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DIET AND SLEEP

Diet and sleep health: a scoping review of intervention studies in adults

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Abstract

Background: Recent research has demonstrated an association between dietary intake and sleep health that can influence chronic disease risk factors. A scoping review of research studies investigating dietary intake and sleep was undertaken to determine the extent and scope of research in laboratory-based, free-living and mixed settings. Additionally, this review determines how well subpopulations and geographical locations are represented and the methodologies used to assess outcome measures.
Methods: Five online databases were used to identify papers published between 1970 and 2017. Included studies were those conducted in adults and reported both outcomes of interest: (i) sleep health, including sleep restriction and sleep hygiene and (ii) dietary outcomes, including altered nutrients, dietary patterns and supplements.
Results: In total, 129 publications were included with the majority being dietary interventions investigating sleep outcomes (n = 109) with fewer being sleep interventions investigating and reporting dietary outcomes (n = 20). Dietary interventions were most often carried out in free-living environments, in contrast to sleep interventions that were most often carried out in laboratory-based environments. The majority of dietary interventions investigated use of a supplement (n = 66 studies), which was predominantly caffeine (n = 49). Sleep interventions investigated sleep duration only, with the majority (n = 17) investigating the effect of partial sleep restriction under 5.5 h per night on dietary intake, while three studies investigating total sleep deprivation.
Conclusions: Investigating broader aspects of dietary such as overall diet quality and dietary patterns and other components of sleep health such as quality, timing and sleep hygiene are important aspects for future research.

Introduction

Individually, poor dietary intake and poor sleep are associated with increased risk of developing obesity and weight-related chronic diseases such as type 2 diabetes and coronary heart disease [1–3]. Sleep disturbance is hypothesised to interfere with the bodies restorative processes that occur during sleep, which can lead to biological risk factors for chronic disease (e.g. decreased insulin sensitivity) [4]. In the USA, 54% of adults are estimated to have a poor quality diet [5] and less than two-thirds of adults sleep for the recommended 7–9 h per night [6,7], whereas one-quarter report poor sleep quality [8].

Poor diet characterised by excessive energy intake, low intakes of core foods such as fruits and vegetables and overall poor diet quality can result in weight gain as a result of an energy imbalance [9] and can contribute to poor sleep. A number of studies have found that dietary intake, particularly in the period before bedtime, can affect various aspects of sleep health (i.e. increased sleep

latency, shorter sleep cycles) [10–12]. Diet has been suggested to influence sleep through the consumption of sleep-promoting and wake-promoting nutrients. Research has reported a range of nutrients that promote sleep, including tryptophan [12], which is an amino acid that is converted in the body to serotonin and melatonin, essential for sleep regulation [13,14], as well as nutrients that inhibit sleep, including caffeine, which is a nervous system stimulant [15] and alcohol, a depressant that often is associated with shorter sleep cycles and poor sleep quality [16]. A previous review of the relationship between diet and sleep reported that a diet rich in fruits, vegetables, whole grains and lean protein sources can improve sleep duration and quality [14].

Sleep is assumed to influence dietary intake, notably energy intake, through impaired executive functioning from insufficient sleep that leads to an increase in the activation of brain regions sensitive to food stimuli, thereby increasing the motivation to eat [17]. Insufficient sleep has also been found increase energy intake by up-regulating appetite hormones leptin and ghrelin and increase intakes of take-out food [18] and increased intakes of energy dense nutrient poor foods to overcome tiredness [19–21].

Existing research indicates a bidirectional relationship in that dietary intake may influence sleep duration and quality, and sleep duration may influence diet. Previous reviews have investigated intervention studies on the effect of sleep on dietary intake; however, the focus has been specifically on the effect of sleep duration [22–24]. These reviews have not examined the scope of the evidence of other dimensions of sleep health (i.e. quality, timing and daytime alertness) and their influence on dietary intake. Furthermore, existing reviews have focused on the dietary outcomes of energy intake and single nutrients, [22,23] without comprehensively examining other aspects, including diet quality or types of foods consumed in response to sleep health.

However, there is no review that has determined the extent/nature of the evidence from studies of the influence of dietary intake on sleep, and the multiple indicators of sleep health. Sleep health is a multidimensional construct that includes sleep duration and quality, as well as sleep timing and daytime alertness [25]. Furthermore, there has been no review conducted on the extent of the evidence on the effect of sleep health on aspects of dietary intake, in addition to energy intake and macronutrient intake, in interventional studies where causal relationships can be determined.

