocrine Science Inc., Calabasa Hills, CA, USA) [52]. One study did not report what method had been used [53].The mean baseline serum 25(OH)D concentration ranged between 25 and 82 nmol L^{-1} [54]. The average concentration exceeded the cut-off level of 50 nmol L^{-1} for defining a sufficient status, in six of the 15 studies [44–46,49,51,52] and, on average, was below that value in eight of them [34,38,42,43,47,48,50,53] and was not reported in one study [55].

All of the studies selected declared that they had a randomised parallel design. Three did not have a placebo group but used a low dose of vitamin D_3 (400 IU day^{-1}) as a control [44,55] or the recommended dose for elderly (800 IU day^{-1}) [42]. One study did not state whether it had been blinded or not [45]. One was a randomised, multicentre, open-label, placebo-controlled study [55]. The randomisation process was usually not sufficiently well described.

Seven of the 15 studies included calcium with vitamin D supplement or placebo [43,45–47,52,53,55]. Three studies assessed the intake of supplements or dietary calcium intake [34,44,51]. One study specified calcium supplementation or dietary intake of calcium of 1300 mg [47]. Two studies assessed the overall nutrient intake [38,50]. One study excluded participants using high-dose (>600 mg) calcium supplements [42]. One study did not consider calcium intake at all [48].

Both season and latitude can be important covariates as a result of internal vitamin D production by ultraviolet-B radiation [21]. The season of blood withdrawal was not stated in six of the 15 studies [34,42,50,53,55] and the geographic latitude was stated in three [38,45,47]. Other covariates of vitamin D status (body mass index, ethnicity, smoking) were usually not considered specifically. The exception was one study that specifically investigated the effect modification of different body mass index groups (normal, overweight and obese) in participants with Caucasian ethnicity [38].

The dropout rate was given in 13 of the studies, and ranged from 0% to 22%. In one of these studies, the dropout rate was given in another publication [56]. In one study, the authors noted that the dropout rate was low, without further details [34]; in one study, the dropout rate was not reported at all [44].

Compliance was not mentioned in four of the 15 studies [43,46,52,55]. In eight of the studies, the compliance was reported to be better than 80% [38,42,44,47,49–51,53]. One study used bolus injections, so that 100% compliance may safely be assumed [48]. In one study, the compliance rate was 100% for the participants completing the study [49]. In one study, the authors stated that a daily compliance calendar had been kept but did not report on compliance [34].

Different metabolites of vitamin D were used, including vitamin D_2 [47,48], vitamin D_3 [34,38,43–45,49,50,52,53] 1,25-dihydroxyvitamin D_3 [51,55], alfacalcidiol [46] or 25(OH) D_3 [42] with various doses, administration routes and treatment periods, ranging from bolus injection of 600 000 IU of vitamin D_2 [48]; 1000 IU daily oral dose of vitamin D_2 [47]; oral vitamin D_3 in doses of 150 000 IU every 3 months [49]; weekly oral dose of 8400 IU vitamin D_3 [43]; and daily oral supplement in doses ranging from 400 to 4000 IU vitamin D_3 [34,38,44,45,50,52,53]. The studies that used 1,25-dihydroxyvitamin D used a daily oral dose of 1,25-dihydroxyvitamin D (0.5 μg) compared to placebo [51] or 125 IU (vitamin D_3) compared to 0.25 μg calcitriol 125 IU^{-1} [55]. One study included four groups comparing different doses of vitamin D3 (800 IU day^{-1} and 5600 IU $week^{-1}$) with 25(OH)D_3 (20 μg day^{-1} and 140 μg $week^{-1}$) [42].

An overview of the methodological quality of the studies is presented in the Supporting information (Appendix S3).

Study outcomes

Measurements of physical performance outcomes are not standardised, and various methods had been used in the clinical studies (see the Supporting information, Appendix S2). Four studies used complex outcome measurements such as the Short Physical Performance Battery (including TUG) [34,43,52] and the aggregate functional performance time [48].

Studies that used single outcome measurements included the knee extension test [34,42,50,53]. Three studies used quadriceps strength (using various protocols thus precluding a formal meta-analysis) [45,46,48],

HGS [38,44,49,51–53,55] and the 3-m TUG [42,45,47,49,50,52]. Other available physical outcome measures were the 4-m TUG, leg muscle strength, leg extension strength, gait speed, Five-Times-Sit-to-Stand-Test, leg extension power, modified Cooper test, stair climbing power, the four square step test, repeated sit-to-stand, knee flexion strength and lower limb muscle strength.

The authors of nine studies concluded that supplementation with vitamin D and/or calcium did not have any beneficial effect on mobility and/or muscle strength [34,38,43,44,48,49,51–53]. In six studies, they found an improvement in mobility and/or muscle strength [42,45–47,50,55]. One of the four studies that used a complex outcome measurement reported a beneficial effect for the mobility outcome [48]. Three of the studies reporting an improvement in either measure only observed this in the subjects who had been weakest and slowest at baseline [47] or in those with pre-existing low levels of 25(OH)D3 [42,46]. In the case of one study [47], no subgroup analysis had been prespecified in the record of the trial registry (clinicaltrials.gov).

The meta-analysis

We performed meta-analyses for the outcomes HGS (kg) and TUG (s).

Hand grip strength

The meta-analysis included seven studies [38,44,49,51–53,55], with 767 participants treated with vitamin D and 639 participants treated with control (low-dose vitamin D or placebo). HGS was measured using various devices and protocols, giving an average HGS at baseline of between 3 and 23 kg. Applying a random effects model, we observed a nonsignificant improvement in HGS after vitamin D supplementation, amounting to 0.2 kg [95% confidence interval (CI) −0.3 to 0.7 kg]. The meta-analysis revealed significant heterogeneity between the studies (I^2 = 97%), which was completely eliminated by omitting the three studies that included subjects with vitamin D deficiency [38,53,55]. After exclusion of these three studies, the effect on the HGS became significant (0.40, 95% CI = 0.37 to 0.43kg). Other sensitivity analyses (Table 1; see also Supporting information, Appendix S4: exclusion of studies using vitamin D_2, using bolus doses of vitamin D or inclusion of calcium supplements) did not diminish the heterogeneity between the studies and did not change the overall result of a marginal effect of vitamin D supplementation on HGS (Fig. 2).

Timed-up-and-go

The meta-analysis included five studies [45,47,49,50,52] with 638 participants treated with vitamin D and 622 participants treated with a control or placebo. The studies reported average TUG results ranging from 5 to 11 s. Applying a random effects model, we observed a significant mean decrease of 0.3 s in TUG (95% CI = 0.1 to 0.5 s) after vitamin D supplementation. Thus, the decrease would mean an improvement of the TUG result after vitamin D supplementation. The meta-analysis revealed significant heterogeneity between the studies (I^2 = 95%) (Fig. 3). A sensitivity analysis excluding Zhu *et al.* [47] (who used vitamin D_2 as a supplement and included participants with an average 25(OH)D concentration lower than 50 nmol L^{-1}) lead to an insignificant overall estimate of 0.2 s (95% Cl = −0.03 to 0.4s) but did not affect the heterogeneity (sensitivity analysis presented in Table 2; see also Supporting information, Appendix S4).

Discussion

The objective of this systematic review and meta-analysis was to investigate whether vitamin D supplementation (with or without calcium) in community-dwelling older persons can improve muscle strength and mobility. For the present review, 15 RCTs were included for revision, whereas 10 were suitable for the meta-analysis. Based on findings in nine of the studies, it was concluded that supplementation with vitamin D and/or calcium did not have any beneficial effect on mobility or muscle strength, or on both [34,38,43,44,48,49,51–53]. The main finding of the quantitative meta-analysis indicated that supplementation with vitamin D did not improve HGS (based on seven studies) to any significant extent but provided a small improvement to the TUG-test (based on five studies). Therefore, vitamin D supplementation appears to be of limited value for the preservation of muscle strength and mobility in an older population.

Study population

The older population is heterogeneous in age and the related frailty, as well as with respect to the prevalence of chronic diseases and their treatment, and dependence in the activities of daily life. It can therefore be expected that studies in older persons in general will yield mixed results unless the population is defined more accurately according to the factors mentioned. We therefore limited the present meta-analysis to community-dwelling older persons in apparently age-related good health, although, in many cases, the health status had not been sufficiently well described.

Community-dwelling older persons are usually in much better health than those hospitalised or living in nursing homes. Targeting these subjects with an intervention

aimed at preserving muscle strength and mobility thus appears sensible. However, in concordance with our findings, studies on vitamin D supplementation in hospitalised older subjects [57,58] or residents in nursing homes [3,7] showed mixed results for the effects of vitamin D supplementation on muscle strength and mobility. Thus, convincing evidence that vitamin D supplementation may be a useful measure is lacking [14,28,59].

Most studies recruited only or predominantly women. Although, at present, there is little evidence that the dietary requirements for vitamin D are different in older men and older women [60], or that the effects of vitamin D on muscle strength are different in older men and women, there is clearly a lack of data on the effect of vitamin D supplementation in men.

Intervention

Vitamin D exists in two different forms (D_3 and D_2). In addition, the inactive form [25(OH)D] and the active form of the hormone [1,25(OH)2D], different routes of administration (oral or intravenous, daily/weekly or bolus supplementation), as well as various doses and various durations of supplementation, can be used. These aspects further complicate comparison of the studies and can introduce heterogeneity between the studies. High-dose bolus supplementation (either oral or intravenous) has the advantage of high compliance, especially in older subjects who already take a number of medicines on a daily basis. Doses of 300 000 IU are an established treatment for vitamin D deficiency and are regarded as safe. However, doses over 500 000 IU should be avoided because adverse effects of such high doses such as increased falls and fracture risk have been reported [61,62].

The studies using a low dose were included in the meta-analysis as a result of studies by Lagari *et al.* [63] and Chao *et al.* [64] stating that 400 IU was inadequate to increase the 25(OH)D concentrations to an acceptable level regardless of baseline 25(OH)D levels in older persons. Because of the high dose of vitamin D_3 used as a control group in the study by Bischoff-Ferrari *et al.* [42], we choose not include the study in our meta-analysis.

Outcomes

The functional improvement in the older persons has been measured using a range of measurements employing different protocols. Among these, the HGS has been shown to be a reliable parameter [65,66] for long-term health outcomes. There is, however, less evidence for the TUG test for long-term health outcomes.

We included only quantifiable outcomes in the present study but not falls or fractures that have been used as measure of reduced muscle strength and as clinical outcomes in other studies [15,67]. However, determining falls may be difficult in community-dwelling older persons because it relies heavily on the subjects' recall and may thus reduce the reliability of this outcome.

We observed a small and nonsignificant improvement in HGS as a result of vitamin D supplementation in the meta-analysis, which was also characterised by a high degree of heterogeneity between studies. However, the magnitude of the effect may also indicate that other health measures, such as exercise and potentially supplementation with other nutrients, should be prioritised. In addition, the huge variation in baseline HGS measurements between studies further complicates the interpretation of the effects of high/increased vitamin D intake. The nonsignificant result may be regarded as contradicting observational studies in community-dwelling older persons because other studies have reported that a doubling of the 25(OH)D concentration from 50 to 100 nmol L^{-1} was associated with a higher HGS in men and in women, with increases of approximately 4.4 and 0.8 kg, respectively [68]. We observed a significant and stronger improvement of HGS and diminished heterogeneity after the exclusion of three studies with low 25(OH)D concentrations at baseline [38,53,55]. Low vitamin D status may reflect a higher degree of frailty [69], and supplementation may therefore be too late to improve muscle strength in those with very low 25(OH)D levels, despite the correction of vitamin D deficiency as indicated by the serum levels.

Although the effect of vitamin D supplementation on the TUG test suggested a positive direction by the reduced time used for the test, this result should be interpreted with caution because the meta-analysis showed a high degree of heterogeneity that was not removed by excluding single studies (Table 2; see also Supporting information, Appendix S4). In addition, the overall magnitude of the effect was very small, suggesting that this change is clinically less meaningful. Overall, the small number of studies and the high degree of heterogeneity precludes any firm conclusions, although further investigations are certainly warranted. It would be interesting to determine whether interventions combined with exercise and/or other nutrients would improve the test outcome. This has already been shown by Bunout *et al.* [12], who used exercise and vitamin D supplements as interventions in vitamin D-deficient community-dwelling older persons and observed a positive effect on TUG.

The importance of calcium supplements should also be considered. Because of the concurrent administration of calcium in most and especially in the larger studies [43,45–47,49,52,53,55], it is impossible to determine any independent effect of either vitamin D or calcium. The use of

calcium supplements for purposes other than improvement of bone health has been strongly debated. It is also plausible to combine vitamin D supplements with calcium because vitamin D increases calcium absorption from the gut but, in the case of insufficient dietary calcium intake, this can also affect bone remodelling [70].

Comparison with previous systematic reviews and meta-analyses

The effect of vitamin D on physical performance has been summarised in systematic reviews [28,30,33] and in three meta-analyses [29,31,32]. These investigations are characterised by either including all age groups [30–32], by including older adults from different settings (community-dwelling and institutionalised, [14,28,29], different study designs [33] and investigating composite outcomes [32], thus making comparisons with our findings difficult. Stockton *et al.* [31] also reported a meta-analysis for HGS and, in line with our findings, reported no significant effect on HGS. The only other meta-analysis that reported TUG as an outcome reported a small, significant improvement of this test, based on three studies [29].

Thus, the overall results are difficult to compare, although they demonstrate the large number of tests used for the assessment of muscle strength, physical performance and mobility. A common test battery would make comparisons between studies much easier.

Strengths and limitations

The strengths of this review include the use of data from 15 RCTs, with approximately 2800 participants treated with vitamin D or a control, and the analysis of quantitative outcomes such as HGS and TUG, which have been shown to be related to other clinical outcomes in the older persons [71].

The main limitation of this review is the small number of studies available for the meta-analysis, mainly as a result of heterogeneity of the measurements used. Another limitation is the variation in study populations, with a wide range of comorbidities. More exact descriptions of the population under study are urgently needed to improve comparability of studies and to increase external validity. We also observed heterogeneity between studies that could not be resolved by subgroup analyses.

In conclusion, we observed no improvement in muscle strength after administration of vitamin D with or without calcium supplements. We did find a small but significant improvement of mobility. This is, however, based on a limited number of studies and participants.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with CONSORT[1]/STROBE[2]/PRISMA[3] guidelines.

Acknowledgments

The authors would like to thank the Norwegian Seafood Research Fund (FHF) for supporting this research through fellowship funding the primary author.

Conflict of interest, source of funding and authorship

The authors declare that they have no conflicts of interest.
Funding support was provided by the Norwegian Seafood and Research Fund (FHF). This is the correct funding. The sponsor had no role in the paper.
HRR and JD designed the study. HRR, US and JD performed the literature search and the meta-analysis. All authors read the included papers and were substantially involved in the writing process. All authors critically reviewed the manuscript and approved the final version submitted for publication.

References

1. Cruz-Jentoft AJ, Baeyens JP, Bauer JM *et al.* (2010) Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* **39**, 412–423.
2. Morley JE (2012) Sarcopenia in the elderly. *Fam Pract* **29** (Suppl 1), i44–i48.
3. Smedshaug GB, Pedersen JI & Meyer HE (2007) Can vitamin D supplementation improve grip strength in elderly nursing home residents? A double-blinded controlled trial. *Scand J Food Nutr* **51**, 74–78.
4. Bacon CJ, Gamble GD, Horne AM *et al.* (2009) High-dose oral vitamin D3 supplementation in the elderly. *Osteoporos Int* **20**, 1407–1415.
5. Gallagher JC (2004) The effects of calcitriol on falls and fractures and physical performance tests. *J Steroid Biochem Mol Biol* **89–90**, 497–501.
6. Malafarina V, Uriz-Otano F, Iniesta R *et al.* (2013) Effectiveness of nutritional supplementation on muscle

mass in treatment of sarcopenia in old age: a systematic review. *J Am Med Dir Assoc* **14**, 10–17.
7. Moreira-Pfrimer LD, Pedrosa MA, Teixeira L *et al.* (2009) Treatment of vitamin D deficiency increases lower limb muscle strength in institutionalized older people independently of regular physical activity: a randomized double-blind controlled trial. *Ann Nutr Metab* **54**, 291–300.
8. Aleman-Mateo H, Macias L, Esparza-Romero J *et al.* (2012) Physiological effects beyond the significant gain in muscle mass in sarcopenic elderly men: evidence from a randomized clinical trial using a protein-rich food. *Clin Interv Aging* **7**, 225–234.
9. Liu CK, Leng X, Hsu FC *et al.* (2014) The impact of sarcopenia on a physical activity intervention: the Lifestyle Interventions and Independence for Elders Pilot Study (LIFE-P). *J Nutr Health Aging* **18**, 59–64.
10. Scanlon TC, Fragala MS, Stout JR *et al.* (2014) Muscle architecture and strength: adaptations to short-term resistance training in older adults. *Muscle Nerve* **49**, 584–592.
11. Hara S, Kishimoto KN, Okuno H *et al.* (2013) Effects of alfacalcidol on back extensor strength gained through back extensor exercise in postmenopausal women with osteoporosis. *Am J Phys Med Rehabil* **92**, 101–110.
12. Bunout D, Barrera G, Leiva L *et al.* (2006) Effects of vitamin D supplementation and exercise training on physical performance in Chilean vitamin D deficient elderly subjects. *Exp Gerontol* **41**, 746–752.
13. Burd NA, Yang Y, Moore DR *et al.* (2012) Greater stimulation of myofibrillar protein synthesis with ingestion of whey protein isolate v. micellar casein at rest and after resistance exercise in elderly men. *Br J Nutr* **108**, 958–962.
14. Latham NK, Anderson CS, Lee A *et al.* (2003) A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). *J Am Geriatr Soc* **51**, 291–299.
15. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB *et al.* (2009) Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ* **339**, b3692.
16. Murad MH, Elamin KB, Abu Elnour NO *et al.* (2011) Clinical review: the effect of vitamin D on falls: a systematic review and meta-analysis. *J Clin Endocrinol Metab* **96**, 2997–3006.
17. Scragg R (2012) Do we need to take calcium with vitamin D supplements to prevent falls, fractures, and death? *Curr Opin Clin Nutr Metab Care* **15**, 614–624.
18. Avenell A, Mak Jenson CS & O'Connell D (2014) Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database Syst Rev* **4**, CD000227.
19. Kojima G (2015) Frailty as a predictor of future falls among community-dwelling older people: a systematic review and meta-analysis. *J Am Med Dir Assoc* **16**, 1027–1033.
20. Deandrea, S, Lucenteforte, E, Bravi, F *et al.* (2010) Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. *Epidemiology* **21**, 658–668.
21. Holick MF (2007) Vitamin D deficiency. *N Engl J Med* **357**, 266–281.
22. Brouwer-Brolsma EM, Bischoff-Ferrari HA, Bouillon R *et al.* (2013) Vitamin D: do we get enough? A discussion between vitamin D experts in order to make a step towards the harmonisation of dietary reference intakes for vitamin D across Europe. *Osteoporos Int* **24**, 1567–1577.
23. Tang BM, Eslick GD, Nowson C *et al.* (2007) Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* **370**, 657–666.
24. Avenell A, Mak JC & O'Connell D (2014) Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database Syst Rev* **4**, CD000227.
25. Bischoff-Ferrari HA, Borchers M, Gudat F *et al.* (2004) Vitamin D receptor expression in human muscle tissue decreases with age. *J Bone Miner Res* **19**, 265–269.
26. Visser M, Deeg DJ & Lips P (2003) Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. *J Clin Endocrinol Metab* **88**, 5766–5772.
27. Dawson-Hughes B (2008) Serum 25-hydroxyvitamin D and functional outcomes in the elderly. *Am J Clin Nutr* **88**, 537s–540s.
28. Annweiler C, Schott AM, Berrut G *et al.* (2009) Vitamin D-related changes in physical performance: a systematic review. *J Nutr Health Aging* **13**, 893–898.
29. Muir SW & Montero-Odasso M (2011) Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* **59**, 2291–2300.
30. Rejnmark L (2011) Effects of vitamin d on muscle function and performance: a review of evidence from randomized controlled trials. *Ther Adv Chronic Dis* **2**, 25–37.
31. Stockton KA, Mengersen K, Paratz JD *et al.* (2011) Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. *Osteoporos Int* **22**, 859–871.
32. Beaudart C, Buckinx F, Rabenda V *et al.* (2014) The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* **99**, 4336–4345.
33. Latham NKK (2003) Effects of vitamin D supplementation on strength, physical performance, and falls in older persons: a systematic review. *J Am Geriatr Soc* **51**, 1219–1226.

34. Ceglia L, Niramitmahapanya S, da Silva Morais M *et al.* (2013) A randomized study on the effect of vitamin D3 supplementation on skeletal muscle morphology and vitamin d receptor concentration in older women. *J Clin Endocrinol Metab* **98**, E1927–E1935.
35. Schulz KF, Altman DG & Moher D (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* **152**, 726–732.
36. The Cochrane Collaboration (2014) *Review Manager (RevMan)*, 5.3 edn. [TNC Center, editor]. Copenhagen: The Cochrane Collaboration.
37. Higgins JPT & Green S (2011) *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0. Available at: www.cochrane-handbook.org. The Cochrane Collaboration.
38. Wood AD, Secombes KR, Thies F *et al.* (2014) A parallel group double-blind RCT of vitamin D_3 assessing physical function: is the biochemical response to treatment affected by overweight and obesity? *Osteoporos Int* **25**, 305–315.
39. Song F, Sheldon TA, Sutton AJ *et al.* (2001) Methods for exploring heterogeneity in meta-analysis. *Eval Health Prof* **24**, 126–151.
40. Yusuf S, Wittes J, Probstfield J *et al.* (1991) Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* **266**, 93–98.
41. Moher D, Cook DJ, Eastwood S *et al.* (1999) Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of reporting of meta-analyses. *Lancet* **354**, 1896–1900.
42. Bischoff-Ferrari HA, Dawson-Hughes B, Stocklin E *et al.* (2012) Oral supplementation with 25(OH)D3 versus vitamin D3: effects on 25(OH)D levels, lower extremity function, blood pressure, and markers of innate immunity. *J Bone Miner Res* **27**, 160–169.
43. Lips P, Binkley N. Pfeifer M *et al.* (2010) Once-weekly dose of 8400 IU vitamin D(3) compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency. *Am J Clin Nutr* **91**, 985–991.
44. Lagari V, Gomez-Marin O & Levis S (2013) The role of vitamin D in improving physical performance in the elderly. *J Bone Miner Res* **28**, 2194–2201.
45. Pfeifer M, Begerow B, Minne HW *et al.* (2009) Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporos Int* **20**, 315–322.
46. Songpatanasilp T, Chailurkit LO, Nichachotsalid A *et al.* (2009) Combination of alfacalcidol with calcium can improve quadriceps muscle strength in elderly ambulatory Thai women who have hypovitaminosis D: a randomized controlled trial. *J Med Assoc Thai* **92**(Suppl 5), S30–S41.
47. Zhu K, Austin N, Devine A *et al.* (2010) A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency. *J Am Geriatr Soc* **58**, 2063–2068.
48. Dhesi JK, Jackson SH, Bearne LM *et al.* (2004) Vitamin D supplementation improves neuromuscular function in older people who fall. *Age Ageing* **33**, 589–595.
49. Glendenning P, Zhu K, Inderjeeth C *et al.* (2012) Effects of three-monthly oral 150,000 IU cholecalciferol supplementation on falls, mobility, and muscle strength in older postmenopausal women: a randomized controlled trial. *J Bone Miner Res* **27**, 170–176.
50. Pirotta S, Kidgell DJ & Daly RM (2015) Effects of vitamin D supplementation on neuroplasticity in older adults: a double-blinded, placebo-controlled randomised trial. *Osteoporos Int* **26**, 131–140.
51. Grady D, Halloran B, Cummings S *et al.* (1991) 1,25-Dihydroxyvitamin D3 and muscle strength in the elderly: a randomized controlled trial. *J Clin Endocrinol Metab* **73**, 1111–1117.
52. Kenny AM, Biskup B, Robbins B *et al.* (2003) Effects of vitamin D supplementation on strength, physical function, and health perception in older, community-dwelling men. *J Am Geriatr Soc* **51**, 1762–1767.
53. Janssen H, Samson MM & Verhaar HJJ (2010) Muscle strength and mobility in vitamin D-insufficient female geriatric patients: a randomized controlled trial on vitamin D and calcium supplementation. *Aging Clin Exp Res* **22**, 78–84.
54. Ross AC, Taylor CL & Yaktine AL (2011) *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press (US).
55. Xia WB, Zhang ZL, Wang HF *et al.* (2009) The efficacy and safety of calcitriol and/or Caltrate D in elderly Chinese women with low bone mass. *Acta Pharmacol Sin* **30**, 372–378.
56. Wood AD, Secombes KR, Thies F *et al.* (2012) Vitamin D3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT. *J Clin Endocrinol Metab* **97**, 3557–3568.
57. Boxer RS, Kenny AM, Schmotzer BJ *et al.* (2013) A randomized controlled trial of high dose vitamin d3 in patients with heart failure. *JACC Heart Fail* **1**, 84–90.
58. Sato Y, Iwamoto J, Kanoko T *et al.* (2005) Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. *Cerebrovasc Dis* **20**, 187–192.
59. Brunner RL, Cochrane B, Jackson RD *et al.* (2008) Calcium, vitamin D supplementation, and physical function in the Women's Health Initiative. *J Am Diet Assoc* **108**, 1472–1479.
60. Cashman KD, Wallace JM, Horigan G *et al.* (2009) Estimation of the dietary requirement for vitamin D in free-living adults >=64 y of age. *Am J Clin Nutr* **89**, 1366–1374.
61. Sanders KM, Stuart AL, Williamson EJ *et al.* (2010) Annual high-dose oral vitamin D and falls and fractures in

older women: a randomized controlled trial. *JAMA* **303**, 1815–1822.
62. Rossini M, Gatti D, Viapiana O *et al.* (2012) Short-term effects on bone turnover markers of a single high dose of oral vitamin D(3). *J Clin Endocrinol Metab* **97**, E622–E626.
63. Lagari VS, Gomez-Marin O & Levis S (2012) Differences in vitamin D3 dosing regimens in a geriatric community-dwelling population. *Endocr Pract* **18**, 847–854.
64. Chao YS, Brunel L, Faris P *et al.* (2013) The importance of dose, frequency and duration of vitamin D supplementation for plasma 25-hydroxyvitamin D. *Nutrients* **5**, 4067–4078.
65. Mijnarends DM, Meijers JM, Halfens RJ *et al.* (2013) Validity and reliability of tools to measure muscle mass, strength, and physical performance in community-dwelling older people: a systematic review. *J Am Med Dir Assoc* **14**, 170–178.
66. Stevens PJ, Syddall HE, Patel HP *et al.* (2012) Is grip strength a good marker of physical performance among community-dwelling older people? *J Nutr Health Aging* **16**, 769–774.
67. Kalyani RR, Stein B, Valiyil R *et al.* (2010) Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis. *J Am Geriatr Soc* **58**, 1299–1310.
68. Toffanello ED, Perissinotto E, Sergi G *et al.* (2012) Vitamin D and physical performance in elderly subjects: the Pro.V.A study. *PLoS ONE* **7**, e34950.
69. Schottker B, Saum KU, Perna L *et al.* (2014) Is vitamin D deficiency a cause of increased morbidity and mortality at older age or simply an indicator of poor health? *Eur J Epidemiol* **29**, 199–210.
70. Uusi-Rasi K, Karkkainen MU & Lamberg-Allardt CJ (2013) Calcium intake in health maintenance - a systematic review. *Food Nutr Res* **57**, doi: 10.3402/fnr.v57i0.21082. Print 2013.
71. Meyer HE, Tverdal A, Falch JA *et al.* (2000) Factors associated with mortality after hip fracture. *Osteoporos Int* **11**, 228–232.
72. Reinhardt T, Horst R, Orf J & Hollis B (1984) A microassay for 1,25-dihydroxyvitamin D not requiring high performance liquid chromatography: application to clinical studies. *J Clin Endocrinol Metab.* **55**, 91–8.
73. Lensmeyer GL, Wiebe DA, Binkely N & Drezner MK (2006) HPLC method for 25-hydroxyvitamin D measurment: comparison with contemporary assays. *Clin Chem* **52**, 1120–6.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. Search terms and search hits in Medline, Embase, Pubmed and Web of Science.

Appendix S2. An overview of the physical performance tests used in the randomised controlled trials included in the systematic review and meta-analysis.

Appendix S3. Summary of CONSORT statements for each study included in the systematic review.

Appendix S4. Sensitivity analysis for hand grip strength (HGS) and timed-up-and-go test (TUG).

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

OLDER PEOPLE

The nutrition and food-related roles, experiences and support needs of female family carers of malnourished older rehabilitation patients

S. Marshall,[1] D. P. Reidlinger,[1] A. Young[2] & E. Isenring[1]

[1]Faculty of Health Sciences and Medicine, Bond Institute of Health and Sport, Bond University, Robina, Qld, Australia
[2]Royal Brisbane and Women's Hospital, Herston, Qld, Australia

Keywords
family carer, nutrition support, protein-energy malnutrition, quality of life, rehabilitation.

Correspondence
S. Marshall, Bond Institute of Health and Sport, Robina, Queensland 4226, Australia.
Tel.: +61 7 5595 5530
Fax: +61 7 5595 3524
E-mail: skye_marshall@bond.edu.au

How to cite this article
Marshall S., Reidlinger D.P., Young A., Isenring E. (2017) The nutrition and food-related roles, experiences and support needs of female family carers of malnourished older rehabilitation patients. *J Hum Nutr Diet*. **30**, 16–26
doi:10.1111/jhn.12397

Abstract

Background: To improve perceived value of nutrition support and patient outcomes, the present study aimed to determine the nutrition and food-related roles, experiences and support needs of female family carers of community-dwelling malnourished older adults admitted to rehabilitation units in rural New South Wales, Australia, both during admission and following discharge.
Methods: Four female family carers of malnourished rehabilitation patients aged ≥65 years were interviewed during their care-recipients' rehabilitation admission and again at 2 weeks post-discharge. The semi-structured interviews were audiotaped, transcribed and analysed reflecting an interpretative phenomenological approach by three researchers. A series of 'drivers' relevant to the research question were agreed upon and discussed.
Results: Three drivers were identified. 'Responsibility' was related to the agency who assumed responsibility for providing nutrition support and understanding family carer obligation to provide nutrition support. 'Family carer nutrition ethos' was related to how carer nutrition beliefs, knowledge and values impacted the nutrition support they provided, the high self-efficacy of family carers and an incongruence with an evidence-based approach for treating malnutrition. 'Quality of life' was related to the carers' focus upon quality of life as a nutrition strategy and outcome for their care-recipients, as well as how nutrition support impacted upon carer burden.
Conclusions: Rehabilitation units and rehabilitation dietitians should recognise and support family carers of malnourished patients, which may ultimately lead to an improved perceived benefit of care and patient outcomes. Intervention research is required to make strong recommendations for practice.

Introduction

Enhancing the effectiveness of nutritional care to improve the overall health of older adults will be key in reducing hospital and aged care facility demand, a priority target of current health service research and policy. [1–3] Protein-energy malnutrition (herein referred to as 'malnutrition') is an expensive consequence and cause of disease and presents a significant burden to rehabilitation facilities, where approximately 14–65% of all older adults are malnourished worldwide. [4–8] Furthermore, a recent study found that malnourished patients admitted to rural rehabilitation units were likely to be discharged with malnutrition and remain moderately malnourished for at least 3 months in their homes. [9] Significantly, although all patients in the study had family carers (herein referred to as 'carers'), these carers were not engaged by the rehabilitation nutrition support services. [9]

There is good evidence that malnutrition-related interventions delivered to carers are able to improve or

prevent decline in nutritional and functional status and quality of life, without increasing carer burden. [10] The engagement of carers as part of the nutrition care team in rehabilitation presents a unique opportunity to improve nutrition care and outcomes because the intervention is centered on the needs and preferences of patients and their family members or friends who provide the majority of their care. The rehabilitation setting is ideal for such interventions because the longer length of stay increases opportunities to engage carers. Importantly, involving the carers supports the primary purpose of rehabilitation, which is to facilitate successful transitioning back to the community or residential aged care.

Exploring the nutrition and food-related roles, experiences and needs of carers of malnourished older adults, both during and following the rehabilitation admission, could ensure the development of intervention strategies that are both patient and carer-centred. Therefore, to inform the design and delivery of future nutrition support interventions for older rehabilitation patients and their carers, a qualitative exploration was undertaken aiming to understand this phenomenon in the interpretive paradigm.

Research question

What are the nutrition and food-related roles, experiences and support needs of female family carers of community-dwelling malnourished older adults admitted to rehabilitation units in rural New South Wales (NSW), Australia, both during admission and following discharge?

Materials and methods

Study design

This longitudinal qualitative investigation was implemented as part of the Malnutrition in the Australian Rural Rehabilitation Community (MARRC) study. Semi-structured interviews were conducted at two time-points with the aim of understanding the carer roles, experience and support needs during and after the rehabilitation stay, with analysis guided by interpretative phenomenological analysis (IPA). This approach was selected because the research was focussed on interpreting the lived experience of carers and informing future interventions to improve health service delivery. [11–13]

Participants and setting

Participants were sampled from two public, general rehabilitation units (24 and 31 beds) in the same local health district in rural NSW, chosen by convenience based on location. Participants were eligible if they were English-speaking female family carers aged ≥18 years, and cared for a community-dwelling inpatient aged ≥65 years with malnutrition (determined by the rehabilitation dietitian). To produce a homogenous sample, female carers were chosen because they represent the majority of family carers; [14] however, reflecting the IPA approach, a 'representative' sample was not sought. For the present study, a family carer was considered to be a family member or close friend who either lived with the older adult or did not live with the older adult but provided assistance with activities of daily living, with point-of-contact ≥4 days per week. Carers were identified from medical records and the older adult inpatient. Exclusion criteria for carers were: a history of abusive or threatening behaviour, as well as an unsafe dwelling or a dwelling located ≥1.5 h driving time from the rehabilitation facility as reported by medical records.

Carers were identified through purposive sampling facilitated by the rehabilitation dietitian (independent of the research team) and the primary researcher (SM): all patients identified as at risk of malnutrition (via the Malnutrition Screening Tool [15]) were referred to the rehabilitation dietitian for full nutritional assessment. With permission from the patient, potentially eligible carers were approached by the researcher to invite them to participate. Reflecting the IPA approach, [16–18] a small sample size of four participants (two daughters and two spouses) was considered appropriate for the present study.

The usual care for care-recipients comprised individualised medical nutrition therapy from the rehabilitation dietitian (0.15 full time equivalent per rehabilitation unit). Involvement of the carer in the nutritional management of the care-recipient occurred opportunistically at the discretion of the carer and rehabilitation dietitian. Usual post-discharge nutrition support may involve referral to publically-funded dietitian outpatient clinics and/or the prescription of subsidised oral nutrition supplements. The researchers were not involved in the care of the care-recipients and provided no intervention.

Ethical considerations

Ethical and governance approvals were obtained as part of the MARRC Study (North Coast Human Research Ethics Committee approval number LNR 063, G108). Written informed consent was obtained from all carer participants. A small travel reimbursement (AU$15) was offered to participants to cover transport costs; however, two participants refused reimbursement. A waiver of consent was granted for the collection of basic demographic data from the rehabilitation inpatients (care-recipients).

Interviews

Care-recipients did not attend interviews. The primary researcher conducted face-to-face semi-structured interviews with carers at two time points (T1 and T2):

T1: during the care-recipients' admission (at least 7 days post-admission) in a private room at the rehabilitation unit.

T2: 2 weeks post-discharge in a private room at the carers' home, workplace or at the rehabilitation unit.

The first carer interview was also a pilot, used to create the interview schedules (see Supporting information, Table S1 and S2) and trial the analysis. The primary researcher collected demographic data about the carer and their care-recipient via interview and medical records. Before and after the interviews, the primary researcher maintained a journal of field observations and thoughts/impressions to aid data analysis.

Data analysis

Interviews were audio-recorded and transcribed verbatim by SM. Identifying information was removed from the transcripts. Codes were developed using qualitative analysis software (NVIVO, version 10. QSR International Pty Ltd, Doncaster, VIC, Australia). Thematic analysis was guided by the IPA method described by Smith *et al.* [17] and Phillips *et al.* [16,19] Specifically:

1 Individual interview transcripts were studied independently and on multiple occasions by SM. Line by line coding was used, and potential themes (words or short phrases) were developed for each interview, including contradictory extracts within a particular theme. A secondary researcher (EI) reviewed transcripts and codes; additional codes were produced and existing codes expanded.

2 Potential themes were discussed and compared by SM and EI until consensus was reached and a long list of themes was created for each interview.

3 Themes with commonality were grouped into 'higher themes' for each interview. Divergences and convergences between linked interviews (T1 and T2 by the same participant) were particularly considered when developing higher themes.

4 The nutrition and food-related significance of the higher themes were considered; those considered to be unrelated to food and nutrition or not relevant to the research question were excluded. Examples were the higher themes of medical status and nonfood-related social interaction. Higher themes and their relevance were assessed by SM and confirmed with EI.

5 Both researchers compared the higher themes across all interviews at each time-point (T1 and T2), producing 'shared themes' that reflected commonalities across all interviews, time-points and the field notes of the primary researcher.

6 Commonalities in shared themes were identified which allowed them to be further grouped into 'super themes', also known as 'drivers'.

7 From the literature, a relevant theoretical framework was selected to help explain and interpret the drivers.

8 The drivers and theoretical framework were used to describe and interpret the experience of carers during their care-recipient's rehabilitation admission and post-discharge, and make suggestions for practice.

An electronic and paper-based audit trail was reviewed by a third, independent researcher (DR). Any disagreements or contested themes were discussed between the three researchers until consensus was reached. Finally, agreed drivers encompassed themes occurring across most accounts and which best answered the research question. The results were integrated with the discussion to support synthesis for the reader. [20]

Results and Discussion

Four female participants were recruited from one rehabilitation unit only (Table 1). Interviews were conducted from July 2015 to January 2016, and all participants attended both interviews (T1 and T2). Each interview was conducted alone with the carer, with the exception of one interview (T1; Joan), which was also attended by Joan's neighbour Vicky (pseudonym used) at the request of Joan. Vicky provided informed consent to participate in the study; however, her contribution was minimal. The T1 interviews were conducted from 11 to 28 days following admission and were 25–36 min in duration, and the T2 interviews were conducted 12–21 days following the care-recipients discharge from rehabilitation and were 6–15 min in duration. The T2 interviews were shorter than expected because the carers' experiences and needs had not significantly changed since T1.

Three inter-related drivers were identified, each with a further two sub-themes (Fig. 1). The drivers and sub-themes were consistent with a theoretical framework (herein referred to as the family caring and health-related outcomes framework), which provides theoretical background for relevant findings. [21] The framework proposes four domains that address the effects of family carers on the health-related outcomes of older adult care-recipients in home health care: type of carer (spouse, offspring, relative, non-relative); nature of caregiving relationship (availability, familiarity, motivation, care-recipient's preference, burden); type of caregiving (psychosocial versus direct care); and internal processes of the care-recipient (psychological, behavioural and physiological processes). These domains are informed by task-specific theory,

Table 1 Demographics of the female family carers and their malnourished care-recipients

Demographic	Amanda*	Jill*	Cindy*	Joan*
Family carer demographics				
Age	45 years	84 years	59 years	85 years
Relationship to care-recipient	Daughter	Wife	Daughter-in-law	Wife
Highest level of education	Trade	Tertiary	Tertiary	Secondary
Marital status	Divorced/separated	Married	Married	Married
Country of birth	Australia	Australia	Australia	England
English as first language	Yes	Yes	Yes	Yes
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian
Religion	No religion	Christianity	Christianity	No religion
Currently dieting	No	No	No	No
Pension	Single parent	Aged	None	Aged
Living with care-recipient	No	Yes	No	Yes
Assist care-recipient with grocery shopping	Yes	Yes	Yes	Yes
Assist care-recipient with food preparation	No	Yes	Yes	Yes
Care-recipient demographics				
Care-recipient*	Velma	Lester	Leona	Alfred
Care-recipient length of rehabilitation stay	36 days	42 days	35 days	32 days
Care-recipient age group	65–69 years	85–89 years	85–89 years	85–89 years
Care-recipient sex	Female	Male	Female	Male
Care-recipient discharge location	Home	Home	Residential aged care facility	Home

*Pseudonyms used.

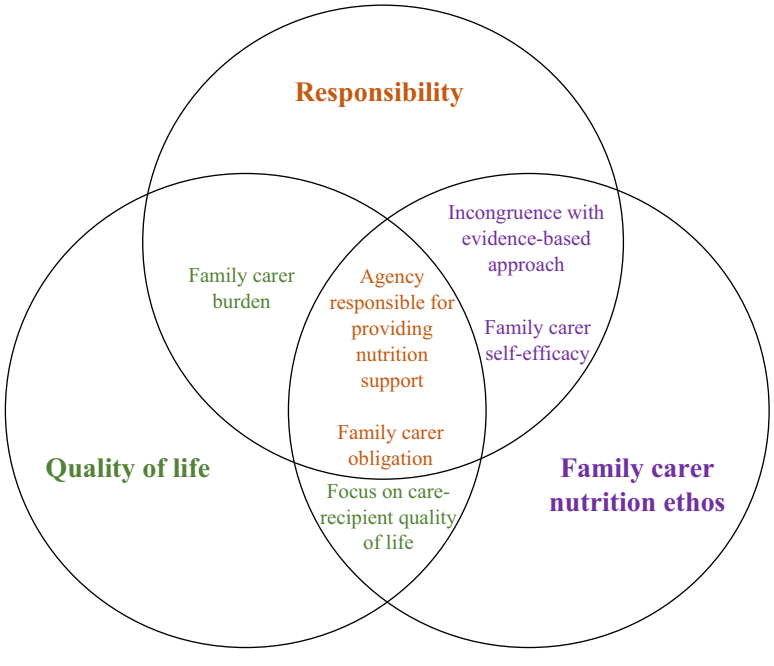

Figure 1 Schematic overview of three interconnected 'drivers' and their sub-themes that represent the nutrition and food-related roles, experiences and support needs of female family carers of malnourished older rehabilitation patients.

hierarchical-compensatory theory, burden theory, direct effect theories and stress-related theories. [21]

Driver: Responsibility

Agency responsible for providing nutrition support

The researchers considered three candidates who may assume responsibility for providing nutrition support for malnourished older rehabilitation patients: carers, the health service (including rehabilitation dietitian) and the care-recipients.

The high responsibility experienced by the carer in providing nutrition support to the care-recipient was strongly expressed across all interviews. The carers saw nutrition support as one of their key roles, which continued during the rehabilitation admission.

'... we had a picnic the other day outside, and we had salmon rolls, and a banana, no, fruit salad I made him. So when I come I bring something, just to boost what he's getting at present' (T1, Jill, carer for Lester)

This finding illustrates the importance of the nature of the caregiving relationship and the motivation of the carer to provide physical and psychosocial care, [21] aligning with the concept that older adults may experience less psychological consequences when care is provided by their preferred person, such as a familiar family carer. [21,22] Interestingly, all carers, at both time-points, recognised that nutrition or eating was a difficulty or problem for their care-recipient but failed to seek formal nutrition support. Although there were multiple reasons why the carers did not seek formal nutrition support in the present study (Table 2), all carers expressed a strong desire to be highly involved in any form of nutrition support that the health service provided to their care-recipient.

'I think it's awfully important to be involved, particularly if he's coming home. I'd have to be. That's, you know, that's the be all and end all of that. I mean, I'd have to be ... I'm buying the food, I'm cooking the food, I'm serving the food ... I must be involved in that' (T1, Joan, carer of Alfred)

It was further interpreted that some carers expected that the health service had a responsibility to provide information to the carers about nutrition support services and, similarly, the rehabilitation dietitian should have actively sought out and engaged with the carer whenever care was provided to a malnourished patient. Similar studies have found that, although carers of older adults may receive praise for their caregiving, they are given little practical assistance by healthcare providers. [23–27] Thus, although previous theory has described formal support as the final preference of elderly care-recipients (coming after care provided by family members), [22] it was clear in the present study that carers themselves

Table 2 Family carers' reasons for not engaging with formal nutrition support provided by the rehabilitation unit during or after their care-recipients' rehabilitation admission

Reason	Quote	Details*
Lack of knowledge of any nutrition support services	Not really aware of any [nutrition services in rehabilitation], apart from, you know, just ... I wasn't really aware of any of them	T1, Amanda, carer of Velma
Belief that if help was needed then the health service would take initiative to intervene and engage the caregiver	Probably because I don't know enough about a nutritionist, how they would work, it would be something that the hospital would have to talk to us about, or the hospital would refer the nutritionist to us	T2, Cindy, carer of Leona
Belief the rehabilitation nutrition support services are unable to assist their care-recipient as a result of inadequate knowledge of the individual	She eats a lot of fish ... they haven't been feeding her fish, and that's all she mainly eats ... That is one of the main reasons she's not eating here	T1, Cindy, carer of Leona
Belief that they have enough knowledge and resources to provide sufficient nutrition support without assistance from formal services	I sort of feel I understand what's needed ... unless I had a problem ... when you asked me 'would a dietitian help me', I thought I knew it all	T2, Jill, carer of Lester
Concern over the cost of formal nutrition support services	But all you think of is 'hang on, if I'm going to get a nutritionist, it's going to cost me an arm and a leg'	T2, Cindy, carer of Leona
Failure to recognise malnutrition and need for a specialised dietary approach	Quite shocked actually [at learning Alfred has malnutrition]. I mean, ah, I suppose he is thin, but I have never known him any other way. I can't say I've looked at Alfred over the last few months even and thought you know, you look thinner than ...	T1, Joan, carer of Alfred

*Pseudonyms used.

perceive such formal support as essential for performing their own role as family carers. In their experience, their contribution in providing nutrition support was not recognised by the health service. A model of care focussed only on the partnership between the health professional and the patient may ignore the overlap between professional and family carers, particularly considering that family carers assume primary responsibility for the care-recipient's overall wellbeing. [28]

Finally, carers experienced that the care-recipient themselves assumed low responsibility for their own nutritional status and dietary intake.

> 'Mum's always been very aware of nutrition, so it's been hard to see her like this, in a state that she's not really ... taking care of what she needs' (T1, Amanda, carer of Velma)
>
> 'He wouldn't listen [to nutritional advice]' (T1, Joan, carer of Alfred)

Amanda's quote represents Velma as undergoing a change in her interest and value in nutrition, and that her current lack of responsibility for her own nutrition support did not reflect her long-term nutrition values in Amanda's experience. Alternatively, Joan gave her experience of Alfred as having a firm and long-standing disinterest in nutrition advice. Overall, all carers' experiences were that their malnourished care-recipients assumed low responsibility for their own nutrition, irrespective of the reason, and this is important in understanding why some care-recipients may have poor adherence to nutrition interventions. In addition, the perceived low responsibility assumed by care-recipients was interpreted to impact upon the carers' assumed responsibility for providing nutrition support. Internal processes of a care-recipient, incorporating self-esteem, meaning of life, obligation to life, loneliness and stress have been linked to healthcare adherence [21] and may provide some insight into the reasons why the care-recipients in the present study were perceived to assume little or no responsibility by their carers.

Family carer obligation

> 'I find it very hard. I find it very constant. I find him extremely unappreciative. He's eating very well now, good meals, because I'm trying to build him up, because he's going in for the operation to get a TURP [crying]. And he needs to be as strong as he can be ... so I'm doing all I can from my side to strengthen him' (T2, Jill, carer of Lester)

This quote exemplifies our interpretation of how the carers' provision of nutrition support was linked to their experience of the care-recipient taking little responsibility, and how this was linked to carer burden (Fig. 1). However, further than that, we interpreted that Jill's provision of nutrition support was voluntary in some ways (as a result of the emotional connection with Lester) and involuntary in other ways (as a result of Lester placing high demands for care on his wife). As discussed earlier, all carers experienced feelings of obligation to provide nutrition support for their care-recipients, although the motivation behind this obligation was diverse, including varying degrees in which this responsibility was voluntarily assumed by the carer. Some carers appeared to naturally assume the responsibility for providing nutrition support on their own volition, whereas others felt this role was involuntarily placed upon them. As the quote by Jill illustrates, the emotion that she expressed revealed how she was personally invested in the wellbeing of Lester. Both Jill and Amanda expressed that, at least partially, they provided their nutrition support out of their feelings of both emotional and self-interested obligation. Because the continued wellbeing of their care-recipients was important to them emotionally, their caregiving was expressed to be more self-initiated and voluntary. Conversely, Cindy expressed her obligation to provide care as a result of societal and/or legal pressures.

> '[if we didn't provide care] ... and you know it looks like we're not doing the right thing by her' (T2, Cindy, carer of Leona)

When initially contacted, Cindy was concerned of negative repercussions if the researcher felt that her care was inadequate. In this case, the researcher perceived that there was less emotional connection to the care-recipient than the other carers because Cindy had only known Leona for 2 years, and her husband (Leona's son) did not have a close relationship with Leona. For Cindy, we interpreted that the provision of care seemed less voluntary than for Amanda and Jill. These findings can be further interpreted by examining the nature of the caregiving relationship, given that the motivations for caregiving may be different depending on the type of carer, such as spouse, offspring or non-relative. [21]

Joan did not see herself as a carer, instead stating that her role as a wife had not changed with Alfred's worsening health status. However, Joan had significant support needs herself, which may have contributed to why she did not recognise her caregiving role. Alternatively, Joan may see caregiving as an extension of her spousal relationship, previously proposed to occur as a consequence of wider sociocultural roles. [21,29]

Previous researchers have proposed that spouse carers experience less role strain than daughters, who have a greater burden as a result of a reversal of roles. [21,30,31] However, Despite the varying origins of carer obligation,

all carers expressed their willingness to assume the responsibility for nutrition support.

Obligation perceived by the carers was interpreted to differ depending on influences from the other drivers. For example, when providing nutrition support was perceived to have a negative impact on the carers' own quality of life (Fig. 1), care provision seemed to be carried out less voluntarily, or with a lower emotional and self-interested sense of obligation. Conversely, other carers tended to be more willing to assume the responsibility, especially if they held a strong nutrition ethos (Fig. 1). Aligning strongly with the family caring and health-related outcomes framework, [21] the quality of the personal relationship between the carer and the care-recipient was identified as a major influence affecting the willingness to provide care, and closely aligned with the emotional sense of obligation.

> 'I've discovered how very much I miss him when he's been away. He's a very big part of my life, and we've been married for 60 years ... It is very important to me that he does as well as he can for as long as he can ... And him being well fed, and getting strong is a very important part of that, you know' (T1, Jill, carer of Lester).
>
> 'She doesn't want to be pushed. Um, as I said, she's a very stubborn lady, but the thing is always "no", whatever you want' (T1, Cindy, carer of Leona)

Driver: Family carer nutrition ethos

Family carer nutrition ethos captures the effect of the nutritional values, beliefs and knowledge of the carers on their persistency and the type of nutrition support strategies that they used. Across the interviews, it was observed that the more value the carer placed on nutrition (or a particular nutritional belief), the more persistent, voluntary or proactive they were with the provision of their nutrition support. The type of nutritional belief, and how strongly it was valued, in turn affected the nutritional priorities and strategies employed by the carer.

> 'It [nutrition] would have to be one of the most important things to me, for me, at this time with my son as well, yeah, very important ... I do tend to keep our diet as restrictive of as much dairy as I can, as much wheat as I can, and I've just recently become vegetarian and on my way to becoming vegan ... [later in the interview] ... so I would like mum to eat kind of more fruit and vegies, you know but she's not going to, so, there's not really.. There's kind of like a bit of a wall with mum' (T1, Amanda, carer of Velma)

However, those who did not hold specific nutritional beliefs or value nutrition as strongly as others saw nutrition support as just another task included as part of their caregiving, and opted for a simple strategy of food provision rather than any particular dietary approach.

> 'Well as far as value [of nutrition] is concerned, I wouldn't put anything. You get up, you prepare breakfast, you have something to eat if you're hungry, you know. I always have plenty of vegetables and stuff' (T1, Joan, carer of Alfred)
>
> 'Well, no, he's eating just the same [as prior to fall and rehabilitation admission]. And I don't know whether it's perhaps lack of exercise, you know, that's making him weak. You see he's not exercising, he's not walking ... mainly because he can't' (T2, Joan, carer of Alfred)

This second quote by Joan was interpreted to reflect that she attributed Alfred's condition to exercise as opposed to dietary intake or nutrition, and did not appear to be highly motivated to provide additional nutrition support despite his continuing malnutrition. However, there may be other reasons Joan was not particularly focused on nutrition support, such as his lack of responsibility and obstinacy against nutrition intervention that she had earlier characterised in him.

Family carer self-efficacy

There was a strong impression that all carers felt the nutrition support strategies they provided were sufficient and effective, and that their current level of nutrition knowledge was adequate. This was a contributing factor to the lack of engagement with formal services such as the rehabilitation dietitian (Table 2). However, there was a divergence in self-efficacy in providing nutrition support overall; specifically, for time availability and receptivity of the care-recipient. The two younger generation carers (daughter and daughter-in-law) expressed time and/or distance constraints limited their ability to provide nutrition support; and two carers (daughter-in-law and wife) expressed the intransigence of their care-recipients as a limitation. Understanding this finding may be enhanced in the context of the nature of the caregiving relationship which includes availability as a key determinant. [21]

> '... I worry about her, and worry about finding the time to come up and do a shop with her ...' (T1, Amanda, carer of Velma)
>
> 'It's alright for me to go through all these, umm, sort of suggestions, but it's another thing getting him to follow it. He is a very, very determined man. He will not do anything he does not want to do' (T2, Joan, carer of Alfred)

Nutrition support strategies used by carers were all highly individualised to cater specifically for their care-recipient's food preferences, lifestyle and culture.

