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INFANT FEEDING

Quality of complementary feeding and its effect on nutritional status in preterm infants: a cross-sectional study

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Abstract

Background: The first 2 years of life represent a critical phase for growth and development, with the quality of the diet at this stage having repercussions throughout adulthood. The present study aimed to develop an Index for Measuring the Quality of Complementary Feeding (IMQCF) for infants, as well as to evaluate diet quality and its effects on the nutritional status of preterm infants.
Methods: This cross-sectional study was conducted at a Brazilian University Hospital. The data were extracted by care protocol of outpatient preterm infants at 2 years of corrected age (CA). Dietary data were collected from 24-h recalls. The diet quality was assessed by the IMQCF composed of nine items based on a Brazilian Food Guide for children aged <2 years. Response options were scored 0–100, with scores closer to 100 representing a better quality diet. Association with growth indicators (*Z*-scores for weight- and length-for-age (WAZ and LAZ) were evaluated via tests of mean difference and multiple linear regression.
Results: The median complementary feeding (CF) score was 72.2 (61.1–77.8) A shorter breastfeeding duration or infant formula use and the early introduction of wheat-based foods, ultra-processed foods and cow's milk in the preterm's diet were the main factors interfering in the adequacy of diet. There was an association between the quality of the diet score and WAZ (0.44; 95% confidence interval = 0.03–0.85; $P = 0.03$).
Conclusions: The introduction of poor quality food in the first 2 years of life interfered with the CF quality of preterm infants and can affect nutritional status at 2 years of CA, possibly in the long term.

Introduction

The prevalence of preterm births and the survival of these newborns has been increasing. Every year, an estimated 15 million babies are born preterm, which represents a rate of 5–18% of babies born across 184 countries, including Brazil (13%) [(1–3)]. Unfortunately, these newborns have more morbidities, particularly those associated with feeding, growth and development [(4)].

Increased risks for chronic noncommunicable diseases in adults (obesity, peripheral insulin resistance, type II diabetes, hypertension and cardiovascular disease) have been associated with inadequate growth in preterms, mediated by effects on metabolic programming [(5,6)]. Risk factors for the aforementioned diseases include the excessive calories and protein supply and the early introduction of complementary feeding (CF) [(5,7)]. It is important to highlight that postnatal growth and development are directly associated with the quantity and quality of food [(8)].

From 2003 onwards, most countries around the world, including Brazil, follow the guidelines for CF of term

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infants proposed by the World Health Organization (WHO) [9–11]. In Brazil, the new version of the Brazilian Food Guide for children aged <2 years had the challenge of exploring the early introduction of ultra-processed foods (UPF) in the diet of toddlers [12]. Until now, there are no specific guidelines for the preterm CF. Nevertheless, there is still no consensus on the appropriate time for the introduction of CF [7,13].

Preterm infants have a higher likelihood of inadequate eating practices. A higher prevalence of weaning rate before 4 months of age was observed when chronological age and CA were considered (95% versus 49%) [14]. In that study, the early introduction of complementary foods (3–4 months of CA) contributed to irritability, stress, choking, nausea and vomiting. Other studies have observed a reduced consumption of fruits, vegetables and fibre and the early introduction of processed foods high in sugar, saturated fat and sodium [10], which may favour early weight gain [15,16].

Besides the food guides, dietary indices based on American recommendations [17,18] have been used to evaluate the quality of diet. Most of these do not have children as their target audience and are not adapted and validated for this age group [16,19]. It is important to note that there is no specific instrument for the preterm population. Thus, there is a need to investigate the quality of the diet with accurate instruments [19–21].

Given all of the above, information is lacking about eating habits during the first few years of premature infants and their relationship with early weaning and malnutrition. Therefore, the present study aimed to: (i) develop an Index for Measuring the Quality of Complementary Feeding (IMQCF) for the population up until 2 years old and (ii) evaluate diet quality and its effect on nutritional status at 2 years of CA in very low birth weight preterm infants (VLBW).

Materials and methods

Design and population study

This was a cross-sectional study conducted at the University Hospital in Rio de Janeiro between February 2008 and December 2018. The sample was a nonprobabilistic of 108 VLBW preterm infants assisted in a specialised outpatient clinic.

Inclusion criteria were preterm births of <1500 g and gestational age (GA) of ≤32 weeks and presenting at least one dietary record every 6 months after the introduction of CF. Those who had conditions that affect fetal growth or situations that may interfere with anthropometric and dietary parameters, such as major malformations, chromosomal disorders, hydrocephalus, necrotising enterocolitis, intraventricular hemorrhage with grade of ≥3, congenital infections, children of diabetic mothers, use of illicit drugs by the mother or severe neuropathy, were excluded. The study was approved by the Research Ethics Committee at the Hospital (number: 3.301.859).

Data collection

Demographic, anthropometric and maternal information were extracted from the attendance protocol regarding to the admission of premature infants at the follow-up clinic. All of these variables are self-explanatory and presented in results as appropriate.

Dietary assessment

Dietary data were collected from 24-h recalls (R-24h) for each patient at the following CA periods: at least two R-24h from 4 to 7 months and one R-24h between 11 and 12 months; one R-24h between 17 and 24 months, totalling a minimum of four R-24h for each infant (607 R-24h were analysed in the present study). A R-24h collected from medical records was obtained with respect to foods, preparations, infant formulas and other drinks consumed by preterm infants the day before the consultation, from the first to the last meal. R24h was evaluated by a trained nutritionist using the *multiple pass method* [22] and was registered in their medical record. For an auxiliary description of the size of the portions consumed and recorded at each visit, a photo album with portions of food was used, in addition to tools and standard measures. Other information obtained from the care protocol was the type and time of exclusive and total breastfeeding (BF) and beginning an evaluation of CF composition during the first 2 years of CA. Preparations involving infant formula (IF) or cow's milk (CM) were evaluated for dilution and addition of other foods. CM introduction was considered precocious when started before 1 year of CA [23].

Measurement tool of diet quality

The quality of CF was measured by a tool created by us called the 'Index for Measuring the Quality of Complementary Feeding – IMQCF]. The instrument consists of gathering the main recommendations for complementary food used worldwide and in Brazil. The starting point to the development of the new instrument for assessing the quality of complementary feeding was the 'Guiding principles for complementary feeding of the breastfed child' [9] and the Brazilian Food Guide for children aged <2 years [12]; additional details of the development are provided in the Supporting information (Table S1). The IMQCF has nine items with four response options in each. The

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responses to items (1, 2, 3 e 4) were recalculated, changing from 0 to 100 according to the equation:

$$\text{Item score} = \left(\frac{R_{ix} - 1}{A}\right) \times 100$$

where R_{ix} is the value of response of each item x and A is the amplitude of the smallest value from the scale to the largest, with A equal to 3 for all items. For example, if item 1 (i_1) was answered with option 4 ($R_{i1} = 4$), the score for this item will be equal to 100: $[(4 - 1)/3] \times 100$. If answer option 1 was answered, the score would be 0.

Item 7 comprises two subitems about the presence of fruits and vegetables in the feeding of the toddler: (i) portion consumption of the fruits and (ii) portion consumption of other vegetables. For items 7_a and 7_b, a single score was generated replacing the 'R' according to the mean values of two scales:

$$\text{Item 7 score} = \left(\frac{\left(\frac{R_{i7a} + R_{i7b}}{2}\right) - 1}{A}\right) \times 100$$

Each item score can range from 0 to 100, where the item score equal to 100 represents total compliance with recommendations, whereas 0 score represents total inadequacy. The intermediary levels represent categories of adequacy with lower impact in any outcome related to the diet. For this, a comparison of the level of the total inadequacy of the diet reason (0 points) with the largest adjustment (100 points) is suggested. The diet quality score of four children was not analysed as a result of a lack of dietary data.

To meet specific peculiarities of the preterm public, the use of IF up to 1 year of CA is considered appropriate, in addition to breast milk, only if it was adequately diluted and without any additions and other industrialised foods. The standard dilution of infant formulas (IF) is a measuring scoop for every 30 mL of water. Below this concentration, the IF was considered diluted and, above this, it was considered concentrated. The addition of sugar, chocolate and wheat-based foods in IF was considered unsuitable for toddler feeding. It is important to highlight that the evaluation of the introduction of complementary foods (questionnaire i_2) follows the recommendations the Guidelines on this theme of the Brazilian Ministry of Health [12].

Anthropometric evaluation

Data on weight and height of preterm infants were obtained from the care protocol by a trained nutritionist. Based on these measures, *Z*-scores of anthropometric indices for weight-for-age (WAZ) and length-for-age (LAZ) or weight to length (WLZ) were calculated considering the child distributions growth reference curves by Fenton *et al.* [24], up to 50 weeks of postnatal GA and the WHO [25] after 50 weeks of postnatal GA.

To estimate the CA of the child, GA, birth weight and the estimated date of delivery were considered, according to the curves and classification proposed by Fenton *et al.* [24]. The preterm infants were classified as small for gestational age, appropriate for gestational age and large for gestational age, with a birth weight percentile of <p10, p10–90 and >p90, respectively. Extremely low birth weight infants weighed <1.000 g and VLBW infants were those who weighed <1.500 g.

Statistical analysis

Descriptive analysis of the study population was conducted using measures of central tendency (mean or median) accompanied by their dispersion [SD or interquartile range (IQR)] depending on the symmetry of their distribution for continuous variables and relative and absolute frequencies for categorical variables.

The associations between descriptive variables collected at birth (gender, race, GA, weight adequacy for gestational age, prematurity status, maternal age, education level and birth weight) and the diet quality in the second year of CA were analysed by Mann–Whitney or Kruskal–Wallis rank tests. In this analysis, the diet quality variable was treated as a continuous variable (score). To evaluate the influence of CF quality on anthropometric indicators in the second year of CA, the quality variable of CF was transformed into a binary variable, dividing the population in deciles (lowest versus highest item score), as a result of the small sample size. In this analysis, anthropometric indicators were tested and presented as continuous variables (*Z*-score) with the diet quality (decile) using the Mann–Whitney test. Differences between proportions obtained from the classification of anthropometric indices were analysed using the chi-squared test. Association between the score of IMQCF (binary variables) with the anthropometric indicators (continuous variables – Z-score) by linear regression was tested. For this analysis, we first tested variables in the bivariate model that could explain the outcome: sex; race; maternal age (years); gestational age; birth weight classification; adequacy for gestational age; gestational age (months); maternal education level; breastfeeding including the combination with IF or not); time exclusively breastfeeding; time to introduction of complementary feeding. Next, for the multivariate analysis, we selected only variables with $P < 0.2$ on univariate analysis for each outcome. We used backward stepwise method to remove variables of the model until all the variables reached $P < 0.05$. Analyses were performed using STATA, version 13.0 (StataCorp LLC,

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College Station, TX, USA), considering a level of significance of 95%.

Results

Infant characteristics

Initially, 140 care protocols were tracked. Among them, 32 were excluded because they did not meet the inclusion criteria and/or did not present sufficient data to perform the research, resulting in a final sample of 108 patients and 607 R-24h. Table 1 shows the baseline characteristics of the study population. Most patients were female (63.4%) and non-white (59.8%), whose birth occurred between 28 and 30 weeks, which is premature to an extreme degree (63.0%). Most newborns were VLBW (89.8%) and small for gestational age (55.6%). Regarding maternal characteristics, 78.4% of mothers completed high school and 29.5% had an advanced age at delivery.

Diet quality

When assessing the characteristics of the BF type of preterm, most of the infants have a discharge hospital diet comprising IF (47.3%, $n = 52$), followed by mixed BF (34.5%, $n = 38$) and exclusive BF (16.7%, $n = 18$). The median total BF was 1 (IQR = 1–4) months, and the use of IF was 8.5 (6–8.5) months. It was found that only seven preterm maintained BF until 6 months and two patients reached the recommendations proposed by the Brazilian Ministry of Health (i.e. ≥24 months of BF) [S].

Table 1 Descriptive characteristics of the preterm infants and mothers

Variables ($n = 108$)	*n*	%	(95% CI)
Sex			
Male	39	36.1	27.5–45.4
Female	69	63.9	54.8–73.0
Race			
White	47	43.5	34.0–53.3
Non-white	61	56.5	46.6–66.0
Gestational age (weeks)			
<28	24	22.2	15.1–30.7
28–30	69	63.9	54.3–72.5
>30–34	10	9.3	5.0–16.5
>34–36	5	4.6	1.9–10.8
Birth weight for gestational age			
Small for gestational age	60	55.6	46.1–64.7
Adequate for gestational age	48	44.4	35.3–53.9
Birth weight			
Extreme	11	10.2	5.4–16.8
Very low	97	89.8	83.2–94.6
Maternal education level (years) ($n = 102$)			
<8	23	22.5	15.2–31.3
8–12	65	63.7	53.1–71.7
>12	14	13.7	8.7–22.4
Maternal age (years) ($n = 105$)			
<35	74	70.5	61.3–78.7
≥35	31	29.5	21.4–38.7

CI, confidence interval.

During the outpatient follow-up, only 29.5% ($n = 28$) of preterm infants were able to maintain the use of IF until 12 months of CA, contributing to the early introduction of CM in more than half of the participants (57.4%). In addition, iregarding artificial feeding, a marked percentage of addition to formulas (CM or IF), or errors in preparation, was observed. The frequency of foods made from or rich in starch addition was high (57.6% and 26.7%, respectively), followed by flour combined with sugar (9.1% and 2.9%, respectively) (data not shown).

Regarding the time of CF introduction, 77.6% ($n = 80$) of premature infants started between 4 and 6 months of CA (40.8% at 6 months), although the main meal (lunch or dinner) was introduced at least in one-quarter ($n = 29$) of patients at an early age and 17.5% ($n = 19$) at a late age, contributing to a mean (SD) age of introduction of 6.5 (1.8) months of CA. The mean (SD) time for main dish introduction was 5.7 (1.8) months and was recorded only to occur early in 15.5% ($n = 17$) of cases. Regarding food contraindicated before 2 years of age, a large proportion of the population had been introduced to inappropriate foods at an early stage because the mean (SD) recorded in corrected months was sweet [12.4 (8.3)], wheat-based foods [(8.2 (3.6)], teas [6.7 (5.7)] and industrialised yogurt (12.2 ± 4.5). Other UPF, such as sugary drinks, sweet and salty cookies, snacks and industrialised yogurt, were also introduced in the preterm's diet before 24 months of CA (data not shown).

The highest scores on the diet score were found among children with a lower consumption of UPF and a higher consumption of vegetables and fruits.

The Supporting information (Table S1) provides details of CF quality using the instrument proposed in the present study. The mean (SD) score was found to be 69.8 (12.3), with a similar median (range) value 72.2 (61.1–77.8).

Distribution values for each item of the elaborated tool are presented in Table 2. Items referring to the introduction of sugar, sweets, soft drinks, teas, sugary drinks and farinaceous were found to result in the lowest score, suggesting the early introduction of these foods. Here, the number of meals and the introduction of semi-solid foods resulted in the highest scores, suggesting greater adequacy.

Diet quality and others variables

A significant increase in quality has been observed as the length of maternal education level increases; higher

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Table 2 Distribution of the score of each item that composes the instrument for evaluation the quality of CF (n = 104)

Items of assessment the quality index of the CF*	Median (IQR)
1 'continued with breast milk or infant formula'	66.7 (33.3–100)
2 'introduction semi-solid foods other than breast milk or infant formula'	100 (83.3–100)
3 'meals per day'	100 (100–100)
4 'introduction of sugar, sweets, soft drinks, teas, sugary drinks and/or some wheat-based foods'	33.3 (0–66.7)
5 'introduction of other un-sweetened ultra-processed foods'	66.7 (33.3–66.7)
6 'evaluation of consistency'	100 (66.7–100)
7 'portions of vegetables and fruit'	83.3 (66.7–100)
8 'groups make up the main meal'	100 (66.7–100)
9 'introduction cow milk and/or dairy products'	66.7 (33.3–66.7)

IQR, interquartile range.
*More details of the instrument used (questions and answer options) are provided in the Supporting information (Table S1).

quality was also observed in children with adequate weight for gestational age and also in white children. Table 3 shows the association between CF quality and descriptive variables of the study population. A higher number of small for gestational age infants was found among premature infants with a non-white skin colour (63.9%) and a birth date before 28 weeks GA compared to white infants (44.7%) and after 28 weeks GA.

Table 3 Median [interquartile interval (IQR)] score according to preterm infants and your mothers characteristics

Variables (n = 104)	n	Median	IQR	P-value
Sex				
Male	36	74.1	65.7–76.9	0.38*
Female	68	70.4	58.3–78.7	
Race				
White	43	75.9	66.7–75.9	0.03*
Non-white	65	66.7	59.3–74.1	
Gestational age (weeks)				
<28	24	66.7	58.3–75.9	0.63†
28–30	65	74.1	66.3–77.8	
>30–34	10	72.3	64.8–77.8	
>34–36	5	70.1	61.1–74.1	
Birth weight for gestational age				
Small for gestational age	59	70.4	59.3–74.1	0.05*
Adequate for gestational age	45	74.1	63.0–81.5	
Birth weight				
Extreme	93	74.1	63.0–77.8	0.43*
Very low	11	64.8	57.4–79.6	
Maternal education level (years) (n = 101)				
<8	22	61.1	55.6–72.2	0.02†
8–12	65	74.1	63.0–77.8	
>12	14	76.9	70.4–79.6	
Maternal age (years) (n = 101)				
<35	72	73.1	60.2–77.8	0.95*
≥35	29	70.4	63.0–75.9	

*Mann–Whitney test.
†Kruskal–Wallis test.

Diet quality and nutritional status

The association between diet quality and growth indicators was not significant on analysis that compare the means/median and proportions (see Supporting information, Table S2). In the same way, regression model indicates that the IMQCF (decile) was not associated with the Z-score of weight for length (β = 0.39; 95% CI = 0.03–0.82; P = 0.07, adjusted for classification of the birth's weight and adequacy for gestational age), nor with length for age (β = 0.27; 95% CI = 0.17–0.72; P = 0.23, adjusted for adequacy for gestational age). Bivariate and multivariate analysis for the outcomes and IMQCF are shown in Table 4. However, the increment in a category of the IMQCF (decile) increases the Z-score of the weight for age by 0.44 (95% CI = 0.03–0.85; P = 0.03) after adjustment for adequacy for gestational age, breastfeeding and gestational age.

Discussion

The present study found that the eating habits of most preterm infants presented inadequacies, impacting on a diet quality score (median 72.2) that was slightly far from ideal (100). This score appears to have been influenced initially by the early introduction of sugar and UPF, especially wheat-based foods, by the insufficient time of total breastfeeding or use of infant formula, and by the early introduction of cow milk and dairy products.

Several international studies, including a recent systematic review [6], emphasise that information on the adequate time for the introduction of CF in preterm infants remains unclear, with a lack of guidelines, requiring more controlled study designs and better scientific evidence [13,26,27], different from that observed for term infants [11,12]. Studies performed with infants aged between 1 and 2 years confirmed that the CF quality was below the desired adequacy level [16,28,29], although dietary assessment was performed using other dietary tools. The findings of the present study report similar results for the preterm population because more than half of our participants did not achieve adequacy of feeding.

In clinical practice, the only difference observed is that the introduction of CF in the preterm follows the corrected age instead of the chronological one. In Brazil and other countries, there are also no differentiated dietary guidelines between term and preterm children [9,10,12],

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Table 4 Bivariate and multivariate analysis for the outcomes and Index for Measuring the Quality of Complementary Feeding (IMQCF)

	Weight for age		Length for age		Weight for length	
Variables	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Bivariate analysis						
IMQCF*	0.32 (−0.11, 0.75)	0.15	0.19 (−0.26, 0.64)	0.40	0.24 (−0.20, 0.69)	0.28
Sex	−0.18 (−0.64, 0.28)	0.45	−0.45 (−0.92, 0.02)	0.06	−0.12 (−0.59, 0.35)	0.62
Race	−0.16 (−0.65, 0.32)	0.51	−0.24 (−0.75, 0.26)	0.34	−0.01 (−0.52, 0.49)	0.96
Maternal age level	0.04 (0.01, 0.07)	0.02	0.02 (−0.02, 0.05)	0.33	0.02 (−0.02, 0.05)	0.35
Gestational age	−0.03 (−0.34, 0.27)	0.83	−0.10 (−0.41, 0.21)	0.54	0.12 (−0.18, 0.44)	0.42
Birth's weight	0.64 (−0.06, 1.34)	0.07	0.06 (−0.68, 0.79)	0.88	1.04 (0.35, 1.72)	<0.01
Adequation to gestational age	0.59 (0.17, 1.02)	0.01	0.52 (0.08, 0.96)	0.02	0.54 (0.10, 0.98)	0.02
Maternal education level	−0.05 (−0.42, 0.32)	0.79	−0.22 (−0.61, 0.17)	0.23	0.16 (−0.22, 0.55)	0.40
Breastfeeding	−0.52 (−0.94, −0.09)	0.02	−0.21 (−0.66, 0.24)	0.35	−0.40 (−0.84, 0.04)	0.08
Exclusive breastfeeding†	0.17 (−0.76, 1.10)	0.72	0.31 (−0.65, 1.27)	0.52	−0.49 (−1.43, 0.45)	0.31
Complementary feeding‡	−0.18 (−0.55, 0.19)	0.33	0.05 (−0.34, 0.45)	0.79	−0.21 (−0.60, 0.19)	0.30
Multivariate analysis						
IMQCF[a]	0.44 (0.03, 0.85)	0.03	0.27 (−0.17, 0.72)	0.23	0.39 (−0.03, 0.82)	0.07
Maternal age	0.03 (0.00, 0.06)	0.05				
Birth's weight					1.03 (0.35, 1,71)	<0.01
Adequation to gestational age	0.70 (0.29, 1.10)	<0.01	0.56 (0.11, 1.01)	0.02	0.52 (0.10, 0.95)	0.02
Breastfeeding	−0.51 (−0.91, −0.10)	0.01				

For multivariate analysis (final model), only variables with $P < 0.2$ on bivariate analysis were included in the model, except for IMQCF, which was mandatorily included for test your predictive value after adjustment for the outcomes.

CI, confidence interval.

*Index for Measuring the Quality of Complementary Feeding: lowest versus highest decile.

†Yes including the combination with infantile formulae versus no.

‡0–3 months versus ≥4 months.

with both groups following the recommendations of the World Health Organization. Accordingly, the instrument created for evaluating the quality of complementary feeding can be appropriated for infants aged <2 years, regardless of whether they are premature or not. However, if the infant has any disease, this tool must be adapted to include the specific nutritional recommendations for each disease. Feeding problems were reported in the early postnatal stages and during childhood in the preterm population compared to full-term infants [4].

Another recommendation present in the Brazilian Food Guide that is applied in the same way for both groups refers to avoiding the early introduction of some foods in early childhood, such as processed yogurts, sweet and salty biscuits, industrialised juices, soft drinks, teas, and gelatin [12]. The UPF restriction is justified because they have a high concentration of sugar, saturated and trans fatty acids and sodium, whereas they are poor in protein, iron and zinc [30], comprising essential nutrients for the growth and development of children, especially if they are premature. In the present study, UPF was one of the items in combination with sugar and sugary drinks that most negatively influenced the quality of the diet.

Regarding nutritional status, our findings revealed that a greater quality of CF can promote an increase in weight for age Z-scores among premature infants. Preterm infants who had the best score on the quality diet were those who ate the lowest amounts of UPF and the most nature foods and also included most food groups in large meals. This information is relevant because the data available in the literature indicate that complementary foods in preterm infants are usually performed with low-energy and/or low-protein foods [31–33], which can affect nutritional status in the long term.

Another relevant point in the present study concerns the type of breastfeeding. At present, despite the numerous known benefits of using exclusive breastfeeding on the health of premature infants [8,10,12], its incidence and duration are generally lower than recommended of this high-risk population [13,31]. In the present study, we found a high prevalence of IF use and low exclusive breastfeeding. The main reasons for this are the late onset of oral feeding as a result of the presence of clinical complications (respiratory distress syndrome, sepsis, necrotising enterocolitis and gastroesophageal reflux, amongst others) to which the premature infants are usually exposed after birth, thus contributing to early weaning during hospitalisation [4,34].

In addition, only 29.5% of preterm infants managed to maintain IF use for up to 12 months of CA, as a result of

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the early introduction of CM in more than one-half of the participants (57.4%). This percentage was greater than twice that found in another study (26%) that investigated the composition of CF in late preterm infants [31].

The major problem associated with the early introduction of CM is its high protein and renal solute content and its association as an independent risk factor for iron-deficiency anaemia [35]. Moreover, CM has also been known as a potentially allergenic food for infants and is associated with the development of atopy [12].

Another point worthy of note in the present study was the high percentage of sugar and wheat-based food additions in IF and CM, as well as dilution errors. These findings were also found in studies reported by Caetano *et al.* [36] and Garg and Chadda [29] that were performed in full-term infants. A study conducted by Labiner-Wolfe *et al.* [37] indicated that an incorrect dilution of formulas was frequently observed to increase the risk of diarrhoea, dehydration, and an inadequate energy and protein supply.

Regarding the time of introducing complementary foods of solid consistency, the results of the present study revealed that 77.6% of preterm infants started CF at between 4 and 6 months of CA, although the main meal was introduced in at least 25% of infants at an early stage and in 17.5% at a late stage. The introduction period was found to be later (4–6 months) compared to most of the other studies performed in preterm infants, in which the CF introduction occurred before 4 months of CA [29,31].

Review studies on preterm feeding, although scarce, suggest that the CA of 3 months (13 weeks) may be an appropriate age for introducing solid foods in most preterm infants [7,13], although limitations of scientific evidence and the likelihood of a risk of choking, infections and allergies were clearly indicated when introducing foods before 4 months [26,29].

When analysing the dietary composition in the present study, fruits were identified as the first 'solid' food prematurely introduced at an early stage in the preterm diet (<4 months), as recorded in 15.5% of cases, and meat was the latest, as recorded in 19.8% of cases. Similar to our results, Carletti *et al.* [38] and Giannì *et al.* [31] reported that fruits were the first food to be introduced into the diet, followed by dairy products and meat. This late meat introduction impairs iron and zinc intakes for a diet and subsequently results in premature growth because it is a food source of protein.

Some factors cited in literature were able to influence the early introduction of CF in infants and/or preterm infants are the higher degree of prematurity, male gender, younger maternal age, low socio-economic status, low educational level, low maternity leave, maternal smoking and early childcare in daycare centers [13,32,39]. In the present study, we found that only birth weight for gestational age, race and maternal education were able to influence the quality of the diet. Non-white infants had lower IMQCF than white premature infants, which can be explained by (i) variations in genetics and physiology of the body and (ii) non-white population tending to be marginalised in terms of their social status, which impacts upon their access to health services and education, and consequently interferes in their health care. Mothers with infants with low birth weight according to gestational age can expect accelerated growth and weight gain, resulting in the introduction of CF earlier, often in an inadequate way, and the introduction of food with a higher energy and macronutrient density.

In relation to maternal educational level, only mothers with >12 years of education had a quality diet score of ≥80 points compared to mothers with less education ($P = 0.02$). Giannì *et al.*[31] found a positive association between low maternal schooling and early introduction of CF in preterm infants. For parents of preterm infants, particularly those with the lowest level of education, chronological age is difficult to distinguish from the CA, and, most of the time, they prefer to start introducing CF at 6 months of chronological age considering that, in this way, they will provide more energy for their children to grow faster [13,40], although some studies still recommend CA for feeding up to 24 months [41,42].

The present study should be interpreted in light of its limitations and strengths. In terms of limitations, we note that the study design was cross-sectional, such that the data source was restricted to the information contained in the patient care protocol, which presents great variability. This design of the study is more susceptible to reverse causality bias. However, this bias could be avoided in prospective longitudinal studies. Another limitation refers to the small sample size and the fact that the instrument does not address the issue of the amount of food consumed.

The main strength is related to the instrument proposed in the present study. The development of a new instrument was based on internationally recognised recommendations, such as 'Guiding principles for complementary feeding of the breastfed child' published by the WHO [9] and the food guide for term children under 2 years of age [12], with the latter addressing questions related to the level of food processing [43]. The proposed IMQCF takes into account the biological and clinical peculiarities of the preterm population, as well as the use of IF as an adequate in the first year of life, in cases when the mother was not able to breastfeed her child. Future research using this instrument in other contexts is needed, as well as studies that address its psychometric properties.

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Another positive aspect of the research refers to the originality of the study because it is the first to evaluate the association between CF quality and nutritional status scores in VLBW preterms infants. More studies on this subject are necessary to understand this relationship.

The present study advances our knowledge by investigating the relationship between CF and nutritional status in premature infants and proposes a new instrument called the Index for Measuring the Quality of Complementary Feeding (IMQCF). The CF quality appears to have been affected mainly by the early introduction of CM and UPF, comprising feeding practices considered inappropriate in early childhood that may contribute to the development of chronic diseases in the long term. The IMQCF appears to have apparent sensibility for predicting nutritional status outcomes: we found a significant association between increases in diet quality score and increases in weight for age in the population investigated. More research involving the proposed instrument and the thematic approach employed in the present study is needed.

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Conflict of interests, source of funding and authorship

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SAR contributed to the research conception, data collection, interpretation of results and critical revision of the article. MCCdR, MCM and ESM contributed to the data analysis and interpretation, drafting, and critical revision of the article. GPCdR and CRM contributed to data collection, as well as the critical revision of the article. All authors agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Transparency declaration

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

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Index for Measuring the Quality of Complementary feeding (IMQCF): items, response options and development process.

Table S2. Association between the quality of CF and anthropometric indexes at 2 years of age.

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INFANT FEEDING

The use of extensively hydrolysed and amino acid feeds beyond cow's milk allergy: a national survey

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Abstract

Background: Extensively hydrolysed formulas (EHFs) and amino acid formulas (AAFs) with proven hypoallergenicity are used for children suffering from cow's milk allergy, when breast milk is not available. However, these feeds are often used in other medical conditions where tolerance and absorption of whole protein is affected, frequently without assessment of efficacy. This practice survey assessed the use of these feeds in paediatric conditions other than cow's milk allergy; aiming to describe the population, growth parameters and micronutrient status.
Methods: Four National Health Service tertiary paediatric centres participated in this practice survey. Inclusion: children between 0 and 18 years, consuming >25% of their estimated energy requirements of an EHF/AAF for any condition other than allergic disease. Anonymised data were collected: (i) descriptive information; (ii) indications; (iii) type and route of feeding; (iv) growth status and nutritional deficiencies; and (v) medication and vitamin and mineral supplementation.
Results: One hundred-and-ninety-one children were included with a median age of 19 months (interquartile range 4–63]. Seventeen percent (33/191) were on AAFs and 83% (158/191) were on EHFs. The feeds were commonly used in cancer for 26% and in critical illness for 31%. The majority (73%) of children had enteral feeds via a nasogastric tube. Nutritional biomarkers were performed in 29% of children and 83% were on a vitamin or mineral supplement.
Conclusions: This practice survey found that EHFs and AAFs were used in a variety of medical conditions. Indications for feed choice varied, and evidence-based research supporting the use was scarce. Awaiting further research, children on these types of feeds should have regular nutritional monitoring.

Introduction

Breast milk represents the optimal source of nutrition for all infants, including those with medical conditions [(1)]. However, for certain conditions, when breast milk is not available or insufficient, specialist feeds may be recommended, which include extensively hydrolysed formulas (EHFs) and amino acid formulas (AAFs) [(2)]. When these feeds are intended for the management of cow's milk allergy (CMA), they have to be assessed according to the criteria by the European Academy for Allergy and Clinical Immunology (EAACI) [(3,4)] and the American Academy of Paediatrics (AAP) [(5)] to be tolerated by 90% of children at a 95% confidence interval (CI) with a challenge proven

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CMA. In addition manufacturers need to also demonstrate safety and efficacy with regard to normal physical growth in infants [6]. However, as a result of the characteristics of EHF and AAF, including peptides, amino acids, glucose polymers and varying levels of medium chain and long chain fatty acids, they are also commonly used in the nutritional support of a variety of acute and chronic childhood illnesses affecting the gastrointestinal tract and are chosen to manage symptoms of gastrointestinal dysmotility [7,8], malabsorption [9–11], drug-induced mucositis [12] and feed intolerance [13], using a wide variety of definitions to characterise an intolerance to a standard feed [14]. The evidence to recommend the use of AAFs and EHFs in many of these conditions is limited [14-16], in addition to lack of defined criteria for the assessment and monitoring of tolerance, efficacy or adequacy. Nutritional requirements differ depending on the clinical diagnosis for both macro- and micronutrients, complicated further by the feeding route (i.e. nasogastric) and polypharmacy [14]. The present survey therefore aimed to describe current clinical practice, including when, how and for whom these feeds were used, to better inform future research and guidelines on use of AAFs and EHFs beyond food allergy.

Materials and methods

In the UK, 20 tertiary National Health Service centres are responsible for the majority of complex paediatric patients. To include a wide range of diagnostic categories, a spread across the UK was considered desirable, and so, for this practice survey, a convenience sample of eight centres with specialist paediatric dietitians was selected, of which four agreed to participate. These were University Hospital Southampton Hospital NHS Foundation Trust, University Hospitals Bristol NHS Foundation Trust, Royal Alexandra Children's Hospital, Brighton University Hospital NHS Trust and King's College Hospital NHS Foundation Trust in London. These centres provide specialist regional services to a variety of children with complex diseases, comprising children with congenital heart disease requiring surgery, critically ill children, infants with gastrointestinal disorders including congenital or acquired intestinal failure, and those with neurodisabilities, cholestatic liver disease and various cancers.

NHS Health Research Authority waived the need for consent because this was classified as a practice survey. An anonymised EXCEL spreadsheet (version 2016; Microsoft Corp., Redmond, WA, USA) was developed by the lead researcher and statistician, and circulated to the four centres with iterative changes until all centres agreed on both the survey data collection sheet and information required. Data were collected from February to October 2018. For this survey, no patient identifiable information was collected and no additional tests, interventions or information was required outside of what was recorded in the medical notes at routine clinic appointments or during hospital stays. Data collection was designed to capture information in the following domains: (i) descriptive information on children prescribed EHFs/AAFs; (ii) indications for use of EHFs/AAFs; (iii) type of feed including feed concentration and route of feeding (e.g. oral, nasogastric); (iv) growth status; (v) nutritional deficiencies as measured by biomarkers; and (vi) medications and vitamin and mineral supplementation. As a result of similarities in protein hydrolysis, glucose polymer and lipid content of semi-elemental and extensively hydrolysed feeds, for the purpose of the present study, all semi-elemental feeds (as long as they were extensively hydrolysed) were grouped under EHFs and all elemental feeds under AAFs (Table 1). EHFs and AAFs included did not required hypoallergenicity testing for suitability for the management of CMA because this survey excluded patients with a CMA.

Inclusion criteria

Children between 0 and 18 years consuming an EHF [17] or AAF as part of their enteral nutrition (including oral and/or tube feeding) providing >25% of estimated energy requirements for any condition other than allergic disease.

Exclusion criteria

1 Children with confirmed immunoglobulin (Ig)E or non-IgE mediated CMA or multiple food allergies which resulted in the prescription of EHFs or AAFs

Table 1 Feeds that were included in this survey

Extensively hydrolysed (semi-elemental) feeds	Amino acid (elemental) feeds
Nutramigen LGG (Mead Johnson, Uxbridge, UK)	E028 (Nutricia Medical Trowbridge, UK)
Pregestimil Lipil (Mead Johnson, Uxbridge, UK)	PurAmino (Mead Johnson, Uxbridge, UK)
Similac Alimentum (Abbott Laboratories, Maidenhead, UK)	Alfamino (Nestle Health Science, Vevey, Switzerland)
Althera (Nestle Health Science, Vevey, Switzerland)	Neocate LCP (Nutricia Medical Trowbridge, UK)
Aptamil Pepti (Nutricia Medical Trowbridge, UK)	Neocate Junior (Nutricia Medical Trowbridge, UK)
Aptamil Pepti Junior (Nutricia Medical Trowbridge, UK)	
Infatrini Peptisorb (Nutricia Medical Trowbridge, UK)	

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2 Children on an elimination diet to confirm suspected non-IgE mediated CMA or multiple food allergy
3 Confirmed (by endoscopy with biopsy) eosinophilic gastrointestinal disease
4 Dietitians from survey centres received a protocol to reflect the survey spreadsheet, with further details on data collection and also describing parameters in more detail to reduce data collection bias (Table 1).

Statistical analysis

Statistical analysis was performed using R, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as medians with interquartile ranges (IQRs) and categorical variables as frequencies and percentages. The Mann–Whitney *U* test was used to examine the differences in *Z*-scores between groups, including AAF versus EHF, gender, time on formula (</> 3 months), medications and symptoms. Pearson's chi-squared test with continuity corrections or Fisher's exact test were used, where appropriate, to compare rates of children in outpatient/inpatient setting and rates of improved growth, as well as assess vitamin/mineral deficiencies and vitamin/mineral supplementation between children on either EHFs or AAFs.

Multiple logistic regression was used to investigate the probability of being prescribed an AAF versus EHF based on diagnoses/symptoms, prematurity, time on the feed, and anthropometric measures with adjustment for potential confounders of age and gender. Only variables that had a statistically significant impact are reported. $P < 0.05$ (two-tailed) was considered statistically significant.

ANTHRO (<5 years of age) and ANTHRO PLUS (>5 years of age) software [World Heath Organization (WHO), Geneva, Switzerland] was used to convert growth parameters into *Z*-scores and malnutrition was expressed in accordance with WHO definitions (Table 2) [18]. For ex-preterm infants, *Z*-scores were corrected using the Fenton growth charts for preterm infants [19].

Results

Subjects

One hundred-and-ninety-one children from the four centres (Table 3) were included: 71% (136/191) inpatients and 29% (55/191) outpatients. Fifty-five percent (106/191) were male and 21% of children (40/191) were born preterm (< 37 weeks gestational age). The median age at the time of data collected was 19 months (IQR = 4–63] and median gestational age of ex-preterm infants at birth was 30 weeks gestational age (IQR = 26–33.1). With regard to prescribed feeds, 17% (33/191) were on an AAF

Table 2 Data collected on growth and indications for feed

Parameter	Description
Diagnostic category	Oncology and haematology (including bone marrow transplant) Paediatric intensive care (PICU) Congenital heart disease – pre/peri-operatively Gastrointestinal disorders including: gastroschisis, volvulus, pseudo-obstruction, duodenal atresia, jejunal atresia, necrotising enterocolitis (NEC), intestinal failure – congenital or acquired including short bowel syndrome – defined as bowel length of <40 cm [20] Cholestatic liver disease Prematurity: <37 weeks gestational age Other: neurodisabilities, chromosomal disorder
Age	Converted into weeks and days Corrected for prematurity
Current growth	Weight in kg Length/height in cm/m Head circumference in cm <2 years of age Converting data to *Z*-scores using WHO Anthro and Anthro Plus software. <37 weeks of gestational age, Fenton Growth calculator was used [19]
Malnutrition	Defined as per WHO guidelines: <−2 *Z*-score moderate malnutrition <−2 *Z*-score weight for age (21) – underweight <−2 *Z*- score weight for height (WHZ) – wasted <−2 *Z*-score height for age (HAZ) – stunted
Indication for feed use	Malabsorption disorder Diarrhoea – defined as Bristol stool chart> 6 and stoma output > 30 mL kg^{-1} Gastroesophageal reflux disease – physician diagnosed Constipation – using criteria from the NICE guidelines Feed intolerance – defined as presence or worsening of diarrhoea/constipation and/or vomiting/abdominal distention on current formula Conjugated jaundice
Feed information	Amino acid formula (AAF) (including elemental feeds) Extensively hydrolysed formula (EHF) (including all semi-elemental feeds that are also extensively hydrolysed) Concentration of feeds: diluted, standard (as per company guidelines) or concentrated or ready to use nutrient-energy dense

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Table 2 Continued

Parameter	Description
Route of feeding	Oral Nasogastric feeding tube Nasojejunal feeding tube Gastrostomy Jejunostomy Parenteral nutrition
Nutritionally related medication and vitamins/minerals	Antacid medication (i.e. proton pump inhibitors and other antacids) Diuretics Antiemetics Immunomodulatory Anticonvulsants Gastric emptying agents Corticosteroids Laxatives Chemotherapy Vitamin supplement Vitamin and mineral supplement Mineral supplement Omega-3 fatty acid supplementation
Presence/ absence of vitamin or mineral deficiencies	Based on available nutritional biomarkers and judged by local cut-offs

and 83% (158/191) on an EHF. Most of the children on an EHF in this practice survey (36%; 57/158) were critically ill on a paediatric intensive care unit (PICU), where half of children were admitted following planned cardiac surgery for congenital heart disease or as a result of acute admission for respiratory failure. The standard practice of this PICU (University Hospital Southampton Hospital NHS Foundation Trust) was to provide nutrient-energy dense whey based EHFs to all infants/children on admission [(20)]. The second most common reason for use of EHFs was a diagnosis of cancer (25%; 39/158), including neuroblastoma, osteosarcoma, rhabdomyosarcoma and acute myeloid leukaemia (Table 4).

This practice survey found no significant difference ($P = 0.99$) in the proportion of prescribed AAFs for an inpatient 17.6% (24/136) or outpatient 16.4% (9/55). In

Table 3 Numbers of patients contributed by individual centres

Hospital	Patients number	Percentage
Brighton University Hospital NHS Trust	23	12%
Bristol University Hospitals NHS Foundation Trust	25	13%
King's College Hospital NHS Foundation Trust	33	17%
Southampton University Hospital NHS Foundation Trust	110	58%

Table 4 Pooled data of diagnostic category, stratified by use of either extensively hydrolysed formula (EHF) or amino acid formula (AAF)

Diagnostic category	Overall percentage	EHF	AAF
PICU All	31% (60/191)	36% (57/158)	9% (3/33)
PICU/other	24% (45/191)	27% (42/158)	9% (3/33)
PICU/cardiac	6% (11/191)	7% (11/158)	0% (0/33)
PICU/prematurity	2% (4/191)	3% (4/158)	0% (0/33)
Cancer	26% (49/191)	25% (39/158)	30% (10/33)
GI disease	18% (34/191)	13% (21/158)	39% (13/33)
Liver	9% (18/191)	9% (15/158)	9% (3/33)
Other*	6% (12/191)	6% (10/158)	6% (2/33)
Prematurity	5% (10/191)	5% (8/158)	6% (2/33)
Cardiac disease	4% (8/191)	5% (8/158)	0% (0/33)

*Neurodisabilities, bone marrow transplant, high dependency unit, long term ventilation and chromosomal disorders. PICU, paediatric intensive care unit; GI, gastrointestinal.

95% of cases, feeds were reconstituted in accordance with the manufacturer's recommendations. Only 5% (9/191) of cases had the feed reconstituted at a higher concentration and 1% (1/191) at a lower concentration. In 60% (114/191) of the population surveyed, EHFs and AAFs contributed >75% of energy requirements (Figure 1).

Seventy-three percent of patients (139/191) received nasogastric tube feeds and 14% had a percutaneous gastrostomy (Table 5). In addition, 10% (20/191) of feeds were used to supplement an oral diet, the majority of which were on EHFs (80%; 16/20). In 11% (21/191) of cases, these feeds were used (via a variety of enteral routes) to supplement parenteral nutrition, of which 52% (11/21) were prescribed an AAF.

Most children were on either EHF or AAF for 1-4 weeks (37%). However, in 29% and 7% of recruited patients, these feeds were used for 3–12 months and >12 months, respectively. A heat map, stratified by reason for admission and time on the feed, found that children on the PICU, where 50% of patients had a planned admission for cardiac surgery, were on the feed for 1-4 weeks and those remaining on these feeds for a longer period of time (3-12 months) were those with cancer and gastrointestinal diseases (Figure 2).

Indications for using an extensively hydrolysed formula and amino acid formula

When assessing the indications for using an EHF or AAF, 32% responded that the use of these feeds was part of their standard practice protocol in their unit and 29% used these feeds when children were considered not to tolerate standard whole protein paediatric feeds, as a result of vomiting 12%, congenital/acquired

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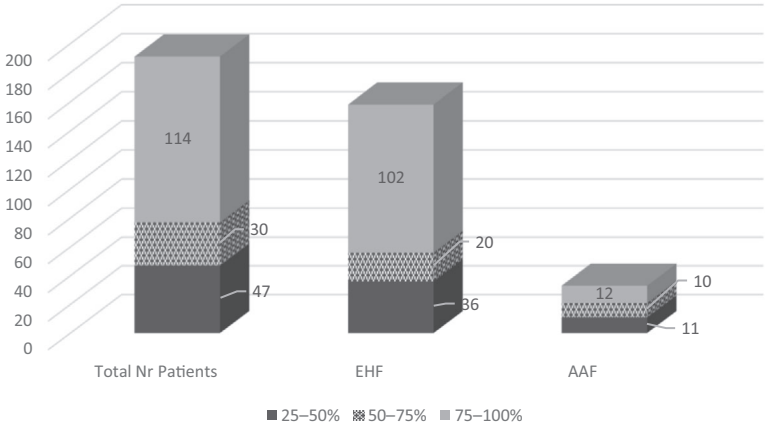

Figure 1 Contribution of extensively hydrolysed formulas (EHFs) and amino acid formulas (AAFs) expressed as percentage of total energy requirements, stratified by feed type.