Given the high prevalence of both poor diet and poor sleep behaviours in the adult populations, the negative implications for health that such behaviours can have, and evidence suggesting there may be a bidirectional relationship between sleep and diet, it is important that the scope of the evidence is explored. A scoping review will increase our understanding of the current evidence base and identify gaps that may exist and highlight areas to explore further, in future research.

The objective of this scoping review is to provide an overview of the evidence of interventions in the adult population that have examined the influence of diet interventions on sleep health outcomes, as well as sleep interventions on dietary outcomes. The primary question was to determine what types of studies, settings and population groups have been used to examine the influence of diet interventions on sleep health outcomes, as well as sleep interventions on dietary outcomes. The secondary questions were to evaluate the type of interventions and the range of outcomes that are reported in published studies.

Materials and methods

This systematic review adheres to the PRISMA statement for scoping reviews (Prisma-SCR) [26] and, as such, the protocol is not registered.

Study criteria

To be eligible for inclusion in this review, a study had to be conducted in an adult population (≥18 years) free of any medically diagnosed health conditions, sleep disorders (e.g. sleep apnoea, narcolepsy, insomnia), eating disorders (e.g. anorexia nervosa, bulimia nervosa), mental health conditions, diabetes, cancer, and cardiovascular disease (CVD). Eligible studies reported an intervention that modified either (i) components of diet (e.g. energy intake, macronutrient intake, intake of a specific food/beverage, or dietary pattern), or (ii) components of sleep health (e.g. sleep duration, sleep efficiency, sleep timing) or sleep hygiene practices, and reported diet or sleep health outcomes. For the purposes of this review, randomised controlled trials (RCTs), randomised and non-randomised cross-over studies, and pre-post studies conducted in free-living, laboratory and mixed settings were included. Reviews, meta-analyses, observational studies, case studies, editorials and conference abstracts were excluded.

Search strategy

Five databases (Medline, EMBASE, Cochrane, SCOPUS and CINAHL) were searched from their inception to November 2017 using predefined keywords (for the full search strategy, see Supporting information, Table S1). Limits were applied to include studies published in the

English language, in humans. A manual search of the reference lists of relevant publications was also conducted to ensure that no relevant articles were missed.

Study selection

Duplicates and articles published before 1970 were removed, as collectively these databases report that they reliably index records from 1970 onward. The remaining title and abstracts were screened by two independent reviewers (SF, research assistant) using the predetermined inclusion/exclusion criterion. Full texts were retrieved and evaluated against the inclusion/exclusion criteria independently. Discrepancies were resolved by a third independent reviewer (TB or MD). Consensus was reached for all included articles.

Data charting

A data extraction form was created jointly by the research team to determine the variables to extract. Two reviewers independently charted the data and extracted the information in a consistent way that were relevant to the review's aims. The form included characteristics and information outlined in Table 1. Any disagreements between reviewers were resolved by discussion with a third reviewer. Data extracted included study design, country, setting (laboratory/free-living/mixed), participant characteristics, the intervention type, and intervention delivery method. For the purpose of this review, dietary interventions were classified into major intervention approach, which included: supplements, altered nutrient (which included interventions where only one aspect of the diet was being modified), fasting/energy restriction, altered overall diet (such as changes in overall dietary pattern, low fat) and 'other' where an intervention could not be classified into one of the aforementioned categories. In a similar mode, sleep interventions were classified as one of the following: sleep duration (restrict or extend), timing, efficiency or quality, or promotion of sleep hygiene practices. Because the objective of a scoping review is to provide an overview of the existing literature relating to a research question, assessments of the methodological quality of included studies are not routinely carried out [26]. Data are summarised using the information presented within studies.

Results

Search results

The search strategy identified 20 424 articles for screening (Figure 1) and nine additional articles were identified through a manual search/searching of references lists of included studies. Following title and abstract screening, 194 studies were identified for full-text review, from which 65 studies were excluded because they did not meet the inclusion/exclusion criteria. In total, 129 studies were included in the current review, with the majority being dietary interventions reporting on sleep outcomes (n = 109) and studies for sleep interventions reporting on dietary intake (n = 20).

Dietary interventions reporting on sleep outcomes

Study designs

For dietary interventions (n = 109), the majority of studies were of a cross-over design (n = 76; 69.72%) where the same population group were exposed to the different intervention conditions. Other study designs included RCTs or controlled trials (n = 26; 24%) where different population groups were allocated to different interventions and compared or pre-post studies (n = 7; 6.42%) where groups were exposed to one condition only.