'... when I did do the, looked at the Polish, um, history ... And I thought "wow, that's really different", here we are trying to introduce a certain type of food to people, and eat breakfast lunch and dinner, they, they don't do that. And I thought, oh, that's really interesting, this is probably why she eats when she wants to eat, because yeah there's no set times ...' (edited text; T1, Cindy, carer of Leona)

The individualised approach used by carers may have led to a high success rate in their provision of nutrition support, in turn contributing to the carers' self-efficacy and subsequent concern over the quality of formal support (Table 2). The family caring and health-related outcomes framework [21] supports this finding, where familiarity is shown to impact upon health outcomes through alignment of understanding and lifestyle between the carer and care-recipient. The high self-efficacy of carers facilitated through familiarity may also link with the high responsibility assumed by carers for providing nutrition support discussed earlier.

Incongruence with evidence-based approach

Amanda's description of her restrictive diet (quoted earlier) demonstrated her strong nutritional belief in the importance of 'whole foods', fruits and vegetables. Although Amanda attached strong values to these foods, all carers considered that a healthy diet with plenty of vegetables was the most important nutritional strategy. This promotion of fruit and vegetables (low-energy and vitamin/mineral-rich foods), although a recognised theme, was less important to the researchers in the analysis than the significance of how this approach does not align with the evidence-based approach for treating malnutrition by promoting energy- and protein-rich foods and beverages. [32]

Similarly, of importance to our interpretation within this sub-theme, there was limited discussion about protein during the carer interviews. Jill had the strongest focus on protein because Lester and Jill had seen a dietitian in acute care where the importance of protein intake was discussed. However, even where the carers recognised the importance of protein, their nutritional knowledge and nutrition support strategies remained inadequate.

'Ah, well, when you asked me "would a dietitian help me", I thought I knew it all. And further to our discussion I realise that the way I see healthy eating, and the way that Lester needs healthy eating to put on weight, are reversed!' (T2, Jill, carer of Lester)

Driver: Quality of life

Focus on care-recipient quality of life

Although the nutrition support strategies described by the carers tended to focus on fruit, vegetables and healthy eating, the reason behind this was interpreted to be strongly related to quality of life. Carers revealed that their purpose in providing nutrition support was to improve the care-recipients' overall quality of life, rather than nutritional or medical outcomes.

'If she starts to enjoy life a little bit more, and starts to enjoy this phase of her life, and enjoy her eating ... its part of life isn't it? Not wanting to eat and actually be amongst it and involved ... it's just such a beautiful thing, so, food is such a beautiful thing, so it would be lovely to see her enjoying that' (T1, Amanda, carer of Velma)

The carers also frequently described non-nutrient-related nutrition support strategies which were directly aimed at improving quality of life.

'Try and make the meal time a happy time, and, umm, perhaps add a glass of port! [Laughs] To make it ... as pleasant time as you can, because I think that does help the appetite' (T2, Jill, carer of Lester)

Therefore, the care-recipients' quality of life was seen as both a strategy and an outcome in nutrition support, overall suggesting that nutrition support was approached holistically with a focus upon quality rather than physical outcomes. Literature has shown that carers frequently provide both psychosocial support as well as direct health-related care, [21] with a carer's influence on a care-recipient's health encouraged through psychosocial processes such as promoting positive obligation to life and reduced stress. [21]

Family carer burden

The carers' own quality of life was important and diverse, both between carers and within the same carer over time.

'So you know, he's not selfish in that way, he's keen for me to have a life as well. Cause you've got to have a life as well, you know ... Even though it might be a tiny bit restricted, it's still a life' (T1, Jill, carer of Lester)

'I find it very hard, very constant ... I find him very unappreciative' (T2, Jill, carer of Lester)

Jill conveyed that burden of care significantly increased following Lester's discharge from rehabilitation. However, this was not the case for all carers. Joan did not report increased burden of care; however, she did require significant additional domiciliary and healthcare support. Amanda did not have the time to visit and assist Velma following her discharge from rehabilitation, although this increased her anxiety regarding her mother as she desired to be able to provide more care. Cindy reported a significant increase in quality of life following Leona's discharge

from rehabilitation; however, unlike the other care-recipients, Leona was not discharged home as originally planned but, instead, discharged to a residential aged care facility.

> 'Exactly, and this is why like carers end up themselves becoming very sick ... this is why really the carers need looking after in their nutritional ... you know, not just nutrition but just being able to have that respite, that care ... [later in interview] ... I've got freedom now! ... I don't have to worry' (T2, Cindy, carer of Leona)

Educating family carers of malnourished older adults has been previously shown to improve patient outcomes but have no effect on carer burden. [10] The present study provides insight on why this may be the case because all carers were already assuming the responsibility for nutrition support and wanted to be involved in any formal nutrition support provided to their care-recipient. However, this does not imply that the carer burden is low because there is good research showing that carers of frail or malnourished older adults have a significant burden of care leading to a lower quality of life. [33–35]

Implications for research and practice

Broadly, the findings of the present study challenge current practice with respect to the nutrition and dietetic care process. [36,37] It is suggested that the way care is delivered in rehabilitation facilities for older malnourished patients should change through the integration of formal and family nutrition support, across both the wider rehabilitation unit and dietetic services. The suggestions for practice described in the present study have been specifically linked to the study findings outlined in the Supporting information (Table S3).

Within rehabilitation units, system changes are required to ensure that family carers are aware of the nutrition support resources available to them, and are assisted to access these services. Specifically for dietetic practice, dietitians should identify and deliberately engage family carers of malnourished patients and recognise that the care-recipient themselves may assume less responsibility for their nutritional intake than the carers. Additionally, dietitians should understand carer nutritional beliefs and the types of nutrition support strategies used by the carer, as well as the motivations behind them, with the aim of making more carer-centred recommendations and correct inappropriate nutrition strategies. Such strategies should still acknowledge the cultural background and food preferences of their patients and provide individualised medical nutrition therapy. In developing strategies, an understanding of the current caregiving concerns of the family carer and joint problem solving is required, so that strategies can be needs-based and provide a meaningful contribution to the pre-existing family carer–care-recipient partnership. Finally, dietitians should recognise that family carers may focus their care upon improving the quality of life of their care-recipients rather than improving nutritional or clinical outcomes. This focus on quality of life should be incorporated in strategies to improve their acceptability to the family carer.

Although these suggestions may improve practice, further research and evidence is required to develop the evidence base. To support the transition of these suggestions to evidence-based recommendations, intervention studies are needed to determine whether the proposed coordination of efforts of the rehabilitation dietitian, the carer and the patient will increase the efficacy of nutrition support. The findings of the present study suggest that such research should consider not only patient outcomes, but also outcomes in the carer. Finally, further qualitative studies should explore the experiences of male carers of malnourished older adults in rehabilitation, as well as carers in other settings, aiming to better improve understanding.

Limitations

The interviews by the four participants in the present study offered rich and diverse themes for exploration and analysis by the researchers; however, the unexpected shorter length of the interviews (particularly T2) and a lack of data on the severity of malnutrition of the care-recipient both represent limitations. In addition, as a result of the purpose of the study, only those themes that were related to the research question were pursued.

As with all qualitative research, there is a potential for bias as a result of the researchers' professional, clinical and personal backgrounds, all of whom were Accredited Practising Dietitians. Reflexivity was used throughout the analysis process and also when reporting the results to acknowledge this.

Conclusions

'Responsibility', 'family carer nutrition ethos' and 'quality of life' were identified as three drivers of female family carers of malnourished older rehabilitation patients. Rehabilitation units and rehabilitation dietitians should recognise and support family carers of malnourished patients during and after the patients' rehabilitation admission, which may lead to improved patient outcomes and perceived benefit of care. Interventional research is required to make strong recommendations for practice.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with RATs [38] guidelines.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

This study received no specific funding. SM was supported by an Australian Postgraduate Award and a research budget of approximately $3000 from Bond University throughout the duration of her PhD Candidature.

SM carried out the data collection, conducted the analysis and interpretation of data, and drafted the manuscript. EI and DR contributed to the data analysis. SM, DR, AY and EI contributed to the study concept and the revision of the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

References

1. The Allen Consulting Group (2007) *The Future of Community Care, Report to the Community Care Coalition*. Melbourne: The Allen Consulting Group.
2. Productivity Commission (2011) *Caring for Older Australians*, Vol. **1**. Canberra: Productivity Commission.
3. Health Workforce Australia (2011) *National Health Workforce Innovation and Reform Strategic Framework for Action 2011–2015*. Adelaide: Health Workforce Australia.
4. Elia M & Stratton R (2005) *The Cost of Disease-Related Malnutrition in the UK and Economic Considerations for the use of Oral Nutritional Supplements (ONS) in Adults*. Redditch: BAPEN.
5. Marshall S, Young A, Bauer J *et al.* (2016) Malnutrition in geriatric rehabilitation: prevalence, patient outcomes and criterion validity of the Scored Patient-Generated Subjective Global Assessment (PG-SGA) and the Mini Nutritional Assessment (MNA). *J Acad Nutr Diet* **116**, 785–794.
6. Pleuss J (2005) Alterations in nutritional status. In: *Pathophysiology, Concepts of Altered Health States*. pp. 217–238 [Porth CM, editor]. 7th edn. Philadelphia, PA: Lippincott Williams & Wilkins.
7. Marshall S, Bauer J & Isenring E (2014) The consequences of malnutrition following discharge from rehabilitation to the community: a systematic review of current evidence in older adults. *J Hum Nutr Diet* **27**, 133–141.
8. Marshall S (2016) Protein-energy malnutrition in the rehabilitation setting: evidence to improve identification. *Maturitas* **86**(7), 7–85.
9. Marshall S, Young A, Bauer J *et al.* (2015) Malnourished older adults admitted to rehabilitation in rural New South Wales remain malnourished throughout rehabilitation and once discharged back to the community: a prospective cohort study. *J Aging Res Clin Pract* **4**, 197–204.
10. Marshall S, Bauer J, Capra S *et al.* (2013) Are informal carers and community care workers effective in managing malnutrition in the older adult community? A systematic review of current evidence. *J Nutr Health Aging* **17**, 645–651.
11. Dibsdall LA, Lambert N & Frewer LJ (2002) Using interpretative phenomenology to understand the food-related experiences and beliefs of a select group of low-income UK women. *J Nutr Educ Behav* **34**, 298–309.
12. Crogan NL, Evans B, Severtsen B *et al.* (2004) Improving nursing home food service: uncovering the meaning of food through residents' stories. *J Gerontol Nurs* **30**, 29–36.
13. Scarpello T, Poland F, Lambert N *et al.* (2009) A qualitative study of the food-related experiences of rural village shop customers. *J Hum Nutr Diet* **22**, 108–115.
14. Van Houtven CH, Coe NB & Skira MM (2013) The effect of informal care on work and wages. *J Health Econ* **32**, 240–252.
15. Marshall S, Young A, Bauer J *et al.* (2016) Nutrition screening in geriatric rehabilitation: Criterion (concurrent and predictive) validity of the Malnutrition Screening Tool (MST) and the Mini Nutritional Assessment-Short Form (MNA-SF). *J Acad Nutr Diet* **116**, 795–801.
16. Wagstaff C, Jeong H, Nolan M *et al.* (2014) The accordion and the deep bowl of spaghetti: eight researchers' experiences of using IPA as a methodology. *Qualitative Rep* **19**, 1–15.
17. Smith JA, Jarman M & Osborn M (2000) Doing interpretative phenomenological analysis. In: *Qualitative Health Psychology*. pp. 218–240. [Murray M & Chamberlain K editors]. London: Sage Publications.
18. Smith JA & Osborn M (2007) *Interpretative Phenomenological Analysis. Qualitative Psychology: A Practical Guide to Research Methods*. 2nd edn. London: SAGE Publications Ltd.
19. Phillips E, Elander J & Montague J (2014) An interpretative phenomenological analysis of men's and women's coping strategy selection during early IVF treatment. *J Reprod Infant Psychol* **32**, 366–376.
20. Burnard P (2004) Writing a qualitative research report. *Accid Emerg Nurs* **12**, 176–181.
21. Cho E (2007) A proposed theoretical framework addressing the effects of informal caregivers on health-

related outcomes of elderly recipients in home health care. *Asian Nurs Res* **1**, 23–34.
22. Cantor MH (1989) Social care: family and community support systems. *Ann Am Acad Pol Soc Sci* **9**, 9–112.
23. Duncan MT & Morgan DL (1994) Sharing the caring: family caregivers' views of their relationships with nursing home staff. *Gerontologist* **34**, 235–244.
24. Powell-Cope GM (1994) Family caregivers of people with AIDS: negotiating partnerships with professional health care providers. *Nurs Res* **43**, 324–330.
25. Thorne SE & Robinson CA (1989) Guarded alliance: health care relationships in chronic illness. Image. *J Nurs Scholarsh* **21**, 153–157.
26. Boland DL & Sims SL (1996) Family care giving at home as a solitary journey. Image: the. *J Nurs Scholarsh* **28**, 55–58.
27. McGarry J & Arthur A (2001) Informal caring in late life: a qualitative study of the experiences of older carers. *J Adv Nurs* **33**, 182–189.
28. Ward-Griffin C & McKeever P (2000) Relationships between nurses and family caregivers: partners in care? *Adv Nurs Sci* **22**, 89–103.
29. Jo S, Brazil K, Lohfield L *et al.* (2007) Caregiving at the end of life: perspectives from spousal caregivers and care recipients. *Palliat Support Care* **5**, 11–17.
30. Johnson CL & Catalano DJ (1983) A longitudinal study of family supports to impaired elderly. *Gerontologist* **23**, 612–618.
31. King AC, Atienza A, Castro C *et al.* (2002) Physiological and affective responses to family caregiving in the natural setting in wives versus daughters. *Int J Behav Med* **9**, 176–194.
32. Wellman NS & Kamp BJ. (2008) Chapter 10: Nutrition in aging. In: *Krause's Food & Nutrition Therapy*. pp. 286–308 [Mahan LK & Escott-Stump S, editors]. 12th edn. St Louis, MO: Saunders Elsevier.
33. McCullagh E, Brigstocke G, Donaldson N *et al.* (2005) Determinants of caregiving burden and quality of life in caregivers of stroke patients. *Stroke* **36**, 2181–2186.
34. Toseland RW, McCallion P, Smith T *et al.* (2004) Supporting caregivers of frail older adults in an HMO setting. *Am J Orthopsychiatry* **74**, 349–364.
35. Salva A, Andrieu S, Fernandez E *et al.* (2011) Health and nutrition promotion program for patients with dementia (NutriAlz): cluster randomized trial. *J Nutr Health Aging* **15**, 822–830.
36. Lacey K & Prichett E (2003) Nutrition Care Process and Model: ADA adopts road map to quality care and outcomes management. *J Am Diet Assoc* **103**, 1061–1072.
37. (2012) *Model and Process for Nutrition and Dietetic Practice*. Birmingham: British Dietetic Association.
38. Clark J (2003) How to peer review a qualitative manuscript. In: *Peer Review in Health Sciences*. pp. 219–235 [Godlee F & Jefferson T, editors]. 2nd edn. London: BMJ Books.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article:
Table S1. The Malnutrition in the Australian Rural Rehabilitation Community (MARRC) Study interview schedule during rehabilitation (T1).
Table S2. The Malnutrition in the Australian Rural Rehabilitation Community (MARRC) Study interview schedule post-rehabilitation (T2).
Table S3. The Malnutrition in the Australia Rural Rehabilitation Community (MARRC) Study findings that support the suggestions for nutrition and dietetics practice in rehabilitations units.

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

OLDER PEOPLE

Supplementation with nutrients modulating insulin-like growth factor-1 negatively correlated with changes in the levels of pro-inflammatory cytokines in community-dwelling elderly people at risk of undernutrition

M. Kim,[1] M. Kim,[1] Y. J. Lee,[2,3] H. J. Song,[2,3] J. K. Shim,[4] D. H. Chang,[5] W. K. Yu,[5] S.-H. Lee[6] & J. H. Lee[1,2,3]

[1]Research Center for Silver Science, Institute of Symbiotic Life-TECH, Yonsei University, Seoul, Korea
[2]National Leading Research Laboratory of Clinical Nutrigenetics/Nutrigenomics, Department of Food and Nutrition, College of Human Ecology, Yonsei University, Seoul, Korea
[3]Department of Food and Nutrition, Brain Korea 21 PLUS Project, College of Human Ecology, Yonsei University, Seoul, Korea
[4]Goyang-si Heendol Community Welfare Center, Goyang, Korea
[5]Yonsei University Dairy R&D Center, Asan, Korea
[6]Department of Family Practice, National Health Insurance Corporation, Ilsan Hospital, Goyang, Korea

Keywords
cytokines, IGF-1, nutritional status, nutritional supplement, the elderly.

Correspondence
J. H. Lee, Department of Food & Nutrition, College of Human Ecology, Yonsei University, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel.: +82 2 2123 3122
Fax: +82 2 364 9605
E-mail: jhleeb@yonsei.ac.kr

How to cite this article
Kim M., Kim M., Lee Y.J., Song H.J., Shim J.K., Chang D.H., Yu W.K., Lee S.-H. & Lee J.H. (2017) Supplementation with nutrients modulating insulin-like growth factor-1 negatively correlated with changes in the levels of pro-inflammatory cytokines in community-dwelling elderly people at risk of undernutrition. *J Hum Nutr Diet*. **30**, 27–35
doi: 10.1111/jhn.12447

Abstract

Background: Suboptimal nutrition accompanied by chronic low-grade increases in circulating cytokine levels is more common in elderly people. We explored the improvement in nutritional status, especially in the level of insulin-like growth factor-1 (IGF-1) and its relationship with changes in circulating cytokine levels, after providing extra protein and energy content to community-dwelling older adults at risk of undernutrition.
Methods: Sixty nondiabetic subjects, aged ≥65 years and living independently in a community for elderly people, with a serum pre-albumin level ≤30 mg dL^{-1} and a body mass index <25 kg m^{-2}, were recruited. The subjects were followed for a 2-week pre-intervention period, during which they maintained routine dietary habits. This was followed by an intervention period, during which they received oral nutritional supplementation for 2 weeks.
Results: Following 2 weeks of intervention, there were significant increases in total lymphocyte count (TLC) and insulin-like growth factor (IGF)-1, pre-albumin and transferrin compared to baseline. Body weight and mid-arm circumference significantly increased without alteration of tricep skinfold thickness at the end of the intervention. There was a significant reduction in interleukin (IL)-6 levels and a trend toward a decrease in the tumor necrosis factor (TNF)-α levels. At baseline, age was negatively correlated with IGF-1 levels and positively correlated with IL-6 and TNF-α levels. The change (△, from baseline) in IGF-1 level was positively correlated with age and negatively correlated with △IL-6 and △TNF-α.
Conclusions: A 2-week intervention with oral nutritional supplementation improved nutritional status and decreased circulating cytokine levels. Specifically, △IGF-1 was negatively correlated with changes in pro-inflammatory cytokine levels in community-dwelling elderly people at risk of undernutrition. (Clinicaltrials.gov: NCT02656186).

Introduction

The percentage of individuals in the USA aged ≥65 years will increase from 15% in 2014 to 24% in 2060 [1]. Providing good health care to the elderly is a major challenge. A balanced diet can have an enormous effect on quality of life, especially among elderly subjects. Therefore, early diagnosis and adequate treatment of undernutrition can provide clear improvements in health and quality of life [2]. To achieve this outcome, relevant clinical evidence is required. There are several reports of the efficacy of nutritional support in hospitalised elderly patients [3–6]. However, because it is difficult to enrol independently living elderly subjects during recruitment for clinical research studies [7], evidence for the effectiveness of nutritional supplements in this population is limited.

Suboptimal nutrition accompanied by chronic low-grade increases in circulating cytokine levels is more common in the elderly age group. There is an age-related decline in the level of insulin-like growth factor (IGF)-1, a sensitive marker reflecting changes in nutritional status, especially in the elderly. Conversely, there is an age-related increase in pro-inflammatory cytokine levels [8]. Therefore, it is important to establish whether diet supplementation is an effective strategy for improving the outcomes of elderly people at risk of a chronic subclinical inflammatory state resulting from undernutrition. The present study aimed to determine the improvement in nutritional status, especially in the level of IGF-1 and its relationship with changes in circulating cytokine levels, after providing extra protein and energy content to community-dwelling older adults at risk of undernutrition. For study precision, we used a nutritional supplement pack that enabled the exact quantification of all micronutrient intake in elderly subjects experiencing difficulties in complementing their normal oral diet.

Materials and methods

Participants

This was a community-based health intervention study. Sixty nondiabetic undernourished subjects who voluntarily agreed to participate and provided their written informed consent, aged ≥65 years with a serum prealbumin level ≤30 mg dL^{-1} and a body mass index (BMI) <25 kg m^{-2} were recruited [7,9] from a pool of 300 subjects at the Goyang-si Heendol Community Welfare Center (Goyang, Korea), which is for elderly people who live independently in the community. Subjects who had an inability to perform oral ingestion, known allergies to milk or eggs, an inability to communicate (e.g. those with Alzheimer's disease), malabsorption syndrome, a history of gastrectomy or enterectomy, diabetes, liver disease, renal disease, neurological disease, pancreatitis, malignancy, cardiovascular or cerebrovascular disease, metabolic syndrome, any other disease requiring treatment, medication or alcohol abuse, or any condition that the investigator considered may put the subjects at under risk were excluded. The study protocol was approved by the Yonsei University Institutional Review Board, which complied with the Helsinki Declaration, and written informed consent was obtained from all study participants. The mean (SD) age of the subjects was 70 (1) years (range 65–86 years); 30.4% were male and 69.6% were female.

Study design

In the present study, the subjects served as their own controls. Subjects who were eligible based on inclusion criteria first entered into a 2-week pre-intervention period, during which they maintained routine dietary habit. This was followed by an intervention period, during which an oral nutritional supplement was used over a period of 2 weeks. All study subjects had been assigned individualised dietary goals to achieve adequate protein and energy content, which were monitored weekly. Each week, the subjects received a nutrition intervention by a dietitian that consisted of individualised nutritional assessments involving 3-day food records.

Serial measurements of nutritional parameters including total lymphocyte counts; serum concentrations of albumin, transferrin, pre-albumin and IGF-1; body weight; mid-arm circumference; and circulating cytokine levels were obtained pre-treatment (week −2), at baseline (week 0) and post-treatment (week 2).

During the intervention period, an oral nutritional supplement was prescribed by a family medicine physician. The subjects received, twice-daily, a 200 mL carton of an orally consumed liquid nutritional supplement (Yonsei University Dairy, Asan, Korea) for 14 days (ClinicalTrials.gov: NCT02656186; http://www.clinicaltrials.gov). Two cartons of oral liquid nutritional supplementation (total 400 mL) contain 16 g of protein, 12 g of fat and 60 g of carbohydrate and provide 1.67 MJ (400 kcal). Each carton (200 mL) also contains 2 g of fibre, 150 μg of retinol equivalents of vitamin A, 0.24 mg of vitamin B_1, 0.3 mg of vitamin B_2, 0.3 mg of vitamin B_6, 20 mg of vitamin C, 2 mg of α-tocopherol, 15 μg of vitamin K, 3.2 mg of niacin equivalents of niacin, 80 μg of dietary folate equivalents of folic acid, 1 mg of pantothenic acid, 1 μg of biotin, 140 mg of Ca, 140 mg of P, 0.16 g of Na, 0.26 g of K, 44 mg of Mg, 2 mg of Fe, 2 mg of Zn, 160 μg of Cu and 0.7 mg of Mn. One supplement was consumed as a morning snack (between breakfast and lunch) and the other as an afternoon snack (between lunch and dinner) [2].

Subjects who were unable to ingest >80% of the prescribed supplement over 2 weeks were removed from the study.

Anthropometric parameters and blood pressure

Body weight (in lightweight clothes and without shoes) (UM0703581; Tanita, Tokyo, Japan) and height (GL-150; G-tech International, Uijeongbu, Korea) were measured in the morning and then BMI was calculated (kg m^{-2}). Waist circumference (directly on the skin) was measured at the umbilical level after normal expiration with the subject in an upright standing posture using a plastic measuring tape to record measurements to the nearest 0.1 cm. Anthropometric parameters were assessed at weeks −2, 0 and 2. During each testing session, systolic and diastolic blood pressure (BP) were assessed in the supine position after a resting period (20 min). BP was measured twice on the left arm using an automatic BP monitor (FT-200S; Jawon Medical, Gyeongsan, Korea); the two measurements were then averaged. Mid-arm circumference was measured using a flexible measuring tape. Tricep skinfold thickness was measured using a Lange skinfold caliper (Cambridge Scientific Industries, Cambridge, MA, USA).

Nutritional status assessment

Serum pre-albumin and transferrin concentrations were measured by an immunoturbidimetric assay using a COBAS INTEGRA autoanalyser (Roche-BM, Rotkreuz, Switzerland). Serum albumin concentrations were analysed via the BCG method using an ALB kit (Roche, Basel, Switzerland) with a Hitachi 7600 autoanalyser (Hitachi Ltd, Tokyo, Japan). Serum iron concentrations were determined via the ferrozine method using a Cobas8000 c702 analyser (Roche). Osmolality was measured via the freezing point depression technique using a Fiske 2400 osmometer (Fiske Associates Inc., Norwood, MA, USA). Serum IGF-1 protein levels were measured by a chemiluminescent immunoassay using an Immulite 2000 XPI immunoassay system (Siemens, Tarrytown, NY, USA).

Biochemical assessment

Blood collection

Blood samples were collected at approximately 08.00 h following an overnight fast of at least 12 h. Venous blood specimens were collected in ethylenediaminetetraacetic acid-treated whole-blood tubes and serum tubes to evaluate clinical characteristics. The blood samples were centrifuged to obtain plasma and serum. The collected samples were stored at −70 °C.

Serum fasting glucose and insulin levels

Serum fasting glucose levels were measured via the hexokinase method using a Hitachi 7600 autoanalyser (Hitachi Ltd). Serum insulin levels were measured via an immunoradiometric assay using commercial kits (DIAsource ImmunoAssays SA, Louvain-la-Neuve, Belgium). The resulting colour reactions were monitored using an SR-300 analyser (Stratec, Birkenfeld, Germany).

Serum lipid profiles

Fasting triglyceride and total and low-density lipoprotein cholesterol levels were measured via enzymatic assays using a Hitachi 7600 autoanalyser (Hitachi Ltd). High-density lipoprotein cholesterol levels were measured via selective inhibition using a Hitachi 7600 autoanalyser (Hitachi Ltd). Serum apolipoprotein (Apo) A-I and Apo B levels were determined by measuring the turbidity at 340 nm using specific anti-sera (Roche).

Liver and renal function

Serum aspartate aminotransferase levels were analysed via the IFCC ultraviolet (UV) method using a Hitachi 7600 autoanalyser. The blood urea nitrogen level was determined via a kinetic UV assay for urea/urea nitrogen using a Hitachi 7600 autoanalyser. Creatinine was analysed via the Jaffe method using a Hitachi 7600 autoanalyser.

Total lymphocyte count and serum high-sensitivity C-reactive protein level

The total lymphocyte count was determined using a HORIBA ABX diagnostic analyser (HORIBA ABX SAS, ParcEuromedicine, Montpellier, France). Serum high-sensitivity C-reactive protein (hs-CRP) levels were measured via the turbidity method by a latex agglutination immunoassay using a Hitachi 7600 autoanalyser.

Serum cytokine levels

The concentrations of tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 in serum were measured using a Bio-Plex™ Reagent Kit and a Bio-Plex™ system (Bio-Rad Laboratories, Hercules, CA, USA) in accordance with the manufacturer's instructions.

Daily energy intake and physical activity measurements

Subjects were instructed to maintain their eating habits and a normal level of physical activity during the study period to ensure that any changes were observed were not a result of alterations in diet or physical activity. A standardised 3-day dietary record (2 weekdays and 1 weekend day) was obtained from each participant. This record was completed at home after the participants

received detailed explanations from a dietitian. This measurement was repeated at weeks −2, 0, and 2. A computerised version of the Korean Nutrition File (Can-Pro 3.0; The Korean Nutrition Society, Seoul, Korea) was used to determine the macronutrient contents of the foods consumed by the participants and the total daily energy intake of the participants. In addition, the participants completed a semi-quantitative food-frequency questionnaire and a 24-h recall questionnaire with the assistance of a dietitian at weeks −2, 0 and 2 to confirm the accuracy of the dietary record. A standardised 3-day physical activity record was also completed at home on the same days during which the dietary record was completed. Total energy expenditure (TEE) (kcal day^{-1}) was calculated from activity patterns, including basal metabolic rate, physical activity over 24 h and specific dynamic action of food. Basal metabolic rate (BMR) for each subject was calculated according to the Harris–Benedict equation. Physical activity level (PAL) was calculated with the equation: PAL = TEE/BMR [10].

Statistical analysis

Statistical analysis was performed using SPSS, version 21.0 (IBM/SPSS, Chicago, IL, USA). Logarithmic transformation was performed on skewed variables. For descriptive purposes, the mean values are presented as untransformed values. One-way repeated-measures analysis of variance for followed by Bonferroni post-hoc analysis was used to determine the significance of differences in variables among the three time points (pre-treatment, baseline and post-treatment). Mauchly's test of sphericity was performed to determine the validity of the assumption of sphericity. The degrees of freedom were adjusted using either the Huynh-Feldt correction (epsilon ≥0.75) or Greenhouse-Geisser correction (epsilon <0.75) when the assumption of sphericity was violated ($P < 0.05$). The Pearson correlation coefficient was used to examine relationships between variables. The results are expressed as the the mean (SE). $P < 0.05$ (two-tailed) was considered statistically significant.

Results

A total of 60 subjects (17 males and 43 females) were included in the present study. Among these, four subjects dropped out during the study period (four females). Three subjects were censored because of incomplete compliance (ingestion of <80% of the prescribed nutritional supplementation), and one subject withdrew consent for participation in the clinical trial. Fifty-six subjects completed the entire study. Of these subjects, 18 took antihypertensive medications. Adverse effects involving oral administration of the supplement were not observed.

Anthropometric parameters, serum protein levels and lymphocyte counts

During the 2-week preingestion period, there were no changes in anthropometric parameters (Table 1), slight but significant decreases in the serum concentrations of albumin (Table 1) and transferrin (Fig. 1), and a significant increase in estimated daily protein intake (Table 1). Following oral intake of the supplement, significant increases in body weight, BMI, mid-arm circumference and total lymphocyte count were observed (Table 1). Mean body weight increased by 550 g ($P < 0.001$) and mid-arm circumference increased by 20 mm ($P = 0.003$) at the end of the study. As shown in Fig. 1, there were significant increases in the serum levels of IGF-1 [from 111.3 (6.31) ng mL^{-1} at baseline to 127.1 (6.30) ng mL^{-1} at week 2, $P < 0.001$], pre-albumin [from 21.5 (0.74) mg dL^{-1} at baseline to 25.5 (0.93) mg dL^{-1} at week 2, $P < 0.001$] and transferrin [from 248.1 (5.14) mg dL^{-1} at baseline to 265.4 (4.67) mg dL^{-1} at week 2, $P < 0.001$] by 14%, 19% and 7%, respectively, at 2 weeks relative to the baseline levels (Fig. 1).

Lipid profiles, levels of aspartate aminotransferase, creatinine, blood urea nitrogen and inflammatory markers, estimated daily nutrient intake and physical activity level

During the 2-week preingestion period, there were no changes in serum lipid profiles, liver or kidney function test results, circulating inflammatory marker levels or estimated nutrient intake; however, daily protein intake was slightly but significantly increased (Table 1). Following oral administration of the supplement, a significant increase in the serum total cholesterol level and a significant decrease in the serum creatinine level were observed. As shown in Table 1, there was a significant decrease in serum IL-6 level ($P = 0.005$) and a trend toward a decrease in serum TNF-α level ($P = 0.072$). The decreases in levels of both IL-6 and TNF-α were 28% at week 2 relative to the baseline levels. Following oral administration of the supplement, dietary energy, carbohydrate, protein and fat intakes, as estimated by the dietary recall method, showed statistically significant increases. Two packs of nutritional supplementation were calculated to increase daily energy intake by 24% and daily protein intake by 26% (Table 1). Therefore, it is likely that the changes observed during the intervention reflect the impact of nutritional supplementation. Lastly, during the 2-week preingestion period, no significant changes were observed for TEE, BMR and PAL. Following oral administration of the supplement, TEE, BMR and PAL showed significant increases (Table 1).

Table 1 Clinical characteristics at time points during the study period

	Pre-treatment (week −2)	Baseline (week 0)	Post-treatment (week 2)	*F*	*P*
Weight (kg)	56.1 (1.05)[b]	56.0 (1.06)[b]	56.5 (1.07)[a]	18.389	<0.001
Body mass index (kg m^{-2})	22.2 (0.28)[b]	22.2 (0.28)[b]	22.4 (0.28)[a]	17.418	<0.001
Waist hip ratio	0.92 (0.01)	0.91 (0.01)	0.91 (0.01)	0.825	0.441
Middle arm circumference (cm)	26.0 (0.31)[a,b]	26.0 (0.31)[b]	26.2 (0.30)[a]	3.856	0.034
Tricep fold thickness (mm)	18.1 (0.77)	18.0 (0.77)	18.1 (0.78)	1.056	0.338
Systolic BP (mmHg)	122.7 (2.04)	120.3 (2.04)	121.9 (2.09)	1.730	0.182
Diastolic BP (mmHg)	77.8 (1.42)	77.2 (1.47)	77.6 (1.57)	0.192	0.826
Total lymphocyte count ($\times 10^3$ μL^{-1})†	2.15 (0.07)[a,b]	2.04 (0.07)[b]	2.22 (0.09)[a]	3.383	0.037
Serum albumin (g dL^{-1})†	4.61 (0.03)[a]	4.56 (0.03)[b]	4.59 (0.03)[a,b]	3.161	0.046
Serum iron (μg dL^{-1})†	111.6 (5.21)	109.3 (4.88)	105.3 (4.17)	0.413	0.663
Osmolality (mOsm per kgH_2O)	305.3 (0.98)	304.5 (1.07)	305.8 (1.15)	0.781	0.460
Glucose (mg dL^{-1})†	86.4 (0.98)	87.5 (1.18)	88.1 (1.46)	0.926	0.390
Insulin (uIU mL^{-1})†	9.30 (0.63)[b]	10.3 (1.11)[a,b]	10.9 (0.83)[a]	3.482	0.034
Total-cholesterol (mg dL^{-1})†	194.1 (4.03)[b]	195.1 (4.51)[b]	204.0 (4.71)[a]	9.097	<0.001
HDL-cholesterol (mg dL^{-1})†	53.2 (1.70)	53.3 (2.01)	55.3 (2.06)	2.915	0.058
LDL-cholesterol (mg dL^{-1})†	116.5 (4.33)	117.7 (4.83)	119.7 (4.93)	0.213	0.678
AST (IU L^{-1})†	24.5 (1.64)	23.8 (1.01)	25.1 (1.00)	2.427	0.093
Creatinine (mg dL^{-1})†	0.85 (0.03)[a]	0.84 (0.03)[a]	0.80 (0.03)[b]	7.044	0.002
Blood urea nitrogen (mg dL^{-1})†	15.7 (0.53)	15.5 (0.52)	16.5 (0.71)	1.902	0.154
TNF-α (pg mL^{-1})†	8.78 (1.14)[a]	8.46 (0.99)[a,b]	6.13 (0.68)[b]	4.479	0.014
IL-6 (pg mL^{-1})†	2.95 (0.50)[a,b]	2.98 (0.36)[a]	2.14 (0.28)[b]	5.268	0.007
IL-1β (pg mL^{-1})†	0.96 (0.08)	1.05 (0.08)	0.99 (0.11)	2.463	0.090
hs-CRP (mg L^{-1})†	1.53 (0.52)	1.24 (0.43)	0.92 (0.12)	0.590	0.556
Estimated daily nutrient intake					
Energy intake MJ [(kcal)]†	6.08 (1.19) [1454.2 (28.6)][b]	6.10 (1.17) [1458.7 (28.0)][b]	7.54 (1.22) [1803.1 (29.2)][a]	1142.615	<0.001
Carbohydrate (g)†	241.0 (6.30)[b]	242.0 (6.26)[b]	279.0 (4.59)[a]	74.891	<0.001
Protein (g)†	55.9 (1.67)[c]	57.0 (1.75)[b]	71.6 (1.20)[a]	130.964	<0.001
Fat (g)†	29.6 (1.20)[b]	29.1 (1.14)[b]	45.3 (0.81)[a]	94.766	<0.001
Total energy expenditure MJ [(kcal)]†	6.85 (1.26) [1638.2 (30.1)][b]	6.87 (1.27) [1641.1 (30.5)][b]	7.01 (1.22) [1675.3 (29.3)][a]	16.890	<0.001
Basal metabolic rate MJ [(kcal)]†	5.26 (1.19) [1256.1 (28.6)][b]	5.25 (1.21) [1254.1 (28.9)][b]	5.30 (1.22) [1266.5 (29.2)][a]	17.747	<0.001
Physical activity level†	1.32 (0.02)[b]	1.33 (0.02)[a,b]	1.34 (0.02)[a]	5.310	0.013

Data are the mean (SE). Data included 56 participants. One-way analysis of variance for repeated measures was used to calculated *P*-values. All alphabetical $P < 0.05$ was derived from Bonferroni post-hoc tests; no significant differences are marked with the same letter and significant differences are marked with a different letters.

†Tested by logarithmic transformation.

AST, aspartate aminotransferase; BP, blood pressure; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; LDL, low-density lipoprotein; TNF, tumour necrosis factor.

Correlations among age, serum protein levels and inflammatory marker levels

At baseline, age was negatively correlated with IGF-1 level ($r = -0.579$, $P < 0.001$) (Fig. 2) and positively correlated with IL-6 level ($r = 0.440$, $P = 0.001$) and TNF-α levels ($r = 0.465$, $P < 0.001$). The change (△, from baseline) in IGF-1 level was positively correlated with age ($r = 0.295$, $P = 0.027$) and negatively correlated with △IL-6 ($r = -0.675$, $P < 0.001$) and △TNF-α ($r = -0.552$, $P < 0.001$) (Fig. 2). There was a correlation between △IL-6 and △TNF-α ($r = 0.655$, $P < 0.001$). There was a positive correlation between △pre-albumin and △transferrin ($r = 0.282$, $P = 0.035$), whereas △hs-CRP was negatively correlated with △pre-albumin ($r = -0.555$, $P < 0.001$) and positively correlated with △IL-1β ($r = 0.328$, $P = 0.014$).

Discussion

Suboptimal nutrition and chronic low-grade increases in circulating cytokine levels are two major risk factors for frailty among elderly people [7,11]. The present study clearly showed that oral liquid nutritional supplementation over a period of 2 weeks significantly improved nutritional status and decreased circulating cytokine levels

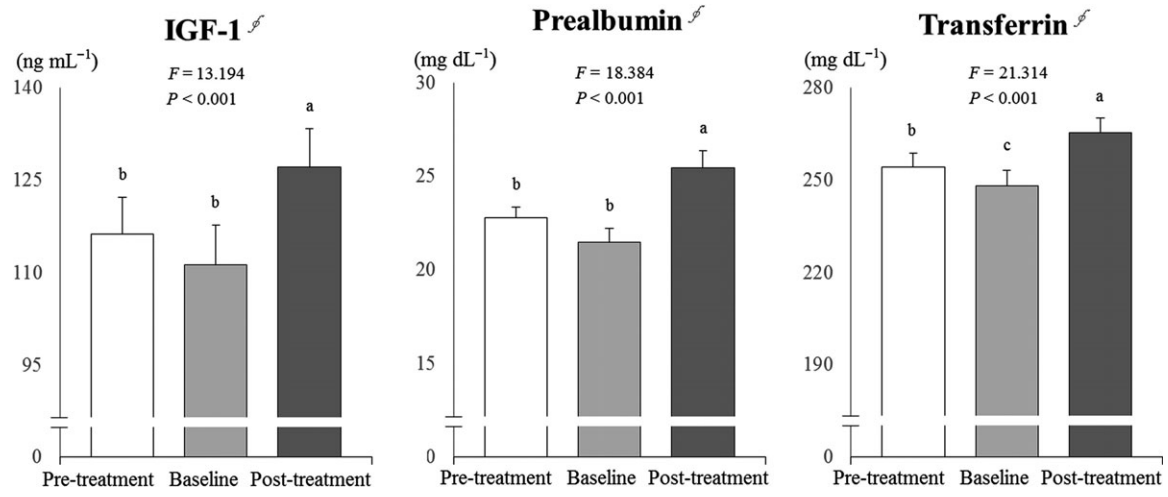

Figure 1 Pre-albumin, transferrin and insulin-like growth factor (IGF)-1 at pre-treatment (□), baseline (▒) and post-treatment (■) during the study period. Data are the mean (SE). Data included 56 participants. §Tested by logarithmic transformation. One-way analysis of variance for repeated measures was used to calculated *P*-values. All alphabetical $P < 0.05$ was derived from Bonferroni post-hoc tests; no significant differences are marked with the same letter and significant differences are marked with different letters.

in older community-dwelling people at risk of undernutrition. Especially, the change in the level of IGF-1, a sensitive marker reflecting nutritional status in the elderly [12], was negatively correlated with △IL-6 and △TNF-α. At baseline, study subjects consumed 108 kJ kg^{-1} day^{-1} (26 kcal kg^{-1} day^{-1}), which was below the recommended daily energy intake of 125 kJ kg^{-1} day^{-1} (30 kcal kg^{-1} day^{-1}) for weight maintenance with moderate activity [13] In practice, our study participants showed characteristics of sedentary activity according to Food and Agriculture Organization (FAO) of the United Nations standard (1.40–1.69, sedentary or light activity lifestyle; 1.70–1.99, active or moderately active lifestyle; 2.00–2.40, vigorous or vigorously active lifestyle) [10] and PAL criteria for Koreans (1.00–1.39, sedentary; 1.40–1.59, low active; 1.60–1.89, active; 1.90–2.50, very active) [14], even though PAL showed significant increase at post-treatment. Additionally, FAO reported that 113 kJ kg^{-1} day^{-1} (27 kcal kg^{-1} day^{-1}) is required for women with a mean age of 70 years and sedentary activity, and 121 kJ kg^{-1} day^{-1} (29 kcal kg^{-1} day^{-1}) is required for men with a mean age of 70 years and sedentary activity [10]. Thus, the consumption 108 kJ kg^{-1} day^{-1} (26 kcal kg^{-1} day^{-1}) was relatively inadequate for our study subjects. Following daily consumption of two packs of nutritional supplementation, daily energy intake was increased by 23% daily protein content was elevated by 25% (from 1.02 g kg^{-1} day^{-1} at baseline to 1.27 g kg^{-1} day^{-1} at week 2) based on the data from food records. One study of nitrogen balance in an ageing population (56–80 years) indicated a greater protein need among the elderly (1.14 g kg^{-1} day) than among the young (0.8 g kg^{-1} day^{-1}) [15]. The increases in the serum levels of IGF-1, pre-albumin and transferrin and in the total lymphocyte count in the present study were 14%, 19%, 7% and 9%, respectively, at week 2 compared to baseline. This result is in agreement with the previous observation of increased IGF-1 expression following daily amino acid supplementation in healthy older women [16]. Additionally, IGF-1 and pre-albumin have been suggested to be more sensitive indicators of malnutrition than classical protein intake markers such as albumin, transferrin and total lymphocyte count [12]. Therefore, the improvements in nutritional status observed after the 2-week intervention likely reflect the impact of nutritional supplementation in the present study.

Protein intake upregulates IGF-1 synthesis and bioactivity, whereas energy restriction is associated with reduced IGF-1 levels [17]. In the present study, nutritional supplement intervention with nutrients modulating IGF-1 induced a weak but significant age-related increase in IGF-1 concentration. This effect might have resulted from the standard age-related decline in the level of IGF-1, a sensitive marker reflecting changes in nutritional status, especially among the elderly [12]. When energy or protein deprivation occurs, there is a significant reduction in the plasma levels of IGF-1 [18]. However, in malnourished subjects consuming food to repletion, the increase in IGF-1 levels has been shown to be much stronger than the changes in levels of serum markers of nutritional status. IGF-1 is an anabolic hormone that plays an active role in the maintenance of muscle mass and strength that promotes muscle protein synthesis [12,19]. In the present study, compared to baseline, oral nutritional

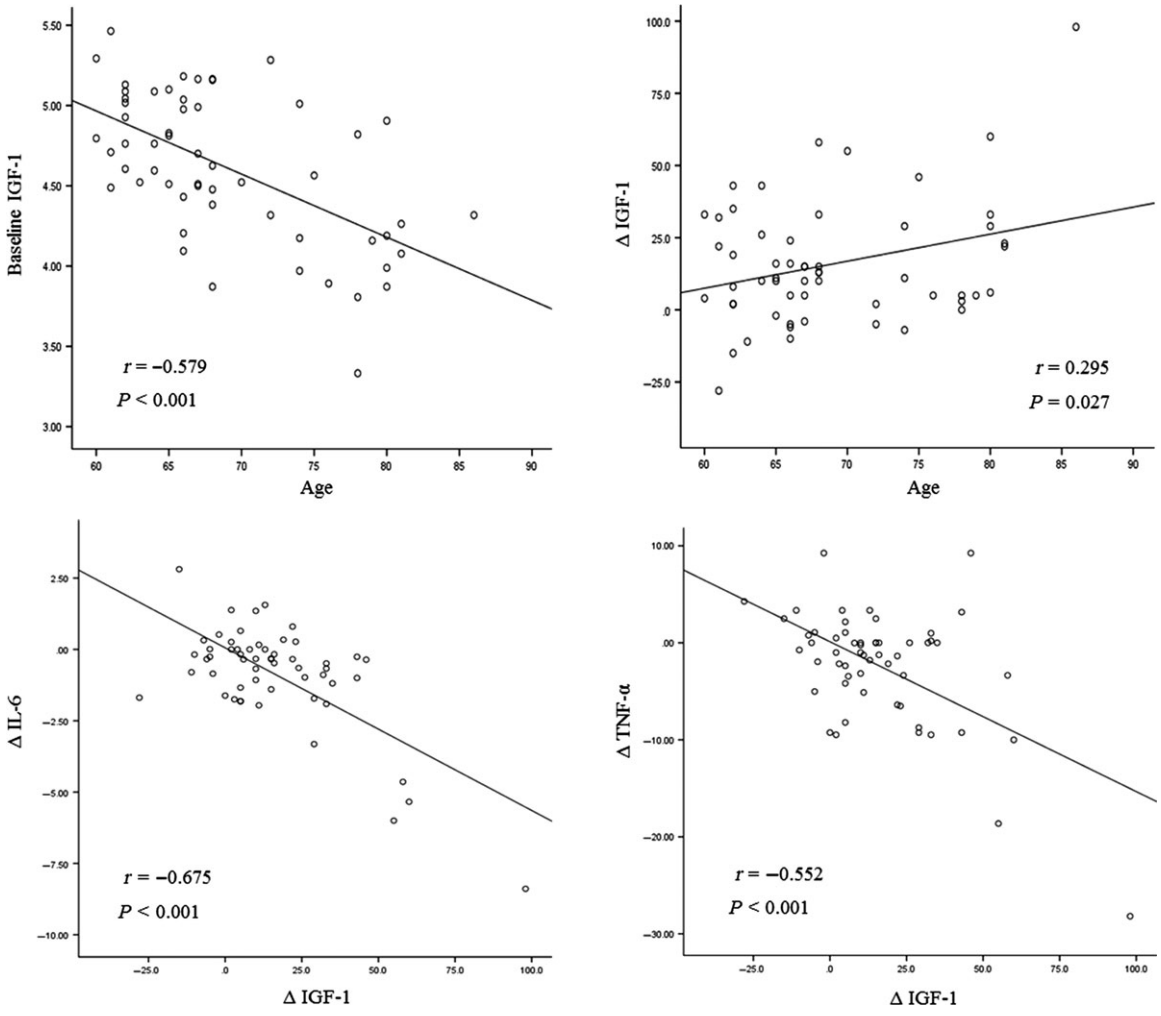

Figure 2 Correlations among age, baseline insulin-like growth factor (IGF)-1 and changes in IGF-1 and inflammatory cytokines. *r*, Pearson correlation coefficient.

supplementation significantly increased body weight and mid-arm circumference at the end of the intervention period without changing the tricep skinfold thickness. Kim *et al.* [20] suggested that increasing protein and energy contents via supplementation can enhance skeletal muscle regeneration in elderly subjects. Moreover, Colbert *et al.* [21] showed a relationship between low circulating IGF-1 levels and small thigh muscle area in a cohort of elderly subjects.

Changes in IGF-1 synthesis and bioactivity warrant special attention because these factors are involved in the integration of nutritional, endocrine and inflammatory pathways [12]. Low IGF-1 levels are associated with high IL-6 and TNF-α levels in community-dwelling elderly subjects [19,22,23]. The circulating levels of inflammatory cytokines increase with age, leading to a subclinical inflammatory state.[8,24] Similar to previous studies, the present study showed an age-related decrease in IGF-1 level and age-related increases in IL-6 and TNF-α levels. Additionally, changes in IGF-1 expression were negatively correlated with changes in the IL-6 and TNF-α levels. Solerte *et al.* [23] also suggested that anabolic conditions are related to IGF-1 availability following oral nutritional supplementation with an amino acid mixture based on their observations of a significant reduction in the serum TNF-α level and a significant increase in the serum IGF-1 level in elderly subjects after the intervention. Furthermore, an antagonistic relationship between levels of inflammation markers and levels of IGF-1 expression and activity has been reported [22]. The present data demonstrated that oral intake of nutritional supplements by community-dwelling elderly subjects at risk of undernutrition resulted in significant changes in levels of inflammatory cytokines and growth factor pathway members. In

effect, we found a reduction in the levels of catabolic cytokines, including IL-6 and TNF-α, and an increase in levels of the anabolic growth factor IGF-1, with consequent increases in IGF-1/IL-6 and IGF-1/TNF-α ratios. Thus, these results demonstrate a transition from catabolic to anabolic conditions.

Although the results of the present stuudy showed a significant benefit of oral nutritional supplementation, one should consider the potential limitations. First, most importantly, the study design was not randomised or placebo-controlled. However, to minimise bias, we implemented a baseline control period followed by an intervention period, and all aspects of therapy (nutritional counseling, etc.) remained constant during these two periods. Second, a gap between actual dietary intake analysis and theoretical values of nutrients was observed. If our study participants ingested the supplement 100% regularly and perfectly maintained their eating habits during the study period, carbohydrate, protein and fat might be 302.0, 73.0 and 41.1 g, respectively (increase of 60 g of carbohydrate, 16 g of protein, and 12 g of fat compared to baseline values) at post-treatment. However, subjects were included in the present study once they ingested greater than 80% of the prescribed supplement. Therefore, a rate of increase of the major nutrient might be below the theoretical level. Additionally, all participants recorded 3-day dietary record by themselves at home. Although they had received detailed explanation regarding a record completion method from a dietitian, habitual eating patterns might be affected by the recording process. Third, the study subjects were provided with oral supplements that they do not intake usually before regular meals; therefore, variables such as satiety might be influenced to the subjects' eating patterns. Indeed, when we analysed daily food patterns using 3-day dietary record, major carbohydrate sources such as cereals, grains and their products, and root/tuber crops and their products, which are the staple food of Koreans, were decreased at post-treatment after excluding the intake amount of oral supplements. However, after considering the intake amount of oral supplement, total carbohydrate consumption was increased. This means that, for nutrition replenishment, the ingestion of oral nutrient supplements above a certain level is surely helpful for undernourished community-dwelling elderly people, even though slight changes in daily food patterns are observed. Finally, we observed a significant increase in BMI after 2-week oral supplementation. Thus, the use of prolonged supplements for more than 2 weeks requires caution because it may lead to obesity.

Despite these limitations, the results of the present study confirm that oral intake of a nutritional supplement by community-dwelling elderly subjects at risk of undernutrition can be conducted with a high degree of compliance and that the nutritional status and anthropometric parameters of these subjects can improve as a result of the use of a supplement. Furthermore, the improvement in nutritional status in the present study, especially the increase in IGF-1 level, suppressed the 'chronic low grade increases in the circulating cytokines' that are typically observed in elderly people [10]. Therefore, nutritional screening and early intervention are important for encouraging the elderly population at risk of undernutrition to comply with nutritional guidelines.

In conclusion, a 2-week intervention with oral nutritional supplementation improved nutritional status and decreased circulating cytokine levels. Specifically, changes in IGF-1 were negatively correlated with changes in the levels of pro-inflammatory cytokines in community-dwelling elderly people at risk of undernutrition. The results observed in the present study suggest a need to reinforce nutrition interventions in prefrail and community-dwelling frail older adults, rather than wait for patients to be institutionalised as a result of increased dependency.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with CONSORT/STROBE/PRISMA guidelines.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

This research was carried out with the support of 'Cooperative Research Program for Agriculture Science & Technology Development (Project title: Development of functional material for immune enhancement using Weissella cibaria, Project No: PJ010835)' Rural Development Administration, Republic of Korea.