Table 5 Feeding route stratified by extensively hydrolysed formula (EHF) and amino acid formula (AAF)

Route of feeding	Overall percentage	EHF	AAF
Oral	10% (20/191)	80% (16/20)	20% (4/20)
Nasogastric tube	73% (139/191)	82% (114/139)	18% (25/139)
Nasojejunal tube	2% (4/191)	75% (3/4)	25% (1/4)
Percutaneous gastrostomy	14% (27/191)	89% (24/27)	11% (3/27)
Percutaneous jejunostomy	1% (1/191)	100% (1/1)	0% (0/1)

*Supplemental parenteral nutrition: Overall 11% (21/191), EHF 48% (10/21) and AAF 52% (11/21).

Reason for admission	Total	<1 week	1–4 weeks	1–3 months	3–12 months	>12 months
PICU ALL	60	17%	70%	3%	8%	2%
PICU / Other	45	20%	69%	4%	4%	2%
PICU / Cardiac	11	9%	64%	0%	27%	0%
PICU / Prematurity	4	0%	100%	0%	0%	0%
Cancer	49	4%	18%	24%	53%	0%
GI disease	34	9%	24%	12%	35%	21%
Liver	18	17%	39%	6%	22%	17%
Other	12	25%	8%	17%	33%	17%
Prematurity	10	10%	40%	30%	20%	0%
Cardiac disease	8	38%	0%	25%	38%	0%

Figure 2 Heat map displaying the length of time feeds were used, stratified by reason for admission.

gastrointestinal pathology 7%, malabsorption 5%, diarrhoea 3%, reflux 1% and constipation 1%. In addition, 10% marked 'other' reasons for using an EHF or AAF. Figure 3, summarises the combined indications for AAF and EHF into a heat map (Figure 3). Outside of the PICU, these feeds were more commonly used in cancer and gastrointestinal diseases, including congenital/acquired gastrointestinal pathology, in addition to children with liver disease.

Variables that significantly increased the likelihood of children being on either EHFs or AAFs were assessed using multiple logistic regression analysis and results are reported as percentage probability in Table 6. Diarrhoea, vomiting or malabsorption as a single variable increased the use of an EHF, but in combination and increased numbers, in particular in association with male gender, the higher the probability of using an AAF.

Nutritional status

The median weight-for-age *Z*-score (WAZ) [21] for the population was −1.2 (IQR = −2.1 to −0.1), height-for-

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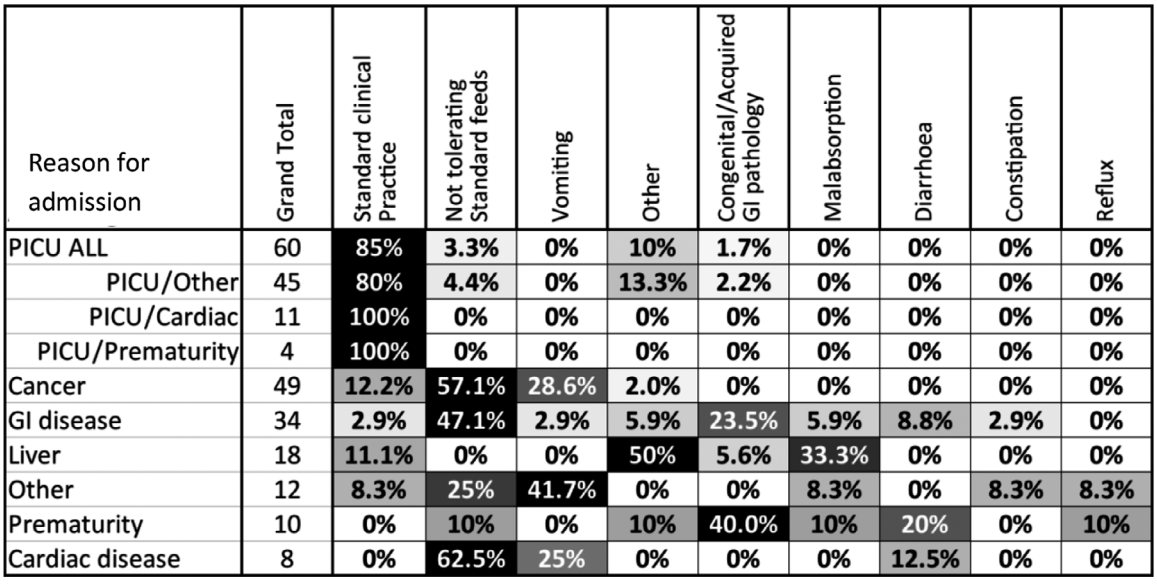

Reason for admission	Grand Total	Standard clinical Practice	Not tolerating Standard feeds	Vomiting	Other	Congenital/Acquired GI pathology	Malabsorption	Diarrhoea	Constipation	Reflux
PICU ALL	60	85%	3.3%	0%	10%	1.7%	0%	0%	0%	0%
PICU/Other	45	80%	4.4%	0%	13.3%	2.2%	0%	0%	0%	0%
PICU/Cardiac	11	100%	0%	0%	0%	0%	0%	0%	0%	0%
PICU/Prematurity	4	100%	0%	0%	0%	0%	0%	0%	0%	0%
Cancer	49	12.2%	57.1%	28.6%	2.0%	0%	0%	0%	0%	0%
GI disease	34	2.9%	47.1%	2.9%	5.9%	23.5%	5.9%	8.8%	2.9%	0%
Liver	18	11.1%	0%	0%	50%	5.6%	33.3%	0%	0%	0%
Other	12	8.3%	25%	41.7%	0%	0%	8.3%	0%	8.3%	8.3%
Prematurity	10	0%	10%	0%	10%	40.0%	10%	20%	0%	10%
Cardiac disease	8	0%	62.5%	25%	0%	0%	0%	12.5%	0%	0%

Figure 3 Heatmap of primary indications for use of formula.

Table 6 Variables significantly contribute towards the likelihood of being on either extensively hydrolysed formula (EHF) or amino acid formula (AAF)

Variable 1	Variable 2	Variable 3	Variable 4	Probability of being on an EHF (%)	Probability of being on an AAF (%)
			Diarrhoea	95	5
	Malabsorption			94	6
		Vomiting		93	7
	Malabsorption		Diarrhoea	85	15
Male			Diarrhoea	84	16
		Vomiting	Diarrhoea	84	16
Male	Malabsorption			79	21
	Malabsorption	Vomiting		79	21
Male		Vomiting		78	22
	Malabsorption	Vomiting	Diarrhoea	60	40
Male		Vomiting	Diarrhoea	58	42
Male	Malabsorption	Vomiting		50	50
Male	Malabsorption	Vomiting	Diarrhoea	28	72

age *Z*-score (HAZ) −1.3 (IQR = −2.7 to 0) and weight-for-length/height (WHZ) *Z*-score was −0.2 (IQR = −1.1 to 0.8). Moderate malnutrition, as defined by a *Z*-score <−2 [18], was present in 29.8% for WAZ (underweight), 10.7% for WHZ (wasted) and 36.4% for HAZ (stunted). When malnourished children were stratified by diagnosis, we found that children with cardiac disorders and ex-preterm infants in the PICU, as well as on the wards, particularly had poor growth parameters, as highlighted in Table 7.

No statistical difference was found in WAZ ($P = 0.97$), HAZ ($P = 0.54$) and WAZ ($P = 0.51$) between children on an EHF versus an AAF. However, children who were on these feeds (EHF or AAF) for> 3 months (compared to < 3 months) had an improved WHZ *Z*-score: 0.0 (IQR = –0.5 to 0.9) versus −0.3 (IQR = –1.4 to 0.6), ($P = 0.02$). The presence of reflux ($P = 0.04$) and malabsorption ($P = 0.003$) had a statistically significant negative impact on WAZ and HAZ, respectively.

Vitamins, minerals and medications

From the patients surveyed, 83% (159/191) were on either a single vitamin/mineral supplement or a multivitamin and mineral supplement (Table 8). However, only 29% (55/191) of children vitamin and mineral status was assessed during the study period. These assessments were more commonly performed in children on an AAF (45%; 15/33) than an EHF (25%; 40/158). Low vitamin D status was most frequently documented (5%), followed by zinc,

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Table 7 Percentage of children with growth parameters of less than −2 *Z*-scores stratified by diagnostic category

Diagnostic category	WAZ	HAZ	WHZ	Body mass index
PICU All	27%	37%	11%	24%
PICU/cardiac	44%	55%	0%	9%
PICU/other	19%	31%	9%	26%
PICU/ex-preterm	75%	50%	50%	50%
Cardiac disease	63%	88%	14%	25%
GI disorders	30%	36%	13%	21%
Cholestatic liver disease	47%	60%	21%	33%
Cancer	11%	11%	0%	9%
Other	33%	63%	0%	13%
Prematurity <37 weeks	56%	57%	17%	29%

GI, gastrointestinal; HAZ, height-for-age *Z*-score; PICU, paediatric intensive care unit; WAZ, weight-for-age *Z*-score; WHZ, weight-for-length/height.

Table 8 Vitamin and/or mineral supplementation

	Overall percentage	EHF	AAF
Multivitamin	44% (84/191)	48% (76/158)	24% (8/33)
Vitamin D	15% (28/191)	12% (19/158)	27% (9/33)
Iron	14% (27/191)	12% (19/158)	24% (8/33)
Multivitamin and mineral	7% (14/191)	7% (11/158)	9% (3/33)
Calcium	1% (2/191)	1% (2/158)	0% (0/33)
Zinc	2% (3/191)	1% (1/158)	6% (2/33)
Probiotic	1% (1/191)	1% (1/158)	0% (0/33)
Omega 3 fatty acids	0% (0/191)	–	–

AAF, amino acid formula; EHF, extensively hydrolysed formula.

Table 9 Medication use stratified by extensively hydrolysed formula (EHF) or amino acid formula (AAF)

	Overall percentage	EHF	AAF
Proton pump inhibitor	40% (77/191)	40% (63/158)	42% (14/33)
Antiemetics	30% (58/191)	30% (47/158)	33% (11/33)
Diuretics	28% (53/191)	33% (52/158)	3% (1/33)
Chemotherapy	25% (48/191)	24% (38/158)	30% (10/33)
Ranitidine	15% (28/191)	15% (23/158)	15% (5/33)
Gastric emptying agents	15% (29/191)	13% (21/158)	24% (8/33)
Laxatives	13% (25/191)	14% (22/158)	9% (3/33)
Corticosteroids	8% (16/191)	9% (14/158)	6% (2/33)
Immunomodulatory medication	7% (14/191)	6% (10/158)	12% (4/33)
Anticonvulsant	4% (7/191)	4% (6/158)	3% (1/33)

vitamin A and phosphate, each at 3%. Numbers were too small to perform further statistical analysis to assess any association of vitamin and mineral deficiencies on either EHF/AAF.

In this practice survey, 30.4% (58/191) were prescribed one medication, 29.8% (57/191) were prescribed two and 21% (41/191) were on three or more medications. Forty percent of children (77/191) were prescribed a proton pump inhibitor (PPI), followed by antiemetics (30%; 58/191) and diuretics (28%; 53/191) (Table 9). The only medication that had an impact on growth was PPI use, which was negative for both WAZ ($P = 0.02$) and HAZ ($P = 0.001$).

Discussion

This practice survey set out to describe the use of EHFs and AAFs in children with various diagnoses to establish when, how and for whom these feeds were used. We found that 83% of children were prescribed an EHF and only 17% an AAF, also reflective of practice for CMA, where AAF is reserved for the more severe cases [22]. The most common diagnostic category where these feeds were used were in critically ill children, followed by cancer and gastrointestinal diseases. A higher percentage (39%) of children with gastrointestinal diagnoses (which included congenital gastrointestinal pathology) were on an AAF, followed by children with cancer diagnoses, prematurity and liver disease. Children on PICU tended to stay on either of these feeds for less than 4 weeks, although those with cancer, gastrointestinal diseases and congenital cardiac disorders remained on either EHF or AAF for a longer period of time. This reflects the nature of the diagnosis and course of disease.

The most common clinical motivation for using either EHFs or AAFs in conditions other than CMA, is to improve perceived feed intolerance, which may include vomiting, raised gastric residual volumes, abdominal distention, diarrhoea and constipation [14]. Our findings indicate that poor tolerance of standard feeds, reflected by vomiting and diarrhoea are common reasons for choosing an EHF or AAF, when not using these feeds as standard practice. Although feeding intolerance is well documented in many paediatric diagnoses [8,23-25], quantifying the severity or frequency of intolerance that requires a feed change is ambiguous and varies between centres and diagnoses. In our practice survey, an energy-dense whey-based EHF was used by one centre as routine practice in their young critically ill children. Marino *et al* [20] reported a lower incidence of feed intolerance, such as vomiting, high gastric residual volumes and diarrhoea in critically ill children, when meeting the prescribed energy requirements when using these feeds. This participating centre in the present study admitted 50% of children for planned cardiac surgery. Dysmotility is well documented not only in children with this diagnosis [26], but also in critically ill children *per se* [23]. Nutritional characteristics of the EHF, including the

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type of protein, the extent of hydrolysis, the osmolality and fat content, and pre- and probiotics, may have all contributed to this positive finding.

Children with cancer commonly have gastrointestinal symptoms including diarrhoea, abdominal pain and vomiting related to both the treatment, as well as the underlying diagnosis [12]. The evidence for either EHF or AAF alleviating these symptoms and improving the delivery of nutrients is limited and mainly consensus based [12]. Chemotherapy frequently induces intestinal mucositis, with morphological changes including the flattening of the villi, villus atrophy and down-regulation of the enterocyte-specific gene expression that is crucial for degradation and absorption of nutrients [27]. The inflammation of the gastrointestinal tract can impact on the brush border, impacting both on the absorption of protein as well as sugars [28]. There may therefore be a role for using either EHF/AAF in paediatric cancer when gastrointestinal symptoms occur but, to date, limited clinical trials exist, supporting their routine use in this cohort.

In complex gastrointestinal disorders, both EHF and AAF use is commonplace. Almost 50% of our gastrointestinal cohort were on these feeds as a result of not tolerating standard protein feeds and 24% had congenital gastrointestinal pathology. The use of AAF was higher in this diagnostic category, which was also highlighted by recent publications on micronutrient adequacy in children with complex gastrointestinal disease [29,30]. Despite its frequent use in gastrointestinal disorders including short gut syndrome, there are only a limited number of studies, often of poor quality [31], evaluating EHFs/AAFs in a variety of gastrointestinal disease [16,32,33]. The motivation for use in gastrointestinal disorders is often based on the different gastric emptying kinetics of whey versus casein [34], peptides and/or amino acids, which have different absorption patterns, type of fat and lactose content. EHF/AAF are a composite of nutrients, which potentially impact on gastrointestinal tolerance not only as a single nutrient, but also in combination. In addition, the heterogeneity of gastrointestinal diagnoses and medical management make it really difficult to establish the efficacy of these feeds.

The use of EHFs for their medium chain triglyceride (MCT) content is common in children with cholestasis [10], although there is little evidence of any beneficial effects of MCT on growth or other outcomes [35]. Unlike long chain triglycerides, the partial water solubility of MCT enables direct absorption into the portal system without the need for bile flow, which may be impaired or absent in cholestasis [36]. If liver disease progresses and children develop cirrhosis and portal hypertension, the result may be intestinal changes such as mucosal oedema resulting in diarrhoea [11]. There may therefore be a benefit to using EHFs if diarrhoea is suspected to be related to portal hypertension [11]; however, to date, there is no convincing evidence for the routine use of an EHF in liver disease.

This practice survey also included children with other diagnoses. Within this category, most notably are children with neurodisabilities where dysmotility is well described [37,38]. The current guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition on the nutritional management of children with neurodisabilities suggest trialling whey-based feeds in children with symptoms of gastro-oesophageal reflux [25]. This suggestion followed studies by Brun *et al* [7,39] and Savage *et al* [40] on improved gastric emptying with whole whey protein in children with cerebral palsy. Khoshoo *et al* [41] also found that energy dense partially hydrolysed whey feeds were better tolerated in this population. However, the aforementioned studies assessed tolerance for partially or whole whey protein, questioning the use of either AAF or EHF in children with neurodisabilities in particular because their macro and micronutrient requirements are often very different.

Almost 10% of children in this practice survey were acutely malnourished and almost 40% had persistent malnutrition. This level of malnutrition was much higher than reported in the study by Hecht *et al* [42] on European hospitalised children where 7.9% were stunted and 5% had a body mass index < -2 *Z*-score. However, this finding is in line with prevalence of malnutrition associated with chronic diseases such as congenital heart disease [43]. There was no difference in the growth parameters between AAF and EHF, although the pooled data indicated that children who remained on either feed for >3 months had better WHZ. Data from this practice survey also found that more than 70% of our population received enteral tube feeding, which is usually started when oral intake does not meet nutritional requirements, particularly in the presence of malnutrition (which was common in our cohort) and during admission to the PICU. We consider that this high prevalence of tube feeding in our practice survey reflects the medical complexity of children on these feeds and is similar to recently published studies on AAF use in children with complex gastrointestinal disease [29]. Furthermore, many of these children are on multiple medications, impacting on the ability to utilise and assimilate nutrients from feeds. Our survey has found a negative association between the PPI and some of the growth parameters. We cannot infer causality, however, because PPI and other medications are known to impact on the bioavailability of nutrients essential for growth [44,45]; further work is required to understand the association between various medications and feed tolerance and growth [44,45].

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We also collected data on vitamin and mineral status, where available. Recent publications have highlighted concerns with regards to phosphate levels in children with complex gastrointestinal conditions receiving an AAF as a sole source of nutrition [29,30]. In only 29% of children, nutritional biomarkers for vitamin and minerals status were taken, although 36% were on these feeds for longer than 3 months. Current British Association for Parenteral and Enteral Nutrition (BAPEN) guidelines for tube fed patients in the UK suggest that electrolytes, B12, folate and a full blood count are assessed until stable and also after this when clinically indicated (no time interval suggested) [46]. Assessment of zinc, copper and selenium levels is recommended only when clinically indicated (no time interval suggested) and vitamin D should be performed every 6 months [46]. In light of the limited data on nutritional adequacy when using either EHF/AAF in children with complex disease, it is prudent that children who are on these feeds for >3 months are monitored at least to the standard set by the BAPEN.

This practice survey has many limitations. The most notable is the bias introduced by the selection of the population. Only eight centres were approached from across the UK and only four of these volunteered to take part and one centre contributed more than half of the patients in this survey. We can therefore not generalise our findings to all paediatric centres in the UK, nor all medical conditions where these feeds may be used. In addition, our survey does not account for the severity of disease, which varies within each category recruited for this survey and may have affected the choice of feed. Although we provided definitions for diarrhoea, we did not clearly define malabsorption disorders, which may have influenced our results on indications for use of EHFs and AAFs. Because this was a survey, we also did not control for growth measurement accuracy, nor the accuracy of nutritional biomarkers. Despite these limitations, this is the first survey to report the use of AAF and EHF in clinical practice and we believe, contributes useful information for future studies.

Conclusions

This practice survey found that EHFs and AAFs are commonly used in a variety of children with complex medical conditions, most of whom are receiving feeds via the enteral route. Our survey found that the primary aim of using either EHF or AAF was to improve tolerance, which may be as part of standard practice. The majority of children on these feeds are fed enterally and are on multiple medications that may impact on the bioavailability of nutrients but are not commonly monitored for vitamin and mineral status. In light of the limited evidence supporting the routine use of these feeds in a variety of conditions, further research is required with respect to better defining the composition of feeds suitable for conditions where whole protein feeds are not tolerated, including safety, indications and the cost–benefit. In the meantime, healthcare professionals need to be aware that children on either EHF/AAF with complex conditions on multiple medications should be monitored regularly to ensure adequate growth including micronutrient status (Box 1).

Box 1. Key learning points for healthcare professionals

- When an extensively hydrolysed formula (EHF) or amino acid formula (AAF) is considered for a child that does not tolerate whole protein feeds, consider the reasons for the change of feed and published data specific to that condition.
- Consider nutritional content of the feed and whether it will meet the nutritional needs for a child with that specific condition.
- Children who do not tolerate standard feeds often have complex conditions that affect multiple organs and are on polypharmacy, which may impact on nutritional adequacy.
- Ensure that the child on either EHF or AAF is regularly monitored for both growth and targeted micronutrients.
- Audit practice of use of EHF and AAF outside of food allergy.
- Initiate research on nutritional adequacy of use of EHF and AAF outside of food allergy

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Conflict of interests, source of funding and authorship

RM: academic lectures for Danone/Nutricia, Mead Johnson, Nestle; LVM: academic lectures for Danone/Nutricia, Abbott Laboratories; CS: academic lectures for Danone/Nutricia, Nestle, Prolacta, Mead Johnson; LS: conference travel funded by Danone/Nutricia.

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RM was responsible for the design of survey, support to collecting centres, help with data analysis and writing the article. CS, LS, SM and LM were responsible for the collection of data and writing the article. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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Transparency declaration

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

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INFANT FEEDING

The use of Breast Milk Fortifier in Preterm Infants by paediatric dietitians in the UK

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Abstract

Background: Breast milk is the feed of choice for premature infants, although its nutritional composition is not always sufficient to meet their raised nutritional requirements. The addition of a multi-nutrient breast milk fortifier (BMF) to breastmilk is recommended; however, international guidelines on the use of BMF are inconsistent. The present study aimed to explore the use of BMF in preterm infants by paediatric dietitians in the UK.
Methods: A questionnaire was designed and sent to members of the British Dietetic Association neonatal specialist group (n = 100) using a secure online platform. Descriptive statistics were calculated.
Results: Forty dietitians completed the survey, all of whom used BMF. Local hospital BMF guidelines were available to 77.5% (n = 31). The most commonly used criteria for commencing BMF were: tolerating a feed volume of 150 mL kg^{-1} day^{-1} (72.5%, n = 29), a gestational age <34 weeks (67.5%, n = 27) and a birth weight <1500 g (60%, n = 24). The primary contraindication for the use of BMF was necrotising enterocolitis (NEC). The majority of respondents used standard fortification, with individualised fortification available to only 12.5% (n = 5). The most common indicators for discontinuing BMF were on discharge home (67.5%, n = 27), satisfactory growth (65%, n = 26) or feeding directly from the breast (62.5%, n = 25).
Conclusions: Although BMF is used more proactively in UK neonatal units than previously, variation in practice remains. Individualised fortification is very uncommon and caution remains regarding risk of NEC. The development of national guidelines on the use of BMF would help to standardise nutritional care in neonatal units.

Introduction

Infants born prematurely, defined as before 37 weeks of gestation, are at increased nutritional risk. They are born before the large accretion of nutrient stores occurs via placental transfer in the third trimester of pregnancy [(1)]. They have less lean tissue than term infants [(2)]; hence, the principal aim of nutrition support in premature infants is to simulate *in utero* growth [(3,4)]. Inadequate nutrition can result in compromised postnatal growth, particularly poorer neurodevelopmental outcomes [(5)]. By contrast, it has been shown that postnatal growth failure in preterm infants is not inevitable, when there is an emphasis on improved nutritional care [(6)].

Providing optimal nutrition for preterm infants remains a challenge with many unanswered questions, particularly with regard to estimation of nutritional requirements. Maternal breast milk is the preferred feed, followed by donor expressed breast milk, provided from women who deliver at term [(1,4,7)]. Breast milk has numerous benefits compared to preterm formula, namely it contains immunoprotective factors, is protective against

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sepsis and necrotising enterocolitis, and has better nutrient bioavailability [8,9]. Breast milk adapts for prematurity, containing higher levels of protein, energy and micronutrients than mature breast milk from mothers who deliver at term [7]. However, the nutrient levels in both preterm and mature breast milk do not always meet the elevated nutritional requirements of preterm infants, particularly for those born with a birth weight <1500 g [1,3,4]. Therefore, in developed countries, a multi-nutrient breast milk fortifier (BMF) is often added to breast milk to provide additional energy, protein, vitamins and minerals [1].

The use of BMF in preterm infants has been found to have beneficial effects on bone mineralisation, weight gain, and linear and head circumference growth [4]; however, international guidance on its use has subtle differences [4,10-12], not least because preterm infants are a heterogeneous group, born into different environments, on a continuum of gestation, development and nutritional status. In 2019, the European Milk Bank Association published guidelines recommending for preterm infants that nutrient fortification of human milk is required to optimise growth; however, further research is required to advance the type and method of fortification [1]. In the UK, BMF is used as part of standard feeding practices in most neonatal units [7]. It is administered as a powder, mostly as a fixed dose sachet and available for inpatient use only [13]. Some specialist hospitals are equipped with human milk analysers, which can measure the exact nutritional composition of the breast milk given to infants. Individualised fortification, either 'targeted' to breast milk composition or 'adjusted' according to an infant's biochemistry, can then be used to supplement with a precise quantity of nutrients required to meet the infant's requirements [1,14]; however, this level of precision is not available in the majority of UK neonatal units [14].

There are currently no national guidelines on when to initiate or discontinue BMF, or what dose should be given per day, potentially leading to inconsistent practices across different neonatal units. A recent UK survey of neonatology healthcare professionals illustrated a number of widely held beliefs regarding the use of BMF, some of which are not supported by current evidence [15]. Similarly, an international survey of neonatologists also demonstrated marked variability in neonatal feeding practices, including the use of BMF [16]. However, neither of these two studies focused on practices by neonatal dietitians, who play an essential role in assessing and enhancing the nutritional status of preterm infants as part of an effective multidisciplinary neonatal team [17,18]. The present study therefore aimed to explore the use of BMF in the UK by neonatal dietitians, with a specific focus on initiation, monitoring, contraindications and discontinuation.

Materials and methods

Participants and recruitment

Participants were recruited from the British Dietetic Association (BDA) neonatal specialist subgroup (n = 100). All members of the BDA neonatal specialist subgroup were eligible to participate provided that they worked with neonatal patients in the UK at the time of completing the survey. The survey was distributed to the groups' mailing list in May 2019 and remained open for 4 weeks, with a reminder sent at the start of the third week. It was also promoted via the official BDA paediatric group social media accounts.

Survey design and piloting

A survey was constructed specifically for this study, based on the study's objectives and a comprehensive review of the literature and similar studies [16,19]. The survey was piloted in April 2019 by six healthcare professionals with neonatal experience. Feedback from respondents was positive, reporting that the survey was simple, having a logical flow of questions and appropriate language.

The final survey consisted of 18 questions and was administered via an online platform 'Online Surveys' (https://www.onlinesurveys.ac.uk). It included preliminary questions on workplace, clinical caseload and years of work experience. Dichotomous questions determined whether BMF was used as part of routine clinical practice and the availability of local BMF guidelines. Multiple-choice questions were then grouped into themes to mirror the study objectives, containing hypothetical examples on initiation of feeds, rate of increase in feeds and cessation of BMF. It also enquired about the use of micronutrient supplements. Further details are provided in the Supporting information (File S1).

Statistical analysis

Data were exported to SPSS, version 24.0 [20]. Quantitative data were analysed using frequencies to describe trends in practice. Differences in practice between the three levels of neonatal units were explored using Fisher's exact test. $P < 0.05$ was considered statistically significant. Responses to an open ended question were assessed and categorised into themes.

Ethical approval was granted by the Faculty of Health and Human Sciences Ethics Committee at University of Plymouth prior to the recruitment of participants (reference number: 18/19-494, 18/19-514).

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Results

Response rate and occupational characteristics

In total, 40 neonatal dietitians completed the survey, indicating a 40% response rate from potential participants. Two participants did not complete the free text question, listing clinical scenarios when breast milk fortifier would be contraindicated. The remainder of respondents answered all questions.

Neonatal units in the UK are categorised into three levels to distinguish the level of specialist care they provide: level 3 Neonatal Intensive Care Units (NICU) look after the most premature and unwell infants; level 2 (Local Neonatal Unit) units include high dependency beds; and level 1 units also known as Special Care Baby Units (SCBU) look after the most stable premature infants. In our sample, over half of respondents worked on level 3 NICUs, some of which had surgical units (65%, $n = 26$). A quarter worked in level 2 neonatal units (25%, $n = 10$), 5% ($n = 2$) worked in level 1 SCBUs and a further 5% ($n = 2$) selected the other response option. The free text responses included a neonatal unit incorporating all levels of care and one participant was a neonatal network dietitian. Over half of respondents (55%, $n = 22$) had greater than 5 years of experience with this patient group. Some 42.5% of respondents ($n = 17$) worked solely with neonatal patients, with 90–100% of their workload dedicated to this patient group.

Use of breast milk fortifier

All of the respondents ($n = 40$) used BMF. Local BMF guidelines were available to 77.5% ($n = 31$) of respondents and one participant used a neonatal network BMF guideline. From a multiple response question, neonatologists or consultant paediatricians were most likely (95%, $n = 38$) to commence BMF, followed by dietitians (87.5%, $n = 35$) and registrars or speciality trainee doctors (45%, $n = 18$).

Criteria for commencing breast milk fortifier

The following data describe responses from the multiple-choice questions where participants could select more than one answer. The free text answers to the 'other' response options were assessed and, if it was felt they represented one of the predetermined survey answers, then they were coded to this. Answers that did not fit the predefined response options were analysed separately and only disregarded if they did not answer the survey question.

A gestational age <34 weeks was most commonly used age criteria for commencing BMF (67.5%, $n = 27$), followed by a gestational age of <32 weeks (27.5%, $n = 11$). There was no difference between level 2 and 3 neonatal units in the gestational age when BMF was commenced ($P = 0.176$).

The use of birth weight as a criterion to commence BMF is shown in Fig. 1. It was commenced most frequently in infants with a birth weight <1500 g ($n = 24$, 60%), followed by a third (32.5%, $n = 13$) of dietitians using BMF with infants with extremely low birth weight (birth weight <1000 g). Four participants (10%) selected the other option, two of which specified a birth weight <2 kg as their criteria for commencing BMF. However, 32.5% ($n = 13$) did not use birth weight as a criterion for starting BMF.

Almost three-quarters (72.5%, $n = 29$) of dietitians started BMF when a feed volume of 150 mL kg^{-1} day^{-1} had been established, with only 12.5% ($n = 5$) starting at a volume of 120 mL kg^{-1} day^{-1}. Five respondents (12.5%) commenced BMF if at least 50% of the total daily enteral feed volume was expressed breast milk. No significant difference ($P = 0.460$) was found between level 2 and level 3 neonatal units and the volume of feed when BMF was commenced.

Most (60%, $n = 24$) of respondents did not use age as a criterion for commencing BMF, although 25% ($n = 10$) did wait until the infant was at least 14 days old. BMF was introduced by 57.5% ($n = 23$) of dietitians when an infant's weight gain fell below 15 g kg^{-1} day^{-1} and by 27.5% ($n = 11$) when an infant's growth had faltered. However, growth was not used in the assessment for starting BMF by 32.5% ($n = 13$) of dietitians. Forty-five percent ($n = 18$) of dietitians did not use serum biochemistry levels to determine whether BMF was commenced, whereas 30% ($n = 12$) and 20% ($n = 8$) of dietitians, respectively, commenced BMF when urea levels fell below 2 mmol L^{-1} or 4 mmol L^{-1}.

Starting dose of breast milk fortifier

Almost all respondents (87.5%, $n = 35$) used standard fortification methods, with only 5% ($n = 2$) and 7.5% ($n = 3$) of dietitians using targeted or adjusted fortification, respectively (i.e. based on analysis of maternal breast milk and monitoring biochemistry). Two dietitians commented that they aspired to using targeted or adjusted fortification but did not have sufficient time or equipment to facilitate these methods. In our sample, BMF was most commonly started by dietitians using a graded introduction approach. Some 40% of respondents ($n = 16$) recommended that BMF was introduced at half strength for 24 h, where 'half strength' equates to 50% of the dose of BMF recommended by manufacturers dissolved in 100 mL of expressed breast milk (EBM). 22.5%

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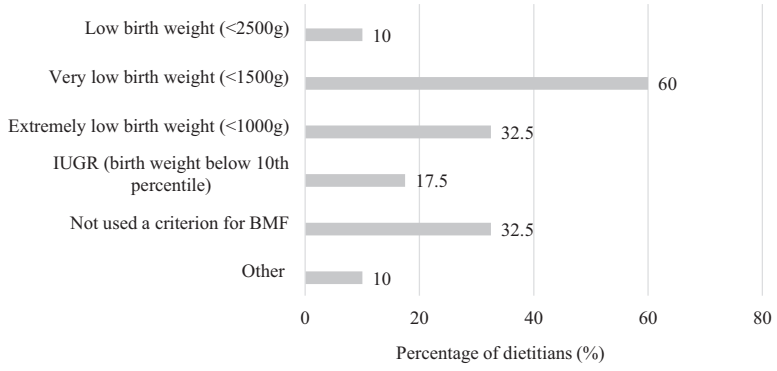

Figure 1 Birth weight used as a criterion for starting breast milk fortifier (BMF). IUGR, *In utero* growth restriction.

(n = 9) of respondents extended the 'half strength' graded introduction to 48 h.

Monitoring of biochemistry and micronutrient supplementation

Serum biochemistry was monitored routinely by 85% (n = 34) of dietitians when preterm infants received BMF in hospital. No neonatal teams conducted routine bloods on infants on BMF once discharged from hospital.

The multiple-choice responses on the use of micronutrients indicated that multivitamins (72.5%, n = 29) and iron (75%, n = 30) were given most commonly alongside BMF. This was followed by phosphate (32.5%, n = 13), folic acid (20%, n = *8*) and vitamin D (12.5%, n = 5). Three dietitians (7.5%) only gave additional micronutrient supplementation if indicated by the infants' biochemistry results or clinically indicated. Two dietitians (5%) did not recommend any additional vitamin or mineral supplements to preterm infants on BMF.

Contraindications for the use of breast milk fortifier

The free text responses (n = 38) to when BMF was contraindicated were grouped into eleven different themes (Table 1). Participants could list more than one contraindication. Necrotising enterocolitis (NEC), either confirmed or suspected, was cited as the most common reason for not using BMF (n = 24), followed poor tolerance or suspected cows' milk protein allergy (n = 12).

Discontinuation of breast milk fortifier

BMF was stopped by 50% (n = 20) of dietitians on discharge from the neonatal unit, with 7.5% (n = 3) using it 'rarely' on discharge. Only one dietitian (2.5%) routinely continued BMF on discharge, with two (5%) using a reduced dose. 35% (n = 14) of dietitians would recommend continuing BMF if the infant required it clinically.

Table 1 Clinical scenarios when breast milk fortifier (BMF) would be withheld or contraindicated (n = 38)

Free text answer	Number of respondents*
NEC/suspected NEC/distended abdomen	24
Poor tolerance/suspected cows' milk protein allergy	12
Infants which had gastrointestinal surgery/high stoma outputs post-surgery	7
Parental request	4
Medical treatment (chemotherapy/steroids/blood transfusion)	3
Absent/reversed end diastolic flow (abnormal placental blood flow)	2
Complex congenital cardiac defects	1
Weight less than 1000 g and on >50% parenteral nutrition	1
Less than 32 weeks of gestation	1
Close to discharge and BMF unavailable in the community	1
Term infant or weight greater than 2.5 kg	1

NEC, necrotising enterocolitis.
*Respondents could list more than one reason for withholding BMF.

The main indicators for discontinuing BMF (Fig. 2) were on discharge home (67.5%, n = 37), closely followed by satisfactory growth as indicated by tracking growth centile lines (65%, n = 26) or feeding directly from the breast (62.5%, n = 25).

Discussion

The present study explored the use of BMF by neonatal dietitians in the UK, with a specific focus on the criteria used to initiate and discontinue BMF, biochemical monitoring and contraindications. The results show that all respondents used BMF routinely in preterm infants, which is higher than previously reported in 2012, when only 69% of UK and Irish neonatal units used BMF as

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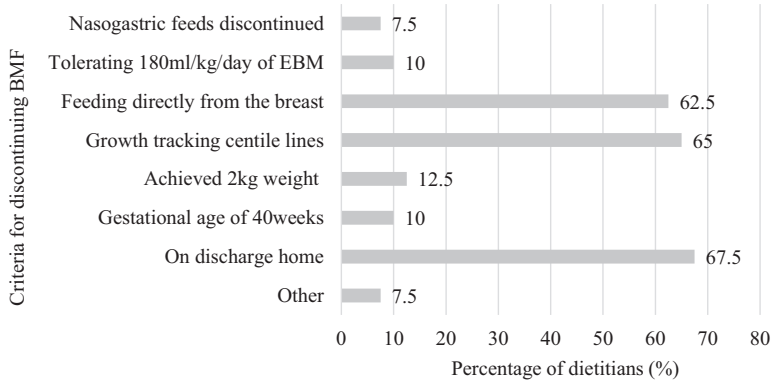

Figure 2 Criteria for discontinuing breast milk fortifier (BMF). EBM, expressed breast milk.

part of standard practice [16]. There was no disparity in the use of BMF between levels of neonatal unit, in contrast to a previous finding that BMF was used more commonly in level 2 versus level 3 neonatal units [15]. Most neonatal units (77.5%) had guidelines on the use of BMF, which is greater than the 49% previously identified [15]. Overall, the present study has demonstrated a positive change in dietetic practice. BMF is commenced proactively to optimise an infant's nutritional status in all levels of neonatal care, rather than postponing usage until there is a decline in nutritional status. However, some inconsistencies and limitations in practice remain, with a cautious approach in relation to the risk of NEC and scarce use of targeted fortification.

The study surveyed the practices of neonatal dietitians in the UK. All respondents were members of the neonatal specialist subgroup of the BDA, a specialist subgroup of the national professional body. Typically dietitians working in neonatal units work as part of a multidisciplinary team including physicians, nurses, pharmacists and other allied health professionals, an approach which has been shown to be effective [18]. The exact responsibility for who makes decisions about nutritional input will vary across different hospitals; generally they are dietetic-led, although made in conjunction with the multidisciplinary team. For example, in the present study, consultant neonatologists/paediatricians (95%), followed closely by dietitians (87.5%), were most likely to recommend starting BMF, although we did not explore the decision-making process any further. The evolving nature of neonatal dietetics has led to debate and discussion within the specialty about best practice and the need for a competence framework [21]. The situation is complicated by the inequality of dietetic service between regions, at different levels of neonatal unit. As such, the BDA neonatal specialist group has published a competency framework that outlines the specific skills and training needed by dietitians working on all levels of neonatal care unit [21]. Aligned to this, nationally endorsed staffing recommendations for all levels of neonatal unit have been developed to ensure that babies and their families receive the best level of care wherever they are treated [22].

There remains a variation in practice for the initiation of BMF; however, the most commonly cited criterion was volume of enteral feeds tolerated, which was closely followed by gestational age at birth, birth weight and rate of growth. Specifically tolerating 150 mL kg^{-1} day^{-1} of enteral feeds, being born before 34 weeks of gestation, having a birth weight <1500 g and gaining <15 g kg^{-1} day^{-1} were the most common indicators for starting BMF. Actual age and biochemistry were the least commonly used criteria in the present study. This change in practice from a previous international study [16] to include the volume of enteral feeds as one of the main criteria for starting BMF could be attributed to wanting to minimise the risk of NEC, by delaying the introduction of BMF until the infant has reached what is considered as a 'safe' enteral feed volume. The reported disparities in practice are reflective of differences between international guidelines. For example, the practice of commencing BMF in infants weighing <1500 g at birth aligns with guidance from the American Academy of Pediatrics [10], whereas the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend a birthweight < 1800 g as a criterion [8]. A minority of respondents (27.5%, $n = 11$) reported using faltering growth as a criterion for commencing BMF, as is recommended by the World Health Organization [10] in 2011, which is no longer considered best practice. However, the majority of dietitians started BMF as soon as the preterm infant started showing signs of suboptimal weight gain (<15 g kg^{-1} day^{-1}). As a consequence of the way that the survey questions were posed, it was not possible to explore every permutation for commencing BMF in more detail.

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The majority of respondents (85%, $n = 34$) routinely monitored serum biochemistry when preterm infants were receiving BMF in hospital. Almost all dietitians used standard fortification methods, with only 12.5% ($n = 5$) using targeted and adjusted fortification of breast milk, possibly because most neonatal units do not have access to breast milk analysers [15]. Standard fortification remains the most widely used fortification method; however, this does not address the issue of protein undernutrition in very low birthweight infants [1]. It is recommended that fortification should start with standard fortification; however, if infants do not grow appropriately, individualised fortification is advisable (either adjustable or targeted), depending on the neonatal unit's experience and facilities [4]. Targeted fortification means that all macronutrients can be supplemented, potentially resulting in a more balanced composition and consistent intake of fat, proteins, and carbohydrates [14]. Although it has been shown to be feasible [14], targeted fortification requires a milk analyser, which requires careful calibration [1] and also requires real-time measurements, estimated to take an additional workload of approximately 5-10 min per milk batch once practitioners have been trained [14]. As it stands, a recent survey indicated that targeted fortification was only available on 36% of UK neonatal units [15], suggesting that there is significant room for improvement; however, this would be dependent on further resources and training being made available on an institutional level. Of note, a recent National Health Service strategy document about improving neonatal care advises that 'all staff are given formal learning opportunities to ensure that staff are adequately trained to undertake their role responsibilities' [23].

Respondents reported that multivitamins (72.5%), iron (75%), phosphate (32.5%), folic acid (20%) and vitamin D (12.5%) were given routinely alongside BMF. However, the questions did not distinguish whether supplementation differed depending on the strength of BMF being administered. The low rates of vitamin D supplementation in our sample are somewhat surprising, despite both brands of BMF not meeting the very high preterm vitamin D requirements (20–25 μg day^{-1}) set by ESPGHAN [1]. This could be the result of a reliance on historic vitamin D supplementation recommendations of 10 μg day^{-1} per day from 2005 [24].

NEC and suspected NEC were listed as the most common contraindications to using BMF. NEC is a severe inflammatory gastrointestinal condition, requiring surgery in 20–40% of cases, and is fatal in 25–50% of cases [25]. There are multiple factors that may contribute to NEC, with different types of nutrition affecting its onset and progression [25]. Although BMF derived from human breast milk is available in some countries [4], the available BMF in the UK is derived from bovine sources. The use of human fortified breast milk has been shown to reduce the risk of NEC compared with bovine-based fortified breast milk in a study of extremely premature infants [26]; however, it is not clear why some infants fed exclusively breast milk still develop NEC [25]. Our finding implies that dietetic practice remains cautious. This is despite evidence of no increased risk of NEC with the introduction of BMF at the infant's first feed or when fed 20 mL kg^{-1} day^{-1} of EBM, compared to delaying fortification until the infant was established on larger volumes of EBM [27,28]. The cautious approach of delaying fortification until feed volumes reach 100 mL kg^{-1} day^{-1} has been heavily criticised as lacking in evidence, being futile and ultimately delaying delivery of full nutrient requirements [29]. Similar to our findings, another UK-based study of predominantly neonatal nurses reported that 43% agreed 'BMF can be implicated in the pathogenesis of NEC' [11]. However, 84% agreed that 'BMF is safe for the majority of preterm infants' and 72% agreed that it 'is well tolerated by preterm infants' [15]. These findings emphasise the need to improve knowledge and ensure practice is based on current evidence.

Poor tolerance or suspected cow's milk protein allergy was the second most common free text response ($n = 12$) for withholding BMF. In preterm infants, cows' milk protein allergy often presents as non-specific gastrointestinal symptoms, making it difficult to distinguish from poor feed tolerance, which is common as a result of gut immaturity [30]. Of note, both BMFs used in the UK are bovine-based, although the degree of protein hydrolysis differs. Fortifiers based on human breastmilk are available in other countries. Optimising human milk-based fortifiers, bioengineered to contain as many bioactive products as possible [4], in addition to further research on development of NEC, may mitigate some of the concerns surrounding feed-related issues and causation of NEC.

In the present study, the most commonly cited reason for discontinuation of BMF was when an infant was discharged home (67.5%, $n = 27$), rather than based on a reaching a target weight. Although ESPGHAN recommends that preterm infants with a suboptimal weight should continue to have BMF following discharge home from hospital [31], more recent guidelines from 2019 conclude there is no consensus on post-discharge nutrition [1]. From a practical perspective, in the UK, BMF is not available on prescription in the community, although 35% ($n = 14$) of our respondents would continue BMF at home if clinically indicated. The inaccessibility of BMF for infants once discharged home means optimal dietetic care planning to support some infants who may need continued nutritional support is not always feasible.

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The next most commonly cited reasons for cessation of BMF were when the infants' weight was tracking a centile line (65%, $n = 26$) or when infants were feeding directly from the breast (62.5%, $n = 25$). Although these findings are consistent with results from a previous survey in the UK and Ireland [14], it is surprising that feeding directly from the breast is one of the most common criteria for ceasing the use of BMF. BMF can be administered in a concentrated format orally prior to a breast feed, commonly known as a BMF 'shot', although some feel that this interferes with breast feeding and may prevent mothers from continuing to breastfeed exclusively [15]. A Cochrane review from 2013 identified only two small trials [32,33] comparing feeding preterm infants with BMF fortified breast milk to unfortified breast milk following hospital discharge, with no long-term data past 18 months of age [34]. Neither trial found a statistically significant difference in the overall duration of breastmilk feeding; however, one of the studies reported that statistically significantly fewer infants in the BMF group remained exclusively breastfed (no formula) at 4 months [33]. Subsequently, a UK-based quality improvement study has demonstrated that the growth trajectory of exclusively breastfed preterm infants discharged home on BMF was improved up to 1 year of age, with parents and healthcare professionals finding the use of home BMF supplement to be acceptable, feasible and safe [13]. Overall, there is an absence of evidence on the effect of using BMF post-discharge on long-term growth and developmental outcomes beyond 1 year corrected age and it is recommended that any future interventions are developed in conjunction with families and consider the potential for interference on breastfeeding [34].

Strengths and limitations

As a result of the absence of a national database for dietitians, it was a challenge to identify all paediatric dietitians working with preterm infants; hence, purposive recruitment was conducted via the BDA neonatal specialist subgroup. Membership of this group is voluntary; therefore, it was not possible to reach all practitioners. Our response rate of 40% was reasonable, although a higher rate would have made the results more externally generalisable. A longer response window or different method of distributing the survey may have elicited a higher response rate. A previous survey of the same specialist group had a higher response rate (66%) but a lower number of respondents ($n = 27$) [13]. Previous studies on the use of BMF in other healthcare professionals have elicited a wide variation in response rates, from an exceptional online response rate of 98% [14] compared to 26% in a postal survey [15]. A strength of the study is the specific focus on dietetic practice. Future research using a mixed-methods design or qualitative approach would enable further details to be explored, given that preterm infants are a heterogeneous group and investigating every permutation is not possible with a questionnaire-based study. It would also be useful to assess whether the dietetic time allocated to a neonatal unit or per neonatal cot influenced the use of BMF and growth outcomes.

Conclusions

In summary, BMF was used routinely by all respondents, across all three levels of neonatal unit, and was commenced proactively before an infants' nutritional status had been compromised. However worryingly, some nutritional practices are outdated and overly cautious, meaning that infants may be discharged with suboptimal nutritional input. The criteria used to commence BMF varied, although it was most commonly commenced in infants tolerating 150 mL kg^{-1} day^{-1} of enteral feeds, born before 34 weeks of gestation, in those with a birth weight <1500 g and gaining <15 g kg^{-1} day^{-1}. NEC or suspected NEC was the most commonly cited contraindication to introducing BMF. Targeted and adjusted fortification was only available to 12.5% of respondents. BMF was most often discontinued when an infant was discharged home or feeding at the breast. BMF guidelines are not available in all neonatal units across the UK, which may explain the differing practices. The development of national guidelines on the use of BMF, alongside investment in development of dietetic services and more widespread use of breast milk analysers, would help to standardise and improve nutritional management in neonatal units.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
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SJ designed the study. SJ collected and analysed data, with supervision from KM. KM and SJ drafted the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

File S1. Survey questions.

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TYPE 2 DIABETES

Substitution among milk and yogurt products and the risk of incident type 2 diabetes in the EPIC-NL cohort

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cohort studies, dairy products, diabetes, milk, substitution models, yogurt.

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[Correction added on 2 June 2020: The author name "M. W. M. Verschuren" has been amended to "W. M. M. Verschuren".]

Abstract

Background: Higher dairy consumption has been associated with lower type 2 diabetes (T2D) risk, whereas dairy product subtypes appear to differ in their T2D risk association. We investigated whether replacing one type of milk or yogurt product with another is associated with T2D incidence.
Methods: Participants of the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort (n = 35 982) were included in the present study. Information on milk and yogurt consumption at baseline was obtained by a validated food frequency questionnaire. T2D cases were identified by self-report or linkage to the hospital discharge registry, and validated by consulting the general practitioner. Multivariable Cox proportional hazard models were used to estimate associations.
Results: During a mean of 15 years of follow-up, 1467 indecent T2D cases were validated. Median total milk and yogurt intake was 1.5 servings (25th percentile to 75th percentile: 0.8–2.4). After adjustment for demographic and cardiovascular risk factors, replacement of one serving (200 g) of whole-fat milk [hazard ratio (HR) = 0.93, 95% confidence interval (CI) = 0.60–1.44], buttermilk (HR = 0.88, 95% CI = 0.58-1.34), skimmed milk (HR = 0.87, 95% CI = 0.57–1.32) or skimmed fermented milk (HR = 0.99, 95% CI = 0.63–1.54) with whole-fat yogurt was not associated with T2D risk. Substitutions among other milk and yogurt products were also not associated with T2D risk. Sensitivity analysis investigating T2D risk halfway follow-up suggested a lower risk for substitutions with whole-fat yogurt.
Conclusions: No evidence was found for the association between substitutions among milk and yogurt products and the risk of incident T2D, although we cannot exclude possible attenuation of results as a result of dietary changes over time. This analysis should be repeated in a population with a wider consumption range of whole-fat yogurt.

Introduction

In 2015, 8.8% of the adults worldwide were diagnosed with diabetes and this number is expected to rise to 10.4% by 2040 [(1)]. This chronic disease results in a decreased quality of life and higher risks of morbidity and mortality, placing a major burden on healthcare systems [(2)]. Identifying modifiable risk factors for type 2 diabetes (T2D) is important for improving public health prevention strategies.

Healthy lifestyle behaviours include several dietary factors that have been associated with a lower T2D risk [(3,4)], including a high consumption of total dairy products [(5)]. The mechanisms behind dairy consumption and a

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reduced T2D risk are not fully understood, although several potential mechanisms have been proposed [6]. Dairy products are heterogeneous as a result of differences in the amount of water, sodium, fats and added sugar, as well as the level of fermentation. The consumption of fermented dairy products has been shown to result in metabolic health benefits by causing a shift in the gut microbial population [7-9]. Pentadecanoic acid and heptadecanoic acid are recognised as markers for dairy fat consumption [10]. Their amounts in erythrocyte membranes are inversely associated with T2D risk [11] and proportions in plasma phospholipids are inversely associated with fasting insulin and glucose [12,13]. Although these fasts have been associated with decreased T2D risk markers, cause and effect relationships remain uncertain. Whey protein consumption has been linked to postprandial stimulate insulin production and activity [14]. Calcium content might play also a role becuase it possibly has antiobesity bioactivity effects [15,16]. In addition, obesity is a major risk factor for the development of T2D and the ability of milk to assist in appetite control might be another relevant contributing factor to the lower risk of T2D being associated with dairy consumption [17].

A dose–response meta-analysis including 22 prospective cohort studies (±580 000 participants; 43 000 cases) observed that total yogurt consumption was associated with a lower risk of T2D, whereas no associations with T2D were observed for the group of whole-fat dairy products and total milk, skimmed milk and whole-fat milk [5]. This meta-analysis is based on studies that compared T2D risk between individuals with different levels of dairy product consumption, at the same time as keeping energy intake at a constant level. As a result of this, individuals differ not only in dairy product intake, but also in the intake of other unspecified energy-providing foods. Hence, the results cannot be interpreted as a direct comparison between individual dairy products.

Substitution modelling can be used to gain further insight into the differences between dairy products and their association with T2D risk because it can be interpreted as a direct comparison between products [18]. Only one study has examined substitution within the group of dairy products so far, and it was observed that consumption of whole-fat yogurt instead of any other milk and yogurt product (i.e. skimmed milk, whole-fat milk, buttermilk or skimmed yogurt) was associated with a lower risk of T2D in a Danish population [19]. We aimed to replicate this previous work by investigating whether substitutions between skimmed milk, whole-fat milk, buttermilk, skimmed fermented milk products and whole-fat yogurt were associated with changes in the incidence of T2D in a Dutch population.

Materials and methods

Study population

Data were sourced from the Dutch contribution to the European Prospective Investigation Into Cancer and Nutrition (EPIC-NL) study. This prospective cohort emerged out of two large cohorts. First, the Prospect-EPIC cohort (n = 17 357), which invited women aged 49–70 years who participated in the nationwide breast cancer screening programme and were living in the Dutch city of Utrecht or its vicinity. Second, the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) cohort (n = 22 654), covering a randomly selected population sample of both males and females aged 20–59 years from three Dutch towns (Amsterdam, Doetinchem and Maastricht). Both cohorts combined provided baseline measurements to form the EPIC-NL cohort of 40 011 individuals. All participants were enrolled in the study between 1993 and 1997 and have been followed up for a mean (SD) of 15 (3) years for the occurrence of T2D. Further details on recruitment and design of the EPIC-NL cohort are described elsewhere [20]. Prior to study inclusion, participants provided their written informed consent and both cohorts were approved by the local medical ethic committees: the institutional review board of the University Medical Centre Utrecht for the Prospect-EPIC cohort and the Medical Ethical Committee of TNO Nutrition and Food Research for the MORGEN cohort. The study was performed in accordance with the Declaration of Helsinki.

From the 40 011 study participants, excluded participants withdrew their permission for inclusion in the study (n = 1); were missing informed consent to retrieve data from the general practitioner, municipal register office or linkage to the hospital discharge diagnoses registry (n = 1789); comprised unvalidated potential T2D cases (n = 488) and participants with type 1 and type 2 diabetes at baseline (n = 820); were missing data on milk and yogurt consumption (n = 172); were non-consumers of milk and yogurt products (n = 209); had an unrealistic reported dietary intake (highest and lowest 0.5% based on the ratio of total energy intake to the estimated basal metabolic rate) (n = 327); were missing data on covariate smoking (n = 104) and education (n = 108); and were participants with a negative follow-up time (n = 11). This left 35 982 individuals for the analysis.

Assessment of diet and milk and yogurt consumption

Dietary intake was measured at study enrolment by a self-administered validated food frequency questionnaire (FFQ) [21]. Participants were asked to report the average intake of 79 main food categories (in times per day, per

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week, per month or per year, or as never) over the past year [22]. Inconsistencies in the FFQ were checked by a dietitian and, if needed, were resolved by contacting the participant [21].

For all milk and yogurt products, total consumption was calculated in grams per day based on serving sizes of 200 g. Products were categorised into five main groups: (i) skimmed milk, including semi-skimmed milk, skimmed coffee milk and semi-skimmed coffee milk; (ii) whole-fat milk, including powdered milk and whole-fat coffee milk; (iii) buttermilk; (iv) skimmed fermented milk products, including skimmed yogurt, drink yogurt and quark; and (v) whole-fat yogurt. The whole-fat groups contained >3 g fat 100 g^{-1}, the skimmed dairy groups contained <3 g fat 100 g^{-1}, and buttermilk groups contained <1 g fat 100 g^{-1}. Other milk products, such as custard, chocolate milk, ice cream and whipped cream, were not included because these products are significantly different in macronutrient composition. Hence, replacement with these products within a diet would unlikely provide health benefits [23].

The relative validity of the FFQ was assessed by comparing collected data on milk product consumption with 12-monthly 24-h recalls among 121 participants. Spearman's rank correlation coefficients for the group of total milk and milk product consumption were 0.69 and 0.77 for males and females, respectively [22].

Additional data on dietary consumption were also collected by the FFQ. The intake of fruits, vegetables, coffee, red meat, processed meat, sugar-sweetened beverages, alcohol and fibre was assessed. Alcohol consumption was categorised in non-consumers, light drinkers 0.1–10 g day^{-1}, moderate drinkers 10–20 g day^{-1} and heavy drinkers >20 g day^{-1}. Fibre consumption was energy adjusted following the nutrient residual model [24] because variation is strongly related to total energy consumption. Energy intake in kilocalories (kcal) per day was calculated based on the total daily consumption with the use of the Dutch Food Composition Table (1996) [25].

Assessment of covariates

Baseline data on potential risk factors for chronic diseases were collected by questionnaires. Smoking status was categorised into current, former or never. Educational level was classified as low (primary education to intermediate vocational education), average (higher secondary education) or high (higher vocational education or university). Physical activity was measured with the validated EPIC questionnaire as used in all EPIC cohorts [26]. Subsequently, the Cambridge Physical Activity Index (CPAI) score was used to categorise participants into inactive, moderately inactive, moderately active and active [27]. As a result of missing values, CPAI-scores could not be calculated for 14% of the study population. Single linear regression modelling was applied to impute the missing scores (missing value analysis procedure in SPSS; IBM Corp., Armonk, NY, USA).

Height (cm) was measured during physical examination and body weight was measured to the nearest 0.5 kg using a floor scale (Seca, Atlanta, GA, USA), without shoes and in light clothing. The body mass index (BMI) was calculated as weight divided by height squared (kg m^{-2}). Presence of hypertension (yes, no) was defined as a mean diastolic blood pressure of >90 mmHg and/or a mean systolic blood pressure of >140 mmHg measured two times in the supine position on the right arm using a Boso Oscillomat (Bosch & Son, Jungingen, Germany) for Prospect-EPIC participants. For MORGEN-EPIC participants, the left arm was measured using a random zero sphygmomanometer. Presence of hypertension was also defined based on self-reported use of antihypertensive medication or physician-diagnosed existence of hypertension. Total serum cholesterol levels and high-density lipoprotein (HDL) concentrations were measured [20]. Total cholesterol to HDL ratio was calculated by dividing total cholesterol by HDL.

Occurrence of type 2 diabetes

A two-step approach was used for the identification and validation of potential T2D cases. For the identification of potential cases, information was obtained through linkage with the hospital discharge diagnosis registry and from follow-up questionnaires. In the hospital discharge diagnoses registry, information on diagnoses was coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) [28]. Code 250 and underlying codes were used to identify potential T2D cases. The follow-up questionnaires collected data on self-reported diabetes diagnosis, and were sent out with intervals of three to five years (1998–2002 questionnaire 1; 2003–07, questionnaire 2; 2011–12, questionnaire 3). Prospect-EPIC participants additionally received a urinary glucose strip test with the first questionnaire. They were asked to self-report whether the strip had turned purple after 10 s, for detection of glucosuria.

All potential T2D cases up to 2006 were validated by consulting the general practitioner or the pharmacist [21]. The pharmacist was only used to confirm presence, not absence, of diabetes. For all potential cases identified after 2006, only the general practitioner was used as verification source. The verification source provided the diagnosis year and we set the diagnosis date for all identified cases at 1 January, in the year of diagnosis. Verification information was available for 81% of the identified

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potential T2D cases. All non-verified potential cases were excluded from the primary analysis because those participants could not be categorised as a case, nor as a non-case. Follow-up was complete until 31 December 2010.

Descriptive analysis

Baseline characteristics were examined per tertile of milk and yogurt product consumption. Results for continuous variables were described as the mean (SD), or as median with the 25th percentile (P_{25}) and 75th percentile (P_{75}) for variables that were not normally distributed. Categorical variables were described in frequencies and percentages. Spearman's rank correlation coefficients were calculated to explore potential correlations between consumption of the different types of milk and yogurt products.

Main survival analysis

Multivariable Cox proportional hazard regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for substitution of milk and yogurt products and incident T2D. Age was used as underlying timescale [29]. Follow-up duration was calculated starting from enrolment date, to the year of T2D diagnosis, date of death, date of emigration or end of follow-up.

We modelled substitution of milk and yogurt products in servings, with a serving size of 200 g. The substitution model included a variable representing the total number of servings of milk and yogurt products consumed per day, and servings consumed of individual milk and yogurt products in subgroups, except for the milk or yogurt subgroup that would be replaced (i.e. four out of five groups were included). As a result, the estimated HR and 95% CI can be interpreted as the risk of T2D for one serving higher intake of the subgroups included in the model at the expense of one serving lower intake of the subgroup not in the model.

Four models to adjust for potential confounding were used. Model 1 was adjusted for sex (male, female) and total energy intake (kcal day^{-1}). Model 2 was further adjusted for smoking status (current, former, never), physical activity (inactive, moderately inactive, moderately active, active), education level (low, average, high), hypertension (yes, no) and alcohol consumption (non-consumers, light drinkers, moderate drinkers and heavy drinkers). Model 3 was further adjusted for the consumption of fruit, vegetables, processed meat, red meat, coffee, sugar-sweetened beverages and energy adjusted fibre (g day^{-1}). Model 4 was additionally adjusted for T2D risk factors that were considered as potential mediators, namely BMI [2] (kg m^{-2}) and the cholesterol ratio [30]. Participants with missing values on these potential mediators were excluded from model 4. Because model 4 included the potential mediators, final conclusions were based on adjusted model 3 and therefore the main results section focus on describing results derived from model 3. Study cohort (Prospect or MORGEN) was included as a stratum variable for all analyses.

Assumptions of the Cox proportional hazard regression model were evaluated. First, the proportional hazards assumption was investigated by plotting scaled Schoenfeld residuals against time. Thereafter, independence between the scaled Schoenfeld residuals and time was tested with chi-squared tests for each covariate and for the overall model. Next, deviance residuals were plotted for all included variables, to check for influential observations. We did not detect violation of the proportional hazard assumption. Martingale residuals including fitted lines with lowess function were plotted against the milk and yogurt subgroups to evaluate linearity. No indications for non-linearity were observed. The assumption of independent delayed entry was investigated by including the date of enrolment in the final adjusted model (model 3). We did not find evidence for violation of this assumption.

Hazard ratios in which the 95% CI did not include 1 were considered statistically significant. Analyses were conducted with the R software environment [31], using the '*survival*' package to create the regression models [32].

Sensitivity analysis

Seven sensitivity analyses were performed with adjusted model 3. First, because the substitution in serving sizes also entails some unspecified residual substitution of kcal from other dietary products, we repeated model 3 in an isocaloric milk and yogurt substitution analysis, modelled in 50 kcal day^{-1}, for comparison. All participants were censored after 7 years to evaluate the influence of unobserved dietary changes over time on associations between milk and yogurt substitutions and T2D risk. Differences in risk associations compared to the main analysis could indicate the occurrence of dietary changes over time. The first 2 years of follow-up were excluded to assess the possible influence of reverse causation. We included non-verified potential T2D cases that were excluded from the study population as incident cases ($n = 488$) to evaluate whether lack of validation of these cases has affected our results because likely the majority of participants in this group will actually be incident cases. Prevalent cases of cardiovascular disease, hypertension and participants with an increased cholesterol ratio (>5) were excluded because those conditions could have resulted in changes in dietary habits [33]. Considering the role of hypertension as a

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confounder or potential mediator in the relationship between milk and yogurt substitution and T2D incidence can be discussed, the model was explored without adjustment for hypertension. We additionally excluded those participants with missing values on the potential mediators cholesterol ratio ($n = 1435$) and BMI ($n = 18$) to investigate study findings in the similar study population as used in model 4. In addition, the baseline characteristics of participants for the complete included study population (model 1-3) were compared with the population characteristics when the participants with missing values on the cholesterol ratio and BMI were additionally excluded (model 4).

For comparison, we investigated the association between the consumption of all milk and yogurt product subgroups and the risk of incident T2D individually, without specified substitutions and adjusted following model 3.

Results

Population characteristics

At baseline, the median milk and yogurt intake was 1.5 servings (P_{25}–P_{75}: 0.8–2.4) per day. Of this milk and yogurt intake, 0.5 servings (P_{25}–P_{75}: 0.2–1.0) were consumed as skimmed milk, 0.2 servings (P_{25}–P_{75}: 0.1–0.3) as whole-fat milk, 0.4 servings (P_{25}–P_{75}: 0.1–1.0) as buttermilk, 0.2 servings (P_{25}–P_{75}: 0.1–0.4) as skimmed fermented milk products and 0.1 servings (P_{25}–P_{75}: 0.0–0.2) as whole-fat yogurt (Table 1).

Two-thirds of the study population represents women. Light alcohol consumption and being physically active were more frequent among participants with a high milk and yogurt intake. Compared to the other milk and yogurt subgroups, high whole-fat yogurt consumers were more likely to be highly educated, less likely to smoke and consumed more fruit (Table 2; see also Supporting information, Tables S1 and S2). The consumption of whole-fat milk and skimmed milk was moderately correlated ($r = 0.76$), as were consumption of whole-fat yogurt and skimmed fermented milk ($r = 0.48$). Correlations between consumption of other milk and yogurt groups were low (all $r < 0.2$) (see Supporting information, Table S3).

Main results

During a mean follow-up of 15 years, 1467 (4.1%) potential incident cases of T2D were validated as an incident T2D case. After adjustment for demographic and T2D risk factors in the final adjusted model (model 3), replacement of whole-fat milk (HR = 0.93, 95% CI = 0.60-1.44), buttermilk (HR = 0.88, 95% CI = 0.58-1.34), skimmed milk (HR = 0.87, 95% CI = 0.57–1.32) or skimmed fermented milk (HR = 0.99, 95% CI = 0.63–1.54) with whole-fat yogurt was not associated with the risk of T2D (Figure 1; see also Supporting information, Table S4). Furthermore, replacing whole-fat milk (HR = 0.94, 95% CI = 0.77–1.15) or buttermilk (HR = 0.89, 95% CI = 0.77–1.04) with skimmed fermented milk, replacing whole-fat milk (HR = 1.07, 95% CI = 0.89–1.29) or skimmed fermented milk (HR = 1.14, 95% CI = 0.98–1.32) with skimmed milk, or replacing whole-fat milk (HR = 1.06, 95% CI = 0.90–1.24) or skimmed milk (HR = 0.99, 95% CI = 0.90–1.08) with buttermilk was also not associated with the risk of T2D. Additional adjustment for potential mediators did not affect the results (see Supporting information, Table S4).

Sensitivity analysis

The isocaloric substitution analysis did not alter conclusions (see Supporting information, Table S5). When censoring after 7 years of follow-up ($n = 35\,981$; 738 cases), associations for substitution with whole-fat yogurt products and reduced T2D risk strengthened because replacing buttermilk (HR = 0.48, 95% CI = 0.26–0.89), skimmed

Table 1 Total milk and yogurt consumption and consumption per milk and yogurt substitution subgroup* in the EPIC-NL cohort ($n = 35\,982$)

	Number of consumers	Daily consumption (g) Median (P_{25}–P_{75})	Daily consumption (servings)† Median (P_{25}–P_{75})
Total milk and yogurt	35 982	302 (158–482)	1.5 (0.8–2.4)
Milk and yogurt subgroups			
Skimmed milk	35 865	93 (31–199)	0.5 (0.2–1.0)
Whole-fat milk	33 468	34 (14–66)	0.2 (0.1–0.3)
Buttermilk	16 957	86 (14–200)	0.4 (0.1–1.0)
Skimmed fermented milk	34 868	31 (11–73)	0.2 (0.1–0.4)
Whole-fat yogurt	34 684	11 (5–31)	0.1 (0.0–0.2)

P, percentile.

*Applicable for the consumers of the specified milk or yogurt products.

†200 g.

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Table 2 Baseline characteristics of participants from the EPIC-NL cohort by tertiles of skimmed milk and whole-fat yogurt consumption (n = 35 982)

	Skimmed milk (g day^{-1})			Whole-fat yogurt (g day^{-1})		
	T_1 18 (8–30)	T_2 93 (65–135)	T_3 295 (198–360)	T_1 2 (1–4)	T_2 11 (8–15)	T_3 41 (30–60)
Number of participants	11 994	11 994	11 994	11 994	11 994	11 994
Female, % (n)	78 (9333)	72 (8606)	74 (8875)	70 (8377)	76 (9079)	78 (9358)
Age at recruitment (years), mean (SD)	50 (11)	48 (12)	49 (12)	48 (12)	49 (12)	50 (12)
Hypertension, % (n)	38 (4592)	35 (4172)	37 (4390)	38 (4562)	36 (4334)	36 (4258)
Total HDL to cholesterol ratio, mean (SD)	4.0 (1.4)	4.1 (1.4)	4.1 (1.5)	4.2 (1.5)	4.0 (1.4)	4.0 (1.4)
CVD, % (n)	1 (153)	1 (138)	1 (154)	2 (184)	1 (146)	1 (115)
High education*, % (n)	22 (2,573)	20 (2,374)	20 (2,438)	17 (2,048)	20 (2,407)	24 (2,930)
Physically active, % (n)	39 (4724)	42 (5035)	45 (5352)	39 (4651)	42 (5075)	45 (5385)
Current smoker, % (n)	30 (3636)	32 (3882)	29 (3415)	40 (4,797)	28 (3,320)	24 (2,816)
Former smoker, % (n)	33 (4010)	30 (3609)	31 (3669)	29 (3492)	32 (3863)	33 (3933)
Light alcohol drinkers[†], % (n)	59 (7115)	63 (7533)	66 (7961)	56 (6742)	65 (7778)	67 (8089)
Body mass index (kg m^{-2}), mean (SD)	25.6 (4.1)	25.5 (3.8)	25.7 (3.9)	26.0 (4.1)	25.7 (4.0)	25.2 (3.7)
Total energy intake (kcal day^{-1}), mean (SD)	1889 (554)	2091 (611)	2183 (616)	1981 (618)	2050 (602)	2132 (591)
Milk and yogurt intake (g day^{-1}), median (P_{25}–P_{75})						
Buttermilk	0 (0–200)	0 (0–57)	0 (0–33)	0 (0–20)	0 (0–86)	7 (0–143)
Whole-fat milk	5 (1–15)	29 (17–49)	63 (43–91)	25 (6–58)	32 (12–63)	36 (14–70)
Skimmed milk	18 (8–30)	93 (65–135)	295 (198–360)	63 (17–165)	105 (35–209)	117 (42–227)
Skimmed fermented milk	22 (6–70)	29 (10–68)	36 (14–77)	6 (2–25)	49 (19–92)	44 (21–83)
Whole-fat yogurt	8 (2–24)	11 (4–30)	15 (6–35)	2 (1–4)	11 (8–15)	41 (30–60)
Total milk and yogurt	136 (56–300)	249 (174–386)	479 (369–641)	197 (70–376)	314 (180–491)	383 (260–551)
Other dietary intake (g day^{-1}), median (P_{25}–P_{75})						
Vegetables	131 (100–170)	129 (101–164)	132 (102–167)	125 (94–163)	131 (102–167)	135 (107–170)
Fruits	238 (129–360)	229 (133–341)	251(150–363)	193 (110–316)	247 (146–359)	260 (163–373)
Coffee	450 (180–625)	450 (225–675)	450 (218–562)	450 (210–675)	450 (210–650)	450 (225–562)
Red meat	60 (33–85)	63 (36–86)	59 (34–83)	65 (37–88)	60 (34–84)	57 (33–83)
Processed meat	19 (8–36)	22 (11–38)	20 (10–36)	24 (11–43)	20 (10–35)	19 (9–34)
SSBs	29 (6–83)	33 (8–90)	30 (7–82)	39 (7–102)	30 (7–82)	26 (7–69)
Fibre[‡]	23 (20–27)	23 (20–26)	23 (20–26)	22 (19– 26)	23 (20–26)	24 (21–27)

CVD, cardiovascular disease; HDL, high-density lipoprotein; P, percentile; SSBs, sugar-sweetened beverages; *T*, tertile.

*Higher vocational education and university.

[†]0.1–10 g alcohol day^{-1}.

[‡]Energy adjusted.

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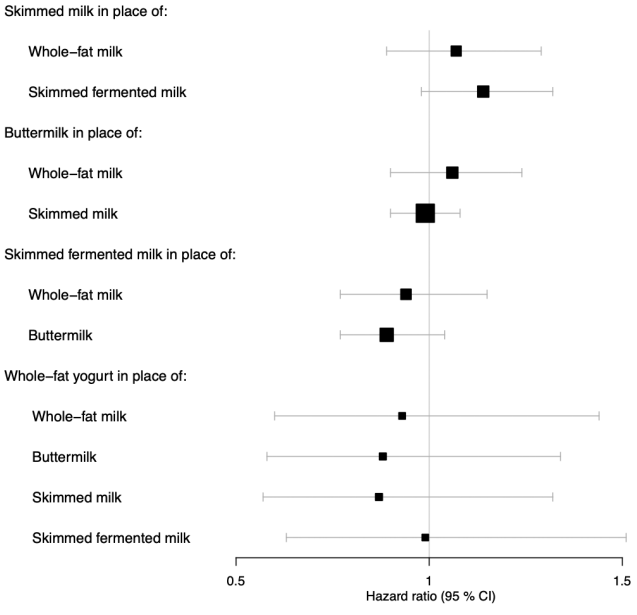

Figure 1 Forest plot of the hazard ratio and 95% confidence interval for substitution of one serving (200 g) of milk or yogurt and the association with type 2 diabetes in the EPIC-NL cohort (n = 35 982; 1467 cases), adjusted for sex (male, female), total energy intake (kcal/day; continuous), smoking status (current, former, never), physical activity (inactive, moderately inactive, moderately active and active), education level (low, average, high), alcohol intake (non-consumer, light, moderate, heavy), hypertension (yes, no) and the dietary intake of fruits, vegetables, processed meat, red meat, coffee, sugar-sweetened beverages and energy adjusted fibre (g day^{-1}; continuous) (model 3).

milk (HR = 0.44, 95% CI = 0.24–0.81) or skimmed fermented milk (HR = 0.48, 95% CI = 0.25–0.91) with whole-fat yogurt was associated with a lower T2D risk (see Supporting information, Table S6). Excluding the first 2 years of follow-up did not change the conclusions, whereas including potential but not verified T2D cases as incident case (n = 488) suggested a potential lower T2D risk for replacement with whole-fat yogurt, although the confidence intervals were wide and the results were not statistically significant (see Supporting information, Table S6). Excluding prevalent cases of cardiovascular disease, hypertension and participants with an increased cholesterol ratio (n = 18 104; 291 cases) resulted in estimates indicating a higher T2D risk for all substitutions, except the replacement of skimmed fermented milk with skimmed milk. However, the results were not statistically significant and the low number of cases and wide confidence intervals suggested low statistical power (see Supporting information, Table S6). When repeating model 3 which adjusted for demographic and T2D risk factors without adjustment for hypertension, and when subjects with missing values on the potential mediators were excluded, the results remained similar (see Supporting information, Table S7). The baseline characteristics after excluding participants with missing values on the potential mediators did not differ from the main study population (see Supporting information, Table S8).

Without specifying substitution, a higher consumption of skimmed milk (HR = 1.11, 95% CI = 1.04–1.19) and buttermilk (HR = 1.09, 95% CI = 1.02–1.16) was associated with increased T2D risk, whereas an increase in the consumption of whole-fat milk (HR = 1.09, 95% CI = 0.95–1.26), skimmed fermented milk (HR = 0.98, 95% CI = 0.86–1.12) and whole-fat yogurt (HR = 1.00, 95% CI = 0.67–1.51) was not (see Supporting information, Table S9).

Discussion

The present study investigated the association between the replacement of milk and yogurt products and the risk of incident T2D among a Dutch study population including 35 982 participants. During follow-up, 1467 (4.1%) validated T2D cases were identified. No evidence was found for an association between the replacement of milk and yogurt products and the risk of incident T2D in the main analysis. However, a lower risk of T2D was suggested when servings of buttermilk, skimmed milk and skimmed fermented milk were replaced by whole-fat yogurt when censoring the follow-up duration to 7 years.

One previous study among a Danish population investigated milk and yogurt product substitutions. In line with the present study, the Danish study did not observe associations with T2D risk when whole-fat milk replaced buttermilk, or skimmed milk replaced whole-fat milk and buttermilk, or skimmed fermented milk replaced skimmed milk, whole-fat milk or buttermilk. Yet, a lower risk of T2D was observed when one serving of whole-fat yogurt was used to replace one serving of skimmed milk (HR = 0.89, 95% CI = 0.83–0.96), whole-fat milk (HR = 0.89, 95% CI = 0.82–0.96), buttermilk (HR = 0.89, 95% CI 0.81–0.97) or skimmed fermented milk (HR = 0.83, 95% CI = 0.71–0.94) [19]. Although our effect estimates are similar to these previous findings, the confidence

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intervals were wider and the results were not statistically significant.

The discrepancies between the study findings are not easily explained because there are no evident sources of heterogeneity between the two studies. One explanation for the discrepancy in findings regarding the whole-fat yogurt may be the lower statistical power in the present study as a result of a smaller study population, as well as a more stringent case definition resulting in a lower number of cases. Another explanation might be the potential influence of dietary changes regarding milk and yogurt product intake in our study population during the 15 years of follow-up. As a result of the use of a single FFQ, only baseline information on dietary intake was available. Furthermore, the sensitivity analysis where we censored after 7 years of follow-up suggested a lower T2D risk for the replacement of buttermilk, skimmed milk and skimmed fermented milk with whole-fat yogurt.

The results from observational studies investigating the association between whole-fat yogurt and T2D risk also report inconclusive results. Some individual cohort studies suggest an inverse association for higher whole-fat yogurt consumption and the risk of T2D [33-36], whereas a previous analysis in a Dutch cohort [37] and the current EPIC-NL analysis suggest a neutral association. It is possible that these discrepancies are driven by differences in adjustment for confounding factors, as well as differences between populations with respect to the food that is consumed instead of whole-fat yogurt. Furthermore, current results from randomised controlled trials investigating dairy product consumption and T2D risk markers often comprise short-term studies conducted in mostly overweight and obese participants, suggesting a null effect or small inverse effects [6]. Long-term experimental studies investigating causal effects between milk and yogurt consumption on intermediate risk markers for T2D (such as fasting glucose levels or insulin response) are necessary.

The present study has several strengths. First, we used a large study population with a long follow-up time with a small degree of loss to follow-up (1.7%). Baseline data collection was extensive, resulting in availability of a wide range of potential confounders. Also, we modelled the substitution of both servings and kilocalories. Finally, we were able to examine the consumption of different types of milk and yogurt because these were measured by the FFQ, and the Dutch population has a relatively high intake of various milk and yogurt products.

There are limitations to consider as well. First, using a FFQ to assess milk and yogurt product intake may have led to misclassification [38,39], although we have no reason to assume that this misclassification is differential and, when comparing collected FFQ data with 12-monthly 24-h recalls, reasonable correlation coefficients were found for the consumption of the total group of milk and milk products [22]. However, the consumption of our specific milk and yogurt subgroups has not been validated against 24-h recalls. Regarding the T2D ascertainment, we did not use the golden standard for diagnosing T2D (i.e. multiple tests of fasting plasma glucose levels) [40]. As an alternative, we used verification information from the general practitioner, who has a complete overview of the medical records, and from the pharmacist, who has information on T2D medication, which is very specific. Furthermore, the substitution model takes a mathematical approach to compare participants at various levels of milk and yogurt product intake, which is not the same as a within-person comparison over time. Repeated measurements of dietary intake would have provided the opportunity to examine milk and yogurt substitution within the same person, although this information is not available. Finally, although we adjusted for a wide range of potential confounders, the possibility of residual confounding cannot be excluded because participants with a higher intake of milk and yogurt products (especially whole-fat yogurt) showed healthier lifestyle behaviours.

In conclusion, we did not find evidence for an association between substitutions within the group of milk and yogurt products and the risk of incident T2D among a Dutch population. Our results therefore indicate that there is no difference between milk and yogurt consumption and the development of T2D. However, we cannot exclude possible attenuation of our results as a result of dietary changes over time. To further clarify the association of milk and yogurt products and T2D risk, this analysis should be repeated in a population with a wider consumption range of whole-fat yogurt to improve the generalisability of the study findings, including follow-up data on the dietary intake. Whole-fat yogurt appears to be particularly relevant in affecting T2D risk and our current analyses were limited by the small intake range of whole-fat yogurt. Swedish or French prospective cohorts may be eligible because these populations have a higher overall milk and yogurt consumption compared to our Dutch population [41]. Furthermore, long-term experimental studies investigating causal effects between milk and yogurt consumption on intermediate risk markers for T2D are needed.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

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IS and LV formulated the research question. JS, LV and IS designed the study, carried it out, analysed the data and wrote the article. All authors provided critical feedback and helped to shape the research and analysis, as well as the final manuscript.

Transparency Declaration

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

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of participants from the EPIC-NL cohort by tertiles of whole-fat milk and skimmed fermented milk consumption (n = 35 982).
Table S2. Baseline characteristics of participants from the EPIC-NL cohort by tertiles of buttermilk consumption (n = 35 982).
Table S3. Correlation between milk and yogurt consumption in the EPIC-NL cohort (n = 35 982).
Table S4. Substitution among milk and yogurt products per one servinga and the associationb with T2D in the EPIC-NL cohort (n = 35 982; 1467 cases).
Table S5. Sensitivity analyses with isocaloric substitution among milk and yogurt products and the association[a] with T2D in the EPIC-NL cohort (n = 35 982; 1467 cases).
Table S6. Sensitivity analyses for the substitution among milk and yogurt products per one serving[a] and the associationb with T2D in the EPIC-NL cohort.
Table S7. Sensitivity analyses for the substitution among milk and yogurt products per one serving[a] and the association[b] with T2D in the EPIC-NL cohort.
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TYPE 2 DIABETES

Under-reporting of the energy intake in patients with type 2 diabetes

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Keywords
dietary assessment, dietary assessment methods, energy intake, type 2 diabetes, under-reporting.

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Abstract

Background: In patients with type 2 diabetes mellitus (DM), an accurate assessment of food intake is essential for clinical nutritional management. Tools such as the food frequency questionnaire (FFQ) and 24-h food record (24HR) identify dietary habits in support of dietary planning. However, it is possible that these tools have reporting errors with respect to assessing food intake, particularly energy intake (EI).
Methods: A cross-sectional study was conducted in patients with type 2 DM. EI was assessed by the FFQ and 24HR tools. Resting energy expenditure (REE) was measured by indirect calorimetry. Data were analysed using a kappa test, *t*-test and Spearman's correlation coefficients. Under-reporting was assessed using the EI/REE ratio. Patients with values <1.18 and <1.10 for FFQ and 24HR, respectively, were considered as under-reporting.
Results: We evaluated 55 patients [mean (SD) 62.7 (5.3) years old, duration of diabetes 11.2 (7.3) years, 52.7% female]. The mean (SD) EI assessed by FFQ was 1797.7 (641.3) and as assessed by 24HR was 1624 (484.8) kcal day^{-1}. The mean (SD) REE was 1641.3 (322.3) kcal day^{-1}. The mean (SD) ratios FFQ/REE and 24HR/REE were 1.11 (0.38) and 1.01 (0.30), respectively. The tools showed a moderate agreement for under-reporting of EI (kappa = 0.404; $P = 0.003$). Moderate and positive correlations between REE were observed with FFQ ($r = 0.321$; $P = 0.017$) and 24HR ($r = 0.364$; $P = 0.006$). According to the tools, the under-reporting was observed in approximately 65% of patients.
Conclusions: The majority of patients with type 2 DM under-reported their calorie intake, as assessed by FFQ and 24HR. REE showed a positive correlation with both tools.

Introduction

Diabetes mellitus (DM) type 2 is the most prevalent form of diabetes and obesity, being associated with approximately 80% of cases [(1)]. The main strategy for the treatment of DM is lifestyle change [(2)]. Overweight and obese patients benefit from changes in reduced energy intake (EI) and an adequate choice of food with a quantity and quality of nutrients that contributes to improved glycaemic control, leading to a reduction of chronic complications of diabetes [(3)]. Thus, knowledge of eating habits is essential for individualised dietary planning in this group of patients.

The assessment tools identifying food consumption habits and patterns provide subsidies for a adequacy of nutritional recommendations to the reality of each patient [(4)]. The instruments most utilised to collect dietary data are the 24-h food recall (24HR) and the food frequency questionnaire (FFQ) [(5)]. However, the limitations of these tools can induce an inaccurate estimate of food intake leading to reporting errors [(6)]. Indeed, it has been reported that individuals tend to report values lower than

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their EI, which does not match their current nutritional status [7]. However, it is also possible to minimise under-reporting errors, as already explained by Goldberg *et al.* [8], where the ratio of EI, as assessed by tools, with resting energy expenditure (REE) may identify under-reporting.

The most commonly identified characteristics associated with under-reporting of EI are obesity [9–11], gender [12–14] and the presence of diabetes [15–16]. Regarding obese individuals in different populations, previous studies have shown that such individuals tend to under-report their EI, and the under-reporting is associated with lifestyle factors as well as the consumption of unhealthy food groups [9,10]. More recently, a study in Iranians that assessed under-reporting through three food consumption instruments found that reporting errors were higher in overweight and/or obese individuals [11].

Gender is also an important variable in food intake reporting studies. A study conducted in Brazil showed that women under and over-reported their EI assessed by the FFQ [12]. These data contributed to a previous study conducted on African American women who also demonstrated under-reporting errors in their EI [13]. A Latin study found a high prevalence of under-reporting of female food intake, and the risk of developing diabetes was also associated with the group with the highest energy intake reporting errors [14].

In patients with DM, under-reporting of food intake also appears to be frequent; however, data are still scarce in this population. A previous study in obese Caucasians with type 2 DM showed under-reporting of EI by approximately 22% and this proportion was higher in women [15]. In black women with type 2 DM, under-reporting errors were also observed, where 46.8% of the evaluated women under-reported their EI and this under-reporting was significantly associated with a higher body mass index (BMI) [16].

Given that most patients with type 2 DM are overweight and obese, and that obesity as well as diabetes are factors associated with EI reporting errors, the present study aimed to evaluate the EI in patients with type 2 DM, through the FFQ and 24HR, as well as the agreement of the tools, the correlations with REE and, finally, the under-reporting of EI evaluated by these instruments.

Materials and methods

Study design and patients

This cross-sectional study included 55 patients with type 2 DM treated at the outpatient clinic of the Hospital de Clinicas in Porto Alegre, Brazil. Diabetes was defined as that occurring subjects over 30 years of age at the onset of diabetes, no previous episode of ketoacidosis or documented ketonuria, and treatment with insulin only after 5 years of diagnosis. The patients were included according to the following criteria: not having received dietary counseling by nutritionist in the last 6 months, age <70 years, serum creatinine <2 mg dL^{-1}, normal thyroid function tests and an absence of severe liver disease, decompensated heart failure or any acute disease. Patients who use medications that could potentially influence body composition (e.g. corticosteroids and diuretics) were excluded. The study protocol was approved by the Ethics Commission of Hospital de Clinicas de Porto Alegre (number 15.0625) and all subjects provided their written informed consent. The study was developed in accordance with the STROBE statement.

Clinical evaluation

Patients were classified as current smokers or not. Usual physical activity was objectively measured by step counting with a pedometer (HJ-321; Omron Healthcare, Inc., Bamockburn, IL, USA) and was classified into five levels: sedentary (<5000 steps day^{-1}), low active (5000–7499 steps day^{-1}), somewhat active (7500–9999 steps day^{-1}), active (≥10 000–12 499 steps day^{-1}) and highly active (≥12 500 steps day^{-1}) [17]. Participants wore pedometer for 7 days, attached to the waistband of their clothing during waking hours, except when bathing or swimming. Participants were encouraged not to alter their usual physical habits during protocol.

Blood pressure was measured twice to the nearest 2 mmHg, after a 10-min rest, using an Omron HEM-705CP digital sphygmomanometer (Omron Healthcare, Inc.). Hypertension was defined as blood pressure ≥140/90 mmHg measured on two occasions or the use of antihypertensive drugs [18].

Body weight and the height of patients (without shoes and coats) were obtained using a calibrated and anthropometric scale (Filizola, Sao Paulo, Brazil). Measurements were recorded to the nearest 100 g for weight and to the nearest 0.1 cm for height. BMI was calculated as weight (kg) divided by the square of the height (m^2). The body composition was performed by means of the electrical bioimpedance (model 230; InBody, Seoul, South Korea) for the determination of fat mass (kg) and fat-free mass (kg).

Dietary assessment, evaluation of energy intake and quality of diet

Two methods of food intake assessment were used: FFQ and three 24HR. The FFQ and 24HR were applied to personal interviews conducted by the same duly trained interviewer. The usual diet was evaluated by the quantitative FFQ previously validated for patients with type 2

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DM, which details 80 items divided into 10 food groups [19]. The 24HR was assessed by 3-day diet recall (two weekdays and one weekend day) through telephone contact [20]. The reported intake of food groups was converted into daily consumption. The Brazilian food composition table was used to evaluate the nutritional composition of the FFQ items [21]. The evaluation of the energy intake from diet records was analysed using the DIETBOX (https://dietbox.me/pt-BR). Data from food intake were expressed as a kcal day^{-1}.

The quality of diet was evaluated by the Goldberg cut-off: the ratio between EI and REE (FFQ or 24HR/REE). Patients with a ratio <1.18 for FFQ and <1.10 for 24HR were considered as under-reporting, respectively [8].

Laboratory evaluation

Blood samples were obtained after a fasting period of 12 h. The plasma glucose level was determined via a glucose-peroxidase-biodiagnostic kit enzymatic colorimetric method, the A1C test by high-precision liquid chromatography (MerckHitachi L-9100; reference values of 4.8–6.0%; Merck Diagnostica, Darmstadt, Germany), total cholesterol and triglycerides by colorimetric enzymatic methods (Merck; Boeringher Mannheim, Buenos Aires, Argentina) and high-density lipoprotein (HDL) by a homogeneous direct method (AutoAnalyzer, ADVIA 1650). Low-density lipoprotein (LDL) was calculated using the Friedewald formula: LDL cholesterol = total cholesterol − HDL cholesterol − triglycerides/5.

Resting energy expenditure measurement

The measurement of REE was performed by indirect calorimetry (IC). The IC protocol consisted of 10 min of rest on a gurney in dorsal decubitus, followed by 30 min of collection of exhaled gases using the canopy dilution technique and a coupled collection device. An open circuit calorimeter (QUARK RMR; Cosmed, Rome, Italy) was used for determining VO_2 (oxygen consumption) and VCO_2 (carbon dioxide production). To calibrate the equipment, the volume of the turbine flowmeter was first calibrated electronically by the system, followed by calibration of the collector plates using a known gas concentration. This process was repeated for each test to standardise the measurement. The first 10 min of gas collection were excluded from the analysis; thus, VO_2 and VCO_2 (L min^{-1}) obtained during the final 20 min of each collection (mean value of the period) were used for the calculation of REE. The equation proposed by Weir [22] was used to obtain values in kcal min^{-1}, which does not require the use of protein metabolism by incorporating a correction factor: $[(3.9 \times VO_2) + (1.1 \times VCO_2)]$. The result (kcal min^{-1}) was multiplied by 1440 min to obtain the value for 24 h. The subjects were asked not to perform any type of physical activity of moderate or high intensity during the 24 h preceding the test, and not to consume alcohol or caffeine. Patients who smoked were instructed not to smoke 12 h before the day of REE measurement. Additionally, subjects were instructed to fast for 12 h prior to the test, with only the *ad libitum* intake of water being permitted, and to have a good night's sleep of at least 8 h. Finally, all subjects came to the test site using a motor vehicle to avoid energy expenditure before the determination of REE. All tests were performed between 06.30 h and 08.00 h in a temperature-controlled (20°C–25°C) and sound-controlled room under low luminosity. All medications in use were maintained during the study period and patients received their usual medication after the IC.