All authors contributed to the conception and design of the paper. MK and MK analysed and interpretated data, and prepared the manuscript. YJL, HJS, JKS, DHC, WKY and S-HL acquired and analysed data. JHL acquired, analysed and interpreted data, and prepared the manuscript. All authors contributed to the critical revision of the paper and have approved the final manuscript submitted for publication.

References

1. Colby SL, Ortman JM. Projections of the size and composition of the US population: 2014 to 2060. Report No. P25-1143. Washington, DC: United States Census Bureau, US Department of Commerce; 2015.
2. Cruz-Jentoft AJ, Calvo JJ, Durán JC *et al.* (2008) Compliance with an oral hyperproteic supplement with fibre in nursing home residents. *J Nutr Health Aging* **12**, 669–673.
3. De Luis DA, De la Fuente B, Izaola O *et al.* (2015) Clinical effects of a hypercaloric and hyperproteic oral suplemment enhanced with w3 fatty acids and dietary fiber in postsurgical ambulatory head and neck cancer patients. *Nutr Hosp* **31**, 759–763.
4. Dupuy C, de Souto Barreto P, Ghisolfi A *et al.* (2015) Indicators of oral nutritional supplements prescription in nursing home residents: a cross-sectional study. *Clin Nutr* **35**, 1047–1052.
5. Myint MW, Wu J, Wong E *et al.* (2013) Clinical benefits of oral nutritional supplementation for elderly hip fracture patients: a single blind randomised controlled trial. *Age Ageing* **42**, 39–45.
6. Sungur G, Sahin H & Tasci S (2015) The effects of implementing a nutritional support algorithm in critically ill medical patients. *J Pak Med Assoc* **65**, 810–814.
7. Piantadosi C, Chapman IM, Naganathan V *et al.* (2015) Recruiting older people at nutritional risk for clinical trials: what have we learned? *BMC Res Notes* **8**, 151.
8. Paik JK, Kim M, Kim M *et al.* (2015) Circulating Lp-PLA_2 activity correlates with oxidative stress and cytokines in overweight/obese postmenopausal women not using hormone replacement therapy. *Age (Dordr)* **37**, 32.
9. Caglar K, Fedje L, Dimmitt R *et al.* (2002) Therapeutic effects of oral nutritional supplementation during hemodialysis. *Kidney Int* **62**, 1054–1059.
10. Nutrition Division. Human energy requirements: Report of a Joint FAO/WHO/UNU Expert consultation. Report No. Y5686. Rome: Food and Agriculture Organization (FAO) of the United Nations, Italy. Agriculture and Consumer Protection; 2004.
11. Kim OY, Chae JS, Paik JK *et al.* (2012) Effects of aging and menopause on serum interleukin-6 levels and peripheral blood mononuclear cell cytokine production in healthy nonobese women. *Age (Dordr)* **34**, 415–425.
12. Maggio M, De Vita F, Lauretani F *et al.* (2013) IGF-1, the cross road of the nutritional, inflammatory and hormonal pathways to frailty. *Nutrients* **5**, 4184–4205.
13. Subcommittee on the Tenth Edition of the Recommended Dietary Allowances; Food and Nutrition Board; Commission on Life Sciences; National Research Council. Recommended dietary allowance; 10th edn. pp. 32-33. Washington, DC: National Academies Press; 1989.
14. Ministry of Health and Welfare, The Korean Nutrition Society. Dietary Reference Intakes for Koreans 2015. Report No. 11-1352000-001537-14. Sejong City: Ministry of Health and Welfare, Korea. Division of Health Promotion; 2015.
15. Campbell WW, Crim MC, Dallal GE *et al.* (1994) Increased protein requirements in elderly people: new data and retrospective reassessments. *Am J Clin Nutr* **60**, 501–509.
16. Dillon EL, Sheffield-Moore M, Paddon-Jones D *et al.* (2009) Amino acid supplementation increases lean body mass, basal muscle protein synthesis, and insulin-like growth factor-I expression in older women. *J Clin Endocrinol Metab* **94**, 1630–1637.
17. Martín MA, Serradas P, Ramos S *et al.* (2005) Protein-caloric food restriction affects insulin-like growth factor system in fetal Wistar rat. *Endocrinology* **146**, 1364–1371.
18. Norat T, Dossus L, Rinaldi S *et al.* (2007) Diet, serum insulin-like growth factor-I and IGF-binding protein-3 in European women. *Eur J Clin Nutr* **61**, 91–98.
19. Maggio M, Ceda GP, Lauretani F *et al.* (2010) Association of plasma selenium concentrations with total IGF-1 among older community-dwelling adults: the InCHIANTI study. *Clin Nutr* **29**, 674–677.
20. Kim JS, Wilson JM & Lee SR (2010) Dietary implications on mechanisms of sarcopenia: roles of protein, amino acids and antioxidants. *J Nutr Biochem* **21**, 1–13.
21. Colbert LH, Rosen CJ, Goodpaster BH *et al.* (2004) Insulin-like growth factor-1. *J Am Geriatr Soc* **52**, 1962–1963.
22. Barbieri M, Ferrucci L, Ragno E *et al.* (2003) Chronic inflammation and the effect of IGF-I on muscle strength and power in older persons. *Am J Physiol Endocrinol Metab* **284**, E481–E487.
23. Solerte SB, Gazzaruso C, Bonacasa R *et al.* (2008) Nutritional supplements with oral amino acid mixtures increases whole-body lean mass and insulin sensitivity in elderly subjects with sarcopenia. *Am J Cardiol* **101**, 69E–77E.
24. Ferrucci L, Corsi A, Lauretani F *et al.* (2005) The origins of age-related proinflammatory state. *Blood* **105**, 2294–2299.

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

CHILDREN

Validity of short food questionnaire items to measure intake in children and adolescents: a systematic review

R. K. Golley,[1] L. K. Bell,[2] G.A. Hendrie,[3] A.M. Rangan,[4] A. Spence,[5] S. A. McNaughton,[5] L. Carpenter,[6] M. Allman-Farinelli,[4] A. de Silva,[6] T. Gill,[4] C.E. Collins,[7] H. Truby,[8] V. M. Flood[4] & T. Burrows[7]

[1]University of South Australia, Adelaide, SA, Australia
[2]Flinders University, Adelaide, SA, Australia
[3]CSIRO, Adelaide, SA, Australia
[4]University of Sydney, Sydney, NSW, Australia
[5]Deakin University, Melbourne, VIC, Australia
[6]University of Melbourne, Melbourne, VIC, Australia
[7]University of Newcastle, Newcastle, NSW, Australia
[8]Monash University, Melbourne, VIC, Australia

Keywords
adolescent, child, food intake, short food question, validity.

Correspondence
R. Golley, School of Pharmacy and Medical Sciences, Division of Health Sciences, University of South Australia, GPO Box 2471, Adelaide, South Australia 5000 IPC CEA 19, Australia.
Tel.: +61 8 8302 2507
Fax: +61 8 8302 2389
E-mail: rebecca.golley@unisa.edu.au

How to cite this article
Golley R.K., Bell L.K., Hendrie G.A., Rangan A.M., Spence A., McNaughton S.A., Carpenter L., Allman-Farinelli M., de Silva A., Gill T., Collins C., Truby H., Flood V.M. & Burrows T. (2017) Validity of short food questionnaire items to measure intake in children and adolescents: a systematic review. *J Hum Nutr Diet*. **30**, 36–50
doi: 10.1111/jhn.12399

The authors are members of the Food and Nutrition stream of the Australian Child and Adolescent Obesity Research Network (ACAORN).

Abstract

Background: Short food questions are appealing to measure dietary intakes.
Methods: A review of studies published between 2004 and 2016 was undertaken and these were included in the present study if they reported on a question or short item questionnaire (≤50 items, data presented as ≤30 food groups) measuring food intake or food-related habits, in children (aged 6 months to 18 years), and reported question validity or reliability. Thirty studies met the inclusion criteria.
Results: Most questions assessed foods or food groups (n = 29), with the most commonly assessed being fruit (n = 22) or vegetable intake (n = 23), dairy foods and discretionary foods (n = 20 studies each). Four studies assessed food habits, with the most common being breakfast and meal frequency (n = 4 studies). Twenty studies assessed reliability, and 25 studies determined accuracy and were most commonly compared against food records. Evaluation of question performance relied on statistical tests such as correlation.
Conclusions: The present study has identified valid and reliable questions for the range of key food groups of interest to public health nutrition. Questions were more likely to be reliable than accurate, and relatively few questions were both reliable and accurate. Gaps in repeatable and valid short food questions have been identified that will provide direction for future tool development.

Introduction

There is growing evidence to suggest that a nutrient-centric approach may lose valuable evidence about the relationship between food, dietary patterns and protection from disease. In recent years, food-based dietary guidelines and compliance with recommended food intakes requires monitoring. A shift in the focus of guidelines away from being nutrient-based has led to increased interest in dietary assessment methods that accurately and reliably measure food intake. Such methods provide the capacity for the rapid reporting of food intake, particularly for monitoring population dietary intake, compliance with dietary guidelines and changes in population intake [1,2].

Short questionnaire-style dietary assessment methods, often called short food questionnaires/surveys/screeners,

or checklists are an appealing brief dietary assessment method. Short food questionnaires (SFQs) can be tailored to the research question or dietary outcome(s) of interest by selecting a tailored combination of relevant items. Although no standard definition exists, they are usually approximately 50 items in length and 'Questionnaire-style' [i.e. they ask about the frequency or servings (portions) of discrete food or beverage items or groups]. Unlike food records, 24-h dietary recalls and traditional Food Frequency Questionnaires (FFQ) that aim to capture the total diet, short instruments assess limited aspects of the diet. They are also quick to administer in a variety of formats (e.g. hard copy, via telephone, via technology such as the Internet or mobile devices), have low a respondent burden, can be self-completed, and can be precoded to aid in data entry and analysis [3].

Similar to any dietary assessment method, the performance of a SFQ needs to be examined in terms of both reliability and accuracy. Traditional questionnaires that measure diet such as FFQ are often lengthy and commonly used for their ranking ability, as well as to derive valid estimates of energy or nutrient intake. By contrast, SFQs need to be evaluated in terms of the performance (validity and reliability) of individual questions (items) to assess food intake. Understanding how SFQs perform in different populations, including children and adolescents, and via different reporting methods (i.e. in person or online) is important. Food intake patterns, portion sizes and cognitive processes differ between adults and children, and the performance of SFQs needs to be demonstrated in different population groups (e.g. age groups, sexes, ethnicities).

To date, evaluation of studies testing the validity of SFQs is limited to unpublished reports aiming to recommend the inclusion of SFQ items in national monitoring surveys [2,4]. A now outdated 2010 report identifying tools internationally appropriate for use in large populations found eleven tools with validation studies, with six measuring children's intake. [5] To our knowledge, no recent or published systematic review of the international scientific literature has been undertaken. The aim of this systematic review is to identify and critique validation studies evaluating the performance of individual SFQ items to measure food intake in children and adolescents.

Materials and methods

A systematic literature search was performed to identify published validation studies evaluating the performance of individual SFQ items estimating food intake or food habits of children and adolescents using *a priori* specified inclusion and exclusion criteria.

Inclusion and exclusion criteria

Types of studies

Studies reporting on the reliability or relative validity of individual food group questions (items) that estimate food intake or habits were included. Studies evaluating cognitive processes (e.g. accuracy of portion size estimation) were excluded.

Types of participants

Studies assessing the dietary intake of healthy children (free of disease) and adolescents (6 months to 18 years) were included. Studies were excluded if infants were exclusively breastfed or formula fed, or no subgroup analysis was reported for the age range of interest. Studies involving samples of preterm infants, children with disabilities, pregnant or lactating females, health conditions (e.g. asthma, cystic fibrosis), behavioural/learning difficulties and clinical samples were also excluded.

Type of dietary assessment tools

Short questionnaire-style dietary assessment methods, such as FFQs, surveys, screeners, questionnaires or checklists, were included. For the purpose of this review, 'short' was defined as being no more than 50 dietary questions/items (e.g. yoghurt, cheese, milk) in length [6] AND reporting food intake on no more than 30 food groups (e.g. dairy) (i.e. food group intake estimated from no more than a few short food questions that could stand alone). 'Questionnaire-style' was defined as including items that ask about the frequency or servings (portions) of discrete food or beverage items or groups. Questions/items could be qualitative, semi-quantitative or quantitative in relation to portion or serving size. Dietary assessment methods such as 24-h recalls, diet histories or food diaries/records were excluded because they are not considered as short tools.

Types of outcome measures

Studies reporting on the reliability or relative validity of questions estimating food (e.g. yoghurt, cheese, milk), food group (e.g. dairy) or food habits (breakfast consumption, meal frequency) were included. Studies reporting only nutrient intake, diet quality (e.g. index or dietary pattern scores), supplementation, infant feeding practices (e.g. breastfeeding/formula feeding, complementary feeding practices), eating behaviours (e.g. eating in absence of hunger, food neophobia), food preferences, other non-food intake outcomes (e.g. food allergies, disordered eating, body image, food security, behavioural outcomes) or parental food intake were excluded.

Other criteria

Studies included were limited to those published between 2004 and March 2016 in the English language.

This time frame was selected because previous reviews have covered studies until 2004 and this is when food-based guidelines begun to arise in the literature and to be used in National recommendations. Studies published in abstract or thesis format only were excluded.

Search and selection of included articles

A comprehensive and systematic search was undertaken of the eight databases: CINAHL, Medline, Medline in Process, EMBASE (Excerpta Medica Database), Web of Science, Scopus, TROVE and PsycINFO. Dietary assessment methodology repositories and Google Scholar were searched to identify any relevant tools or papers in the grey literature. These were cross-checked with the published literature. Search terms were pilot tested, refined and tailored to each database by an information technologist expert. Keywords were searched within four categories (using 'OR') and then combined (using 'AND'): (i) population (e.g. *infant*, *toddler*, *preschool*, *child*, *boy*, *girl OR adolescent*) AND (ii) dietary assessment tool/data collection method (e.g. questionnaire, diet surveys, record, checklist OR screener/screening) AND (iii) dietary outcome (e.g. *food*, *diet*, *beverages*, *meal/s*, *eat OR snack*) AND (iv) type of study (e.g. *validity*, *reliability*, *reproducibility OR performance*). The search strategy specific terms used in each database are provided in the Supporting information, Tables 1-5). After searching, duplicates were removed and lists of all identified studies were screened for additional studies. The title and abstract of each study was screened independently against the inclusion/exclusion criteria by two reviewers. Full texts of remaining articles were then screened against the review criteria by two reviewers. Where disagreements were identified, a third reviewer made a final decision.

Data extraction and analysis

Data from each included study were extracted and checked by two reviewers into standardised tables. Data extracted included sample characteristics (age, ethnicity, weight status) and dietary assessment methodology details (tool type, foods captured, response variable, recall period, administration method), as well as reliability and relative validity data for individual SFQs. Two reviewers independently scored the validation study methodology quality using the tool described in Serra-Majem *et al.* [7], which has been used previously [8] but was adapted for the current review as described below. Scores range from 0 (poorest quality) to a maximum of 7 (highest quality) with components including sample and sample size (maximum 1 point), type of statistics used to assess validity (3 points), administration method (0.5 points), food grouping detail provided (1.0), frequency scale and portion size consideration (1.0 point), and consideration of seasonality (0.5 points). A summary score of the components was calculated. The maximum score was seven and studies were rated as: poor (≤2), acceptable (≥2.5 to <3.5), good (≥3.5 to <5) or excellent (≥5.0). Any discrepancies were resolved by a third reviewer.

Data were assessed and synthesised based on the interpretation of a range of statistics to evaluate the performance of individual SFQs in terms of reliability (i.e. tool reproducibility or repeatability using a test–retest procedure [9,10] and relative validity [i.e. the ability to accurately measure food consumption data that represents the true intake of the individual [10,11], determined by comparison with an already validated tool/method]. Each SFQ was coded using standardised criteria, which was determined by expert consensus at the annual meeting of the Food and Nutrition Stream of the Australasian Child and Adolescent Obesity Research Network. Tool items were coded as reliable and/or accurate (i.e. performed well) based on three criteria: (i) nonsignificant difference between measures if $P > 0.05$ or with a confidence interval that includes 1.0 in mean or median intakes between repeated measures of a tool or between two methods; (ii) adequate association with a Pearson or Spearman correlation of >0.5[12]; and (iii) adequate agreement demonstrated by an intra-class correlation >0.5[13] or kappa statistic > 0.6 (Table 1). Where possible, the strength of agreement was interpreted as poor (kappa = <0.20), fair (kappa = 0.21–0.40), moderate (kappa = 0.41–0.60), good (kappa = 0.61–0.80) or very good (kappa = 0.81–1.0). Bland–Altman and percentage agreement analyses were also considered as tests of agreement between methods. However, these data are interpreted in the text where available because no critique criteria could be identified for these statistics. Data were then summarised according to common food groups. Food groups included 'core' foods and beverages [e.g. fruits; vegetables; cereals (e.g. bread, rice, pasta, noodles); meat and alternatives (e.g. fish, eggs, nuts); dairy; fats and oils; water]; and/or discretionary (energy-dense, high added saturated fat/sugar/sodium, low nutrient) foods [14,15]. For some of the mentioned food groups, several questions were separated out. These included: juice intake, legume intake, wholegrains and artificially sweetened (diet) versions of sweetened drinks. Where food groups were based on several items, the intake estimate was considered reliable and/or accurate (i.e. performing well) if >50% of items for that food group met the criteria outlined above.

Results

Study characteristics

Thirty articles met the review criteria (Fig. 1) and are described in Table 2. The majority of studies were conducted in the USA (n = 12) and Australia (n = 8). Study sample size ranged from 35 [16,17] to 4487 [1], with the majority (n = 18 studies) having a sample size greater than 100. The majority of samples were of Caucasian (European) ethnicity, with studies from the USA tending to include multi-ethnic samples. Child age within study samples ranged between 1 and 18 years, with five studies focusing on children aged <5 years, 13 studies on children aged 5–11 years and eight studies on children ≥12 years. Scoring against a validation study methodology quality tool [7] showed that eight studies were rated as poor, four as acceptable, 11 as good and seven as excellent quality. In addition, 11 studies reported on study sample weight status. Of those described as percentage overweight or obese (n = 7), participants ranged from 16% overweight/obese

Table 1 Criteria for interpretation and coding of reliability and accuracy data

Statistical approach	Statistical tests considered	Criteria indicating adequate performance
Group differences between administrations (reliability) or between methods (accuracy)	*t*-tests	$P > 0.05$* or CI includes 1.0*
Tests of association between administrations (reliability) or between methods (accuracy)	Pearson or Spearman correlation	$r > 0.5$
Tests of agreement between administrations (reliability) or between methods (accuracy)	ICC	ICC > 0.5
	kappa statistic	kappa > 0.6

*Adequate performance where no significant difference between repeated measures of a tool or between two methods is observed. CI, confidence interval; ICC, intraclass correlation.

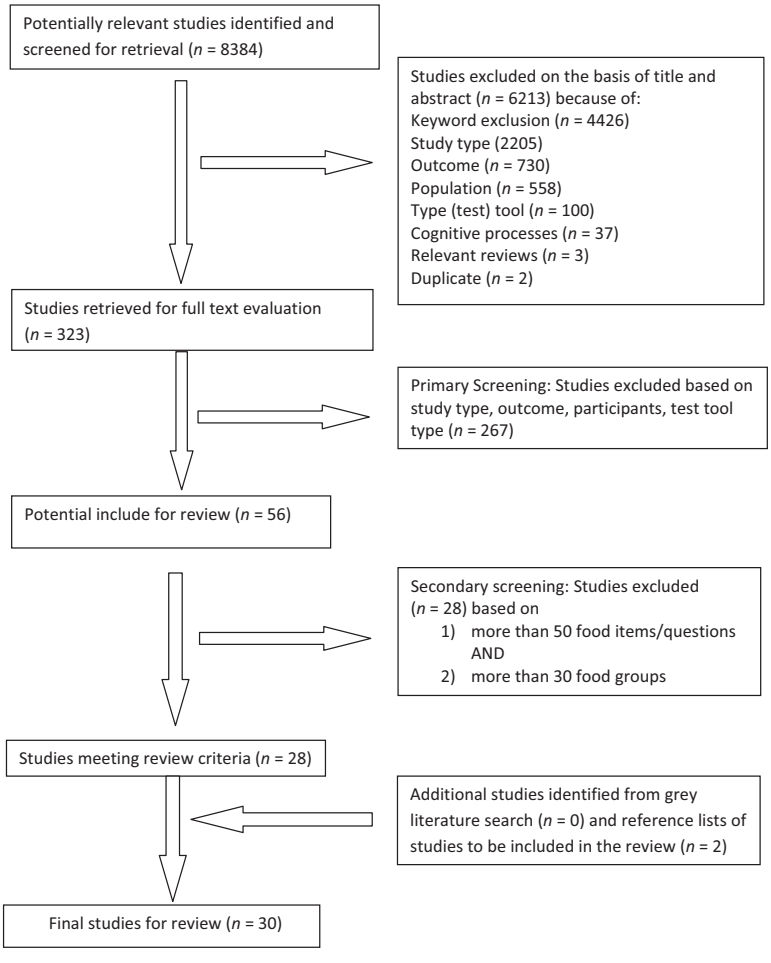

Figure 1 QUOROM flow diagram [34]. Validation studies assessing children's food intake using short food questions.

Table 2 Study sample characteristics and questionnaire details of included studies

Study	Questionnaire details			Administration method		Population				Reliability	Validity	Study quality[†]
Study, first author (year), country	Tool type: number of items[‡]	Response variables	Recall period	Respondent or interviewer: paper or computer assisted	Intake reported by:	Sample size; ethnicity[§]	Age range mean (SD)	Sex	Weight status	Period between repeat administ-ration	Reference method	Score (/7)
Antonogeorgos (2013), Greece [22]	FFQ: 63	Fq	Usual	Respondent: Paper	Parent	*n* = 124; NR	10–12 y 10.9 (1.2) y	37% M	27% ow/ob	NA	3DFR	4
Bell (2014), Australia [21]	FFQ: 19	Fq & portion size	7 d	Respondent: Paper	Parent	*n* = 111	12–36 mo 23.0 (6.9) mo	54% F	NR	1–11.9 wks, mean (SD) 3.2 (1.8)	FFQ	2.5
Bennett (2009), Australia [35]	Q: NR	no. serves	1 d	Respondent: Paper	Parent	*n* = 90	2–5 y 3.98 (0.98) y	56% F	NR	NA	1 × 24HDR	1.5
Bjelland (2014) Norway [36]	Q44	Fq	Usual	Respondent: Paper	Child	*n* = 440	14.3 (0.6); 91% Norwegian	52% F	NR	10–14 d	NA	4
Davis (2009), USA [17]	Screener: 22	Fq & no. times	1 mo	Respondent: Paper	Child	*n* = 35, Latino	14–17 y NR	100% F	100% ow/ob	7–14 d	3DFR	2
Eaton (2013), USA [37]	SFS: 14	Fq & no. cups	7 d & 1 d & usual	Respondent: Paper	Child	*n* = 610; Multi-ethnic	14–18 y NR	51% F	NR	NA	1 × 24HDR	2
Economos (2008), USA [38]	SFQ: 8	Yes/no variable	1 d	Interviewer; Paper	Child	*n* = 84	6–9 y 8.3 (1.1) y	54% F	NR	1–2 h	Observation	2
Fahlman (2012), USA [28]	SFS: 20	no. times	1 d	Respondent: Paper	Child	*n* = 387; Multi-ethnic	NR13 (0.4–1) y	52% F	NR	5 h	1 × 24HDR	3.5
Flood (2014), Australia [24]	FFQ: 17	Fq & servings & no. cups	1 y	Interviewer: Phone	Parent	*n* = 77 (reliability), *n* = 64 (validity)	2–5 y 3.6 (0.94) y	NR	NR	2 wks	3DFR	5.5
Guldan, (2015), China [39]	Q: 17	Fq+2	NR	Respondent; paper	Child	*n* = 1301 (reliability), *n* = 357 (validity)	11.6 (0.7) y (reliability), 11.5 (0.6) y (validity)	54% M (reliability), 55% M (validity)	NR	2 wks	3 × 24HDR	3
Gwynn (2011), Australia [19]	FFQ: 28	Fq & food type	Usual	Respondent: Paper	Child	*n* = 241 (reliability) *n* = 205 (validity); included indigenous	10–12 y 10.8 (0.7) y	42% M	NR	2 wks	1 × 24HDR	4.5
Haraldsdottir (2005), Europe[¶] [40]	FFQ:6	Fq	Usual	Respondent: Paper	Child	*n* = 60–74 (reliability) *n* = 43–60 (validity)	11–12 y NR	39–69% F	NR	7–12 d	7DFR	5
Hendrie (2013), Australia [1]	SFS: 3	no. serves & food type	Usual	Respondent: Computer assisted	Parent (2–8 y); Child (9–16 y)	*n* = 4487	2–16 y NR	50% M	27.2% ow/ob	NA	1 × 24HDR	5
Hendrie (2014), Australia [18]	SFS: 38	no. serves & no. cups & no. times	Usual	Respondent: Computer assisted	Parent	*n* = 63	4–11 y 7.1 (2.1) y	56% M	15.9% ow/ob	1 wk	1 × 24HDR	6

Table 2. Continued

Study	Questionnaire details			Administration method		Population				Reliability	Validity	Study quality†
Study, first author (year), country	Tool type: number of items‡	Response variables	Recall period	Respondent or interviewer: paper or computer assisted	Intake reported by:	Sample size; ethnicity§	Age range mean (SD)	Sex	Weight status	Period between repeat administ-ration	Reference method	Score (/7)
Huybrechts (2009), Belgium [23]	FFQ:6	Fq	1 y	Respondent: Paper	Parent	*n* = 650 (validity) *n* = 124 (reliability)	2.5–6.5 y NR	NR	NR	5 wks	3DFR	6
Leatherdale (2013), Canada [29]	Q: 4	Servings	1 d	Respondent: Paper	Child	*n* = 178	14–15 y NR	53% F	NR	7 d	7DFR (online)	4
Lillegaard (2012), Norway [20]	FFQ: 21	Glasses/mo, week or day & Fq/mo, week or day	1 y	Respondent: Paper	Child	*n* = 733 (9 y) *n* = 904 (13 y)	9 y 8.9 (0.3 y 13) y 12.9 (0.3) y	50–52% F	NR	NA	4-d precoded FR	3.5
Lim (2015), USA [26]	Q: 2	Cups per day'	Most days	Respondent: paper	Child	*n* = 100; multi-ethnic	3rd grade	50% M	NR	NA	24HDR	5.5
Magarey (2009), Australia [25]	Q: 28	Variety & Fq	1 wk or 1 d	Interviewer/ Respondent; Paper	Parent	*n* = 193 (validity) *n* = 116 (reliability)	4–16 y NR	NR	16% ow	10 d (5–57 d)	7 d food checklist	4
Nelson (2009), USA [41]	Screener: 22	Fq & portion size & no. times/mo, week or day	1 mo	Respondent: Paper	child	*n* = 59 (validity) *n* = 33 (reliability)	11–18 y NR	45% M	NR	2–21 d (most 7–14 d)	3 × 24HDR	2
Neuhouser (2009), USA [42]	FFQ:19	Fq	1 wk	Respondent: Paper	Child	*n* = 46	7th grade 12.7 y	61% F	NR	4–6 wks	4DFR	1
Olsen (2014), USA [43]	SFS: 7	no. times or no. glasses	7 d	Respondent: Paper	Child	*n* = 610; Multi-ethnic	Grade 9–12 NR	51% F	NR	NA	3 × 24HDR	4
Penkilo (2008), USA [27]	Q: 43	Fq	1d	Respondent: Paper	Child	*n* = 322; Multi-ethnic	9–12 y 9.71 y	52% F	NR	2 h	NA	1.5
Prochaska (2004), USA [44]	Screener: 2	no. serves	Usual	Respondent: Paper & computer assisted	Child	*n* = 138; Multi-ethnic	NR 12.1 (0.9) y	65% F	NR	0 d–1 mo	3DFR	5.5
Randall Simpson (2008), Canada [45]	Screener: 17	Fq	NR	Respondent: Computer assisted	Parent	*n* = 140; Multi-ethnic	3–5 y NR	94% F	NR	2–4 wks	Interviewer DH	3
Thiagarajah (2008), USA [46]	FFQ: 54	Fq	1 d	Respondent: Paper	Child	*n* = 110; Multi-ethnic	9–11 y 10.31 (0.5) y	53% F	NR	NA	1 × 24HDR	3.5
Vandevijvere (2013), Europe[47]	FFQ: 15	Fq	1 d	Respondent: Paper	Child	*n* = 390	12.5–17.5 y 14 (1) y	42% M	NR	NA	2 × 24HDR	1.5
Vereecken (2008), Belgium Italy [48]	FFQ: 14	Fq	Usual	Respondent: Paper	Child	*n* = 112 Flemish, *n* = 114 Italian	11–12 y 11 (0.5) y	36–52% M	NR	1 wk	7DFR	4.5

Table 2. Continued

Study	Questionnaire details			Administration method		Population				Reliability	Validity	Study quality[†]
Study, first author (year), country	Tool type: number of items[‡]	Response variables	Recall period	Respondent or interviewer: paper or computer assisted	Intake reported by:	Sample size; ethnicity[§]	Age range mean (SD)	Sex	Weight status	Period between repeat administ-ration	Reference method	Score (/7)
Wilson (2011), Australia [13]	Q: 14	Fq	1 d & 7 d	Respondent: Paper	Child	n = 134 (reliability), n = 117 (validity)	10–12 y NR	62% F	20% ow/ob	8–36 d	7DFR	3.5
Wright (2011), USA [16]	Q: 19	Fq & food type & yes/no	1 mo	Respondent: Paper	Child	n = 35; 54% Hispanic, 34% black	7–16 y 11.8 (2.3) y	63% M	43% ow/ob	1–4 wk	1 × 24HDR	2.5

24HDR, 24-h dietary recall; 3DFR, 3-day food record; CA, computer assisted; d, day; DH, diet history; F, female; FFQ, food frequency questionnaire; Fq, frequency of intake; I, interviewer; M, male; mo, month; NA, not assessed; no., number; NR, not reported; NS, national survey; nw, normal weight; ob, obese; ow, overweight; P, paper; Q, questionnaire; R, respondant; SFS, short food survey; uw, underweight; wk, week; y, year.

[†]Study quality assessed using an adapted version of the study quality scoring tool described in Serra-Majem *et al.* [7].

[‡]Short food survey defined as ≤50 dietary questionnaire items and ≤30 food groups.

[§]Ethnicity, as stated by the authors.

[¶]Austria, Belgium, France, Germany, Greece, Hungary, Italy, Spain and Sweden.

[18] to 100% overweight/obese [17]. Indicators of socio-economic status were rarely reported (data not shown).

Dietary assessment tool characteristics

The tools were described as (short) food frequency questionnaires (n = 11), short food questions/surveys (n = 6), screeners (n = 4) or questionnaires (n = 9) (Table 2). The majority of tools were designed to self-report intake; 21 used child-report and nine used parents as a proxy (6/8 were for children <6 years). Twenty-six tools were administered in paper format, with only four studies administered via computer, with a tendency for these being published 2008 onwards. Response options were most commonly qualitative frequencies (n = 24), with some tools also utilising serves/portions (n = 8) or food category (n = 4). The dietary recall period ranged from 1 day to 1 year. Information regarding average completion times was rarely reported. The mean number of questions per tool was 19.

Description of individual questions/items

Most questions assessed individual foods or food group intake (n = 29). The food groups most frequently assessed were fruit (n = 22) or vegetable (n = 23) intake. Questions on dairy foods (n = 20) and discretionary foods (n = 20) were the next most common (Table 3). One study included questions relating to all the nine food and beverage (including water) groups [19], with a further five studies assessing seven food and beverage groups apart from water [18,20–23]. Fruit juice was assessed in 13 studies and two studies asked specifically about wholegrains. The most popular food habits assessed were meal frequency (n = 4) and breakfast (n = 4), followed by the use of vitamin supplements and snacking (n = 2 studies each).

Tool performance

Tools were assessed in terms of their ability to reliably and/or accurately estimate food/beverage or food group intake.

Reliability

Twenty-one studies assessed reliability, with the period between repeat administrations ranging from 1 to 2 h to 1–12 weeks (Table 2). The statistical approach varied between studies but most commonly utilised tests of association (e.g. Pearson or Spearman correlation) and/or tests of agreement (e.g. intraclass correlations or kappa statistic) Tables 4 and 5 identify studies where the estimate of food or beverage group intake was considered

Table 3 A summary of food groups assessed by short food questionnaire within the included studies

Reference, first auuthor (year)	Fruit	Vegetables	Fruit and vegetables	Meat and alternatives	Grains and starchy foods	Dairy foods	Discretionary foods	SSB	Water	Fats†	Habits
Antonogeorgos (2013)	✓J	✓ L		✓	✓	✓	✓				
Bennett (2009)	✓ J	✓				✓	✓ P	✓	✓		
Bell (2014)	✓	✓		✓	✓	✓	✓	✓		✓	
Bjelland (2015)		✓						✓			✓ MF
Davis (2009)						✓	✓ P	✓ D	✓		
Eaton (2013)	✓ J	✓									
Economos (2008)	✓	✓									
Fahlman (2012)	✓	✓ L		✓	✓ WG		✓	✓			
Flood (2014)	✓ J	✓		✓		✓	✓	✓ D	✓		✓ BF, Dinner
Guldan (2015)	✓ J	✓				✓	✓	✓			✓ BF
Gwynn (2011)	✓ J	✓ L		✓	✓	✓	✓ P	✓	✓	✓	
Hendrie (2013)	✓	✓				✓					
Hendrie (2014)	✓	✓		✓	✓	✓	✓	✓		✓	
Haraldsdottir (2005)	✓ J	✓	✓								
Huybrechts (2009)	✓ J	✓		✓	✓	✓	✓	✓			
Magarey (2009)			✓			✓	✓	✓			
Nelson (2009)						✓	✓ P	✓ D	✓		
Lillegaard (2012)	✓ J	✓		✓	✓ WG	✓	✓ P	✓ D			
Lim (2015)	✓	✓									
Leatherdale (2013)			✓	✓	✓	✓					
Neuhouser (2009)			✓				✓				
Olsen (2014)	J					✓		✓ D	✓		
Penkilo (2008)	✓ J	✓ L				✓	✓	✓ P			✓ BF, MF, S, Vit
Prochaska (2004)			✓								
Randall Simpson (2008)	✓	✓			✓	✓	✓	✓ P	✓		
Thiagarajah (2008)	✓ J	✓ L			✓	✓	✓	✓ P	✓		✓ BF, MF, S, Vit
Vandevijvere (2013)	✓	✓		✓							
Vereecken (2008)	✓	✓			✓	✓	✓ P	✓ D			
Wilson (2011)	✓	✓					✓	✓	✓		
Wright (2011)	✓ J	✓				✓	✓	✓	✓		✓ MF

BF, breakfast; D, separate questions available superficially on diet versions of SSBs; J, separate question(s) available about juice intake; L, separate question(s) available about legume intake; MF, meal frequency; P, partially assessed; S, snack; SSB, sugar sweetened beverages; Vit, vitamin pill; WG, separate question(s) available about wholegrain intake.

†For example, butter, margarine.

Table 4 A summary of the reliability and validity results of short food questions in the included studies for core food groups

		Fruit	Fruit juice	Vegetables	Legumes	Fruit and vegetables	Meat and alternatives	Grains and starchy foods	Whole grains	Dairy products	Water	Eating habits
Reliability[†]												
Group difference	Yes	3 [13,18,23]	1 [23]	3 [13,18,23]	0	0	3 [18,23]	2 [18,23]	0	3 [23]	0	0
	No	0	0	0	0	0	0	0	0	0	1	0
Association	Yes	9 [23,27,28,40,48]	7 [23,27,40]	15 [23,27,28,36,40,48]	2 [27,28]	7 [29,40,42]	2 [23,28]	6 [23,27–29,45]	1 [28]	7 [17,23,27,29,41,48]	0	3 [27,36]
	No	1	0	0	0	0	1	0	0	0	0	2
Agreement	Yes	4 [13,18,23,24]	3 [19,23,27]	6 [13,18,23,24,27,45]	2 [19,27]	2 [25,29]	4 [18,19,23,28]	5 [18,23,24,28,29]	1 [28]	6 [21,23–25,27,29]	5 [13,17,19,24,41]	2 [27,39]
	No	9	2	7	4	1	6	5	1	6	3	2
Summary	Yes all measures	1 [23]	1 [23]	1 [23]	–	–	1 [23]	1 [23]	–	1 [23]	–	–
Accuracy[‡,§]												
Group difference	Yes	6 [18,35,37,40]	1 [35]	6 [13,19,24,35,40]	0	2 [40]	1 [24]	2 [18,23]	0	3 [24,35,48]	2 [13,19]	0
	No	9	11	9	0	2	3	2	1	4	3	0
Association	Yes	6 [23,24,26,28,40]	2 [23,40]	6 [23,24,26,28,40]	2 [28,46]	4 [25,29,40,42]	2 [28]	4 [28,46,48]	0	4 [20,23,29]	0	1 [46]
	No	9	2	10	1	4	6	3	1	6	4	0
Agreement	Yes	1 [28]	0	2 [28]	2 [28]	1 [29]	2 [28]	1 [28]	0	1 [29]	0	0
	No	4	2	3	1	0	4	5	0	5	3	1
Summary	Yes all measures	–	–	–	–	–	–	–	–	–	–	–

A number represents the total number of studies that meet that criteria and the corresponding number in brackets represents the reference number of the study. –, No studies met this criteria.
Yes = question performs well based on criteria in Table 1 (does not include Bland–Altman).
No = question did not perform well based on criteria in Table 1.
[†]*n* = 8 studies did not assess reliability of questions.
[‡]*n* = 2 studies did not assess validity of questions.
[§]Studies assess association and/or agreement.

Table 5 A summary of the reliability and validity results of short food questions[†] in the included studies for discretionary choices

		Discretionary choices	Confectionary	Cakes/biscuits	Dairy desserts	Savoury snacks	Potatoes Fries	Processed meats	Composite/takeaway foods	SSB	SSB diet varieties	Fats
Reliability[‡]												
Group difference	Yes	3 (13,18,23)	0	0	0	0	0	0	0	3 (13,18,23)	0	0
	No	0	0	0	0	0	0	0	0	0	0	0
Association	Yes	3 (23,28,42)	3 (27,48)	1 (27)	1 (27)	0	4 (23,27,48)	1 (28)	4 (27,41,48)	3 (17,28,36,41,48)	4 (17,41,48)	0
	No	0	0	0	0	0	0	0	0	2	0	0
Agreement	Yes	4 (18,23,25,28)	2 (24,27)	3 (17,24,27)	1 (27)	2 (19,24)	4 (19,24,27,48)	1 (28)	2 (24,27)	8 (13,18,21,23–25,28,41)	2 (24,41)	4 (19,21)
	No	1	5	4	1	6	4	6	5	5	1	0
Summary	Yes all measures	(23)	–	–	–	–	(23)	–	–	(23)	–	–
Accuracy[§,¶]												
Group difference	Yes	2 (23)	2 (24,35)	1 (35)	0	3 (20,24,35)	3 (19,23,24)	0	3 (19,20)	6 (19,23,24,35,43,48)	4 (20,24,43,48)	0
	No	1	2	1	0	2	4	1	3	6	1	0
Association	Yes	3 (28,42)	0	0	0	0	1 (46)	2 (28)	0	5 (23,25,28,48)	1 (24)	0
	No	3	6	2	1	4	7	2	4	8	4	0
Agreement	Yes	2 (28)	0	0	0	0	0	2 (28)	0	3 (17,28)	0	0
	No	2	1	1	1	0	1	1	1	3	1	0
Summary	Yes all measures	–	–	–	–	–	–	–	–	–	–	–

Yes = question performs well based on criteria in Table 1.

No = question did not perform well based on criteria in Table 1.

[†]Total number of samples in which that food group had a question assessed (greater than the number studies because some had multiple samples in the same paper).

[‡]n = 8 studies did not assess reliability of questions.

[§]n = 2 studies did not assess validity of questions.

[¶]Studies assess association and/or agreement.

reliable based on the interpretation of one or more statistical test. For core food groups, analyses based on *t*-tests or tests of association tended to suggest reliable tool performance (Table 4). Similar results are described for categories of discretionary foods (Table 5). However, questions asking about discretionary foods or sugar-sweetened beverages as a generic category of food products tended to perform reliably across all statistical testing reported.

Accuracy/relative validity

Twenty-eight studies assessed accuracy; specifically, relative validity. A range of reference standards were used as the comparison tool (24-h recalls, $n = 13$; 3–7-day food records/pre-coded diary, $n = 12$; long form FFQ, $n = 1$; direct observation, $n = 1$; interviewer diet history, $n = 1$). No studies utilised any biomarkers to test validity. The statistical approach varied between studies but most commonly utilised *t*-tests to assess group differences and/or testing of association (Tables 4 and 5). Only 14 studies utilised tests of agreement between methods, with five of these performing Bland–Altman analyses [18,22,24–26].

Tools were assessed in terms of their ability to accurately estimate food/beverage or food/beverage group intake based on the interpretation of one or more of the statistical tests presented (Table 4 and 5). No tools performed well across all statistical analyses undertaken, although, for each food group, there were examples of questions that could be considered accurate (Table 4). Similar results were found for categories of discretionary foods (Table 5), although a number of tools were considered to provide accurate estimates of discretionary foods or sugar sweetened beverages as a generic group.

To assess the agreement between SFQs and their comparative method, four studies utilised Bland–Altman plots [18,22,24,26]. Although kappa statistics were reported, there was limited formal evaluation of the agreement between the two measures. The plots illustrated in these studies limit the determination of absolute agreement values, which limits the direct comparisons that could be made. Hendrie *et al.* [18] reported 84% agreement for the SFQ compared to the dietary guidelines index. Additionally, Hendrie *et al.* [18] reported a kappa of 0.76, classifying it as good agreement. The studies by Flood *et al.*[24] and Lim *et al.*[26] did not report kappa statistics, whereas Antonogeogros *et al.*[22] reported very good agreement (kappa values of 0.9 or above) for food groups of refreshments/juices, starchy products, fish and fruit.

Reliability and relative validity

Eighteen studies assessed both reliability and validity/accuracy. No tool could be considered both reliable and accurate across the range of food groups they assessed (see Supporting information). The Belgium tool reported by Huybrechts *et al.* [23] performed consistently across both the range of food groups and statistical analysis performed. Three Australian tools (Flood *et al.* [24]; Hendrie *et al.* [18]; Magarey *et al.* [25]) have been evaluated rigorously and perform well across the range of food groups assessed in this review. The US tools developed by Penkilo *et al.* [27] and Fahlman *et al.* [28] also show promise for the majority of food groups assessed.

Discussion

The present review has identified 30 validation studies that evaluated the reliability and accuracy of individual SFQ items used to estimate food intake in children and adolescents. Although study samples were relatively homogenous, variation in study quality, the period between administration to test reliability, reference standard to test relative validity and statistical analysis hindered direct comparison between studies. This review has identified valid and reliable questions for the range of key food groups of interest to public health nutrition for use in Europe [23], North America [27,28] and Australia [18,24,25]. However, SFQ questions were more likely to be reliable than accurate, and relatively few questions were both reliable and accurate.

Questions measuring the intake of fruit and/or vegetables, discretionary food/beverages and dairy foods were the most common SFQs assessed. This probably reflects the public health nutrition importance of these food groups and their being a proxy for other healthy foods, particularly given the recent focus on child obesity. SFQs asking about meat and alternatives, grain-based foods, water and fats were less common, and also tended to perform poorly compared to their reference method. This may reflect the range of foods and eating contexts (e.g. eaten as part of mixed dishes and/or low daily frequency of meat and alternatives) of these food groups. Although these food groups might be difficult to measure using these existing tools, it is important that valid questions are available to enable assessment of overall dietary intake, particularly for monitoring population intake against food-based dietary guidelines. As discussed further below, cognitive testing of these SFQs to understand how respondents interpret and process these questions is likely to aid improvement of their performance.

Of the included studies, the SFQ tools that provided the most comprehensive set of questions that can be compared against dietary guidelines included those of Huybrechts *et al.* [23], who assessed seven food groups + juice (total of 8), all which performed well against predefined criteria; Hendrie *et al.* [18], who assessed seven food groups of which six (four core food groups and 2

discretionary questions) performed well; and Flood *et al.* [24], who assessed seven food groups (+ juice and diet beverages) with a more comprehensive breakdown of discretionary food choice and the inclusion of two additional items on breakfast and dinner consumption, which performed well on five categories of food/beverage assessed. When considering individual items from within the included studies, Fahlman *et al.* [28] and Leatherdale *et al.* [29] had questions that performed well for fruit and vegetables, meat/alternatives and grains and Penkilo *et al.* [27] provided an assessment of discretionary choices.

The information examined in this review is timely given the increased focus on food-based dietary guidelines and recommendations internationally. Specifically, it has been almost 10 years since the performance of SFQs in Australian children have been comprehensively assessed, particularly for SFQs other than those relating to fruit, vegetables consumption or type of milk. National Australian data suggest there are some food groups that the population is continuing to consume inadequately (i.e. vegetables and legumes) [2] and, accordingly, there is an increasing need to track intakes of such food groups between surveys because extended periods of time may elapse before national surveys are recompleted.

Strengths and limitations of the current literature

Assessment of the study methodology quality based on the tool described by Serra-Majem *et al.* [7] indicated that study quality was variable, with just over half considered as good or excellent. Most studies were conducted in samples greater than 100, as recommended in the literature [30], and were well described. Although a number of studies utilised multiple statistical tests to comprehensively characterise the validity performance of the SFQs evaluated, this remains the key area for improvement in this body of the literature. Very few studies have provided explanations of how mixed dishes were handled, which has relevance for groups such as vegetables because they may often be components of meals rather than be consumed solely on their own. There was a reliance on the use of correlations that test association but not agreement. Only three included studies used Bland–Altman methods and, within those, only plots were reported rather than agreement using kappa values, which made comparison difficult [31]. An improvement in the reporting of weight status and socio-demographics in dietary studies would aid in an improved understanding of the population in which the SFQ has been tested because several subgroups such as those who are overweight have been identified as being more prone to misreporting[32]. Additionally the validity/reliability across these groups needs further work because the results may vary.

Strengths and limitations of the review methodology

Central to the review aim was the intent to interpret the data extracted to provide guidance and recommendations on SFQ items to use in future research. However, recommendations of that nature require consensus on cut-offs or criteria for assessing acceptable reliability and validity. Although the present review used existing and published criteria, these may be considered as arbitrary. In addition, they may also be considered as lenient, and therefore the recommendations of this review may be considered as a 'best case' scenario. Further consensus is required on requirements for acceptable reliability and validity.

Furthermore, it is acknowledged that the choice of reference standard will influence the results observed. Two important considerations in evaluating relative validity are (i) that both the test method and reference method must measure the same underlying concept over the same time period [10,30] and (ii) that the measurement error from the test method and from the reference method should be uncorrelated [10]. It is often very difficult to design validation studies where the test and reference method comparison meet these two considerations, and many of the studies reviewed here did not. This review was limited to English language studies published after 2004 and did not include any thesis studies. The heterogeneity of the studies reviewed made comparisons across studies difficult, limited the ability to conduct sub-analysis by reference standard and was challenging to incorporate into the synthesis of results.

A particular challenge faced when developing the review protocol was related to the definition of a 'short food question'. Preliminary scoping identified a lack of validated individual questions that measured child or adolescent food intake and therefore the focus of the review was broadened to include short questionnaire-style dietary assessment methods where the intent was to estimate intake of a food group in a few questions. A previously reported definition of a 'short' food question was adopted [6] and the focus was on identifying studies where data were reported on the individual food items or food groups compared to an evaluation of energy or nutrient intake, which tends to be the outcome of interest in more traditional validation studies. The results of the present review provide an understanding of the validity of short dietary assessment tools and more generally highlight some food groups that are easier or harder to measure as can be assessed by alternate methods. This is useful in explaining and directing the development of dietary assessment methods for estimating energy and nutrient intakes.

Conclusions

Recommendations for future studies

The review highlights a number of areas for further development and testing. Evaluation of SFQs in terms of responsiveness or sensitivity to change is urgently needed to ensure the valid and accurate monitoring of population trends in food intake, particularly after public health nutrition interventions. Furthermore, a closed SFQ structure achieved through limited response categories is ideal, although this requires an understanding of the range and distribution of responses to be expected. This has been evaluated in very few tools [19], although it should be tested more in the future to minimise respondent and researcher burden and also maximise accuracy by omitting 'unexpected' responses. However, this approach makes it difficult to identify change within intervention studies if individuals fall within the same response category. Finally, SFQ may benefit from a range of cognitive testing, including provision of memory cues, assessment of frequencies or portion size, and use of tools designed to enhance cognitive processing, to improve our understanding of whether SFQs are clearly understood particularly in relation to food group definition and serving size estimation. This type of testing is likely to prove most useful in refining SFQs so that they perform better in terms of reliability and validity.

Recommendations for future studies considering the use of SFQs in research should consider use of technology to assist in administration, which could include prompts of 3D visual aids and portion sizes to increase accuracy. In this review, only eight studies utilised parents to report food intake and this tended to be for children aged less than 5 years. Recent studies have shown that differences exist in dietary reporting depending on who is being asked to report or record dietary or food intake. Traditionally, in research studies, it is the mother who is asked to report; however, compared to the child and father, mothers have been shown to be least accurate with respect to gold standard methods of doubly-labelled water [33].

Guidance in selecting questions that measure children's food intake

The ideal set of questions to measure children and adolescent's food intake will depend on the study sample and research question of interest. However, the findings and practical tables of this review can be used to guide this process. For example, Table 3 aids with the quick identification of validated individual items for food groups of interest. Combined with the validity data critique presented in Tables 4 and 5, researchers can choose a single or a tailored combination of valid questions relevant to their research questions. Finally, the review findings can also enable researchers to develop new sets of short food questions (i.e. short food tools) for improving the validity of short dietary assessment tools that can comprehensively measure total diet, energy and nutrient intake. This is only possible through the improved understanding of the properties of individual items.

Acknowledgments

We thank the following students who assisted in the review process, including-retrieving articles, quality checks, data extraction: Kuok Kueng Chan, Natalie Logan and Anna Bullivant.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest. Funding was provided by the Australasian Child and Adolescent Obesity Research Network (stream funds). RG and TB guided the research. RG, LB, TB, AS, SAM and LC completed extractions and checks. All authors reviewed and collated the data. All authors critically reviewed the manuscript and approved the final version submitted for publication.

References

1. Hendrie GA & Riley MD (2013) Performance of short food questions to assess aspects of the dietary intake of Australian children. *Nutrients* **5**, 4822–4835.
2. Flood, VM, Webb, K & Rangan, A. (2005). Recommendations for short questions to assess food consumption in children for the NSW Health Surveys. *Nutrition NCfPH* http://ro.uow.edu.au/hbspapers/364.
3. Magarey A, Watson J, Golley RK *et al.* (2011) Assessing dietary intake in children and adolescents: Considerations and recommendations for obesity research. *Int J Pediatr Obes* **6**, 2–11.
4. Marks GC, Webb K, Rutishauser I *et al.* (2001) Monitoring food habits in the Australian population using short questions. *Care CDoHaA*.
5. Roberts K & Flagherty S (2010) *Review of Dietary Assessment Methods in Public Health*: Oxford: National Obesity Observatory.
6. Calfas KJ, Zabinski MF & Rupp J (2000) Practical nutrition assessment in primary care settings: a review. *Am J Prev Med* **18**, 289–299.