Statistical analysis

Patients were recruited from a convenience sample. The results were expressed as the median (25–75th), percentage (%) or the mean (SD). Spearman's correlation coefficient was used to assess the correlation between EI estimated by FFQ and 24HR with measured REE. The under-reporting agreement between the FFQ and 24HR instruments was calculated using the kappa coefficient. Kappa varies from 0–1: a value <0.2 indicates poor agreement; 0.2–0.4 indicates fair agreement; 0.4–0.6 indicates moderate agreement; 0.6–0.8 indicates substantial agreement; and >0.8 indicates almost perfect agreement [23]. The differences among the ratio EI/REE according to BMI categories were analysed used Student's *t*-test. Pearson's chi-squared test was used to evaluate the proportion of under-reporting by the estimated by FFQ or 24HR/REE ratio according to the BMI in both instruments. Calculations were performed using SPSS, version 23.0 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Results

In total, 55 patients with type 2 DM were evaluated [mean (SD) 62.7 (5.3) years of age; 11.2 (7.3) years of DM duration; and 52.7% women]. The selection process is illustrated in Fig. 1. Most patients in the present study were sedentary (56.4%) and 83.6% were overweight/obese. Also, the presence of hypertension was observed in all patients (100%). The lipid profile was within normal limits; however, the glycaemic control expressed by fasting glucose and the A1c test showed altered levels, as expected in diabetic patients. With regard to drug treatment, all patients used oral antihyperglycaemic agents.

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The characteristics of the patients are described in Table 1.

Table 2 shows anthropometric characteristics, body composition and evaluation of diet quality. The mean (SD) weight was 81.3 (15.2) kg, height was 164.3 (10.6) cm, BMI was 29.9 (4.1) kg m^{-2}, and body composition comprised 34.8 (11.9) kg fat-free mass and 29.0 (9.2) kg fat mass. The mean REE (kcal day^{-1}) assessed by IC was 1641.3 (322.3) kcal day^{-1}. The mean total EI assessed by the FFQ was 1797.7 (641.3) kcal day^{-1} and as assessed by 24HR was 1624 (484.8) kcal day^{-1}. The ratios FFQ/REE and 24HR/REE were 1.11 (0.38) and 1.01 (0.30), respectively. A percentage of under-reporting of 65.5% and 63.6% was observed according to FFQ and 24HR, respectively. In, addition, the tools showed moderate and significant agreement to assess under-reporting of EI (kappa = 0.404; $P = 0.003$).

When we evaluated the under-reporting according to the sex, we did not observe significant differences between reporting errors in men and women by the FFQ and 24HR instruments.

Figure 2 shows the correlation between the EI estimated by the FFQ and 24HR with the REE measured by IC. A positive and significant correlation was observed between REE with FFQ ($r = 0.321$; $P = 0.017$) and 24HR ($r = 0.364$; $P = 0.006$).

Figure 3 demonstrates differences among the ratio EI (estimated by FFQ or 24HR)/REE according to BMI categories. EI/REE ratios <1.18 in FFQ and <1.10 in 24HR were considered as under-reporting. When assessing under-reporting according to BMI, diabetic patients with BMI ≥30 kg m^{-2} had a higher proportion of under-reporting by FFQ (69.2% versus 62.1%; $P = 0.577$) and 24HR (69.2 % versus 58.6%; $P = 0.414$), although without statistical significance. Still, patients with BMI ≥30 kg m^{-2} had a lower EI/REE ratio compared to patients with BMI <30 kg m^{-2}, in both tools; however, the differences were not significant.

Table 1 Clinical and laboratory characteristics of the 55 patients with type 2 diabetes mellitus

Variable	Characteristics*
Age (years)	62.7 (5.3)
Duration of diabetes (years)	11.2 (7.3)
Sex (female)	29 (52.7%)
Physical activity (steps $week^{-1}$)	5324 (1560–18097)
Sedentary (%)	56.4
Hypertension (%)	55 (100%)
Fasting plasma glucose (mg dL^{-1})	153.4 (46.8)
A1C test (%)	7.6 (5.2–12.0)
Total cholesterol (mg dL^{-1})	161.6 (38.7)
LDL cholesterol (mg dL^{-1})	83.4 (29.3)
HDL cholesterol (mg dL^{-1})	45.8 (12.2)
Triglycerides (mg dL^{-1})	145.0 (111.2–191.0)
Medications	
Oral antihyperglycaemic	55 (100%)
Antihypertensive agents	55 (100%)
Hypolipidaemic agents	38 (69.1%)

A1C, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Data are presented as the median (25th–75th), percentage (%) or mean (SD).

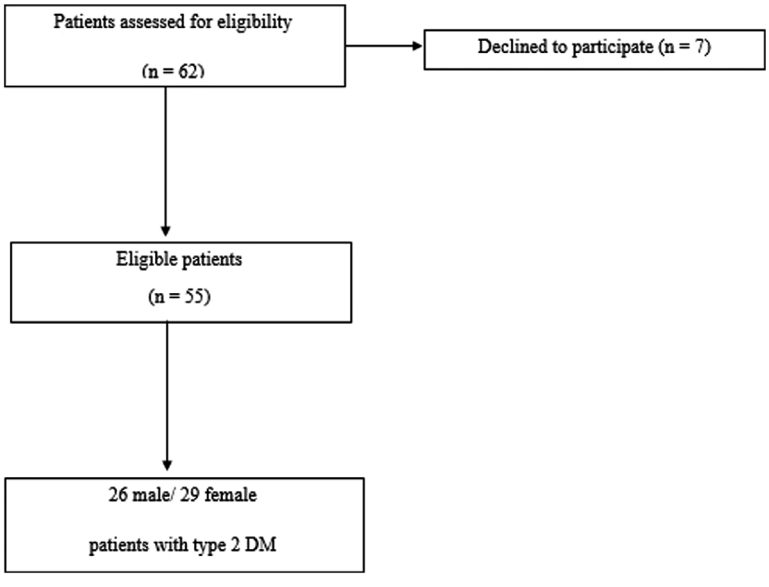

Figure 1 Flowchart for patient selection, DM, diabetes mellitus.

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Table 2 Nutritional characteristics and evaluation of energy intake of the 55 patients with type 2 diabetes mellitus

Variable	Characteristics*
Weight (kg)	81.3 (15.2)
Height (cm)	164.3 (10.6)
BMI (kg m^{-2})	29.9 (4.1)
Overweight/obese (%)	83.6
Fat-free mass (kg)	34.8 (11.9)
Fat mass (kg)	29.0 (9.2)
BMR by IC (kcal day^{-1})	1641.3 (322.3)
EI by FFQ (kcal day^{-1})	1797.7 (641.3)
FFQ/BMR (ratio)	1.11 (0.38)
EI by 24HR (kcal day^{-1})	1624.0 (484.8)
24HR/BMR (ratio)	1.01 (0.30)
Under-reporting by FFQ	36 (65.5%)
Under-reporting by 24HR	35 (63.6%)

24HR, 24-h dietary recalls; BMI, body mass index; BMR, basal metabolic rate; EI, energy intake; FFQ, food frequency questionnaire; IC, indirect calorimetry.
*Data are presented as a percentage (%) or the mean (SD).

Discussion

Under-reporting of EI is a problem in studies evaluating food intake, in particular, in calorie consumption data [6]. In the present study, in type 2 DM patients, under-reporting of EI was similar according to the FFQ assessment (65.5%) and the 24HR (63.6%). Studies conducted in the general population, which compared different food consumption assessment instruments, showed variations in their results regarding the under-reporting rates of EI [11,12,24]. A recent study of 118 Iranian adults, which evaluated three methods of food consumption, showed that the highest under-reporting rate was observed in the 24HR instrument and also that this was associated with the highest BMI [11]. The FFQ showed lower rates of under-reporting of EI [11]. However, a study conducted in 65 Brazilian women, which also evaluated the reports of EI from three instruments, showed that 24HR had lower rates of under-reporting compared to FFQ, further suggesting that FFQ has limitations that can lead to under-reporting, regardless of individual characteristics [12]. Indeed, a previous study conducted in American adults had also shown a lower prevalence of under-reporting in the 24HR method compared to FFQ [24]. In the present study, the food intake assessment tools, FFQ and 24HR, showed a moderate and significant agreement for the occurrence of under-reporting of EI.

Reporting errors are also been associated with other variables such as obesity, diets, unhealthy food groups and conditions such as smoking and age, as shown in a study of Jamaican adults [9]. In this same study, it was also observed that women tend to under-reporting more than men (38.6% versus 22.5%) [9].

Gender is also an important variable in food intake assessment. Studies in different ethnicities assessing EI errors in both genders showed that women under-report a higher and more significant proportion than males [9,15,25,27]. In the present study, when we stratified according to gender, we observed that women were more likely to under-report in the FFQ, although without any significant difference between genders.

Age, presence of obesity and diabetes have also showed associations with calorie notification errors, as assessed by different food consumption instruments. A study of 41 healthy elderly subjects (mean age of 67 and 68 years for

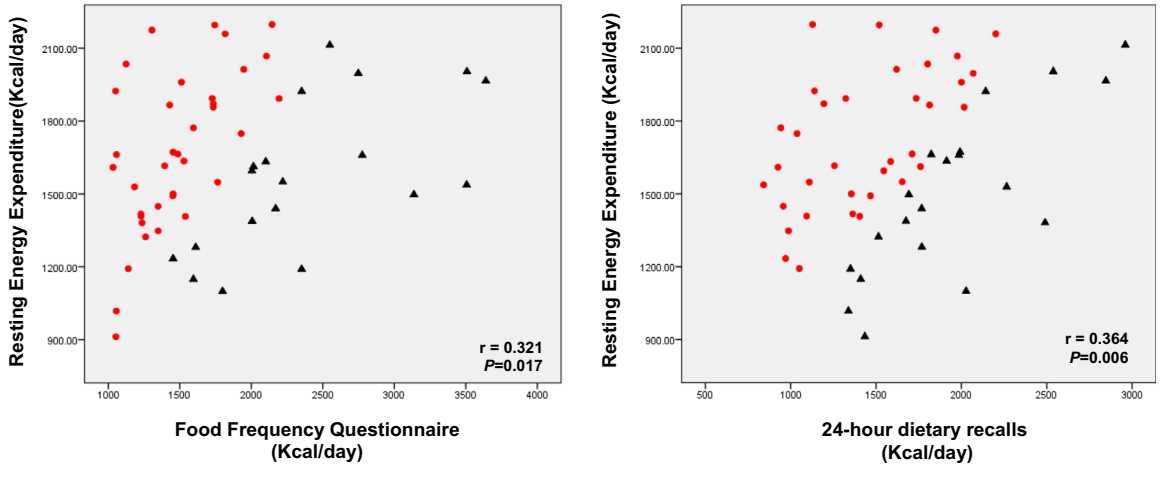

Figure 2 Correlation of energy intake estimated by food frequency questionnaire (FFQ) and 24-h dietary recall (24HR) with resting energy expenditure (REE) by indirect calorimetry (IC). *r*, Spearman's correlation. Statistical significance: $P \leq 0.05$. ●, under-reporting of energy intake (EI); ▲, acceptable notification of EI.

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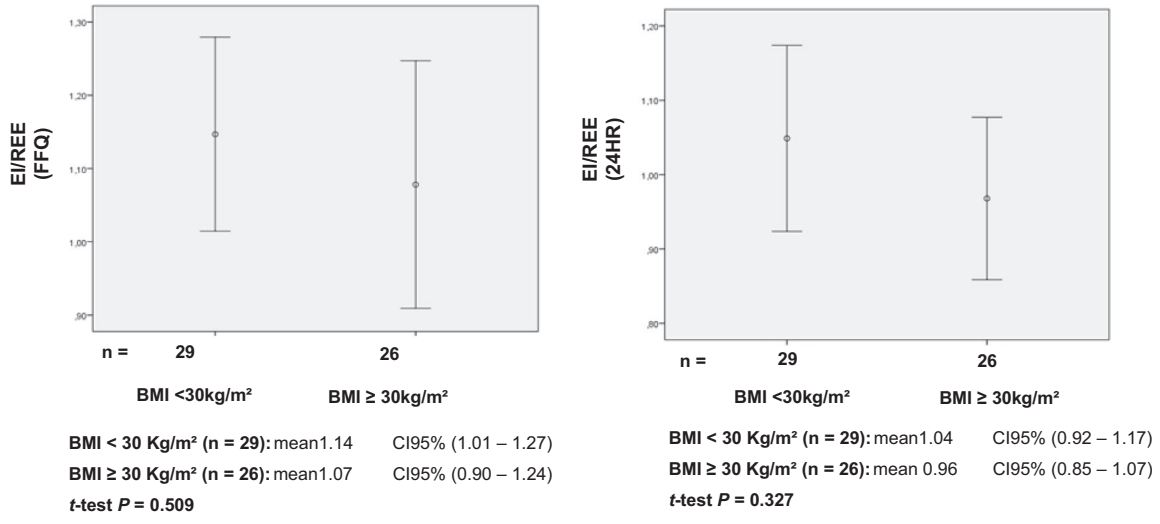

Figure 3 Differences among the ratio energy intake (EI), as estimated by food frequency questionnaire (FFQ) or 24-h dietary recall (24HR)/resting energy expenditure (REE) according to body mass index (BMI) categories. CI, confidence interval. Statistical significance: $P \leq 0.05$.

women and men, respectively) showed under-reporting of calories as assessed by 24HR (31%) and FFQ (40.5%) [25]. Still, under-reporting was more frequent in older women with a higher body fat percentage [25]. In the present study, no association was observed between age and under-reporting of EI (data not shown).

Obesity has been the factor most negatively related to the accuracy of the intake report, regardless of the food intake assessment instrument used. Also, the fear of a negative assessment has also been reported as a predictor of under-reporting of EI [26]. In the present study, type 2 DM individuals had a mean (SD) BMI of 29.9 (4.1) kg m^{-2}, demonstrating that most of the patients evaluated were overweight and/or obese. When evaluating notification errors according to BMI, we observed a tendency for under-reporting with BMI ≥30 kg m^{-2}; however, these differences were not significant in patients with BMI <30 kg m^{-2}. The association between overweight and under-reporting was demonstrated in a cross-sectional study of 331 Brazilian non-diabetic subjects, for which EI was assessed by the mean of two 24HR and it was demonstrated that 15.1% under-reporting was associated with being overweight and those individuals expressing dissatisfaction with their body weight were more likely to under-report their intake.[10] In Latin individuals at high risk of developing type 2 DM and who used the average of 24HR to assess EI, an association between under-reporting and higher BMI was observed [14].

Type 2 DM, as a result of its important association with obesity [1], is confirmed to be a component in under-reporting errors; however, studies are scarce in individuals with DM [13,15,16,27]. A study of 185 African American women with type 2 DM showed that 58% of under-reporting of EI, as assessed by the average of three 24HR, was associated with a higher BMI [13]. In 21 obese patients (12 patients with type 2 DM), it was shown that diabetic patients under-reported their EI, as assessed by the 3-day dietary record, with values being much lower than those for REE [15]. In addition, sub-reports were significantly lower in obese diabetic patients compared to non-diabetic patients, and women, with and without DM, underestimated more in both groups [15]. A study in black women with type 2 DM, for which EI was assessed from a combination of dietary recall with modified FFQ, showed caloric under-reporting in 46.8% and an association with a higher BMI [16]. These data support the classic study of under-reporting in patients with type 2 DM, for which food intake was assessed by 3-day dietary records, and where it was observed that obese individuals with type 2 DM reported a lower EI compared to non-obese individuals, particularly females, and also that reports of diets obeyed the recommended treatment prescription rather than their actual usual intake [27].

The REE assessment is relevant in food consumption studies because its measurement or estimate allows the identification of notification errors through cut-offs obtained by the ratio between EI (measured by the instruments) and the REE [8]. In the present study, the ratios found for FFQ and 24HR were 1.11 and 1.01, respectively, demonstrating under-reporting of EI in this group of type 2 DM patients. When we evaluated the correlation of the instruments with REE, we observed that both instruments demonstrated a positive and significant correlation with REE, as measured by IC. In this sense, from the data found in the present study, we consider that any of the instruments can be used to assess food intake in patients with

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type 2 DM; however, the results of dietary data should be interpreted with caution, considering that this population showed a large proportion of under-reporting of EI.

The present study had some limitations. We did not follow weight changes during the dietary data collection period. The FFQ was applied on the day of clinical evaluation and the 3 days of 24HR by telephone. However, no significant weight loss was reported by patients dusing telephone contacts. In the assessment of REE, we did not consider the physical activity factor because most of our patients are considered as 'low active' according to the number of steps $weeks^{-1}$. Indeed, if we consider the activity factor, we could lead to even greater under-reporting errors, which might not portray the reality for this group of patients. Another limitation of the present study may be the small sample size. However, our study collaborates with the few studies developed in patients with type 2 DM that evaluated food intake notifications errors. In addition, we evaluated REE by a reference criterion, IC, and not by prediction equations, which reinforces the relevance of the study and the reported data.

In conclusion, in the present study, the majority patients with type 2 DM under-reported their EI, as assessed by FFQ and 24HR. Studies in patients with type 2 DM with a larger sample size and stratified according to gender are necessary and relevant for a better evaluation of which food consumption instrument is the best for use in this population.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
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Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned (please add in the details of any organisation that the trial or protocol has been registered with and the registration identifiers) have been explained.

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TYPE 2 DIABETES

Cost effectiveness of dietitian-led nutrition therapy for people with type 2 diabetes mellitus: a scoping review

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Abstract

Background: The management of diabetes costs in excess of $1.3 trillion per annum worldwide. Diet is central to the management of type 2 diabetes. It is not known whether dietetic intervention is cost effective. This scoping review aimed to map the existing literature concerning the cost effectiveness of medical nutrition therapy provided by dietitians for people with type 2 diabetes.

Methods: Thirteen scientific databases, including MEDLINE, EMBASE and CINAHL, as well as multiple official websites, were searched to source peer-reviewed articles, reports, guidelines, dissertations and other grey literature published from 2008 to present. Eligible articles had to have assessed and reported the cost effectiveness of dietetic intervention for adults with type 2 diabetes in developed countries. Experimental, quasi-experimental, observational and qualitative studies were considered.

Results: Of 2387 abstracts assessed for eligibility, four studies combining 22 765 adults with type 2 diabetes were included. Dietetic intervention was shown to be cost-effective in terms of diabetes-related healthcare costs and hospital charges, at the same time as also reducing the risk of cumulative days at work lost to less than half and the risk of disability 'sick' days at work to less than one-seventh.

Conclusions: The findings highlight the importance of advocacy for medical nutrition therapy for people with type 2 diabetes, with respect to alleviating the great global economic burden from this condition. Further studies are warranted to elucidate the factors that mediate and moderate cost effectiveness and to allow for the generalisation of the findings.

Introduction

Type 2 diabetes mellitus has emerged as a global chronic epidemic, accounting for 90% of all diabetes [1-3]. Diabetes results in significant human, social and economic costs, placing enormous demands on healthcare systems [3]. The International Diabetes Federation reports half a billion people in the world living with diabetes [4]. The global economic burden of diabetes was estimated in 2015 at $1.3 trillion, corresponding to approximately 1.8% of the global gross domestic product [5]. People with type 2 diabetes exhibit a high healthcare resource utilisation that may include hospital inpatient and outpatient care; visits to general practitioners, endocrinologists and other specialists; a greater use of allied health services such as podiatry, dietetics, optometry and others; and extensive prescription drug and medical supply use [6]. Diabetes prevalence rates increase with age, predicting further increases in the global economic burden of disease, considering our ever-increasing ageing population [7]. The recent changes to the food supply and dietary patterns, combined with less physical activity, means that most populations are experiencing more obesity and more diabetes [8]. Indeed, the World Health Organization is reporting rising numbers for type 2 diabetes [9].

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Type 2 diabetes has been shown to go into remission with lifestyle modifications alone, such as by following a healthy diet and being physically active [10]. Diet and exercise work synergistically to control blood glucose concentrations and adiposity, by improving insulin sensitivity and facilitating a healthier body composition. Although diet is crucial for both the prevention and management of type 2 diabetes, changing individual eating habits is a complex undertaking that involves detailed nutrition knowledge; skills in food preparation; access and affordability for healthy foods such as vegetables, fish and wholegrains of low glycaemic index; and an individual's motivation to change [11-12] Dietitians have the expertise and experience to deliver the counselling, and support the patient journey to achieve the dietary patterns that optimise the control of blood glucose concentration, as well as that of other risk factors such as dyslipidaemia, hypertension and obesity.

Research has established that better clinical outcomes, such as better regulation of glycaemia and greater weight loss, are achieved when the dietary intervention is led by a dietitian as opposed to any other healthcare professional [13]. Even a single session with a dietitian improves HbA1c levels [14]. For these reasons, international guidelines emphasise the importance of medical nutrition therapy (MNT) delivered by accredited dietitians for people with type 2 diabetes [15-17]. Dietitians are the only health professionals trained in MNT. Yet, despite the proven benefits of consulting with a dietitian, many people with type 2 diabetes never consult with one [18-20]. Furthermore, some patients prefer to obtain nutrition advice from general practitioners (GPs) [21] despite global reports highlighting a lack of nutrition education in medical curricula [22,23]. In addition to GPs' lack of the required expertise in the field of nutrition to deliver the care needed to patients, their appointments are generally more costly, therefore also justifying this service being conducted by a dietitian from a cost efficiency point of view. Yet, a current review of the proven cost effectiveness of dietetic intervention for people with type 2 diabetes is lacking.

A preliminary search was conducted in February 2020 for existing narrative, scoping and systematic reviews of cost effectiveness of dietetic interventions in the following databases: CINAHL, the Cochrane Database of Systematic Reviews, Epistemonikos, JBI Database of Systematic Reviews and Implementation Reports, MEDLINE and PROSPERO. The search did not identify any recent (less than 10 years old) reviews on the cost effectiveness of dietitian-led nutrition intervention in people with type 2 diabetes. Hence, to inform healthcare services planning funding policies in countries with both private and government-subsidised health systems, we conducted a scoping review to map the existing literature concerning the cost effectiveness of MNT provided by dietitians for people with type 2 diabetes in developed countries.

Materials and methods

Data sources and search strategy

Thirteen databases were searched: AMED (Ovid), Business Source Ultimate (EBSCO), CINAHL (EBSCO), Cochrane CENTRAL (Wiley), EMBASE (Ovid), ERIC (Ovid), Academic Search Ultimate (EBSCO), Global Health (Ovid), Health Business Elite (EBSCO), MEDLINE (Ovid), PsychINFO (Ovid), Scopus (Elsevier) and Web of Science (Clarivate Analytics). Sources of unpublished studies and grey literature searched were Google, Trove, MedNar and OpenGrey; official websites of international and government organisations such as the World Health Organization website and its international clinical trial registry; the Australian, European Union and the US clinical trials registers; the American Diabetes Association, Diabetes UK and Diabetes Australia websites; websites of professional and accreditation bodies such as the Academy of Nutrition and Dietetics, the British Dietetic Association, and the Dietitians Association of Australia; websites of leading consulting firms such as Deloitte, KPMG, PwC, Ernst & Young, Accenture, Boston Consulting Group, McKinsey & Company, Bain & Company, Capgemini, Roland Berger, Strategy&, Oliver Wyman, At Kerney, LEK, Monitor, OC&C Strategy Consultants, Mercer, American Healthcare Consulting, Australian Healthcare Associates, Illuminate Health Consulting; finally, advocacy groups and other industry-related websites were also searched.

The search strategy was optimised to extract both published and unpublished studies, as well as other reviews. An experienced research librarian facilitated the development of the search strategy. Initially, proposed search terms were tested against a list of relevant articles in three online databases (CINAHL, EMBASE and MEDLINE). Identified text words contained in the title and/or abstracts of relevant papers informed the initial set of terms, and the resulting improved search terms were used to conduct a second search, this time across all included databases. The complete search strategy for Ovid MEDLINE is provided in Appendix 1. Moreover, the reference lists of identified relevant articles and reports were searched for additional studies. The authors of identified studies were contacted to confirm the involvement of dietitians in the intervention, as well as to provide unpublished data and further information.

Study eligibility and selection criteria

The PICOTS (Population, Intervention, Comparator, Outcome, Time and Setting) framework was used to

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identify eligible studies. Studies were considered if they included a (i) nutrition intervention delivered by (ii) accredited dietitians, in (iii) adults with (iv) type 2 diabetes. Both studies including dietitians or nutritionists were considered because the latter may be used in different countries to describe the same profession. To ensure consistency, the authors were contacted to confirm that the dietitian or nutritionist possessed a formal qualification and national accreditation to practice in a clinical setting. If this confirmation could not be obtained, the study was excluded. Studies needed to include a (v) comparator in which the nutrition intervention is delivered by other healthcare professionals, such as nurses or physicians, or followed usual care that did not include a referral to a dietitian. The outcome of interest was (vi) cost effectiveness. Studies that reported on clinical effectiveness but did not include cost effectiveness data were excluded. Both direct cost effectiveness outcomes, such as cost of intervention in dollars ($) or other currencies, as well as indirect ones, such as Quality-Adjusted Life Years gained (QALYs), were considered. Only contemporary studies and reviews published in (vii) English language (viii) after 1 January 2008 were considered. To facilitate comparisons between different countries and healthcare systems, this review was limited to studies from (ix) developed countries that have established guidelines in regards to the nutritional management of people with type 2 diabetes [15-17]. It is recognised that the delivery of health care varies even between developed countries, although some comparisons can be made. Including studies from developing countries would likely increase the heterogeneity of the settings substantially, hindering insightful comparisons; therefore, studies from countries that do not report guidelines for the nutritional management of people with type 2 diabetes were excluded. To aid with this, countries listed by the World Bank as 'developing' were excluded from this review [24]. (x) Both studies conducted in primary care and hospital settings were included. (xi) Any type of study was considered for inclusion, including experimental, quasi-experimental, analytical, descriptive observational, qualitative and case studies, as well as reports found in grey literature.

Two researchers from the present study (GS and LW) assessed titles and abstracts against the eligibility criteria. Full-text articles were retrieved and assessed for eligibility when the title and abstract did not contain sufficient information to determine study eligibility. Any disagreements were resolved by consensus.

Data extraction and charting

Two researchers from the present study (GS and LW) extracted the data: publication details of the research (article identification number, type of article, title, journal, year), author details (names, affiliations, funding, conflict of interest), study details (location, year, setting, design, purpose, inclusion criteria, blinding method, randomisation method, statistics, conclusions), participant details (sample size, recruitment process, demographics, retention rate, adherence and compliance), intervention (description of intervention, primary and secondary endpoints, duration), outcomes (cost effectiveness, other outcomes, measurement methodology) and key findings.

Data were charted in a tabular form that aligns with the scope of this review. A narrative summary accompanies the tabulated findings and describes how the results relate to the review's objective and questions.

Results

The search yielded 3540 records in total: 3383 records were identified by searching scientific databases and another 157 were identified by searching the grey literature and the reference lists of identified eligible articles. One thousand one hundred and fifty-three (1153) duplicates were removed and the remaining 2387 abstracts were assessed for eligibility (Figure 1). Two thousand three hundred and thirty-four (2334) articles were excluded during the primary exclusion round and a further 49 were excluded after assessing the full-text articles. Reasons for exclusion included 'no cost effectiveness reported', 'study not conducted in a developed country', 'intervention being carried out by a multidisciplinary team' with the involvement of dietitian being uncertain, 'the control group also receiving education by the dietitian', 'not clear if the intervention was led by a dietitian' (communication attempted with the authors to no avail) and articles not relevant (e.g. position papers, guidelines and conference abstracts). The complete list of full-text articles excluded along with the detailed reasons for exclusion of these articles are shown in Appendix 2. Four studies were included in the scoping review [25-28].

Study characteristics

All four studies were conducted in outpatient settings. Two involved a parallel randomised control trial (RCT) design [26,28], with one employing cluster randomisation [26], and two were retrospective cohort studies [25,27]. Three studies were conducted in the USA [25,27,28] and one in Australia [26]. The reported conflicts of interest and funding sources are shown in Appendix 3. In total, 22 765 adults with type 2 diabetes, representing a diverse range of participants, were included (Table 1).

Table 1 charts the study characteristics. Three studies [25,26,27] reported a mean age of participants in their fifties

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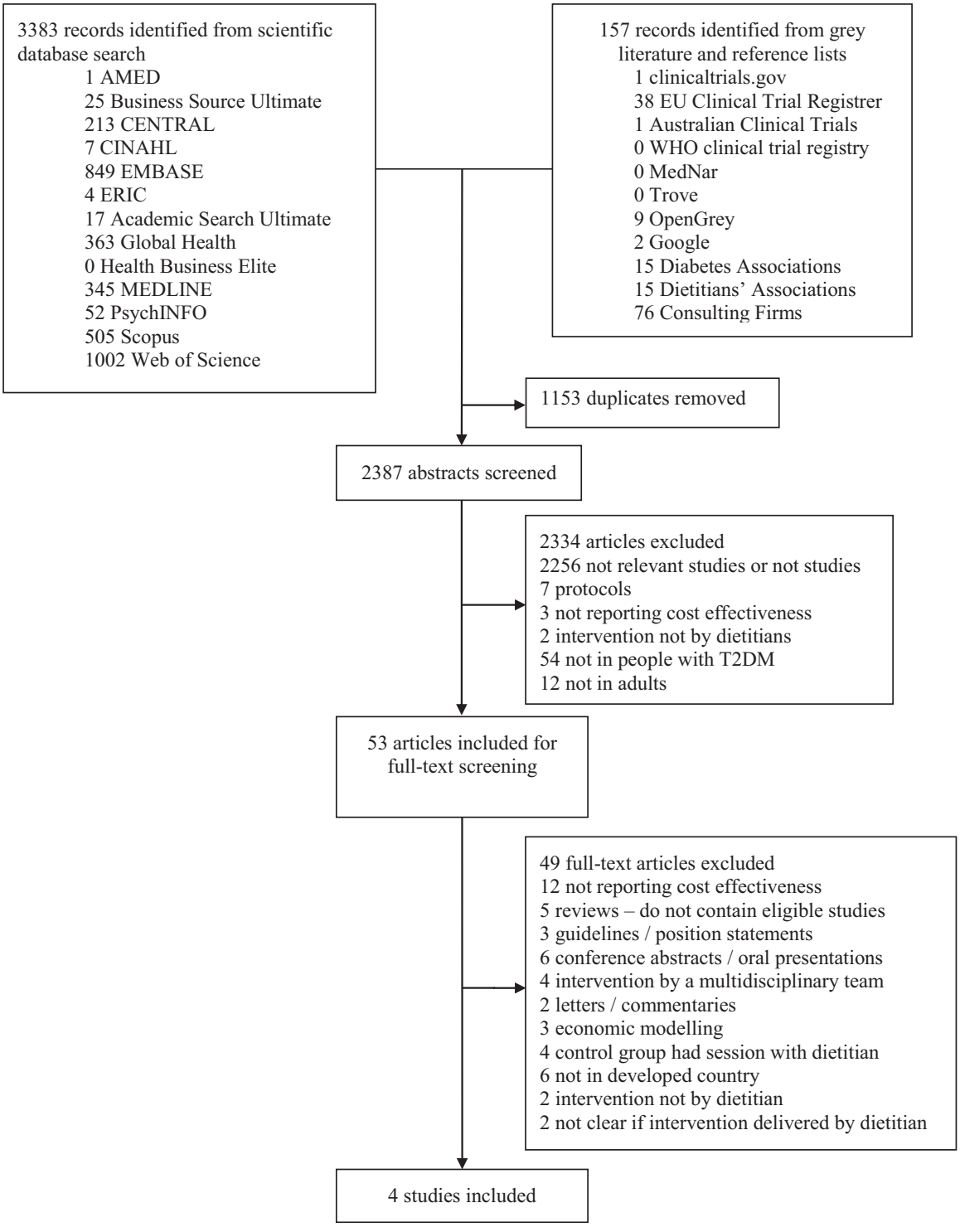

Figure 1 Study selection. T2DM, type 2 diabetes mellitus.

(56, 58.2 and 53 years old), with Robbins *et al.* [27] not reporting on mean age. In two studies [25,28], the majority of participants were white Caucasian; in one [27], they were African American; with Graves *et al.* [26] not reporting on ethnicity. Three studies [26,27,28] recruited more female participants (61%, 57% and 60% women, respectively), with one study [25] having a more even gender distribution (53.5% men).

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Table 1 General characteristics of the included studies

Author (year) (Country)	Study design	Setting	Duration	Participants	Intervention
Dalal *et al.* (2014) (USA) [25]	Retrospective Cohort	Outpatient (98%)	12 months	26 700 subjects; mean age: 56 years; men: 53.5%; white: 67%	524 subjects received nutrition counselling and 1822 received diabetes education Subjects not in the C/E group did not receive counselling or education 1890 subjects in the C/E group were propensity matched with an equivalent number of subjects from the non-C/E group
Graves *et al.* (2009) (Australia) [26]	Cluster RCT, parallel groups	Outpatient	12 months and then extrapolated to 10 years	434 subjects; mean age: 58.2 years; men: 39%; BMI: 31.1 kg m^{-2}	228 intervention subjects had 18 telephone behavioural counselling sessions for diet and physical activity 206 control subjects did not receive counselling.
Robbins *et al.* (2008) (USA) [27]	Retrospective Cohort	Inpatient	4.7 years (mean)	18 404 subjects; men: 43.3%; 73% African-American	1683 subjects saw the nutritionist (25% were RDs) at least once for education. The remaining subjects did not receive education
Wolf *et al.* (2009) (USA) [28]	RCT, parallel groups	Outpatient	12 months	147 subjects; mean age: 53 years; men: 40%; 80% Caucasian; BMI: 35.6 kg m^{-2}; HbA1c: 7.7%	74 subjects received education and MNT from a RD 73 control subjects received standardised written educational material

BMI, body mass index; C/E, counselling and/or education; HbA1c, haemoglobin A1c; MNT, medical nutrition therapy; RCT, randomised control trials; RD, registered dietitian; T2DM, type 2 diabetes mellitus.

The intervention lasted for 12 months in three studies [25,26,28], with one study [27] reporting a mean duration of intervention of 4 years and 8 months. The intervention involved nutrition education and counselling [25-28] and one study additionally emphasised behavioural change techniques [26]. In two of the studies, the nutrition intervention was exclusively conducted by registered dietitians [26,28]. Dalal *et al.* [25] reported 73% of participants receiving nutrition/diet counselling and Robbins *et al.* [27] reported that 25% of the 'nutritionists' in their study were registered dietitians. Following contact with the authors, it could not be established how many of the remaining 'nutritionists' were dietitians who were not registered with the professional body. The frequency of consults varied, with one study [27] reporting at least one session, another study [26] stating eighteen telephone counselling sessions, and the other two studies [25,28] not reporting on frequency. The duration of the educational sessions with the dietitian was not clear.

Economic outcomes

Table 2 charts the economic measures assessed by the different studies, their methodologies and the outcomes. Three studies [25-27] reported healthcare costs, with two [25,27] reporting direct costs and one [26] indirect costs. One study [28] reported on days missed at work and on days with disability. Favourable overall economic outcomes were reported for the intervention groups by all four studies.

In the study by Dalal *et al.* [25], 524 middle-aged white adults received nutrition education from a dietitian and another 1822 received diabetes education. The education resulted in $2335 less cost per patient in diabetes-related healthcare costs at 1 year follow-up. However, the total healthcare costs of the intervention participants increased at the 1-year follow-up mark (from $20 076 ± $53 741 to $24 747 ± $57 670), whereas total healthcare costs for the comparator decreased (from $22 432 ± $45 030 to ($18 378 ± $37 522). Although data were available for a large cohort of people with type 2 diabetes, only a small number of cases could be used in the economic analyses, comprising the nutrition education and counselling and the diabetes education. The authors reported limitations including the use of medical insurance claims data and the intrinsic coding error possibility; the retrospective cohort design that could not allow for causality inference; and the privately medically insured study

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Table 2 Economic measures and outcomes of included studies

Author (year) (Country)	Economic measures	Timeframe assessed	Method	Findings
Dalal *et al.* (2014) (USA) [25]	Total health care and diabetes-specific costs. Diabetes costs included medications, visits to endocrinologist, supplies (lancets/glucose test strips) – claim had to include a diabetes code	12 months	Propensity score matching at a ratio of 1:1 was used to construct a comparator group that closely matched the intervention. A total of 1890 subjects per group were compared Intergroup comparisons (dietetic intervention vs control) of healthcare costs were evaluated using χ^2 and t tests to detect differences	The intervention group incurred \$2335 per patient less in diabetes-related healthcare costs at 12 months ($P = 0.002$), but their total healthcare costs were higher by \$6369 ($P < 0.001$)
Graves *et al.* (2009) (Australia) [26]	Healthcare costs including consultations with GPs and other healthcare practitioners, hospital admissions and outpatient visit costs and health benefits	12 months – extrapolated to 10 years	Costs assessed using a state-transition Markov model that predicted the progress of participants through five health states related to changes in physical activity and diet for 10 years after recruitment. Total cost and QALY outcomes for the intervention and usual care control groups were compared However, usual care resulted in treatment effects so a control whereby no changes in physical activity and diet states occurred as is existing practice was constructed for comparison	Telephone diet and physical activity counselling vs control costs \$29 375 per QALY gained and is cost effective. Counselling vs usual care costs \$78 489 per QALY gained is not cost-effective
Robbins *et al.* (2008) (USA) [27]	Costs for all hospitalisations during follow-up	4.7 years (mean follow-up time)	Linear regression models for associations of each educational visit with hospital charges (total charges for all hospitalisations during follow-up)	Nutrition intervention incurred \$13 872 less in hospital charges (95% CI = \$7799 to \$19 945; $P < 0.001$). Each nutrition visit was associated with \$6503 less in hospital charges (95% CI = \$3421 to \$9586; $P < 0.001$)
Wolf *et al.* (2009) (USA) [28]	Group differences in cumulative days missed at work or with disability	12 months	Due to skewed distributions of outcomes, unadjusted differences in mean cumulative days missed between groups were evaluated using Mann–Whitney *U*-tests	Dietetic intervention reduced risk of cumulative days missed at work by 64.3% ($P \leq 0.01$) compared to control (annual accumulation: C: 3.49 days vs. I: 0.92 days, ($P = 0.01$) and risk of disability days by 87.2% ($P = 0.003$) compared to control (annual accumulation: C: 5.3 days vs. I: 0.94 days, ($P \leq 0.001$)

95% CI, 95% confidence interval; GP, general practitioner; QALY, quality-adjusted life year.

population that may not be representative of the general US population.

Graves *et al.* [26] reported on 228 middle-aged obese adults receiving nutrition counselling over the telephone. The nutrition intervention was cost-effective compared to the existing practice (\$29 375 per QALY gained) but not compared to usual care control (\$78 489 per QALY gained). Of note, the authors reported that the 'existing practice' group was the one more closely resembling the usual care practices, and that the group named as 'usual care' in fact did receive intervention, although this was less than that received by the 'intervention' group. The authors reported the economic model used (Markov) as the main strength of the study, with its 10-year horizon allowing for policy making. However, the authors also stated that the extrapolation of their 12-month data to an additional 9 years means that an assumption of continuation of current trends has been made. Another limitation

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noted was the conservative assumptions of equal mortality rates for the intervention and control groups, when the literature indicates a reduction in mortality with diet improvements. Furthermore, participants were recruited from a low socio-economic community, and the majority had three or more comorbidities, limiting the generalisability of the findings.

In the study by Robbins *et al.* [27], 1683 mostly African-American adults visited the nutritionist at least once for education. Approximately one-quarter of the nutritionists in this study were registered dietitians. The nutrition intervention reduced hospital charges by \$13 872 (95% confidence interval = \$7799 to \$19 945), with each nutritionist visit being associated with a \$6503 reduction in hospital charges (95% confidence interval = \$3421 to \$9586). The authors reported the possibility of confounding, acknowledging that this is an inherent limitation of observational studies. They reported that middle-aged patients (i.e. between the ages of 45 and 64 years) were more likely to receive educational visits. However, when the analysis was restricted to this group, the conclusions were not different. The authors reported that the long time period between recruitment and final follow-up (mean of 4.7 years) means that diabetes education was not uniform as a result of the change in care practices that took place within that time frame.

Finally, Wolf *et al.* [28] reported on 74 Obese Class II middle-aged Caucasian adults receiving education and MNT. The intervention reduced the risk of cumulative work days lost by 64.3% ($P \leq 0.01$) compared to control and decreased the risk of disability days by 87.2% ($P = 0.003$). 'Cumulative work days lost' report absenteeism rates, comprising the loss of productivity as a result of employees not attending work because of sickness. The term 'disability days' is a measure of presenteeism i.e. the loss of productivity as a result of unwell employees who choose to attend work but underperform because of illness. The authors highlighted the self-reported outcome measures, the small sample size and the lack of generalisability of the findings as the main limitations of the study. However, they stated that this means of outcomes reporting is standard practice in these studies.

Discussion

This scoping review is the first to map the existing literature on the cost effectiveness of dietitian-led nutrition intervention for people with type 2 diabetes in developed countries. Four studies, combining 22 765 adults with type 2 diabetes, indicated that dietetic intervention is cost-effective in terms of diabetes-related healthcare costs and hospital charges, at the same time as also reducing the risk of absenteeism to less than half and the risk of disability days to less than one-seventh.

Of some concern, nutrition intervention in the study by Dalal *et al.* [25] increased the total healthcare costs. It was postulated that the education may have increased the health care-seeking behavior of the participants in the intervention group. Indeed, health education has been shown to increase the consumption of health care. [29] Also, although nutrition intervention was cost-effective compared to the existing practice alternative (real control) in the study by Graves *et al.* [26], it was more costly than the 'usual care'. Graves *et al.* [26] stated that the 'usual care' group underwent extensive health behavior assessment and it did not appropriately reflect the existing practice that decision makers prefer to use as the comparator for alternate programs. Specifically, the 'usual care' group received a brief intervention that included physical activity. Therefore, Graves *et al.* [26] proposed that improvements seen in the 'usual care' group might have been the result of physical activity. This becomes more likely because, for all dietary outcomes, the improvement seen in the diet-led telephone intervention group at 12 months was significantly greater than that of the 'usual care' group. The 'existing practice' group did not receive any intervention. Robbins *et al.* [27] found that nutrition counselling had better cost and hospitalisation outcomes than diabetes classes. This finding reinforces the need for nutrition intervention not only for the proven better clinical outcomes, but also to reduce hospitalisation rates and associated costs. Wolf *et al.* [28] reported a reduction in absenteeism and presenteeism rates with dietitian-led nutrition intervention. Costs associated with presenteeism have been shown to be five- to 10-fold higher than those associated with absenteeism, across a geographically, culturally and economically diverse set of eight countries [30].

This review has several limitations. First, only a small number of studies met the inclusion criteria, representing populations in just two countries, therefore limiting the generalisability of the findings. However, two of the studies included large sample sizes with some ethnic diversity and thus the findings could be generalisable within the context of countries such as the USA, UK and Australia. Second, two of these studies were retrospective cohort studies rather than randomised trials, offering a lower level of evidence. Because successful nutrition intervention requires behavioural change, greater participation by patients that are ready and willing to receive dietetic counselling and adopt, comply and adhere to MNT intervention may have been more likely to have occurred. Further RCTs are warranted to address this. Third, we restricted our searches to articles in English language and

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thus we may have missed articles published in other languages. Fourth, having conducted a scoping review that aimed to map the current literature, and being consistent with the principles of this type of review, we did not systematically rate the quality of evidence from each study. However, we strove to describe the characteristics of the included studies in detail aiming for readers to understand their methodologic strengths and limitations.

The cost effectiveness of dietetic intervention has been previously investigated in other populations, including people at risk of developing diabetes [31–33], a mixed population of type 1 and type 2 diabetes [34,35], and people with dyslipidaemia [36], as well as in the general population [37,38]. Our scoping review is the first review to assess the cost effectiveness of dietitian-led nutrition intervention in people with type 2 diabetes in developed countries. Our findings, obtained from a small number of studies in only two countries, but with 22 765 participants, indicate the cost effectiveness of dietitian-led nutrition intervention in people with type 2 diabetes. This finding reinforces the importance of advocacy for MNT for people with type 2 diabetes, with respect to alleviating the global economic burden of a condition that is projected to increase from $1.3 in 2015 to almost double that in 2030 [39]. It is also essential to ensure that MNT commences with the diagnosis of diabetes, aiming to prevent the advancement of this condition, because the cost of treating diabetes and its complications at late stages has been shown to be eighteen times the cost at early stages [40].

Future studies should inform the cost effectiveness of MNT in developed countries other than the USA and Australia. Moreover, assessing the cost effectiveness in developing countries warrants exploration. The use of different economic tools and research methods to assess cost effectiveness, even by the small number of studies presented in this review, means that a synthesis of the findings is currently not feasible. Therefore, this scoping review has also identified a lack of uniformity in reporting economic outcomes of dietetic interventions in people with type 2 diabetes. It will be useful for future studies to report economic findings in a standardised way, such as QALYs or Disability-Adjusted Life Years (DALYs), to facilitate the integration of data from across the globe, by conducting robust meta-analyses that will provide the required insight to inform healthcare services planning and funding policies in countries with both private and government-subsidised health systems. Finally, the factors that mediate and moderate cost effectiveness, such as the frequency of visits with the dietitian and the optimal duration of the session to achieve favourable clinical outcomes at the same time as being cost-effective, should be examined.

Conflict of interests, source of funding and authorship

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GS conceived the idea for the review. GS and MAF designed the review protocol. GS and LW searched the literature and extracted the data. All authors analysed and interpreted the data. GS drafted the manuscript. The authors thank University of Sydney's academic liaison librarian for advising with the literature search strategy and assisting with the database searches. All authors critically reviewed and revised the manuscript.

Transparency declaration

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

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dietitian nutritionists for management of dyslipidemia: a systematic review and meta-analysis. *J Clin Lipidol* **12**, 1113–1122.
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Appendix 1
Search strategy for Ovid MEDLINE

1 diabetic* OR diabetes
2 type 2 OR t2 OR tii
3 1 AND 2
4 t2d OR t2dm OR tiid OR tiidm
5 3 OR 4
6 diet* OR nutrition*
7 advi* OR counsel* OR program* OR therap* OR educat* OR interven*
8 6 AND 7
9 5 AND 8
10 cost* OR econom* OR finance* OR fisc*
11 effect* OR effic* OR assess* OR analys* OR evaluat* OR apprais* OR perform* OR success* OR benefit* OR saving* OR valu* OR reduc* OR impact* Or burden* OR incentiv*
12 10 AND 11
13 qualy* OR daly* OR dfly* OR healy* OR qale* OR dale* OR dfle* OR hale* OR pyll* OR icer* OR ceac* OR return on investment* OR return-on-investment* OR roi
14 12 OR 13
15 9 AND 14
16 limit 15 to english language
17 limit 16 to yr='2008 -Current'
18 limit 70 to 'all adult (19 plus years)'

A pilot search was conducted on the 11 March 2020 in Ovid MEDLINE, yielding:

- 1070 records, when no limits applied.
- 1022 records, when the English language limit applied.
- 727 records, when the English language limit and studies after 2008 limits applied.
- 345 records, when the English language limit, studies after 2008 and adult limits applied.

Appendix 2
List of excluded full texts with reasons for exclusion

1. Idris, I. (2015). A review of diet and exercise shown to be cost effective for people with type 2 diabetes. *Diabetes Obesity & Metabolism* **17**: 908.
Reason: Commentary

2. American Diabetes Association (2013). Standards of medical care in diabetes – 2013. *Diabetes Care* **36** (Suppl. 1): S11–S66.
Reason: Guidelines paper

3. American Diabetes Association (2014). Standards of medical care in diabetes – 2013. *Diabetes Care* **37** (Suppl. 1): S14–S80.
Reason: Guidelines paper

4. Agee, M. D., *et al.* (2018). Effect of medical nutrition therapy for patients with type 2 diabetes in a low-/no-cost clinic: a propensity score-matched cohort study. *Diabetes Spectrum* **31**: 83-89.
Reason: No cost effectiveness reported

5. Alkhder, H., *et al.* (2019). To assess clinical and cost effectiveness of an integrated diabetes care model in Solihull (SoLID) general practice. *Diabetic Medicine* **36** (Suppl. 1): 158-159.
Reason: Conference Abstract

6. Al-Maskari, F., *et al.* (2010). Assessment of the direct medical costs of diabetes mellitus and its complications in the United Arab Emirates. *BMC Public Health* **10**.
Reason: No cost effectiveness reported

7. Araja, D., *et al.* (2018). Impact of nutrition-related diseases on public expenditures. *New Challenges of Economics & Business Development*: **111**.
Reason: No cost effectiveness reported

8. Bahia, L. R., *et al.* (2011). The costs of type 2 diabetes mellitus outpatient care in the Brazilian Public Health System. *Value in Health* **14** (5 Suppl.): S137–S140.
Reason: Not in developed country

9. Bhanpuri, N. H., *et al.* (2018). Estimated reduction in medication cost during first year of a continuous care intervention for treatment of type 2 diabetes. *Value in Health* **21** (Suppl. 1): S73.
Reason: Conference Abstract

10. Dalton, J. E. (2008). Web-based care for adults with type 2 diabetes. *Canadian Journal of Dietetic Practice and Research* **69**: 185–191.
Reason: Review – No relevant study after 2008

11. Dave, R., *et al.* (2019). The impact of multiple lifestyle interventions on remission of type 2 diabetes mellitus within a clinical setting. *Obesity Medicine* **13**: 59–64.
Reason: Not in developed country

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12. Davis, R., *et al.* (2011). Cost effectiveness of a telehealth-based diabetes self-management (DSME) intervention in a rural community. *Diabetes* **60**: A325.

Reason: Conference Abstract

13. De Feo, P., *et al.* (2011). An innovative model for changing the lifestyles of persons with obesity and/or Type 2 diabetes mellitus. *Journal of Endocrinological Investigation* **34**: E349–E354.

Reason: Intervention by a multidisciplinary team

14. Delahanty, L. M., *et al.* (2008). Implications of the Diabetes Prevention Program and Look AHEAD Clinical Trials for Lifestyle Interventions. *Journal of the American Dietetic Association* **108** (Suppl. 1): S66.

Reason: No cost effectiveness reported

15. Delahanty, L. M., *et al.* (2020). Effectiveness of Lifestyle Intervention for Type 2 Diabetes in Primary Care: the REAL HEALTH-Diabetes Randomized Clinical Trial. *Journal of General Internal Medicine*.

Reason: Control group also saw the dietitian

16. Delahanty, L. M., *et al.* (2015). Improving diabetes outcomes through lifestyle change – a randomized controlled trial. *Obesity* **23**: 1792.

Reason: Control group also saw the dietitian

17. (2013). Dietitians New Zealand Conference: Increasing the Voice, Impacting the Future, Sky City, Auckland, New Zealand, 1-4 September 2013. *Nutrition & Dietetics* **70**: 1–15.

Reason: Conference proceedings

18. Dunbar, S. B., *et al.* (2015). Randomized clinical trial of an integrated self-care intervention for persons with heart failure and diabetes: quality of life and physical functioning outcomes. *Journal of Cardiac Failure* **21**: 719.

Reason: No cost effectiveness reported

19. Dutton, G. R., *et al.* (2015). The Look AHEAD Trial: Implications for Lifestyle Intervention in Type 2 Diabetes Mellitus. *Progress in Cardiovascular Diseases* **58**: 69–75.

Reason: No cost effectiveness reported

20. Eakin, E. G., *et al.* (2008). The Logan Healthy Living Program: a cluster randomized trial of a telephone-delivered physical activity and dietary behavior intervention for primary care patients with type 2 diabetes or hypertension from a socially disadvantaged community – Rationale, design and recruitment. *Contemporary Clinical Trials* **29**: 439.

Reason: No cost effectiveness reported

21. Early, K. B., *et al.* (2018). Position of the Academy of Nutrition and Dietetics: the role of medical nutrition therapy and registered dietitian nutritionists in the prevention and treatment of prediabetes and type 2 diabetes. *Journal of the Academy of Nutrition and Dietetics* **118**: 343–353.

Reason: Position statement

22. Fuller, N. R., *et al.* (2013). A within-trial cost-effectiveness analysis of primary care referral to a commercial provider for weight loss treatment, relative to standard care – an international randomised controlled trial. *International Journal of Obesity* **37**: 828–834.

Reason: Intervention not led by dietitian

23. Gagliardino, J. J., *et al.* (2012). Patients' education, and its impact on care outcomes, resource consumption and working conditions: data from the International Diabetes Management Practices Study (IDMPS). *Diabetes & Metabolism* **38**: 128–134.

Reason: Not in developed country

24. Goel, A. (2019). In type 2 diabetes, a primary care-led weight management program increased weight loss and diabetes remission at 2 years. *ACP Journal Club* **171**: JC17.

Reason: Letter

25. Griffie, D., James, L., Goetz, S., Balotti, B., Shr, Y. H., Corbin, M., & Kelsey, T. W. (2018). Outcomes and economic benefits of Penn State Extension's Dining With Diabetes Program. *Preventing Chronic Disease* **15**: E50.

Reason: Not clear if intervention delivered by dietitian

26. Grimmer-Somers, K., *et al.* (2010). Enhanced primary care pilot program benefits type ii diabetes patients. *Australian Health Review* **34**: 18–24.

Reason: No cost effectiveness reported

27. Hakeem, R., *et al.* (2008). Efficacy of dietetics in low resource communities: dietary intake and BMI of type 2 diabetics living in Karachi before and after receiving dietician's guidance. *Pakistan Journal of Biological Sciences* **11**: 1324-1329.

Reason: No cost effectiveness reported

28. Howatson, A., *et al.* (2015). The contribution of dietitians to the primary health care workforce. *Journal of Primary Health Care* **7**: 324–332.

Reason: Review – No relevant study after 2008

29. Huckfeldt P.J., *et al.* (2019). 347-OR: The long-term effects of an intensive lifestyle intervention on medicare outcomes. *Diabetes* **68** (Suppl. 1)

Reason: Oral presentation

30. Kirkman, M. S., *et al.* (2012). Diabetes in older adults. *Diabetes Care* **35**: 2650–2664.

Reason: No cost effectiveness reported

31. Kogut, S. J., *et al.* (2012). Evaluation of a program to improve diabetes care through intensified care management activities and diabetes medication copayment reduction. *Journal of Managed Care Pharmacy* **18**: 297–310.

Reason: Control group also saw the dietitian

32. Laiteerapong, N., *et al.* (2018). Individualized glycemic control for U.S. adults with type 2 diabetes: a cost-effectiveness analysis. *Annals of Internal Medicine* **168**: 170–178.

Reason: Economic modelling

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33. Lammers, M., *et al.* (2012). Cost-benefit analysis of dietary treatment. SEO Report No. 2012-76A. *SEO Economic Research*.

Reason: Review – Does not contain any relevant study published after 2008

34. Lean, M. (2011). VLED and formula LED in the management of type 2 diabetes: defining the clinical need and research requirements. *Clinical Obesity*: 41–49.

Reason: No cost effectiveness reported

35. Nerat, T., *et al.* (2016). Type 2 diabetes: cost-effectiveness of medication adherence and lifestyle interventions. *Patient Preference and Adherence* **10**: 2039–2049.

Reason: Review – No relevant study after 2008

36. Randolph, S., *et al.* (2010). Economic analysis of a diabetes-specific nutritional meal replacement for patients with type 2 diabetes. *Asia Pacific Journal of Clinical Nutrition* **19**: 1–7.

Reason: Economic modelling

37. Shurney, D., *et al.* (2012). Chip lifestyle program at Vanderbilt university demonstrates an early ROI for a diabetic cohort in a workplace setting: a case study. *Journal of Managed Care Medicine* **15**: 5–15.

Reason: Control group also saw the dietitian

38. Signorovitch, J., *et al.* (2014). Which newly-diagnosed diabetics should receive dietary counselling services? Estimating individualized treatment allocations that optimize cost-effectiveness in real-world data. *Value in Health* **17**: A358.

Reason: Conference Abstract

39. Singh, K., *et al.* (2018). Cost-effectiveness of interventions to control cardiovascular diseases and diabetes mellitus in South Asia: a systematic review. *BMJ Open* **8**.

Reason: Not in developed country

40. Smith, E. (2014). Effectiveness and cost-effectiveness of providing a local dietetic service to general practitioner (GP) practices for people with Type 2 diabetes and those at significant risk of developing hyperglycaemia. *Diabetic Medicine* **31**: 94–94.

Reason: No cost effectiveness reported

41. Sullivan, S. D., Dalal, M. R., & Burke, J. P. (2013). The impact of diabetes counseling and education: clinical and cost outcomes from a large population of US managed care patients with type 2 diabetes. *The Diabetes Educator* **39**: 523–531.

Reason: Not clear if intervention delivered by dietitian

42. Suseelal, T., *et al.* (2017). A study to assess the cost effectiveness of home based education programme among clients with diabetes mellitus (DM) at selected villages in Kancheepuram district, Tamil Nadu, India. *International Journal of Pharmaceutical Sciences and Research* **8**: 3552–3556.

Reason: Not in developed country

43. Urbanski, P., *et al.* (2008). Cost-effectiveness of diabetes education. *Emerging Trends in Diabetes Prevention and Control – Applications to Practice*. **108** (Suppl. 1): S6–S11.

Reason: Review – No relevant study after 2008

44. Wang, H., *et al.* (2019). Cost-effectiveness analysis of comprehensive intervention programs to control blood glucose in overweight and obese type 2 diabetes mellitus patients based on a real-world setting: Markov modeling. *Annals of Translational Medicine* **7**: 676.

Reason: Not in developed country

45. Wilson, K. J., *et al.* (2015). Cost-effectiveness of a community-based weight control intervention targeting a low-socioeconomic-status Mexican-origin population. *Health Promotion Practice* **16**: 101–108.

Reason: Economic modelling

46. Xin, Y., *et al.* (2019). Cost of the counterweight-plus weight management programme to achieve diabetes remission and its one year cost-effectiveness: results from the diabetes remission clinical trial (DiRECT). *Diabetic Medicine* **36** (Suppl. 1): 92.

Reason: Intervention by a multidisciplinary team

47. Xin, Y., *et al.* (2019). Type 2 diabetes remission: economic evaluation of the DiRECT/Counterweight-Plus weight management programme within a primary care randomized controlled trial. *Diabetic Medicine* **36**: 1003–1012.

Reason: Intervention by a multidisciplinary team

48. Xin, Y., *et al.* (2019). Within-trial cost and 1-year cost-effectiveness of the DiRECT/Counterweight-Plus weight-management programme to achieve remission of type 2 diabetes. *The Lancet. Diabetes & Endocrinology* **7**: 169–172.

Reason: Intervention by a multidisciplinary team

49. Yu, D. H., *et al.* (2017). Population-level impact of diabetes integrated care on commissioner payments for inpatient care among people with type 2 diabetes in Cambridgeshire: a postintervention cohort follow-up study. *BMJ Open* **7**.

Reason: Intervention not led by dietitian.

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Appendix 3
Reported conflicts of interest and funding sources

Study	Conflict of interest statement	Funding	Funding details	Conflict of interest exists
Dalal *et al*. (2014)	'Dr. Dalal is an employee of, and Dr. Sullivan is a consultant for, Sanofi U.S. Mr. Robinson is an employee of Premier, Inc., which received funding from Sanofi U.S. to carry out this work.'	Industry	Sanofi US	Not known
Graves *et al*. (2009)	'The authors have declared that no competing interests exist.'	Non-industry	National Health and Medical Research Council (NHMRC) Project Grant #290519, and by a Queensland Health Core Research Infrastructure Grant and NHMRC Program Grant funding (#301200). 'The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.'	No
Robbins *et al*. (2008)	No	Non-industry	National Institute of Diabetes, Digestive, and Kidney Diseases (grant #R21DK064201)	Not known
Wolf *et al*. (2009)	No	Non-industry	Grants from the American Dietetic Association, National Institute of Diabetes and Digestive and Kidney Diseases (R18 DK062942) and a grant to the University of Virginia General Clinical Research Center, MO1 RR00847	Not known

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DIETETIC PROFESSION

Do images of dietitians on the Internet reflect the profession?

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Keywords
authentic, dietitian, images, Internet, perception, recruitment.

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Abstract

Background: The image of dietitians presented on the Internet shapes public perception of the profession, which in turn may influence engagement with professionals. The aim was to describe the portrayal of the dietetic profession on the Internet and how this aligns with international professional demographics.
Methods: In this cross-sectional observational study, images appearing in two Google image searches using the word 'dietitian' were analysed for content by two independent researchers. A coding framework was used to identify personal characteristics of professionals and others presented in the image, as well as the work setting. These were compared to demographic data of members of professional associations in Australia, the United Kingdom (UK) and the United States of America (USA).
Results: The dietitian portrayed in the images (n = 339) was most often female (88%), Caucasian (72%), aged between 26–39 years (63%), pictured alone (78%), pictured with food (78%) and in a setting that could not be determined (76%). The age and gender profile presented matches the characteristics of the international workforce; however, there was an absence of images illustrating dietitians in authentic work roles.
Conclusions: The images resulting from an online search for 'dietitian' do not fully illustrate the profession. There are opportunities to create and share authentic images online that show the breadth of work roles and diversity of professionals' age, gender, cultural background and size.

Introduction

Internet usage has rapidly increased from 2000 onward, with 53.6% of the global population, or 4.1 billion people, estimated to use the Internet in 2019 [(1)]. Reflections from leaders in the Academy of Nutrition & Dietetics describe the dramatic impacts that these technological advances have had on society, including in the provision of healthcare and food systems [(2)]. The importance of digital literacy within the curriculum and the increased demand for dietitians who have technological expertise highlight the translation of the digital age into the profession [(2)]. The need for dietitians to shape the technological future that we desire has also been noted, including the need for the profession to utilise higher-level skills and services that cannot be automated or programmed into expert systems [(2)].

With such high usage, the Internet provides a medium for the public to identify information and images of nutrition professionals, which influences their perception and engagement with the profession. Lordy and Dubè [(3)] report that 50% of dietetic students chose dietetics as a career based on information sourced from the media (print, television, radio and Internet communication). This is not surprising given that students making university entry decisions may fall into the 17–30 year age range, so called 'digital natives' [(4)]. The Internet is also a key source of health information, with 70% of adults in the USA turning first to the Internet [(5)].

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Data from a representative sample of US adults found that 25% reported to know 'a lot' about the role of a dietitian, whereas 10% reported knowing 'a lot' about what a nutrition scientist does [6]. A favourable view among participants was reported by 51% towards nutrition scientists and 60% towards dietitians [6]. Other researchers have suggested that the role of the dietitian to those outside healthcare is not clearly defined beyond the profession. Researchers have previously reported that 26% of the public consider that dietitians distribute and collect hospital menus, whereas 21% think that dietitians prepare meals in hospital [7]. Dietitians compete with celebrity chefs, fitness professionals, wellness bloggers and influencers as the 'face' of nutrition expertise in the public space. Self-concept and professional identity are derived from public image, work environment and values [8], and so it is important that our Internet presentation reflects the profession. Improving the public profile and perception of dietitians has been identified as the number one priority for the profession [9]. Intervening and shaping how nutrition professionals are represented on the Internet is one way of achieving this.

Previous research has investigated the presentation of healthcare professionals on the Internet. Kalisch *et al.* [10] found that nurses were largely represented on websites as intelligent and educated, and as having specialised knowledge and skills [10]. Analysis of online images by Koo *et al.* [11] identified that nurses were mostly female and Caucasian. They were predominately represented to be caring for patients or documenting information, with a lack of images of nurses undertaking non-clinical tasks (e.g. research and education) [11]. In the 10 most viewed YouTube clips representing nurses, researchers identified three identity types: a skilled knower and doer, a sexual plaything, and a witless incompetent [12]. Hence, stereotypes of nurses were both favourable and derogatory. Content analysis of websites determined that the speech pathology profession was predominantly presented as a female providing individual therapy [13]. Narrow professional demographics and client groups (e.g. paediatrics) were portrayed.

To our knowledge, no previous rigorous assessment of the dietetics profession on the Internet has been undertaken. The present study aimed to describe the portrayal of the dietetic profession on the Internet and how this aligns with international professional demographics.

Materials and methods

This was a cross-sectional observational study, with online searches of images from Google (https://www.google.com) conducted at two time points, 17 months apart. Images were analysed using a deductive content analysis methodology to classify what they portrayed [14]. This approach has been successfully completed to analyse Internet images of speech pathologists [13] and nurses [10,11].

Ethical approval

The Human Research and Ethics Committee at Monash University confirmed that ethics approval was not required because the data were publically accessible and no humans or animals were involved.

Search strategy

Google images was searched for images retrieved using the term 'dietitian'. Although there are two common spelling variations ('dietitian' and 'dietician'), the spelling of 'dietitian' with a *t* was used. This term is officially correct [15] and is utilised by the professional dietetic associations in Australia, the USA and the UK. Additionally, users searching 'dietician' are prompted by Google to search for 'dietitian' instead.

The searches were completed in Australia in February 2018 (search 1) and again in July 2019 (search 2). The searches were conducted in 'incognito' mode, when signed out of personal Google accounts to avoid the influence of past searches and personalisation on the results. No restrictions (e.g. image size, region, file type, usage rights) were applied in the search settings of Google. One researcher (RS) conducted the first search and another researcher (SA) conducted the second search.

Coding process

The first 250 images in Google were considered. Images were copied into EXCEL 2013 (Microsoft Corp., Redmond, WA, USA), where data management, coding and analyses occurred. Analyses occurred at the time when the searches were conducted.

Two researchers (RS & JP search one; SA & JP search two) independently coded each image using a predetermined coding framework. Discrepancies were resolved by a third researcher (JC). Images that did not depict a professional were recorded and counted for data management purposes, although they were excluded from the coding process.

The coding framework (Table 1) was developed by two researchers (JC, JP) based on a framework used in a previous study of Internet images of speech pathologists [13]. The final coding framework consisted of four items that described the age, gender and ethnicity of the professional, the number, age and gender other individual/s (if present), accessories (e.g. equipment, technology) and the type of work depicted. Ethnicity of professionals was only

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Table 1 Coding framework used to analyse images from the internet portraying dietitians

Item	Data collected or coding options
Image	Copy of actual image Image URL
Image source	1 = personal page; 2 = nutrition or dietetic service; 3 = university or professional association webpage; 4 = stock image; 5 = other
Does the image include a dietitian?	1 = yes; 2 = no (no further coding)
Characteristics of the dietitian	
Sex	1 = male; 2 = female; 3 = cannot determine
Age	1 = under 25 years; 2 = 26–39 years; 3 = 40–55 years; 4 = over 55 years; 5 = cannot determine
Ethnicity	1 = Caucasian; 2 = Black; 3 = Asian; 4 = other ethnicity; 5 = cannot determine
Work setting	1 = bed-based clinical (includes public and private hospital); 2 = ambulatory clinical (including community health, private practice, group education); 3 = academic/research; 4 = industry; 5 = other setting ; 6 = cannot determine
Characteristics of others in the image	
Number	1 = none; 2 = individual; 3 = group
Sex	1 = male; 2 = female; 3 = cannot determine
Age	1 = baby; 2 = child (2–17 years); 3 = young adult (18–25 years); 4 = 26–39 years; 5 = 40–55 years; 6 = over 55 years; 7 = combination; 8 = cannot determine
Accessories	
Technology	1 = yes; 2 = no
Medical equipment	1 = yes; 2 = no
Lab equipment/attire	1 = yes; 2 = no
Cooking equipment/attire	1 = yes; 2 = no
Food	1 = yes; 2 = no
Books/clipboard	1 = yes; 2 = no
Other	1 = yes; 2 = no

determined where the individual's face was visible. Adjustments were made to the original framework [13] that was geared towards therapy (i.e. professional-client consult), aiming to ensure that the broad range of work completed by dietitians was captured. Code options for age and work setting were based on categories of data provided by professional associations, aiming to ensure that images were coded in a manner that allowed for meaningful comparison with actual demographic data. Code options for accessories were based on common items appearing in images identified in preliminary searches. In addition to the coding framework, the source of each image (e.g. personal page, industry-based organisation, university, stock image, etc.) was recorded.

Demographic data

Demographic data of the dietetic profession were sought to enable a comparison of images with the demographics of the dietetic workforce internationally. The British Dietetic Association, Dietitians Association of Australia and the Academy of Nutrition and Dietetics in the USA were contacted in February 2018 to request aggregate data on the characteristics of their membership.

Statistical analysis

Descriptive characteristics (number, percent) were calculated in EXCEL to identify the portrayal of the professional, other individual(s) (if present), accessories and work setting in the images, at each time point.

Results

Image selection

Overall, of the 500 Google images retrieved, 339 (n = 170 images from search 1; n = 169 from search 2) contained an image of one or more dietitians and were analysed for content (Figure 1). This included two images that were a collage of four images, and another comprising a collage of two images that were considered separately for coding analysis.

Descriptive characteristics

The majority of Google images retrieved in the search were from websites advertising dietetic/nutrition services (154/332 images; 46%) followed by 'other' sources including online news and magazine articles (87/332 images; 26%), personal blogs/newsletters (59/332 images; 18%), stock images (17/332 images; 5%) and university or professional association web content (15/332 images; 5%).

Findings

The content analysis of images is summarised in Table 2. Some images contained more than one dietitian, resulting in a total of 355 professionals analysed from the 339 images (n = 175 professionals from search 1; n = 180 search 2). The majority of professionals (n = 355) in all images retrieved were female (88%), aged 26–39 years (63%) and Caucasian (72%) (Table 1). Characteristics could not be fully determined for up to one-fifth of

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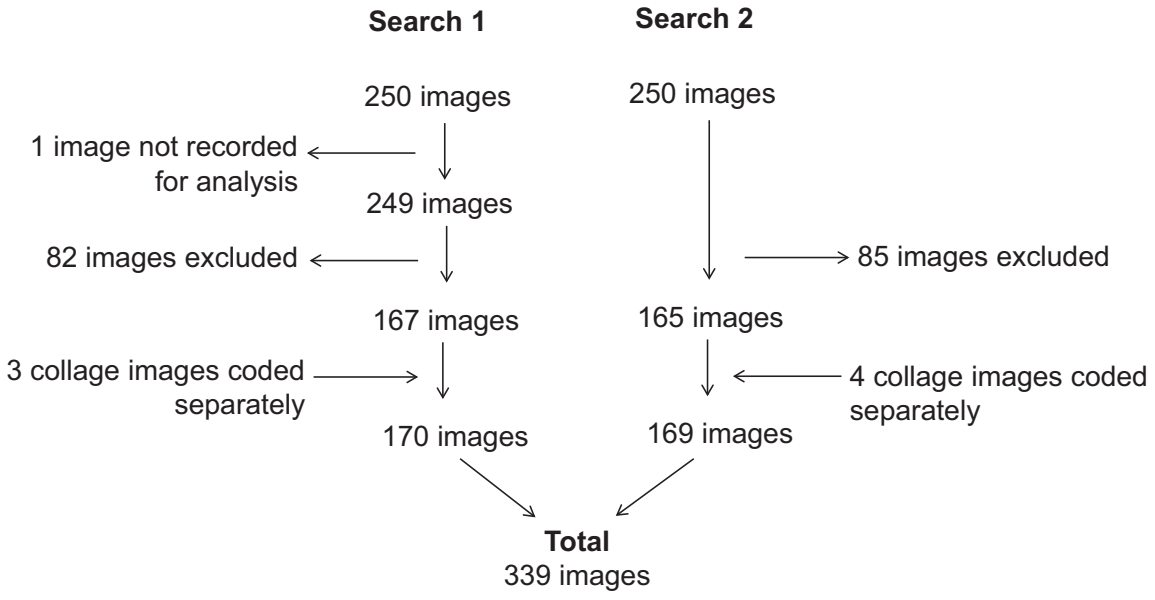

Figure 1 Flow diagram of image selection process.

professionals presented in images. Excluding these increased the proportion of young, white, female dietitians in images. Ninety percent of professionals in images where gender was apparent (n = 346) were female and 10% were male. When age could be determined (n = 289), 3% were < 25 years, 77% were 26–39 years, 18% were 40–55 years and 2% were >55 years old. Of the 287 images able to be assessed for ethnicity, 89% were Caucasian, 2% were black, 8% Asian and 1% were of other ethnicities.

The gender profile of dietitians from Australia, the UK and the USA (Table 3) was inconsistent with content of Google images, with a higher percentage of males presented than indicated in the membership of professional associations. The majority of dietitians were reported to be aged 26–39 years (Table 3) and this was the most common age of professionals portrayed in images, however, a much lower proportion of dietitians aged 40 years and over were represented in images than the proportion in the actual workforce (Table 3).

The work setting depicted could not be determined in the majority of images (76%) because most images appeared to be staged profile shots of a professional rather than candid images of dietitians at work. As such, these images were generic and gave no indication of the work setting. For the images that did capture a dietitian in the workplace, they were more likely to be in the ambulatory clinical setting (e.g. outpatient consultation, private practice consultation) than the inpatient setting, despite this being the most common employment setting in the US and the UK (Table 3). There were also very few images of dietitians engaged in academic or research roles, again not depicting the contribution of the membership.

Where images depicted the dietitian accompanied with someone else (19%), a female adult was the most common person illustrated. They often were illustrated as a client or a colleague. Approximately four out of every five images (78%) portrayed food in the image with the dietitian; this was the most common prop or accessory depicted. Images also commonly portrayed dietitians with medical equipment (31%) (usually a stethoscope), laboratory equipment or attire (41%) (usually wearing a lab coat) or books and/or a clipboard (35%).

Discussion

The present study aimed to investigate whether images of dietitians presented on the Internet match the reality of the dietetic profession. In an era where Internet enabled devices are constantly within arms' reach, the images that we encounter online influence our perceptions and opinions of a subject area. The results indicate that an online search for 'dietitian' yields images that are not a full and accurate depiction of the profession. Dietitians were mostly portrayed as young females, which is line with characteristics of the workforce in Australia, the US and the UK. However, their work roles were poorly illustrated, hampering a true representation of the wide scope of practice of nutrition professionals. These findings are in keeping with published research on images for nursing [10] and speech pathology [13], professions also portrayed in the form of a narrow stereotype that is not in keeping with the current reality.

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Table 2 Characteristics of dietitians portrayed in images (n = 339) from the Internet

	Search 1, *n* (%)	Search 2, *n* (%)	Total *n* (%)
Gender of professional	*n* = 175	*n* = 180	*n* = 355
Male	17 (10)	18 (10)	35 (10)
Female	154 (88)	157 (87)	311 (88)
Could not determine	4 (2)	5 (3)	9 (2)
Age of professional	*n* = 175	*n* = 180	*n* = 355
Under 25 years	7 (4)	0 (0)	7 (4)
26–39 years	109 (62)	114 (63)	223 (63)
40–55 years	27 (15)	26 (14)	53 (15)
Over 55 years	5 (3)	1 (1)	6 (2)
Could not determine	27 (15)	39 (22)	66 (19)
Ethnicity of professional	*n* = 175	*n* = 180	*n* = 355
Caucasian	130 (74)	124 (69)	254 (72)
Black	3 (2)	3 (2)	6 (2)
Asian	13 (7)	10 (6)	23 (6)
Other	1 (1)	3 (2)	4 (1)
Could not determine	28 (16)	40 (22)	68 (19)
Work setting depicted	*n* = 170	*n* = 169	*n* = 339
Bed-based clinical	5 (3)	1 (1)	6 (2)
Ambulatory clinical	29 (17)	38 (22)	67 (20)
Academic/research	2 (1)	2 (1)	4 (1)
Industry	2 (1)	4 (2)	6 (2)
Could not be determined	132 (78)	124 (73)	256 (76)
Number of others in the image	*n* = 170	*n* = 169	*n* = 339
None	133 (78)	132 (78)	265 (78)
One (individual)	31 (18)	34 (20)	65 (19)
More than one (group)	6 (4)	3 (2)	9 (3)
Gender of others in the image	*n* = 37	*n* = 37	*n* = 74
Male	13 (35)	11 (30)	24 (32)
Female	17 (46)	23 (62)	40 (54)
Combination of male and female	6 (16)	2 (5)	8 (11)
Could not determine	1 (3)	1 (3)	2 (3)
Age of others in the image	*n* = 37	*n* = 37	*n* = 74
Baby	0	0	0
Child 2–17 years	5 (14)	4 (11)	9 (12)
Young adult 18–25 years	0	0	0
26–39 years	9 (24)	4 (11)	13 (18)
40–55 years	6 (16)	5 (14)	11 (15)
Over 55 years	6 (16)	15 (41)	21 (28)
Combination	3 (8)	1 (3)	4 (5)
Could not determine	8 (22)	8 (22)	16 (22)
Accessories in the image*	*n* = 170	*n* = 169	*n* = 339
Technology	24 (14)	21 (12)	45 (13)
Medical equipment	48 (28)	56 (33)	104 (31)
Laboratory equipment/attire	59 (35)	81 (48)	140 (41)
Cooking equipment/attire	37 (22)	29 (17)	66 (19)
Food	138 (81)	127 (75)	265 (78)
Books/clipboard	50 (29)	70 (41)	120 (35)
Other	40 (24)	22 (13)	62 (18)

Bed-based clinical includes public and private hospital. Ambulatory clinical includes community health, private practice, group education.
*Categories are not mutually exclusive; each item was coded as yes or no.

In dietetics, a number of factors add a layer of complexity to the image of the profession. Our personal experience across many years of practice is that dietitians are commonly considered by the general public as someone whose job is to help people lose weight. Furthermore, the relationship between food, health and body weight means that there may be an expectation that dietitians are thin. Although eating disorders have been reported to be more

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Table 3 Characteristics of dietitians in Australia, United Kingdom and United States

Country	Characteristic	
Australia* (n = 6515)	Gender n (%)	
	Male	363 (6)
	Female	5490 (84)
	No answer	662 (10)
US† (n = 6461)	Gender n (%)	
	Male	237 (4)
	Female	6118 (95)
	No answer	106 (1)
	Years of age n (%)	
	Under 25	123 (2)
	26–39 years	2873 (44)
	40–55 years	1766 (27)
	Over 55 years	1662 (26)
	No answer	37 (1)
	Primary work setting n (%)§	
	Bed-based clinical	2198 (36)
	Ambulatory clinical	1440 (23)
	Academic/research	407 (7)
	Industry	254 (4)
	Community or public health	411 (7)
	Government/non profit agency or professional association	576 (9)
	Foodservice	320 (5)
	Other	529 (9)
	Not reported	8 (0)
UK¶ (n = 9200)	Gender %**	
	Male	4%
	Female	96%
	Years of age n (%)	
	Under 25	863 (9)
	26–39 years	3842 (42)
	40–55 years	2769 (30)
	Over 55 years	1036 (11)
	No answer	690 (8)
	Primary work setting %**	
	National Health Service	65%

*Data provided by DAA in February 2018 for their membership, no information available on age or work setting.
†Data from *Compensation & Benefits Survey of the Dietetics Profession 2017* Exhibit 7.04, 7.05, 7.17 for Registered Dietitian Nutritionists (RDNs) currently employed in a nutrition/dietetics-related position.
§% calculated using denominator of n = 6144.
¶Data provided by BDA in February 2018 for their membership.
**Data provided as percentage only, data on other gender or work setting categories not available.

prevalent in dietitians compared to the general population [16], our observations are that dietitians work across a range of practice settings and that body composition comprises a range of shapes and sizes. Although assessing the physical appearance of those captured in the Internet images was beyond the scope of the present study, 'thin, young, pretty, white and female' broadly describes the images identified in this research.

The representation of dietitians attired in white lab coats or with laboratory equipment occurred in over one-third of the images. The white coat may have become synonymous with a clinician as a result of pop-culture references (e.g. US medical-based TV shows) depicting medical doctors dressed in this way. Although medical doctors in the US do wear white coats, we have spent time in healthcare settings in Australia, the UK and the US, and have not observed dietitians doing so.

There was also a limited diversity in ethnicity, where 89% of professionals in images were Caucasian. Comparisons could not be made with international membership information because ethnicity data are rarely collected. However, compared with the similar image study of nurses

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where 66.1% were Caucasian [11], more could be done to promote the cultural diversity of the dietetic profession.

The limited number of images representing dietitians in academic and research roles is also problematic. This finding is consistent with a previous study in nursing where scientific activities such as research were absent in stock images [11]. Recent research has shown an increasing academic output from dietitians [17–19], and this should be represented through authentic images of research across settings. Additionally, the majority of images were staged photographs of an individual posing with fresh fruit and vegetables. Although dietitians' work often relates to nutrition, food and diets, there are very few work settings in the modern day where dietitians actually handle food as a core task.

Misconceptions of the image of health professions have a range of consequences, including the impact on health-seeking behaviours of the public and recruitment and retention within the profession. Prospective students who do not see a similarity between themselves and people depicted in dietitian images may be less likely to choose nutrition and dietetics as a career if they perceive they will not fit. This is a factor contributing to lack of gender and cultural diversity across the profession. Dietetic services are provided to many individuals (and groups) of diverse backgrounds[20], as such, diversity within the profession is needed.

The data obtained from professional associations in the present study indicated that there continues to be a relatively small proportion of males in the profession. Literature in nursing has identified that society's perception of nursing is the most commonly identified barrier to the entry of males into nursing [21]. A qualitative study of male dietitians undertaken in Canada reported males' feeling different and their need to adapt to a female dominated culture, as well as the need to construct their unique professional identity [22]. Although the images of males in the present study were proportionally higher than the membership data, the need for marketing of the profession to enhance equality and diversity within dietetics was included as a recommendation for developing the dietetic workforce of the future in the UK [9].

Cultural diversity in the profession may also be limited by the public perception of the dietitian and the findings of the ethnicity analysis undertaken in the present study. Research undertaken in minority and male dietitians in the 1990s reported that lack of knowledge about the profession, lack of role models and a view of the profession as 'closed' were some of the main reasons why minority groups were under-represented [23]. This research, as well as that of Suarez and Shanklin [24], recommended that visibility of dietetics needed to be increased to attract prospective students from minority groups.

The Internet provides an opportunity to improve both the image and knowledge of the scope of practice of dietitians to a mass audience. Increased visibility and true representation of the profession is needed. This is now particularly important with the rise of alternate nutrition experts: celebrity chefs, fitness professionals and wellness bloggers.

More dietitians need to seek and take up opportunities to promote their work in the media. A larger sample size will naturally lead to a more diverse representation; however, in the short term, positive discrimination or incentivisation for 'non-traditional dietitians' (e.g. male, older or culturally diverse individuals) to engage in media opportunities may be useful. There is a role for professional associations to provide adequate media and communication training, as well as for members to support and unite with their peers who choose to take up media roles. Microcredentials and other short courses post-qualification could also provide the support needed for practitioners to more actively engage in media opportunities.

We need to consider a less polished and more authentic 'look'. Social media presents an opportunity to disseminate still or moving images, alone or alongside written content, to a broad and large audience. 'Live' platforms, such as Facebook live or Instagram and Snapchat 'stories', as well as videos and images on Twitter, can be used to offer a 'real life' snapshot of dietitians going about their day-to-day tasks.

Social media campaigns showcasing real dietitians appear impactful because they harness the collective communication power of the profession to reach a wide audience with a united message. The #WhatDietitiansDo photo competition run by the British Dietetics Association for dietitians in 2019 and 2020 is a standout example of professional leadership to illustrate the diversity of the profession [25]. Future research should catalogue the image of dietitians in social media (e.g. Instagram, twitter, Facebook, YouTube) to complement this research.

Longitudinal change using data from the present study as a baseline will provide an indicator of the success of these strategies. Diversity in people and settings, as well as images that authentically present the dietetics profession, can best showcase the true work carried out by dietitians.

Strengths and limitations

Because the coding process was subjective, it was influenced by the position of those undertaking the work. All researchers were nutrition professionals, and therefore analyses occurred through the lens of individuals with knowledge and experience of the profession. It is unclear whether others (e.g. members of the public) would classify images of dietitians in the same way. The researchers

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were two students studying Nutrition Science (RS) and Dietetics (SA), a qualified dietitian with over 20 years of experience in research, clinical dietetics, management and teaching (JP), and a qualified dietitian with 9 years of experience in research, clinical dietetics, foodservice and teaching (JC). The different levels of experience of the researchers strengthened the trustworthiness of the content analysis. Coding was completed in duplicate by two researchers and checked by a third, which further enhanced rigour. Web searches were conducted in Australia and, as such, the results may be influenced by local Internet traffic restrictions.

Conclusions

The representation of dietitians on the Internet does not reflect the true picture of practising dietitians. The age and gender profile is similar, although there are discrepancies between the work settings of dietitians that may be fostering a stereotype of a dietitian to prospective students and clients that does not align with reality. Dietitians can increase their engagement with the media, including through sharing and promoting authentic images of themselves in the workplace, aiming to rectify the mismatch between the Internet representation of dietitians and reality.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

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JC and JP conceptualised the study. JP coded data and JC verified codes. JC and JP wrote the manuscript. Both authors approved the final copy of the manuscript submitted for publication.

Transparency declaration

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

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DIETETIC PROFESSION

Digital disruption of dietetics: are we ready?

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Abstract

Digital health is transforming the delivery of health care around the world to meet the growing challenges presented by ageing populations with multiple chronic conditions. Digital health technologies can support the delivery of personalised nutrition care through the standardised Nutrition Care Process (NCP) by using personal data and technology-supported delivery modalities. The digital disruption of traditional dietetic services is occurring worldwide, supporting responsive and high-quality nutrition care. These disruptive technologies include integrated electronic and personal health records, mobile apps, wearables, artificial intelligence and machine learning, conversation agents, chatbots, and social robots. Here, we outline how digital health is disrupting the traditional model of nutrition care delivery and outline the potential for dietitians to not only embrace digital disruption, but also take ownership in shaping it, aiming to enhance patient care. An overview is provided of digital health concepts and disruptive technologies according to the four steps in the NCP: nutrition assessment, diagnosis, intervention, and monitoring and evaluation. It is imperative that dietitians stay abreast of these technological developments and be the leaders of the disruption, not simply subject to it. By doing so, dietitians now, as well as in the future, will maximise their impact and continue to champion evidence-based nutrition practice.

Introduction

Seventeenth-century German scientist Georg Christoph Lichtenberg is famous for his proclamation, 'I cannot say whether things will get better if we change; what I can say is they must change if they are to get better'. This assertion has never been more relevant for today's health systems with respect to managing the complications of a rapidly ageing global population with multimorbidity [(1)]. With the majority of disease burden attributable to modifiable lifestyle factors, such as poor diet and physical inactivity [(1)], health and social care services face a considerable challenge in how to meet medical, lifestyle and personal health needs of populations they serve. A daunting challenge for healthcare managers is how to provide the required care in a scalable, clinical and cost-effective way, within finite budgets. One strategy to mitigate the burden on healthcare systems has been to empower individuals to self-manage their health, through health system and service delivery innovations [(2)].

Digital health has been around for the last two decades in the form of medical informatics and simple telehealth, but it is only within the past 5 years that there has been a proliferation of literature on this topic [(3)]. Digital health employs routine and innovative forms of information and communications technology to address health needs and remotely deliver effective health interventions [(4)]. Digital health includes electronic health (eHealth), such as standalone and web-based software; mobile health (mHealth) such as smartphone applications (apps), text messaging

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programs and wearable devices; health information technology; telehealth/telemedicine; electronic medical records (EMRs); and emerging areas such as the use of advanced computing sciences in big data, genomics and artificial intelligence [4]. Digitally enabled systems, comprising health systems that are adopting technology to help improve the quality, delivery and management of patient care, have the potential to transition our healthcare model to harmonise primary and secondary care with self-management as the central pillar.

Here, we outline how digital technologies are disrupting the traditional delivery of nutrition care and how dietitians can embrace the digital world to support delivery of the Nutrition Care Process (NCP).

Dietetics in the digital world

It has been two decades since the *Journal of Human Nutrition and Dietetics* published 'Dietitians and the Internet: are dietitians embracing the new technology?' [5]. It provided fascinating insights and a yardstick to the subsequent digital disruption that has occurred since. It was found only 66% of dietitians had Internet access in the workplace and, perhaps even more tellingly, only 13% of dietitians reported seeing information obtained by patients from the Internet [5]. Fast-forward 20 years and we are not discussing *if* dietitians are using 'new' technology, but *how* dietitians can shape the development and implementation of technologies to leverage their expertise and improve patient outcomes [6]. The recent British Dietetic Association (BDA) workforce strategy for Dietetics 2020–2030 calls on dietitians to embrace advances in science and technology alongside a growing recognition that this will re-define how dietitians develop and deliver medical nutrition therapy [7]. Ubiquitous and almost limitless access to information is transforming dietetic roles from being gatekeepers of nutrition knowledge to facilitating and motivating patients to access and implement scientifically sound, evidence-based care. Technology has advanced exponentially over the last 20 years, with cost and barriers to access dropping considerably [8,9], resulting in dietitians and patients now surrounded by an increasingly digital, highly connected world. As a result of increasing connectivity to 5G wireless networks, portable smartphone devices with various applications, integrated EMRs, and telehealth, the consequent increasing complexity brings opportunities for dietetics to innovate and support patients with respect to managing their own nutrition (an overview of digital technologies that can complement the NCP is provided in Fig. 1).

The proliferation of available technologies for healthcare delivery in recent years continues to expand in the context of COVID-19 and its immediate impact on dietetic practice. Some innovations showcase the potential for dietetic practice to be improved via digital health. For example, from 2017 onwards, dietitians in the UK have had access to free, on-demand webinars (www.patientwebinars.co.uk) for patients, as part of their treatment and/or education on specific gastroenterology conditions [10]. In the past 6 months, this resource has been used across the UK by primary care practices and dietetic departments. Furthermore, during the shutdown of traditional service delivery as a result of COVID-19, dietitians worldwide have turned to telephone and video consultations to deliver high-quality nutrition care, services that are comparable to face-to-face delivery modalities [11]. This rapid adoption of virtual care has been supported by policy change in many jurisdictions, to pave the way for a future where this practice is commonplace [12].

Despite these recent advancements, the literature indicates that the adoption of technology into healthcare practice has been relatively slow in recent years. Although dietitians typically use face-to-face consultations, patients may be more interested in technology-assisted consultations [13]. A 2019 survey by Abrahams *et al.* [14] demonstrated that most dietitians did not consider technology to play an important role in their current practice. This may be the result of a lack of e-readiness [15], training and professional development, remuneration, or exposure to the opportunities that it provides to enhance the efficiency and delivery of patient-centred care [11].

This year, an editorial in the *Journal of Human Nutrition and Dietetics* clearly outlined that dietitians who do not adopt or understand the transforming digital dietetics landscape run the risk of being replaced [6]. It is therefore paramount that dietitians be the leaders of this digital disruption, rather than be subject to it. We believe that this is a critical time in our profession to ensure dietetic services remain relevant and supported in digital healthcare futures, at the same time as ensuring practice is underpinned by a robust evidence base.