7. Serra-Majem L, Frost Andersen L, Henrique-Sanchez P *et al.* (2009) Evaluating the quality of dietary intake validation studies. *Br J Nutr* **102**(Suppl 1), S3–S9.
8. Burrows T, Golley RK, Khambalia A *et al.* (2012) The quality of dietary intake methodology and reporting in child and adolescent obesity intervention trials: a systematic review. *Obes Rev* **13**, 1125–1138.
9. Margetts, BM & Nelson, M (1997) The Validation of Dietary Assessment. In: *Design Concepts in Nutritional Epidemiology*. pp. 241–272, 2nd ed. [Nelson M, editor]. Oxford: Oxford University Press.
10. Gleason PM, Harris J, Sheean PM *et al.* (2010) Publishing nutrition research: validity, reliability, and diagnostic test assessment in nutrition-related research. *J Am Diet Assoc* **110**, 409–419.
11. Peat, JK (2001). Health Science Research. In: *A Handbook of Quantitative Methods*. pp. 181–187. [Mellis C. Williams K & Xuan W, editors]. Victoria: Allen & Unwin.
12. Pallant J (2011) *SPSS Survival Manual: A Step by Step Guide to Data Analysis Using SPSS*. 4th edn. Crows Nest: Allen and Unwin.
13. Wilson AM, Magarey AM & Mastersson N (2008) Reliability and relative validity of a child nutrition questionnaire to simultaneously assess dietary patterns associated with positive energy balance and food behaviours, attitudes, knowledge and environments associated with healthy eating. *Int J Behav Nutr Phy Act* **5**, 1–11.
14. National Health and Medical Research Council (2013) *Australian Dietary Guidelines*. Canberra: Commonwealth of Australia.
15. National Health and Medical Research Council (2013) *Australian Guide to Healthy Eating (AGHE)*. Canberra: Commonwealth of Australia.
16. Wright ND, Groisman-Perelstein AE, Wylie-Rosett J *et al.* (2011) A lifestyle assessment and intervention tool for pediatric weight management: the HABITS questionnaire. *J Hum Nutr Diet* **24**, 96–100.
17. Davis JN, Nelson MC, Ventura EE *et al.* (2009) A brief dietary screener: appropriate for overweight Latino adolescents? *J Am Diet Assoc* **109**, 725–729.
18. Hendrie GA, Viner Smith E & Golley RK (2014) The reliability and relative validity of a diet index score for 4–11-year-old children derived from a parent-reported short food survey. *Public Health Nutr* **17**, 1486–1497.
19. Gwynn JD, Flood VM, D'Este CA *et al.* (2011) The reliability and validity of a short FFQ among Australian Aboriginal and Torres Strait Islander and non-Indigenous rural children. *Public Health Nutr* **14**, 388–401.
20. Lillegaard ITL, Overby NC & Andersen LF (2012) Evaluation of a short food frequency questionnaire used among Norwegian children. *Food Nutr Res* doi: 10.3402/fnr.v56i0.6399.
21. Bell LK, Golley RK & Magarey AM (2014) A short food-group-based dietary questionnaire is reliable and valid for assessing toddlers' dietary risk in relatively advantaged samples. *Br J Nutr* **112**, 627–637.
22. Antonogeogros G, Grigoropoulou D, Papadimitriou A *et al.* (2011) Validation of a food frequency questionniare designed for children 10-12 years: The Panacea FFQ. *Pediatr Res* **70**, 778.
23. Huybrechts I, De Backer G, De Bacquer D *et al.* (2009) Relative validity and reproducibility of a food-frequency questionnaire for estimating food intakes among Flemish preschoolers. *Int J Environ Res Public Health* **6**, 382–399.
24. Flood VM, Wen LM, Hardy LL *et al.* (2014) Reliability and validity of a short FFQ for assessing the dietary habits of 2-5-year-old children, Sydney, Australia. *Public Health Nutr* **17**, 498–509.
25. Magarey A, Golley R, Spurrier N *et al.* (2009) Reliability and validity of the Children's Dietary Questionnaire; a new tool to measure children's dietary patterns. *Int J Pediatr Obes* **4**, 257–265.
26. Lim SS, Gold A, Gaillard PR *et al.* (2015) Validation of 2 brief fruit and vegetable assessment instruments among third-grade students. *J Nutr Educ Behav* **47**, e1.
27. Penkilo M, George GC & Hoelscher DM (2008) Reproducibility of the school-based nutrition monitoring questionnaire among fourth-grade students in Texas. *J Nutr Educ Behav* **40**, 20–27.
28. Fahlman M, McCaughtry N, Martin J *et al.* (2012) Assessing the eating behaviors of low-income, urban adolescents. *Am J Health Educ* **43**, 165–171.
29. Leatherdale ST & Laxer RE (2013) Reliability and validity of the weight status and dietary intake measures in the COMPASS questionnaire: are the self-reported measures of body mass index (BMI) and Canada's food guide servings robust? *Int* **10**, 42.
30. Cade J, Thompson R, Burley V *et al.* (2002) Development, validation and utilisation of food frequency questionnaires. *Public Health Nutr* **5**, 567–587.
31. Altman DG & Bland JM (1983) Measurement in medicine: the analysis of method comparison studies. *The Statistician* **32**, 307–317.
32. Elliott S, Davies P, Nambiar S, *et al.* (2011) A comparison of two screening methods to determine the validity of 24-h food and drink records in children and adolescents. *Eur J Clin Nutr* **65**, 1314–1320.
33. Burrows T, Truby H, Morgan P *et al.* (2013) A comparison and validation of child versus parent reporting of children's energy intake using food frequency questionnaires versus food records: Who's an accurate reporter? *Clin Nutr* **32**, 613–618.
34. Moher D, Cook D, Eastwood S *et al.* (1999) Improving the quality of reports of randomised controlled trial: the QUAROM statement. *The Lancet* **354**, 1896–1900.
35. Bennett CA, de Silva-Sanigorski AM, Nichols M *et al.* (2009) Assessing the intake of obesity-related foods and beverages in young children: comparison of a simple

population survey with 24 hr-recall. *Int J Behav Nutr Phys Act* **6**, 71.
36. Bjelland M, Hausken SE, Sleddens EF *et al.* (2014) Development of family and dietary habits questionnaires: the assessment of family processes, dietary habits and adolescents' impulsiveness in Norwegian adolescents and their parents. *Int J Behav Nutr Phys Act* **11**, 130.
37. Eaton DK, Olsen EO, Brener ND *et al.* (2013) A comparison of fruit and vegetable intake estimates from three survey question sets to estimates from 24-hour dietary recall interviews. *J Acad Nutr Diet* **113**, 1165–1174.
38. Economos CD, Sacheck JM, Kwan Ho Chui K *et al.* (2008) School-based behavioral assessment tools are reliable and valid for measurement of fruit and vegetable intake, physical activity, and television viewing in young children [Erratum appears in J Am Diet Assoc. 2008 Nov;108(11):1936 Note: Irizzary, Laura (corrected to Irizarry, Laura)]. *J Am Diet Assoc* **108**, 695–701.
39. Guldan GS, Lau TS & Lee HM (2014) Validity and reliability of a two-minute assessment rapid dietary questionnaire measuring healthy eating behaviours among Hong Kong primary school students. *Hong Kong Med J* **20** (Suppl 7), 30–33.
40. Haraldsdottir J, Thorsdottir I, de Almeida MD *et al.* (2005) Validity and reproducibility of a precoded questionnaire to assess fruit and vegetable intake in European 11- to 12-year-old schoolchildren. *Ann Nutr Metab* **49**, 221–227.
41. Nelson MC & Lytle LA (2009) Development and evaluation of a brief screener to estimate fast-food and beverage consumption among adolescents. *J Am Diet Assoc* **109**, 730–734.
42. Neuhouser ML, Lilley S, Lund A *et al.* (2009) Development and validation of a beverage and snack questionnaire for use in evaluation of school nutrition policies. *J Am Diet Assoc* **109**, 1587–1592.
43. Olsen EO, Eaton DK, Park S *et al.* (2014) Comparing methods for assessing beverage intake among high school students. *Am J Health Behav* **38**, 114–123.
44. Prochaska J & Velicer W (1997) Behaviour change: the transtheoretical model of health behaviour change. *Am J Health Promot* **12**, 38–48.
45. Randall Simpson JA, Keller HH, Rysdale LA *et al.* (2008) Nutrition Screening Tool for Every Preschooler (NutriSTEP): validation and test-retest reliability of a parent-administered questionnaire assessing nutrition risk of preschoolers. *Eur J Clin Nutr* **62**, 770–780.
46. Thiagarajah K, Fly AD, Hoelscher DM *et al.* (2008) Validating the food behavior questions from the elementary school SPAN questionnaire. *J Nutr Educ Behav* **40**, 305–310.
47. Vandevijvere, S, Geelen, A, Gonzalez-Gross, M *et al.* (2013) Evaluation of food & nutrient intake assessment using concentration biomarkers in European adolescents from the Lifestyle, Healthy in Europe by Nutrition in Adolescence study. *Br J Nutr* **109**, 736–747.
48. Vereecken CA, Rossi S, Giacchi MV *et al.* (2008) Comparison of a short food-frequency questionnaire and derived indices with a seven-day diet record in Belgian and Italian children. *Int J Public Health* **53**, 297–305.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article:
Table S1. Symbols used in this document.
Table S2. Database(s): MEDLINE 1946 to Present with Daily Update.
Table S3. Database(s): Embase Classic+Embase 1947 to 2014 September 12.
Table S4. Database(s): MEDLINE In-Process & Other Non-Indexed Citations.
Table S5. Database(s): PsycINFO 1806 to September Week 1 2014.
Table S6. CINAHL.

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

CHILDREN

Association between gestational weight gain and risk of obesity in preadolescence: a longitudinal study (1997–2007) of 5125 children in Greece

S. P. Mourtakos,[1] K. D. Tambalis,[1,2] D. B. Panagiotakos,[1] G. Antonogeorgos,[1] C. D. Alexi,[1] M. Georgoulis,[1] G. Saade[3] & L. S. Sidossis[1,4]

[1]Department of Nutrition and Dietetics, Harokopio University, Athens, Greece
[2]Department of Physical Education and Sport Science, University of Athens, Athens, Greece
[3]Department of Obstetrics and Gynecology, University of Texas Medical Branch at Galveston, Galveston, TX, USA
[4]Department of Internal Medicine, Sealy Center on Aging, Institute for Translational Sciences and Shriners Hospital for Children, University of Texas Medical Branch at Galveston, Galveston, TX, USA

Keywords
child, childhood obesity, infant, IOM category, maternal weight gain, newborn, preadolescence, pregnancy.

Correspondence
L. S. Sidossis, University of Texas Medical Branch at Galveston, 301 University Blvd, Galveston, TX 77555-0177, USA.
Tel.: +409 266 9690
Fax: +848 932 9512
E-mail:lasidoss@utmb.edu

How to cite this article
Mourtakos S.P., Tambalis K.D., Panagiotakos D.B., Antonogeorgos G., Alexi C.D., Georgoulis M., Saade G., Sidossis L.S. (2017). Association between gestational weight gain and risk of obesity in preadolescence: a longitudinal study (1997–2007) of 5125 children in Greece. *J Hum Nutr Diet*. **30**, 51–58
10.1111/jhn.12398

Abstract

Background: The present study aimed to investigate the association between gestational weight gain (GWG) and birth weight, as well as the body mass index (BMI) status, of children at the ages of 2 and 8 years.
Methods: Population-based data were obtained from a database of all 7–9-year-old Greek children who attended primary school during 1997–2007. The study sample consisted of 5125 children matched with their mothers, randomly selected according to region and place of residence, and equally distributed (approximately 500 per year) throughout the study period (1997–2007). A standardised questionnaire was applied; telephone interviews were carried out to collect maternal age, BMI status at the beginning and the end of pregnancy and GWG, birth weight of offspring and BMI status at the ages of 2 and 8 years, as well as several other pregnancy characteristics (e.g. pregnancy duration, gestational medical problems, maternal smoking and alcohol consumption habits, and lactation of offspring after pregnancy).
Results: Gestational weight gain was positively associated with the weight status of offspring at all three life stages studied: newborn (birth weight), infant (BMI) and child (BMI) [$b = 0.008$ (0.001), $b = 0.053$ (0.009) and $b = 0.034$ (0.007), respectively, all $P < 0.001$], after adjusting for maternal age at pregnancy (significant inverse predictor only at age 2 years). The same applied to excessive GWG, as defined by the Institute of Medicine guidelines.
Conclusions: Excessive GWG was associated with a higher risk of greater infant size at birth and a higher BMI status at the ages of 2 and 8 years. Healthcare providers should encourage women to limit their GWG to the range indicated by the current guidelines.

Significance statement

The study is important to the research community because it explored the potential association between gestational weight gain (GWG) and the offspring's weight status at three different developmental stages (e.g. newborn, 2 and 8 years) and explored the consistency of this association across time (e.g. 1997–2007). It confirms that GWG is associated with a risk of obesity at various life stages of the offspring (e.g. newborn, infant at age 2 years

and child at age 8 years). When a mother gains excess weight during pregnancy, the risk that her offspring will be born with excess weight and be overweight or obese during childhood increases significantly. In this respect, healthcare providers should advise women to start their pregnancy with a BMI in the normal weight category and limit their GWG to the range specified for their prepregnancy BMI according to Institute of Medicine (IOM) guidelines.

Introduction

Childhood obesity is a recognised epidemic in most developed and developing countries [1]. The number of children who are overweight is expected to rise by 1.3 million per year and more than 300 000 become obese each year [2]. Childhood obesity rates in Greece are among the highest not only in Europe [3], but also worldwide and are similar to those of the USA [4]. In particular, we recently reported a dramatic increase (by 52%) in the prevalence of childhood obesity in Greece [3]. Furthermore, a significant increase was observed, by approximately 30%, in the rates of overweight 8–9-year-old children of both sexes in Greece during the last decade [3,5].

Obesity during adulthood often has its roots in childhood [6]. Therefore, understanding the determinants of childhood obesity will have broad implications for health. Factors contributing to childhood obesity that have been the focus of recent intensive study include the prenatal maternal characteristics. Observational studies suggest that childhood obesity could be associated with specific characteristics of pregnancy, such as maternal weight status, gestational weight gain (GWG), infant birth weight, smoking habits during pregnancy, maternal gestational diabetes and breast feeding [7–9], whereas GWG has also been associated with greater offspring body mass index (BMI) into early adulthood [10]. Assessment of the Institute of Medicine (IOM) recommendations revealed that 42% of women in the USA began pregnancy in 2004–2007 when they were overweight or obese and 51.2% gained excessive weight [>50 lb (>22.68 kg)] during their pregnancy [11].

Despite the alarming rates of obesity in various countries, there is a limited number of studies providing evidence related to the effect of the gestational period and the related maternal characteristics with the offspring's weight status in preadolescence. Moreover, the consistency of this effect across time and offspring age has never been evaluated. Therefore, the present study aimed to determine the effect of GWG on the offspring's weight status at different life stages (e.g. newborn, 2 and 8 years) and to explore the consistency of this association across time (e.g. 1997–2007) and offspring age.

Materials and methods

A health survey in Greek primary schools (1997–2007)

During the years 1997–2007, with the exception of 2002, 11 nationwide, school-based health surveys were performed (i.e. 85% participation rate for schools); schools that did not participate were from borderland areas, with small numbers of children. A total of 671 715 primary school pupils, aged 7–9 years old, were enrolled (51% boys and 49% girls). Socio-demographic (age, sex, city and area of school and contact information for children), anthropometric [weight (kg), height (cm)] and physical activity data were obtained from almost all children who went to the primary school in these years (87% participation rate). Measurements were performed by two trained physical education (PE) teachers in each school and were collected yearly, during the spring of each year. PE teachers followed a specific protocol taught in corresponding seminars held by the Greek General Secretariat of Sports. Following an official request to the Ministry of Education, the database was obtained by our study group aiming to test several research hypotheses.

Working sample

To test the research hypothesis, a sample of 5500 children (0.8% of the enrolled population) was randomly extracted from the database after the completion of the 1997–2007 school-based health surveys. Random extraction was performed using SPSS, version 18.0 (SPSS Inc. Chicago, IL. USA). The number of 5500 subjects was adequate to achieve statistical power greater or equal to 99% for evaluating a 0.10 ($\pm$ 0.05) change in the regression coefficients at a 5% significance level (two-sided) for the tested hypotheses. The random sampling was stratified according to the region and place of living (e.g. rural/urban), and in accordance with the National Statistical Agency, and was equally distributed during the study period (i.e. 500 mothers per year). For each child, a telephone interview with their mothers was requested by the study's investigators. Of the 5500 mothers, 192 (3.5%) did not provide full information about their children and 183 (3.3%) did not want to participate; thus, 5125 mother–child dyads that covered all geographical regions of Greece (e.g. mainland Greece and the islands) participated in the present study. All mothers were of Greek nationality. Originally, 7500 children and their families were randomly extracted from the database through stratified random sampling and contacted by our research team. From these, 5500 (73%) agreed to participate in the study. No specific information regarding the characteristics among the responders and the nonresponders group is available. However, the nonresponding rate

showed no differences among the sampling strata, thus minimising any selection bias in the final sample.

Measurements

The information needed to test the research hypothesis was obtained using a standardised questionnaire, the Childhood Obesity Pregnancy Determinants (ChOPreD) questionnaire, designed and developed in collaboration with the Department of Nutrition and Dietetics of Harokopio University and the Department of Internal Medicine-Geriatrics, Sealy Centre on Aging at the University of Texas Medical Branch. The ChOPreD questionnaire was tested and internally revised by the study investigators during a pilot study, which confirmed its construct validity. Moreover, to validate the telephone interview process, 100 face-to-face interviews were conducted to check for discrepancies with the information collected through the telephone. No such discrepancies were noted in any variables measured (all $P > 0.90$).

The information obtained was: mother's nationality (Greek or other), parents' educational level, duration of pregnancy (in weeks), potential medical problems during pregnancy (i.e. development of diabetes, hypertension), lifestyle behaviours during pregnancy (smoking, alcohol consumption and eating habits), physical exercise during pregnancy, maternal lactation after pregnancy, and parental anthropometric data. With regard to anthropometric evaluation, mothers were asked to report their body weight at the beginning and the end of the pregnancy, as recorded in their prenatal records (e.g. ultrasound). GWG was calculated based on the difference between the mother's weight at the last and first visits. Only mothers that had Greek nationality and had full-term pregnancy (e.g. duration >37 weeks) were retained in the study. Relative GWG was calculated based on the difference between the last visit compared to the first. Each mother was categorised according to the IOM guidelines: (i) for mothers who are underweight at the start of pregnancy, adequate GWG is 12.5–18 kg; (ii) for mothers at normal weight at the start of pregnancy, adequate GWG is 11.5–16 kg; (iii) for mothers who are overweight at the start of pregnancy, adequate GWG is 7–11.5 kg; and (iv) for mothers who are obese at the start of pregnancy, adequate weight gain is 5–9 kg. Mothers who gained more or less weight than beyond these ranges were categorised as IOM excess or inadequate, respectively [12].

Moreover, children's anthropometric data, such as height and weight, at various developmental age stages (e.g. birth, 2 and 8 years) were also recorded. The data for the children were retrieved from two sources: mothers were asked to provide information that related to their child's birth weight and height, and their height and weight at the age of 2 years as they appeared in the health records for each child. The weight and height at the age of 8 was retrieved from the records of the database (measured by the investigators). BMI status of the offspring at the age of 2 and 8 years was determined based on age- and sex-specific cut-off points suggested by the International Obesity Task Force [13].

The study was approved by the Bioethics Committee of Harokopio University. Oral approval was obtained from all mothers who agreed to participate in the study and written informed consent was obtained from those participants who took part in the validation process of the study.

Statistical analysis

Continuous variables are presented as the median and quartiles (1st to 3rd) or the mean (SD). Categorical variables are presented as absolute and relative frequencies. Histograms and P-P plots were applied to evaluate the normality of the distribution of the continuous variables. To test the research hypothesis, multiple linear regression analysis, with the offspring's birth weight or BMI at the age of 2 and 8 years as the dependent outcome, was carried out with the independent variables: maternal age and GWG (Model 1) and maternal age and IOM Category (Excess) (Model 2). Normality of the residuals derived from the linear regression models was tested using the Kolmogorov test and P-P plots; homoscedacity was evaluated by fitting scatterplots of standardised residuals against predicted values. The variance inflation factor was calculated to test for colinearity of the independent variables and the Durbin–Watson criterion was applied to evaluate serial dependency of BMI. The annual effect of the association of maternal age and GWG with BMI at the age of 2 and of 8 years was studied during the entire 10-year-period using linear trend analysis. To assess the potential effect of maternal age and GWG on obesity status (e.g. overweight/obese versus normal) of the offspring, logistic regression analysis was applied and odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) were calculated. Hosmer and Lemeshow's test was conducted to evaluate the model's goodness-of-fit and residual analysis was implicated using the dbeta, the leverage and Cook's distance D statistics to identify outliers and influential observations. All analyses were performed using SPSS, version 18.0 (SPSS Inc.). $P \leq 0.05$ (two-sided) was considered statistically significant.

Results

The characteristics of the mothers and their offspring are presented in Table 1. The median maternal age at pregnancy was 28 years (1st, 3rd quartile: 25, 30), the

maternal age range was 15–48 years. The median GWG was 13 kg (1st, 3rd tertile: 10, 18) with a mean (SD) of 14.3 (3.45) kg (range 5–45 kg), whereas the median relative GWG (over maternal weight at first visit) was 21.7% for the entire sample, 27.9% (1st, 3rd tertile: 21.2%, 40.0%) for underweight mothers, 22.0% (17.5%, 30.0%) for normal weight mothers, 18.6% (14.0%, 25.7%) for overweight mothers and 12.9% (9.7%, 18.8%) for obese mothers. The majority of mothers started their pregnancy with a normal BMI (79.9%), 3.8% were underweight, 14.8% were overweight and 2.5% were obese. However, 48.1% of mothers were overweight at the end of the pregnancy, 26.5% were obese and only 25.4% retained a normal BMI. As far as the IOM category is concerned, 34.1% of the mothers gained adequate/normal weight during pregnancy, whereas 31.5% gained less and 34.4% gained more than recommended. The offspring had an mean (SD) birth weight of 3.33 (0.50) kg (range 1.20–5.80 kg). The mean (SD) BMI at the age of 2 years (infant) and at the age of 8 years (child) was 16.5 (2.28) kg m^{-2} and 17.6 (3.01) kg m^{-2}, respectively.

Table 1 Characteristics of the studied sample of mothers and their offspring (n = 5125)

Offspring characteristics	
Males, *n* (%)	2686 (52.4)
Females, *n* (%)	2439 (47.6)
Birth weight (kg)*	3.33 (0.50) (1.20–5.80)
BMI at age 2 years (infant) (kg m^{-2})*	16.5 (2.28) (9.07–28.40)
BMI at age 8 years (child) (kg m^{-2})*	17.6 (3.01) (10.20–46.29)
Maternal characteristics	
Maternal age at pregnancy (years)	27.84 (15, 48)
Gestational weight gain (GWG) (kg)	14.3 (3, 45)
Relative gestational weight gain (% kg)	21.7 (16.7, 29.9)
Maternal BMI status in first visit, *n* (%)	
Underweight	194 (3.8)
Normal	4044 (78.9)
Overweight	757 (14.8)
Obese	130 (2.5)
Maternal BMI status in last visit, *n* (%)	
Normal	1302 (25.4)
Overweight	2467 (48.1)
Obese	1356 (26.5)
IOM category, *n* (%)	
Inadequate	1613 (31.5)
Adequate	1747 (34.1)
Excess	1765 (34.4)

Data are presented as absolute and relative frequencies or median (quartiles) unless stated otherwise.
*Mean (SD) and range.
BMI, body mass index; IOM, Institute of Medicine.

Results from the multiple linear regression analysis (Table 2) revealed that GWG change was positively associated with the offspring's birth weight and BMI at age of 2 and 8 years (Model 1); no association was observed with maternal age, except for offspring's BMI at age 2 years. Moreover, excess weight gain according to IOM Categories (Model 2) was associated with birth weight or BMI at different life stages (i.e. at age 2 and 8 years), after adjusting for maternal age. The adjusted r^2 for Model 1 was 0.9% for newborns (F = 23.730, $P < 0.001$), 2.9% for infants aged 2 years (F = 24.007, $P < 0.001$) and 5% (F = 11.760, $P < 0.001$) for children aged 8 years, which indicates that the change in GWG explains a considerable and gradually higher proportion of the variance in offspring BMI level at the various ages. A similar pattern was observed for Model 2, for which the adjusted r^2 was 0.1% for newborns (F = 1.759, $P < 0.172$), 2% for infants aged 2 years (F = 11.038, $P < 0.001$) and 6% (F = 10.592, $P < 0.001$) for children aged 8 years.

Table 2 Results from multiple linear regression models that were estimated to evaluate the association between maternal age and gestational weight gain (GWG) (independent predictors) with birth weight (newborn) or body mass index (dependent outcomes) at the age of 2 and 8 years

	Predictors	*b* (SE)	Beta	*P*
Model 1				
Age 0 years (newborn)	Maternal age, per 1 year	0.0001 (0.002)	0.001	0.929
	GWG, per 1 kg	0.008 (0.001)	0.098	<0.001
Age 2 years	Maternal age, per 1 year	−0.042 (0.012)	−0.087	<0.001
	GWG, per 1 kg	0.053 (0.009)	0.142	<0.001
Age 8 years	Maternal age, per 1 year	0.006 (0.009)	0.010	0.485
	GWG, per 1 kg	0.034 (0.007)	0.068	<0.001
Model 2				
Age 0 Years (newborn)	Maternal age, per 1 year	0.001 (0.002)	−0.004	0.828
	IOM Category (Excess)	0.032 (0.017)	0.032	0.063
Age 2 years	Maternal age, per 1 year	−0.045 (0.014)	−0.094	0.002
	IOM Category (Excess)	0.472 (0.136)	0.103	0.001
Age 8 years	Maternal age, per 1 year	0.004 (0.011)	0.007	0.696
	IOM Category (Excess)	0.476 (0.104)	0.079	<0.001

IOM, Institute of Medicine.

Trend analysis revealed that the effect of maternal age or GWG during pregnancy on offspring BMI status at 2 or 8 years was similar across time (1997–2008) in that no significant linear slope (trend) was revealed on the beta-coefficients of the applied models (all $P > 0.05$).

The aforementioned analyses were also stratified by maternal body weight status at the beginning of pregnancy (i.e. underweight, normal weight, overweight and obese). It was observed that the effect of GWG on infant birth-weight was statistically significant for normal weight [0.008 (0.001), $P < 0.001$] and overweight mothers [0.008 (0.003), $P = 0.014$] per 1 kg gain, but not significant for underweight and obese mothers. The effect of GWG on BMI status at age 2 years was statistically significant for normal weight mothers at 0.056 (0.010) ($P < 0.001$) per 1 kg gain and for overweight mothers at 0.061 (0.026) ($P = 0.020$) per 1 kg gain, but not significant for underweight and obese mothers; the effect of GWG on BMI status at age 8 years was 0.079 (0.029) ($P = 0.006$) per 1 kg gain for underweight mothers, 0.033 (0.008) ($P = 0.0005$) for normal weight and 0.059 (0.020) ($P = 0.003$) for overweight mothers, but not significant for obese mothers.

Logistic regression analysis was conducted to assess the potential effect of maternal age and GWG on the probability of overweight and obesity of the offspring at the age of 2 and 8 years. The analysis revealed that 1 kg weight gain during pregnancy was significantly associated with a 1.054-times higher odds of the offspring being overweight (95% CI = 1.022–1.087) at the age of 2 years, a 1.036-times higher odds of the offspring being overweight (95% CI = 1.014–1.058) at the age of 8 years, as well a 1.077-times higher odds of the offspring being obese (95% CI = 1.046–1.109) at the age of 2 years and a 1.048-times higher odds of the offspring being obese (95% CI = 1.024–1.072) at the age of 8 years, after adjusting for maternal age.

Furthermore, a 10% relative increase in maternal body weight compared to weight at first visit was associated with a 42% higher likelihood of the offspring being overweight/obese at the age of 2 years (95% CI 28–59%), whereas relative GWG was not significantly associated with the offspring's obesity status at the age of 8 years. When the previous analysis was stratified by maternal obesity status at the beginning of pregnancy (i.e. underweight, normal weight, overweight and obese), we found that relative GWG was associated with an increased likelihood of having an overweight/obese offspring at the age of 2 years for underweight (OR per 10% change = 1.42; 95% CI = 1.00–1.96), normal weight (OR = 1.45; 95% CI = 1.28–1.64), as well as overweight mothers (OR = 1.79; 95% CI = 1.21–1.67), but not for obese ones (OR = 1.00; 95% CI = 0.97–1.87). No significant effect of maternal relative GWG was observed on offspring obesity status at the age of 8 years when the analysis was stratified by maternal obesity status at the beginning of pregnancy (e.g. all $P > 0.05$). When the analysis was focused on birth weight, relative GWG was positively associated with infant weight for normal weight mothers [0.003 (0.001), $P < 0.001$] and overweight mothers [0.004 (0.002), $P = 0.041$] but not for underweight mothers [0.0002 (0.002), $P = 0.339$] or obese mothers [0.006 (0.005), $P = 0.254$].

Discussion

The present study aimed to determine how GWG is related to the offspring's weight status at different life stages (e.g. newborn, 2 and 8 years) and to explore the consistency of this association across time. The results of the present study revealed that excessive GWG (expressed as an absolute scale or based on IOM recommendations) in Greek women was positively associated with the risk of obesity at all three stages of their offspring's life that were studied (e.g. newborn, infant and child), irrespective of maternal age. With respect to consistency over time, there were no changes in the effect of maternal age and GWG on the weight status of the offspring throughout the decade studied (1997–2007).

There are many mechanisms by which a mother's increased GWG in pregnancy might confer a risk of obesity to her child, including the child's inheritance of genes that confer susceptibility to obesity, the effects of maternal increased weight on the intrauterine environment, and the maternal role in shaping the child's postnatal eating and physical activity environment. Regardless of the exact mechanisms, the presence of obesity is associated with various metabolic and vascular abnormalities in childhood. Therefore, the prevention of the offspring's obesity through modification of the mother's pre- and perinatal characteristics is of great public health importance [14–16]. It is also worth emphasising that, besides offspring weight status, a higher maternal prepregnancy BMI has been associated with higher systolic blood pressure, insulin, glucose and insulin resistance levels in adolescence, indicating an adverse cardiometabolic profile [17]. The results of the present study suggest the need for pregnant women to adhere to recommended GWG.

Epidemiological support for the hypothesis that GWG is associated with the offspring's future obesity status comes from studies showing a positive correlation between maternal BMI before pregnancy or in its early stages and the BMI of the offspring in later life [18–22]. For example, in a study based on reports of families who participated in the Special Supplemental Nutrition Programme for women, infants and children in Ohio (with a

sample of more than 5000 children), strong and linear correlations were found between maternal BMI during the first trimester of pregnancy and the risk of developing childhood obesity until the age of 4 years [18]. This relationship was independent of a range of other factors, such as birth weight, socio-economic status and maternal smoking status during pregnancy.

Two epidemiological studies that examined the relationship between GWG and weight of the child at the age of 3 years reported that GWG is linked to a higher risk for obesity in childhood. The first study involved 1044 mother–child pairs. Women with adequate or excess GWG had an approximately four-fold greater risk of having a child with BMI above the 95th percentile compared to women whose GWG was under the levels suggested by IOM [23]. The second study examined 208 mother–child pairs in rural areas of upstate New York and found a significant interaction between maternal BMI before pregnancy, the GWG, and the weight of the child at the age of 3 years. Although no independent effect of GWG on offspring's weight in their overall multivariate model was found, they attributed this to their small sample size. The risks of childhood obesity based on GWG as well as the BMI before pregnancy were also determined [24]. Other studies have investigated the connection of GWG and obesity in older children/adolescents. Oken *et al.* [25] examined approximately 12 000 children aged 9–14 years and found that every 5-lb (2.268 kg) increase in the GWG was associated with 1.09 OR of obesity of the offspring. Compared with GWG in the IOM guidelines in 1990, an increase over the guidelines was associated with a 1.42 OR of developing obesity. Maternal BMI before pregnancy did not alter the relationship between childhood obesity and GWG.

The present study revealed that the median GWG was 13 kg and that, based on the 2009 IOM recommendations, 62.6% of the mothers gained adequate/normal weight during pregnancy, whereas 34.4% gained excess weight. Egan *et al.* [26] noted an excessive GWG in 59% of women, whereas Chung *et al.* [27], Walsh *et al.* [28] and He *et al.* [29] reported an excessive GWG of 73%, 43% and 14%, respectively. The differences between populations may be a result of an under-reporting of GWG by some, or some populations may be properly informed and advised by their physicians and/or are more sensitive to weight gain for various reasons.

Besides the absolute GWG, the present study indicated that maternal excess GWG according to IOM recommendations was also related to an increased risk of having an offspring with higher weigh at birth and higher BMI at the age of 2 and 8 years. This is in accordance with the findings reported by the prospective national Norwegian Mother and Child Cohort Study (MoBa), which involved 56 101 pregnant women. This study reported that weight gain in excess of the IOM recommendations (e.g. GWG > IOM recommendations) among other variables (e.g. pregnancy hypertension, etc.) significantly increased the risk for a high birth weight infant [30]. Moreover, in the prospective study conducted by Alberico *et al.*[31], which collected data on mode of delivery and maternal/neonatal outcomes in eleven hospitals in Italy, the researchers reported that maternal obesity, excess GWG and diabetes should be considered as independent risk factors for newborn macrosomia. They reported significant ORs of developing offspring macrosomia for pregestational BMI overweight and obese mothers, as well as for GWG that is higher than IOM recommendations. Moreover, Walsh *et al.* [28] reported that women with an excessive weight gain during pregnancy had higher foetal weights and foetal adiposity, whereas infant birth weight and birth weight centiles were also higher in those who exceeded the guidelines.

The major strength of the present study is that it explored the potential association between GWG and the offspring's weight status at three different developmental stages (e.g. newborn, 2 and 8 years) and explored the consistency of this association across time (e.g. 1997–2007). However, the present study has several limitations. The information that was collected during the telephone interviews was self-reported and, although mothers could provide information based on health records for themselves and their children, this constitutes a study limitation. Moreover, in the current cohort, 17.3% of women were overweight/obese before their pregnancy, which is a relatively low prevalence in comparison to published reports for the corresponding population [32,33]. This could be attributed to deliberate under-reporting, or recall bias for the self-reported prepregnancy anthropometric data (body weight and height) [34]. Similar observations have been reported previously in Greece by Manios *et al.* [35] in 2009 and it is a common limitation in similar studies [36]. Another limitation of the present study lies in the fact that data could not be collected for year 2002, which might have affected the analysis with respect to consistency across time. Moreover, the sample of mothers included in the present study did not show statistically significant levels of other risk factors related to intrauterine or foetal growth (i.e. gestational diabetes, increased blood pressure, etc.). Thus, the analysis concentrated only on the risks associated with GWG and maternal age at pregnancy. Finally, it should be noted that, although several characteristics related to pregnancy and gestational maternal habits were assessed (given that the main purpose of the present study was to explore the effect of gestational characteristics on childhood obesity),

other factors that could affect offspring's weight status, such as offspring's lifestyle habits (dietary and physical activity habits) and general health status during infancy and childhood, were not evaluated and not included as confounding factors in our analyses.

Conclusions

The present study indicated that GWG was associated with the risk of obesity at various life stages of the offspring (e.g. newborn, infant at age 2 and child at age 8 years). Specifically, according to our results, when a mother gains excess weight during pregnancy, the risk that her offspring will be born with excess weight and be overweight or obese during childhood increases significantly. With respect to consistency over time, our results indicate that there are no changes in the effect of maternal age and GWG on the offspring's risk for becoming overweight or obese throughout the decade studied (1997–2007, except 2002). Our study supports previous reports and confirms the detrimental role of excess weight gain during pregnancy on childhood obesity, as already addressed in the current IOM guidelines for weight gain during pregnancy. Under this scope, healthcare providers should continue to encourage and support women to start their pregnancy with a BMI in the normal weight category and limit their GWG to the range specified for their prepregnancy BMI.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with CONSORT[1]/STROBE[2]/PRISMA[3] guidelines.

Ethical standards

The study was approved by the Bioethics Committee of Harokopio University. Oral approval was obtained from all mothers who agreed to participate in the study and written informed consent was obtained from those participants who took part in the validation process of the study.

Acknowledgments

The authors want to thank the study subjects for their willingness to participate. We also want to thank Dr Sarah Toombs Smith for editorial assistance. We also very grateful to Mrs Stavroula Parastatidou, Markella Symeopoulou and Mema Lampropoulou for their assistance with the data collection.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
This study was conducted with the support of the Institute for Translational Sciences at the University of Texas Medical Branch, supported in part by a Clinical and Translational Science Award (UL1TR000071) from the National Centre for Advancing Translational Sciences, National Institutes of Health, OPAP SA – Greece, Nestlé -Greece, and also received support from the Harokopio University Post Graduate program on Nutrition and Dietetics.
SM, DP, GS, KT and LS guided the design, analysis, interpretation and writing of the manuscript. GS, KT and GA revised the manuscript during the review process and performed the statistical analysis. MG, SM, CA and conducted the individual interviews, read the transcripts and developed the analytical framework. All authors contributed to the interpretation of the analysis and critically revised the manuscript. All authors approved the final version submitted for publication.

References

1. James WP (2008) The epidemiology of obesity: the size of the problem. *J Intern Med* **263**, 336–352.
2. Kosti RI & Panagiotakos DB (2006) The epidemic of obesity in children and adolescents in the world. *Cent Eur J Public Health* **14**, 151–159.
3. Tambalis KD, Panagiotakos DB, Kavouras SA *et al.* (2010) Eleven-year prevalence trends of obesity in Greek children: first evidence that prevalence of obesity is leveling off. *Obesity (Silver Spring)* **18**, 161–166.
4. Ogden CL, Carroll MD & Flegal KM (2008) High body mass index for age among US children and adolescents, 2003–2006. *JAMA* **299**, 2401–2405.
5. Tambalis KD, Panagiotakos DB, Psarra G *et al.* (2011) Inverse but independent trends in obesity and fitness levels among Greek children: a time-series analysis from 1997 to 2007. *Obes Facts* **4**, 165–174.
6. Elks CE, Loos RJ, Hardy R *et al.* (2012) Adult obesity susceptibility variants are associated with greater childhood weight gain and a faster tempo of growth: the 1946 British Birth Cohort Study. *Am J Clin Nutr* **95**, 1150–1156.
7. Rooney BL, Mathiason MA & Schauberger CW (2011) Predictors of obesity in childhood, adolescence, and

adulthood in a birth cohort. *Matern Child Health J* **15**, 1166–1175.
8. Mamun AA, Callaway LK, O'Callaghan MJ *et al.* (2011) Associations of maternal pre-pregnancy obesity and excess pregnancy weight gains with adverse pregnancy outcomes and length of hospital stay. *BMC Pregnancy Childbirth* **11**, 62.
9. Gaskins RB, LaGasse LL, Liu J *et al.* (2010) Small for gestational age and higher birth weight predict childhood obesity in preterm infants. *Am J Perinatol* **27**, 721–730.
10. Arenz S & Von Kries R (2009) Protective effect of breast-feeding against obesity in childhood: can a meta-analysis of published observational studies help to validate the hypothesis? *Adv Exp Med Biol* **639**, 145–152.
11. Park S, Sappenfield WM, Bish C *et al.* (2011) Assessment of the Institute of Medicine recommendations for weight gain during pregnancy: Florida, 2004-2007. *Matern Child Health J* **15**, 289–301.
12. Medicine Io (2009) *Subcommittee on Nutritional Status and Weight Gain during Pregnancy, Weight Gain during Pregnancy: Reexamining the Guidelines*. Washington, DC: National Academy Press.
13. Cole TJ, Flegal KM, Nicholls D *et al.* (2007) Body mass index cut offs to define thinness in children and adolescents: international survey. *BMJ* **335**, 194.
14. Ebbeling CB, Pawlak DB & Ludwig DS (2002) Childhood obesity: public-health crisis, common sense cure. *Lancet* **360**, 473–482.
15. Whitaker RC & Dietz WH (1998) Role of the prenatal environment in the development of obesity. *J Pediatr* **132**, 768–776.
16. Catalano PM (2003) Obesity and pregnancy – the propagation of a viscous cycle? *J Clin Endocrinol Metab* **88**, 3505–3506.
17. Gaillard R, Welten M, Oddy WH *et al.* (2016) Associations of maternal prepregnancy body mass index and gestational weight gain with cardio-metabolic risk factors in adolescent offspring: a prospective cohort study. *BJOG* **123**, 207–216.
18. Whitaker RC (2004) Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy. *Pediatrics* **114**, e29–e36.
19. Laitinen J, Power C & Jarvelin MR (2001) Family social class, maternal body mass index, childhood body mass index, and age at menarche as predictors of adult obesity. *Am J Clin Nutr* **74**, 287–294.
20. Li C, Kaur H, Choi WS *et al.* (2005) Additive interactions of maternal prepregnancy BMI and breast-feeding on childhood overweight. *Obes Res* **13**, 362–371.
21. Parsons TJ, Power C & Manor O (2001) Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal study. *BMJ* **323**, 1331–1335.
22. Stettler N, Tershakovec AM, Zemel BS *et al.* (2000) Early risk factors for increased adiposity: a cohort study of African American subjects followed from birth to young adulthood. *Am J Clin Nutr* **72**, 378–383.
23. Oken E, Taveras EM, Kleinman KP *et al.* (2007) Gestational weight gain and child adiposity at age 3 years. *Am J Obstet Gynecol* **196**, 322 e1-8.
24. Olson CM, Strawderman MS & Reed RG (2004) Efficacy of an intervention to prevent excessive gestational weight gain. *Am J Obstet Gynecol* **191**, 530–536.
25. Oken E, Rifas-Shiman SL, Field AE *et al.* (2008) Maternal gestational weight gain and offspring weight in adolescence. *Obstet Gynecol* **112**, 999–1006.
26. Egan AM, Dennedy MC, Al-Ramli W *et al.* (2014) ATLANTIC-DIP: excessive gestational weight gain and pregnancy outcomes in women with gestational or pregestational diabetes mellitus. *J Clin Endocrinol Metab* **99**, 212–219.
27. Chung JG, Taylor RS, Thompson JM *et al.* (2013) Gestational weight gain and adverse pregnancy outcomes in a nulliparous cohort. *Eur J Obstet Gynecol Reprod Biol* **167**, 149–153.
28. Walsh JM, McGowan CA, Mahony RM *et al.* (2014) Obstetric and metabolic implications of excessive gestational weight gain in pregnancy. *Obesity (Silver Spring)* **22**, 1594–1600.
29. He X, Hu C, Chen L *et al.* (2014) The association between gestational weight gain and substantial weight retention 1-year postpartum. *Arch Gynecol Obstet* **290**, 493–499.
30. Haugen M, Brantsaeter AL, Winkvist A *et al.* (2014) Associations of pre-pregnancy body mass index and gestational weight gain with pregnancy outcome and postpartum weight retention: a prospective observational cohort study. *BMC Pregnancy Childbirth* **14**, 201.
31. Alberico S, Montico M, Barresi V *et al.* (2014) The role of gestational diabetes, pre-pregnancy body mass index and gestational weight gain on the risk of newborn macrosomia: results from a prospective multicentre study. *BMC Pregnancy Childbirth* **14**, 23.
32. Krassas GE, Kelestimur F, Micic D *et al.* (2003) Self-reported prevalence of obesity among 20,329 adults from large territories of Greece, Serbia and Turkey. *Hormones (Athens)* **2**, 49–54.
33. Manios Y (2006) Design and descriptive results of the 'Growth, Exercise and Nutrition Epidemiological Study In preSchoolers': the GENESIS study. *BMC Public Health* **6**, 32.
34. Villanueva EV (2001) The validity of self-reported weight in US adults: a population based cross-sectional study. *BMC Public Health* **1**, 11.
35. Manios Y, Grammatikaki E, Kondaki K *et al.* (2009) The effect of maternal obesity on initiation and duration of breast-feeding in Greece: the GENESIS study. *Public Health Nutr* **12**, 517–524.
36. Brawarsky P, Stotland NE, Jackson RA *et al.* (2005) Pre-pregnancy and pregnancy-related factors and the risk of excessive or inadequate gestational weight gain. *Int J Gynaecol Obstet* **91**, 125–131.

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

CHILDREN

Growth status of children with autism spectrum disorder: a case–control study

K. Barnhill,[1] A. Gutierrez,[1] M. Ghossainy,[2] Z. Marediya,[1] C. N. Marti[3] & L. Hewitson[1]

[1]The Johnson Center for Child Health and Development, Austin, TX, USA
[2]The University of Texas at Austin, Austin, TX, USA
[3]Abacist Analytics, LLC, Austin, TX, USA

Keywords
anthropometric, autism, body mass index, growth status, physical status.

Correspondence
K. M. Barnhill, The Johnson Center for Child Health and Development, 1700 Rio Grande, Suite 200, Austin, TX 78701, USA.
Tel.: +1 512 732 8400
Fax: +1 512 732 8353
E-mail: kbarnhill@johnson-center.org

How to cite this article
Barnhill K., Gutierrez A., Ghossainy M., Marediya Z., Marti C.N., Hewitson L. (2017) Growth status of children with autism spectrum disorder: a case–control study. *J Hum Nutr Diet*. **30**, 59–65
doi:10.1111/jhn.12396

Abstract

Background: Children with autism spectrum disorder are at risk of a compromised dietary intake and nutritional status that could impact growth over both the short and long term. The limited body of published research addressing this concern has been contradictory and inconclusive to date.
Methods: This case–control study investigated the height, weight, body mass index (BMI) and other anthropometric measurements of children diagnosed with autism spectrum disorder (ASD). Eighty-six children with ASD and 57 healthy controls participated in the study. Caregivers of participants who met the inclusion criteria completed a health history questionnaire, provided information on dietary intake and feeding behaviour, and completed a nutrition physical with a healthcare professional, which provided all of the anthropometric measurements required for the study.
Results: Body mass index and BMI *Z*-scores for females with ASD and corresponding healthy controls were significantly different. Female participants with ASD had significantly lower BMI and BMI *Z*-scores than control participants. The prevalence of risk for failure-to-thrive status was consistent across ASD subjects and controls. The prevalence of overweight and obesity was consistent across ASD subjects and controls. Children with ASD comprised 60% of the total number of children across BMI categories and mid-arm muscle circumference percentile ranges, which is consistent with the proportion of children in the overall sample.
Conclusions: More research is needed to fully assess physical status and potential growth concerns of children with ASD. A full physical assessment should be a component of primary care for all children with ASD.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by deficits in social interaction and communication, as well as restricted, repetitive or stereotyped behaviour, with an onset before 3 years of age [(1)]. The prevalence of ASD in the USA is approximately 1 in 68, and it is more common in boys than in girls [(2)]. The Centers for Disease Control and Prevention (CDC) found that US boys were almost five times more likely to receive an ASD diagnosis than girls, indicating that approximately one in 42 boys is currently diagnosed with ASD. Recent CDC autism prevalence data indicate that, as of 2015, this total population figure could be as high as one in 45 children [(3)].

Two factors that are known to be risks in ASD and potentially influence growth are food selectivity behaviour and gastrointestinal health status. Selective dietary intake could play a significant role in the growth status of children with ASD. Children with ASD are more likely to have food selectivity and feeding issues resulting in challenging behaviours surrounding food intake than their typically developing peers [(4,5)]. Food selectivity continues to be highly reported in children with ASD, and is simply defined as the

consumption of an abnormally limited variety of food [6]. This behaviour affects food choices, which, in turn, can affect nutritional status and growth [7–9]. For children with food selectivity behaviour, a refusal to consume one or more food groups is common, and anxiety and tantrums can be associated with the introduction of new foods [6,9].

Furthermore, a higher incidence of gastrointestinal symptoms has been documented in children with ASD [10]. Caregiver-reported frequencies of gastrointestinal symptoms, abnormalities or disorders in children with ASD range between 9% and 70% [4,11]. Common gastrointestinal symptoms reported include constipation, diarrhoea, abdominal pain, encopresis, bloating and gastro-oesophageal reflux disease [10–13]. Research indicates that children with ASD and gastrointestinal issues have a higher risk of developing problem behaviours (e.g. sleep disturbance, self-injury and aggression) than children with ASD who do not present these symptoms [10–12,14]. Additional research raises concerns over gastrointestinal flora associated with ASD and its corresponding impact on behavioural symptoms and autism severity [14]. Although these differences are now noted clearly in the literature, the prevalence of gastrointestinal abnormalities in children with autism is not well understood.

Anthropometric measurements, including height, weight, body mass index (BMI), triceps skinfold (TSF) and mid-arm circumference (MAC), are an effective method of evaluating dietary intake, growth status and nutritional status in children with ASD [15]. As noted, the effects of gastrointestinal symptoms and food selectivity can lead to an inadequate dietary intake, resulting in abnormal anthropometric measurements [16]. In some studies, no differences in BMI were reported between children with ASD and their typically developing peers, whereas other studies have reported higher rates of underweight children with ASD compared to their typically developing peers [16,17]. For these reasons, we chose to evaluate the physical status of children with ASD by means of a detailed dietary evaluation and anthropometric assessment. Comprehensive information on dietary intake will be published separately. The present study aimed to determine the growth status of children aged 2–13 years who were diagnosed with ASD in comparison with healthy controls.

Materials and methods

Eighty-six children with ASD and 57 healthy controls were enrolled in the present study. All children included in the ASD group either received a clinical ASD diagnosis prior to study participation or completed a comprehensive diagnostic assessment at the time of study enrolment. All prior formal diagnostic assessments were completed by appropriately trained clinicians, including psychologists, psychiatrists, developmental paediatricians or neurologists. These diagnoses were confirmed at the time of study initiation by an appropriately research-trained professional. Diagnostic assessment at the time of study enrolment was completed by a psychologist utilising Social Communication Questionnaire (SCQ), ADI-R (Autism Diagnostic Interview-Revised) and ADOS (Autism Diagnostic Observation Schedule) instruments. All study participants met the criteria for an ASD diagnosis regarding age of onset, repetitive, stereotypical behaviour, and significant deficits in social interaction and communication. For the control group, all subjects underwent a developmental screening using the Adaptive Behaviour Assessment System-Second Edition (ABAS-II) as assessed by a psychologist. Control subjects were excluded if their score on the ABAS-II suggested developmental concern as well as the need for further evaluation. Exclusion criteria also included those children with a co-morbid diagnosis that could affect growth status or dietary intake, those with a history of major chronic disease, and those who had used medication known to affect growth or nutritional status at any time. The present study was approved by the Austin Multi-Institutional Review Board and the procedures followed were in accordance with the ethical standards of the responsible institutional committee on human experimentation and in accordance with the Helsinki Declaration of 1975 as revised in 1983. Written informed consent was obtained from the parent or legal guardian of all children who participated in the study.

All anthropometric data were collected by either a licensed, registered dietitian (RD) or a registered nurse (RN) at the time of the study appointment. Both the RD and RN received training and ongoing assessment in appropriate collection of anthropometric data. The height and weight of all research and control participants were recorded using a wall-mounted stadiometer measurement instrument (Detecto Scale Ltd, Bury Saint Edmunds, UK) with a moveable measuring rod and a Detecto physician model standard balanced beam weight scale (Detecto Scale Ltd). Body mass index (BMI) was then calculated from these height and weight measurements.

Anthropometric measurements also taken included TSF and MAC, which is also referred to as mid-upper arm circumference [15]. TSF and MAC were evaluated to assess the nutritional status in this population. These measurements were collected with standard steel precision callipers for use with all paediatric patients. The accuracy of all instruments was confirmed before use. MAC measurements below 11.5 cm are indicative of severe undernutrition (a result of prolonged undernutrition that results in declining rates of linear growth and growth stunting); those between 11.5 and 12.4 cm are indicative of moderate undernutrition (undernutrition resulting in BMI or

length-for-height values below the average range); and those between 12.4 and 13.5 cm are indicative of at-risk for undernutrition (typically an acute and brief undernutrition situation resulting in weight loss or a decrease in weight gain trajectory). This information is recommended for use in the assessment of children aged 1–5 years and adults in acute settings. MAC is a standard for determining acute malnutrition in developing countries but is also used (although to a lesser extent) in well-nourished and developed countries. This technique has become a more common and standard measure, particularly in hospital settings, in developed countries in recent years [18].

Finally, mid-arm muscle circumference (MAMC) was calculated based on TSF and MAC measurements and evaluated using a standardised reference table. This is a relatively simple calculation: MAMC = MAC – 3.14 (TSF). According to national standards, an MAMC measurement of less than the fifth percentile indicates severe protein-calorie malnutrition. An MAMC measurement falling to less then the 10th percentile indicates moderate protein-calorie malnutrition.

At the time of data analysis, every effort was made to age-match all participants. ASD and control participants were compared using linear regression models that included age and sex as control variables, with the exception of models in which either age was the dependent variable or models were fit for a single sex. Additionally, ASD and control participants were compared across four BMI categories (underweight, healthy, overweight, obese). BMI *Z*-scores and percentiles were computed from CDC growth charts that are based on five national health examination surveys. Fisher's exact test of independence assessed whether there were differences in these weight categories across the ASD and control groups. Follow-up tests were conducted within each BMI category using an exact binomial test to determine whether the observed proportions of ASD cases differed from the sample proportions. All the statistical tests were two-tailed $\alpha = 0.05$. All data analysis was conducted using R, version 3.2.2 (The R Project for Statistical Computing, Vienna, Austria).

Results

The participants in this study included 86 children aged 2–13 years diagnosed with ASD, based on the criteria set forth in both the DSM-IV and DSM-5, as well as 57 aged-matched healthy control children who did not have ASD, based on the data collected in a health history questionnaire. Using CDC charts and the percentile rankings obtained, children were classified in one of four categories: obese (BMI >95th percentile), overweight (BMI >85th percentile to 95th percentile), healthy (BMI >5th percentile to <85th percentile) and underweight (<5th percentile). Means (SDs) for ASD and controls for the entire sample, as well as by sex, are reported in Table 1. Additionally, Table 1 presents a summary of the baseline characteristics of the study subjects (age, weight, height, BMI and BMI *Z*-score).

The results indicate statistically significant age differences between ASD and non-ASD participants ($t_{140} = 2.81$, $P = 0.006$). First, ASD participants were significantly younger than the control participants. This effect was driven by the male participants only ($t_{124} = 2.89$, $P = 0.005$), specifically in male participants under the age of 3 years ($t_7 = 3.47$, $P = 0.010$) (data not shown). Despite these age differences, weight and height did not differ between groups, regardless of sex, suggesting that ASD and non-ASD participants were comparable on these measures. The results did reveal that female ASD participants had significantly lower BMI and BMI *Z*-scores than female control participants ($t_{14} = 2.24$, $P = 0.042$ and $t_{14} = 2.23$, $P = 0.043$, respectively).

Table 2 illustrates the distribution of children with and without ASD who fall within each of four BMI categories (underweight, healthy weight, overweight and obese.) The results revealed that the majority of children in both ASD and non-ASD groups were classified as having a healthy weight. There was no significant association between ASD status and any BMI categories, and the distribution of ASD and control participants did not differ across the four BMI categories as measured by Fisher's exact test for count data ($P = 0.644$). Furthermore, the proportion of children with ASD in each BMI percentile range did not differ significantly from the proportion of children with ASD in the overall sample. Children with ASD comprised 60% of the total number of children within each BMI category, as well as the population as a whole. Additionally, the prevalence of overweight and obesity in control participants mirrors that of recently published work on paediatric overweight and obesity status in the general US population [19].

Anthropometric measurements of MAC and TSF were evaluated. With regard to MAC measurements for children with and without ASD, no participants met the criteria for any category of undernutrition or risk of undernutrition. The evaluation of MAMC, which is calculated through the use of TSF and MAC measurements, was also conducted. The resulting MAMC values and percentiles for all study participants are presented in Table 3. The results indicate no significant association between ASD status and MAMC percentile range as measured by Fisher's exact test ($P = 0.268$). Finally, the proportion of children with ASD in each percentile range did not differ significantly from the proportion of children with ASD in the overall sample. As with the BMI classification,

Table 1 Main characteristics of children with and without autism spectrum disorder (ASD)

Baseline characteristic	Children with ASD (n = 86) n (%), mean (SD)			Children without ASD (n = 57) n (%), mean (SD)			P-value (95% CI)		
	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls
	86 (100)	79 (92)	7 (8)	57 (100)	47 (82)	10 (18)			
Age (months)	66.19 (19.94)	67.33 (19.42)	53.31 (22.77)	74.38 (22.30)	77.82 (20.12)	58.22 (25.98)	0.006 −16.71, −2.90	0.005 −17.66, −3.31	0.693 −30.90, 21.08
Weight (kg)	20.55 (5.35)	20.86 (5.41)	17.07 (3.28)	22.91 (5.94)	23.61 (6.01)	19.62 (4.51)	0.250 −2.04, 0.54	0.478 −1.94, 0.91	0.113 −4.22, 0.50
Height (cm)	112.13 (12.31)	112.86 (12.31)	103.96 (9.46)	117.52 (13.65)	119.61 (12.40)	107.95 (15.70)	0.194 −3.51, 0.72	0.255 −3.62, 0.97	0.600 −7.71, 4.62
BMI	16.15 (2.04)	16.19 (2.11)	15.66 (0.58)	16.32 (1.88)	16.20 (1.90)	16.85 (1.79)	0.597 −0.89, 0.51	0.963 −0.76, 0.79	0.042 −2.64, −0.06
BMI Z-score	0.16 (1.17)	0.17 (1.21)	0.05 (0.58)	0.25 (1.07)	0.14 (1.08)	0.76 (0.93)	0.528 −0.52, 0.27	0.936 −0.46, 0.42	0.043 −1.56, −0.03

ASD, autism spectrum disorder; BMI, body mass index; CI, confidence interval.

children with ASD comprised 60% of the total number of children within each MAMC percentile range.

Discussion

We chose to fully evaluate the nutritional and growth status of children with ASD and their typically developing peers given the limited amount of data available regarding this topic, incomplete work in prior datasets, and the conflicting results that have been reported to date [20]. Regarding the study groups, there was a statistically significant difference in age between the ASD and control participants, with younger children being enrolled in the ASD group. Examining this age difference across sexes, we found no age difference between females in each group; instead, we found that males in the ASD group were significantly younger than their non-ASD counterparts, particularly in children aged 3 years and younger. Despite these age differences, there were no significant differences between ASD participants and non-ASD participants with respect to weight or height, suggesting that these two groups were comparable on these measures.

Our results did reveal a significant difference in BMI score for females (but not males) with and without ASD. Female participants with ASD had significantly lower BMI scores than their non-ASD counterparts. Marí-Bauset *et al.* [21] reported similar results in their work focusing on children aged 6–9 years with respect to total participants with ASD compared to healthy controls. However, this was noted in the participant group as a whole and not in any female subset in particular. Sadowska and Cierebiej [22] identified a lower body weight despite height being within the normal range for children with ASD, with 30% of all participants with ASD meeting the criteria for the low body weight classification. Furthermore, among our sample, we found no significant difference in the proportion of children with and without ASD across any of the BMI categories. Finally, the majority of children in both groups were classified as having a healthy weight.

Little research has been published on physical status in children with ASD to date. Our work is in agreement with that of other researchers in suggesting that children with ASD tend to have a lower BMI status and may be at risk of protein malnutrition [22–24]. Although not statistically significant, the percentage of children with ASD meeting the criteria for the overweight/obese classification was lower compared to that of control participants. Additionally, although these values are also not statistically significant, the percentage of children with ASD meeting the criteria for moderate and severe protein-calorie malnutrition per MAMC evaluation is higher than that of control participants. These trends mirror the results that we see in children in clinical practice on a daily basis.

Table 2 Proportion of children in each body mass index (BMI) category

Percentiles BMI	Total	Underweight	Healthy weight	Overweight	Obese
Children with ASD	86 (100%)	4 (5%)	65 (76%)	9 (10%)	8 (9%)
Children without ASD	56 (100%)	3 (5%)	39 (70%)	10 (18%)	4 (7%)
P-value*		1.00	0.619	0.349	0.773

Fisher's exact test for count data $P = 0.644$.

*The *P*-values indicate whether the proportion of autism spectrum disorder (ASD) cases within each percentile range (corresponding to underweight, healthy weight, overweight, obese) differed from the sample proportions.BMI, body mass index.

Table 3 Proportion of children in each protein-calorie nutrition category as measured by mid-arm muscle circumference (MAMC)

Percentiles MAMC	Total	>5th percentile	5–10th percentile	10–25th percentile	25–50th percentile	50–75th percentile	75–90th percentile	>90th percentile
Children with ASD	85 (100%)	26 (30.6%)	15 (17.64%)	7 (8.2%)	19 (22.35%)	12 (14.11%)	2 (2.35%)	4 (4.71%)
Children without ASD	57 (100%)	15 (26.31%)	7 (12.28%)	11 (19.29%)	9 (15.78%)	6 (10.52%)	3 (5.26%)	6 (10.52%)
P-value*		0.75	0.52	0.09	0.45	0.64	0.40	0.21

Fisher's exact test for count data $P = 0.268$.

*The *P*-values indicate whether the proportion of autism spectrum disorder (ASD) cases within each MAMC percentile range differed from the sample proportions.

Additional work does indicate that children with ASD tend toward being overweight or obese, although it also identifies a subset of children at risk for malnutrition or failure to thrive [25–30]. For example, Ho *et al.* [26] found that a high proportion of study participants met the criteria for obesity, whereas Xia *et al.* [30] found that over 30% of study participants with ASD met the criteria for overweight or obesity.

The limitations of the present study include a variation in the number of cases and controls (86 and 57, respectively) as well as a significant difference in age for male participants. Although our analyses indicate that this difference did not significantly impact the data outcome, enrolling additional control participants could have produced different information. Additionally, the present study included primarily male participants in the ASD group (79 males versus 7 females), which is likely a result of the increased prevalence of ASD in boys (2). Enrolling sufficient females with ASD in research studies is a common problem for autism researchers [31] and, by including many more boys than girls with ASD in the present study, we were unable to thoroughly investigate sex-specific differences in nutritional status in children with ASD. Interestingly, the ratio of male to female participants enrolled in the present study was somewhat higher than that typically found in the ASD population. Finally, variability in the accuracy of anthropometric measurements, despite appropriate training, measurement validation and consistency of those completing all measurements, can also be noted as a potential study limitation.

Overall, the results of the present study indicate that anthropometric measurements of children with ASD are similar to those of healthy peer controls. There were significant differences in measurements of height, weight and BMI across female participants in this study. However, despite the lack of statistical significance, when anthropometric measurements for participants as a whole are evaluated more closely, two main conclusions can be drawn: (i) the percentage of children with ASD within the present study who met the criteria for being overweight or obese (18%) was lower than that of their healthy control peers (25%) and (ii) the differences in the calculated MAMC in children with ASD compared to controls approached significance, given that 48.24% of participants with ASD met the criteria for severe or moderate protein-calorie malnutrition, whereas 38.59% of healthy controls fell within the same category. This trend indicates that, within our study, ASD participants were more likely to evidence protein malnutrition than their non-ASD peers.

This case–control study adds to the existing literature by means of a detailed evaluation of multiple factors that may impact growth in children with ASD. Because there are few studies in this arena and the results remain mixed, our work contributes further to the understanding of the complexities of growth status in this population. Additionally, the present study is the first to evaluate and present MAMC as a factor in establishing protein-calorie malnutrition in children with ASD. Based on these findings, our recommendations are two-fold: (i) a comprehensive physical and anthropometric assessment should be completed for all

children with ASD in a primary care setting as a baseline measurement to evaluate the need for referral for more specialised evaluation and potential intervention on a case-by-case basis and (ii) further research in the area of food selectivity behaviours, gastrointestinal concerns and other factors that may influence dietary intake, nutritional status and growth in children with ASD is necessary. This work could include ongoing and targeted behavioural evaluations regarding food selectivity, the expansion of novel research evaluating the impact of the gastrointestinal microbiome on food choices, gastrointestinal symptoms and growth patterns, and the identification of differences in each of these based on ASD subtype.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with CONSORT/STROBE/PRISMA guidelines.

Acknowledgments

The authors would like to thank all the parents whose children participated in this research study. We are very grateful to all of the staff at the Johnson Center for their support of this research, particularly Dr Claire Schutte for performing diagnostic assessments, and Kirsten Bell, RD, LD and Rebeca Flores, RN for collecting the anthropometric assessments. The authors would like to acknowledge the JBJ Foundation for their financial support.

Conflict of interest, source of funding and authorship

The authors declare that they have no conflicts of interest.
No funding is declared.
KB, AG, MG and LH designed the research. KB, AG and MG conducted the research. KB, MG and CNM analysed the data. KB, ZM, CNM, MG and LH wrote the paper. KB had primary responsibility for the final content. All authors read and approved the final manuscript submitted for publication.

References

1. American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders*. 5th edn. Washington, DC: American Psychiatric Association Publishing.
2. Centers for Disease Control (2014) *Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years – Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010*. MMWR 63 (SS02), 1–21.
3. Zablotsky B, Black LI, Maenner MJ, *et al.* (2015) Estimated prevalence of autism and other developmental disabilities following questionnaire changes in the 2014 National Health Interview Survey. *National health statistics reports; no 87*. Hyattsville, MD: National Center for Health Statistics.
4. Emond A, Emmett P, Steer C *et al.* (2010) Feeding symptoms, dietary patterns, and growth in young children with autism spectrum disorders. *Pediatrics* **126**, 337–342.
5. Bandini L, Anderson S, Curtin C *et al.* (2010) Food selectivity in children with autism spectrum disorders and typically developing children. *J Pediatr* **157**, 259–264.
6. Dovey T, Staples P, Gibson E *et al.* (2008) Food neophobia and picky/fussy eating in children: a review. *Appetite* **50**, 181–193.
7. Evans E, Must A, Anderson S *et al.* (2012) Dietary patterns and body mass index in children with autism and typically developing children. *Res Autism Spectr Disord* **6**, 399–405.
8. Herndon A, DiGuiseppi C, Johnson S *et al.* (2009) Does nutritional intake differ between children with autism spectrum disorders and children with typical development? *J Autism Dev Disord* **39**, 212–222.
9. Ernsperger L & Stegen-Hanson T (2004) *Just Take a Bite*. Arlington, TX: Future Horizons, Inc..
10. Ibrahim S, Voigt R, Katusic S *et al.* (2009) Incidence of gastrointestinal symptoms in children with autism: a population-based study. *Pediatrics* **124**, 680–686.
11. Erickson C, Stigler K, Corkins M *et al.* (2005) Gastrointestinal factors in autistic disorder: a critical review. *J Autism Dev Disord* **35**, 713–727.
12. Chaidez V, Hansen R & Hertz-Picciotto I (2014) Gastrointestinal problems in children with autism, developmental delays, or typical development. *J Autism Dev Disord* **44**, 1117–1127.
13. Buie T, Campbell D, Fuchs G *et al.* (2010) Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics* **125**, S1–S18.
14. Adams J, Johansen L, Powell L *et al.* (2011) Gastrointestinal flora and gastrointestinal status in children with autism – comparisons to typical children and correlation with autism severity. *BMC Gastroenterol* **11**, 22.
15. Fryar CD, Gu Q & Ogden CL (2012) Anthropometric reference data for children and adults: United States, 2007–2010. National Center for Health Statistics. *Vital Health Stat* **11**, 1–48.
16. Mari-Bauset S, Llopis-Gonzalez A, Zazpe I *et al.* (2015) Anthropometric measures of Spanish children with autism spectrum disorder. *Res Autism Spectr Disord* **9**, 26–33.

17. Mari-Bauset S, Zazpe I, Sanchis A *et al.* (2012) Are there anthropometric differences between autistic and healthy children? *J Child Neurol* **28**, 1226–1232.
18. Powell-Tuck J & Hennessey E (2003) A comparison of mid upper arm circumference, body mass index and weight loss as indices of undernutrition in acutely hospitalized patients. *Clin Nutr* **22**, 307–312.
19. Ogden C, Carroll M, Kit B *et al.* (2012) Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. *JAMA* **307**, 483.
20. Marí-Bauset S, Zazpe I, Mari-Sanchis A *et al.* (2015) Anthropometric measurements and nutritional assessment in autism spectrum disorders: a systematic review. *Res Autism Spectr Disord* **9**, 130–143.
21. Marí-Bauset S, Zazpe I, Mari-Sanchis A *et al.* (2013) Food selectivity in autism spectrum disorders: a systematic review. *J Child Neurol* **29**, 1554–1561.
22. Sadowska J & Cierebiej M (2011) Evaluation of the nutrition manner and nutritional status of children with autism Preliminary investigations. *Pediatr Współcz Gastroenterol Hepatol Zywienie Dziecka* **13**, 155–160.
23. Al-Farsi Y, Al-Sharbati M, Waly M *et al.* (2011) Malnutrition among preschool-aged autistic children in Oman. *Res Autism Spectr Disord* **5**, 1549–1552.
24. Bicer A & Alsaffar A (2013) Body mass index, dietary intake and feeding problems of Turkish children with autism spectrum disorder (ASD). *Res Dev Disabil* **34**, 3978–3987.
25. Curtin C, Anderson S, Must A *et al.* (2010) The prevalence of obesity in children with autism: a secondary data analysis using nationally representative data from the National Survey of Children's Health. *BMC Pediatr* **10**, 11.
26. Ho H, Eaves L & Peabody D (1997) Nutrient intake and obesity in children with autism. *Focus Autism Other Dev Disabl* **12**, 187–192.
27. Mouridsen S, Rich B & Isager T (2008) Body mass index in male and female children with pervasive developmental disorders. *Pediatr Int* **50**, 569–571.
28. Mouridsen S, Rich B & Isager T (2002) Body mass index in male and female children with pervasive developmental disorders. *Acta Paediatr Jpn* **6**, 197–205.
29. Whiteley P, Dodou K, Todd L *et al.* (2004) Body mass index of children from the United Kingdom diagnosed with pervasive developmental disorders. *Pediatr Int* **46**, 531–533.
30. Xia W, Zhou Y, Sun C *et al.* (2010) A preliminary study on nutritional status and intake in Chinese children with autism. *Eur J Pediatr* **169**, 1201–1206.
31. Lai M, Lombardo M, Auyeung B *et al.* (2015) Sex/gender differences and autism: setting the scene for future research. *J Am Acad Child Adolesc Psychiatry* **54**, 11–24.

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

CLINICAL NUTRITION

Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet

D. Q. Holt,[1,2,3] B. J. Strauss[2] & G. T. Moore[2,3]

[1]Clinical Nutrition and Metabolism Unit, Monash Health, Clayton, VIC, Australia
[2]School of Clinical Sciences, Monash University, Clayton, VIC, Australia
[3]Department of Gastroenterology & Hepatology, Monash Health, Clayton, VIC, Australia

Keywords
beliefs, Crohn's disease, dietary advice, eating patterns, ulcerative colitis.

Correspondence
D. Holt, Clinical Nutrition and Metabolism Unit, Monash Health, 246 Clayton Road, Clayton, Victoria 3168, Australia.
Tel.: +61 3 95943177
Fax: +61 3 95946250
E-mail: darcy.holt@monashhealth.org

How to cite this article
Holt D.Q., Strauss B.J. & Moore G.T. (2017) Patients with inflammatory bowel disease and their treating clinicians have different views regarding diet. *J Hum Nutr Diet*. **30**, 66–72
doi: 10.1111/jhn.12400

Abstract

Background: Diet and body composition play unclear roles in the pathogenesis, activity and symptoms of inflammatory bowel disease (IBD). Evidence-based guidance regarding dietary modification in IBD is lacking. We aimed to determine the attitudes of IBD patients and clinicians to diet.
Methods: The present cross-sectional study comprised an online questionnaire distributed to members of a national IBD patient organisation, assessing demographics, anthropometry, disease phenotype and dietary beliefs. Dietitians, gastroenterologists and surgeons were targeted for a similar questionnaire as a result of membership of national professional bodies.
Results: Nine hundred and twenty-eight patients (72.2% female; mean age 39.5 years; age range 5–91 years) responded. Two-thirds of the patients had Crohn's disease. The mean reported body mass index was 24.9 kg m^{-2} and was significantly skewed to the right. Patients who had taken >10 courses of steroids were had a greater probability of being overweight or obese, independent of disease complications. Most patients (71%) assumed that their diet affected their IBD; 61% considered their IBD specialist disregarded the importance of diet. Of the 136 clinicians who responded, the majority felt that diet was a factor in symptoms and intestinal microbiota. More gastroenterologists (44%) than dietitians (17%) considered that diet had a role in the pathogenesis of IBD ($P = 0.003$). Twenty-six percent of patients reported receiving dietary advice from their IBD specialist, whereas 98% of gastroenterologists reported advice provision. Patients received diverse advice. Half of the patients followed recommendations provided by a clinician.
Conclusions: The present study demonstrates that IBD patients consider diet to be important in their disease. IBD clinicians from different disciplines have diverse views of the role of diet. Advice given to patients is heterogeneous, often perceived as inadequate and poorly followed.

Introduction

Although exclusive enteral nutrition has been shown to be effective in the induction of remission of Crohn's disease (CD) [1,2], the role of diet and body habitus in the pathogenesis and activity of inflammatory bowel disease (IBD) is unclear. Protein-energy malnutrition was reported to be prevalent in patients with IBD [3–7], although recently published series [8–12] have shown a 10–55% prevalence of being overweight or obese in patients with IBD. Obesity has been associated with the need for earlier surgery [13] and faster disease progression [14] in patients with CD. Intestinal dysbiosis is a known feature of IBD, and reduced gut microbial gene richness is associated with obesity and inflammation; dietary interventions were shown to increase bacterial gene richness [15,16].

A recent systematic review revealed a lack of clear, evidence-based guidelines regarding dietary modification in

IBD [17]. Some dietary interventions, such as a reduction in fibre or fermentable carbohydrates, may provide symptomatic improvement, although evidence from studies of dietary intervention is limited [18] because randomised controlled trials in this area are lacking and blinding is not possible.

Although there is evidence suggesting that IBD patients consciously modify their diets [19,20], there is sparse literature available regarding the attitudes of treating clinicians to the role that diet plays in IBD. In recently published data, 80–89% of IBD patients considered dietary advice to be important, although only 8–16% felt that their treating clinician had provided sufficient information [21]. The present study aimed to determine the attitudes of IBD patients, as well as clinicians who have frequent contact with IBD patients, regarding the role of diet in the pathogenesis and symptomatology of IBD.

Materials and methods

An anonymous online questionnaire (Google Docs; Google Inc., Mountain View, CA, USA) was advertised to members of the Crohn's and Colitis Australia mailing list. Members of this large national patient support group (with a membership of 3916 in April 2015; personal communication) (Dr Gregory Moore) were asked structured questions regarding demographics, anthropometric data, their IBD phenotype and treatment, and diet-related beliefs (Table 1; see also Supporting infromation, Appendix S1).

A separate anonymous online questionnaire was distributed to members of the Australian Inflammatory Bowel Disease Association (a section of the Gastroenterological Society of Australia comprising members nominating an interest in gastrointestinal tract infection and inflammation) and the Dietitians Association of Australia (Appendix S2).

Statistical analysis

A descriptive analysis was performed with Fishers exact test being used to analyse differences between groups. The D'Agostino & Pearson omnibus normality test was used to assess normality of the continuous data series. Questionnaires remained open for responses from August to December 2012. Only valid responses to each question were included in analyses. $P < 0.05$ was considered statistically significant.

Ethical considerations

The Southern Health (now Monash Health) Human Research Ethics Committee approved the present study (application 11264A).

Table 1 Demographic details, diet-related beliefs and supplement use of Crohn's and Colitis Australia respondents

	N	%
Female	648	72.2
Mean age (years)	39.5 (range 5–91, SD 15.0)	
Crohn's disease	558	63.9
Ulcerative colitis	315	36.1
Montreal classification of Crohn's disease [41]		
A1 (age <16 years)	83	14.7
A2 (age 17–40 years)	369	65.3
A3 (age >40 years)	113	20.0
L1 (ileal)	158	28.0
L2 (colonic)	133	23.5
L3 (ileocolonic)	262	46.4
L4 (isolated upper gastrointestinal)	12	2.1
B1 (not penetrating/stricturing)	229	39.6
B2 (stricturing)	113	19.5
B3 (penetrating)	237	40.9
Weight change subsequent to diagnosis		
None	237	26.5
Loss	244	27.3
Gain	412	46.1
Believe weight change as a result of IBD	471	52.9
Believe weight change as a result of treatment	415	46.8
Believe weight contributes to severity of IBD	219	24.8
Treatment		
Azathioprine	420	41.0
Mercaptopurine	182	17.8
Methotrexate	148	14.5
No immunomodulator	274	26.8
Anti-tumour necrosis factor	233	27.5
Previous IBD surgery	264	30.4
Believe diet affects IBD	679	76.0
Believe IBD specialist places importance in diet	298	34.4
Over the counter supplements		
Vitamin D	245	27.2
Multivitamin	182	20.2
Calcium	167	18.5
Marine omega-3	159	17.6
Iron	117	13.0
Probiotics	70	7.8
Vitamin B	62	6.9
Vitamin C	61	6.8
Vitamin B_{12}	54	6.0
Folic acid	52	5.8
Magnesium	39	4.3
Zinc	39	4.3
Glucosamine	13	1.4
Aloe vera, flaxeed oil, slippery elm, evening primrose oil		<1

% refers to the percentage of respondents to each particular question. IBD, inflammatory bowel disease.

Results

Patient responses

Demographics

There were 928 respondents (72% female; mean age 39.5 years; age range 5–91 years who) who replied to the advertisement for patients with IBD, which is an estimated response rate of 24% (comprising an expected rate of response for an e-mail-based survey without reminders or incentives) [22,23]. In total, 64% were identified as having CD and 36% were identified as having ulcerative colitis (UC) (Table 1).

Most patients described a disease duration of more than 5 years. Patients with CD had a self-reported mean body mass index (BMI) of 24.7 kg m^{-2} (median 23.9 kg m^{-2}, SD 5.1 kg m^{-2}); for patients with UC, the mean BMI was 24.9 kg m^{-2} (median 24.0 kg m^{-2}, SD 5.6 kg m^{-2}; difference not statistically significant). The distribution of BMI values was asymmetrical, with a long tail to the right (skewness: CD 1.060; UC 1.247). A BMI <18.5 kg m^{-2}, meeting the World Health Organization definition of being underweight [24], was reported in 5.8% of respondents with CD and 6.3% of subjects with UC (not significant).

Of the 366 (39%) patients with a BMI >25 kg m^{-2}, 77% considered themselves as overweight, 22% as normal weight and 1% as underweight.

Treatment for inflammatory bowel disease

Of the 44% of patients who gained weight subsequent to their diagnosis of IBD, 67% considered the change to be a result of treatment for IBD (Table 1). Overall, 55% of respondents attributed a change in weight to treatment (58% CD compared to 50% UC; $P = 0.04$) There was no significant difference in BMI between the 39% who had complicated CD (Montreal classification) and those who did not. Patients who had taken more than 10 courses of steroids were more likely [odds ratio 1.59 (range 1.14–2.23)] to be overweight or obese [50.4%; BMI ≥25 kg m^{-2}, mean (SD) 25.72 (6.04) kg m^{-2}] than those who had taken 0–3 courses of steroids [40.0%; BMI ≥25 kg m^{-2}, mean (SD) 23.67 (5.21) kg m^{-2}] ($P = 0.008$). There was no difference between types of IBD and proportion of patients who had taken more than 10 courses of steroids (25.9% CD, 26.2% UC; $P = 0.933$). More than half (51%) of those patients reporting more than 10 courses of steroids considered that they had gained weight subsequent to the diagnosis of IBD compared to 44% of those who had taken fewer than three courses ($P = 0.115$). There was no significant correlation between WHO classifications of BMI (underweight/normal weight/overweight/obese) and rates of surgery for IBD, or the prevalence of complicated (stricturing or penetrating) CD.

Dietary advice and beliefs

One quarter (26%) of patients reported receiving dietary advice from their IBD specialist, whereas 98% of gastroenterologists reported providing dietary advice to patients. The large majority (91%) of patients referred to a dietitian by either their general practioner or specialist had seen a dietitian compared to 46% of all respondents. Significantly more CD patients than those with UC had seen a dietitian (56.1% versus 40.8%; $P < 0.001$). There was no difference in perception of diet (as either healthy or as requiring improvement) between patients who had seen a dietitian and those who had not. Patients who had seen a dietitian were more likely to consider that diet affected their IBD (81.4% versus 72.4%; $P = 0.002$) Half (50%) of patients reported following dietary advice provided by a clinician. Supplement or vitamin use was more prevalent among patients who had seen a dietitian (76.2% versus 69.1%; $P = 0.025$) or a naturopath (81.5% versus 70.8%; $P = 0.005$). Familiarity with a low FODMAP diet (fermentable, oligo-, di-, mono-saccharides and polyols) was reported by 38% of patients; the proportion was twice as high in patients who had seen a dietitian as those who had not ($P < 0.001$). Three-quarters (72%) had used (or were aware of) probiotics (Fig. 1). Almost half of the patients had knowledge of a low residue diet; there was no significant difference in awareness between patients with stricturing disease and those without.

Most patients (71%) considered that diet affected their IBD, with symptoms being worsened by spicy foods in more than half of respondents; high fibre foods, dairy and nuts were similarly implicated. Avoidance of particular foods was more common in patients who had surgery for IBD (84.5% versus 77.1%; $P = 0.033$), with a rate of 93% amongst patients reporting stricturing disease. Food avoidance rates did not differ between CD and UC patients.

The majority (61%) of respondents felt their IBD specialist did not place importance in the role of diet, with significantly fewer UC patients than CD patients considering this to be the case (38.2% versus 26.7%; $P < 0.001$).

Responses from clinicians

The clinician survey was completed by 136 practitioners (including 46 gastroenterologists, 12 surgeons and 73 dietitians; response rates not defined). Half (49%) of the respondents spent less than 10% of their working time with IBD patients. However, the proportion of working time spent on IBD by the respondent gastroenterologists was significantly higher: 39% reported this occupying more than half of their time, with a further 24% reporting one quarter to half their time being occupied.

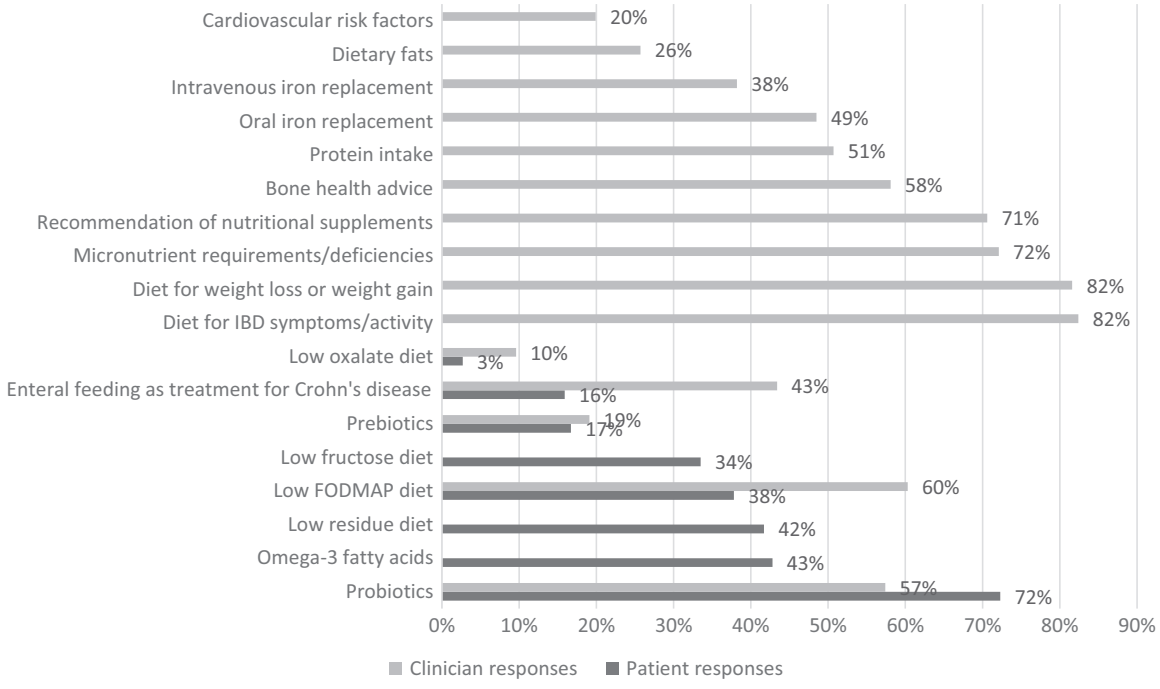

Figure 1 Dietary advice provided by clinicians and received by patients. FODMAP, fermentable, oligo-, di-, mono-saccharides and polyols; IBD, inflammtory bowel disease.

Most (79%) respondents felt that less than one quarter of their IBD patients were overweight or obese. The majority of clinicians felt that diet was a factor in symptoms (94%; 99% of dietitians) and intestinal microbiota (79%; 52% of dietitians); more gastroenterologists (44%) than dietitians (17%) considered diet to have a role in the pathogenesis of IBD ($P = 0.003$). Eighty-two percent of clinicians had advised dietary measures with regard weight loss or gain (Fig. 1), with 72% addressing specific micronutrient deficiencies and 60% providing education about FODMAPs. By contrast to the majority opinion of the patient group, 42% of clinicians considered that they held similar views to their patients regarding the role of diet.

Discussion

The role of diet in IBD may be considered in terms of pathogenesis, symptomatology and nutritional deficiency as a result of malabsorption or dietary restriction.

An analysis of practice guidelines from large dietetic and gastroenterology societies and patient support associations in the USA, Europe and Japan revealed that advice to clinicians regarding micronutrient supplementation was common, although recommendations regarding screening for deficiency varied. Dietary modifications also varied, with common themes of reducing fibre consumption during disease activity and avoidance of dairy if lactose intolerant, although some guidelines suggest the need for a reduction in excess fat, as well as excess or fermentable carbohydrates [25]. This diversity in practical advice was reflected in the responses provided by professionals in the present study.

Although enteral nutrition is an effective treatment for CD, a recent comprehensive review has identified an absence of published data regarding its use in UC [2]. It is not established that the role of diet is different in these types of IBD. We aimed to determine variances in attitude or experience between CD and UC patients. For the majority of categorical and continuous variables identified, there was no significant difference. The only identified distinctions between patient groups were: a higher proportion of CD patients considering a change in their weight was a result of IBD treatment, a lower rate of UC patients having seen a dietitian, and CD patients more often considering that their specialist places importance in the role of diet.

Previous studies have demonstrated the high importance patients with IBD place on the role of diet. In a series of patients surveyed on admission to a French IBD unit, diet was felt to be an initiating factor in the development of IBD by 15.6%, whereas 57.8% considered that food could cause a relapse [19]. A larger proportion of patients in the present study (76%) felt that diet affected

their IBD but, in both studies, over 70% had received dietary advice, and a majority had modified their diets to avoid a disease relapse. The idea that diet played an important role in IBD was more prevalent among patients who had seen a dietitian; this may be either cause or effect. Vitamin or supplement use was higher in patients who had sought dietetic or naturopathic advice. Qualitative analysis in our Australian cohort found that spicy foods, high fibre, dairy and nuts were implicated in worsening symptoms. A variety of foods were considered to contribute to symptoms and these were similar to those reported in another study implicating spicy foods, fat, raw fruits and vegetables, and carbonated beverages [19]. A structured dietary questionnaire administered to a well-described cohort of New Zealand CD patients did not consistently identify foods that were beneficial or detrimental; curry was the most generally detrimental food, and fish, banana and yoghurt were among the most commonly reported beneficial foods [26]. Similar results in terms of dietary preferences were seen in an Internet-based cohort of 2329 American IBD patients [20] and a single-centre survey of CD patients [27]. Yoghurt, bananas, fish and potatoes were among several foods identified as being beneficial in a novel study analysing the diet of subjects with UC in the week prior to a grading sigmoidoscopy; beneficial foods were considered to be those consumed in higher proportions in subjects with low endoscopic activity indices [28]. We found that previous surgery for IBD and stricturing disease were associated with higher incidences of food avoidance.

Dietary restrictions and modifications may lead to suboptimal micronutrient intake. In a study of ambulatory CD patients, diet analysis revealed less than the recommended levels of folate (in 100% of subjects), vitamin C (approximately 40%), vitamin E (almost all subjects) and calcium (approximately 90%) [6], despite an adequate energy intake, normal BMI and mild disease activity. In another cohort, 40–90% of IBD patients had vitamin levels <15th centile of normal [29]. Similar results have been published with respect to a Canadian IBD outpatient population [30]. British patients with UC demonstrated poor adherence to healthy-eating guidelines, although, during flares and treatment, they generally avoided contraindicated foods [31]. In our patient group, awareness of dietary restrictions may explain the widespread (68%) use of supplemental vitamins, minerals or herbal extracts (Table 1).

A significant proportion of patients reported knowledge of diets low in FODMAPs, with 9.2% of respondents using a free text field in the survey to comment on the utility of this diet. Familiarity with this diet was much higher among patients who had seen a dietitian, and this may reflect Australian clinical practice because a majority of clinicians reported providing advice about FODMAPs. There is an evidence basis for this advice: when a recall questionnaire was used in a cohort of IBD patients, it appeared that a reduction in the intake of FODMAPs reduced abdominal symptoms such as pain, diarrhoea, bloating and wind [32]. It has been postulated that increased FODMAP intake in a changing Western diet may explain the rising incidence of CD, implicating diet in disease pathogenesis [33]. Aside from the disease-specific effects of these fermentable carbohydrates, their consumption is strongly associated with worsening symptoms of irritable bowel syndrome [34], which is a condition that is two- to three-fold more prevalent in IBD patients in long-term remission than in the general population [35], although such symptoms may represent occult inflammation [36]. Quality of life improved in a small study evaluating the use of a 'half elemental diet' in CD patients in remission [37]; whether this is the result of a reduction in FODMAP consumption is uncertain. A recent systematic review found very little good-quality evidence regarding the use of indigestible carbohydrates in CD [38]. In a randomised controlled study of fibre supplementation in patients in remission from UC, gut transit time was altered by resistant starch and wheat bran consumption, whereas carbohydrate fermentation and short-chain fatty acid production were unchanged [39]. Similarly, a low FODMAP diet caused a reduction in total bacterial abundance, no effect on relative abundance of bacterial groups with putative health benefits and no effect on increased faecal butyrate excretion [40].

Despite a systematic review showing a reduced BMI in 37% of CD patients and 20% of UC patients [41], the self-reported incidence of an underweight BMI in this large Australian cohort was similar to that reported in the 2011–2012 Australian National Health Survey; rates of being overweight or obese were only slightly lower. The self-reported mean BMI for the general Australian population was 27.9 kg m^{-2} for men and 27.2 kg m^{-2} for women [42]. Steroid use was associated with increased weight, suggesting a drug-related effect because complicated disease in itself was not associated with a significant difference in weight. A high degree of knowledge of CD biology and relevant anatomy has been demonstrated in members of a patient support group [43], providing some validation to responses regarding disease phenotype and treatments in our cohort.

A strength of the present study is the large number of individual responses from members of a national association, matched with clinicians treating the same population. In this patient group, a wide variety of opinions regarding diet existed, and knowledge regarding probiotics, omega-3 fatty acids, low residue and low FODMAP diets was prevalent. However, adherence to dietary advice was poor. This may reflect a lack of efficacy or a paucity of firm evidence.

Conclusions

This present study emphasises that IBD clinicians from different disciplines have diverse views of the role of diet in IBD; for example, gastroenterologists are significantly more likely to place importance in the role of diet in the pathogenesis of IBD. The advice given to patients is heterogeneous, often perceived as inadequate and poorly followed. Further work in this field is needed to provide an evidence base from which to offer the guidance that patients expect.

Transparency statement

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with STROBE guidelines.

Acknowledgments

We thank Crohn's and Colitis Australia for allowing distribution of the questionnaire hyperlink, as well as the members of each organisation who participated.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
Researchers contributing to this work were funded by the Angela McAvoy AM Fellowship from Crohn's and Colitis Australia, as well as by an Emerging Researcher Fellowship from Monash Health.
DH, GM and BS formulated the questionnaires and designed the study. DH performed the statistical analyses and prepared the manuscript. BS and GM critically revised the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

References

1. O'Morain C, Segal AW & Levi AJ (1984) Elemental diet as primary treatment of acute Crohn's disease: a controlled trial. *Br Med J (Clin Res Ed)* **288**, 1859–1862.
2. Triantafillidis J-K, Vagianos C & Papalois AE (2015) The role of enteral nutrition in patients with inflammatory bowel disease: current aspects. *Biomed Res Int* **2015**, Article 197167; 1–12.
3. Krok KL & Lichtenstein GR (2003) Nutrition in Crohn disease. *Curr Opin Gastroenterol* **19**, 148–153.
4. Donnellan CF, Yann LH & Lal S (2013) Nutritional management of Crohn's disease. *Therap Adv Gastroenterol* **6**, 231–242.
5. Gassull MA (2003) Nutrition and inflammatory bowel disease: its relation to pathophysiology, outcome and therapy. *Dig Dis* **21**, 220–227.
6. Aghdassi E, Wendland BE, Stapleton M *et al.* (2007) Adequacy of nutritional intake in a Canadian population of patients with Crohn's disease. *J Am Diet Assoc* **107**, 1575–1580.
7. Nguyen GC, Munsell M & Harris ML (2008) Nationwide prevalence and prognostic significance of clinically diagnosable protein-calorie malnutrition in hospitalized inflammatory bowel disease patients. *Inflamm Bowel Dis* **14**, 1105–1111.
8. Sousa Guerreiro C, Cravo M, Costa AR, Miranda A, Tavares L, Moura-Santos P *et al.* (2007) A comprehensive approach to evaluate nutritional status in Crohn's patients in the era of biologic therapy: a case-control study. *Am J Gastroenterol* **102**, 2551–2556.
9. Kugathasan S, Nebel J, Skelton JA *et al.* (2007) Body mass index in children with newly diagnosed inflammatory bowel disease: observations from two multicenter North American inception cohorts. *J Pediatr* **151**, 523–527.
10. Long MD, Crandall WV, Leibowitz IH *et al.* (2010) Prevalence and epidemiology of overweight and obesity in children with inflammatory bowel disease. *Inflamm Bowel Dis* **17**, 2162–2168.
11. Steed H, Walsh S & Reynolds N (2009) A brief report of the epidemiology of obesity in the inflammatory bowel disease population of Tayside, Scotland. *Obes Facts* **2**, 370–372.
12. Nic Suibhne T, Raftery TC, McMahon O *et al.* (2013) High prevalence of overweight and obesity in adults with Crohn's disease: associations with disease and lifestyle factors. *J Crohns Colitis* **7**, e241–e248.
13. Hass DJ, Brensinger CM, Lewis JD *et al.* (2006) The impact of increased body mass index on the clinical course of Crohn's disease. *Clin Gastroenterol Hepatol* **4**, 482–488.
14. Blain A, Cattan S, Beaugerie L *et al.* (2002) Crohn's disease clinical course and severity in obese patients. *Clin Nutr* **21**, 51–57.
15. Cotillard A, Kennedy SP, Kong LC *et al.* (2013) Dietary intervention impact on gut microbial gene richness. *Nature* **500**, 585–588.
16. Albenberg LG & Wu GD (2014) Diet and the intestinal microbiome: associations, functions, and implications for health and disease. *Gastroenterology* **146**, 1564–1572.
17. Richman E & Rhodes JM (2013) Review article: evidence-based dietary advice for patients with inflammatory bowel disease. *Aliment Pharmacol Ther* **38**, 1156–1171.

18. Charlebois A, Rosenfeld G & Bressler B (2015) The impact of dietary interventions on the symptoms of inflammatory bowel disease: a systematic review. *Crit Rev Food Sci Nutr* **10**, 1370–1378.
19. Zallot C, Quilliot D, Chevaux J-B *et al.* (2013) Dietary beliefs and behavior among inflammatory bowel disease patients. *Inflamm Bowel Dis* **19**, 66–72.
20. Cohen AB, Lee D, Long MD *et al.* (2013) Dietary patterns and self-reported associations of diet with symptoms of inflammatory bowel disease. *Dig Dis Sci* **58**, 1322–1328.
21. Wong S, Walker JR, Carr R *et al.* (2012) The information needs and preferences of persons with longstanding inflammatory bowel disease. *Can J Gastroenterol* **26**, 525–531.
22. Sheehan K. B. (2001) E-mail Survey Response Rates: A Review. *Journal of Computer-Mediated Communication* **6**, 0. doi: 10.1111/j.1083-6101.2001.tb00117.x.
23. Edwards P, Roberts I, Clarke M *et al.* (2002) Increasing response rates to postal questionnaires: systematic review. *BMJ* **324**, 1183.
24. World Health Organization (1995) Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. Technical Report Series no. 854. WHO: Geneva.
25. Brown AC, Rampertab SD & Mullin GE (2011) Existing dietary guidelines for Crohn's disease and ulcerative colitis. *Expert Rev Gastroenterol Hepatol* **5**, 411–425.
26. Triggs CM, Munday K, Hu R *et al.* (2010) Dietary factors in chronic inflammation: food tolerances and intolerances of a New Zealand Caucasian Crohn's disease population. *Mutat Res* **690**, 123–138.
27. Zutshi M, Hull TL & Hammel J (2007) Crohn's disease: a patient's perspective. *Int J Colorectal Dis* **22**, 1437–1444.
28. Magee EA, Edmond LM, Tasker SM *et al.* (2005) Associations between diet and disease activity in ulcerative colitis patients using a novel method of data analysis. *Nutr J* **4**, 7.
29. Fernandez-Banares F, Abad-Lacruz A, Xiol X *et al.* (1989) Vitamin status in patients with inflammatory bowel disease. *Am J Gastroenterol* **84**, 744–748.
30. Vagianos K, Bector S, McConnell J *et al.* (2007) Nutrition assessment of patients with inflammatory bowel disease. *JPEN J Parenter Enteral Nutr* **31**, 311–319.
31. Walton M, Walton M, Alaunyte I *et al.* (2014) Do patients living with ulcerative colitis adhere to healthy eating guidelines? A cross-sectional study *Br J Nutr* **112**, 1628–1635.
32. Gearry RB, Irving PM, Barrett JS *et al.* (2009) Reduction of dietary poorly absorbed short-chain carbohydrates (FODMAPs) improves abdominal symptoms in patients with inflammatory bowel disease-a pilot study. *J Crohns Colitis* **3**, 8–14.
33. Gibson PR & Shepherd SJ (2005) Personal view: food for thought – western lifestyle and susceptibility to Crohn's disease. The FODMAP hypothesis. *Aliment Pharmacol Ther* **21**, 1399–1409.
34. Shepherd SJ, Parker FC, Muir JG *et al.* (2008) Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin Gastroenterol Hepatol* **6**, 765–771.
35. Simrén M, Axelsson J, Gillberg R *et al.* (2002) Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol* **97**, 389–396.
36. Keohane J, O'Mahony C, O'Mahony L *et al.* (2010) Irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease: a real association or reflection of occult inflammation? *Am J Gastroenterol* **105**, 1788, 1789–1794.
37. Takagi S, Utsunomiya K, Kuriyama S *et al.* (2009) Quality of life of patients and medical cost of 'half elemental diet' as maintenance therapy for Crohn's disease: secondary outcomes of a randomised controlled trial. *Dig Liver Dis* **41**, 390–394.
38. Lee J, Allen R, Ashley S *et al.* (2014) British Dietetic Association evidence-based guidelines for the dietary management of Crohn's disease in adults. *J Hum Nutr Diet* **27**, 207–218.
39. James SL, Christophersen CT, Bird AR *et al.* (2015) Abnormal fibre usage in UC in remission. *Gut* **64**, 562–570.
40. Halmos EP, Christophersen CT, Bird AR *et al.* (2015) Diets that differ in their FODMAP content alter the colonic luminal microenvironment. *Gut* **64**, 93–100.
41. Bryant RV, Trott MJ, Bartholomeusz FD *et al.* (2013) Systematic review: body composition in adults with inflammatory bowel disease. *Aliment Pharmacol Ther* **38**, 213–225.
42. Australian Bureau of Statistics (2012) Australian Health Survey: First Results, 2011–12. ABS: Canberra.
43. Eaden JA, Abrams K & Mayberry JF (1999) The Crohn's and colitis knowledge score: a test for measuring patient knowledge in inflammatory bowel disease. *Am J Gastroenterol* **94**, 3560–3566.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article:
Appendix S1. Inflammatory bowel disease and diet questionnaire.
Appendix S2. Clinician questionnaire: diet and inflammatory bowel disease.

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

CLINICAL NUTRITION

Adding glucose to food and solutions to enhance fructose absorption is not effective in preventing fructose-induced functional gastrointestinal symptoms: randomised controlled trials in patients with fructose malabsorption

C. J. Tuck, L. A. Ross, P. R. Gibson, J. S. Barrett & J. G. Muir

Department of Gastroenterology, Monash University, The Alfred Hospital, Melbourne, VIC, Australia

Keywords
FODMAPs, food intolerance, fructose, functional bowel disorders, irritable bowel syndrome, malabsorption.

Correspondence
C. J. Tuck, Department of Gastroenterology, Central Clinical School, Monash University, Level 6, The Alfred Centre, 99 Commercial Road, Melbourne, VIC 3004, Australia.
Tel.: +61 3 9903 0264
Fax: +61 3 9903 0556
E-mail: caroline.tuck@monash.edu

How to cite this article
Tuck C.J., Ross L.A., Gibson P.R., Barrett J.S. & Muir J.G. (2017) Adding glucose to food and solutions to enhance fructose absorption is not effective in preventing fructose-induced functional gastrointestinal symptoms: randomised controlled trials in patients with fructose malabsorption. *J Hum Nutr Diet*. **30**, 73–82
doi: 10.1111/jhn.12409

Abstract

Background: In healthy individuals, the absorption of fructose in excess of glucose in solution is enhanced by the addition of glucose. The present study aimed to assess the effects of glucose addition to fructose or fructans on absorption patterns and genesis of gastrointestinal symptoms in patients with functional bowel disorders.
Methods: Randomised, blinded, cross-over studies were performed in healthy subjects and functional bowel disorder patients with fructose malabsorption. The area-under-the-curve (AUC) was determined for breath hydrogen and symptom responses to: (i) six sugar solutions (fructose in solution) (glucose; sucrose; fructose; fructose + glucose; fructan; fructan + glucose) and (ii) whole foods (fructose in foods) containing fructose in excess of glucose given with and without additional glucose. Intake of fermentable short chain carbohydrates (FODMAPs; fermentable, oligo-, di-, monosaccharides and polyols) was controlled.
Results: For the fructose in solution study, in 26 patients with functional bowel disorders, breath hydrogen was reduced after glucose was added to fructose compared to fructose alone [mean (SD) AUC 92 (107) versus 859 (980) ppm 4 h^{-1}, respectively; $P = 0.034$). Glucose had no effect on breath hydrogen response to fructans ($P = 1.000$). The six healthy controls showed breath hydrogen patterns similar to those with functional bowel disorders. No differences in symptoms were experienced with the addition of glucose, except more nausea when glucose was added to fructose ($P = 0.049$). In the fructose in foods study, glucose addition to whole foods containing fructose in excess of glucose in nine patients with functional bowel disorders and nine healthy controls had no significant effect on breath hydrogen production or symptom response.
Conclusions: The absence of a favourable response on symptoms does not support the concomitant intake of glucose with foods high in either fructose or fructans in patients with functional bowel disorders.

Introduction

Fructose is a dietary 6-carbon monosaccharide that is present in commonly consumed foods such as apples, pears and fruit juices, and is also used as a sweetener [1]. It is also found as part of the disaccharide sucrose and the plant oligosaccharide fructan [1,2]. Fructose has been implicated in multiple health problems, such as obesity [3] and depression [4], although it is unknown whether the relationship is cause and effect. Dietary fructose is one inducer of abdominal symptoms in patients with functional bowel disorders (FBD), including irritable bowel

syndrome (IBS). This is a result of its slow absorption in the small intestine with resultant passive diffusion increasing small intestinal luminal water content and, in some individuals, its malabsorption with fermentation in the proximal colon. Restricting the intake of fructose in excess of glucose is part of the dietary restriction in the low FODMAP (fermentable, oligo-, di-, monosaccharides and polyols) diet, which provides symptom improvement in IBS [5–8]. An alternative strategy is to improve the rate of absorption of fructose.

Small intestinal fructose absorption principally involves the transporters, GLUT5 and GLUT2 [9]. GLUT5 is specific to fructose and provides carrier-mediated facilitative diffusion. However, its low capacity leads to slow uptake of luminal fructose that occurs along the length of the small intestine [10]. In the presence of high luminal glucose concentrations, GLUT2 can insert into the apical membrane, providing a high capacity pathway for fructose absorption [11]. Hence, the concentration of luminal glucose plays a key role in the rate of fructose absorption. At equal or greater concentrations of glucose, fructose will be largely absorbed rapidly via GLUT2 [12]. When fructose is present in excess of glucose, it is dependent upon the slower GLUT5 pathway [13,14], and hence fructose molecules remain in the small intestinal lumen for longer. The passive diffusion exerted by fructose in the lumen is the most likely reason for the increased luminal water content and distension [15]. Some fructose fails to be absorbed and enters the large intestine resulting in malabsorption [9]. The degree of malabsorption will depend not only upon the efficiency of GLUT5, but also the dose of fructose and the time available for its absorption [9]. The malabsorbed fructose which reaches the large intestine is then available for fermentation by the colonic microbiota, resulting in hydrogen and/or methane production, depending on the type of microbiota present. Some of this gas produced can then travel to the lungs via the bloodstream, and can be measured through exhaled breath [16].

One therapeutic technique used to enhance the absorption of fructose is to elevate the concentration of luminal glucose by its co-ingestion with foods containing fructose in excess of glucose. When glucose is added to ingested fructose solutions or fruit juices in healthy subjects, both fructose malabsorption (using breath hydrogen as a marker) [17–21] and small intestinal water content (using magnetic resonance imaging) [15] are reduced. The optimal reduction in breath hydrogen has been observed when glucose and fructose are in a ratio of 1 : 1 [17]. However, whether this strategy improves fructose absorption and subsequent symptom induction when the fructose is contained within whole food, as well as solutions, has not been investigated in patients with FBD.

The present study aimed to address the hypotheses that glucose addition to solutions and whole foods containing fructose in excess of glucose will enhance fructose absorption and improve symptoms in patients with FBD. Randomised, blinded, cross-over studies in patients with FBD and in healthy subjects with fructose malabsorption were undertaken using breath hydrogen and symptoms as end-points.

Materials and methods

Subjects

Subjects were recruited via advertising through the Monash University website, social media, dietitian private practice clinics and breath-testing clinics, in Melbourne, Australia. Inclusion criteria required participants to be aged 18–70 years, and, within the past 3 months, to have fructose malabsorption identified by breath hydrogen rise of ≥15 ppm after 35 g of fructose. Two groups of fructose malabsorbers were recruited: healthy subjects (without gastrointestinal symptoms) and patients with FBD, as determined by a gastroenterologist using the Rome III criteria. Exclusion criteria included inadequate breath hydrogen production (<15 ppm) after 35 g of fructose, pregnancy or breastfeeding, diabetes, other gastrointestinal disorders such as coeliac disease, antibiotic or probiotic use in the past 2 weeks, and the taking of colonoscopy preparations in the past 4 weeks. Those who expressed interest but had a positive fructose breath test more than 3 months prior were asked to repeat the fructose breath test prior to enrolment and only if fructose malabsorption was retained were they then invited to enrol.

Study protocol: fructose in solution

The fructose in solution study was a randomised, double-blind, placebo-controlled, cross-over trial. After careful instruction, participants were asked to complete tests involving six separate sugar solutions (Table 1) performed at home on separate days at least 2 days apart. The solutions used included glucose alone, sucrose alone (negative controls), fructose alone (fructose control), fructose and glucose (co-administration intervention), fructans (positive control), and fructans and glucose (co-administration intervention). A dose of 25 g of fructose was used, with equal quantities of glucose added to the combined solution to give a total of 50 g. To provide an equivalent dosage, 50 g of sucrose and 50 g of glucose were used. As a positive control for induction of symptoms, a fructan (Oligofructose Orafti P-95; Beneo-Orafti, Oreye, Belgium) was used because they are short-chain (degree of polymerisation of four) and not digested in the small intestine. A dose of 10 g was used as larger

Table 1 Composition of sugar solutions used in the experiments in the fructose in solution study

Sugar solution	Quantity (g)	Volume (mL)	Concentration (%)	Osmolarity (mOsm kg^{-1})
Glucose	50	375	13.3	837
Sucrose	50	375	13.3	504
Fructose	25	375	6.6	442
Fructose + Glucose	25 + 25	375	13.3	856
Fructans	10	375	2.6	87
Fructans + Glucose	10 + 25	375	9.3	461

quantities were more likely to be poorly tolerated [22], with the equivalent glucose of 25 g added to the combined solution. Dosage and volumes used for the sugar solutions were chosen to ensure a suitable osmolarity to be tolerated by the participants as shown in Table 1. The order of sugar solution consumption was randomised (www.randomizer.org). All sugar solutions were made up to 375 mL in water and had 3 g of orange sugar flavouring (containing 3 g of sucrose; Vitafresh, Hansells, Auckland, New Zealand) added. Solutions were labelled 'A' to 'F' by a department member who was not involved in data collection or analysis to aid in the blinding of both participants and researchers.