Digital health records and the Nutrition Care Process

EMR is a digital form of patient records that allows for both current and historic assessment information to be collected seamlessly [16] and has proven efficient in the documentation of administrative and clinical processes for healthcare purposes. EMRs result in improved dietitian access to nutrition information, increased numbers of resolved nutrition diagnoses, and an enhanced capacity and efficiency of dietetic services [17].

Despite increasing use of electronic, Internet-enabled records (over 50% annually since 2013) [18], coordination gaps remain, such as a lack of interoperability across

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Figure 1 Digital technologies to compliment the Nutrition Care Process. Each '!' on the peripheral represents barriers to address for wider adoption in primary and secondary care. BP, blood pressure; ECG, electrocardiogram; PREM, patient-reported experience measures; PROM, patient-reported outcome measures.

multiple digital health platforms and systems, as well as technical barriers experienced by clinicians [19,20]. The growing adoption of personal health records is assisting with addressing this problem, giving patients the ability to access, manage and share their health information, as well as that of others for whom they are authorised, in a private, secure and confidential manner [21]. Personal health records differ from standard EMRs and have already been implemented in many countries, including Australia, Austria, Denmark, Estonia, Finland, France, Norway and Sweden; in the USA, they are variably offered through private health providers [21].

Digitally disrupting nutrition assessment

Digital health lends itself well to enhancing nutrition assessment by leveraging the plethora of technologies on the market, including smartphone apps, sensors and wearables, together with drawing relevant data from EMRs and cloud computing systems.

Chen *et al.* [22] highlight how dietitians can make use of mobile apps in nutrition assessment; for example, to track patients' body weight and/or blood glucose levels, their activity through a pedometer and exercise diary, and for documenting dietary intake [22]. Key conclusions from

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the review highlighted that mobile apps have great potential to complement nutrition care delivered by dietitians and enhance the efficiency of the nutrition care process, allowing more time for counselling patients [22]. The Pt-Global app is a nutrition assessment app that facilitates simple and systematic nutrition risk screening using the validated Patient-Generated Subjective Global Assessment (PG-SGA) for interventional triaging, and for nutritional monitoring during and after intervention [23]. However, nutrition-related apps must be utilised correctly (i.e. users record data accurately) and contain evidence-based algorithms to be effective, and so they are not considered appropriate for standalone use. However, when combined with dietitian prescription, critical thinking and monitoring, these apps may support individualised, patient-centred nutrition care [22].

Wearable devices, defined as infrastructures that interconnect technology with wearable sensors through wireless connections [24], offer a simple and non-invasive mechanism to inform nutrition assessment. Wearables typically sync with a software system or mobile app that can be used to digitally exchange nutrition assessment parameters. Examples of wearables that may assist nutrition assessment are summarised in Fig. 1 and include: wireless tracking of body weight (via Bluetooth connected scales or weight tracking mobile apps) [25], continuous glucose monitors and smart insulin pens (that track dose/time and recommend correct insulin type/dosage) [26], smartwatches (e.g. Apple watch) and activity monitors (e.g. Fitbits; tracking activity, heart rate, sleep patterns), vital sign patches (that wirelessly track and monitor a patient's heart rate, respiration, temperature, steps taken, sleep cycle, stress levels, and whether a user has fallen or otherwise become incapacitated) [27], wireless electrocardiogram monitors [28], and wearable blood pressure monitors [29].

Technology-based methods for dietary intake assessment have also been systematically evaluated. A review found that one-third of such tools used image-based methods and two-thirds used integrated databases to estimate energy or nutrient intakes using predominantly self-reported data [30]. In addition to mobile apps to assess dietary intake [22], technology-assisted dietary assessment includes web-based methods in individuals with and without disabilities [31] and automated electronic methods among low income adults [32]. Some devices have been proposed to automatically scan and track dietary intake [33] and analyse food diaries for their nutrient profiles using machine learning algorithms by photographing meals [34]. One novel hybrid dietary assessment tool currently under development (Voice-Image-Sensor technologies for Individual Dietary Assessment; VISIDA) uses an image-voice food record app, wrist sensor, web-based analysis platform and machine learning models, and will undergo iterative development and piloting in low income countries [35].

The validity of apps for nutrition assessment is important for dietitians to consider. Studies have shown that dietary assessments conducted through mobile phones and nutrition apps have similar validity and reliability [36,37]. Pedometers and activity trackers can reliably collect activity measures for structured ambulatory activity; however, have low validity for predicting energy expenditure [38]. By contrast, the accuracy, clinical validity and quality of mobile health apps for blood glucose monitoring in diabetes management require further scrutiny [39]. It is important to acknowledge that many of the available commercial health apps may not be validated and are not endorsed by reputable authorities [40] and seldom include evidence-based behaviour change techniques [41].

It is important for dietitians to understand the availability and benefits of these technology-assisted nutrition assessment tools. The main barriers to virtual nutrition care delivery include difficulties in taking accurate anthropometric measurements and identifying clinical signs of nutrient deficiencies [42]. The imperative for dietitians to be abreast of such technology is recognised by professional agencies such as the BDA via strategic partnerships [43] to assist dietitians in understanding how to leverage digital health to support and improve their practice [6]. Libraries of apps are also becoming widely available to support dietitians in providing evidence-based digital resources and suggestions for devices and mobile apps in their practice (Table 1). If dietitians require patients to collect nutrition assessment data using technology, they should also engage with patients prior to the consultation to outline what technology needs to be downloaded or installed. Next, patients should be shown how to record anthropometric measurements using home-scales, pedometers and wearables, or told how to request such measurements to be taken by other practitioners working in the patient's location.

Digitally disrupting nutrition diagnosis

Many programs and computer software platforms exist for guiding dietitians in making an appropriate nutrition diagnosis, as recently overviewed by Chen *et al.* [22]. Some promising technologies being used to inform nutrition diagnosis are artificial intelligence (AI) and deep machine learning. AI has the capability to read EMR data via text recognition with natural language processing, including medical history, medications, and results from physical assessments, imaging and pathology, as well as contextualise it to generate diagnosis and/or treatment decisions and possibilities [44]. There have been calls for the

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Table 1 Selected mHealth databases, resources and frameworks to evaluate and implement evidence-based digital care

Framework/online resource	Description
The mobile Nutrition Care Process grid (mNCP framework) *Australia* [22]	The mNCP was designed to support dietitians in their use of apps and technology throughout the NCP
Framework for evaluating app quality and utility *Australia* [40]	This preliminary framework has been developed to enable government agencies and decision makers to decide which apps should be endorsed and which could then be recommended with confidence by clinicians to their patients
The Handbook of Non-Drug interventions (HANDI) is a tool available to general practitioners *Australia* [115]	HANDI includes electronic resources for nutrition interventions in primary care such as diet pattern interventions, low FODMAP diets, weight control, allergy prevention and nutrition in pregnancy, all of which is evidence-based and has been developed by the HANDI Project team Although HANDI is targeted towards general practitioners, this platform is an example of an evidence-based database with patient resources that can be used to improve nutrition and patient outcomes. In the future, mHealth platforms, programs and resources may be added to HANDI (or a similar database), which dietitians can use to facilitate education interventions in practice
The NHS Apps Library *UK* [87]	The NHS Apps Library is an evidence-based library of health apps that can be used across health disciplines to prescribe appropriate apps to patients App developers can use the framework provided to answer a range of required digital assessment questions, designed to ensure only safe and secure apps and digital tools are published on the NHS Apps Library
Orcha health app reviews and prescription services *UK* [86]	Orcha is a private initiative in UK which evaluates and grades health apps and has a web-based platform for practitioners can subscribe to (for a fee) Although this is not as rigorous as scientific evaluations in the literature, it is a practical tool with app prescription advice and portal services and is an example of a digital platform that can assist clinicians in making informed decisions on app prescriptions for their patients
Nutritools database of validated dietary assessment tools *UK* [116]	Nutritools is an expert-led website which hosts a details library and resource bank of validated interactive dietary assessment tools for research and clinical practice, for both dietitians and other clinicians to access
Patient webinars *UK* [118]	Patient webinars is an online resource providing access to reliable nutrition information from qualified dietitians. Recorded webinars are provided free and on-demand for patients as part of their treatment and or education on specific gastroenterology conditions such as IBS, coeliac disease, IBD In addition, there are webinars on the Patient Webinars website (https://patientwebinars.co.uk) spanning, advice for children, constipation, diabetes, food allergy, kidney health and malnutrition – with each newly developed webinar submitted to the BDA for endorsement
The American Psychiatric Association's App Evaluation Model *USA* [117]	The App Evaluation Model can be used across (all) health disciplines to evaluate the evidence, usability, functionality of an app to improve health behaviour

BDA, British Dietetic Association; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; HANDI, Handbook of Non-Drug interventions; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; mNCP, mobile Nutrition Care Process; NCP, Nutrition Care Process; NHS, National Health Service.

development of algorithm-driven decision-aid technology in nutrition; for example, in predicting the risk of malnutrition using blood biomarkers [45]. However, despite great promise in dietetics, there are limited examples to date of AI and deep learning are being used to predict nutrition diagnoses.

We only need to look at the uptake and application of AI and deep learning in the wider medical literature to find examples of traditional human tasks being automated by computer-driven AI. Recent studies show how elements of chronic disease management can be improved through AI; for example, one study has demonstrated that deep learning of EMR data can predict risk of disease progression, future medical outcomes and care decisions in diabetes and mental health [46]. Such technology could be used to streamline nutrition diagnosis by collating information already captured in EMRs such as anthropometric, biochemical, clinical and nutrition care data, and then using it to predict nutrition diagnoses.

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Digitally disrupting nutrition intervention

Effective nutrition interventions rely on individual behaviour change. The principles of long-term behaviour change and maintenance are well recognised and include motivation, self-regulation, access to resources (both psychological and physical), habit formation, and environmental and social influences [47]. Technology-assisted dietetic services, including telephone/video consultations, on-demand webinars, mHealth and eHealth, comprise intervention delivery modalities particularly useful for facilitating behaviour change and improving chronic disease self-management [48-52] and are slowly seeing uptake in clinical systems [53,54]. Text-message programs delivered by dietitians are reported to be effective at improving dietary behaviour in people with cardiovascular disease [55,56], and web-based nutrition interventions have been shown to improve dietary behaviour among patients with obesity [57] and type 2 diabetes [58]. Similarly, community-based dietetic mHealth and eHealth interventions have demonstrated the capacity to improve dietary behaviour in single studies among people with type 2 diabetes [59], hypertension [60], chronic kidney disease [61] and eating disorders [62]. Although these interventions have the potential to improve a variety of health-related behaviours both in hospital- and community-based dietetic services, it is important to note there are a similar number of studies suggesting these interventions may not be effective [63-66]. Hence, larger and more robust clinical trials are needed to confirm the clinical benefits of these methods in practice before integration into usual care systems.

The ubiquitous nature of technology means that consumers have greater access to digital resources than ever before [67]. A 2015 survey demonstrated that 58% of smartphone users had downloaded a health-related app for their lifestyle self-management [68]. Natural language processing, AI and machine learning have also driven increased availability of point-of-care health information such as chatbots, which can provide lifestyle and medical advice through conversational interactions with the user. There are many established AI chatbots commercially available; for example, Woebot, Your.MD, Babylon and HealthTap, where patients can input their symptoms and advice is generated instantly [69]. Nutrition-specific examples are emerging too, such as Health Hero [70], Tasteful Bot [71] Lark [72] and Forksy [73], which all provide tailored nutrition advice using AI algorithms via Facebook messenger or smartphone app platforms.

Smart voice assistants or conversation agents, such as Amazon Alexa and Google Home, are being increasingly used to support people at home via AI-driven conversations. Interactive conversations with smart voice assistants may enable patient-centred and patient-engaged approaches to care, which can empower and motivate patients to take more control of their health [74]. A limited number of trials have evaluated smart voice assistants for behaviour change purposes. A systematic review of conversational agents in healthcare showed these agents are commonly used for both patient support (providing education and training for health-related aspects of their lives) and clinician support (used to autonomously conduct clinical interviews with diagnostic purposes in mental health and sleep disorders, as well as assist with data collection and decision support in referral management) [74]. One randomised controlled trial found that a conversational agent improved targeted health behaviours, including fruit and vegetable intake (+3 serves per day), compared to a control group [75]. Another study evaluated an automated and interactive telephone program designed by dietitians to improve Dietary Approaches to Stop Hypertension (DASH)-diet adherence among African Americans with hypertension. Significant improvements in diet quality, fibre intake and daily energy expenditure were found, along with trends towards reductions in blood pressure and improved medication adherence, however no differences were observed between intervention and control groups and uptake was modest (15%) [76]. This highlights the importance of including end-users in the design of technology-assisted models of care.

In the not too distant future, AI and machine learning may be used to conduct rapid quality improvement projects and analyse outcome data captured by dietitians through NCP terminologies. Hypothetically, variations in nutrition interventions used in standard clinical practice could be evaluated in real time, with the potential for algorithms to inform recommendations for the most appropriate nutrition intervention for each clinical case. This is an example of a move towards precision nutrition, which can further personalise recommendations [44], at the same time as supporting dietitians in complex clinical decision making via electronic decision pathways [77].

Digitally disrupting nutrition monitoring and evaluation

Routine self-monitoring encourages self-efficacy and motivation and is therefore important for long-term behaviour change. Digital health has the potential to improve self-monitoring behaviours by collecting live health information that can facilitate remote reviewing and monitoring. Similarly, the implementation and adoption of personal health records allows individuals to share health data with their dietitian, which can be used to track and evaluate nutrition- and health-related goals.

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Mobile apps are another efficient way to track diet and health data, with over 60% of dietitians working in various practice areas (including both private practice and hospital) using mobile apps with their clients to record food intake and track progress [78-80]. Digital health also offers the opportunity to facilitate collection of patient-reported outcome and experience measures (PROMs/PREMs) [81], which can be used to enhance nutrition review and evaluation [82]. As automation and computer systems advance, PROM and PREM data may disrupt the NCP further. For example, electronic patient-reported data have potential to flag patients needing further support or monitoring, and additional intervention modification may be possible through AI and deep learning based on PROMs and PREMs inputs recorded in the system.

Digital tools can allow dietitians to remotely monitor and evaluate nutrition care outcomes and advance nutrition research and evidence-based practice. One example is the Academy of Nutrition and Dietetics Health Informatics Infrastructure (ANDHII) [83]. ANDHII is an electronic web-based tool that could potentially enable efficient evaluation of NCP chains in large datasets. A feasibility study showed that dietitians could use the platform with negligible impact on their practice time, at the same time as ensuring evidence-informed practice [84]. Wider adoption of platforms with similar capabilities as ANDHII will continue to occur, saving time and automating many tasks involved in monitoring and evaluating the NCP. Other technologies to engage patients in monitoring their own nutrition are also emerging, such as a program that allows patients to track their dietary intake alongside their individual nutrition requirements from the hospital bedside [85]. This not only encourages patient-centred and patient-driven care, but also could enable finite dietitian time to be directed to more high value clinical activities by allowing patients to conduct simple tasks themselves (e.g. recording their own dietary intake). Future nutrition monitoring and evaluation modalities may involve deep machine learning and/or AI algorithms to detect appropriate monitoring parameters in EMR and generate suggested review times. As dietitians embrace these technologies, we are likely to see more effective use of dietitian time and the efficient evaluation of nutrition interventions, supporting the advocacy for workforce funding and technology-supported models of care.

Digital dietetic frameworks and resources

Nutrition care supported by mHealth appears to be a highly accepted, safe and effective way to support self-management among people with chronic conditions [50,51], causing some groups to recommend the wider adoption of digital nutrition interventions. Numerous online databases, resources and frameworks are available to support health professionals to select, implement and evaluate mHealth technologies (as summarised in Table 1).

The active role of dietitians will never be lost to machines; however, the dietetic profession will need to adapt to these digital education delivery platforms in ways that may challenge conventional service delivery. Just as it is the responsibility of dietitians to maintain contemporary knowledge on clinical evidence in their area of practice, dietitians will be increasingly required to be aware of available technology and the evidence underpinning its use. Organisations such as ORCHA [86] and the National Health Service (NHS) Apps Library [87] are valuable for dietitians to access knowledge of what is available and evidence-based (Table 1). Professional organisations also recognise their critical role in ensuring dietitians stay abreast of current technology, and are also making resources and training more available; for example, practice guides, webinars and resources [88-90], as well as position statements [11]. If dietetic professionals stay up to date with this growing evidence base, future interventions may well include provision of evidence-based digital resources, devices and mobile apps.

Tertiary programs must consider the professional training the next generation of dietitians need so that they are be equipped with the skills and confidence to deliver high-quality nutrition care using technology in the era of digitally disrupted healthcare systems. Appropriate and effective use of technology in practice is a key competency outlined in many international dietetics training standards, including Australia [91], Canada [92] and the UK [93]. These standards also emphasise the need for education on the use of digital health technologies for patient education and counselling, as well as throughout other important areas of professional practice. Integrating digital heath skills in undergraduate dietetic teaching, or as continuing professional development, has been shown to improve understanding of concepts essential for using technology-supported mediums [94].

Barriers: equity, data security, software and policy considerations

Although technology presents endless opportunities for the dietetic profession, we must be aware of inherent inequities that may occur. Such challenges include healthcare systems' budgets and whether individuals can afford/have access to technology hardware or reliable phone/Internet services as result of financial disadvantage. For example, it may not be appropriate for a dietitian to ask a patient to purchase a wearable, or download an app if they cannot afford one or have limited mobile/internet usage

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allowances. This highlights the need for carefully considered research into telehealth tools and technology-supported models of care that considers the advantages and disadvantages of minority groups (whom generally lack representation in telehealth research), ensures equal access and overcomes literacy barriers to engaging underserved communities; otherwise, there will be a significant danger of perpetuating or escalating current disparities [95].

An important environmental enabler of digital health implementation is policy support. Many countries have digital health policies in place, or are in the process of developing them; for example, Australia, China, France, Germany, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sweden, Thailand, the European Union, the USA and Vietnam currently have relevant policies in place for eHealth and/or the Internet of Things for healthcare [96,97]. The UK created a digital health action framework in 2014 to support frontline staff, patients and citizens with respect to taking better advantage of digital health technologies in practice [98] and this has subsequently seen a number of supporting policies [99]. The World Health Organization reports that over 66% of countries have at least one health information system policy, 58% have an eHealth policy or implementation strategy and over 25% have policies for telehealth [100]. In addition, the World Health Organization maintains an updated directory of relevant digital health policies for each country in its online database [101]. Digital health applications that support clinical decision-making processes often require medical device approval [102] and strong policy surrounding these approvals is required. As such, resources are available in certain countries to support developers in designing digital devices that meet regulations [103,104].

Implementing digital health services is only possible when widely accepted and adopted by consumers, clinicians and health systems collectively. One of the biggest barriers to this scaled implementation comprises concerns around data safety and confidentiality. For example, one 2016 study showed that many mobile apps' manifest file privacy declarations did not match those in the source code, raising questions around app quality and highlighting potentially negative impacts on the safety and reliability of mHealth-related applications [105]. Further questions exist concerning who owns, can view and controls the health data stored on cloud services, suggesting that the use of digital health systems requires careful strategic planning and transparent guidelines.

The interoperability of digital health devices and systems presents another threat to wider adoption of digital health services. Semantic interoperability refers to the ability for digital devices to communicate and exchange information with each other, which is necessary for the sharing of nutrition tracking information with EMRs and also for big data techniques to support decision-making processes [106]. There has been significant effort made in recent years to introduce international standards across health technology platforms, with organisations such as Health Level Seven (HL7) International leading the way with the Fast Health Interoperability Resources (FHIR) [107]. FHIR aims to accelerate the interoperability between EMRs and mHealth solutions and thus increase access to health data for large scale analytics [108]

Finally, remuneration for dietetic services delivered via technology has historically been challenging for dietitians and the wider health community [109,110]. Many countries such as Australia, Canada, China, Italy, UK and United States [12,111-114] have recently (and temporarily) adopted remuneration policies around virtual care (telehealth) in response to COVID-19. These efforts to reduce barriers to telehealth implementation underscore the potential to reframe traditional models of dietetic interventions into virtual and distance modalities [12]. Future evaluations will give insight into the long-term policy decisions of telehealth-delivered dietetic services. However, these policies do not include asynchronous digital health modalities (one-way communication at any time; e.g. text messaging and web-portals), which means these services still require fee-for-service models in practice. It is time for decision makers and private health payers to strongly consider the evidence for expanding telehealth to include mHealth and eHealth. These technologies can be used alongside telephone or video conferencing modalities or in-person delivery because they improve access to effective nutrition services and support people with chronic conditions to optimise their diet-related health and well-being, regardless of their location, income or literacy level.

Conclusions

There are many examples of effective technology-supported dietetic programs that can enhance the delivery of medical nutrition therapy as part of the Nutrition and Dietetic Care Process, aiming to improve dietary and clinical outcomes for patients and populations. To achieve widespread adoption of digital nutrition care interventions, issues of data security, policies and regulations, interoperability and remuneration require attention. The digital disruption of traditional NCP delivery is here, we call on dietitians around the world to be the leaders of this disruption, not the subject of it. It is imperative that dietitians stay abreast of technological developments and understand how digital health can be used to support and improve their current practice, ensuring that dietitians remain effective and are the champions of evidence-based nutrition care.

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Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. This is a narrative review and no reporting guidelines were used. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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OBESITY AND WEIGHT MANAGEMENT

Exploring the role of social support and social media for lifestyle interventions to prevent weight gain with young adults: Focus group findings

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Keywords
social media, young adults, overweight and obesity, lifestyle, social identity theory, social influence model of consumer participation.

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Abstract

Background: Young adults gain more weight annually than other adults and may be destined for future obesity. Effective interventions are needed, and social support may be a key element for success. The present study explores how best to leverage social media to support young adults with their health goals in a healthy lifestyle programme.
Method: Young adults aged 18–25 years were recruited from the community to a series of four focus groups led by an experienced facilitator who used a discussion guide developed *a priori*. The discussion explored their opinions regarding which social media platforms were appropriate for providing social support, the types of support that were relevant (family and friends versus strangers) and factors that would encourage peer-to-peer communication in a healthy lifestyle intervention. Sessions were audiotaped, transcribed and analysed using the qualitative software, NVIVO, version 11 (QSR International Pty Ltd., Melbourne, VIC, Australia). Themes were generated using an inductive approach informed by the Theory of Social Identity and Social Influence Model of Consumer Participation.
Results: Thirty-three people (12 male) participated. Facebook was the most popular platform for facilitating social support as a result of its private group capabilities and already being embedded into their daily routines. The preference was to be grouped with strangers who shared similar goals in smaller groups of participants. The discussions highlighted the integral role of a credible and relatable health coach to serve as a mentor, mediator and role model.
Conclusions: The learnings from this research will be applied to optimise engagement within social media support groups in lifestyle interventions.

Introduction

Young adults in countries such as the UK, USA and Australia are an at-risk group for unhealthy weight gain.[1,2,3] The period of transition from childhood through adolescence and young adulthood is frequently characterised by less healthy behaviours, such as poor diet quality, decreases in physical activity and binge drinking.[4,5] Qualitative research suggests generic public health messages around healthy eating and exercise are unappealing to young adults.[6] Lifestyle interventions specifically tailored for young adults and using communication delivery channels with which they engage are suggested solutions to this apparent failure to reach them.[7]

Social support from family and peers is one key component of health behaviour change including weight management.[8–12] In the past decade, researchers have attempted to harness social networking sites for healthy lifestyle interventions both as the sole means of intervention delivery[13] or to provide additional social support to participants via coach and peers.[14–19]

A recent review of social media use in behaviour change interventions found that functions for peer grouping improved perceptions of social support and social

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support coping.[20] This reinforces the important role of social networking platforms in interventions to provide peer support rather than be restricted to delivery of information.

Early attempts at using social media for peer interaction in lifestyle interventions among adolescents and young adults used blogs or discussion boards as platforms for social support, finding limited engagement and efficacy of the lifestyle-related outcomes.[14,17,21] More recent research has harnessed modern social networking sites such as Facebook and Twitter.[15,16,22] However, active peer-to-peer engagement through commenting and sharing posts remains poor and declines over the length of the intervention with these media. Passive behaviours such as viewing and liking informative posts shared by a health professional are more common.[23,24]

Clearly, further research is needed to determine how to effectively employ social networking features to provide social support in lifestyle interventions and promote peer-to-peer engagement among young adults. This includes developing a better understanding of the preferred platforms for delivery, the types of support, and from whom they desire social support be it existing networks with friends or family or new networks. Given that past studies have found limited and short-term engagement with peer interaction in groups that include all an intervention treatment arm, some discussion around size of groups, as well as composition, is indicated.[18,19]

Thus, the current research aims to gather opinions of young adults (18–25 years) on the types of social support that would be helpful to them during a healthy lifestyle intervention to better understand the role social media may play. Focus group methods offer an opportunity for participants to interact with each other to consider similar and opposing views. Some consensus may be reached, although divergent opinions can also be expressed in the respectful environment created by the facilitator.[25] These focus group attributes are in common with the ideas for social media support groups. Thus, focus groups were the preferred approach to gain understanding of the complex reasons for young adults' attitudes and opinions. The present study also includes an investigation of the perceived advantages and disadvantages of leveraging social media for providing social support and determining what factors would motivate young adults to actively share their own material and interact with material of other group members.

Materials and methods

Sample

Young adults aged 18–25 years were recruited from across the greater Sydney area, Australia. Flyers were placed around university campuses and advertisements emailed to young adults registered on a volunteer list for research participation. Interested participants completed an online screener, supported on the Research Electronic Data Capture (REDCAP) secure platform,[26] for eligibility and those meeting the selection criteria were contacted by a member of the research team to organise a focus group. Consent for participation was collected online at the end of screening. To be eligible, participants needed to have experienced unwanted weight gain, be interested in changing their diet or physical activity to prevent further gains and promote wellbeing, and be regular users of social networking sites. No exclusions based on body mass index or health status were imposed. They did not need previous participation in any lifestyle programmes either online or face-to-face. Young adults who were currently or previously had undertaken a degree in a health-related area such as nutrition, exercise physiology or occupational therapy were excluded. Consecutive sampling was used until data saturation was achieved with no new ideas generated during a focus group. An AUD $50 gift voucher was provided to participants at the conclusion of the focus group as compensation for their time and travel expenses.

Design

The procedure of the focus groups was approved by the Institutional Human Research Ethics Committee (approval number 2018/890). The Consolidated criteria for reporting qualitative studies (COREQ) checklist has guided the writing of this manuscript.[27] Each focus group ran for approximately 60 min and was led by an experienced female researcher (PhD and credentialed dietitian) with an additional dietitian researcher observing at three of the four sessions. The focus groups were held in three locations in Greater Sydney to attract a more representative sample. The method used to facilitate the session was informed by the procedures outlined by Kruger and Casey.[28]

The focus groups explored views on three key areas: (i) the types of social support that would be helpful during a healthy lifestyle intervention and by whom; (ii) the perceived advantages and disadvantages of social media as a platform for social support including preferred platform; and (iii) factors that would motivate young adults to actively engage within an online social support group. A predetermined prompt sheet with open-ended questions based on the main research issues was used by the group moderator to guide a semi-structured group discussion (see Supporting information, Table S1). Upon arrival, participants were briefed with the focus group objectives and a succinct introduction. They were asked to consider the scenario that they were part of a healthy lifestyle

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programme giving them access to a health professional coach via phone to support them to attain their goals. Each discussion began by prompting participants to reflect on an appropriate online/electronic platform that could be used to allow participants in the lifestyle programme to support each other.

Analysis

The discussions were audio-taped and transcribed once all the focus groups had been conducted. The identity of focus group participants was withheld from transcripts and they were not circulated to participants for further comment.

The thematic analysis was conducted in six stages in accordance with Braun & Clarke's framework.[29] To begin, each transcript was reviewed twice by the main coding researcher and early impressions were documented. The transcripts were then loaded into coding software, NVIVO, version 11.0.0.317 (QSR International Pty Ltd., Melbourne, VIC, Australia). An open coding system was used so that, as similarities in participant observations emerged, they were clustered together under a code. For example, comments regarding mobile apps as a communication platform were grouped under a separate code to comments made about social media platforms. Codes were refined and modified during a second round of transcript analysis. The researcher then progressed to the third stage of analysis in which codes sharing commonalities were clustering into overarching themes. For example, all of the codes regarding communication platforms were thematically categorised under the theme 'appropriate platforms for social support'. These themes were then reviewed to ensure they were coherently distinct from one another. The fifth step of the qualitative analysis procedure involved formulating a descriptive summary for each theme, interpreting the key message and selecting representative quotes that highlighted participant views. If opposing opinions were found, example quotes presenting these exceptions were included. A second researcher read all transcripts and checked the coding, organisation of themes and representative quotes. In the final stage, the two researchers provided an interpretative description of the key themes under subheadings interpreted in the context of two existing theories, Social Identity Theory[30] for forming social groups and Social Influence Model of Consumer participation[31], which derives in part from the former theory, and is used to explain participation in virtual communities.

Results

One hundred and sixteen people completed the screener and 75 were eligible and contacted to confirm attendance at one of the focus group locations. Thirty-nine participants could not attend a group at the nominated times or locations and three failed to attend on the day. In total, 33 young adults (12 male) attended one of the four focus groups conducted between January and February 2019. Groups ranged in size from seven to 11 persons. Thirteen out of 28 participants who provided their education level had completed university, five had trade qualifications and 10 had completed high school. Regarding socio-economic status (SES), 14 were of higher SES, 10 were lower SES and five were middle SES, with four not reporting SES. Only two participants reported they had prior experience with a lifestyle programme. One had joined a telephone coaching service and the other joined a large Reddit online community discussion website as an observer.

Major themes

Major themes that emerged from the focus groups were categorised under five key subheadings with two themes split into sub-themes: (i) defining social support -purpose of social support and friends and family versus strangers; (ii) appropriate platforms for social support; (iii) cultivating functional groups – role of health professional and group size; (iv) factors motivating peer engagement; and (v) advantages and disadvantages of social support through social media. The findings generated were examined for convergence with Social Identity Theory[30] that hypothesises behaviour among social groups relates to their need to differentiate themselves from others and see their group in a positive way, and the Social Influence Model of Consumer Participation[31] that builds from the former theory. Explanations in terms of other theories have been introduced as required.

Defining social support

Purpose of social support

Participants reflected that the key purpose of engaging in a social support group while participating in a lifestyle intervention was to receive feedback from peers and the professional health coach. This aligns with Social Identity theory[30] and The Social Influence Model of Consumer participation[31] that posit value is added to the individual with approval as a result of contributing to the group. Furthermore, other stated purposes of sharing the journey with like-minded people to maintain motivation throughout the programme and posting personal goals, achievements and milestones within the support group to receive encouragement and inspiration to overcome challenges is also recognised within The Social Influence Model of Consumer participation. Sharing of common goals (group

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norms) within virtual communities would increase willingness to participate.

> 'Just say you're trying a different type of exercise and you want to see who else this is working for, or is this the appropriate thing and you get responses from the coach and your peers' (Female)

> '... If I am with people who are supportive and encouraging, then maybe I would want to do something' (Female)

> '... At least you would have some support there, like you can see where you are at and where your mates are at' (Male)

> 'Milestones ... steps along the way to achieving your larger goal. Just how your day went, the ups and downs and something like that' (Female)

The role of friends and family versus strangers

Predominantly, these young adults preferred to be supported by strangers rather than people within their existing networks such as friends and family. They suggested being grouped with strangers provided a sense of anonymity and greater level of comfort to share their progress with their health goals. Social Identity Theory explains the importance of maintaining a positive identity and comparisons within your group should reinforce that identity. Friends or family were viewed as judgmental. Thus, the theory suggests that if the group reacts in a way to create a negative self-identity then the individual seeks an alternate group, as would appear to be the case here and indicates why they align with strangers rather than with friends. A small number of participants suggested they would value the opportunity to be supported by a friend who also joined the programme, although this suggests the friend has similar goals and is non-judgmental within the group and derives a positive self-identity themselves from belonging to the group.

> 'When they are strangers you feel more comfortable about disclosing your failures and that is more relatable' (Female)

> 'It's a safe space, because you probably don't know anyone in there so you can post honestly about your failures ...' (Female)

> 'I prefer if my friends and family were not part of the group, because that way I could speak more freely. Generally I enjoy a bit of anonymity that online platforms offer' (Male)

Appropriate platforms for social support

Facebook was the most popular communication medium for facilitating social support because it was embedded in their lives and preferable to using and learning an additional new platform such as a dedicated mobile application (app). Other modes of communication such as websites (e.g. Reddit) were discussed but they did not emerge as preferred platforms. It was stated that Snapchat or Instagram, although popular, would not be suitable for creating a record of comprehensive information. Participants also disregarded the use of emails as social support because they often ignored or deleted messages. Consistent with the Technology Acceptance Model,[32] approval of the platform was determined by 'ease of use' and viewed as useful.

> 'I think in the past I have had separate apps for all different things, but I never tend to use them. So I think integration into an app that I already use, something like Facebook ... rather than an external app where I have to go into to check' (Male)

> '... Here is the problem with using an app, you will take some time to learn the interface, so it's better to have a Facebook private group because you are familiar with the interface' (Male)

Cultivating functional groups

Role of the health professional coach

The health professional coach was seen as a pivotal part of the lifestyle intervention and social support. The role of the coach was to be a mentor to guide and motivate group members through the process of achieving their lifestyle goals and a role model who inspired them. The authenticity of the coach centred around his/her own experiences in achieving health, consistent with Social Identity Theory and inter-group constructs around similar values and goals.

> 'because this person is going to help you achieve your goal, knowing what their goal was and how they achieved their own goal and that they are capable ... that would be important' (Female)

> 'Somebody who is not just perfect all the time, because that is often the image portrayed on social

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media, like they always eat healthy, they are always exercising well and doing all these things' (Female)

'... the health coach is a genuine person that is actually succeeding and not just this team of people who have come together to show you how you can do it' (Male)

The credibility of the coach as a source of relevant and valid information was viewed as critical. Source Credibility Theory explains how the persuasiveness of a communication is somewhat dependent on the perceived credibility of the source.[33] Hence, the coach needs to be expert to ensure the validity of the shared group information.

'lead and continue the conversation, to give the validation. They can also help relate the other people's posts to the rest of the community' (Male)

'I think it would be important for me to know the qualifications of the person. I feel like in the world of health, there are a lot of people making things up' (Male)

Although less commonly raised in discussion, some male participants felt that they would only be able to relate to a male health professional coach but the young females did not see gender as important for building rapport with the coach.

Group size

The Social Influence Model of Consumer participation introduces two categories of consumers groups in virtual communities those who prefer large network-based and those preferring small-group based.[31] The small group has similar beliefs, and so the values of the group have a large influence, whereas, in the large group, the self-values play a greater role because the closeness, agreement and belonging are less. A shared sense of purpose becomes influential in a smaller group creating higher levels of motivation to engage than would appear to come from the large network and hence likelihood of sharing becomes more in small groups. Twice as many participants were in favour of small groups rather than a large group (50 or more members), because a small group would generate a sense of belonging to a community. Many participants expressed their concern that, if a group was too large, their voice would not be heard because their posts would be dispersed among the excessive content shared. However, a minority stated that they liked the anonymity of the large group, suggesting group sizes ranging from 50 to 1000 participants. This might also allow them to gain a greater depth of insight and opinions from many different people.

'I would want the group to be small enough that you could actually get to know people. It is not like you turn up every week and there is someone new' (Female)

'Smaller group you can get more input, but bigger group it is hard to control how content is shared' (Male)

'I have chosen the larger group, because I have joined the group to get different opinions from different people, like I said from 50–200 means you can have diversity in the group, so like you get the suggestions and opinions' (Male)

Group categorisation

Participants indicated that, to facilitate greater social support, people should be categorised into groups according to their health goals and/or similar sociodemographic such as their profession. This suggestion is in keeping with Social Identity Theory and the Social Influence Model of Consumer participation that people will form in groups with like characteristics and goals.[30,31] It was suggested that students be grouped with others at their institution and, for workers, similar professions should be grouped. Others suggested that grouping participants according to their local area would enable greater connectedness by providing an opportunity for in-person meet-ups to exercise together or attend local health-related events with the group. Other suggestions were to group participants according to food preferences and dietary habits (e.g. vegan, love of cooking).

'Different demographics will have different goals. I would probably have different goals to a professional businessman, so being in the same group as them, I wouldn't be able to relate to what they post. Whereas if it was someone similar to me doing the same thing, I would be inspired by what they are doing' (Male)

'... also a good thing would be a sort of geographical categorisation, so that way, if you go to the same gyms ... like I would be open to meeting up in real life with people' (Female)

Factors motivating peer engagement

In all groups, the idea of an orientation session to allow members of the social support group to meet in-person,

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get to know each other and discuss the aims of the group emerged as enabling creation of a safe social media environment. Such a group would allow participants to engage in peer-to-peer interaction to support each other.

> '... I think it would make me more engaged on the online side of things if I knew them' (Female)

About half the young adults in each focus group indicated they tend to be 'silent lurkers' or 'observers' on social networks. When prompted to express what would encourage them to engage in conversation within an online support group, they indicated that it would be important for members to share personal stories. Social Influence Model of Consumer Participation indicates that motivation comes from a strong sense of identifying with the group. Regular validation by peers would enable engagement. This would include posting about personal successes or failures, daily challenges and progress and growing the sense of belonging. It was noted commenting and providing support to others could be established as 'expectation' or 'requirement' of participation in the social support group. A small group rather than the large online network more readily enables participation and 'rules'.

> 'If you share the same struggles, we have some common things, we can communicate and help each other' (Female)

> 'I think the validation might be important ... If you just give a like, it's different to a comment. A comment shows the person you really appreciate what they have done ... Like if you have eaten bad all week and then eat well and post about it, people's comments would encourage you to do it again' (Male)

> 'If it was expected that everyone would post, then I would do something' (Male)

Advantages and disadvantages of social support through social media

Participants primarily communicated that a healthy lifestyle support group on social media would provide a constant reminder embedded into their daily routine of the goals they were trying to achieve and make them more accountable to take action. Group members would aim to continue to present a social identity that the group would positively reinforce.

> 'I think that sense of community and sense of accountability comes from having a group where you kind of post and upload and that type of thing. So say it's a smaller group, someone might follow-up if you haven't done something for a while and ask how you are doing' (Male)

> 'It being a constant reminder, it's often going to be in your feed. So even if you're not commenting or interacting, you're seeing it and it's reminding you and you're not forgetting because it's integrated into your Facebook when you're scrolling through, its subconsciously going through your mind, so maybe later when you are deciding what to eat you might remember a meal someone cooked and think, I don't want to go to Maccas [McDonalds], I'll make my own meal because that looked really good' (Male)

Some participants talked about less positive experiences with social media groups, such as toxic environments or bullying. The importance of having a strict 'no-bullying policy' and a dedicated moderator (likely the health professional coach) to monitor content and comments would be essential to ensure participants felt safe to remain engaged. Inter-group communication should remain positive or as Social Identity Theory suggests, participants would leave and seek a new group.[30]

> 'Sometimes the group culture can become toxic, if rules aren't followed, there might be things that make you feel uncomfortable or like people could be rude that might push you away from participating' (Female)

As raised by some focus groups, there was the possibility that the social media support group became stagnant because people started to ignore content that seemed personally irrelevant or information saturation was reached. The participants suggested a search function that allowed participants to filter personally relevant information would be helpful. In effect, the inter-group dynamics would be broken if the group member no longer had like goals and values and the focus groups have identified a technical means of 'removing' these people from their group.

> '... A search function would be important, like I want dinner recipes and I can look up the answers'

Although only mentioned across two focus groups, the young adults expressed that a considerable disadvantage of engaging in an online social support group was that they would be overwhelmed by too many postings. It was suggested a predetermined schedule of postings might address this.

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Discussion

Young adults could see value in participating in a social support group to receive feedback from peers and a professional coach when attempting lifestyle changes. The sharing of successful methods and achievements and honesty about lapses by peers were viewed as providing opportunity and motivation to change behaviours. This qualitative research dispelled some common misconceptions around the use of social media as the channel to provide this support. It was not the support of family and friends that was seen as providing the best approach to encourage change and achieve their lifestyle-associated goals, rather that of strangers with common goals and similar backgrounds. Despite the growing popularity of other social media among youngest adults, they viewed Facebook as the best means to deliver the social support during a healthy lifestyle intervention. This was accredited to its pervasiveness in their current daily routine and ability to form a private group. The credibility, authenticity and ability of the health professional with respect to relating to the group were important to them. However, they still voiced some reluctance to actively engage and post comments unless it was clearly a condition of participation in a peer support group so that all members were actively assisting others and validating individual's achievements. The size of the support group on social media was also an important consideration and might explain why some previous multicomponent interventions have failed to actively engage peer support.

Social support is a key behaviour change technique and young adults are active users of social media. However, the evidence from lifestyle interventions for healthy eating and prevention of harmful weight gain shows a lack of active participation in peer support via social media. Young adults are interested in the provision of credible health information via social media and may 'lurk' to read comments from others without posting themselves but, overwhelmingly, engagement quickly diminishes.[34] Most attempts at providing social media-enabled support have used one or more additional delivery channels in their health promotion interventions. In many, the size of the treatment arm will have overwhelmingly exceeded the small group size suggested by most of these young adults. Two US large, well-designed, 2-year long multicomponent studies conducted in 18–35-year-olds for the prevention of weight gain used two different channels to provide social support. One used a private website with a discussion forum[18] and the other used public Facebook.[16] Both were moderated by trained interventionists and included information and gaming to accumulate points for prizes or challenges and competitions. Both trials showed initial engagement, with 50% and 69% of participants posting at least once, although only 16–40% could be seen as long-standing active participants. Even using the embedded social media channel that young adults have suggested is the best to deliver this type of social support, Facebook, participation was no better compared to the private discussion forum that would have required additional training and log-ins. The size of these groups was approximately 200 and exceeds that suggested by most of the young adults participating in these focus groups. The small-group based virtual reality social media support described by the Social Influence Model of Consumer Participation may be the preferred means of support for many, young adults to improve their lifestyles.[30,31] Those with like goals and values group to share and support and influence each other.

However, size may not be the only consideration for an apparent lack of engagement. Two smaller studies used Facebook and reported the engagement. One mostly included women and the other was exclusively in men, although it should be noted the duration of the studies was only 2 and 3 months, respectively. The sizes of the arms receiving social media support were 17 and 18 in one study[15] and 25 in the other,[35] which is closer to the magnitude agreed upon in this qualitative research. One study had 20 participants make at least one post[15] but the other had only one participant post during the 11-week intervention.[35] A possible explanation for the lack of engagement in the latter is the inclusion of face-to-face sessions.[35] It is highly likely that the once weekly in-person meetings with the health professional and peers negated the need for the online social support. Smaller groups may help participants to feel more comfortable to make a post but, as indicated in the current focus groups, some additional push may still be needed to become an active participant rather than a 'lurker'. Our young adults suggested an expectation of membership might be that participants regularly post and Beetham[36] did so in a 2-month long study in which weekly posts were threshold to receiving their US $50 for participation. The groups were small, comprising seven to nine participants, and each had a lifestyle coach moderator but social media engagement was poor. Again, one group had weekly face-to-face intervention sessions and the others had weekly telephone calls from the health coach and weekly clinic weigh-ins albeit by a research assistant with no advice offered. Thus, social media support might only be required if interventions have no face-to-face contact. The focus group participants did suggest that an initial meeting face-to-face among the peer group would enhance later engagement.

Another suggestion was that the social media support groups are formed among people who share common traits, such as being university students, having a similar profession or living in a similar area. Many of the studies

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in US college students will have accommodated some of these suggestions as students leave home and live on campus but this is not the case in many countries (e.g. Australia). However, as both Social Identity Theory and Social Influence Model of Consumer Participation propose, the other important idea about forming groups is that the members share common goals. Matching people who share an interest in specific forms of physical activity and like similar cuisines is an approach that warrants further research. A pilot study of post-partum women used a private Facebook group for a 12-week weight loss programme. The group was small (n = 19) and the women had commonalities in their goals. The engagement was maintained throughout and, in the final 4 weeks, all of the women had posted or commented or at least 'liked' a post.[37] Social Identity theory explains that people want to form positive appraisals of their social group and differentiate it from other groups that do not possess the desirable behaviours. People will strive towards removing any negative aspects of identity of their group to enhance the individual and shared identity.[30]

Another important consideration when planning social support groups via social media might be to ensure the relatedness of the health professional coach. Not only are their professional credentials important, but also it might be important that they have shared generational, social and cultural values. In a previous effective multicomponent intervention conducted in 18–35-year-olds, the participants reported that the young dietitians who coached them were the most helpful aspect of the programme.[38] Credibility is central to effective communication and behaviour change.[33]

There are several limitations of the current research. More females than males participated in the groups, although the opinions offered by the groups did not appear to be overwhelmingly gender-dependent with the exception of some males desiring a male coach. A range of socio-economic groups were represented but the group is mostly well educated. The overall sample size was at the lower limit usually suggested for focus group research, although theme saturation appeared to be reached. All participants expressed an interest in participating in a diet and physical activity programme but only one had participated in such a programme and only one other observed an online group environment, and so suggestions could be considered somewhat hypothetical. When it comes to generalising the results to all young adults, we are uncertain whether the results from an Australian group would characterise young adults internationally, although it is noted there are commonalities in the social media environment encountered across countries such as the US and UK. It is also important to recognise that these suggestions for using social media are specific to young adults wanting to change their lifestyle to prevent unwanted harmful weight gain. Our findings may not necessarily apply to social support groups for young adults with diseases or morbid obesity. However, because the opinions gathered align closely with theories about the construction of social groups and the behaviour within groups, as well as why people select one type of virtual community over another one, these findings could be explored in patient groups.

In conclusion, the findings from this qualitative research suggest that young adults would like social media support groups to be smaller in size with members drawn from strangers but who have common goals and some similarities in personal characteristics. It is important that there are some rules surrounding expectation to contribute constructive posts and also that the health professional ensures the information is credible and they are an authentic coach who acts as a role model. Further interventional research is required aiming to test whether a social media support group based on all these constructs is more successful in engaging the young adults and achieving the desired outcomes.

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Conflict of interests, source of funding and authorship

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This research was funded by a grant from the office of the Deputy Vice Chancellor of Research at the University of Sydney. MAF has received funding from the National Health and Medical Research Council, the Australian Research Council and Cancer Council NSW, and NSW Health, Australia but not for the current study.
MAF and MN contributed equally to the design of the focus groups. MN led the focus groups (MAF observed). MAF and MN contributed to the analysis of data and interpretation of results. Both authors contributed to writing the paper and take responsibility for the final version of the manuscript submitted for publication.

Transparency declaration

The authors affirm that this manuscript is an honest, accurate and transparent account of the study being reported. The authors affirm that no important aspects of

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the study have been omitted and that any discrepancies from the study as planned have been explained.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Interview guide for focus group discussion.

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OBESITY AND WEIGHT MANAGEMENT

A study using semi-structured interview and Delphi survey to explore the barriers and enabling factors that influence access and utilisation of weight management services for people living with morbid obesity: A patient and professional perspective

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Keywords
barriers, commissioning, education, obesity, weight management.

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Abstract

Background: A quarter of the United Kingdom's population are living with obesity, a disease that causes an estimated 30 000 deaths each year. This coincides with an under-utilisation of weight management services across the country with the majority of patients with morbid obesity having no record of any weight loss intervention at all. This study explores the factors that influence patient access to weight management services.
Methodology: Expert opinion was obtained using semi-structured interviews and the Delphi methodology. Participants were selected from primary and secondary healthcare settings. Healthcare professionals (HCPs) had experience working in weight management services or in services dealing with obesity-related comorbidities. Patients had experience in attending a variety weight management services.
Results: Nineteen participants completed all aspects of the study. The main barriers included negative perceptions, low mood/depression, obesity not being considered as a serious disease, lack of access to services for housebound patients and disproportionate commissioning. Suggested facilitating factors to improve access included the education of all HCPs about obesity, improving HCP communication with patients, and broadening the number of HCP's that are able to refer to weight management services.
Conclusions: Future services must prioritise the education of all HCPs and the public to combat the stigma of obesity and its impact on health. National commissioning guidelines in partnership with advocates of obesity should seek to streamline referral pathways, broaden referral sources and increase the availability of specialist services. Awareness of these factors when designing future weight management services will help to improve their utilisation.

Introduction

Obesity affects a quarter of the United Kingdom's adult population and is estimated to result in ~30 000 excess deaths each year [(1)]. The treatment of this disease along with its associated comorbidities is set to cost close to £10 billion per year by 2050 [(2)]. Current treatment strategies include dietary/lifestyle intervention, psychological intervention, pharmacotherapy and bariatric surgery; all of which have a strong evidence base [(3)]. In reality, synergy across these treatment modalities will provide the most effective means to reduce these excess deaths. The National Institute of Clinical Excellence's clinical guidance (CG189) 2014 advises that the identification, assessment

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and management of obesity should follow a tiered structure. This tiered structure is based on cardiovascular disease risk simplified to the product of level of Body Mass Index (BMI kg m^{-2}) and presence of morbidity, with an increase in cardiovascular disease risk requiring an increase in need for multidisciplinary specialist intervention. Figure 1 outlines the tiers of weight management in the UK.

In order for treatment strategies to be effective it is important to ensure that they are accessible to those individuals requiring them. The apparent under-utilisation of weight management services in the UK was highlighted by Booth *et al.* [4], showing that up to 60% of patients with morbid obesity (BMI $\geq$ 40 kg m^{-2}) had no record of primary care level weight intervention during a 7-year period. It is also reflected in the number of eligible people undergoing bariatric surgery, with the UK having some of the lowest operation rates in Europe [5] despite robust evidence for its cost-effectiveness [6-8]. Primary care provides an opportunity to give frontline weight management advice and referral into the available local services. However, in reality the topic of weight loss may not often be raised by the healthcare professional due to inadequate documentation of patients' weights, time constraints, limited understanding about obesity and not having the resources to raise a potentially sensitive topic with the patient [9]. From the individual's perspective, the lack of time, cost implications, stigma and attitudes to health are examples of barriers that may affect access to specialist services [10,11]. Access to NHS weight management services across the UK currently lacks consistency, with significant disparities existing regarding the availability of weight management service provision. Inconsistencies in the process of commissioning weight management services through local government authorities, local clinical commissioning groups and national bodies has resulted in fragmentation of NHS weight management services.

The need to identify, define and address the main factors that influence access to weight management services has never been as apparent as it is currently. It was therefore the aim of this study to identify the primary and secondary care viewpoints on this topic from both the patient and healthcare professional's (HCPs) perspective. This was achieved by investigating the most agreed upon barriers and facilitating factors that influence access to weight management services and therefore provide the foundations needed for future models of care.

Methods

Subjects

The subject group included a mix of experienced patients and health care professionals (HCP) involved in obesity management from both primary and secondary care settings to form an 'expert' panel. A recruitment target for the "expert" panel was set at 20–30 participants. Eligible experienced patients were those living with obesity having either a BMI of >40 kg m^{-2} or >35 kg m^{-2} with obesity related comorbidity. All patients had previous experience in accessing recognised weight management services. Primary care recruitment settings included a community weight management clinic and a GP practice. Secondary

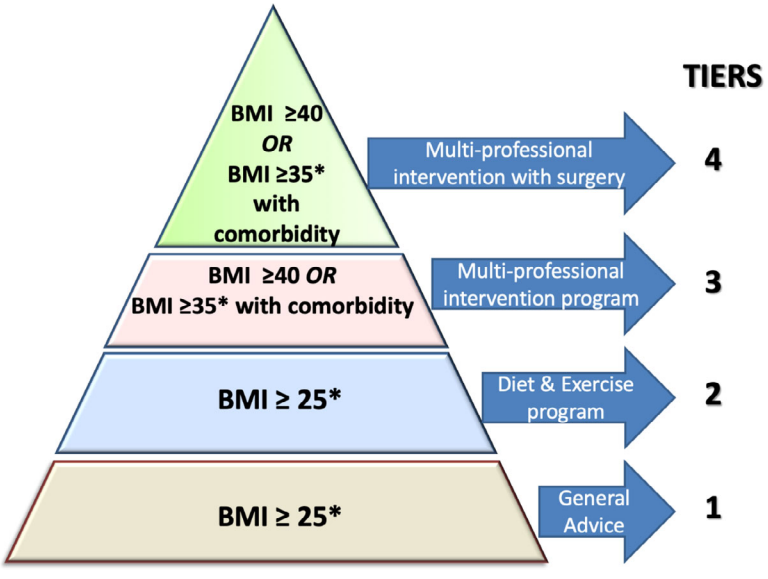

Figure 1 Tiered structure for weight management intervention in the UK. *Black African, African-Caribbean and Asian (South Asian and Chinese) groups use a lower BMI threshold. (Tier 1/2 = 23 kg m^{-2}; Tier 3/4 = 32.5 kg m^{-2})

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care recruitment settings included a bariatric clinic within a University Hospital, a bariatric patient support group and medical out patients department. Participants were directly approached at random by members of the research team and provided with information leaflets prior to undertaking a formal consent process.

Study design

A qualitative study was undertaken involving the use of semi-structured interviews to identify the main barriers and enabling factors when accessing weight management services. Private one-to-one interviews were performed in mid-late 2018 by an experienced Registered Associate Nutritionist at either the place of recruitment, over the phone or in a setting of the participant's choice. Each interview began with an open-ended phrase such as – 'What do you think are the key barriers for somebody accessing weight management services? This can be any service from lifestyle advice to bariatric surgery'. Prompts were used during the interview when necessary for expansion on responses. Interview time lasted no longer than 20 min or finished when the interview reached a natural end.

Data was collated from each interview and analysed for repetitive responses. Responses were grouped into themes before applying Delphi methodology to capture consensus of opinion via online surveys. A two round process was utilised to capture each groups option without compromising the response rate. The survey consisted of all unique responses grouped in themes with a 5-point linear scale 1='*not important*' to 5='*extremely important*'. Participants were also invited to comment if they felt statements could be changed to improve ease of rating. This online survey was emailed to all participants. Completed surveys were analysed prior to the administration of a second-round survey consisting of the unique responses where consensus had not been agreed (Fig. 2). The final analysis of the study was completed in March 2019.

Consensus

Consensus was defined as having an interquartile range of less than 1 on the 5 point linear scale. Responses with consensus from the first round were not included in the second round of questionnaire.

Ethical statement

Ethical approval for this research was granted by the Health Research Association and local Research Ethics Committee.

Results

Participant characteristics

A total of 28 participants (7 primary care HCP, 7 secondary care HCP, 6 primary care patients, 8 secondary care patients) completed the semi-structured interviews with 19 participants (3 primary care HCP, 7 secondary care HCP, 3 primary care patients, 6 secondary care patients)going on to complete all rounds of the Delphi method consensus study. Belonging to the HCP group were dietitians, psychologists, psychotherapists, nurses, doctors and weight management advisors. Professional experience in weight management ranged from 12 months to 15 years. The patient group captured a variety of experiences in weight management services including commercial slimming groups, community tier 3 clinics, hospital-based tier 3 clinics and bariatric surgery services (see Table 1 for a breakdown of participants that completed all aspects of the study).

Themes

All responses obtained from the interviews were grouped into 5 main themes: knowledge and education of HCPs, public perception/stigma, healthcare resources, previous experience of healthcare and service design/provision.

Barriers to weight management services

In total, 44 barriers were identified in the HCP group compared to 41 in the patient group. The top 10 most important consensus responses that act as barriers to weight management services in both groups are listed below in Table 2 with similarities highlighted.

Enabling factors to weight management services

In total, 31 enabling factors were identified in the HCP group compared to 20 in the patient group. The top 10 most agreed upon enabling factors in both groups are listed below in Table 3.

Discussion

Delphi methodology & participants

Our aim was to determine the current option concerning what is perceived as being the top barriers and enablers to accessing weight management services for people living with obesity. The opinions of both healthcare professionals and 'expert' patients from both primary and secondary healthcare settings were sort in order to ensure a diversity of perspectives. The Delphi method was used as

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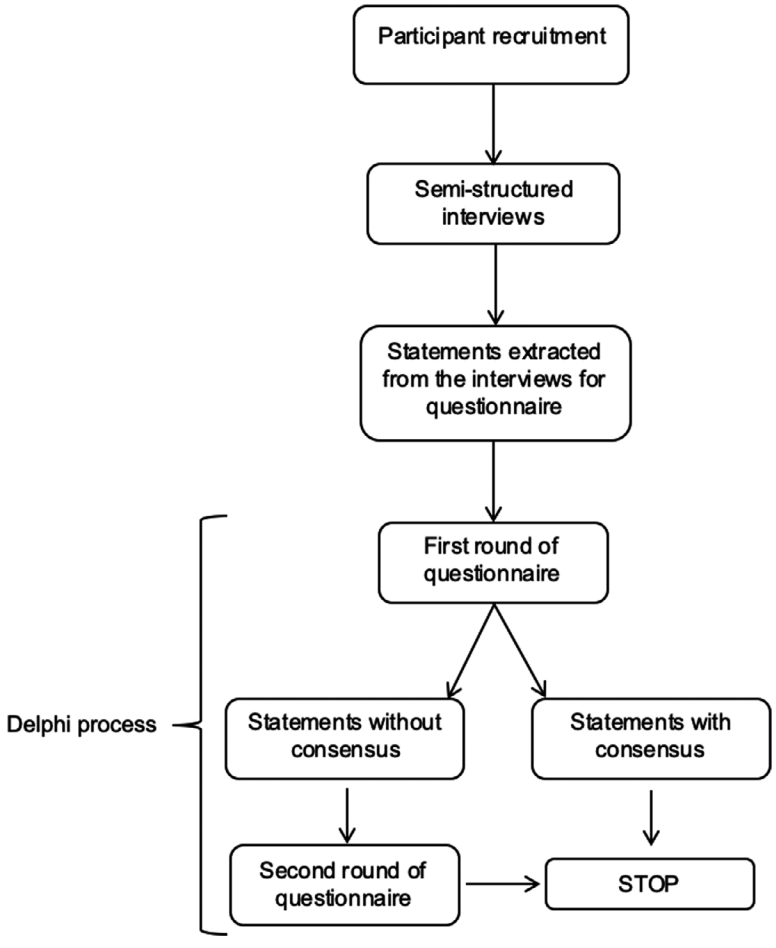

Figure 2 Study process

it captures a wide consensus of expert responses whilst avoiding biased/dominating opinions from an individual or sub-group [12].

Whilst the participant size in this study is relatively small, it has captured a wide array of opinions from both patients and professionals with experience in weight management. Unfortunately, there were no male participants recruited into the 'expert' patient group. The lack of a male 'expert' patient perspective restricts the ability to generalise some of the study's conclusions. However, the 'expert' patient group does in partial reflect the national picture with men being notoriously underrepresented in all settings of weight management [13,14]. Reasons for this include embarrassment, services being perceived as 'feminine' spaces and a general lack of desire for lifestyle change when compared to women [15-17]. Perhaps this also demonstrates that gender itself is a barrier when it comes to men accessing weight management services. More research is needed to gain a greater insight into this gender disparity for accessing weight management services.

Patient responses

The top ranked patient barriers identified in this study often involved previous engagement with and/or the perceptions of HCPs. Unfortunately, this confirms the reality that an individual living with obesity may already be at a disadvantage before even discussing their weight with their healthcare team. Sadly, as the BMI of a patient increases there can bean associated decrease in respect from the healthcare professional. This subconscious prejudice (stigma) has an adverse influence on the quality of care provided and may even prevent an individual from seeking medical help [18].

The 'expert' patient group felt as though HCPs often do not treat obesity as a serious medical condition that requires treatment, despite often being advised to lose weight in order to improve their health. Stigma towards obesity in the healthcare setting is unfortunately well documented [19] and highlights an apparent weight bias that often influences the care of individuals living with this condition, further driving the stigma around obesity

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Table 1 Characteristics of participants that completed all aspects of the study

	Healthcare professional	Patient
Sex		
Male	2	0
Female	8	9
Healthcare setting		
Primary	4	4
Secondary	6	5
Main service type		
Community tier 3	3	4
Hospital-based tier 3	2	1
Tier 4	4	4
Other	1	-
Professional experience		
0–12 months	1	-
2–5 years	1	-
6–10 years	6	-
>10 years	2	-
Occupation		
Specialist bariatric dietitian	3	-
Specialist bariatric nurse	1	-
Specialist diabetes nurse	1	-
Weight management advisor	1	-
Psychologist/psychotherapist	2	-
Consultant physician	1	-
GP	1	-

which often damages the relationship between patient and HCP. Interestingly, this weight bias has also been identified within the healthcare student population [20–22], suggesting that obesity stigma is passed on through the education system and on to the future healthcare workforce. It is therefore not surprising that the most important agreed enabling factor by the 'expert' patient group was the need for education of all HCPs on effective treatment of people living with obesity. As this may serve to reduce obesity stigma across all healthcare settings and improve the treatment of obesity. This point is also supported by other enabling factors identified in this study such as empowering more HCPs, including dietitians, nurses and physiotherapists to refer into weight management services.

The third most highly ranked enabling factor as considered by the 'expert' patient group was the provision of weight loss advice within the local healthcare setting. This has been highlighted in previous studies, but continues to be an on-going issue [23,24]. This important enabling factor may reflect just the practicality of traveling time & cost. However, the effectiveness of current weight loss intervention strategies in primary care settings has been brought into question as highlighted by a meta-analysis of 15 randomised controlled trials including 4539

Table 2 Top 10 ranked barriers to accessing weight management services. Arrows highlight crossover between participant groups

Rank	Healthcare professionals	Cross-over	Patients
1st	The way weight management services are commissioned frequently means that housebound patients cannot be access them		Healthcare professionals sometimes have a negative perception of bariatric surgery
2nd	The frequent commissioning and decommissioning of services make it difficult to stay up to date with referral criteria and pathways		Negative perceptions of obesity can inhibit taking steps to lose weight
3rd	Healthcare professionals are not actively referring appropriate patients to weight management services		Negative emotions (i.e. low mood or depression) can inhibit weight loss
4th	Funding shortages disproportionately affects weight management services		Healthcare professionals sometimes do not consider obesity to be a serious medical condition that requires treatment
5th	The lack of weight management advocates means that commissioners do not always understand where funding is most effectively directed		Previous negative experiences with healthcare professionals inhibit seeking help
6th	There is a perception that healthcare professionals have a negative opinion on weight loss surgery		Negative public attitudes concerning weight loss surgery
7th	Healthcare professionals are often not aware of what weight management services are available		GP practices do not know what local weight management services are available
8th	Some healthcare professionals have the perception that weight management services do not work and/or are a waste of time		Healthcare professionals are not proactive at discussing the effects obesity has on health
9th	Healthcare professionals may not address weight management issues with patients as it can be time consuming		The fear of failure if you are unsuccessful at losing weight

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Table 2 Continued

Rank	Healthcare professionals	Cross-over	Patients
10th	Negative emotions (i.e. embarrassment) can prevent patients from seeking help		Healthcare professionals usually say the same things about how to lose weight and aren't very helpful

participants, showing less than 5% total body weight loss after 12 and 24 months [25]. Suggesting that whilst local primary care settings are the preferred location of weight management services there remains the need for more specialist regional services for when further weight loss intervention is required.

Despite bariatric surgery being a cost-effective treatment option for patients with morbid obesity [26,27], the 'expert' patient group felt that work is still needed to combat the negativity that some HCPs have towards bariatric surgical intervention. This, alongside changes in commissioning responsibilities, may be a contributing factor to the relatively low rates for bariatric surgical operations seen in the UK when compared to across the rest of Europe.

Negative emotions were ranked as the third most important barrier that patients with obesity face when considering accessing weight loss interventions in this study. Negative emotions and low mood are known to be associated with patients living with obesity [28-30], but it is unclear whether obesity causes these or whether it just has a strong influence on the development of them. However, it has been demonstrated that weight loss can improve mental wellbeing of people living with obesity [31]. For this reason, it appears important to address mental wellbeing and emotions alongside weight intervention to enhance the readiness to make lifestyle and behavioural changes to increase engagement in weight management services. Obesity is not the only chronic disease in which negative emotions and low mood have been identified as barriers to self-management, others include diabetes, hypertension, COPD, multiple sclerosis and prostate cancer [32–35].

Health Care Professional responses

Interestingly, the most agreed upon barrier in the HCP group was the lack of provision of weight loss intervention for housebound patients. As the obesity epidemic continues to grow, one can only imagine that the number of housebound individuals living with obesity will

Table 3 Top 10 ranked enablers to accessing weight management services. Arrows highlight crossover between participant groups

Rank	Healthcare professionals	Cross-over	Patients
1st	Make the referral process easier and less confusing		Educate all healthcare professionals on effective methods to help people with obesity related problems
2nd	Provide frontline advice weight loss advice in GP practices		Improve the communication and referral process from GP/community services
3rd	Enable GPs to discuss weight loss with their patients		Enable GP practices to provide weight loss advice/services
4th	Simplify the referral process into weight management services		Enable all healthcare professionals to refer into weight management services (i.e. nurses, dietitians, physiotherapists)
5th	Enabling all healthcare specialists to refer into weight management services		Develop social media forums where people can ask questions and get information about weight management services
6th	Increase funding to promote the benefits of weight loss		Encourage all healthcare professionals to listen and provide support in regard to weight loss
7th	Improve the communication links between primary and secondary care services		Provide all healthcare professionals with the information concerning weight loss services and referral processes
8th	Ensure commissioned services are adaptable and can evolve with the service users over time		Educate all healthcare professionals about the negative health consequences of obesity
9th	Educate primary healthcare professionals in how to deal with obesity		Challenge the negative perceptions of weight loss services (e.g. bariatric surgery services) belonging to healthcare professionals
10th	Develop links between all the services involved in weight management (i.e. council, hospital, commercial and community services)		Better promotion of the positive experiences of weight management services in order to challenge misperceptions

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increase. The majority of specialist weight management services rely on the patient attending appointments in a specific, often clinical location and do not provide domiciliary visits. The rise of telemedicine and 'web-based distance management clinics' may be of benefit in this patient group, however this has sometimes been met with reluctance from the patient as it requires a level of competence with using technology [36,37]. It therefore appears that finding ways to access housebound patients may need further research to enable the appropriate commissioning of future weight management services.

In fact, responses focusing on the process of commissioning for weight management services were some of the highest ranked barriers in the HCP group. The lack of uniformity in the provision of services across the country, with some areas not having any specialist services available at all, often leads to either established centres having to increase their geographic catchment without a proportionate rise in resources or the denial of patients having access to weight management services. The perpetual issue of NHS funding of services that disproportionately affects individuals living with obesity was highly ranked as a barrier by the HCP group.

The paucity of weight management 'advocates' in the commissioning process is also considered a contributing barrier for patients accessing weight management services. In the UK the responsibility of commissioning multidisciplinary weight management services currently lies with the local Clinical Commissioning Groups (CCGs) of which there are 191 CCGs across the country. Therefore, it is no surprise that there are now disparities in access and quality of weight management services nationally leading to health inequalities. It is hoped that with time advocates from both patient and HCP organisations will exert more influence on commissioners and reduce these inequalities.

It is striking that half of the most agreed upon barriers in the HCP group included the negative actions and attitudes towards obese patients by HCPs themselves. There is clearly a need to resolve myths concerning the effectiveness of weight management interventions and services available to patients. Therefore, it is no surprise that some of the highest ranked enabling factors seen are to combat these barriers were the education of all HCPs on obesity and its treatment. The learning and development of HCPs is an on-going process and opportunities to adapt curricula need to be explored. Given the prevalence of obesity in the UK and the associated negative impacts on health, all HCPs should be enabled to appropriately discuss weight management with patients in a similar fashion to which alcohol and smoking is currently discussed. This may be as part of a brief intervention, or as a signposting of services/support to the patient. Whilst not being the top enabling factor by HCP's, this was the top factor for patients. There was also strong agreement between the patients and HCP's that the future learning and development needs of HCP's should be a top priority. Therefore, curricula adaptions are urgently required to alter attitudes and up-skill the next generation of healthcare professionals.

In conclusion the results of this study highlight the current opinions of both expert patients and HCP's concerning existing barriers and enabling factors that people living with obesity face when accessing weight management services in the UK. Awareness of these factors when commissioning new weight management services will help to improve their utilisation. It is clear that current HCP education programs need to be updated and adapted to increase obesity awareness to combat the stigma surrounding obesity if weight intervention services of the future are to maximise their effectiveness. Nationally agreed commissioning guidelines developed in partnership with weight management advocates are required to enable integration of established weight management services and streamlining of referral pathways focusing on broadening the source of referral and empowering local CCG's to provide effective tiered weight loss services to their population.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
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Guy Holt (Study coordinator) was responsible for drafting of the paper, data collection and interpretation of results. David Hughes (Principal/chief investigator) was responsible for study conception and design, interpretation of results and contributions to the final paper. All authors critically reviewed the manuscript and approved the final version submitted for publication.

Ethical statement

Ethical approval for this research was granted by the Health Research Association and local Research Ethics Committee.

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Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported.

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CANCER

Burden of colorectal cancer attributable to diet low in milk in China, 1990–2017: findings from the global burden of disease study 2017

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China, colorectal cancer, diet low in milk, disability-adjusted life-years, Global Burden of Disease Study, mortality.

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[*]These authors contributed equally to the present study.

Abstract

Background: Colorectal cancer (CRC) has emerged as a major public health concern. However, little is known about the burden attributable to specific risk factors. The present study aimed to estimate the temporal trends and geographical variation of CRC burden attributable to a diet low in milk in China.

Methods: Following the general analytic strategy used in the 2017 Global Burden of Disease study, we assessed the age-, sex-, and province-specific mortality and disability-adjusted life-years (DALYs) of CRC caused by a diet low in milk in China from 1990 to 2017.

Results: In 2017, a diet low in milk contributed 32 032 [95% uncertainty interval (UI) = 11 350–53 806] deaths and 726 710 (95% UI = 256 651–1 218 153) DALYs for CRC with a population attributable fraction of 17.1%. The age-standardised mortality and DALY rates per 100 000 were 1.7 (95% UI = 0.6–2.9) and 36.8 (95% UI = 13.0–61.7), respectively. An upward trend with age in rates of mortality and DALYs was observed. Males had higher age-standardised rates than females. The number of deaths and DALYs increased significantly from 1990 to 2017, whereas the corresponding age-standardised rates showed relatively stable trends. In 2017, Hunan and Liaoning were ranked as the top two provinces in terms of disease burden. Socio-demographic index had a weak correlation with the age-standardised mortality ($r = 0.348$, $P = 0.047$).

Conclusions: The present study shows a substantial increase in the CRC burden attributable to a diet low in milk over the past three decades. Greater priority in CRC prevention should be given to males and the elderly population throughout China, particularly in less-developed provinces.

Introduction

Colorectal cancer (CRC) ranks as the third most commonly diagnosed malignant neoplasm and the second leading cause of death among cancers globally, with an estimated 1.8 million cases diagnosed and 896 thousand deaths in 2017 [1–3]. CRC incidence and mortality rates have stabilised or declined in economically developed countries, which had the highest CRC burden, whereas the rates are increasing rapidly in many low-income and middle-income countries [4,5]. In China, rapid economic development, demographic transitions and lifestyle changes over the past 30 years have led to CRC being reported as the fourth most common cancer and the fifth leading cause of death in 2013 [6,7].

The striking variation in the global incidence rates for CRC suggests that lifestyle factors including diet play a pivotal role in the development of the disease [8]. Milk, as

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a common diet, is recommended by many dietary guidelines and consumed in most populations of the world, and its consumption accounts for a large proportion of dairy product consumption [9–11]. Most systematic reviews and meta-analysis of prospective studies consistently showed a decreased risk of CRC associated with a higher consumption of milk or total dairy products [9,12–14]. However, some studies showed contradictory results [15,16]. In view of this, the Global Burden of Disease (GBD) study 2017 established the convincing causality for a diet low in milk–CRC pairing by systematically evaluating all existing epidemiological evidence and summarising the important characteristics of the relationship [17]. Currently, a diet low in milk, as the third largest contributor to CRC burden in the globe [3], has not been described in detail elsewhere and its contribution to disease burden could be an important estimate to report in different populations.

In China, dairy consumption per capita had increased significantly over past decades, although it was still at quite a low level (33.6 kg year^{-1} in 2013) compared to that worldwide (107.2 kg year^{-1}) [18]. Previous studies have evaluated the ever-growing incidence and mortality of CRC in China, as well as the fraction of CRC cases and deaths caused by selected risk factors [19–24]. However, to the best of our knowledge, there are no adequate national level data that identify the dietary risk factor of low milk intake and its contribution to CRC. In the present study, based on the GBD 2017 study, we systematically assessed the mortality and disability-adjusted life-years (DALYs) of CRC attributable to a diet low in milk in China from 1990 to 2017 by sex, age and geographical area. The results obtained will help to identify the current status and trends for the CRC burden and provide evidence for policy makers that highlights the need to take targeted interventions with respect to future prevention and management.

Materials and methods

Data sources

In the present study, all data and analysis on CRC in China originated from the Global Burden of Diseases, Injuries, and Risk Factors Study 2017, which provided comprehensive and systematic assessments of the prevalence and years lived with disability (YLDs) for 354 diseases and injuries, age-sex-all cause and cause-specific mortality and years of life lost (YLLs) for 282 causes, and 84 risk factors in 195 countries and territories from 1990 to 2017 [2,17,25]. Details of the general methodology used in GBD 2017, as well as the specific methodology used for CRC in China, have been extensively described previously [2,17,25,26]. The present study focused on the burden of CRC attributable to a diet in low milk based on the standardised metrics of mortality and DALYs in China from 1990 to 2017.

Estimates for CRC mortality were mostly from five data sources: the Disease Surveillance Point system, the Maternal and Child Surveillance System, the Child Cancer Registry, the cause-of-death reporting system collected by the Chinese Center for Disease Control and Prevention (CDC), and some important nationwide surveys [27]. In general, the GBD study conducted a systematic review of literature to identify nationally and sub-nationally representative surveys of consumption of dietary factors, and more details are given in the appendix of that paper [28]. For a diet low in milk, data from the Chinese Health and Nutrition Survey in 2002, the Chronic Disease and Risk Factor Surveillance in 2013, and published epidemiological surveys for China were mainly used. Specific data sources used for China included in GBD can be accessed via the Global Health Data Exchange (http://ghdx.healthdata.org/geography/china). The relative risk (RR) between a diet low in milk and CRC was obtained from meta-analysis of prospective observational studies and randomised controlled trials conducted anywhere across the globe [17]. In addition, a total of 33 province-level administrative units, including 31 mainland areas and the Hong Kong and Macao Special Administrative Regions (SAR), were analysed. In the 10th revision of the International Classification of Diseases (ICD), these cancers, coded as C18–C21, D01.0–D01.2 and D12–D12.8, were considered to be CRC [25]. An average daily intake of less than 435 g of milk including non-fat, low-fat and full-fat milk, excluding soy milk and other plant derivatives, was considered as exposure to a diet low in milk [17].

Estimates of disease burden

For GBD 2017, DisMod-MR 2.1, a Bayesian meta-regression tool, was used as the main method of estimation to ensure consistency between rates of incidence, prevalence, remission, and cause of death for each condition [25]. Mortality estimates for CRC were generated using the Cause of Death Ensemble model (CODEm). During the process, the incidence and mortality data from different sources generated the crude mortality-to-incidence (MI) ratios using multiple linear models. Final MI ratios were generated through a Gaussian process regression and combined with incidence data to the mortality data estimates. A detailed description of the CODEm approach can be found in previous publications [2,29]. YLLs were estimated by multiplying deaths and the reference life expectancy at each age. YLDs were estimated by multiplying the prevalence of disease or injury and its disability weights, which represent the severity of health loss associated with CRC. DALYs were calculated by summing up

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the YLLs and YLDs. All age-standardised results were calculated by the GBD reference population [26]. Furthermore, the socio-demographic index (SDI) [26], a summary measure determined by lag-distributed income per capita, total fertility rate and educational attainment, was developed to explore the association between CRC burden as a result of a diet low in milk with socioeconomic development across provinces in China.

For each dietary risk factor, the GBD study quantified the proportion of disease burden that could have been prevented if the exposure level had been sustained at the lowest risk level. This level of exposure was defined as the theoretical minimum-risk exposure level (TMREL). For a diet low in milk, the TMREL was considered to be 350–520 g per day [17]. The exposure data and effect size (RR) evaluated had been adjusted for study- and country-level relevant covariates and potential mediators [17]. Furthermore, for a diet low in milk–CRC pairing, the population attributable fraction (PAF) represented the proportional reduction in CRC burden that would occur in a given population and in a given year if the exposure to a diet low in milk had been reduced to the counterfactual level of the TMREL in the past [17]. The PAF was calculated in GBD study using:

$$PAF_{r,c,p,t,s,a} = \frac{\int_{x=l}^{u} RR_{r,c,p,s,a}(x) P_{r,p,t,s,a}(x)\mathrm{d}x - RR_{r,c,p,s,a}(TMREL_{r,s,a})}{\int_{x=l}^{u} RR_{r,c,p,s,a}(x) P_{r,p,t,s,a}(x)\mathrm{d}x}$$

where $PAF_{\mathrm{r,c,p,t,s,a}}$ is the population attributable fraction for a risk factor r attributed to cause c in province p, year t, sex s and age group a. $RR_{\mathrm{r,c,p,s,a}}$ (x) is the relative risk as a function of exposure level x for a risk factor r for cause c, province p, sex s and age group a with the lowest level of observed exposure as l and the highest as u; $P_{\mathrm{r,p,t,s,a}}$ (x) is the distribution of exposure at x for risk r, province p, year t, sex s and age group a; $TMREL$r,s,a is the TMREL for risk factor r, sex s and age group a.

Next, the deaths and DALYs for CRC attributable to a diet in low milk could be estimated by multiplying the total deaths and DALYs of CRC by the PAF for the risk-outcome pair by each age, sex, province and year.

Our present report calculated the 95% uncertainty interval (UI) for each quantity used in the analysis. These UIs were estimated on the basis of the 25th and 975th ranked values across all 1000 draws [25].

Statistical analysis

Linear correlation analysis, which was conducted using SPSS, version 21.0 (IBM Corp., Armonk, NY, USA), was used to explore the associations between SDI values and age-standardised mortality rates or DALY rates by province. $P < 0.05$ (two-tailed) was considered statistically significant.

Results

Colorectal cancer burden attributable to a diet low in milk in China

As shown in Table 1, a diet low in milk contributed 32 032 (95% UI = 11 350–53 806) deaths and 726 710 (95% UI = 256 651–1 218 153) DALYs for CRC in 2017 in China. The age-standardised mortality and DALY rates per 100 000 were 1.7 (95% UI = 0.6–2.9) and 36.8 (95% UI = 13.0–61.7), respectively. As for the overall trend from 1990 to 2017, the number of deaths and DALYs in 2017 increased significantly by over 100.0% compared to 1990, whereas the age-standardised DALY rate decreased slightly by 3.9%. By decomposing the DALY numbers into YLLs and YLDs, it could be found that YLLs of CRC caused by a diet low in milk were the main contributor to DALYs, with a proportion of 97.8% in 1990 and 95.0% in 2017.

Colorectal cancer burden attributable to a diet low in milk stratified by age and sex

Higher mortality rates of CRC attributable to a diet low in milk were seen in older individuals (Fig. 1a). In 2017, the rate was less than 1 per 100 000 populations in age groups less than 45 years. It increased gradually with age and reached a peak in the age group of over 80 years (24.8 per 100 000) with a PAF of 17.1% (95% UI = 6.0%–28.9%). Compared to that in 1990, the mortality rates for population aged 25–59 years were decreased in 2017, whereas the rates increased for the population aged over 60 years. Figure 2a shows that, from 1990 to 2017, the all-age mortality rose rapidly by 104.5% from 1.1 (95% UI = 0.4–1.9) to 2.3 (95% UI = 0.8–3.8) per 100 000, whereas the age-standardised mortality was basically stable. All-age and age-standardised mortality rates were higher for males than females.

Similar to the mortality trends, DALY rate for CRC caused by a diet low in milk increased with age (Fig. 1b). The all-age DALY rates were less than 100 per 100 000 population in age groups less than 60 years in 2017, and the peak occurred in the age group of over 75–79 years (239.0 per 100 000) with a PAF of 17.2% (95% UI = 5.9%–29.0%). The trends in DALY rates of all age groups from 1990 to 2017 were consistent with the trends in mortality rates. From 1990 to 2017, the all-age DALY rate per 100 000 population showed an upward trend from 30.3 (95% UI = 11.0–52.8) to 51.4 (95% UI = 18.2–86.2), whereas a slight downward trend was observed in the age-standardised rate from 38.3 (95% UI = 13.9–66.3) in 1990 to 36.8 (95% UI = 13.0–61.7) in 2017 (Fig. 2b). All-age and age-standardised DALY rates for males were higher than that for females from 1990 to 2017. Especially in 2017, males had approximately 1.5

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Table 1 All-age deaths, years of life lost (YLLs), years lived with disability (YLDs), disability-adjusted life-years (DALYs) and their age-standardised rates for colorectal cancer attributable to a diet low in milk in China, 1990 and 2017

	Numbers			Age-standardised rate (per 100 000)		
Variable	1990	2017	Change (%)	1990	2017	Change (%)
Deaths	13 272 (4834–22 971)	32 032 (11 350–53 806)	141.3	1.6 (0.6–2.8)	1.7 (0.6–2.9)	4.9
YLLs	355 166 (129 685–618 045)	690 063 (244 748–1 158 905)	94.3	37.4 (13.6–65.0)	34.9 (12.4–58.6)	–6.7
YLDs	7821 (2671–14 401)	36 647 (12 532–68 398)	368.6	0.9 (0.3–1.6)	1.9 (0.6–3.5)	113.5
DALYs	362 987 (132 222–631 592)	726 710 (256 651–1 218 153)	100.2	38.3 (13.9–66.3)	36.8 (13.0–61.7)	–3.9

Numbers in brackets are 95% uncertainty intervals.

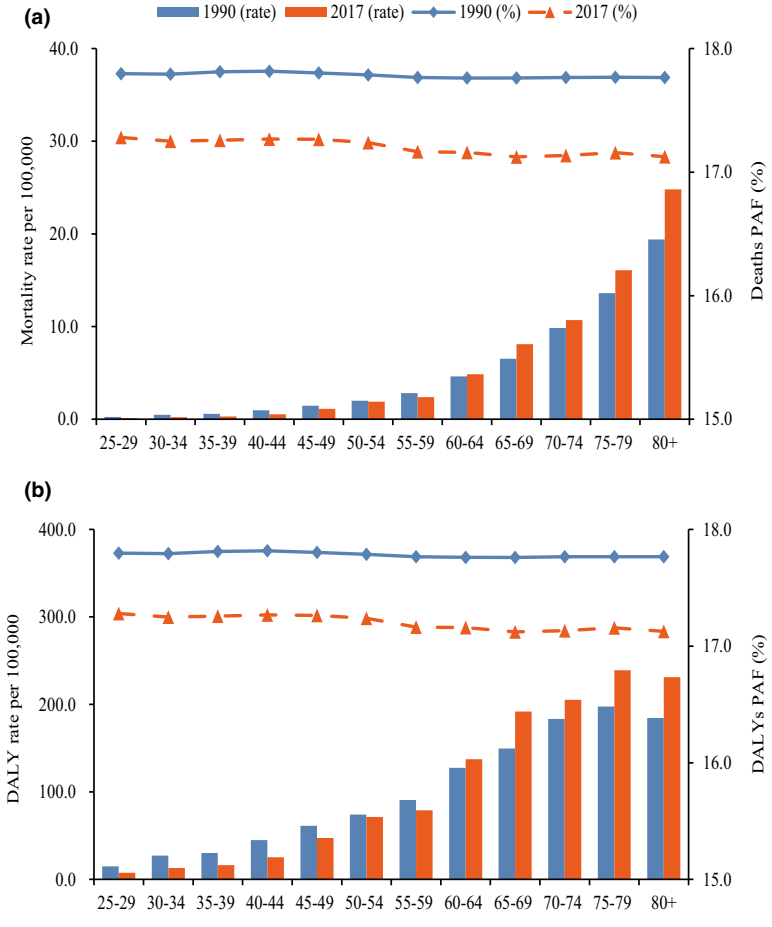

Figure 1 Age-specific mortality (a) and disability-adjusted life-year (DALY) (b) rates and their population attributable fractions (PAFs) for colorectal cancer attributable to a diet low in milk in China in 1990 and 2017.

times greater all-age and age-standardised DALY rates than females.

Colorectal cancer burden attributable to a diet low in milk stratified by provinces

Figure 3 shows the age-standardised mortality and DALY rates for each of the 33 provinces in 2017. The age-standardised mortality rates were highest in provinces such as Liaoning, Hong Kong SAR, Hunan, Shanghai and Fujian, which showed one- to two-fold differences compared to the lowest rates in provinces such as Shanxi, Ningxia, Hainan, Tibet and Shaanxi. The highest age-standardised DALY rates were observed in provinces such as Hunan, Liaoning, Guizhou, Fujian and Sichuan, which showed one- to two-fold differences compared to the

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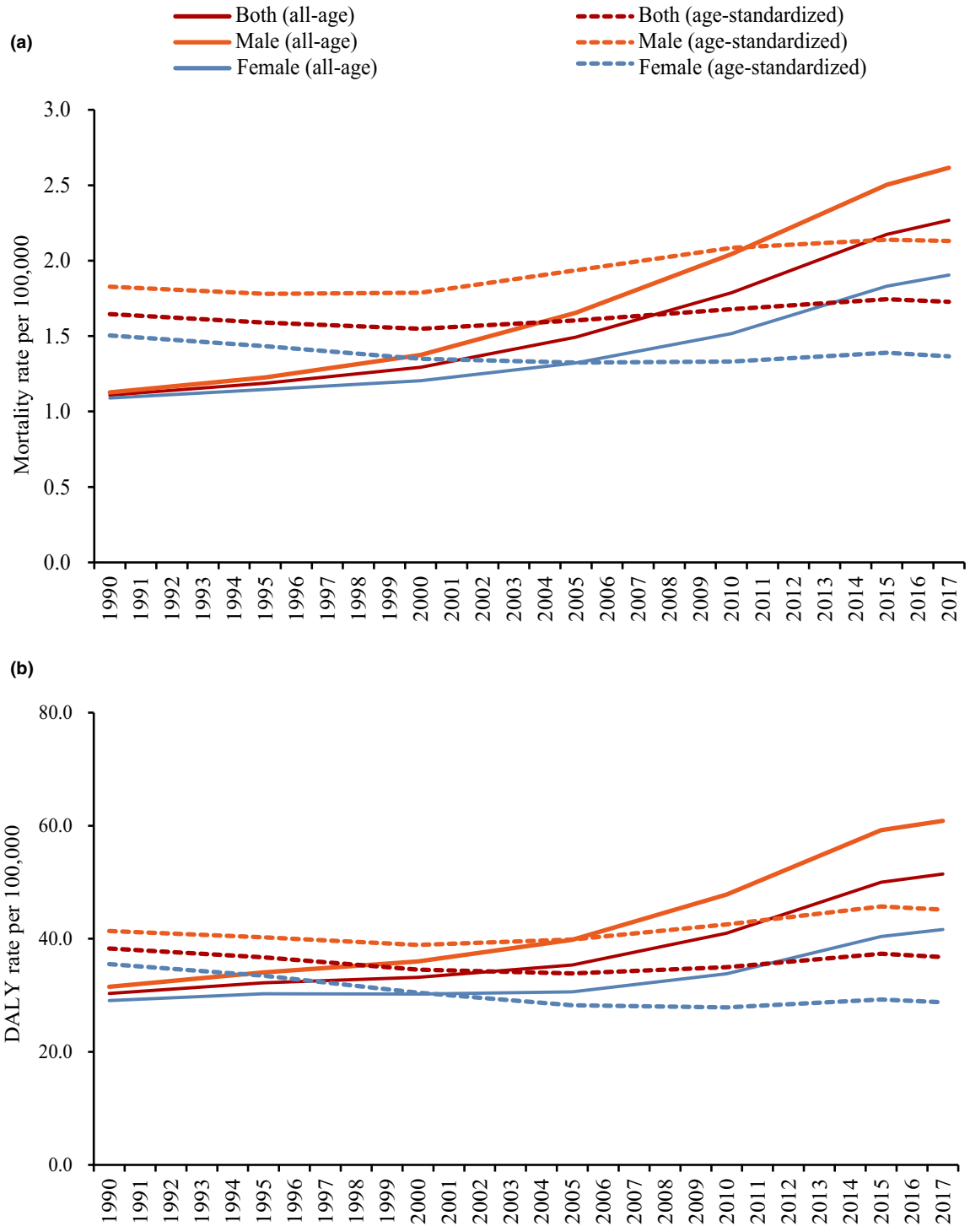

Figure 2 The trends of mortality (a) and disability-adjusted life-year (DALY) (b) rates for colorectal cancer attributable to a diet low in milk by sex in China from 1990 to 2017.

lowest age-standardised DALY rates in provinces such as Shanxi, Tibet, Hainan, Ningxia and Shaanxi. Moreover, the PAF of CRC burden as a result of a diet low in milk was 17.1% in 2017, with the highest PAFs of CRC deaths and DALYs observed in provinces with less-developed economies, such as Gansu, Guizhou, Anhui and Jiangxi, as well as the lowest PAFs in provinces with well-developed economies, such as Hong Kong and Macao SAR,

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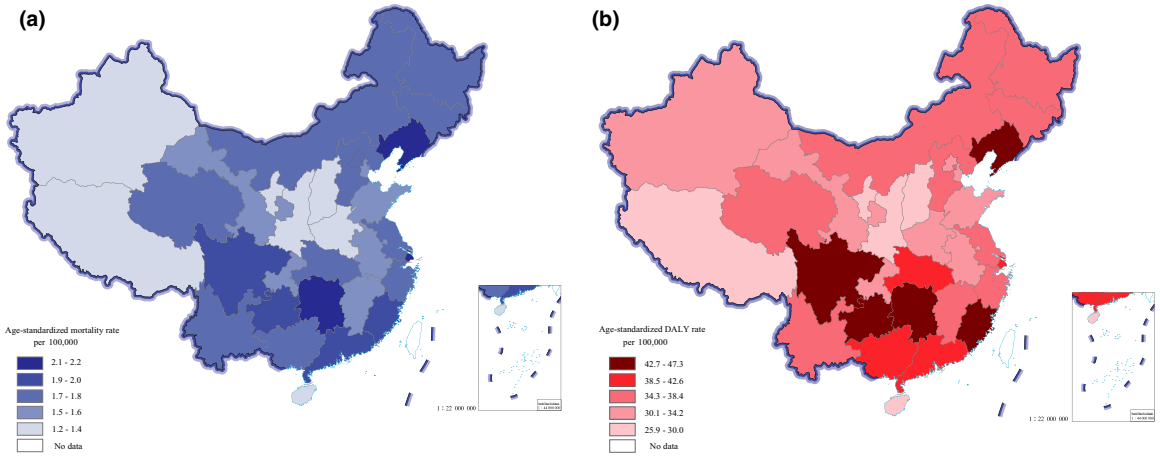

Figure 3 Age-standardised mortality (a) and disability-adjusted life-year (DALY) (b) rates of colorectal cancer attributable to a diet low in milk for 33 provinces in China in 2017.