Participants were instructed to follow a diet low in FODMAPs and fibre, which they provided themselves for 24 h prior to each test. After an overnight fast, a baseline breath sample was taken, the sugar solution was consumed within 5 min and breath samples collected every 20 min for the next 4 h. Participants were asked to refrain from eating during this time. Hourly breath samples were taken for a further 8 h. Participants were provided with lunch, dinner and snacks to consume after the test solution. All of the food provided was low in FODMAPs (including lactose-free) to minimise other sources of breath hydrogen production. Samples of the meals and snacks made were analysed for their total FODMAP content according to previously described protocols [1,23]. The nutrient analysis (analysed using FOODWORKS PROFESSIONAL, version 7; Xyris Software Pty Ltd, Brisbane, QLD, Australia) and FODMAP content of the foods consumed are provided in the Supporting information (Table S1).

Study protocol: fructose in foods

The fructose in foods study was a randomised, single-blind, cross-over trial using whole foods as the source of fructose with and without added glucose. During a 36-h low FODMAP run-in period, followed by a 24-h test day, all food was provided (see Supporting information, Table S2). Breath hydrogen samples were collected hourly for 14 h on two consecutive days, commencing before breakfast each day. For the test day, participants were randomised to either a diet high in fructose with no added glucose (high fructose diet) or high in fructose with glucose added to give a 1 : 1 ratio of free fructose to free glucose (fructose/glucose co-administration diet). Following a 1-week washout period, participants crossed over to the alternative diet. For both test diets, foods included were naturally high in fructose in excess of glucose (including watermelon, apple/guava juice, pear and apple muffins). The remainder of the diet was low in total FODMAP content.

For the fructose/glucose co-administration diet, glucose was co-ingested by participants in tablet form (Glucodin tablets; Reckitt Benckiser, West Ryde, NSW Australia) when whole pieces of fruit were eaten (see Supporting information, Table S2). Participants were asked to consume the glucose tablets at the time of meal consumption. Glucose powder (Glucodin Powder; Reckitt Benckiser) was added during the baking process for apple muffins and premixed with apple/guava juice. For the high fructose diet, sucrose cubes and powder replaced the glucose to aid in blinding the participants.

The high fructose foods provided 11 g of fructose in excess of glucose. The diets provided during the two run-in periods were identical. The two high fructose diets were also identical apart from the addition of sucrose and/or glucose. There were no differences in macronutrient content between the two test diets, including total carbohydrate, starch, dietary fibre and total sugar levels.

Hydrogen breath testing

The methodology for the breath testing followed that reported previously by Ong *et al.*[8]. Breath samples were collected in collection bags (Wagner Analysen Technik Pty Ltd, Carlton, VIC, Australia). Breath hydrogen concentrations were analysed using a gas chromatography (Microlyzer Model DP Plus and Model SC; Quintron Instrument Co., Milwaukee, WI, USA). The machine was calibrated prior to sample analysis.

Symptom scores

At the end of the each day, participants were asked to score their symptoms on a previously validated 100-mm

visual analogue scale (VAS) [24]. The symptom diaries requested participants to rate overall abdominal symptoms, abdominal pain, bloating, wind, nausea and fatigue. Participants were also asked 'During the past day, were your symptoms adequately controlled (meaning not troublesome for you) – yes or no?'.

Ethics approval

All participants provided informed consent prior to commencing the study. Ethics approval was received for the fructose in solution study from The Alfred Ethics Committee (Number 124/12) and Eastern Health Research and Ethics Committee (E57/1112). For the fructose in foods study, approval was received from Deakin University Human Research Committee (EC 37-2008) and Eastern Health Ethics committee (E52/0708). The trials were registered with the Australian New Zealand clinical trials registry (Number ACTRN12614000176662 and ACTRN12616000766415).

Statistical analysis

For the fructose in solution study, a sample size of 20 participants in the FBD subgroup was required to detect a 30% change in the primary end-point, breath hydrogen, with a power of 80%. $P \leq 0.05$ was considered statistically significant. An interim analysis after 16 patients with FBD had completed the fructose in solution study was planned. This was performed by an independent statistician examining only the primary end-point. An additional 10 participants with FBD were then recruited. No power calculations were conducted for the healthy subgroup or the whole food study.

Statistical analysis was carried out using IBM SPSS, version 22 (IBM Corp., Armonk, NY, USA). Breath hydrogen data are displayed as both average and area-under-the-curve (AUC) using the mean (SD), as reported previously [8]. Per-protocol analyses were undertaken, hydrogen data were corrected for baseline and outliers (>2 SD above mean) were removed. For the fructose in solution study, hydrogen data were assessed at both the 4- and 12-h time points via one-way repeat analysis of variance and pairwise comparisons with Bonferroni correction. Greenhouse–Geisser correction was used for problems with homogeneity of covariance. For the fructose in foods study, hydrogen production between the two test diets was compared using paired *t*-tests. The symptom data for both the fructose in solution and fructose in foods studies were analysed using nonparametric analysis and outliers were removed (>2 SD above mean). Friedman's test and Wilcoxon signed ranks test were used and expressed using the median and interquartile range. As a result of uneven subject numbers in the FBD versus healthy subject groups in the fructose in solution study, no statistical comparisons could be made between the two groups.

Results

Subjects

In the fructose in solution study, 26 FBD [mean (range) age 40 (22–65) years; 23 female] and six healthy [mean (range) age 35 (26–52) years; five female] participants were recruited. Functional bowel disorder subtypes included 21 IBS (three constipation-predominant; nine diarrhoea-predominant; eight mixed; one un-subtyped); one functional constipation, three functional bloating and one functional diarrhoea. In the fructose in foods study, 10 FBD [mean (range) age 50 (31–76) years; nine female] and nine healthy [mean (range) age 47 (22–65) years; nine female] participants were recruited, one FBD participant was a clear outlier and was removed from all analysis. Participants with FBD were well matched demographically with the healthy subjects in each part of the study. Details of the subject recruitment process and subsequent participation are provided in the Supporting information (Fig. S1). For the fructose in solution study, intake of individual FODMAP subgroups and total FODMAP intake were similar across the test days, with the exception of the content of the sugar solutions. Intake of macronutrients and fibre was similar between the healthy and FBD subgroups, with the exception of fat during the fructose + glucose sugar solution test day which was significantly higher in the FBD group ($P = 0.005$) as shown in the Supporting information (Table S1). All subjects consumed the entire 375 mL of sugar solution.

Fructose in solution

Breath hydrogen excretion

Average breath hydrogen production across the 12-h collection period for the FBD subject group is shown in Fig. 1(a). The 4-h breath hydrogen response expressed as AUC following the fructose test drink [mean (SD) fructose 859 (984) ppm 4 h^{-1}] was reduced with the addition of glucose [fructose + glucose, 92 (107) ppm 4 h^{-1}; $P = 0.034$; *t*-test], which was similar to that with glucose alone [glucose, 143 (186) ppm 4 h^{-1}; $P = 1.00$] (Fig. 2). The greatest production of breath hydrogen was in response to fructans [fructan, 2951 (1415) ppm 4 h^{-1}] and this was unaffected by the addition of glucose [fructan + glucose, 2200 (1421) ppm 4 h^{-1}; $P = 1.000$]. The AUC data when expressed over the 12-h period were similar (Fig. 2), except there was no longer any statistical

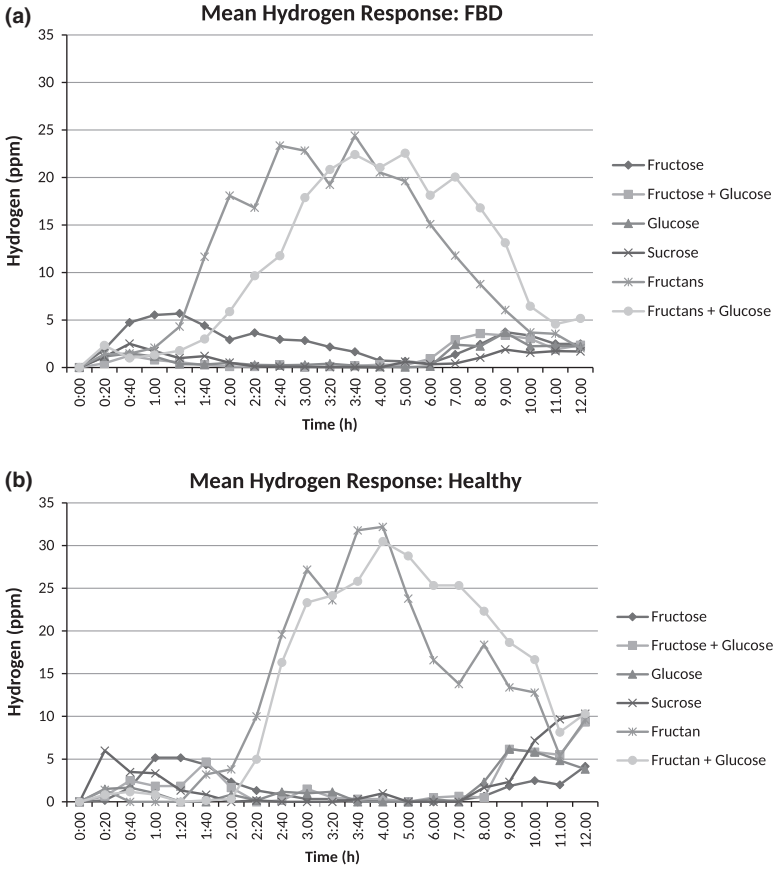

Figure 1 Average hydrogen production following ingestion of various sugar solutions in (a) patients with functional bowel disorders (FBD) (n = 26) and (b) healthy subjects in the fructose in solution study (n = 6). There was significantly greater breath hydrogen response to fructans compared to that to fructose ($P < 0.001$) in the FBD group. Breath hydrogen response from FBD and healthy subgroups were similar.

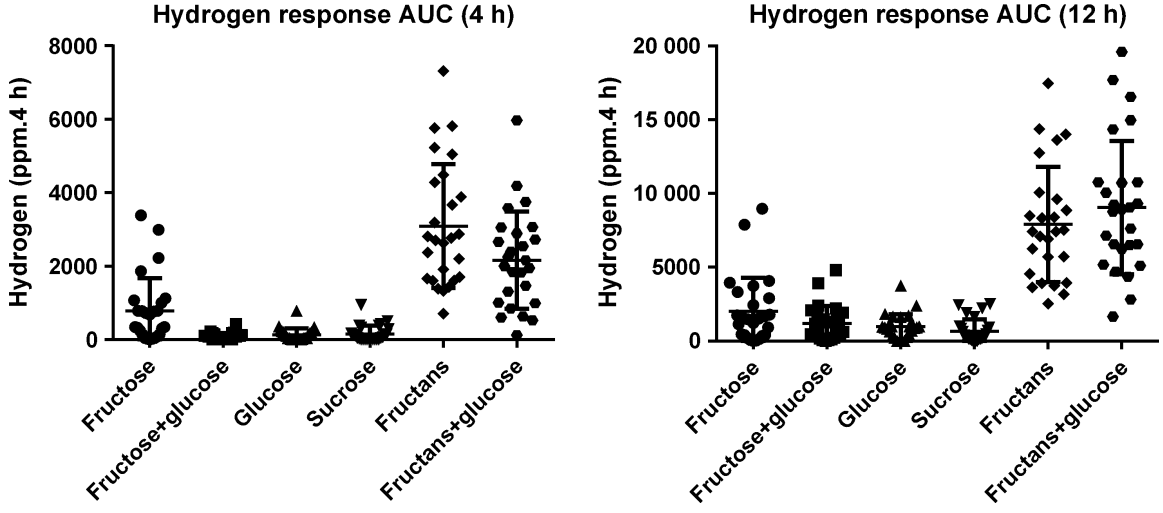

Figure 2 Hydrogen response expressed as area-under-the-curve (AUC) for the functional bowel disorders (FBD) subgroup at 4 and 12 h following ingestion of various sugar solutions in the fructose in solution study (n = 26). Breath hydrogen response following fructose alone [mean (SD) 859 (980) ppm 4 h^{-1}] was significantly greater than that when glucose was added to fructose [92 (107) ppm 4 h^{-1}; P = 0.034; t-test]. There was no significant difference in breath hydrogen response with the addition of glucose to fructans (P = 1.000). The AUC data when expressed over the 12-h period was similar, except there was no longer any statistical difference between fructose alone and fructose with added glucose [1527 (1319) versus 1023 (1097) ppm 12 h^{-1}].

difference between fructose alone and fructose with added glucose [1528 (1319) versus 1023 (1097) ppm 12 h^{-1}; $P = 1.00$]. There was significantly greater breath hydrogen response to fructans compared to fructose ($P < 0.001$).

The pattern of breath hydrogen responses in the six healthy participants was similar compared to the patients with FBD, as shown for the 12-h data in Fig. 1(b). The breath hydrogen response to 25 g fructose [mean (SD) 1186 (786) ppm 12 h^{-1}] or to fructans [13300 (5291) ppm 12 h^{-1}] did not significantly change with addition of glucose [2035 (1106) ppm 12 h^{-1}; $P = 0.157$ and 12874 (4876) ppm 12 h^{-1}; $P = 1.000$, respectively]. Breath hydrogen response after fructans was significantly higher compared to that following fructose ($P = 0.000$).

Symptoms

As shown in Fig. 3, the addition of glucose did not alter the overall symptom score compared to those for either fructose (median 15, interquartile range 2–46 versus 5, 1–35; $P = 0.236$, Wilcoxon signed-rank test) or fructans alone (19, interquartile range 2–32 versus 17, 2–46; $P = 0.926$). The addition of glucose to fructose worsened nausea (1, interquartile range 0–3 versus 2, 1–11; $P = 0.049$).

From minimal baseline symptoms reported, no differences for overall or individual symptoms were observed in the healthy subgroup for any of the sugar combinations. Three subjects experienced symptoms ≥20 mm above baseline and these comprised of overall symptoms and bloating following fructan with glucose ($n = 1$), wind following fructan ($n = 1$), lethargy following sucrose ($n = 1$) and bloating following glucose ($n = 1$).

Fructose in foods

Breath hydrogen excretion

For breath hydrogen excretion, only subjects who had a significant rise in breath hydrogen and hence still demonstrated fructose malabsorption following ingestion of the high fructose foods were analysed. An increase in breath hydrogen ≥15 ppm was noted in five FBD participants and five healthy controls**.** As shown in Fig. 4**,** addition of glucose to the diet high in fructose in excess of glucose had no discernible effect on the increment of breath hydrogen production in those with FBD [mean (SD) 5049 (1949) versus 4362 (1641) ppm 14 h^{-1}; $P = 0.620$] but tended to fall in the healthy controls [8690 (4540) versus 4809 (2504) ppm 14 h^{-1}; $P = 0.076$].

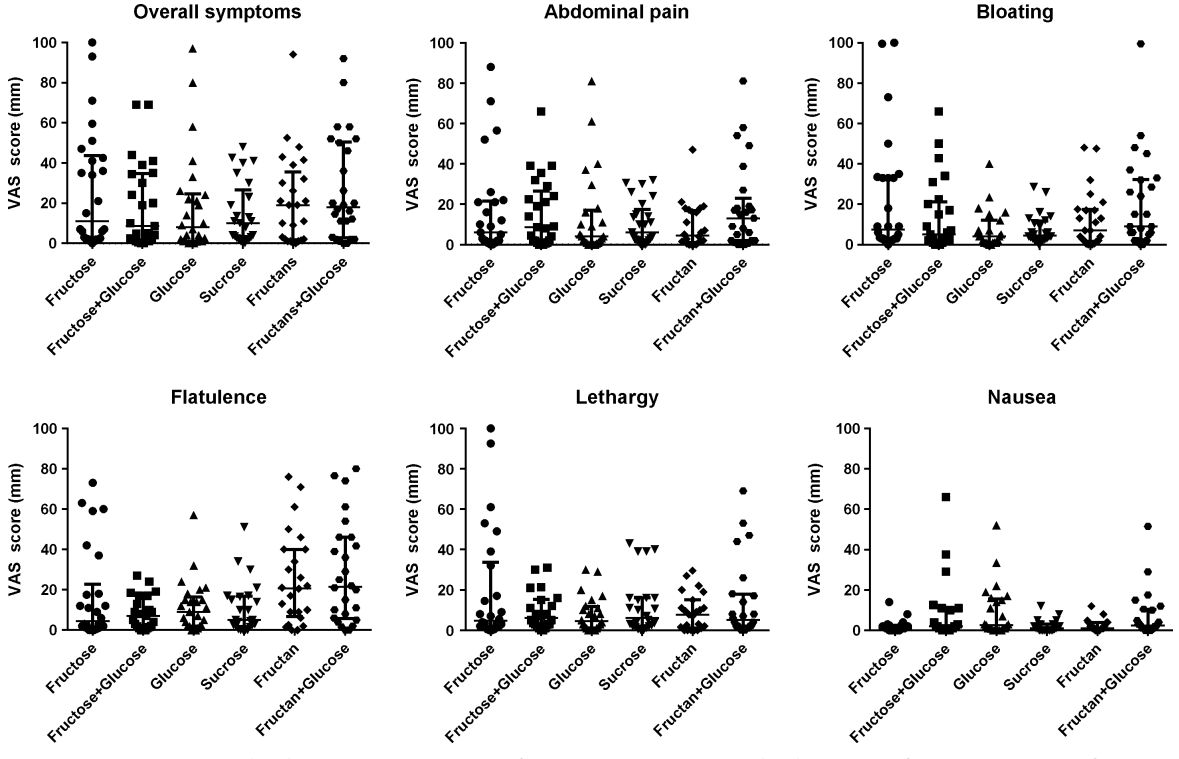

Figure 3 Visual analogue scale (VAS) symptom scores in the functional bowel disorders (FBD) subgroup following ingestion of various sugar solutions in the fructose in solution study ($n = 26$). No statistical differences were shown with the addition of glucose to fructose or fructans with the exception of nausea which was increased when glucose was added to fructose compared to fructose alone (median 1, interquartile range 0–3 versus 2, 1–11; $P = 0.049$).

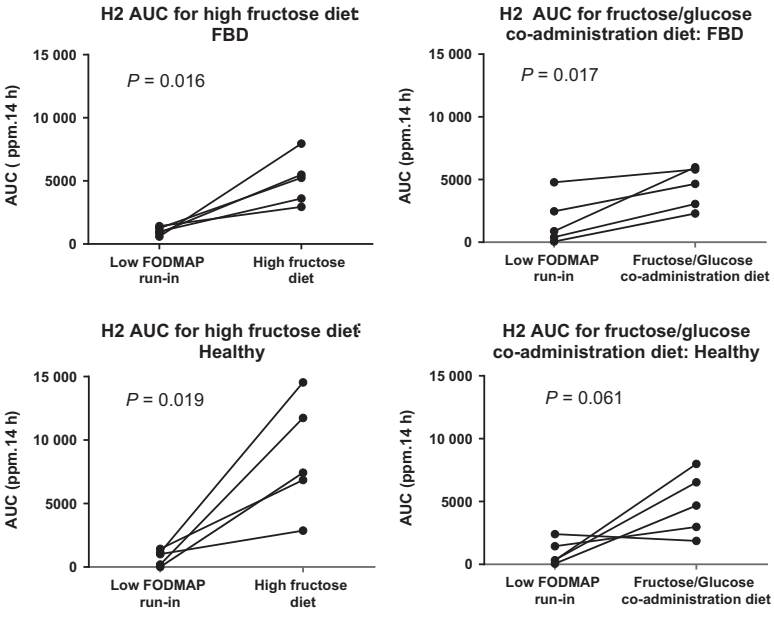

Figure 4 Hydrogen response expressed as area-under–the-curve for the functional bowel disorders (FBD) and healthy subgroups when consuming food containing fructose in excess of glucose without glucose or with glucose in the fructose in foods study (n = 5). Both groups had a significant increase in breath hydrogen with the addition of the foods containing fructose in excess of glucose compared to the low FODMAP run-in period [FBD mean (SD) 1030 (324) versus 5049 (1949) ppm 14 h^{-1}, P = 0.016; Healthy 756 (624) versus 8690 (4540) ppm 14 h^{-1}, P = 0.019; paired t-test]. During the fructose/glucose co-administration diet, breath hydrogen remained higher for the FBD group [1719 (1944) versus 4362 (1641) ppm 14 h^{-1}, P = 0.017]; however, in the healthy group, this change was no longer seen [920 (984) versus 4809 (2504) ppm 14 h^{-1}, P = 0.061]. AUC, area-under-the-curve; H2, breath hydrogen production.

Symptoms

All nine patients with FBD were analysed in terms of symptom response. Overall symptoms were not changed with the addition of glucose [median 27, interquartile range 13–47 versus 33, 9–49; P = 0.990]. The addition of foods containing fructose in excess of glucose was associated with a worsening of symptoms (VAS increase of ≥10 mm from baseline) in three of five with fructose malabsorption and two of four without on breath hydrogen criteria.

Discussion

This two-part study has shown that, although the addition of glucose to fructose in sugar solution and whole food can reduce breath hydrogen, it does not assist in improving symptoms associated with fructose intake in FBD. The practice of adding glucose to meals containing fructose in excess of glucose to enhance absorption of fructose and consequently reduce symptoms is largely based upon breath hydrogen response following challenges in healthy subjects with pure sugar solutions [15,17–19,21]. The present study confirms this response also occurs in patients with FBD. However, whether this strategy has any clinical utility must be questioned because the present study failed to show the addition of glucose to fructose solutions had any significant impact on symptom induction and does not appear to improve fructose absorption or symptoms when applied to whole food containing fructose in excess of glucose.

The patterns of breath hydrogen responses to sugars in the six healthy controls in the present study confirmed previous demonstrations that fructose malabsorption is a normal physiological phenomenon [25] and that equimolar glucose is effective in promoting rapid fructose absorption [17]. In 11 FBD patients with fructose malabsorption and 15 controls, small bowel biopsy found no differences in expression of GLUT5 and GLUT2 transporters [26]. Minimal symptoms were produced in our healthy controls, as would be expected in an asymptomatic population. Thus, the methodologies and protocols used in the present study were valid. The lack of symptom response in the healthy controls also emphasises that dietary fructose is of relevance only when fructose malabsorption occurs in the presence of functional gastrointestinal symptoms.

The major focus of the present study was the responses in patients with FBD, which have received minimal attention. First, there is a disparity between fructose malabsorption and symptom induction by foods containing fructose in excess of glucose in patients with FBD. This suggests that malabsorption of fructose is not the main mechanism by which fructose induces symptoms, which rather may arise principally as a result of small intestinal distension from the passive diffusion created by slowly-absorbed fructose. This was illustrated by Murray *et al.*[15], where magnetic resonance imaging in 16 healthy controls demonstrated that the degree of distension was independent of the malabsorption of fructose. In a study of symptoms experienced by 1372 FBD patients undergoing a fructose breath test, symptoms during breath testing

correlated more strongly with symptom response to subsequent dietary change rather than malabsorption during the breath test [27]. In another study involving 306 patients, only a weak correlation between a positive 25 g of fructose breath test and symptoms was found [28]. For mannitol or sorbitol, both slowly absorbed FODMAPs similar to fructose, the development of symptoms in patients with IBS after an acute challenge bore no relationship to whether malabsorption occurred [29].

Second, glucose enhanced fructose absorption in the FBD group. One feature of the patients in the present study was that their breath hydrogen response to 25 g of fructose was not vigorous. This dose was chosen for practical reasons to permit glucose matching without reducing the tolerability of the final solution. The patients were identified as fructose malabsorbers after routine clinical testing with 35 g of fructose. Malabsorption of fructose is dose-dependent [30]; for example, in 20 healthy subjects, none malabsorbed a dose of 15 g, 10% malabsorbed 25 g and 80% malabsorbed 50 g [31], and most healthy subjects can absorb up to 25 g of fructose [13,32]. Thus, it was not surprising then that breath hydrogen responses to 25 g of fructose were relatively attenuated. However, they still permitted the positive effect of glucose on improving the absorption of fructose solutions.

Third, despite such reduction in fructose malabsorption, supplemental glucose had no consistent and statistically significant effect on fructose-induced symptoms in the patients with FBD, except paradoxically by increasing nausea. The mechanism for the increase in nausea is unknown, although it may be related to the high sugar load given. These results further challenge the importance of fructose malabsorption *per se* on symptom genesis. However, it might have been anticipated that the reduction of its malabsorption assessed by breath hydrogen would have reflected improved fructose absorption in the small bowel and thus reduced the small bowel water content increase caused by passive diffusion, as demonstrated on magnetic resonance imaging [15]. Such an observation raises the question of what does generate abdominal symptoms when free fructose is ingested in patients with IBS.

Fourth, and as anticipated, the addition of glucose to fructans did not provide any reduction in breath hydrogen or symptom induction. Fructans are oligosaccharides consisting of short chains of fructose units with a single D-glucosyl unit at the nonreducing end [33]. Mammals lack the enzymes to hydrolyse the glycosidic linkages with subsequent malabsorption and delivery of fructans to the large intestine. This was reflected in the relatively vigorous hydrogen response to 10 g of fructans compared to a small response to 25 g of fructose. Glucose addition delayed the rise in breath hydrogen response to fructan, which is possibly related to changes in intestinal transit, although the magnitude of the rise in breath hydrogen was unchanged. The practice of adding glucose to reduce symptoms associated with high fructan foods that has been anecdotally reported to occur commonly in the community should be strongly discouraged.

It was important to observe whether concomitant glucose ingestion could influence the rate of food-delivered fructose absorption. The results of the present study indicate that such a strategy is not successful. Breath hydrogen responses were not significantly attenuated in patients or in healthy controls and food-induced symptoms were not altered. The lack of positive effects may be related to mixing issues with the gastrointestinal tract and/or the fact that the rapid absorption of glucose may reduce its luminal concentration relative to fructose that is being less rapidly released from food during digestion. Whatever the explanation, the results provide further evidence that glucose co-ingestion is an ineffective strategy to reduce fructose-related abdominal symptoms. Such a conclusion is welcome given the potential negative health implications of strategically increasing the intake of refined sugar and total energy intake.

The challenges and limitations of designing and implementing dietary studies to control for confounding factors were exemplified in the present study [34]. In an attempt to limit such factors, the present study was carefully designed to ensure randomisation, blinding of subjects in both studies, as well as investigators in the fructose in solution study, the use of a placebo and a cross-over design. The control of diet through providing low FODMAP meals was used to limit the effects of variations in food choice by the subjects. Moreover, a combination of hydrogen breath testing and symptom scores enabled accurate associations to be made. Despite such methodological rigour, the effects of small amounts of fermentable undigested carbohydrates present in the meals provided were still evident with the increased variability of the 12-h breath hydrogen data. Furthermore, designing a diet in which foods containing fructose in excess of glucose but not of other potentially malabsorbed sugars is difficult because fructose in excess of glucose often co-exists with sorbitol in foods. The use of pear that contains sorbitol may have confounded results. Hence, the approach taken in the present study was to concurrently test both foods and pure sugar solutions. Physiological observations with pure sugar solutions may not reflect the physiology when those sugars are presented in a food matrix. Malabsorption from food is likely to be less than sugar solutions as a result of slower gastrointestinal transit. For example, hydrogen and symptom responses have been found to be greater following ingestion of fructose in excess of glucose compared to high

fructose corn syrup containing glucose [35]. It may also reflect the limited release of fructose when contained within the food matrix, hence limiting absorption. One could also argue that, if fructose in excess of glucose is difficult to find without the presence of other FODMAPs, then the use of glucose may be of limited benefit because of the presence of other FODMAPs whose absorption is independent of glucose. Glucose and sucrose given on alternate diets did not appear the same and, despite the use of orange flavouring to disguise taste, the sweetness of the sugar solutions did vary, which may have influenced the blinding. However, it is unlikely that subjects would understand these differences and should not have affected the placebo response. In addition, the different sugar content of the solutions leads to differences in osmolarity, which may have affected symptom response, although this is unlikely because the solutions with highest osmolarity had the lowest breath hydrogen and symptom response.

In conclusion, when applied to pure sugar solutions, adding glucose to solutions in excess of fructose improves its absorption, although it appears to have an attenuated effect, if any, when added to whole food containing fructose in excess of glucose. In both studies, no evidence was obtained that this approach reduced the induction of gastrointestinal symptoms in patients with FBD. The addition of glucose had no impact on the effect of fructans. These observations, together with the potential induction of nausea, do not support the strategy of adding glucose to lessen the impact of dietary FODMAPs on functional gastrointestinal symptoms.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with CONSORT guidelines. The trials were registered with the Australian New Zealand clinical trials registry (ANZCTR) (Number ACTRN12614000176662 and ACTRN12616000766415) http://www.anzctr.org.au/.

Acknowledgments

The authors would like to thank the volunteers who participated in the present study. They would also like to thank Dr Greg Yelland for assistance with interim and final statistical analysis and Gastrolab for assistance with study advertising.

Conflict of interests, source of funding and authorship

LAR and JSB declare that they have no conflicts of interest.
CJT was supported by an Australian Postgraduate Award Scholarship. The Department of Gastroenterology financially benefits from the sales of a digital application and booklets on the low FODMAP diet. PRG has published an educational/recipe book on diet. JGM declares no conflict of interest.
JGM, JSB and PRG designed the study. CJT and LAR conducted the research. CJT, JGM and PRG analysed data. CJT, PRG, JGM and JSB wrote the paper. CJT had primary responsibility for final content. All authors read and approved the final manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

References

1. Muir JG, Shepherd SJ, Rosella O *et al.* (2007) Fructan and free fructose content of common Australian vegetables and fruit. *J Agr Food Chem* **55**, 6619.
2. Beyer PL, Caviar EM & McCallum RW (2005) Fructose intake at current levels in the United States may cause gastrointestinal distress in normal adults. *J Am Diet Assoc* **105**, 1559–1566.
3. Bray GA, Nielsen SJ & Popkin BM (2004) Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr* **79**, 537–543.
4. Ledochowski M, Widner B, Bair H *et al.* (2000) Fructose- and sorbitol-reduced diet improves mood and gastrointestinal disturbances in fructose malabsorbers. *Scand J Gastroenterol* **35**, 1048–1052.
5. Halmos EP, Power VA, Shepherd SJ *et al.* (2014) A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology* **146**, 67–75.e5.
6. Staudacher HM, Whelan K, Irving PM *et al.* (2011) Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. *J Hum Nutr Diet* **24**, 487–495.
7. De Roest RH, Dobbs BR, Chapman BA *et al.* (2013) The low FODMAP diet improves gastrointestinal symptoms in patients with irritable bowel syndrome: a prospective study. *Int J Clin Pract* **67**, 895–903.
8. Ong DK, Mitchell SB, Barrett JS *et al.* (2010) Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. *J Gastroenterol Hepatol* **25**, 1366–1373.

9. Tuck CJ, Muir JG, Barrett JS *et al.* (2014) Fermentable oligosaccharides, disaccharides, monosaccharides and polyols: role in irritable bowel syndrome. *Expert Rev Gastroenterol Hepatol* **8**, 819–834.
10. Blakemore SJ, Aledo JC, James J *et al.* (1995) The Glut5 Hexose transporter is also localized to the basolateral membrane of the human jejunum. *Biochem J* **309**, 7–12.
11. Jones HF, Butler RN & Brooks DA (2011) Intestinal fructose transport and malabsorption in humans. *Am J Physiol Gastrointest Liver Physiol* **300**, G202–G206.
12. Gouyon F, Caillaud L, Carrière V *et al.* (2003) Simple-sugar meals target GLUT2 at enterocyte apical membranes to improve sugar absorption: a study in GLUT2-null mice. *J Physiol* **552**, 823–832.
13. Frieling T, Kuhlbusch-Zicklam R, Kalde S *et al.* (2011) Fructose malabsorption: how much fructose can a healthy subject tolerate? *Digestion* **84**, 269–272.
14. Fujisawa T, Riby J & Kretchmer N (1991) Intestinal absorption of fructose in the rat. *Gastroenterology* **101**, 360–367.
15. Murray K, Wilkinson-Smith V, Hoad C *et al.* (2013) Differential effects of FODMAPs (Fermentable Oligo-, Di-, Mono-Saccharides and Polyols) on small and large intestinal contents in healthy subjects shown by MRI. *Am J Gastroenterol* **109**, 110–119.
16. Gasbarrini A, Corazza G, Gasbarrini G *et al.* (2009) Methodology and indications of H2-breath testing in gastrointestinal diseases: the Rome Consensus Conference. *Aliment Pharmacol Ther* **29**, 1–49.
17. Rumessen JJ & Gudmand-Hoyer E (1986) Absorption capacity of fructose in healthy adults. Comparison with sucrose and its constituent monosaccharides. *Gut* **27**, 1161.
18. Truswell AS, Seach JM & Thorburn A (1988) Incomplete absorption of pure fructose in healthy subjects and the facilitating effect of glucose. *Am J Clin Nutr* **48**, 1424–1430.
19. Hoekstra JH, van den Aker JH, Kneepkens CM *et al.* (1996) Evaluation of $^{13}CO_2$ breath tests for the detection of fructose malabsorption. *J Lab Clin Med* **127**, 303–309.
20. Densupsoontorn N, Jirapinyo P, Thamonsiri N *et al.* (2007) Fructose malabsorption in Thai adult. *Asia Pac J Clin Nutr* **16**, 209–212.
21. Kneepkens CM, Jakobs C & Douwes AC (1989) Apple juice, fructose, and chronic nonspecific diarrhoea. *Eur J Pediatr* **148**, 571–573.
22. Shepherd SJ, Parker FC, Muir JG *et al.* (2008) Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin Gastroenterol Hepatol* **6**, 765–771.
23. Muir JG, Rose R, Rosella O *et al.* (2009) Measurement of short-chain carbohydrates in common Australian vegetables and fruits by high-performance liquid chromatography (HPLC). *J Agr Food Chem* **57**, 554.
24. Bengtsson M, Persson J, Sjölund K *et al.* (2013) Further validation of the visual analogue scale for irritable bowel syndrome after use in clinical practice. *Gastroenterol Nurs* **36**, 188–198.
25. Barrett JS, Irving PM, Shepherd SJ *et al.* (2009) Comparison of the prevalence of fructose and lactose malabsorption across chronic intestinal disorders. *Aliment Pharmacol Ther* **30**, 165–174.
26. Wilder-Smith CH, Li X, Ho SS *et al.* (2014) Fructose transporters GLUT5 and GLUT2 expression in adult patients with fructose intolerance. *United Eur Gastroenterol J* **2**, 14–21.
27. Wilder-smith CH, Materna A, Wermelinger C *et al.* (2013) Fructose and lactose intolerance and malabsorption testing: the relationship with symptoms in functional gastrointestinal disorders. *Aliment Pharmacol Ther* **37**, 1074–1083.
28. Enko D, Kriegshäuser G, Kimbacher C *et al.* (2015) Carbohydrate Malabsorption and Putative Carbohydrate-Specific Small Intestinal Bacterial Overgrowth: Prevalence and Diagnostic Overlap Observed in an Austrian Outpatient Center. *Digestion* **92**, 32–38.
29. Yao C, Tan HL, Langenberg D *et al.* (2013) Dietary sorbitol and mannitol: food content and distinct absorption patterns between healthy individuals and patients with irritable bowel syndrome. *J Hum Nutr Diet* **27**, 264.
30. Latulippe ME & Skoog SM (2011) Fructose malabsorption and intolerance: effects of fructose with and without simultaneous glucose ingestion. *Crit Rev Food Sci Nutr* **51**, 583–592.
31. Rao SSC, Attaluri A, Anderson L *et al.* (2007) Ability of the Normal Human Small Intestine to Absorb Fructose: evaluation by Breath Testing. *Clin Gastroenterol Hepatol* **5**, 959–963.
32. Erdogan A, Adame EC, Yu S *et al.* (2014) Optimal testing for diagnosis of fructose intolerance: over-dosage leads to false positive intolerance test. *J Neurogastroenterol Motil* **20**, 560.
33. Roberfroid M & Delzenne NM (1998) Dietary fructans. *Annu Rev Nutr* **18**, 117–143.
34. Yao CK, Gibson PR & Shepherd SJ (2013) Design of clinical trials evaluating dietary interventions in patients with functional gastrointestinal disorders. *Am J Gastroenterol* **108**, 748–758.
35. Skoog S, Bharucha A & Zinsmeister A (2008) Comparison of breath testing with fructose and high fructose corn syrups in health and IBS. *Neurogastroenterol Motil* **20**, 505–511.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Subject recruitment process and subsequent participation..

Table S1. Actual dietary intake on the test day of each sugar solution during the fructose in solution study.

Table S2. Diets provided during the fructose in food study.

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

CLINICAL NUTRITION

Nutritional status of Vietnamese outpatients with chronic obstructive pulmonary disease

D. Hogan,[1] L. T. T. Lan,[2] D. T. N. Diep,[3] D. Gallegos[1] & P. F. Collins[1,4]

[1]Nutrition and Dietetics, School of Exercise and Nutrition Sciences, Faculty of Health, Queensland University of Technology, Kelvin Grove, QLD, Australia
[2]Respiratory Care Center, University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam
[3]Nutrition Center, Ho Chi Minh City, Vietnam
[4]Department of Nutrition and Dietetics, Princess Alexandra Hospital, Woolloongabba, QLD, Australia

Keywords
body mass index, chronic obstructive pulmonary disease, malnutrition, subjective global assessment, Vietnam.

Correspondence
P. F. Collins, School of Exercise and Nutrition Sciences, Faculty of Health, Queensland University of Technology, Victoria Park Road, Kelvin Grove, Brisbane, QLD 4059, Australia.
Tel.: (+61) 07 3138 3524
Fax: 07 3138 3980
E-mail: pf.collins@qut.edu.au

How to cite this article
Hogan D. , Lan L.T.T., Diep D.T.N., Gallegos D. & Collins P.F. (2017). Nutritional status of Vietnamese outpatients with chronic obstructive pulmonary disease. *J Hum Nutr Diet.* **30**, 83–89 doi: 10.1111/jhn.12402

Abstract

Background: Nutritional screening and assessment is not currently part of routine clinical practice in Vietnam. Therefore, the present study aimed to investigate the utility of the commonly used methods for identifying malnutrition in outpatients with chronic obstructive pulmonary disease (COPD).
Methods: A cross-sectional pilot study and a larger retrospective study were carried out in outpatients with COPD who were attending a respiratory clinic in Ho Chi Minh City, Vietnam. Routine clinical data were collected [body mass index (BMI), forced expiratory volume in 1 s (FEV_1)]. Nutritional screening and assessment were performed using the Malnutrition Screening Tool (MST) and Subjective Global Assessment (SGA) as the gold standard to diagnose malnutrition.
Results: In total, 393 outpatients had documented BMI and 29 were prospectively assessed using SGA: males, $n = 25$; females, $n = 4$; mean (SD) age 69.7 (9.6) years; mean (SD) BMI 21.0 (3.4) kg m^{-2}; mean (SD) FEV_1 percentage predicted 57.0% (19.7%). Malnutrition risk was identified in 20.7% ($n = 6$) of patients using the MST (38% sensitivity; 94% specificity). However, 45% ($n = 13$) were diagnosed as malnourished using the SGA (31% mild/moderate; 14% severe). All malnourished patients not identified by the MST had evidence of muscle wasting. BMI had a strong negative correlation with muscle wasting as assessed using the SGA ($r = -0.857$, $n = 28$; $P < 0.001$) and all malnourished patients had a BMI <21 kg m^{-2} (range 14.6–20.8 kg m^{-2}, nourished range 20.0–27.6 kg m^{-2}).
Conclusions: Malnutrition is common in Vietnamese outpatients with COPD. A BMI threshold of <21 kg m^{-2} appears to represent a useful and pragmatic cut-off point for identifying outpatients requiring comprehensive nutritional assessment and support.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide [(1)] and is predicted to continue to increase in both developed and developing counties [(2)]. Vietnam is predicted to have the highest COPD prevalence in the Asia-Pacific region at 6.7%, which is related to high levels of tobacco smoking and air pollution [(3)]. Malnutrition is a common problem in patients with COPD, with respiratory and extrapulmonary effects of the disease frequently resulting in a loss of body weight and particularly muscle wasting [(4–7)]. Malnourished COPD patients experience greater gas trapping, lower lung diffusing capacity, reduced exercise tolerance, impaired immunity and a poorer quality of life [(8,9)]. Indeed, a low body mass index (BMI) has been identified

as an independent risk factor for mortality in patients with COPD [5,10]. The causes of malnutrition in COPD are complex and multifactorial, and are determined not only by pulmonary impairment, but also by skeletal muscle pathology [11]. The prevalence reported in COPD varies widely depending on the method of nutritional assessment used, ranging from 10% to 45% in outpatients [12]. The only published study to date to have explored malnutrition in Vietnamese hospitals identified the greatest prevalence in respiratory inpatients at 65% [13].

Despite COPD being progressive, irreversible and associated with an increased malnutrition risk, malnutrition does appear to be amenable to nutritional treatment if identified. Recent meta-analyses have found that nutritional support in malnourished COPD outpatients results in improvements in nutritional status, functional capacity and quality of life [14,15]. In addition, nutritional support involving oral nutritional supplements in hospitalised COPD patients is associated with reduced lengths of hospital stay and the associated costs [16]. To date, no research has been carried out investigating nutritional screening and assessment methods in Vietnamese COPD outpatients, and there are no guidelines formally recommending nutritional assessment as part of routine care. The Subjective Global Assessment (SGA) tool is a validated method of identifying and categorising malnutrition status [17] and has previously been used in Vietnamese surgical [18] and general inpatients [19]. The SGA explores data relating to weight change, recent dietary intake, nutritional impact symptoms and a physical examination of subcutaneous fat loss and muscle wasting [17]. However, given the time and training required for use and the limited Vietnamese nutrition and dietetics workforce, simple nutrition screening methods are needed. The Malnutrition Screening Tool (MST) is a simple, validated tool [20] that has been used previously in the inpatient setting in Vietnam [19,21] demonstrating 78% sensitivity and 86% specificity compared to the SGA as gold standard [21]. However, the muscle wasting that is common in COPD [22] might be overlooked with simple screening methods alone. An alternative means of nutritional assessment and one routinely measured in Vietnam is the BMI. A World Health Organization expert consultation with respect to Asian counties with concurrent problems of undernutrition and overnutrition suggested population BMI thresholds of <18.5 kg m^{-2} (underweight) and 18.5–23 kg m^{-2} (i.e. an increasing but acceptable risk) [23]. However, these recommendations are for the general population and may be inappropriate in the presence of a chronic progressive disease characterised by wasting. The BMI, Airflow Obstruction, Dyspnoea, and Exercise Capacity (BODE) Index for COPD includes a BMI <21 kg m^{-2} as an indicator of increased risk of morbidity and mortality [24] and has been shown to have good predictive validity in an Asian population [25]. Similarly, the American Thoracic Society and European Respiratory Society proposed a BMI threshold of <21 kg m^{-2} to indicate being underweight in patients with COPD [26]. How these different BMI thresholds translate to a Vietnamese COPD population is currently unclear and is complicated in a population where both over- and undernutrition are common [28], as well as by the limitations of interpreting the BMI in patients in a disease characterised by muscle wasting. BMI is often included as a component of several commonly used nutritional screening and assessment tools, although the BMI cut-offs used to define being underweight vary: <18.5, <20 and <21 kg m^{-2} [25,26,29-31]. The present study aimed to explore the utility and effectiveness of different nutritional screening and assessment methods in identifying malnutrition in a cohort of Vietnamese COPD outpatients.

Materials and methods

This cross-sectional pilot study took place during June 2014, in Ho Chi Minh City (HCMC), Vietnam. It involved the analysis of both a prospective and retrospective cohort of outpatients with COPD. Ethics approval was awarded by Queensland University of Technology's Human Research Ethics Committee (approval number 1400000439).

Prospective study

Twenty-nine COPD outpatients were assessed during routine respiratory outpatient clinic attendance throughout June 2014. Only those patients with a confirmed diagnosis of COPD [forced expiratory volume in 1 s (FEV_1)/forced vital capacity <0.7] were included and COPD disease-severity was classified according to GOLD criteria [4]. Written informed consent for participation was obtained from all patients and nutritional assessment tools were translated from English to Vietnamese by a back-translation method and administered with assistance from a trained Vietnamese interpreter . Variables including age, smoking status and pack years were sourced from the participant's medical records. Smoking status was categorised as non-smoker, ex-smoker or current smoker. BMI was categorised by WHO [31] guidelines as underweight (<18.5 kg m^{-2}), normal weight (18.5–24.9 kg m^{-2}), overweight (25–29.9 kg m^{-2}) or obese (>30 kg m^{-2}) and also analysed at different BMI threshold for being underweight. On arrival at the respiratory clinic, all anthropometric measurements were collected by a trained undergraduate research dietetic student. Malnutrition risk was examined using the MST to produce a score that classified a patient as at risk of malnutrition (score ≥2) or not at risk of malnutrition (score <2) [20]. Comprehensive nutritional assessment using the SGA

was used to establish malnutrition status, where outpatients were classified as nourished (A), mildly/moderately malnourished (B) or severely malnourished (C) [17].

Retrospective study

Medical records of 536 COPD outpatients who consecutively attended the clinic between June 2013 and June 2014 were examined for inclusion. Outpatients who had a confirmed diagnosis of COPD and data available on height and weight were included and only data from the initial presentation to the clinic during the observation period were analysed.

Statistical analysis

Statistical analysis was performed using SPSS, version 21 (IBM Corporation, Armonk, NY, USA). Continuous variables were assessed for outliers, as well as normality using the Shapiro–Wilk test, and expressed as the mean (SD). Categorical variables are expressed as frequency (%). Variation of mean data between more than two groups was examined using one-way analysis of variance (ANOVA). A contingency table was used to determine the sensitivity and specificity of the MST and BMI thresholds in diagnosis malnutrition versus SGA [32]. Correlations between parameters were evaluated using Spearman's rank correlation analysis. $P < 0.05$ was considered statistically significant.

Results

Prospective study

The characteristics of the 29 outpatients assessed for malnutrition are summarised in Table 1. The mean (SD) age was 69.7 (9.6) years; 86.2% were male; 58.3% were ex-smokers, 25.0% were current smokers and 16.7% were nonsmokers.

Severity of chronic obstructive pulmonary disease

The sample included patients with mild (6.9%), moderate (51.7%), severe (34.5%) and very severe (6.9%) COPD according to the GOLD classifications [4]. There was no difference in mean $FEV_{1\%}$ predicted according to smoking status (ex-smoker 54 SD 18%; current smoker 60 SD 7%; nonsmoker 52 SD 17%; $P = 0.69$ ANOVA), sex (male 58 SD 20%; female 53 SD 17%; $P = 0.65$) or residential location (HCMC 57 SD 16%; Provincial 55 SD 16%; $P = 0.80$).

Nutritional status

Of the 29 outpatients, 13 (44.8%) were identified using the SGA to be malnourished; nine (31%) with mild/moderate malnutrition and four (13.8%) with severe malnutrition. Mean (SD) BMI of the sample was 21.1 (3.4) kg m^{-2} (range 14.6–27.6 kg m^{-2}). According to WHO [31] classifications, 27.6% were underweight (<18.5 kg m^{-2}), 62.1% were normal weight (18.5–24.9 kg m^{-2}), 6.9% were overweight (25–29.9 kg m^{-2}) and none were classified as obese. SGA was significantly associated with WHO BMI categories, although the sample was small ($P < 0.001$, chi-squared test), with eight out of 12 malnourished patients having a BMI <18.5 kg m^{-2}. However, four patients with mild/moderate malnutrition had a BMI between 18.5 and 20.9 kg m^{-2} and therefore fell within the normal weight range. The MST only identified six patients (20.7%) to be at risk of malnutrition (38% sensitivity and 94% specificity) and a BMI cut-off value of <18.5 kg m^{-2} had a sensitivity of 66% and a specificity of 100%. However, when a BMI cut-off of <21 kg m^{-2} was imposed, which has been recommended to identify malnutrition in COPD [24], this threshold demonstrated a sensitivity of 100% and a specificity of 94% against the gold standard SGA ($P < 0.001$, Fisher's exact test) (Table 2). There was also a significant moderate correlation between malnourished patients missed by the MST and muscle wasting as assessed by the SGA during physical examination of lean body stores ($r_s = -0.585$, $P < 0.001$). All malnourished patients had moderate or severe muscle wasting and there was a significant negative association with a reduced BMI (Fig. 1).

Table 1 Prospective study outpatient characteristics

Participant characteristics	*N* (%)
Sex	M 25 (86.2)F 4 (13.8)
Smoking status	
Nonsmoker	4 (13.8)
Smoker	6 (20.7)
Ex-smoker	14 (48.3)
Residence location	
City	11 (37.9)
Province	15 (51.7)
COPD severity [4]	
Mild COPD	2 (6.9)
Moderate COPD	15 (51.7)
Severe COPD	10 (34.5)
Very severe COPD	2 (6.9)
	Mean (SD)
Age (years)	69.7 (9.6)
BMI (kg m^{-2})	21.1 (3.4)
FEV_1 (% predicted)	57.0 (19.7)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; F, female; FEV_1, forced expiratory volume in 1 s; M, males

Factors related to nutritional status

Body weight and BMI were significantly associated with SGA classification; however, mean FEV_1 (% predicted) was not associated with malnutrition status (Table 3). Binary logistic regression confirmed BMI to be

Table 2 Sensitivity and specificity of malnutrition screening methods in reference to the Subjective Global Assessment

Method	True +ve	False +ve	True −ve	False −ve	Sensitivity (%)	Specificity (%)	PPV	NPV
MST	5	1	15	8	38	94	83	65
<18.5 kg m^{-2}	8	0	16	4	66	100	100	80
<20 kg m^{-2}	9	0	16	3	75	100	100	84
<21 kg m^{-2}	12	1	15	0	100	94	92	100
<22 kg m^{-2}	12	3	13	0	100	81	80	100

BMI, body mass index; MST, Malnutrition Screening Tool; NPV, negative predictive value; PPV, positive Predictive value.

significantly and independently associated with malnutrition status ($P < 0.001$) after adjustment for age ($P = 0.605$) and disease severity ($P = 0.624$).

Retrospective study

Of the 536 medical records examined retrospectively, 393 records met the inclusion criteria. The mean (SD) age was 65 (12) years; 92% were male; 44.3% were ex-smokers, 29.5% were current smokers and 6.9% were non-smokers. Comparison of the characteristics of the prospective ($n = 29$) and retrospective ($n = 393$) cohorts resulted in no statistical differences, suggesting that the smaller prospective sample is generally representative of the COPD population attending this particular clinic during the previous 12 months.

Disease severity

The study population included patients with mild (7.6%), moderate (45.6%), severe (36.6%) and very severe (10.2%) COPD. There were no associations between age, number of smoking pack years and COPD disease severity. However, there was a significant association between BMI and disease severity [mean (SD), mild: 21.9 (3.7) kg m^{-2}, moderate: 21.4 (3.2) kg m^{-2}, severe: 20.4 (3.2) kg m^{-2}, 20.1 (3.9) kg m^{-2}; $P = 0.005$, ANOVA].

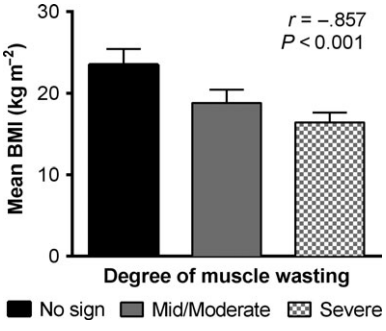

Figure 1 Mean body mass index of patients according to muscle wasting classification assessed by the Subjective Global Assessment. BMI, body mass index.

Factors related to nutritional status

The mean (SD) BMI of the cohort was 21.1 (3.9) kg m^{-2}, ranging from 14.6 kg m^{-2} to 27.6 kg m^{-2}. According to the WHO [31] classifications, 26% of patients were underweight (<18.5 kg m^{-2}), 63% were normal weight (18.5–24.9 kg m^{-2}), 9.2% were overweight (25–29.9 kg m^{-2}) and 1.5% were obese (>30 kg m^{-2}). However, the prevalence of being underweight according to a recommended BMI threshold of 21 kg m^{-2} in COPD patients was 51%. Age was significantly associated with a reduced BMI [mean (SD), underweight: 68 (12) years, normal weight: 66 (11) years, overweight: 58 (12) years, obese: 55 (16) years; $P < 0.001$, ANOVA]. Regression analysis confirmed both disease severity and age to be significantly and independently associated with a reduced BMI.

Discussion

The present study is the first to assess the utility of commonly used nutritional screening and assessment methods with the aim of identifying malnutrition in Vietnamese COPD outpatients. Within the larger retrospective cohort, malnutrition was found to be a common clinical problem, with half of all patients assessed found to be at nutritional risk (BMI <21 kg m^{-2}). A similar prevalence (45%) was found within the smaller prospective cohort when full nutritional assessment was completed using the

Table 3 Characteristic of patients according to malnutrition status

Variable	SGA-A: Well nourished	SGA-B: Mild/moderately malnourished	SGA-C: Severely malnourished	*P* value
Weight (kg)	60.3 (9.0)	49.3 (5.1)	41.3 (3.3)	<0.001
BMI (kg m^{-2})	23.5 (1.9)	18.7 (1.6)	16.1 (1.2)	<0.001
FEV_1 (% predicted)	54 (14.2)	66.7 (26.8)	46.6 (19.8)	0.211

Values are presented as the mean (SD). BMI, body mass index; FEV_1, forced expiratory volume in 1 s; SGA, Subjective Global Assessment.

SGA (51%). To date, there have been very few studies using the SGA in this patient group; two previous studies reported a prevalence of malnutrition of 42% ($n = 60$) [33] and 40% ($n = 163$) [34], which is comparable to the present study. The high prevalence of malnutrition in a Vietnamese COPD population is not unexpected given the country's burden of malnutrition, with 17% of the general adult population previously identified as being underweight in 2009–2010 [35]. More recent findings suggest the burden of undernutrition in Vietnam to be improving, with 9% of the general population found to have a BMI <18.5 kg m^{-2} [36]. Despite the economic growth and improvements in nutritional status over the past decade, malnutrition is still common in Vietnam, particularly within the hospital setting [13] and areas of social deprivation [3,37].

The SGA was considered the gold standard for nutritional assessment in the present study because it is valid in both acute and outpatient settings, and assesses anthropometric, dietary, functional, gastrointestinal and physical changes to diagnose malnutrition [17]. Currently in Vietnam, medical doctors with nutrition expertise are the healthcare professionals who are predominantly responsible for the nutritional management of patients. However, the first specifically trained dietitians are scheduled to graduate university in Vietnam in 2018. This is a huge milestone for the profession of dietetics in a country of approximately 92 million and is likely to have a significant impact on the nutritional care that patients receive. Because completion of the SGA requires time and trained individuals, the primary aim of the present study was to explore the utility of alternative nutrition screening methods. Given the importance of routine nutritional screening to enable early initiation of nutritional support, the selection of a sensitive screening tool is of clinical importance [38]. In the present study, the MST demonstrated a poor sensitivity of 38% with 94% specificity in comparison with the SGA. These findings differ from those of a previous study reporting the MST to have a sensitivity and specificity of 78% and 86%, respectively, in Vietnamese inpatients [21]. The discrepancy with the present study may be a result of the increased risk of fat-free mass depletion commonly observed in COPD patients [39], which is not assessed within the MST. Indeed, all of the malnourished patients in the present study who were undiagnosed by the MST were identified to have signs of muscle wasting when physical assessment was undertaken as part of the SGA. This highlights the challenge with respect to identifying those patients who are at nutritional risk in routine clinical practice. Simple nutritional screening tools may not have the sensitivity to identify those patients at risk of malnutrition who are showing signs of nutritional depletion without marked changes in body weight. However, the present study did find that using a BMI of <21 kg m^{-2} to indicate nutritional risk was 100% sensitive and 94% specific in identifying malnutrition against the reference method. Although this BMI threshold has previously been recommended as a means of identifying those patients who are at nutritional risk, the BMI is limited in that it does not assess body composition. COPD is characterised as a wasting disease and muscle wasting is known to occur in patients across all BMI classifications [40]. The identification of muscle wasting is clinically important in COPD patients and muscle mass depletion has been found to be a better predictor of mortality than BMI [41,42]. However, the present study demonstrated a very strong significant inverse relationship between muscle wasting and BMI and all patients with a BMI <21 kg m^{-2} were considered to have muscle depletion.

Vietnam is a country that is going through socio-economic transition and experiencing concurrent states of undernutrition and growing levels of overnutrition. It is likely that the sensitivity of BMI as a screening method for malnutrition is reduced with increasing body fat and thus physical assessment of muscle stores becomes more difficult. In such a case, direct measurement of muscle stores is preferable using technologies such as dual-energy X-ray absorptiometry and bioelectrical impendence analysis; however, there are availability and cost issues in a Vietnamese context. The current cohort had a mean BMI of 21.9 kg m^{-2} and less than 11% were identified as being overweight or obese, making the identification of muscle depletion easier and allowing a stronger correlation between BMI and muscle wasting. The clinical utility of BMI as a means of highlighting nutritional risk will likely continue to be debated, particularly in elderly populations and those with chronic wasting diseases such as COPD, as well as in Asian populations. In light of the findings of the present study, as well as the current American Thoracic Society and European Respiratory Society's recommendation of a BMI cut-off of <21 kg m^{-2} [27], this would appear to be a simple and pragmatic means of highlighting those who are at nutritional risk and require further nutritional assessment by a trained individual. However, with a growing prevalence of overnutrition in Vietnam, it is more likely that a comprehensive assessment of fat-free mass will be needed in the future.

The cross-sectional and retrospective design of the present pilot study are limitations. However, although the sample size of the prospective cohort is small, the characteristics of the cohort were similar to those of the larger retrospective cohort, suggesting it to be representative of the cohort attending that clinic. A sex imbalance was observed in the cohort, with a predominance of male (92.1%) over female patients (7.9%), which is reflective

of the Vietnamese COPD population. A recent study of 1506 participants found the prevalence of COPD to be three times greater in males than females in Vietnam [43]. Although the unicentric nature of the study does prevent the generalisability of the findings, it is hoped they will be confirmed in future multicentre studies. However, the prevalence of malnutrition reported in the present study does fall within previously reported ranges for COPD outpatients in European studies, providing additional confidence in the findings of the present study. The burden of COPD to Vietnam is considerable and growing [43], and the different nutritional phenotypes that exist within the Vietnamese COPD population are yet to be fully explored.

In conclusion, the present study highlights malnutrition as being a common clinical problem in COPD, with half of all Vietnamese patients being at nutritional risk. As a result of the wasting nature of the disease, simple nutritional screening tools that do not include an assessment of body weight or BMI may not be able to identify all of those who are at risk. The present study found that a BMI threshold of <21 kg m^{-2} had appropriate sensitivity and specificity as a nutritional screening method and it was significantly associated with the presence of muscle wasting. Given the clinical significance of malnutrition in COPD, and the fact that, if it is identified, it is amenable to treatment, consideration of nutrition screening methods is imperative.

Conflict of interests, source of funding and authorship

All authors had no conflicts of interest to declare.
This study was supported by the Australian Government Department of Education Asia Bound Grant.
All authors contributed to the development of the study design and wrote, reviewed and approved the final version submitted for publication. DH was responsible for the integrity of the data collection and analysis. DH and PFC contributed substantially to the data interpretation and the writing of the manuscript. PFC had primary responsibility for the final content.

Transparency declaration

The lead author affirms that the manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with CONSORT1/STROBE2/PRISMA3 guidelines.

References

1. Bousquet J, Khaltaev NG & Cruz AA (2007) *Global Surveillance, Prevention and Control of Chronic Respiratory Diseases: A Comprehensive Approach*. Geneva: World Health Organization.
2. Lopez AD, Shibuya K, Rao C *et al.* (2006) Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J* **27**, 297–412.
3. Regional COPD Working Group (2003) COPD prevalence in 12 Asia-Pacific countries and regions: projections based on the COPD prevalence estimation model. *Respirology* **8**, 192–198.
4. Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Available at: http://www.goldcopd.it/materiale/2015/GOLD_Pocket_2015.pdf (accessed June 2016).
5. Landbo C, Prescott E, Lange P *et al.* (1999) Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **160**, 1856–1861.
6. Wouters E, Creutzberg E & Schols AM (2002) Systemic effects in COPD. *Chest* **121**, 127–130.
7. Bernard, S, LeBlanc, P, Whittom, F *et al.* (1998) Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **158**, 629–634.
8. Ezzell L & Jensen GL (2000) Malnutrition in chronic obstructive pulmonary disease. *Am J Clin Nutr* **72**, 1415–1416.
9. Wilson DO, Rogers RM, Wright EC *et al.* (1989) Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. *Am Rev Respir Dis* **139**, 1435–1438.
10. Schols AM, Slangen J, Volovics L *et al.* (1998) Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **157**, 1791–1797.
11. Schols AM (2009) Nutritional rehabilitation: from pulmonary cachexia to sarcoPD. *Eur Respir J* **33**, 949–950.
12. Stratton R, Green C & Elia M (2003) *Disease-Related Malnutrition: An Evidenced Based Approach to Treatment*. Oxford: CABI Publishing.
13. Hanna, KL, Glen KD, Lau, BT *et al.* (2016) Relationship between malnutrition and selected risk factors in two hospitals in Vietnam. *Nutrition & Dietetics* **73**, 59–66.
14. Collins PF, Elia M & Stratton R (2013) Nutritional support and functional capacity in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Respirology* **18**, 616–629.
15. Collins PF, Stratton RJ & Elia M (2012) Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Am J Clin Nutr* **95**, 1385–1395.
16. Snider JT, Jena AB, Linthicum MT *et al.* (2015) EFfect of hospital use of oral nutritional supplementation on length

of stay, hospital cost, and 30-day readmissions among medicare patients with copd. *Chest* **147**, 1477–1484.
17. Detsky AS, McLaughlin JR, Baker JP *et al.* (1987) What is subjective global assessment of nutritional status? *J Parenter Enteral Nutr* **11**, 8–13.
18. Pham, NV, Cox-Reijven, PL, Greve JW (2006) Application of subjective global assessment as a screening tool for malnutrition in surgical patients in Vietnam. *Clin Nutr* **25**, 102–108.
19. Lau B, Gallegos D, Hanna K *et al.* (2013) Prevalence of hospital malnutrition and association with risk factors in Vietnam [Abstract]. *Nutrition & Dietetics* **70**, 4–25.
20. Ferguson M, Capra S, Bauer J *et al.* (1999) Development of a valid and reliable malnutrition screening tool for adult acute hospital patients. *Nutrition* **15**, 458–464.
21. Glen K, Hanna K, Gallegos D *et al.* (2013) Validation of the MST in Vietnam using the SGA [Abstract]. *Nutrition & Dietetics* **70**, 4–25.
22. Mathur S, Brooks D & Carvalho C (2014) Structural alterations or skeletal muscle in COPD. *Front Physiol* **5**, 104.
23. World Health Organization (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* **363**, 157–163.
24. Celli BR, Cote CG, Marin JM *et al.* (2004) The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* **350**, 1005–1012.
25. Ong K-C, Earnest A & Lu S-J (2005) A multidimensional grading system (BODE index) as predictor of hospitalization for COPD. *Chest* **128**, 3810–3816.
26. American Thoracic Society/European Respiratory Society Task Force (2004). *In Standards for the Diagnosis and Management of Patients with COPD*, vol. 1.2. New York, NY: American Thoracic Society.
27. Celli BR, MacNee W, Agusti A *et al.* (2004) Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* **23**, 932–946.
28. Walls HL, Son PT, Quang NN *et al.* (2009) Prevalence of underweight, overweight and obesity in urban Hanoi, Vietnam. *Asia Pac J Clin Nutr* **18**, 234.
29. Isenring E, Cross G, Kellett E *et al.* (2010) Nutritional status and information needs of medical oncology patients receiving treatment at an Australian public hospital. *Nutr Cancer* **62**, 220–228.
30. Elia, M (2003) Screening for malnutrition: a multidisciplinary responsibility. *Development and use of the Malnutrition Universal Screening Tool ('MUST') for Adults. Redditch: BAPEN*.
31. World Health Organization (1995) *Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Consultation*. WHO Technical Report Series Number 854. Geneva: World Health Organization.
32. Gabrielson DK, Scaffidi D, Leung E *et al.* (2013) Use of an abridged scored Patient-Generated Subjective Global Assessment (abPG-SGA) as a nutritional screening tool for cancer patients in an outpatient setting. *Nutr Cancer* **65**, 234–239.
33. Yuceege MB, Salman SO, Duru S *et al.* (2013) The evaluation of nutrition in male COPD patients using subjective global assesment and mini nutritional assesment. *J Intern Med* **2**, 1–5.
34. Günay E, Kaymaz D, Selçuk NT *et al.* (2013) Effect of nutritional status in individuals with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation. *Respirology* **18**, 1217–1222.
35. National Institute of Nutrition (2011) *A Review of the Nutrition Situation in Vietnam 2009–2010*. Hanoi: Medical Publishing House.
36. Ho-Pham L, Lai T, Nguyen M *et al.* (2015) Relationship between body mass index and percent body fat in Vietnamese: implications for the diagnosis of obesity. *PLoS ONE* **10**, e0127198.
37. Khan NCKH (2008) Double burden of malnutrition: the Vietnamese perspective. *Asia Pac J Clin Nutr* **17**, 116–118.
38. Mueller C, Compher C & Ellen DM (2011) A.S.P.E.N. clinical guidelines: nutrition screening, assessment, and intervention in adults. *J Parenter Enteral Nutr* **35**, 39–39.
39. Schols AM (2015) The 2014 ESPEN Arvid Wretlind Lecture: metabolism & nutrition: shifting paradigms in COPD management. *Clin Nutr* **34**, 1074–1079.
40. Maltais F (2014) Body composition in COPD: looking beyond BMI. *Int J Tuberc Lung Dis* **18**, 3–1.
41. Martinez-Garcia, MA, Navarro, M & Salcedo, E *et al.* (2005) Mid-arm muscle area is a better predictor of mortality than body mass index in COPD. *Chest* **128**, 2108+.
42. Schols AM, Broekhuizen R, Weling-Scheepers CA *et al.* (2005) Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* **82**, 53–59.
43. Nguyen Viet N, Yunus F, Nguyen Thi Phuong A *et al.* (2015) The prevalence and patient characteristics of chronic obstructive pulmonary disease in non-smokers in Vietnam and Indonesia: an observational survey. *Respirology* **20**, 602–611.

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

CLINICAL NUTRITION

Dietary carbohydrate composition is associated with polycystic ovary syndrome: a case–control study

G. Eslamian,[1] A.-R. Baghestani,[2] S. Eghtesad[3] & A. Hekmatdoost[4]

[1]Students' Research Office, Faculty of Nutrition and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Liver and Pancreatobiliary Disease Research Center, Digestive Disease Research Institute, Shariati Hospital, Tehran, Iran
[4]Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Keywords
carbohydrate, fibre, glycaemic index, glycaemic load, polycystic ovarian syndrome.

Correspondence
A. Hekmatdoost, Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, No 7, West Arghavan Street, Farahzadi Blvd., Zip Code 1981619573, PO Box 19395-4741, Tehran, Iran.
Tel.: +98 21 22360658
Fax: +98 21 22360657
E-mail: a_hekmat2000@yahoo.com

How to cite this article
Eslamian G., Baghestani A.-R., Eghtesad S., Hekmatdoost A. (2017) Dietary carbohydrate composition is associated with polycystic ovary syndrome: a case–control study. *J Hum Nutr Diet*. **30**, 90–97
doi: 10.1111/jhn.12388

Abstract

Background: The present study aimed to investigate the association between dietary carbohydrate components and polycystic ovary syndrome (PCOS) in Iran.
Methods: In this case–control study, the diagnosis of PCOS was made based on the Rotterdam criteria in hospital clinics. Dietary assessments were performed using a validated semi-quantitative food frequency questionnaire. In total, 281 women with incident PCOS and 472 age-matched controls were assessed. Participants were interviewed through the clinics in Tehran, Iran, from February 2012 until March 2014. Average dietary glycaemic index (GI) and glycaemic load (GL) were calculated using GI of Iranian Foods Table and international tables of GI and GL values. We also assessed total dietary carbohydrate, refined grains, whole grains and fibre intakes.
Results: Participation rates were 97.5% among cases and 96.3% among controls. Mean (SD) dietary GI values among the controls and cases were 51.8 (4.7) and 59.7 (5.9) ($P = 0.02$) and GL values were 155.34 (35.2) and 173.6 (39.1) ($P < 0.001$), respectively. The multivariate adjusted odds ratio (OR) comparing the highest tertile of dietary GI and GL with the lowest tertile were 2.18 [95% confidence interval (CI) = 1.29–3.81; *P*-test for trend = 0.012] and 2.39 (95% CI = 1.23–3.01; *P*-test for trend = 0.001), respectively, with a significant trend. Fibre intake was inversely associated with PCOS (OR = 0.73; 95% CI = 0.49–0.91; *P*-test for trend = 0.013).
Conclusions: The findings of the present study suggest that high dietary GI and GL and low fibre intake are significantly associated with PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a multifactorial endocrinopathy, affecting 5–21% of women worldwide [(1–3)]. The reported prevalence of PCOS ranges between 7.1% and 14.6% in Iran, depending on the definition of PCOS used [(4)]. The diagnosis of PCOS has life-long implications, increasing the risk of numerous morbidities including infertility, obstetrical complications, type 2 diabetes mellitus, cardiovascular disease, metabolic syndrome, endometrial carcinoma, and mood and eating disorders [(5)]. Women with PCOS are also at an increased risk of developing insulin resistance [(6)].

Multiple environmental and/or genetic factors contribute to the pathogenesis of PCOS [(5,7,8)]. Lifestyle modifications are considered as the first-line treatment for women with PCOS [(9–11)]. The effects of a diet high in glycaemic index (GI) and glycaemic load (GL) on the risk of developing PCOS have been debated intensively in recent years [(12,13)]. Altieri *et al.* [(9)] found that women with PCOS consumed more high-GI starchy sweets (cakes, biscuits, snacks), compared to normoandrogenic

women. Evidence implicating hyperinsulinaemia/insulin resistance and refined carbohydrates in the aetiology of PCOS suggests that refined carbohydrate, high GI and GL and low fibre diets are associated with PCOS [11,12,14]; however, this evidence is inconsistent and there is a lack of data, specifically in developing countries.

To increase the understanding of the role of dietary carbohydrates in the aetiology of PCOS, we designed the present case–control study aiming to evaluate whether or not dietary GI, GL, refined grains, whole grains, total carbohydrate and fibre intakes are associated with PCOS. To our knowledge, no previous studies have assessed this association in a developing county.

Materials and methods

Study design and subjects

This case–control study was conducted in outpatient clinics from February 2012 until March 2014 in Tehran, Iran. During this period, 288 females (aged 20–35 years) with a confirmed diagnosis of PCOS (within 3 months of the study) referred to these clinics and agreed to participate in this study. A diagnosis of PCOS was made by having at least two out of the three symptoms on the international Rotterdam Criteria 2003 [15]. Ninety-eight percent of the patients had hyperandrogenism and polycystic ovaries, and matched to type C phenotype. Age-matched controls comprised 491 patients who had also been referred to the same hospital clinics for a range of diseases such as orthopaedic problems, ear/nose/throat diseases or elective surgeries; all controls had regular menstrual cycles without ovulatory abnormalities, hyperandrogenism and polycystic ovary. None of the participants reported following a special diet. Pelvic ultrasound and serum endocrine hormones were assessed on the third day of the menstrual cycle in all controls. Data were collected at the outpatient clinics at the same time as recruitment.

Eighteen participants were excluded from analysis because log scales of their total energy intake were either >3 or <3 SD from the mean, leaving 281 PCOS cases (97.5% participation rate) and 472 controls (96.3%) for the final analysis.

Ethical considerations

The ethics board of the Shahid Beheshti University of Medical Sciences approved the study protocol. Written informed consent was obtained from each participant after them having been told about the purpose of this research. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 [16].

Dietary assessment

A validated semi-quantitative food frequency questionnaire (FFQ), developed for the Iranian population, was used to assess the usual dietary intake of the participants [17]. Using this FFQ, past nutritional intake for a single 1-year period (generally the year before the interview for controls and the year before diagnosis for cases) was assessed. Trained dietitians collected dietary data in the clinics. Consumption frequency was asked on a daily (e.g. bread), weekly (e.g. meat) or monthly (e.g. fish) basis. The average daily intake was calculated for every food item on the questionnaire by multiplying the consumption frequency of each food by its standard item-specific portion size; these scores were then summed to estimate carbohydrate intake.

The mean daily intakes of energy and nutrients for each individual were assessed using the USDA food composition table [18] (FCT) and the Iranian FCT [19]. To analyse the energy and nutrient contents of mixed food items (e.g. pizza), usual restaurant recipes were used. Alcohol consumption was not assessed in the FFQ as a result of its cultural and religious ban, and was not included in the analysis.

The GI and GL values for foods were obtained according to the Iranian Food Table of GI and GL [20]; those foods that were not included in this database were obtained from International Tables of GI and GL Values: 2008 [21]. The GI values of foods not reported in those databases were estimated based on the GI of foods that had similar nutritional composition and methods of preparation or were calculated using recipes. Dietary GI and GL values were calculated using the formulas described by Levitan *et al.* [22] [Dietary GI =$\sum$ foods carbohydrate (g) in a serving of food $\times$ frequency of consumed food $\times$ GI$\sum$ foods carbohydrate (g) in a serving of food; Dietary GL = $\sum$ foods Carbohydrate (g) in a serving of food $\times$ Frequency of consumed food $\times$ GI/100]. The procedure developed by Jacobs *et al.* [23] to classify grains as whole or refined was applied in the present study. Specifically, whole-grain foods included dark breads, barley bread, popcorn, cornflakes, whole wheat biscuits, wheat germ and bulgur. Refined grains included white breads, iceberg bread, noodle, pasta, rice, milled barley, sweet bread, white flour, starch and biscuits.

Nondietary exposure assessment

A general questionnaire was used to collect participants' socio-demographic and lifestyle information, including physical activity, occupational and educational history, familial history of PCOS, obesity and other diseases, smoking status and history of medication and supplement use.

Weight and height were measured in light clothing and without shoes. Weight was measured using digital scales (Soehnle, Berlin, Germany) and this was recorded to the

nearest 100 g. Height was measured using a nonstretch tape measure fixed to a wall and was recorded to the nearest 0.5 cm. Body mass index (BMI) was calculated by dividing the weight (kg) by height (m) squared. Waist circumference (WC) was measured at the umbilical site, using a tape and was recorded to the nearest 0.1 cm. These measurements were carried out by one trained examiner to avoid random observer error.

Physical activity information was obtained through interviews using a valid questionnaire and expressed as metabolic equivalent hours per day (MET h day^{-1}) [24,25]. This questionnaire consisted of nine different MET categories on a scale ranging from sleep/rest (0.9) to high-intensity activities (>6). Multiplying the time spent in each activity by the MET value corresponding to that activity, the MET h for an activity was calculated. Total MET h day^{-1} was then calculated by adding the MET h values for different activities in a day.

Endocrine function tests including serum follicle-stimulating hormone (FSH), luteinising hormone (LH), prolactin (PRL) and testosterone were assessed using enzyme-linked immunosorbent assay biochemical kits (serum prolactin, FSH, LH and IBL: Pishtaz Teb Zaman Diagnostics, Tehran, Iran; testosterone: IBL GmBH, Hamburg, Germany).

Statistical analysis

All analyses were conducted using SPSS, version 20 (IBM Corp., Armonk, NY, USA). Chi-squared or Fisher's exact tests were used to check differences in the distribution of categorical variables (e.g. smoking) and an Independent *t*-test or a Mann–Whitney test were used to assess differences in the distribution of continuous variables (e.g. BMI). Carbohydrate variables were adjusted for total energy consumption using the residual method as suggested by Willet and Stampfer [26]. Carbohydrate variables were categorised into tertiles. The first tertile served as the reference category for all regression analyses. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for tertile categories of carbohydrate variables were derived from the unconditional multivariate logistic regression. For comparison purposes, a base regression model and a fully-adjusted model for each analysis was calculated. The base model was adjusted for the matching variable (i.e. age in years), which was automatically controlled for by design. The fully-adjusted model, on the other hand, included the covariates: age (5-year groups), BMI (kg m^{-2}), WC (cm), physical activity (MET h day^{-1}), familial history of PCOS (yes/no) and noncarbohydrate energy intake (kcal day^{-1}) as potential confounders. These confounders were included in the fully-adjusted model based on the review of literature and comparison of cases and controls. $P < 0.05$ (two-tailed) was considered statistically significant.

Results

Table 1 presents the general characteristics of the cases ($n = 281$) and controls ($n = 472$). The mean (SD) age of participants was 28.8 (7.6) and 29.4 (7.5) years in cases and controls, respectively, demonstrating the age-matched design. MET h day^{-1} was significantly lower, whereas mean energy intake was significantly higher in cases compared to controls ($P < 0.05$). Compared to controls, BMI and WC were higher in the case group, as was the incidence of PCOS within their families ($P < 0.001$).

The mean intakes of dietary carbohydrate variables for cases and controls are listed in Table 2. There were no significant differences between the two groups in the mean starch and total sugar intakes ($P = 0.062$ and 0.059, respectively). Mean intakes of carbohydrate, refined grains, GI and GL were significantly higher among PCOS cases ($P < 0.05$). On the other hand, the controls consumed significantly more dietary fibre and whole grains ($P < 0.005$). Table 3 shows multivariate adjusted ORs (95% CIs) for the case group, according to the tertile of each dietary carbohydrate variable. Dietary GI and GL were significantly associated with PCOS. The adjusted ORs comparing the highest tertile of dietary GI and GL with the lowest tertile were 2.18 (95% CI = 1.29–3.81; *P*-test for trend = 0.012) and 2.39 (95% CI = 1.23–3.01; *P*-test for trend = 0.001), respectively, with a significant trend. Further adjusting for GI did not change the observed association of GL with PCOS (*P*-test for trend =0.007). Refined grain intake was directly associated with PCOS (OR = 2.35, 95% CI = 1.68–3.39; *P*-test for trend = 0.007). There was no significant association or dose–response trend for higher intakes of total sugar, starch and carbohydrate. Inverse associations were observed between the highest tertile of total fibre intake (OR = 0.73, 95% CI = 0.49–0.91; *P*-test for trend = 0.013) and whole grain intake (OR = 0.61, 95% CI = 0.34–0.89; *P*-test for trend = 0.008) and PCOS.

Discussion

To our knowledge, the present study is the first to evaluate the association between dietary carbohydrate composition and PCOS in a developing country. The results show that a higher dietary GI and GL and a lower fibre intake are significantly associated with PCOS.

Our results are consistent with studies in western countries indicating that women with PCOS consumed more high-GI foods compared to normoandrogenic women [9,10,14,27]. Graff *et al.* [27] have shown that dietary GI is associated with less favourable anthropometric and metabolic profiles in women

Table 1 General characteristics of study participants in cases and controls

Characteristic	PCOS women (n = 281)	Control women (n = 472)	P value*
Age (years), mean (SD)	28.8 (7.6)	29.4 (7.5)	0.775
Age at menarche (years), mean (SD)	13.7 (1.9)	10.8 (1.5)	0.002
Familial history of PCOS, n (%)	93 (33.1)	75 (15.9)	<0.001
BMI (kg m^{-2}), mean (SD)	31.2 (7.5)	25.9 (3.8)	<0.001
Waist circumference (cm), mean (SD)	93.3 (8.2)	80.1 (6.5)	<0.001
Physical activity (MET h^{-1} day^{-1}), mean (SD)	48.6 (5.1)	59.8 (7.5)	0.005
Energy intake (kJ day^{-1}) [kcal day^{-1}], mean (SD)	13451 (3016) [3215 (721)]	10413 (2347) [2489 (561)]	<0.001
Endocrine parameters, mean (SD)			
Testosterone (nmol L^{-1})	14.1 (4.5)	12.5 (3.8)	0.025
Luteinising hormone (IU L^{-1})	13.5 (3.4)	9.0 (2.2)	0.014
Follicle-stimulating hormone (IU L^{-1})	13.4 (3.5)	12.9 (2.8)	0.525
Prolactin (pmol L^{-1})	398 (126)	386 (123)	0.112
Cigarette smoker, n (%)			
Never smoker	145 (51.6)	221 (46.8)	0.176
Ex-smoker, pack years <10	19 (6.8)	47 (10.0)	
Ex-smoker, pack years ≥10	25 (8.9)	50 (11.0)	
Current smoker, pack years <20	59 (21.0)	118 (25.0)	
Current smoker, pack years ≥20	33 (11.7)	36 (7.6)	
Education, n (%)			
Less than high school	42 (14.9)	63 (13.3)	0.749
High school diploma	146 (52.0)	269 (57.0)	
Bachelor's or higher	93 (33.1)	140 (29.7)	
Monthly family income, US $, n (%)			
<300	196 (69.8)	344 (72.9)	0.241
≥300	85 (30.2)	128 (27.1)	
Vitamin mineral use, n (%)	54 (19.2)	105 (22.2)	0.783

*Student's t test, Mann–Whitney test, chi-squared test and Fisher's exact test.
BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinising hormone; PRL, prolactin; PCOS, polycystic ovary syndrome.

Table 2 Energy-adjusted dietary variables among cases with polycystic ovary syndrome (PCOS) and matched controls

Dietary factors mean (standard deviation)	Range	PCOS women (n = 281)	Control women (n = 472)	P value*
Glycaemic index†	39–69	59.7 (5.9)	51.8 (4.7)	0.02
Glycaemic load†	119–263	173.6 (39.1)	155.3 (35.2)	<0.001
Carbohydrate (g)	361–499	418.1 (39.5)	323.5 (43.4)	0.003
Dietary fibre (g)	5–41	12 (5.3)	29.5 (4.9)	<0.001
Starch (g)	59–111	93.6 (16.3)	89.3 (23.8)	0.062
Sugar (g)	91–191	140.3 (33.5)	135.7 (31.6)	0.059
Refined grains (g)	139–278	205.1 (59)	190.6 (51)	0.002
Whole grains (g)	45–169	88.3 (33)	97.2 (39)	0.004
Protein (g)	85–141	111.6 (21.3)	110.0 (19.5)	0.458
Fat (g)	63–170	120.9 (26.7)	83 (14.6)	0.006
Saturated fatty acids (g)	4–19	12.3 (5.6)	9.1 (3.9)	0.007

*Student's t test, Mann–Whitney test.
†Units were based on a scale where the glycaemic index of pure glucose = 100.

with PCOS. Barr *et al.* [28] have shown that total energy intake, total fat intake and dietary GI were higher in women with PCOS compared to healthy women.

Furthermore, some clinical trials have shown the beneficial effects of a low GI diet on some PCOS characteristics. Barr *et al.* [13] showed that an isocaloric low GI diet improves insulin sensitivity in women with PCOS. Mehrabani *et al.* [29] reported that the combination of high-protein and low-GL foods in a modified diet caused a significant increase in insulin sensitivity and a decrease in high-sensitivity-C-reactive protein levels compared to a conventional diet. Marsh *et al.* [12] demonstrated that a low GI diet, compared to a conventional healthy diet, improved menstrual cycles in PCOS women. Herriot *et al.* [30] reported that a reduced GL diet in combination with medication may contribute to improvements in symptom relief in patients with PCOS.

In the present study, a significant association was seen between the risk of PCOS and a higher dietary GI and GL and a lower fibre intake. Although this association remained significant after adjusting for other known PCOS risk factors, it was weaker in a full adjustment model, indicating that this relationship might be a result of the role of other metabolic risk factors such as general and abdominal obesity in the pathogenesis of PCOS. These results support previous studies indicating that a high GL diet can augment metabolic aberrance in PCOS [31] through the anabolic

Table 3 Adjusted odds ratio (OR) estimates and 95% confidence intervals (CIs) for polycystic ovarian syndrome according to the tertile of each dietary carbohydrate variables*

Carbohydrate variables	Tertiles of intake			*P* for trend
	1st	2nd	3rd	
GI				
Number of cases/number of controls	48/157	109/158	124/157	
Base model†	1.00 (reference)	1.71 (1.03–2.07)	2.43 (1.32–3.75)	0.002
Full model‡	1.00 (reference)	1.66 (0.98–2.03)	2.18 (1.29–3.81)	0.012
GL				
Number of cases/number of controls	57/157	98/158	126/157	
Base model†	1.00 (reference)	2.01 (1.13–2.57)	2.55 (1.93–3.07)	<0.001
Full model‡	1.00 (reference)	1.97 (1.23–2.44)	2.39 (1.23–3.01)	0.001
Total carbohydrates (g)				
Number of cases/number of controls	90/157	88/158	103/157	
Base model†	1.00 (reference)	1.19 (0.43–1.57)	1.25 (0.73–1.81)	0.125
Full model‡	1.00 (reference)	1.07 (0.83–2.08)	1.33 (0.83–2.19)	0.229
Starch (g)				
Number of cases/number of controls	89/157	93/158	99/157	
Base model†	1.00 (reference)	1.32 (0.49–1.59)	1.62 (0.39–2.75)	0.225
Full model‡	1.00 (reference)	1.03 (0.73–2.18)	1.73 (0.73–2.98)	0.339
Sugar (g)				
Number of cases/number of controls	93/157	90/158	98/157	
Base model†	1.00 (reference)	1.78 (0.33–2.91)	1.68 (0.21–3.20)	0.598
Full model‡	1.00 (reference)	1.58 (0.13–3.22)	1.59 (0.24–3.69)	0.711
Refined grains				
Number of cases/number of controls	44/157	97/158	140/157	
Base model†	1.00 (reference)	1.43 (1.11–2.92)	2.41 (1.45–3.06)	<0.001
Full model‡	1.00 (reference)	1.72 (1.32–2.81)	2.35 (1.68–3.39)	0.007
Whole grains				
Number of cases/number of controls	128/157	94/158	59/157	
Base model†	1.00 (reference)	0.64 (0.47–1.02)	0.57 (0.37–0.98)	0.003
Full model‡	1.00 (reference)	0.71 (0.39–0.97)	0.61 (0.34–0.89)	0.008
Total fibre (g)				
Number of cases/number of controls	121/157	100/158	60/157	
Base model†	1.00 (reference)	0.76 (0.57–1.08)	0.69 (0.30–0.88)	0.009
Full model‡	1.00 (reference)	0.88 (0.42–1.05)	0.73 (0.49–0.91)	0.013

*An unconditional logistic regression model.
†Adjusted for age (5-year categories).
‡Adjusted for age (5-year categories), body mass index, waist circumference, noncarbohydrate energy intake, familial history of PCOS and physical activity. GI, glycaemic index; GL, glycaemic load.

effects of insulin and changes in energy expenditure, as well as food intake [32,33]; this process leads to obesity and an increase in fatty tissue, further increasing insulin resistance in a vicious circle. Thus, it appears that a diet with a low GI and GL but high in fibre could prevent the occurrence or propagation of this vicious cycle by reducing insulin resistance and its related complications such as obesity and metabolic disorders [33].

In the present study, we used a valid and reliable FFQ to assess the usual dietary intake of the participants. Although using dietary recall might be more robust in portion size assessment, the use of a FFQ gives us more accurate data on the usual dietary habits of the subjects over 1 year before the diagnosis of the disease. Moreover, using a FFQ is superior to dietary recall for case–control studies because the patients might change their dietary intakes after the diagnosis of the disease. Furthermore, it has been shown that this FFQ provides valid data showing acceptable correlation with 24-h recall [17,34].

The most important strength of the present study lies in the fact that it is the first study to assess the association of dietary carbohydrate quantity and quality with PCOS in a developing country. Developing countries provide unique opportunities for assessing associations between diet and diseases because, where there is severe restriction in economic resources, food intake is strongly linked to income, such that even small economic differences are directly reflected in the diet and increase between-person variation [35]. This between-person variation provides us with an opportunity to evaluate the

effects of different dietary intakes on the development of disorders, which is not possible where there is only limited dietary intake variations in a population. The participation rate in the present study was high, which was a strength of the study. Only those individuals who were diagnosed with PCOS 3 months (at the most) prior the interview were included in the study, aiming to reduce the possibility of recall bias. This is because the dietary data collected at the time of disease might not truly reflect past intakes or intakes during the disease development and cases might have changed their diets as a result of disease symptoms. Controls were also carefully selected from only those patients with conditions not related to diet or other major risk factors for PCOS. Detailed assessment and adjustment for several important confounders and noncarbohydrate energy intake are other important strengths of the study.

Finally, a number of limitations need to be considered. Measurement errors were inevitable because dietary intake was assessed using a FFQ, which might have led to error in the estimation of associations; with that said, the FFQ used in the present study has good validity and reproducibility among the Iranian population [17] and participants under-/over-reporting their energy intakes were excluded. Moreover, the recruitment of patients with other diseases as controls is a weakness because their exposure may not be representative of the general population [36]; however, recruiting controls from the same hospitals provided us with the advantage of similarity in their socio-economic status, which, as explained, may have a great impact on nutrition in a developing country. Control participants might also have had nutritional diseases such as nutrient deficiencies diluting the association of carbohydrate intake and the risk of PCOS; however, we preferred clinic controls (as opposed to community controls) to avoid selection bias and also because of their higher participation and cooperation rates. To compensate for this limitation, controls with only a small range of diagnoses were selected to be included in the present study. Furthermore, although residual confounding cannot be entirely ruled out as a result of imprecise measurements of important covariates, it is unlikely that errors in measuring the covariates were so extreme because the crude and multivariable results were essentially the same. Another limitation of the present study is that serum testosterone and not sex hormone-binding globulin (SHBG) was measured because SHBG is somehow dependent on the protein intakes of the subjects. Finally, it would have been ideal to match cases and controls for BMI values to be able to confidently compare them from a metabolic stand point. Being more overweight affects the severity of PCOS and the women in the present study represent those who were more severely affected because past research has shown that clinic populations of PCOS are more overweight than community populations [37]. At the same time, we did not match for BMI as a result of concerns about an overmatching problem. This could lead to a loss of efficiency because matching could narrow the exposure range.

Conclusions

The most obvious finding to emerge from the present study is that women with PCOS consumed a diet with higher GI and GL and lower fibre compared to women without PCOS. There is abundant room for further progress in determining the mechanism behind this association, such as measuring blood glucose levels and insulin demands in future studies.

Transparency declaration

Azita Hekmatdoost affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with STROBE guidelines.

Acknowledgments

The authors are thankful to all participants and the research assistants who participated in this project for their effort in soliciting cases and controls and conducting interviews. They also acknowledge Ms Leyla Perkins for editing the English language in the manuscript submitted for publication.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
This study is financially supported by Shahid Beheshti University of Medical Sciences, Tehran, Iran.
AH had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. AH and GE conceived and designed the study and provided administrative, technical or material support, analysed and interpreted the data, and drafted the manuscript. AH, GE and SE critically revised the manuscript for important intellectual content. All authors critically reviewed the manuscript and approved the final version submitted for publication.

References

1. Azziz R, Woods KS, Reyna R *et al.* (2004) The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab* **89**, 2745–2749.
2. Solomon CG (1999) The epidemiology of polycystic ovary syndrome. Prevalence and associated disease risks. *Endocrinol Metab Clin North Am* **28**, 247–263.
3. Rose S & Laan MJ (2009) Why match? Investigating matched case–control study designs with causal effect estimation. *Int J Biostat* **5**, Article 1.
4. Tehrani FR, Simbar M, Tohidi M *et al.* (2011) The prevalence of polycystic ovary syndrome in a community sample of Iranian population: Iranian PCOS prevalence study. *Reprod Biol Endocrinol* **9**, 39.
5. Goodarzi MO, Dumesic DA, Chazenbalk G *et al.* (2011) Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. *Nat Rev Endocrinol* **7**, 219–231.
6. Chun-Sen H, Chien-Hua W, Wan-Chun C *et al.* (2011) Obesity and insulin resistance in women with polycystic ovary syndrome. *Gynecol Endocrinol* **27**, 300–306.
7. Jeanes YM, Barr S, Smith K *et al.* (2009) Dietary management of women with polycystic ovary syndrome in the United Kingdom: the role of dietitians. *J Hum Nutr Diet* **22**, 551–558.
8. Rodrigues AM, Martins LB, Franklin AM *et al.* (2015) Poor quality diet is associated with overweight status and obesity in patients with polycystic ovary syndrome. *J Hum Nutr Diet* **28**(Suppl 2), 94–101.
9. Altieri P, Cavazza C, Pasqui F *et al.* (2013) Dietary habits and their relationship with hormones and metabolism in overweight and obese women with polycystic ovary syndrome. *Clin Endocrinol* **78**, 52–59.
10. Marsh K & Brand-Miller J (2005) The optimal diet for women with polycystic ovary syndrome? *Br J Nutr* **94**, 154–165.
11. Moran LJ, Ko H, Misso M *et al.* (2013) Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines. *J Acad Nutr Diet* **113**, 520–545.
12. Marsh KA, Steinbeck KS, Atkinson FS *et al.* (2010) Effect of a low glycemic index compared with a conventional healthy diet on polycystic ovary syndrome. *Am J Clin Nutr* **92**, 83–92.
13. Barr S, Reeves S, Sharp K *et al.* (2013) An isocaloric low glycemic index diet improves insulin sensitivity in women with polycystic ovary syndrome. *J Acad Nutr Diet* **113**, 1523–1531.
14. Douglas CC, Norris LE, Oster RA *et al.* (2006) Difference in dietary intake between women with polycystic ovary syndrome and healthy controls. *Fertil Steril* **86**, 411–417.
15. ESHRE/ASRM. (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* **19**, 41–47.
16. Williams JR (2008) The declaration of Helsinki and public health. *Bull World Health Organ* **86**, 650–652.
17. Mirmiran P, Esfahani FH, Mehrabi Y *et al.* (2010) Reliability and relative validity of an FFQ for nutrients in the Tehran lipid and glucose study. *Public Health Nutr* **13**, 654–662.
18. Food and Nutrition Information Center, US Department of Agriculture (2009) *Food composition table (FCT)*. Beltsville, MD. Secondary Food and Nutrition Information Center, US Department of Agriculture: Food composition table (FCT). Beltsville, MD. Available at: http://www.nal.usda.gov/fnic/foodcomp.
19. Azar, M & Sarkisian, E (1980) *Food Composition Table of Iran. Tehran: National Nutrition and Food Research Institute*. Tehran: Shahid Beheshti University Press.
20. Taleban, F & Esmaeili, M (1999) *Glycemic Index of Iranian Foods*. 1st edn. Tehran: National Nutrition and Food Technology Research Institute Shahid Beheshti University of Medical Sciences.
21. Atkinson FS, Foster-Powell K & Brand-Miller JC (2008) International tables of glycemic index and glycemic load values: 2008. *Diabetes Care* **31**, 2281–2283.
22. Levitan EB, Westgren CW, Liu S *et al.* (2007) Reproducibility and validity of dietary glycemic index, dietary glycemic load, and total carbohydrate intake in 141 Swedish men. *Am J Clin Nutr* **85**, 548–553.
23. Jacobs DR Jr, Meyer KA, Kushi LH *et al.* (1998) Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa women's health study. *Am J Clin Nutr* **68**, 248–257.
24. Aadahl M & Jorgensen T (2003) Validation of a new self-report instrument for measuring physical activity. *Med Sci Sports Exerc* **35**, 1196–1202.
25. Kelishadi R, Ghatrehsamani S, Hosseini M *et al.* (2010) Barriers to physical activity in a population-based sample of children and adolescents in Isfahan, Iran. *Int J Prev Med* **1**, 131–137.
26. Willett W & Stampfer MJ (1986) Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* **124**, 17–27.
27. Graff SK, Mario FM, Alves BC *et al.* (2013) Dietary glycemic index is associated with less favorable anthropometric and metabolic profiles in polycystic ovary syndrome women with different phenotypes. *Fertil Steril* **100**, 1081–1088.
28. Barr S, Hart K, Reeves S *et al.* (2011) Habitual dietary intake, eating pattern and physical activity of women with polycystic ovary syndrome. *Eur J Clin Nutr* **65**, 1126–1132.
29. Mehrabani HH, Salehpour S, Amiri Z *et al.* (2012) Beneficial effects of a high-protein, low-glycemic-load hypocaloric diet in overweight and obese women with polycystic ovary syndrome: a randomized controlled intervention study. *J Am Coll Nutr* **31**, 117–125.
30. Herriot AM, Whitcroft S & Jeanes Y (2008) An retrospective audit of patients with polycystic ovary syndrome: the effects of a reduced glycaemic load diet. *J Hum Nutr Diet* **21**, 337–345.

31. The DCCT Research Group (1988) Weight gain associated with intensive therapy in the diabetes control and complications trial. *Diabetes Care* **11**, 567–573.
32. Ryan M, Livingstone MB, Ducluzeau PH *et al.* (2008) Is a failure to recognize an increase in food intake a key to understanding insulin-induced weight gain? *Diabetes Care* **31**, 448–450.
33. Bhupathiraju SN, Tobias DK, Malik VS *et al.* (2014) Glycemic index, glycemic load, and risk of type 2 diabetes: results from 3 large US cohorts and an updated meta-analysis. *Am J Clin Nutr* **100**, 218–232.
34. Esfahani FH, Asghari G, Mirmiran P *et al.* (2010) Reproducibility and relative validity of food group intake in a food frequency questionnaire developed for the Tehran lipid and glucose study. *J Epidemiol* **20**, 150–158.
35. Willett WC, Koplan JP, Nugent R *et al.* (2006) Prevention of chronic disease by means of diet and lifestyle changes. In: Jamison DT, Breman JG, Measham AR, *et al.*, eds. *Disease Control Priorities in Developing Countries*. 2nd ed. Washington, DC: World Bank.
36. Lewallen S & Courtright P (1998) Epidemiology in practice: case–control studies. *Community Eye Health* **11**, 57–58.
37. Ezeh U, Yildiz BO & Azziz R (2013) Referral bias in defining the phenotype and prevalence of obesity in polycystic ovary syndrome. *J Clin Endocrinol Metab* **98**, E1088–E1096.

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

CLINICAL NUTRITION

Patient adherence in following a prescribed diet and micronutrient supplements after laparoscopic sleeve gastrectomy: our experience during 1 year of follow-up

L. Schiavo,[1] G. Scalera,[1] V. Pilone,[2] G. De Sena,[1] F. R. Ciorra[1] & A. Barbarisi[1]

[1]Department of Anaesthesiology, Surgery and Emergency Sciences, Integrated Assistential Department of General and Special Surgery (Cappella Cangiani), IX Division of General Surgery, Vascular and Applied Biotechnology, Second University of Naples, Naples, Italy
[2]Department of Medicine and Surgery, University of Salerno, Salerno, Italy

Keywords
barriers to recommended adherence, laparoscopic sleeve gastrectomy, post-operative dietary adherence, post-operative micronutrient supplement adherence.

Correspondence
L. Schiavo, Department of Anaesthesiology, Surgery and Emergency Sciences, Second University of Naples, Integrated Assistential Department of General and Special Surgery (Cappella Cangiani), IX Division of General Surgery, Vascular and Applied Biotechnology, Via Pansini n° 5, 80131, Naples, Italy.
Tel.: +39 081 5665377
Fax: +39 081 290700
E-mail: luigi.schiavo@unina2.it

How to cite this article
Schiavo L., Scalera G., Pilone V., De Sena G., Ciorra F.R. & Barbarisi A. (2017) Patient adherence in following a prescribed diet and micronutrient supplements after laparoscopic sleeve gastrectomy: our experience during 1 year of follow-up. *J Hum Nutr Diet*. **30**, 98–104
doi: 10.1111/jhn.12427

Abstract

Background: One of the most effective surgeries for sustainable weight loss in morbidly obese patients is laparoscopic sleeve gastrectomy (LSG). The present study aimed to assess the adherence of LSG patients with respect to following post-operative dietary requirements and micronutrient supplementation, as well as to investigate their perceived barriers in achieving optimal adherence.
Methods: Retrospective data analysis was performed (3, 6, 9 and 12 months after LSG) using the medical records of 96 morbidly obese patients who had undergone LSG at our institution during 2011–2013. Data collected from patient records were: adherence to prescribed diet; adherence to prescribed consumption of fruit, vegetables, legumes and cereals; use of prescribed micronutrient supplements; and barriers to diet and micronutrient therapy adherence. Data were analysed using SPSS, version 14.0 (SPSS Inc., Chicago, IL, USA).
Results: At 3, 6, 9 and 12 months post-LSG, the rates of patient non-adherence to a prescribed diet were 39%, 45%, 51% and 74%, respectively. In particular, there was a low consumption of fruit, vegetables, legumes and cereals compared to the post-surgery prescription. In addition, the rates of patient non-adherence to prescribed micronutrient supplements at 3, 6, 9 and 12 months post-LSG were 43%, 51%, 59% and 67%, respectively. The main reasons for patient non-adherence to diet were poor self-discipline (72%) and poor family support (11%) whereas difficulty swallowing pills or capsules (61%) and cost (20%) were reported as the main barriers to post-LSG adherence.
Conclusions: Morbidly obese patients who have undergone LSG do not follow exactly the post-operative dietary guidelines, including micronutrient therapy.

Introduction

Laparoscopic sleeve gastrectomy (LSG) is one of the most commonly performed bariatric surgical procedures [(1)]. Although LSG influences the volume of food consumed, it does not necessarily improve the quality of food consumed or adherence with respect to following recommended micronutrient supplement usage, leaving nutrition care and food choice as important lifelong considerations. Therefore, morbidly obese patients who have undergone LSG must adhere to many lifestyle and nutritional recommendations, including micronutrient therapy [(2)].

After LSG, early satiety and a gastric volume that is restricted to approximately 15% of original capacity

impacts on dietary intake [3]. Although LSG does not cause malabsorption, it appears to alter nutrient utilisation, in particular of vitamin B_{12} and iron [4–6]. Hence, a strict adherence to a post-operative prescribed diet and multivitamin and mineral supplements is a lifelong recommendation [2].

Therapeutic adherence includes patient adherence not only with respect to medication, but also regarding diet, exercise or lifestyle changes. Thus, therapeutic non-adherence occurs when an individual's health seeking or maintenance behaviour lacks congruence with recommendations as prescribed by a healthcare provider [7]. Although not perfect, the term 'adherence' is preferable to 'compliance' because the latter implies patient submission to the healthcare professional's orders without mutual negotiation [7].

As reported in the American Society for Metabolic and Bariatric Surgery (ASMBS) Guidelines [2], nutrition assessment and dietary management in surgical weight loss is a vital component of the bariatric surgery process. The goal should be to create a plan for post-operative dietary intake that will enhance the likelihood of success. The above mentioned document also highlights the importance for the bariatric patient to regularly take vitamin and mineral supplements not only to prevent nutrient deficiencies that can arise after surgery, but also because some nutrients, such as calcium, can enhance weight loss and help prevent weight regain.

Nutrient deficiencies constitute one of the most important long-term complications of LSG [8] because they may lead to haematological, metabolic and especially neurological disorders [9–11]. Poor post-operative nutrient intake, recurrent vomiting and food intolerance are important and well-recognised risk factors after LSG [12–15].

New research indicates that other causes of nutrient deficiency after bariatric surgery involve patients who do not follow exactly the post-operative dietary guidelines or the prescribed intake of regular supplements of vitamins and minerals [16].

Up-to-date data on patient adherence with respect to following a prescribed diet and micronutrient supplements after LSG are scarce. The present study aimed to assess the adherence of LSG patients with respect to following post-operative dietary requirements and micronutrient supplementation, as well as to investigate their perceived barriers in achieving optimal adherence.

Materials and methods

Patient selection

The present study aimed to determine adherence with respect to following a prescribed diet and micronutrient supplements given by healthcare practitioners to patients who had undergone LSG at our institution during the years 2011–2013. The reasons for non-adherence to diet and micronutrient supplement recommendations were also evaluated. A total of 96 participants were recruited, comprising 72 women and 24 men. After surgery, patients were instructed to follow a post-operative diet and to use micronutrient supplements, and were motivated with respect to understanding the role of diet and vitamin/mineral therapy in the management of their condition. This education in lifestyle modification was performed by a trained nutritionist in periodic and individualised consultations, as established in the service protocol, which is based on the American Society for Metabolic and Bariatric Surgery dietary recommendations [2]. Retrospective data analysis was performed using the medical records of patients who had been followed for at least 12 months after LSG. Barriers to diet and micronutrient supplement adherence were investigated using a face-to-face interview. Patients were individually assessed every 3 months over 12 months. Informed written consent was obtained from each participant after the objectives of the study had been explained to them. None of the patients who were approached for recruitment declined to take part in the study.

Post-laparoscopic sleeve gastrectomy dietary adherence assessment and barriers to diet adherence

In accordance with the nutritional guidelines for the surgical weight loss patient [2], after discharge on the sixth post-operative day, patients followed a diet specifically devised for LSG recipients: a liquid diet that was changed to a puree-based diet after 10–15 days and to a soft solid food diet after an additional 3–4 weeks. One month after the surgery, patients were instructed to follow a Mediterranean protein enriched diet (MPED), which we recently demonstrated to be useful in determining a significant reduction in body weight, fat mass and visceral mass without a significant loss of fat-free mass [17]. MPED food plans were developed using NUTRIGEO, version 8 (Progeo, Ascoli Piceno, Italy) by assigning a specific quantity to individual food items. Each food plan [50.21 MJ day^{-1} (1200 kcal day^{-1})] consisted of 141 g of carbohydrates (45%), 35 g of fats (25%) and 80 g of protein (30%). Dietary recommendations proposed by a healthcare professional included a Mediterranean diet comprising a daily serving of certain food (fruits, vegetables, bread, pasta, rice, other grains, potatoes, olive oil, beans, nuts, legumes, seed, herbs and spices); food to be consumed at least two times per week (fish and seafood); food to be consumed in moderate portions, daily to 1 week (poultry, eggs, cheese and yogurt); and, finally, food to be consumed less often (sweets and red meats), as well as small

amounts of fats, oils, refined sugars and salt. Adherence with respect to following the prescribed diet (every 3 months over 12 months) were performed using 3-day estimated food records and 72-h recalls [18]. To measure nutritional intake and obtain a broad idea regarding the diets consumed during a typical week, all participants had to complete a dietary record for three consecutive days (Sunday to Tuesday; breakfast to bedtime) and a daily food diary to record any deviations from their prescribed diet. A trained nutritionist conducted secondary assessments by administering a 72-h recall questionnaire in which patients were requested to precisely describe their food and non-alcoholic beverage intake during the previous 3 days. All participants repeated the 72-h recall for purposes of analytical repeatability. Nutrient intakes were calculated from the 72-h recalls and 3-day dietary records using NUTRIGEO, version 8. In addition, during the counselling session, patients who were found to not regularly follow the prescribed diet were individually asked to answer the question: what made it difficult to follow the regularly prescribed diet? The patient was not asked to answer a question with multiple answers but to explain his/her main barriers/motivations verbally. The nutritionist registered the individual patient answers for the statistical analysis.