Zhejiang, Beijing, and Shanghai (see Supporting information, Table S1).

The association between CRC burden attributable to a diet low in milk and SDI at the provincial level is presented in the Supporting information (Figure S1). SDI had a weak correlation with the age-standardised mortality rate ($r = 0.348$, $P = 0.047$) and no correlation with the age-standardised DALY rate ($r = 0.129$, $P = 0.476$).

Declines in the age-standardised mortality and DALY rates for CRC as a result of a diet low in milk were observed in most provinces of China from 1990 to 2017 (see Supporting information, Table S2). The largest decreases in the disease burden were found in provinces with a high SDI, such as Hong Kong SAR, Macao SAR and Beijing. By contrast, other provinces experienced upward trends in disease burden, and the greatest increases in age-standardised mortality and DALY rates were seen in provinces with a mid-level SDI, such as Hebei, Sichuan and Henan.

Discussion

The present study is the first comprehensive assessment of the ever-growing burden of CRC attributable to a diet low in milk in China, with more attention paid to temporal and spatial trends. In 2017, a diet low in milk contributed to 32 032 CRC deaths, constituting 0.3% of all deaths and 17.1% of CRC deaths in China [2,3]. In addition, the CRC burden as a result of an insufficient intake of milk was common in males and older people.

Significant increasing trends in numbers and all-age rates of mortality and DALYs for CRC burden caused by a diet low in milk were observed during the study period. The following aspects might explain the above situation. First, liquid milk was the main source of dairy products consumed by Chinese residents [30,31]. Data from the Chinese Nutrition and Health Surveillance showed that, from 1989 to 2015, the dairy consumption rate among adults rose from 1.45% to 17.0%, and the average daily intake rose from 2.06 g day^{-1} to 21.3 g day^{-1} [30,32]. However, the proportions of liquid milk (or an equivalent dairy food) intake of more than 300 g day^{-1} (the recommended dairy intake of the dietary guidelines for Chinese residents) among adult residents and consumers in 2015 were only 0.6% and 3.8%, respectively [30,33]. Dairy consumption among Chinese residents has improved significantly, although there is still a huge gap with respect to the recommended level and the exposure level of milk intake in the present study. Second, a slight decrease in the age-standardised DALY rate of CRC caused by a diet low in milk was observed, which might be linked to growth and ageing of the population [26]. Third, it is possibly explained by the continuously improving diagnosis and treatment measures, such as colonoscopy screening, neoadjuvant chemoradiotherapy, standardised surgical methods, targeted therapy, and so on [34,35]. In addition, by decomposing the DALYs numbers into YLLs and YLDs, we found that YLLs of CRC caused by a diet low in milk were the main contributor to DALYs, which was similar to previous studies on DALYs of CRC for all causes [3,20]. A diet low in milk therefore was an important risk factor of CRC burden in China, such that reducing the number of premature deaths and improving the survival rate of CRC patients could be effective measures for controlling the growth of CRC burden.

The patterns of CRC burden caused by a diet low in milk varied with respect to sex and age in the present study. Both mortality and DALY rates were higher among men compared to women. There are some studies that support this result [3,5,36]. The reasons for a higher

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burden in men are not completely understood, although it could reflect aetiological factors associated with complex interactions between risk factor exposures and sex hormones [37,38]. Similar to most cancers in China, there was a strong trend for higher mortality and DALY rates of CRC caused by a diet low in milk in older individuals. Furthermore, CRC was rare for those who were aged 0–-24 years old. There is some evidence indicating that females and people aged 60 years and above had significantly higher consumption rates and a daily intake per capita of dairy products than their counterparts [30,32,39]. This might be explained by women and older individuals usually receiving more advice to increase their milk intake for the prevention of osteoporosis [40]. On the other hand, males and older population generally had a relatively low awareness about the symptoms of CRC and the benefits of early screening. Special attention and greater efforts should be paid to the education, awareness and prevention measures among these high-risk populations.

Geographical differences across provinces should be highlighted in the epidemiological characteristics of CRC attributable to a diet low in milk in China. In line with the global spatiotemporal patterns of CRC morbidity and mortality [3,41], our study observed that provinces with developed economies had higher age-standardised mortality rates and larger decreases in the disease burden during the study period. These spatial characteristics might be largely attributed to disparities in dietary factors and lifestyles, levels of socio-economic development and conditions of local health care among regions [42–44]. Studies have demonstrated that dairy consumption frequency and daily intake increased with the development of improvements in a region, as well as an increase in household income and an improvement in education background [30,39]. Although the intake of dairy products in urban areas (55.7 g day^{-1}) was much higher than that in rural areas (6.0 g day^{-1}) in 2015 [30], it still remained at quite a low level. The present study also showed that the highest PAFs of CRC deaths and DALYs occurred in provinces with less-developed economies, which could be explained by people living in these areas having a lower education level and being less likely to receive any type of screening for CRC. Thus, it is necessary to improve access to health services for early cancer screening and treatment, especially in those less-developed provinces.

There are marked differences in the burden of CRC attributable to a diet low in milk in different regions worldwide. Data from the GBD 2017 illustrated that, from 1990 to 2017, the age-standardised mortality of CRC caused by a low milk intake declined globally, with significant decreases in America and Europe, and the opposite trends in Asia and Africa. Notably, in 2017, a low milk intake contributed to 1.75 deaths per 100 000 in Europe, followed by Asia (1.65), Africa (1.45) and America (1.43) (http://ghdx.healthdata.org/gbd-results-tool). These discrepancies could be explained by differences in exposure level and genetic factors associated with milk consumption in different populations. For example, daily milk intake ranged from less than 200 g to more than 600 g in western populations [45,46], whereas it ranged from less than 42.4 g to more than 82.6 g in Asian populations [47,48]. Although milk and dairy products are important foods and ingredients, they are relatively expensive and less frequently used in Chinese foods or meals in other low- and middle-income countries compared to in western foods in high-income countries. In addition, the prevalence of lactose intolerance varied by ethnic population, ranging from less than 10% in northern Europe to as high as 50% in Asia [49]. On the other hand, differences in CRC burden may be interpreted partly as a result of improvements in survival through the adoption of best practices in cancer treatment and management in developed countries [4].

Previous studies on the association between milk or dairy product consumption with CRC also showed inconsistent results. For example, a recent study in China reported that there was no significant association between high milk intake and CRC, and also that people with a high milk intake (750 mL $week^{-1}$) had a 33% higher risk of total cancer mortality [15]. However, the consumption level could be classified to a low intake according to the GBD study. A case–control study from the Basque Country indicated that a higher consumption of milk or dairy products was associated with an increased CRC risk, probably as a result of a small sample size ($n = 616$) [16]. Meanwhile, the potential reasons for this were that cut-offs for the highest milk or dairy product intake categories in different studies varied by geographical region, and also different studies had adjusted for different confounding factors, which biased the results and led to different estimates [50]. The potential protective effects of milk and dairy products against CRC could be related to calcium, vitamin D, fats and other components such as lactoferrin or lactic bacteria in fermented dairy products milk [12,51]. In addition to milk, other dairy products, such as yogurt, cheese, ice cream and milk tea, have high-fat contents, particularly saturated fat, which might increase the risk of CRC by increasing bile acid levels in the colon [51,52]. The beneficial effects of milk or dairy products may be masked by their harmful effects to some extent. This may also explain the inconsistent results between CRC and dairy products or milk consumption in different studies.

The present study had several limitations. First, all of the limitations of the GBD methodology described previously also existed in our study [2,3,17,25,26]. The GBD

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estimates could not capture the most recent changes in health information because there was a lag in data availability. Second, our estimates relied largely on the data sources available. The trend in incidence of CRC caused by a diet low in milk, which was related to the screening participation rate, was not analysed in the present study. Changes in exposure to a diet low in milk during the study period by sex, age and province were not taken into account when we analysed the epidemiological patterns of CRC. Furthermore, China had a well-established vital registration system and improved quality of coding of ICD in death certificates, although large differences still existed across provinces. Third, we did not analyse the urban–rural stratification of the results, which would be beneficial for understanding the gap and guiding the appropriate health policy and programmes [53]. Fourth, although the GBD study endeavoured to evaluate the effect size that had controlled for major confounders, potential interactions between dietary components and residual confounding cannot be excluded.

In conclusion, the present study has provided evidence of a substantial increase in CRC burden attributable to a diet low in milk in China over past decades. To reduce the CRC burden in China, more targeted strategies should be carried out by focusing on males, especially in older individuals. Moreover, the highest age-standardised mortality rates of CRC caused by a diet low in milk in 2017 were found in those with a high SDI, despite greater improvements having occurred in them during the study period. Given the limited health resources, targeted cost-effective interventional strategies for CRC prevention and treatment are needed.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
No funding declared.
ML conceived and designed the research. ZW and LZ wrote the first draft of the paper. WG, YG, XL, YZ and JL performed the data analysis. ML and MZ reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript submitted for publication.

Transparency declaration

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

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Relationship between the burden of colorectal cancer attributable to a diet low in milk and socio-demographic index (SDI) at the provincial level in 2017. (a) Age-standardised mortality rate versus SDI. (b) Age-standardised disability-adjusted life-year (DALY) rate versus SDI.

Table S1. Population attributable fractions (PAFs) of colorectal cancer attributable to a diet low in milk by province in China in 1990 and 2017.

Table S2. Age-standardised mortality and disability-adjusted life-year (DALY) rates of colorectal cancer attributable to a diet low in milk by province in China in 1990 and 2017.

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Cancer cachexia: an overview of diagnostic criteria and therapeutic approaches for the accredited practicing dietitian

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Abstract

Background: Cancer cachexia (CC) is a multifactorial syndrome characterised by ongoing skeletal muscle loss that leads to progressive functional impairment driven by reduced food intake and abnormal metabolism. Despite the traditional use of non-volitional weight loss as the primary marker of CC, there is no consensus on how to diagnose and manage CC.
Methods: The aim of this narrative review was to describe and discuss diagnostic criteria and therapeutic approaches for the accredited practicing dietitian with respect to identifying and managing CC.
Results: Available diagnostic criteria for cachexia include the cancer-specific (Fearon and Cachexia Score) and general criteria (Evans and Global Leadership Initiative on Malnutrition). These include phenotypic criteria [weight loss, body mass index, (objective) muscle mass assessments, quality of life] and aetiological criteria (disease burden, inflammation, energy expenditure, anorexia and inadequate food intake) and can be incorporated into the nutrition care process (NCP). This informs the nutrition diagnosis of 'chronic disease- or condition-related malnutrition (undernutrition) as related to increased nutrient needs, anorexia or diminished intake due to CC'. Optimal nutrition care and management of CC is multidisciplinary, corrects for increased energy expenditure (via immunonutrition/eicosapentaenoic acid), suboptimal protein/energy intake and poor nutrition quality of life, and includes a physical exercise intervention. Monitoring of intervention efficacy should focus on maintaining or slowing the loss of muscle mass, with weight change as an alternative gross indicator.
Conclusions: Dietitians and the NCP can play an essential role with respect to identifying and managing CC, focusing on aspects of nutrition screening, assessment and intervention.

Introduction

Cancer cachexia (CC) is 'a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Its pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism' [1,2]. CC compromises the ability of patients to receive, tolerate and respond positively to anticancer therapies and is associated with a poorer quality of life [1,3].

Cachexia is a form of disease-related malnutrition, characterised by weight loss, increased inflammatory

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response and muscle wasting [4]. Although anorexia and reduced food intake play a role in this wasting syndrome, these are related to abnormal metabolism and not to 'starvation'. Because of the multifactorial nature of cachexia, it is hard to recognise or identify it and, so far, there is no consensus on the diagnosis of CC. Three frameworks that were suggested by cachexia experts in the fields are well known and often referred to as the 'Evans' [5], 'Fearon' [1] and Cachexia Score (CASCO) criteria [6], and will be discussed in this review.

In addition to the CC frameworks, the Global Leadership Initiative on Malnutrition (GLIM) consensus criteria for diagnosing malnutrition (including CC) [7] were recently published and proposed to identify CC.

Despite the availability of a range of diagnostic criteria for CC, the systematic review by Healy *et al.* [8] reported that, of the 31 extant nutrition risk screening instruments, all instruments failed to consider risk factors specific to CC, screening only the domains of starvation-related malnutrition [i.e. weight loss, body mass index (BMI) and dietary intake]. Similarly, the GLIM criteria do not include anorexia, a hallmark of CC; instead, they only refer to anorexia as a supportive indicator to help identify poor food intake. The limitations of this are discussed later.

The emergence of diagnostic criteria for CC and the increasing adoption of the multidisciplinary team in modern-day health care means that we are ideally positioned to implement a multimodal approach to identify and manage CC, with nutrition remaining a cornerstone of therapy [9]. Early recognition and management of CC may improve clinical outcomes [4]. In this regard, understanding the physiology and metabolism underpinning CC and having a clear process for identifying those who are cachectic and potentially responsive to nutrition care are essential. The present review aims to describe and discuss diagnostic criteria and therapeutic approaches provided by the accredited practising dietitian (APD) with respect to identifying and managing CC. Thus, CC and the role of the APD in its assessment, diagnosis and intervention will be discussed in the context of the nutrition care process (NCP) [10]; an evidence-based model designed to standardise and promote consistent, high-quality nutrition care [11].

Methods

This narrative literature review discusses the pathophysiology, definition and management of cachexia in patients with cancer from the angle of the NCP.

Results

Nutrition assessment

The purpose of nutrition assessment is to obtain and interpret data needed to identify nutrition-related problems, their aetiology and significance, forming the foundation for the subsequent phases of the NCP [10,12]. It can be split into phenotypical and aetiological assessments. Table 1 provides an overview of diagnostic tools for CC, and the suggested criteria and cut-offs for each criterion.

Phenotypical assessment

Anthropometric measurements (weight loss, body mass index, muscle mass). Non-volitional weight loss is the traditional diagnostic criterion for CC and is associated with inflammation, the acute phase protein response (APPR) and hypermetabolism [13]. The systematic review by Blum *et al.* [14] on weight loss in cancer patients found that studies were heterogeneous and many failed to provide a criteria or time frame over which the weight was lost. Where the rate of weight loss was described, the usual cut-offs of 5% or 10% over an ascribed time period were considered arbitrary and lacked data demonstrating that these changes were specific to CC [14]. Furthermore, weight loss does not always reflect changes in body composition. In starvation-related malnutrition, weight is lost from fat mass, whereas CC is characterised by the loss of lean mass with or without loss of fat mass [15]. The activation of proteolysis is an early event during tumour growth and skeletal muscle may be compromised long before weight loss is apparent [15,16]. Despite its limitations, when weight loss was evident, it was associated with poor outcomes, such as reduced quality of life [17,18], suboptimal nutritional status [18], chemotherapy-related toxicity [19], diminished response to anti-cancer treatments and poor survival [19]. Therefore, monitoring weight changes in patients is valuable, particularly where body composition data are not available, assuming that its limitations are considered.

Being underweight or having a low BMI have been used as additional parameters to identify depletion [1,7]. It should be acknowledged that weight loss can be present in overweight or obese patients, indicating that BMI cannot be used as a sole anthropometric parameter. Moreover, it is unclear which BMI cut-offs to use for Asian populations [7].

Muscle wasting is the most clinically relevant symptom of CC. The reprioritisation of amino acids from the pool required for muscle anabolism to that for APPR reactant synthesis could be a significant contributor to the net loss of body nitrogen and muscle loss [15]. Loss of muscle mass in cancer is associated with poorer overall survival [20–22], chemotherapy toxicity and premature treatment cessation [22,23]. Furthermore, sarcopenia is a significant independent predictor of survival [20] and chemotherapy toxicity [21] in patients with cancer [24].

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Table 1 Overview of criteria and cut-offs in diagnostic tools for cancer cachexia, as adapted from Evans *et al*. [5], Fearon *et al*. [1], Argiles *et al*. [6] and Cederholm *et al*. [7]

	Phenotypic criteria			Aetiological criteria	
Tool	Weight loss	Low BMI	Low muscle mass*/function	Reduced food intake	Disease burden/inflammation
Evans 2008 [5]					
Cachexia	>5% in 12 months	<20 kg m^{-2}	Low FFMI, decreased muscle strength (upper-limb hand-grip dynamometry or lower-limb extension strength testing)	Anorexia	Increased C- reactive protein or interleukin-6 Low serum albumin (<3.2 g L^{-1})
Fearon 2011 [1]					
Precachexia	<5%	NA	NA	Anorexia	Metabolic change
Cachexia	>5% in 6 months	<20 kg m^{-2} and weight loss >2%	ASMI consistent with sarcopenia (males <7.26 kg $m.^{-1}$; females <5.45 kg m^{-1})† and weight loss >2%	Reduced food intake	Systemic inflammation
Cachexia Score (CASCO) 2011[6]					
No cachexia	<5%	-	No change in LBM QoL questionnaire: mild issues	Simplified Nutrition Assessment Questionnaire – No	5 mg L^{-1} ≤ C-reactive protein ≤ 10 mg L^{-1} 4 pg mL^{-1} ≤ Interleukin-6 ≤10 pg mL^{-1} Plasma albumin <3.2 g dL^{-1} Plasma pre-albumin <16 mg dL^{-1}
Cachexia	≥5%, mild ≥10%, moderate ≥15%, severe ≥20%, terminal	-	Loss of LBM >10% Low: Total activity Physical performance, Handgrip strength questionnaire, or monitoring Stairs climb 6-min walk distance QoL questionnaire: moderate/severe issues	Simplified Nutrition Assessment Questionnaire – Yes	Plasma C-reactive protein: 10 mg L^{-1} <C-reactive protein ≤20 mg L^{-1}, or C-reactive protein >20 mg L^{-1} Plasma interleukin-6: 10 pg mL^{-1} <Interleukin-6 ≤30 pg mL^{-1}, or Interleukin-6 >30 pg mL^{-1} Plasma albumin: ≥3.2 g dL^{-1} Plasma lactate: >2.2 mM Plasma triglycerides >200 mg dL^{-1} Anaemia: haemoglobin <12 g dL^{-1} Plasma urea >50 mg dL^{-1} Oxidative stress: reactive oxygen species plasma levels >300 FORT U Glucose tolerance test or HOMA index: altered
GLIM criteria 2018 [7]					
Stage 1. Moderate malnutrition	5–10% in 6 months or 10–20% beyond 6 months	<20 kg m^{-2} if <70 years‡ <22 kg m^{-2} if ≥70 years‡	Mild to moderate deficit§	Reduced food intake ≤50% of estimated requirements >1 week; or any reduction for>2 weeks; or any chronic gastrointestinal condition that adversely impacts food assimilation or absorption	Acute disease/injury-related (e.g. burns or trauma) or chronic disease-related (e.g. cancer)

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Table 1 Continued

	Phenotypic criteria			Aetiological criteria	
Tool	Weight loss	Low BMI	Low muscle mass*/function	Reduced food intake	Disease burden/inflammation
Stage 2. Severe malnutrition	>10% in 6 months or >20% beyond 6 months	<18.5 kg m^{-2} if <70 years‡ <20 kg m^{-2} if ≥70 years‡	Severe deficit§		

ASMI, appendicular skeletal muscle index; FORT, free oxygen radicals testing; HOMA, homeostatic model assessment; LBM, lean body mass; NA, not available; QoL, quality of life.

*By a validated body composition technique.

†A generally accepted rule is an absolute muscularity below the fifth percentile. This can be assessed as follows: mid upper-arm muscle area by anthropometry (men <32 cm, women <18 cm); appendicular skeletal muscle index determined by dual energy X-ray absorptiometry (men <7.26 kg m^{-1}; women <5.45 kg m^{-1}); lumbar skeletal muscle index determined by CT imaging (men <55 cm m^{-1}; women <39 cm m^{-1}); whole body fat-free mass index (FFMI) without bone determined by bioelectrical impedance (men <14.6 kg m^{-1}; women <11.4 kg m^{-1}). A direct measure of muscularity is recommended in the presence of fluid retention, a large tumour mass, or obesity (overweight).

‡Low body mass index (BMI) for Asian populations indicated at <18.5 kg m^{-2} if <70 years and <20 kg m^{-2} if ≥70 years; however, consensus is still required to determine cut-offs for the severity of malnutrition.

§For example: appendicular lean mass index (kg m^{-2}) by dual-energy absorptiometry or corresponding standards using other body composition methods such as bioelectrical impedance analysis, computed tomography or magnetic resonance imaging. When not available or by regional preference, physical examination or standard anthropometric measures such as mid-arm muscle or calf circumferences may be used. Functional assessments sucvh as hand-grip strength may be used as a supportive measure.

In the clinical setting, body composition measures should be chosen for the depth of information that they provide, their ability to monitor changes over time and their availability [14]. To date, clinical trials have predominantly used total body composition analysis with dual energy X-ray absorptiometry (DXA), where image data is used to calculate the appendicular skeletal muscle index. However, as with bioelectrical impedance analysis, the reliance of DXA on predictive equations means that it can overestimate fat-free mass in patients with fluid retention (a common issue in cancer or disease progression) [25]. Furthermore, DXA can incur a cost per scan and is not always available. Transverse computed tomography (CT) imaging can be used to quantify skeletal muscle density and quantity because it allows for differentiation between tissue types [25,26]. The most common landmark for CT body composition analysis is the lumbar vertebra (L3) cross-section, which correlates strongly with whole body muscle and adipose tissue and has been validated for use in cancer [26,27]. The cost of CT scans and the additional radiation dosage means that, even in research, CT scans are used opportunistically. Although these scans provide the best information, they might not be available in a clinically relevant time (within 30–60 days of the nutrition assessment), at the L3 landmark level or for follow-up assessments.

An initial nutrition assessment in patients with cancer should capture body composition. Follow-up assessments provide the opportunity to assess the dynamic changes in lean mass. In an observational study of mostly lung and colorectal cancer patients ($n = 241$), Blauwhoff-Buskermolen *et al.* [28] found that there was an 85% disagreement on the presence of low muscle mass between mid-arm muscle circumference, bioelectrical impedance analysis, DXA and CT. Therefore, changes in lean mass should be evaluated by repeating the same method over time.

Nutrition-focused physical findings. Physical examination can be used to identify physical manifestations of malnutrition and muscle wasting. In the context of CC, physical examination should be focus on the overall appearance of patients and the level of muscle and fat wasting [29].

In addition, it is important to consider functional indicators such as physical activity and muscle strength. In 2006, the CC Study Group showed [30] that weight loss alone did not fully predict the effect of CC on physical function and prognosis; this was only achieved using a combination of weight loss, reduced food intake and systemic inflammation. This reflects the multifactorial nature of CC and the need to look at the full spectrum of CC parameters, and not just weight loss.

In clinical practice, strength is often used as a proxy measure of physical function, predominantly via hand grip dynamometry; a valid and reliable tool representative of whole-body strength [31]. In CC, those with poorer hand grip strength have poorer strength, appetite,

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performance status and quality of life [32]. Poorer values of hand grip strength are associated with sarcopenia and loss of lean body mass in those with CC [31]. However, there is no consensus on the reference values for 'low' grip strength and it might not be sufficiently sensitive to identify small deteriorations. Also, grip strength can vary according to posture and encouragement, and so measurements need to be standardised.

Another strength measure includes limb muscle function. A study of gastrointestinal cancer patients ($n = 54$) reported reduced lower limb and quadriceps strength in male patients with CC, but not in females. This was associated with reduced physical function and increased fatigue scores [33]. In precachectic patients with non-small cell lung cancer, exercise capacity was assessed using a cycle ergometer with increased loading and, in addition to increased inflammatory markers, patients had a lower peak oxygen consumption than healthy controls, indicating a reduced exercise capacity. The Geriatric 8 and Timed Get Up and Go tests have been applied in a few studies in older patients with cancer and are able to predict functional decline [34]. However, research on the sensitivity of these relatively new instruments in patients with CC is required.

Physical activity levels (PALs) are an indicator of performance status and quality of life and are associated with muscle mass and physical function. Patients with cancer often have a lower physical activity compared to the healthy population. One study reported a lower energy expenditure with respect to activity in 24 patients with pancreatic cancer compared to the predicted value for healthy individuals (PAL 1.24 versus 1.50) [35]. Dahele *et al.* [36] reported that patients receiving palliative chemotherapy for gastrointestinal cancer ($n = 20$) spent less energy on activities and had 43% less steps per day than matched healthy controls ($n = 13$). However, in their study, energy spent on activities and steps/day did not correlate to physical functioning, fatigue or global health status or quality of life [36]. Patients with lung and upper gastrointestinal cancer took <5000 steps day^{-1} and spent two-thirds or more of their waking time either sitting or lying [36]. Lower levels of physical activity could be explained by systemic inflammation. In patients with advanced cancer, anorexia and fatigue was reported more in patients with higher C-reactive protein (CRP) levels, and those with higher CRP levels needed more assistance with activities of daily living [37].

Assessment, monitoring and evaluation tools. The four existing consensus-based criteria that have been proposed for CC are the Evans, Fearon, CASCO and GLIM criteria (Table 1). They differ with regards to the type of criteria and parameters included, cut-offs used and severity grading.

The Evans criteria describe non-condition-specific cachexia criteria requiring >5% weight loss in 12 months or a BMI < 20 kg m^{-2} with at least three of the following: decreased muscle strength; fatigue; anorexia; low fat-free mass index; and/or abnormal biochemistry. Fearon *et al* [1] described a cancer-specific consensus-based framework delineating CC into three stages of clinical relevance, each characterised by varying degrees of anorexia and deranged metabolism: precachexia, cachexia and refractory cachexia. The CASCO and simplified Mini CASCO consider weight loss, body composition, inflammation, metabolic disturbances, immunosuppression, physical performance, anorexia and quality of life [6]. The comprehensiveness of cachexia criteria highlights the complexity of CC, particularly when trying to identify precachexia. Furthermore, a body of evidence exists to validate the instruments against nutrition-related markers such as anorexia, body composition, dietary intake, inflammatory markers or survival outcomes [38,39].

The European Society of Clinical Nutrition and Metabolism (ESPEN) GLIM criteria include a two-step model including screening for nutrition risk, malnutrition assessment and severity grading, based on a set of phenotypic (weight loss, BMI and muscle wasting) and aetiological (reduced food intake and inflammation) criteria. The severity of malnutrition is determined by the phenotypic criteria [7]. The GLIM process assumes that CC is identifiable through screening with existing nutrition risk instruments because it recommends the use of validated instruments to identify nutrition risk.

Aetiological assessment

Food-/nutrition-related history (anorexia, dietary intake, medications and supplements). As a result of the dysregulation of the neuroendocrine axis, anorexia is considered a hallmark of CC, potentially serving as an early indicator of the syndrome. Anorexia might be present long before any changes in body composition appear. In the validation study by Blum *et al.* [39], those with CC had significantly worse anorexia than non-cachectic patients. Interestingly, anorexia is not necessarily correlated with dietary intake [14,40]. In a multicentre, cross-sectional study of 885 non-small cell lung cancer patients, 25% of those exhibiting anorexia reported unchanged or increased dietary intake [41]. Similarly, in a study of 128 cancer patients, anorexia and early satiety did not affect energy or macronutrient intakes [40]. Therefore, it is important to evaluate the presence and severity of anorexia irrespective of any changes in dietary intake because it can be an early indicator of CC [42].

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Where patients with CC do not necessarily alter their premorbid dietary habits, they might fail to meet their requirements as a result of potential increases in metabolic demand. Any increases in energy demands (e.g. such as those that may be present in precachexia) that are not met through the diet will have detrimental effects on body composition. A reduction in the supply of energy and protein or an increased demand leads to substrates being drawn from existing body stores. Additionally, amino acids are preferentially utilised for the synthesis of glucose in CC as a result of increased Cori cycle activity. For protein synthesis to occur, an adequate supply of amino acids as nitrogen donors is required, as well as glucose, to satisfy any increases in metabolic demand [43]. It has been calculated that an elevation of just 12% of the metabolic rate with no dietary intake correction could account for 1–2 kg body weight loss per month [44]. This loss is likely reflective of skeletal muscle losses because muscle provides the largest pool of amino acids. Muscle appears to be the major site of protein loss in patients with CC, highlighting the importance of ongoing weight and body composition monitoring.

As part of the diet history, information on medication and supplements should be recorded. Potential medicines used are appetite stimulants, anabolic agents, cytokine and metabolic inhibitors [45]. Amino acid supplements may include essential amino acids (EAAs) or branched chain amino acids (valine, isoleucine, leucine, creatine) [46].

Biochemical data, medical tests and procedures. Because the metabolic alterations in CC are related to the presence and severity of the disease and systemic inflammation, relevant biochemical or medical tests for CC relate to disease burden or inflammation [1,7]. Below, we discuss the following indicators of disease burden and inflammation: proinflammatory cytokines, APPR, resting energy expenditure (REE), and the hormones insulin-like growth factor 1 (IGF-1) and insulin.

The metabolic disruption of CC is driven by proinflammatory cytokine-dependent hyperactivation of metabolic pathways. Proinflammatory cytokines are key signals for lipolysis and proteolysis. These cytokines (Table 2) change the balance from adaptive protein sparing and fat utilisation as seen in starvation to uncontrolled muscle wasting [5] and, as such, are indicators of CC presence and severity. Although proinflammatory cytokines are elevated in cancer, the levels are not CC-specific. Preclinical studies indicate that, although anti-cytokine antibodies successfully relieved anorexia in mice [47], no single antibody completely reversed the effects of CC. This suggests that CC is driven by a suite of mediators acting in composite as opposed to any one cytokine, limiting their use as a solo biomarker [47].

The systemic response to inflammation, the APPR, provides other potential CC markers. During the APPR, hepatic synthesis of positive reactants (e.g. CRP and fibrinogen) is up-regulated, whereas negative reactant (e.g. albumin) synthesis is down-regulated. CRP may be more useful than cytokines as a result of its clinical availability because it is a commonly used proxy for the presence and magnitude of inflammation [48]. It rapidly responds to cytokines as a result of a short plasma half-life (19 h) and constant clearance rate. CRP has been shown to distinguish between weight-stable and weight-losing cancer patients, highlighting the role of inflammation in CC [14]. Elevated levels of CRP at the time of hospital admission are indicative of an increased risk for all-cause cancer mortality, with levels as high as 80 mg L^{-1} resulting in a 23-fold increase in mortality [18]. Further evidence for its utility as a CC marker is provided by Blum *et al.* [39] (n = 861 advanced cancer patients), who reported that those diagnosed with CC based on the criteria of Fearon *et al.* [1] had significantly higher CRP levels compared to those who did not. Unfortunately, CRP is elevated in all cancer patients; thus, to be useful for CC assessment, a higher CRP cut-off (10–30 mg L^{-1}) should be considered [14].

With regard to REE, the 2017 ESPEN guidelines on nutrition in cancer patients estimate energy requirements of cancer patients at 25–30 kcal kg^{-1} body weight day^{-1}, similar to healthy people [49].

However, a recent meta-analysis of REE (via indirect calorimetry, 14 studies) as related to lean mass reported cancer patients (n = 1453) [50] reported a 8–9% higher REE than healthy controls (n = 1145). REE varied by cancer subgroup, with a significant mean difference of 22.7 (liver), 9.5 (pancreatic), 6.5 (lung), 6 (head and neck/oesophageal) and 3.9 (urological) kJ kg^{-1} fat free mass day^{-1}. There was no elevation in REE in gastric cancer and no significant difference between sexes, nor between healthy versus hospitalised/diseased cancer patients or between weight losing cancer patients versus healthy controls.

The presence of CC would be expected to influence REE as a result of chronic inflammation, metabolic demands of the tumour and the futile Cori-cycling of glucose and lactate between the tumour and the host at the expense of energy [51]. Furthermore, proinflammatory cytokines (e.g. IL-1) [51] mimic the effect of leptin on the neuroendocrine axis, inhibiting ghrelin activity and resulting in sustained anorexia and REE [15,47]. However, in an observational study of non-small cell lung cancer patients (n = 148), those with CC (using Fearon criteria [1]) had a significantly lower calculated mean (SD) basal metabolic rate compared to non-cachectic patients: 1188 (114) versus 1258 (118) kcal day^{-1} (P = 0.02) [51]. Additional

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Table 2 Cytokines associated with cancer cachexia and their mechanisms of action

Cytokine	Mechanism of action [48]	Clinical parameters
Tumour necrosis factor-α	• Stimulates apoptosis, gluconeogenesis, lipolysis and proteolysis • Reduces protein, glycogen and lipid synthesis • Stimulates the expression of other proteolytic proteins	Sarcopenia Anorexia Poorer survival
Interferon-γ	• Accelerates proteolysis via the adenosine triphosphate-dependent ubiquitin proteasome pathway (major system that regulates skeletal muscle mass and strength) • Up-regulation of Adenosine triphosphate-dependent ubiquitin proteasome pathway in the skeletal muscle of weight-losing cancer patients • Components of the adenosine triphosphate-dependent ubiquitin proteasome pathway are up-regulated in the skeletal muscle of weight-losing cancer patients versus both healthy subjects and weight-stable cancer patients	Weight loss
Interleukin-1	• Associated with elevated C-reactive protein and low albumin • Catabolic programming in muscle, inducing atrophy	Weight loss Weakness Anorexia Sarcopenia Increased length of hospital stay Poorer survival
Interleukin-6	• Independently associated with elevated C-reactive protein and low albumin • Stimulates muscle protein breakdown and myocyte apoptosis	Sarcopenia Physical weakness Anorexia Poorer quality of life Poorer survival

variations in REE may be the result of CC stage. Evidence from preclinical studies indicates that hypermetabolism in rats was associated with worsening precachexia and cachexia [52], the rats then reached a stable metabolic phase before progressing to a preterminal (refractory cachexia) hypometabolic phase. Further human research is needed to profile the REE at different CC stages, particularly by tumour type.

Hormones are also involved in anabolism and catabolism. Emerging evidence suggests that IGF-1 and testosterone are down-regulated in the skeletal muscle of cancer patients and might serve as an early marker of CC [47,53]. In the systematic review (71 studies of 6325 cancer patients) by Blum *et al.* [14], weight-losing cancer patients had elevated fasting plasma insulin (with no insulin resistance), fatty acid oxidation, lipolysis and fatty acid clearance. Whole body protein breakdown was elevated, and the circulating branched chain amino acids were depleted. However, the utility of these indicators is yet to be confirmed with respect to diagnosing CC.

Client history. The risk and progression of CC depends on cancer type and stage, and therefore these medical history details should be recoded as part of nutrition assessment [1].

Nutritional diagnosis

It is important that a nutrition diagnosis identifies and describes a specific problem that can be resolved or improved through a nutrition intervention [10]. Although CC is viewed as a medical issue that is not responsive to conventional nutrition support, we would argue that an initial diagnosis of CC provides context and direction for the subsequent nutrition interventions. For a diagnosis of CC, the NCP Terminology (NCPT) code is 'chronic disease- or condition-related malnutrition (undernutrition)' (NC-4.1.2) [10] as related to increased nutrient needs, anorexia or diminished intake due to CC. Signs and symptoms include non-volitional weight loss, loss of subcutaneous adipose tissue or muscle mass, inadequate energy intake, deterioration of physical function and the presence of malignancy. Non-volitional weight loss should be considered clinically relevant at ≥10% in 6 months or ≥5% in 1 month [10] or ≥2% in the presence of sarcopenia when measured by a readily available objective measure [1]. Inflammation should be considered where CRP >10 mg L^{-1} and an anorexia where an Edmonton Symptom Assessment Score score of >3 [39] (Table 1). These parameters help to clarify an otherwise unclear diagnosis of CC, and help to stage CC, particularly precachexia [39] which would otherwise be missed. Furthermore, a

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statement that the patient has CC would clarify the diagnosis, particularly in the multidisciplinary clinical setting where other health disciplines may not be familiar with NCPT.

The increased nutrient needs are a consequence of 'increased energy expenditure' (NI-1.1) resulting in 'inadequate energy intake' (NI-1.2) and 'inadequate protein intake' (NI-5.6.1).

Increased energy expenditure (NI-1.1) [10] relates to inflammation and/or the presence of a hypermetabolic malignancy (e.g. liver cancer). Signs and symptoms include measured REE >25–30 kcal kg^{-1} body weight day^{-1} [49] and non-volitional weight loss (≥10% in 6 months or ≥5% in 1 month). The signs and symptoms of 'inadequate energy intake' (NI-1.2) [10] include an estimated intake less than measured REE or estimated REE with or without non-volitional weight loss. We suggest wherever possible to measure REE because the current estimating equations do not factor in cancer type, cancer treatment, body composition and CC stage, which influence REE [54].

A study of predictive equations for REE [55] reported that fixed factor equations (e.g. 30 kcal kg^{-1} day^{-1}) demonstrated one of the largest prediction error rates and that the Food and Agricultural Organisation/World Health Organisation/United Nations University (1985) equation had the smallest prediction error in adult inpatients, outpatients, and underweight patients. However, this equation underestimates low REE and overestimates high REE [55].

There is also variability in the definition of inadequate intake, with the NCPT [11] stating <75% of estimated energy for 1 month, and the 2017 ESPEN guidelines [49] stating 'unable to eat for >1 week' or 'if patients fail to meet ≥60% of their energy requirements for 1–2 weeks'. The GLIM criteria [7] state '≤50% for >1 week' or 'any reduction for >2 weeks' (Table 1). At this stage, it is suggested that clinicians use the most recent and least conservative criteria; the GLIM criteria. The signs and symptoms of 'inadequate protein intake' (NI-5.6.1) [10] include estimated intakes insufficient to meet protein requirements (<1.0–1.5 g kg^{-1} body weight per day) [49]. Although there is guidance for estimating protein requirements in cancer, there are no CC-specific estimating equations. Furthermore, dietitians should be aware of the potential limitations of protein estimating equations which are based on body weight, not body composition and, as such, might over- or underestimate protein requirements when accounting for the variations in lean mass [56]. Despite these criticisms, no model has been proposed to more accurately estimate protein requirements in the clinical setting.

Finally, patients with CC are subject to 'poor nutrition quality of life' (NB-2.5) [10] as related to food and nutrition-related knowledge deficit, altered body image and/or lack of social support for implementing changes. The signs and symptoms of this diagnosis are quite complex. Oberholzer *et al.* [57] reported the damaging effect of misinformation and poor understanding around the role of eating during refractory cachexia on the psychological wellbeing of and relationship between the patients and their carers. This is particularly so with respect to the visible physical changes, physical weakness, loss of independence and possible social isolation leading to psychosocial effects [57]. These effects arose when there were expectations that improved dietary intake would stop weight loss at the refractory stage of CC.

Nutrition intervention

Correcting increased energy expenditure

The definition of CC states that muscle loss cannot be fully reversed by conventional nutrition support. Therefore, nutraceuticals or immunonutrition supplements, including eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid from fish oil have been investigated. *In vitro* studies demonstrated that EPA mediates the down-regulation of proteolytic pathways and the APPR and improves insulin sensitivity, energy and protein intake [58]. Similarly, in humans, there is evidence to support modest benefits on some aspects of quality of life and PALs [2,59].

Recent preclinical studies [60–63] have suggested that resistance to platinum-based chemotherapy might be induced by endogenous hexadeca-4,7,10,13-tetraenoic [16:4(*n*-3)] acid synthesis in response to omega-3 fatty acid supplementation. However, a secondary analysis of a fish oil supplementation trial [64] suggests that, although those taking fish oil had a greater increase in plasma 16:4(*n*-3), there was no difference in 16:4(*n*-3) between those who did and did not respond to cancer treatment. Interestingly, the study also showed that 16:4 (*n*-3) was already present in the plasma prior to the commencement of platinum-based chemotherapy, suggesting that omega-3 fatty acids are safe for use in patients undergoing platinum-based chemotherapy. The 2017 ESPEN guidelines [49] recommend EPA use in advanced cancer patients undergoing chemotherapy who are at risk of weight loss or already malnourished and state that supplemental intakes with doses of 4–6 g day^{-1} fish oil or 1–2 g day^{-1} EPA diminish inflammatory markers.

Correcting suboptimal protein and energy intake

A systematic review of dietary treatments (five studies) in CC reported that, although there is some evidence that

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dietary counselling alone improves dietary intake, corresponding improvements in body weight were not evident [65]. In studies where cancer patients increased their dietary intake and weight through dietary counselling, parenteral/enteral nutrition or appetite stimulants, significant improvements in muscle mass were not evident [47,65–67].

This is partly because CC patients achieve an anabolic response to feeding through a decrease in protein breakdown, whereas healthy controls exhibit both a reduction in protein breakdown and an increase in protein synthesis [68]. Engelen *et al.* [69] demonstrated that a nutrition supplement of 14 g EAAs resulted in a higher net protein anabolism in non-small cell lung cancer patients. In addition, net protein anabolism in their study was positively correlated with the amount of EAA in the systemic circulation, irrespective of weight loss, inflammation or survival duration [69]. EAAs control the balance between muscle synthesis and degradation; changing the dimensions of this equation, as occurs in CC, alters this balance [43]. EAAs also regulate the cellular expression of amino acid transporters, thereby indirectly controlling cellular amino acid concentrations [43]. A minimum requirement in the dietary management of CC is the inclusion of the appropriate ratio of EAAs in the diet provided on a background of adequate energy intake for supplemental amino acids to be effective with respect to promoting muscle protein synthesis. However, there are currently no EAA ratio reference values for CC. Once established, an additional diagnosis of 'intake of types of amino acids inconsistent with needs' (NI-5.7.1) could be included and addressed with the appropriate nutrition intervention.

In summary, even though estimated protein requirements can be satisfied through protein-rich foods and conventional nutrition supplements, protein quality is not always optimal for anabolism, where protein quality is the extent to which the amino acids match the amino acid needs and how well they are extracted from the diet [65]. Therefore, the effectiveness of any corrective actions on protein intake and quality should be conducted by monitoring body composition.

Correcting poor nutrition quality of life

Because APDs undertake the nutritional management of patients with CC, they are ideally situated with respect to educating the multidisciplinary team and counsel patients with CC and their carers about what to expect throughout the CC trajectory. It is important that everyone involved in the care of patients with CC are informed of the symptomology and progressive nature of the condition, particularly with regard to precachexia (where nutrition intervention would be most effective) and refractory cachexia. The psychosocial effects of CC on the patient should be managed from diagnosis [1].

Nutrition monitoring and evaluation

The goals of nutrition intervention in CC are to stabilise weight and muscle mass, by correcting increased energy expenditure, poor nutrition quality of life, and suboptimal protein and energy intake [2]. Evaluation of nutrition intervention by the APD includes assessment of macronutrient and energy intake, physical activity, anthropometry (weight, muscle mass), biochemical or medical tests (disease burden/inflammation), physical examination (appearance, appetite, muscle status) and patient outcomes (quality of life, self-rated health and wellbeing, physical function). Obviously, most of these outcomes will also be discussed and assessed by other disciplines, such as the oncologist, or other allied health services, and multidisciplinary treatment and coordination of care is essential in CC.

An ongoing trial investigating a multimodal treatment in CC is a good example: the Multimodal – Exercise, Nutrition and Anti-inflammatory medication for Cachexia (MENAC) Trial (NCT02330926). The MENAC Trial is a multicentre, 6-week, Phase III randomised, open label trial evaluating the effectiveness of a multimodal intervention on the body weight of advanced cancer patients undergoing chemotherapy. The MENAC trial recognises the multifactorial nature of CC and addresses each aspect of the syndrome. Dietary counselling with oral nutritional supplements comprising 542 kcal and 30 g day^{-1} protein is provided to maintain energy and protein balance. Non-steroidal anti-inflammatories (1200 mg per day ibuprofen) and 2 g of EPA and 1 g of docosahexaenoic acid (separately or as part of the oral nutrition supplement) are also included to address inflammation. A physical exercise programme using resistance and aerobic training is included to increase anabolism.

With the emergence of interdisciplinary teams in modern health care, it is expected that therapeutic approaches are multimodal with nutrition remaining the cornerstone of therapy [9].

Discussion

In summary, muscle wasting is the most obvious and clinically relevant symptom of CC and is caused by a disruption in eating behaviour, energy expenditure and metabolism, resulting in a negative protein balance. This disruption is driven by inflammatory processes driving lipolysis and proteolysis. Thus far, no single metabolic parameter has been identified to diagnose CC; however,

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consensus diagnostic criteria and staging have been proposed. Precachexia or the risk of developing CC might be identified by existing cachexia tools where indicators of inflammation and metabolic alterations are included. However, the exact cut-offs of the clinically available markers for predicting CC need further investigation. In addition to markers of inflammation, a full nutrition assessment for CC should consider REE, anorexia severity irrespective of its impact on dietary intake, and objective measures of body composition, particularly lean body mass. Measured REE is preferable because there is a high variability of REE across CC stages and in relation to lean mass. Dietary intake and the presence of anorexia should both be evaluated because precachectic patients may be asymptomatic, exhibiting no reduced dietary intake, weight loss or loss of physical function, despite underlying physiological changes. Monitoring of intervention efficacy should focus on maintaining or slowing the loss of muscle mass. However, if assessment methods are unavailable, weight change could be used as a gross indicator. Future interventions are likely to be multimodal, with nutrition remaining the cornerstone of any therapy.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent narrative literature review. The lead author affirms that no important aspects of the literature review have been omitted and that any discrepancies from the literature review as planned have been explained.

Conflict of interests, source of funding and authorship

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BM and LT conceived the review, performed article searches and wrote the manuscript, AM and EI wrote and reviewed the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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