Post-laparoscopic sleeve gastrectomy micronutrient therapy assessment: face-to-face interview

Micronutrient supplementation was started in all patients after discharge. To ensure that all patients consumed similar micronutrients, they all received the same commercially available mineral and vitamin supplement (FitForMe Optimum capsules; FitForMe, Orte, Italy), which was specially formulated for obese patients and/or for people who have undergone LSG.

The percentage of patients who were non-adherent to micronutrient supplementation was assessed at 3, 6, 9 and 12 months after LSG surgery. Each candidate was counselled individually about his adherence with respect to regularly taking the prescribed micronutrient supplements.

Face-to-face interviews were performed to assess barriers to micronutrient supplement adherence, during which each patient was asked to answer the questions: (i) did you take the prescribed micronutrient supplements daily and (ii) what makes it difficult for you to regularly follow the prescribed micronutrient supplementation? The patient was not asked to answer a question with multiple answers but to explain verbally his/her main barriers/motivations. The nutritionist registered the answers of individual patients for the statistical analysis.

Statistical analysis

Data were collected from 1 September 2011 to 31 December 2013 using 3-day estimated food records and 72-h recalls, and entered into EXCEL (Microsoft, Redmond, WA, USA) and then subsequently exported to SPSS, version 14.0 (SPSS Inc., Chicago, IL, USA) for analysis. The variables were analysed with descriptive statistics using simple frequency distributions: percentages, frequencies, averages, SDs and minimum and maximum values. The number of servings eaten by each participant was classified as either within, less or exceeding recommendations. Data regarding age, initial weight and initial body mass index (BMI) are reported as the mean (SD).

Results

Baseline characteristics of participants

As shown in Table 1, 96 patients, comprising 72 females (75%) and 24 males (25%), with a mean (SD) age of 45 (12.2) years, as well as a mean (SD) initial weight and BMI of 174 (21.1) kg and 56.1 (10.5) in males and 138 (16.9) kg and 50.7 (18.7) kg m^{-2} in females, respectively, were studied. All participants underwent LSG at our University Hospital.

Concerning weight loss and BMI, and based on the repeated measurements during the follow-up period, we observed a significant ($P < 0.01$) reduction of both parameters at month 12 in both sexes [male = mean weight and BMI of 116 (19.6) kg and 37.4 (19.3) kg m^{-2}, respectively; female = mean weight and BMI of 102 (12.4) kg and 37.5 (13.4) kg m^{-2}, respectively].

Table 1 Distribution of participant's baseline characteristic

Characteristic	Pre-LSG	Post-LSG (follow-up 12 months)
Number of patients	96	90
Female	72 (75%)	68 (75%)
Male	24 (25%)	22 (25%)
Age (years)	45 (12.2)	46 (11.8)
Weight (kg)	Male: 174 (21.1)	Male: 116 (19.6)
	Female: 138 (16.9)	Female: 102 (12.4)
BMI (kg m^{-2})	Male: 56.1 (10.5)	Male: 37.4 (19.3)
	Female: 50.7 (18.7)	Female: 37.5 (13.4)
Living alone	12 (12.5%)	12 (12.5%)
Living with parents	24 (25%)	24 (25%)
Married or co-habiting	64 (62.5%)	64 (62.5%)
Employed	72 (75%)	72 (75%)
Unemployed	24 (25%)	24 (25%)

BMI, body mass index; LSG, laparoscopic sleeve gastrectomy.

Reasons for non-adherence in following the prescribed post-laparoscopic sleeve gastrectomy diet

We analysed patient adherence with respect to following the dietary prescriptions after surgery. The dietary prescription included fruit, vegetables, cereals and legumes. The data are presented as a percentage of the food diet compared to that of patients at months 3, 6, 9 and 12.

As shown in Fig. 1a, patient non-adherence with the dietary prescription increased every month throughout a 12-month follow-up period; from an average of 39% at month 3 to an average of 45% at month 6, 51% at month 9 and 74% at month 12. In addition, as shown in Fig. 1b, patient non-adherence concerning fruit, vegetables, cereals and legumes consumption also increased every month throughout a 12-month follow-up period.

Concerning barriers for non-adherence with respect to following the prescribed post-LSG diet, poor-self-discipline and poor support by family members were the two primary barriers identified in 72% and 11% of the patients, respectively. In addition, financial constraints and eating out were the two secondary barriers identified in 9% and 8% of the patients, respectively.

Reasons for non-adherence in following the prescribed post-laparoscopic sleeve gastrectomy micronutrient supplements

The other data that we analysed were patient adherence with respect to following the prescribed micronutrients supplements after LSG. The reasons listed by patients for not following the prescription were: difficulty swallowing pills or capsules, cost, forgetting or patients feeling that they are not necessary. As shown in Fig. 1c, patient non-adherence with micronutrient supplement prescription increased every month. Concerning barriers to micronutrient therapy adherence, difficulty swallowing pills and/or capsules and the high cost of the supplements were the two primary barriers identified in 61% and 20% of the patients, respectively, whereas 8% of the patients said that they did not think they needed to take micronutrient supplements and 11% said they forgot to take them.

Discussion

The main finding of the present study is that morbidly obese patients who have undergone LSG do not follow exactly the post-operative dietary guidelines, including micronutrient therapy. The primary reasons for patient non-adherence to follow the prescribed post-LSG diet were poor self-discipline and poor family support, whereas the principal motives for patient non-adherence to regularly take the prescribed micronutrient supplements were difficulty swallowing pills or capsules and the high cost of the supplements.

The present study showed that, only 3 months after surgery, more than one-third (39%) and almost half (43%) of the participants did not adhere to diet and micronutrient supplements, respectively, and this lack of

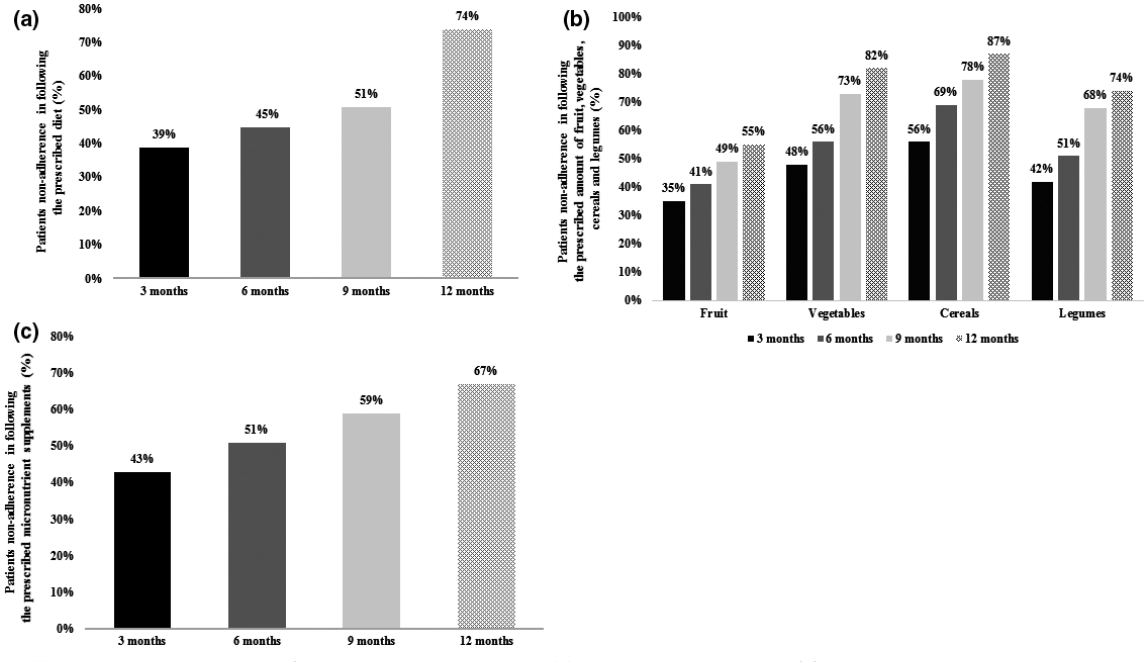

Figure 1 (a) Patients non-adherence in following the prescribed diet, (b) the prescribed amount of fruit, vegetables, cereals and legumes and (c) the prescribed micronutrient supplements after laparoscopic sleeve gastrectomy (LSG). Values obtained at 3, 6, 9 and 12 months after LSG are reported.

adherence increased every month throughout a 12-month follow-up period.

In particular, we always observed that the average consumption of fruit, vegetables, legumes and cereals was already lower than the post-LSG recommended amounts, at post-operative month 3, and non-adherence increased every month throughout a 12-month follow-up period.

The rate of non-adherence to diet in the present study compared well with those reported in other countries where similar studies were conducted. In particular, the results are similar to those reported by Soares *et al.* [16] who, aiming to evaluate food quality in the late post-operative period on bariatric surgery, used the bariatric food pyramid, showing that more than half of 172 patients studied had insufficient intake of fruit, vegetables and cereals, at both 6 months and 1 year, in comparison with the recommendations.

Despite each candidate being counselled individually before starting the post-LSG diet, the majority still gave various reasons for their non-adherence to the recommendations. In the present study, the most frequently reported reasons for non-adherence to dietary recommendations were poor self-discipline and poor support by family members. These data are crucial because they demonstrate that, despite the bariatric procedures performed in morbidly obese patients, dietary change is not easy because it requires alterations in personal and familiar habits that are built up over a long period of time. Therefore, our data are in accordance with the study by Moreira *et al.* [19], who aimed to assess participant adherence to their provided diet over the 6-month duration of the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy, and showed that dietary adherence is good when patients are highly motivated.

Considering that bariatric surgery patients have a high risk of micronutrient deficiencies, which can be caused by decreases in fruit and vegetable intake [20,21], we thus recommend the need for more research to determine appropriate strategies aimed at improving patient adherence with a dietary prescription that has a positive impact on preventing deficiencies of micronutrients after bariatric procedures, such as LSG.

Concerning post-operative micronutrient therapy, despite preoperative education regarding the need for daily micronutrient therapy, we observed that the average adherence with respect to following the prescribed supplement was lower than recommended at 3, 6, 9 and 12 months, suggesting poor long-term post-operative adherence to supplements. However, despite our data confirming previous data reported in other studies performed in different populations who underwent bariatric surgery [22], the data concerning the adherence of bariatric surgery patients with respect to following post-operative micronutrient supplementation are still controversial [23].

In the present study, difficulty in swallowing multivitamins was the primary barrier identified (61%). Interestingly, difficulty swallowing multivitamins already became prominent 3 months after the surgery. This finding could be the result of a change in taste and deglutition and, in our opinion, this is crucial because it demonstrates how, in morbidly obese patients who underwent bariatric surgery, the inability to eat solid food for several weeks after surgery may hinder the ability of a patient to swallow a large multivitamin pill or capsule, suggesting that more research to determine appropriate strategies aimed at improving patient adherence with post-operative micronutrient supplements (i.e. micronutrient supplements in drops and/or in liquid formulation).

It is widely recognised that LSG patients are at risk from macro- and micronutrient deficiencies because of several mechanisms, including preoperative micronutrient deficiency [24–26], as well as post-operative reduced intake, nausea and vomiting, poor food choice, and food avoidance because of intolerance [27]. In our opinion, the data obtained in the present study could have important clinical implications because they would allow us to postulate that nutritional deficiencies observed in LSG patients are not only caused by gastric modifications, as induced by interventions and reduced food intake, but also are a result of patients not following exactly the post-operative dietary guidelines, as well as patients not taking regular supplements of vitamins and minerals as prescribed. Considering that, as recently shown by Calleja-Fernández *et al.* [28], bariatric surgery procedures enhanced by nutritional education appear to improve their results by achieving an adequate weight loss, we recommend that more research is conducted to determine appropriate strategies aimed at improving patient adherence with micronutrients and dietary prescriptions for a positive impact in preventing nutritional deficiencies that may have a role in post-LSG long-term complications.

The present study has certain limitations. First, patient adherence in terms of sex was not investigated to determine whether one sex followed the prescription more than the other. Another limitation of the present study is the fact that the amount of information obtained from the quantity of food taken is limited and relied only on a patient's honesty. Nevertheless, the results obtained provide valuable information about patient adherence in following the prescribed diet and micronutrient supplementation after bariatric surgery. The need to improve preoperative nutritional counselling to instruct patients to regularly follow a post-operative diet and use micronutrient supplements is highlighted. Clearly, more research is needed to determine appropriate strategies aimed at improving

patient adherence with micronutrients and dietary prescription. This would have a positive impact in preventing nutritional deficiencies after bariatric procedures.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
No funding declared.
LS and AB contributed to the conception, design and interpretation of the data and the drafting of the manuscript. GS, VP, GD and FC contributed to the data acquisition. All procedures performed in the present study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments. All authors critically reviewed the manuscript and approved the final version submitted for publication.

Transparency declaration

The lead author (LS) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, and that no important aspects of the study have been omitted.

References

1. Angrisani L, Santonicola A, Iovino P *et al.* (2015) Bariatric surgery worldwide 2013. *Obes Surg* **25**, 1822–1832.
2. Allied Health Sciences Section *Ad Hoc* Nutrition Committee, Aills L, Blankenship J *et al.* (2008) ASMBS Allied health nutritional guidelines for the surgical weight loss patient. *Surg Obes Relat Dis* **4**, S73–S108.
3. Melissas J, Daskalakis M, Koukouraki S *et al.* (2008) Sleeve gastrectomy – a 'food limiting' operation. *Obes Surg* **18**, 1251–1256.
4. Xanthakos SA (2009) Nutritional deficiencies in obesity and after bariatric surgery. *Pediatr Clin North Am* **56**, 1105–1121.
5. Gehrer S, Kern B, Peters T *et al.* (2010) Fewer nutrient deficiencies after laparoscopic sleeve gastrectomy (LSG) than after laparoscopic Roux-Y-gastric bypass (LRYGB) – a prospective study. *Obes Surg* **20**, 447–453.
6. Jàuregui-Lobera I (2013) Iron deficiency and bariatric surgery. *Nutrients* **5**, 1595–1608.
7. World Health Organization (2003) Defining adherence – The adherence project. Available at: http://www.who.int/chp/knowledge/publications/adherenceSection1.pdf
8. Sarkhosh K, Birch DW, Sharma A *et al.* (2013) Complications associated with laparoscopic sleeve gastrectomy for morbid obesity: a surgeon's guide. *Can J Surg* **56**, 347–352.
9. Aarts EO, Janssen IM & Berends FJ (2011) The gastric sleeve: losing weight as fast as micronutrients? *Obes Surg* **21**, 207–211.
10. Malinowsky SS (2006) Nutritional and metabolic complications of bariatric surgery. *Am J Med Sci* **331**, 219–225.
11. Berger JR (2004) The neurological complications of bariatric surgery. *Arch Neurol* **61**, 1185–1189.
12. Donadelli SP, Junqueira-Franco MVM, de Mattos Donadelli CA *et al.* (2012) Daily vitamin supplementation and hypovitaminosis after obesity surgery. *Nutrition* **28**, 391–396.
13. Toh SY, Zarshenas N & Jorgensen J (2009) Prevalence of nutrient deficiencies in bariatric patients. *Nutrition* **25**, 1150–1156.
14. Alvarez-Leite JI (2004) Nutrient deficiencies secondary to bariatric surgery. *Curr Opin Clin Nutr Metab Care* **7**, 569–575.
15. Snyder-Marlow G, Taylor D & Lenhard MJ (2010) Nutrition care for patients undergoing laparoscopic sleeve gastrectomy for weight loss. *J Am Diet Assoc* **110**, 600–607.
16. Soares FL, Bissoni de Sousa L, Corradi-Perini C *et al.* (2014) Food quality in the late postoperative period of bariatric surgery: an evaluation using the bariatric food pyramid. *Obes Surg* **24**, 1481–1486.
17. Schiavo L, Scalera G, Sergio R *et al.* (2015) Clinical impact of Mediterranean-enriched-protein diet on liver size, visceral fat, fat mass, and fat free mass in patient undergoing sleeve gastrectomy. *Surg Obes Relat Dis* **11**, 1164–1170.
18. Schröder H, Covas MI, Marrugat J *et al.* (2001) Use of a three-day estimated food record, a 72-h recall and a food-frequency questionnaire for dietary assessment in a Mediterranean Spanish population. *Clin Nutr* **20**, 429–437.
19. Moreira EA, Most M, Howard J *et al.* (2011) Dietary adherence to long-term controlled feeding in a calorie-restriction study in overweight men and women. *Nutr Clin Pract* **26**, 309–315.
20. Bordalo LA, Teixeira TF, Bressan J *et al.* (2011) Bariatric surgery: how and why to supplement. *Rev Assoc Med Bras* **57**, 113–120.
21. Vargas-Ruiz AG, Hernández-Rivera G & Herrera MF (2008) Prevalence of iron, folate, and vitamin B12 deficiency anaemia after laparoscopic Roux-en-Y gastric bypass. *Obes Surg* **18**, 288–293.
22. Cooper PL, Brearley LK, Jamieson AC *et al.* (1999) Nutritional consequences of modified vertical gastroplasty in obese subjects. *Int J Obes Relat Metab Disord* **23**, 382–388.
23. James H, Lorentz P & Collazo-Clavell ML (2016) Patient-reported adherence to empiric vitamin/mineral supplementation and related nutrient deficiencies after

Roux-en-Y gastric bypass. *Obes Surg*, doi: 10.1007/s11695-016-2155-7. [Epub ahead of print]
24. Wolf E, Utech M, Stehle P *et al.* (2015) Preoperative micronutrient status in morbidly obese patients before undergoing bariatric surgery: results of a cross-sectional study. *Surg Obes Relat Dis* **11**, 1157–1163.
25. Ben-Porat T, Elazary R, Yuval JB *et al.* (2015) Nutritional deficiencies following sleeve gastrectomy – can they be predicted pre-operatively? *Surg Obes Relat Dis* **11**, 1029–1036.
26. Schiavo L, Scalera G, Pilone V *et al.* (2016) Micronutrient deficiencies in patients candidate for bariatric surgery: a prospective, preoperative trial of screening, diagnosis, and treatment. *Int J Vitam Nutr Res*, doi: http://dx.doi.org/10.1024/0300-9831/a000282. [Epub ahead of print]
27. Damms-Machado A, Friedrich A, Kramer KM *et al.* (2012) Pre- and postoperative nutritional deficiencies in obese patients undergoing laparoscopic sleeve gastrectomy. *Obes Surg* **22**, 881–889.
28. Calleja-Fernández A, Pintor-de-la-Maza B, Diez-Rodríguez R *et al.* (2015) Relationship between diet and body composition after biliopancreatic diversion. *Obes Surg* **25**, 2093–2099.

BDA The Association of UK Dietitians
THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

DIETARY GUIDELINES

How much is '5-a-day'? A qualitative investigation into consumer understanding of fruit and vegetable intake guidelines

C. Rooney,[1] M. C. McKinley,[1] K. M. Appleton,[2] I. S. Young,[1] A. J. McGrath,[1] C. R. Draffin,[1] L. L. Hamill[1] & J. V. Woodside[1]

[1]Centre for Public Health, Queen's University Belfast, Belfast, UK
[2]Department of Psychology, Bournemouth University, Poole, UK

Keywords
food-based dietary guidelines, fruit and vegetables, portion size, understanding.

Correspondence
J. Woodside, Centre for Public Health, Institute of Clinical Sciences, Block B, Grosvenor Road, Belfast BT12 6BJ, UK.
Tel.: +44 (0)2890978942
Fax: +44 (0)2890235900
Email: j.woodside@qub.ac.uk

How to cite this article
Rooney C., McKinley M.C., Appleton K.M., Young I.S., McGrath A.J., Draffin C.R., Hamill L.L. & Woodside J.V. (2017) How much is '5-a-day'? A qualitative investigation into consumer understanding of fruit and vegetable intake guidelines. *J Hum Nutr Diet*. **30**, 105–113
doi: 10.1111/jhn.12393

Abstract

Background: Despite the known health benefits of fruit and vegetables (FV), population intakes remain low. One potential contributing factor may be a lack of understanding surrounding recommended intakes. The present study aimed to explore the understanding of FV intake guidelines among a sample of low FV consumers.

Methods: Six semi-structured focus groups were held with low FV consumers (n = 28, age range 19–55 years). Focus groups were recorded digitally, transcribed verbatim and analysed thematically using NVIVO (QSR International, Melbourne, Australia) to manage the coded data. Participants also completed a short questionnaire assessing knowledge on FV intake guidelines. Descriptive statistics were used to analyse responses.

Results: The discussions highlighted that, although participants were aware of FV intake guidelines, they lacked clarity with regard to the meaning of the '5-a-day' message, including what foods are included in the guideline, as well as what constitutes a portion of FV. There was also a sense of confusion surrounding the concept of achieving variety with regard to FV intake. The sample highlighted a lack of previous education on FV portion sizes and put forward suggestions for improving knowledge, including increased information on food packaging and through health campaigns. Questionnaire findings were generally congruent with the qualitative findings, showing high awareness of the '5-a-day' message but a lack of knowledge surrounding FV portion sizes.

Conclusions: Future public health campaigns should consider how best to address the gaps in knowledge identified in the present study, and incorporate evaluations that will allow the impact of future initiatives on knowledge, and ultimately behaviour, to be investigated.

Introduction

The World Health Organisation (WHO) set a minimum daily target of 400 g of fruit and vegetables (FV), which has subsequently been translated into the '5-a-day' public health message within the UK [1,2]. Despite these guidelines, current population intakes remain suboptimal [3].

Knowledge is potentially an important predictor of FV intake [4–7]. Few studies have investigated consumer understanding of the meaning of the '5-a-day' message, including which foods are included in the guidelines and what counts as a portion of FV. Greater awareness of the amounts and types of FV needed to achieve the recommended guidelines might promote better adherence and increased intake. For example, improved comprehension of what constitutes a portion of FV may enhance consumers' capability and motivation to achieve the recommendations [8]. It might also help individuals to

accurately assess their current FV intake and, consequently, plan dietary changes. Discordant findings between people's perception of their FV intake and their actual intake have been observed. For example, one study [9] found that, amongst 426 elderly participants, 83% were aware of FV intake guidelines and 35% considered that they were eating sufficient FV. However, a closer examination (using a dietary recall of typical FV intake) of the latter group showed that some individuals were consuming as little as two portions of FV per day. One explanation for this discrepancy might be that the individuals considered they were eating sufficient FV for their health personally, and so did not need to meet the intake guidelines [10]. However, another possibility is that participants did not understand how to quantify a portion of FV.

The few studies that have been conducted to date on consumer understanding of FV intake guidelines have primarily investigated knowledge amongst American [7,11–14], Australian [8,15–17] and New Zealand consumers [18]. Only two studies [19,20] have investigated knowledge within the UK, and these studies used samples of University students and socially-deprived individuals. Given that FV-based public health campaigns, intake recommendations and portion size (PS) guidance vary greatly between countries (see Supporting information, Table S1), the majority of evidence to date cannot necessarily be generalised to a UK context. Hence, the present study aimed to explore the awareness and understanding of FV intake guidelines, with a particular emphasis on sources of FV and FV PS, within a sample of low FV consumers.

Materials and methods

Study sample and recruitment

The current sample comprised participants taking part in a pilot randomised controlled feeding study, entitled the Biomarkers of Fruit and Vegetable (BIOFAV) study. Full details of the pilot trial have been reported elsewhere [21]. In brief, it was designed to investigate novel biomarkers of FV consumption amongst 32 healthy, low FV (≤2 portions) consumers. Participants were recruited through an intranet advertisement published within Queen's University Belfast, and through word-of-mouth. The study was approved by the School of Medicine, Dentistry and Biomedical Sciences research ethics committee of Queen's University Belfast, and participants provided their written informed consent.

Focus group discussions

Six focus groups (FGs) were conducted between August 2011 and May 2012, during the first week of the 4-week BIOFAV study. The FGs ranged in size between four and six participants. They lasted 45–60 min and were recorded digitally.

The FGs were moderated by the first investigator (CR), with assistance from another researcher (CRD/AJMcG). Moderators received formal training in conducting FGs. To ensure consistency, a semi-structured topic guide was developed based on a prior literature search. The guide was piloted on a group of four research students (age range 20–30 years); sample questions are provided in the Supporting information (Table S2). The co-moderator ensured that all topic areas were covered within each session and volunteers were encouraged to fully express their views, provided that the conversation was relevant to the aims of the research. At the end of each session, participants were asked if they had any other issues they would like to raise.

Questionnaire

Prior to the FGs, demographic information was collected on the sample. A questionnaire about the '5-a-day' FV guidelines was also administered. The purpose of the questionnaire was to provide some context on the sample and also to aid with the interpretation of participant responses during the qualitative discussions.

The questionnaire covered four areas: (i) awareness of the '5-a-day' message; (ii) knowledge on foods that are classified as a fruit or vegetable according to the '5-a-day' message; (iii) PS of commonly consumed FV; and (iv) knowledge on portions provided by combinations of FV (to reflect normal dietary consumption patterns). Participants were firstly asked 'Are you aware of the '5-a-day' message about FV consumption?', to which they could answer 'yes', 'no' or 'not sure'. Secondly, participants were given a categorisation task requiring them to identify foods that counted as a fruit or vegetable according to the '5-a-day' message from a list of 39 commonly consumed foods. A third question showed a list of 27 FV with specific quantities (e.g. four spears of broccoli) and asked participants to record how many portions of fruit or vegetables each would contribute towards the '5-a-day' message (e.g. half portion). Finally, the questionnaire presented seven combinations of FV (e.g. one medium apple, one medium pear and two medium glasses of fruit juice) and asked participants to specify how many portions each set would equate to if eaten within the course of 1 day.

Statistical analysis

FGs were transcribed verbatim by CR. Another study team member listened to the audio recordings and checked this against the transcripts. Data were analysed

using Braun and Clarkes' inductive thematic analysis framework [22]. This involved six steps: (i) familiarisation with data; (ii) initial descriptive coding of data; (iii) search for themes; (iv) review of themes; (v) naming and defining of themes; and (vi) writing up of results. CR carried out this process, and the transcripts were then read by MCMcK and the codes were checked and compared. Few between-researcher discrepancies were found and consensus was reached through discussion. NVIVO, version 8 (QSR International, Melbourne, Australia) was used to facilitate data coding and management.

Questionnaire responses were analysed using PASW (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to describe the demographic profile of participants. Categorical data are presented as frequencies and percentages, whereas continuous data are shown as the median and interquartile range (IQR) (as a result of the small sample size). For questionnaire analysis, correct responses were given a score of one, whereas incorrect and 'don't know' responses were given a score of zero, making a maximum possible score of 74. The percentage of correct responses was calculated for each participant for the questionnaire as a whole and for each of the four questionnaire domains. Descriptive statistics were used to report the frequency of correct and incorrect responses, and percentage knowledge scores for the sample are presented as the median and IQR. The small sample size did not permit statistical testing of responses by demographic variables.

Results

Twenty-eight participants took part in the FGs (sample characteristics are shown in Table 1). The main themes that emerged from the analysis of the transcripts were: (i) knowledge; (ii) education; and (iii) suggestions for improving FV PS knowledge (for a full list of themes, subthemes and quotations, see the Supporting information, Table S3).

Knowledge

Although the majority of participants claimed to be aware of the '5-a-day' campaign, a lack of knowledge was evident regarding the specifics of the message (Quote 1 in Table 2). For example, most participants were confused as to which foods counted as a fruit or vegetable according to the '5-a-day' message. Additionally, when prompted by the moderator, some expressed their surprise at foods such as tomato-based sauces, which they would not have previously classified as a fruit or vegetable (Quote 2 in Table 2). Some participants also said they were unaware that potatoes were not classified as a vegetable according to the guidelines. Most ambiguity existed with regard to composite foods (e.g. spaghetti bolognaise and stew), with many participants stating they did not normally count these foods towards their FV intake (Quote 3 in Table 2). One participant also indicated that they were uncertain about what conditions a food needed to satisfy to be classified as a fruit or vegetable (Quote 4 in Table 2).

Most participants also expressed a lack of awareness surrounding PS for FV, and this was the prevailing topic of conversation during the FG discussions about the '5-a-day' message. Respondents mentioned varieties they considered particularly difficult, including lettuce, and the heterogeneity in PS for different FV was highlighted as a factor that made it more difficult to identify a portion of FV (Quote 5 in Table 2). When additional FV guideline rules were discussed (e.g. that fruit juices can only count

Table 1 Demographic profile of participants (n = 28)

Characteristics	Overall	Focus Group 1	Focus Group 2	Focus Group 3	Focus Group 4	Focus Group 5	Focus Group 6
Participants (*n*)	28	4	6	4	4	4	6
Women (*n*)	15	1	0	4	4	4	2
Men (*n*)	13	3	6	0	0	0	4
Age (years)*	21 (20–31)	23.5 (19.3–30)	20 (19.8–20.3)	20 (20–20)	31.5 (30.3–33.5)	29 (22.8–48.8)	32 (19–49.8)
Range (years)	19–55	19–31	19–21	20	30–34	21–55	19–55
Occupation (*n*)							
Employed	10	1	0	0	2	2	5
Unemployed	1	0	1	0	0	0	0
Student	17	3	5	4	2	2	1
Education (years)*	15 (14.3–17.0)	16.5 (15.3–19.3)	15.0 (14.8–15.5)	16.0 (15.3–16.0)	19.5 (15.3–21.5)	18.0 (14.8–21.3)	14.0 (12.8–15.0)
BMI (kg m^{-2})*	22.9 (21.5–25.3)	21.7 (18.7–24.0)	21.5 (21.0–22.5)	24.0 (22.3–31.9)	24.2 (20.9–25.3)	23.0 (22.5–24.9)	27.3 (21.0–31.2)

BMI, body mass index; IQR, interquartile range.
*Median (IQR).

Table 2 Example quotations from focus group discussions

Quotation number	Quotation
Knowledge	
1	It's the big '5-a-day' rather than saying what '5-a-day' (FG2, M, 19 years)
2	I'm very surprised, I wasn't counting tinned tomatoes as a portion (FG5, F, 55 years)
3	Also the sauces, I didn't realise like in bolognaise with a tomato base would have been a portion you know, or even on pizza, I didn't think that would be a portion (FG4, F, 31 years)
4	So this one of five a day, what makes a fruit and vegetable qualify for it, must be a measure of vitamins and mineral levels? (FG1, M, 19 years)
5	And fruit and that have a huge range of what's [a portion], some of the stuff is nothing, some stuff is huge amounts (FG2, M, 19 years)
6	If you eat two oranges does that count as two portions, but if you drink two portions of orange juice it doesn't count? ... why does that make sense again? (FG2, M, 21 years)
7	It's fine for stuff like bananas and all you know is a portion, but whenever you get down to ... stuff that's in sandwiches and in your meals at dinner time ... I think that's a lot harder to work out then (FG3, F, 20 years)
8	Up until a few days ago, I actually thought that it was five portions of veg and five portions of fruit a day (FG2, M, 20 years)
9	Most of my friends wouldn't realise it's five different ones do you know (FG4, F, 30 years)
10	I didn't realise how much fruit and veg I probably ate, because you put so much into dinners and that, and you don't realise but (FG2, M, 20 years)
11	So maybe, you're right, things like the cans of tomatoes and stuff that I would use in cooking, I maybe didn't realise I was getting portions, but on the other hand, I think the fruits I thought I was eating was less (FG5, F, 30 years)
Education	
12	I would read it on the packets, like because I get pre-packed foods (FG3, F, 20 years)
13	I think the last time someone talked to me about that was probably at primary school ... when they talked about eating your fruit and veg (FG5, F, 30 years)
14	Probably grams are the easiest, when you buy it and checking the packaging, you know how much is in there (FG1, M, 20 years)
15	But what's the difference, say it was 75 g or 83 g you know, it's not really that big a difference between them, so being exact isn't really ... (FG2, M, 20 years)
16	I think tablespoons would be a lot easier, cause it takes out the weighing (FG2, M, 20 years)
17	I think it depends on the size of your hands [laughs]. My boyfriend's hands are twice the size of mine, does that mean he needs bigger portions? I'm not too sure, does that mean there is less portions in his meal than there is in mine? Confusing yeah (FG4, F, 32 years)
18	I think it's easier to base it on emm size, like maybe an apple ... it's more difficult with like berries or something, but even if you think you can hold an apple in your hand, and like fit as many blueberries into your hand as you can (FG3, F, 20 years)
19	I would never think of trying to up my consumption to five a day, just cause I wouldn't really know what five, like how much of everything I would need to make five up. But if you knew exactly what I was getting ... I would probably do it (FG1, M, 20 years)
20	It would definitely help me to know what a portion is, it would be general knowledge to me then (FG6, M, 33 years)
21	If I cook, I wouldn't measure one portion, two portions, I won't do that (FG1, M, 31 years)
22	Emm but I don't think I would improve apart from that really, just because it's the fact that for me it's all preparation (FG4, F, 32 years)
Suggestions for improving portion size knowledge	
23	Or even someone standing there to talk to you, to you know, to ... (FG5, F, 55 years)
24	I would hate that (FG5, F, 21 years)

Table 2. *(Continued)*

Quotation number	Quotation
25	I think like leaflets through doors or, if all packets said on them how much of your five a day that is, you'd be more willing (FG3, F, 20 years)
26	If you had a board like that said you were getting a chicken sandwich with whatever vegetables, how many portions it is a day (FG4, F, 31 years)
27	I think when you're faced with like your meal plan*, and like what you eat in the day, you feel very aware of how you could drop in a couple of portions easily (FG5, F, 21 years)
28	I really just think if you let people know that they can put this veg or this fruit in something easily, they're just going to end up doing it (FG2, M, 19 years)

F, female; M, male; FG, focus group.
*Participants were asked to adhere to set meal plans as part of the Biomarkers of Fruit and Vegetable (BIOFAV) study.

as a maximum of one portion per day), some participants questioned the reasoning behind this rule (Quote 6 in Table 2). Generally, it was suggested by participants that PS for fruit were easier to establish than vegetables, with some mentioning fruit as 'more discrete' (FG1, male, 19 years) and the fact that you could 'use the whole thing' (FG2, male, 20 years). Most participants claimed that composite food dishes including FV (e.g. sandwiches, stew and soup) were particularly difficult to quantify in terms of the number of portions that were provided in one serving (Quote 7 in Table 2).

Variety was a key concept discussed in multiple FGs. First, some participants claimed that they had misinterpreted the '5-a-day' message as meaning five portions of fruit, plus five portions of vegetables a day (Quote 8 in Table 2). Many participants also alluded to the fact that they were not previously aware that FV intake should ideally be comprised of a variety of FV, and some thought that eating five of the same type of fruit or vegetable would be sufficient to meet recommendations (Quote 9 in Table 2).

Finally, in relation to their lack of knowledge of FV PS, some participants expressed that they had difficulty estimating their current intake of FV (Quotes 10 and 11 in Table 2).

Education

Overall, findings from the FGs suggested that participants had received little or no information on what constituted a portion of FV according to intake guidelines. However, some sources of education mentioned included front-of-pack labelling, as well as school and magazine articles (Quotes 12 and 13 in Table 2). There were mixed opinions with regard to the preferred unit of measurement for FV PS. Some said grammes were superior because this is a universal measurement and is used on packaging (Quote 14 in Table 2). Others expressed concern that they were not familiar with grammes as a form of measurement, it would be a hassle to weigh FV before eating, and there was no need to be so precise (Quote 15 in Table 2). Tablespoons and handfuls were both generally perceived as more useful measures for FV PS (Quote 16 in Table 2). However, some participants considered that handfuls could be confusing because individual hand sizes differ (Quote 17 in Table 2). In two FGs, participants stated that they preferred to guess FV PS based on the size of well-known FV such as an apple (Quote 18 in Table 2).

On the whole, participants agreed that having more information on what constitutes a portion of FV would impact positively on their current FV consumption (Quotes 19 and 20 in Table 2). With increased information, some said they would feel 'more informed' and 'more aware', and that the guidelines would seem 'more achievable'. However, others said they did not think about FV PS, instead preferring to eat depending on their appetite. Some participants also suggested that increased FV PS information would not overcome other barriers towards FV consumption, including routine and preparation (Quotes 21 and 22 in Table 2).

Suggestions for improving portion size knowledge

Suggestions for improved future communication of FV PS included increased information on packaging and displays in the FV produce section of supermarkets. Some participants said they would like personal assistance when shopping for FV (i.e. somebody to inform you of how much you need to make up a portion of FV) (Quote 23 in Table 2), although this idea was refuted by younger participants (Quote 24 in Table 2).

Other proposals included increased FV PS information in eateries that could be used when ordering food, governmental campaigns and more promotional material, including leaflets or posters (Quotes 25 and 26 in Table 2). Assistance with meal planning and FV PS information in recipe books were also suggested as possible motivators for increasing FV intake (Quotes 27 and 28 in Table 2).

Questionnaire results

A summary of the scores from each domain of the FV guidelines questionnaire is provided in the Supporting information (Table S4). All participants were aware of the '5-a-day' FV guidelines and the majority were able to correctly identify foods that counted as a fruit or vegetable (median knowledge score 91%). Only 39.3% and 42.9% of participants correctly stated that jacket potatoes and potatoes, respectively, were not included in the FV count (see Supporting information, Table S5).

The median knowledge score for identifying the portions provided by different amounts of individual types of FV was 37% (see Supporting information, Table S6). For most foods (59%), less than half of the sample correctly answered the portions provided by the stated quantities of FV. More than 50% of participants correctly identified the portions provided by 10 foods only. These were mostly in the form of one 'piece' of fruit or vegetable (e.g. one apple, one banana).

Apart from one combination of FV (one apple, one banana, one glass of fruit juice), the majority of participants (≥50%) incorrectly assessed the number of portions provided by different selections of FV (see Supporting information, Table S7). The median knowledge score for this task was 21.4%.

Discussion

Despite awareness of the UK government's '5-a-day' recommendation for FV, the present study demonstrated a lack of knowledge with regard to the specifics of the message. Some misunderstandings of '5-a-day' exist, notably the belief that it recommends five fruit *and* five vegetables per day, and not appreciating the importance of variety. There were also knowledge gaps regarding what is included in the FV recommendation, and a lack of knowledge about what constitutes a portion of FV, or how to actually achieve the recommended intake target.

Identification of fruit and vegetables within the context of the '5-a-day' guidelines

The FG discussions highlighted a lack of clarity with regard to which foods count as a fruit or vegetable according to the '5-a-day' message. Specifically, individuals demonstrated a deficit of knowledge about whether certain composite foods counted towards FV guidelines. This is in line with the findings reported from another study [14] suggesting that FV consumed in composite dishes were the most difficult to classify for American consumers. The exclusion of composite foods when assessing FV intake can have important implications in terms of the conclusions that are reached regarding current consumption. For example, a study [23] showed that excluding composite foods from FV estimates can misclassify participants as low/nonconsumers of FV. Indeed, a possible explanation for the increase in FV consumption observed in UK adults in the National Diet and Nutrition Survey between 2002 [24] and 2012 [4] (2.8 portions FV day^{-1} versus 4.1 portions FV day^{-1}, respectively) is that the most recent survey used disaggregated data for a wider range of composite dishes. Composite foods account for as much as 20–30% of vegetable intake and 10% of fruit intake, thus illustrating the need for consumers to be better informed of the value of FV-rich meals in relation to achieving FV guidelines [25]. Additionally, the public should be made aware of how to easily incorporate portions into commonly consumed meals. Such information could have a positive impact in terms of making the '5-a-day' target seem more achievable; a point that was strongly advocated in the FGs within the present study.

Although the sample scored well in the questionnaire when asked to identify foods that are classified as a fruit or vegetable, as voiced in the FGs, there was some uncertainty in relation to potatoes, chickpeas and lentils. The international variation in the classification of potatoes, with some countries, such as the USA, including potatoes as a vegetable, and others, such as the UK, excluding potatoes from their FV guidelines (in accordance with recommendations set by the WHO/Food and Agriculture Organization), may be confusing for individuals as indicated by the data gathered in the present study. Regardless of the reason, this is an important finding because it emphasises that some consumers may count potatoes towards their daily intake of FV, and thus they may be over-estimating their consumption. Future education resources should endeavour to clarify this for the general public.

Understanding of fruit and vegetables portion sizes within the context of the '5-a-day' guidelines

Another key finding from the FGs was that the majority of participants had trouble conceptualising a portion of different types of FV, which is a key skill required in understanding the '5-a-day' message. This finding is

consistent with previous studies conducted in the area [8,12,14,15,18–20]. Participants generally found it more challenging to decipher the portions provided by FV that were not in the form of one whole food/piece, with some stating that this was the main reason why vegetables were often more difficult to determine in terms of portions compared to fruit. The questionnaire responses reinforced this finding, and also revealed that, when faced with a list of FV, most respondents were unable to tell how many portions the combination would provide. When translated into a normal day-to-day dietary context, this suggests that these consumers are unlikely to be able to accurately assess their own daily intake of FV, and this was acknowledged within the FGs. Hence, it is possible that individuals in the sample are making dietary choices regarding FV consumption based on ill-informed perceptions about their current intake. Regarding another key finding, some participants considered that the '5-a-day' guidelines required the consumption of five portions of fruit in addition to five portions of vegetables per day. This notion has been observed elsewhere [26], and could potentially be demotivating, thus suggesting a need for the refinement of '5-a-day' to facilitate better consumer understanding. There may be some merit, for example, in providing separate intake recommendations for FV, as is the case in Australia ('Go for 2&5' campaign).

From a nutrition research perspective, the lack of PS knowledge presented within the present study emphasises the complexities of measuring FV intake using self-report measures. Some measures of dietary intake, including FFQs, require respondents to report their frequency of consumption of FV based on an 'average portion'. As highlighted in the present study, people are not necessarily aware of what a standard portion of FV equates to and hence the validity of such data might be compromised. In terms of implications for the assessment of FV intake in the future, researchers should provide assistance to respondents when quantifying FV intake (e.g. through the use of a food PS atlas).

One of the key messages advocated by the '5-a-day' campaign is the importance of consuming a variety of FV; however, the present study demonstrates that this message is not well understood. For example, during the FGs, a number of individuals indicated that they believed eating five of the same FV would suffice in terms of achieving the '5-a-day' guidelines. Similarly, Carter *et al.*[16] also found that a sample of Australian participants were unclear as to whether FV intake guidelines stipulated that five different FV needed to be consumed each day. Again, these are important findings in terms of the probability that people are misjudging the adequacy of their FV intake. Participants in the present study also conveyed the notion that eating five of the same FV was unappealing and an unrealistic target in relation to their satiety. Hence, education on consuming a variety of FV, particularly within meals, could make the guidelines more achievable.

There are a number of proposed explanations regarding why consumers lack an understanding of FV intake guidelines including PS. The first, and perhaps most obvious reason, could simply be a result of a lack of education. Within the present study, for example, the majority of participants claimed to have been exposed to limited information about FV PS, except occasionally from packaged FV sources. A second potential reason, as raised by participants, is the confusion generated by the substantial variation in the amounts of FV needed to achieve one portion.

In terms of the future and regarding how knowledge on achieving a portion of FV could be increased, the results from the FGs suggested that a collaborative effort is required from the food industry (e.g. packaging), retailers (e.g. supermarket displays and eateries) and health promotion bodies (e.g. campaigns and promotional material) to address key misconceptions or deficits in knowledge. With regard to PS information on packaged FV, it is worth noting that no regulations exist within the UK in relation to making claims on the portions provided by FV products. Manufacturers are not obliged to display such details, and thus there is great inconsistency with regard to the level of information currently provided. Furthermore, there is variability in the methods used to communicate PS information to consumers (e.g. various logos have been employed).

What is ambiguous from the present study was how PS information would best be communicated in terms of grammes/household measures. Future studies should seek to clarify this issue. Furthermore, public health campaigns should investigate not only whether increasing PS information can reduce confusion and increase understanding (knowledge), but also whether it has the potential to facilitate long-term increases in FV consumption (behaviour) and overcome other barriers towards FV intake such as those mentioned in the present study (appetite, routine, preparation).

Strengths and limitations

The present study provides some of the first evidence about consumer understanding of FV guidelines within the UK, including the novel topic area of FV PS. However, the findings should be interpreted in light of some limitations. Firstly, the sample comprises a small number of mostly well-educated young adults, with a normal body mass index; thus, the findings may not be generalisable to other groups in the population. However, this

sample of low FV consumers represented an ideal opportunity to investigate understanding of intake guidelines. Secondly, although the FGs were held as close as possible to the start of the 4-week intervention, participants may have sought information on FV from the research team during prior feeding sessions, which could have influenced their attitudes. Similarly, although the quantitative questionnaire was distributed at the beginning of the study, it is possible that participants may have acquired some information on FV during the screening visits. However, this was unavoidable because the questionnaire could not have been distributed before individuals were deemed eligible, and consented into the study. Furthermore, the question assessing knowledge of the '5-a-day' message may have facilitated guessing, which could have potentially inflated the accuracy score. Finally, the questionnaire was neither validated, nor formally piloted prior to use. Although one existing validated questionnaire contains questions on FV PS knowledge [20], it assessed knowledge on a limited number of foods and did not examine the understanding of sources of FV, which was a key aspect of the present study. In comparison with most previous studies assessing knowledge of FV intake guidelines, including FV sources and FV PS, the questionnaire used in the present study measured knowledge based on a greater number of items, making it one of the most comprehensive measures to date.

In conclusion, the present study showed some misunderstanding surrounding the UK '5-a-day' message, including what foods are included within the guidelines. It also emphasised a lack of knowledge with regard to FV PS. Future public health campaigns should attempt to address these misconceptions and gaps in knowledge, and incorporate evaluations that will allow the impact of future initiatives on knowledge, and ultimately behaviour, to be investigated.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with STROBE guidelines.

Acknowledgments

We are very grateful for the volunteers who took part in this research. We also thank Drs Shrobona Bhattacharya and Sarah Gilchrist for providing technical assistance.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
Funding for the BIOFAV study was provided by the Medical Research Council (G0901793) to investigate the development of novel biomarkers of fruit and vegetable consumption. We also gratefully acknowledge the Centre of Excellence for Public Health Northern Ireland for providing the funding to write this manuscript.
CR contributed towards the design of the PS questionnaire, conducted qualitative data collection, carried out all analyses and drafted the manuscript. JVW designed the study and was principal investigator on the grant application. ISY, MCMcK and KMA were co-investigators on the grant application, and MCMcK assisted with the analysis and interpretation of the qualitative data. KMA developed the first draft of the PS questionnaire and provided advice on its analysis. CRD, LLH and AJMcG were responsible for participant recruitment and completion of the study protocol. CRD and AJMcG also assisted with the FG discussions. All authors critically reviewed and approved the manuscript.

References

1. Food and Agriculture Organisation and World Health Organisation (2004) *Fruit and Vegetables for Health*. Available at: http://www.who.int/dietphysicalactivity/publications/fruit_vegetables_report.pdf (accessed September 2015).
2. National Health Service (2013) *5 A DAY - Live Well - NHS Choices*. Available at: http://www.nhs.uk/Livewell/5ADAY/Pages/5ADAYhome.aspx (accessed September 2015).
3. Bates B, Lennox A, Prentice A, *et al.* (2014) *National Diet and Nutrition Survey: Results from Years 1-4 (combined) of the Rolling Programme (2008/2009-2011/12). Executive summary*. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/310997/NDNS_Y1_to_4_UK_report_Executive_summary.pdf (accessed September 2015).
4. Shaikh AR, Yaroch AL, Nebeling L, *et al.* (2008) Psychosocial predictors of fruit and vegetable consumption in adults a review of the literature. *Am J Prev Med* **34**, 535–543.
5. Spronk I, Kullen C, Burdon C, *et al.* (2014) Relationship between nutrition knowledge and dietary intake. *Br J Nutr* **111**, 1713–1726.
6. Erinosho TO, Moser RP, Oh AY, *et al.* (2012) Awareness of the Fruits and Veggies-More Matters campaign, knowledge of the fruit and vegetable recommendation, and fruit and

vegetable intake of adults in the 2007 Food Attitudes and Behaviors (FAB) Survey. *Appetite* **59**, 155–160.
7. Wolf RL, Lepore SJ, Vandergrift JL, *et al.* (2008) Knowledge, barriers, and stage of change as correlates of fruit and vegetable consumption among urban and mostly immigrant black men. *J Am Diet Assoc* **108**, 1315–1322.
8. Pollard CM, Daly AM & Binns CW (2009) Consumer perceptions of fruit and vegetables serving sizes. *Public Health Nutr* **12**, 637–643.
9. Appleton KM, McGill R, Neville C, *et al.* (2010) Barriers to increasing fruit and vegetable intakes in the older population of Northern Ireland: low levels of liking and low awareness of current recommendations. *Public Health Nutr* **13**, 514–521.
10. Miles S & Scaife V (2003) Optimistic bias and food. *Nutr Res Rev* **16**, 3–19.
11. Young LR & Nestle M (1998) Variation in perceptions of a 'medium' food portion: implications for dietary guidance. *J Am Diet Assoc* **98**, 458–459.
12. Britten P, Haven J & Davis C (2006) Consumer research for development of educational messages for the MyPyramid Food Guidance System. *J Nutr Educ Behav* **38**, S108–S123.
13. Shah M, Adams-Huet B, Elston E, *et al.* (2010) Food serving size knowledge in African American women and the relationship with body mass index. *J Nutr Educ Behav* **42**, 99–105.
14. Thompson FE, Willis GB, Thompson OM, *et al.* (2011) The meaning of 'fruits' and 'vegetables'. *Public Health Nutr* **14**, 1222–1228.
15. Glasson C, Chapman K & James E (2011) Fruit and vegetables should be targeted separately in health promotion programmes: differences in consumption levels, barriers, knowledge and stages of readiness for change. *Public Health Nutr* **14**, 694–701.
16. Carter OBJ, Pollard CM, Atkins JFP, *et al.* (2011) 'We're not told why – we're just told': qualitative reflections about the Western Australian Go for 2&5® fruit and vegetable campaign. *Public Health Nutr* **14**, 982–988.
17. Kothe EJ & Mullan BA (2011) Perceptions of fruit and vegetable dietary guidelines among Australian young adults. *Nutr Diet* **68**, 262–266.
18. Ashfield-Watt PA (2006) Fruit and vegetables, 5+ a day: are we getting the message across? *Asia Pac J Clin Nutr* **15**, 245–252.
19. Herbert G, Butler L, Kennedy O, *et al.* (2010) Young UK adults and the 5 a day campaign: perceived benefits and barriers of eating more fruits and vegetables. *Int J Consum Stud* **34**, 657–664.
20. Buyuktuncer Z, Kearney M, Ryan CL, *et al.* (2014) Fruit and vegetables on prescription: a brief intervention in primary care. *J Hum Nutr Diet* **27**, 186–193.
21. McGrath AJ, Hamill LL, Cardwell CR, *et al.* (2015) Combining vitamin C and carotenoid biomarkers better predicts fruit and vegetable intake than individual biomarkers in dietary intervention studies. *Eur J Nutr* http://dx.doi.org/10.1007/s00394-015-0953-7.
22. Braun V & Clarke V (2006) Using thematic analysis in psychology. *Qual Res Psychol* **3**, 77–101.
23. O'Brien MM, Kiely M, Galvin M, *et al.* (2003) The importance of composite foods for estimates of vegetable and fruit intakes. *Public Health Nutr* **6**, 711–726.
24. Henderson L, Irving K & Gregory J *et al.* (2004) T*he National Diet & Nutrition Survey: adults aged 19 to 64 years. Volume 1: Types and quantities of food consumed*. Available at: http://tna.europarchive.org/20110116113217/http:/www.food.gov.uk/multimedia/pdfs/ndnsfour.pdf (accessed September 2015).
25. Agudo A (2005) *Measuring intake of fruit and vegetables.* Available at: http://www.who.int/dietphysicalactivity/publications/f&v_intake_measurement.pdf (accessed September 2015).
26. Booth AO, Lowis C, Dean M, *et al.* (2013) Diet and physical activity in the self-management of type 2 diabetes: barriers and facilitators identified by patients and health professionals. *Prim Health Care Res Dev* **14**, 293–306.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article:
Table S1. Example of the variation in fruit and vegetable recommendations, public campaigns and portion size information between countries.
Table S2. Sample questions from the topic guide.
Table S3. Knowledge of fruit and vegetable intake guidelines: findings from thematic analysis.
Table S4. Overall and domain scores for fruit and vegetable knowledge questionnaire (n = 28).
Table S5. Percentage defining foods as a fruit or vegetable plus overall percentage of correct scores per food item.
Table S6. Percentage correctly identifying portions provided by different amounts of individual fruit and vegetables.
Table S7. Percentage of correct answers when identifying portions provided by combinations of fruits and vegetables.