Settings and geographical locations

The majority of studies recruited participants from a community/free-living setting (n = 106; 97.25%), with a small number of studies recruiting participants from clinics (n = 3; 2.75%). Most studies were carried out in the free-living environment (n = 80; 73%), whereas a smaller proportion were carried out in laboratory settings (n = 29; 27%) (Figure 2a,b). All dietary interventions were delivered face to face with the majority (n = 100) delivered at an individual level, group-based (n = 4) and n = 5 classified as mixed (individual and mixed). The average number of diet study participants was 30 (range 6–390 participants). Most studies were performed in the USA (n = 39; 35.78%), followed by the UK (n = 20; 18.35%), Australia (n = 8; 7.34%), Japan (n = 6; 5.5%) and Canada (n = 5; 4.59%) (Figure 2a,b).

Participant characteristics

The mean (SD) age range of participants derived from reported values in studies was 19.5 (5.7) 1.8–72.1 years. The age range of participants derived from reported values was 18–85 years; however, the age of participants was not reported in 26 studies. The majority of dietary studies included a mix of participants from both sexes (n = 63; 57.8%) (Figure 2c). In forty-one (37.61%) studies, participants were exclusively male and, in four (3.67%) studies, participants were exclusively female. In one study the sex of participants was not reported [27]. In total, 73 studies reported the body mass index (BMI) of participants and this ranged from 17.6 to 42 kg m^{-2} with the mean BMI of study participants being above healthy weight (BMI >25) in eight studies only.

Table 1 Characteristics of included studies

Author, Year	Country	Study design	Participants (*n*)		Age, mean (SD) (range)	Sex	BMI, mean (SD) (range)	Setting	Intervention approach	Mode
			Total	Per group [randomised controlled trial (RCT)]						
Diet interventions										
Adam 1980 [50]	UK	Cross-over	16	NR	59.0 (52–67)	Male/ Female	NR	Community/ free living	Diet/ Supplement	Malted milk
Afaghi *et al.* 2007 [51]	Australia	Cross-over	12	NR	NR (18–35)	Male	NR (18.5–25.0)	Laboratory	Diet/Altered nutrient	High glycaemic index (GI) versus low GI carbohydrate (CHO)
Afaghi *et al.* 2008 [52]	Australia	Cross-over	14	NR	23.6 (4.1) (18–35)	Male (M)	23.4 (1.9)	Laboratory	Diet/Altered nutrient	Very low CHO
Alfaris *et al.* 2015 [53]	USA	RCT	390	Usual care = 130, Brief lifestyle counselling (LC) = 131, Enhanced LC = 129	51.5 (11.5)	Male/ Female	38.5 (4.7)	Community/ free living	Diet/Fasting	Usual care, brief LC or enhanced LC (with Orlistat)
Ali *et al.* 2015 [54]	New Zealand	Cross-over	10	NR	24.0 (4.0)	Female	NR	Community/free living	Diet/Supplement	Caffeine
Almeneessier *et al.* 2017 [55]	Saudi Arabia	Cross-over	8	NR	26.6 (4.9) (20–35)	Male	23.7 (3.5)	Laboratory	Diet/Fasting	Ramadan fasting
Anderson *et al.* 2006 [27]	UK	Cross-over	10	NR	24.4 (14.4)		NR (22–25)	Laboratory	Diet/ Supplement	Sugary drink
Arnulf *et al.* 2002 [56]	France	Cross-over	17	NR	26.0 (5.9) (18–38)	Male/ Female	22.2 (4.3) (17.6–33.0)	Laboratory	Diet/Altered nutrient	Tryptophan depletion
Beaumont *et al.* 2004 [57]	France	RCT	27	Placebo = 9, Slow release caffeine (SRC) = 9, Melatonin = 9	35.3 (8.1)	Male/ Female	NR Weight (kg) = 77.6 (15.8)	Laboratory	Diet/Supplement	SRC/melatonin
Beaumont *et al.* 2005 [58]	France	Cross-over	16	NR	23.0 (2.0) (19–27)	Male	NR Weight (kg) = 73.3 (3.7)	Laboratory	Diet/Supplement	Slow release caffeine
Boelsma *et al.* 2010 [59]	Netherlands	Cross-over	21	NR	33.0 (14.0) (19–57)	Male	22.4 (2.5) (18.7–26.3)	Laboratory	Diet/ Altered overall diet	Low protein/high CHO or high protein/low CHO
Bonnet *et al.* 1992 [60]	USA	Controlled study	12	NR	NR (18–30)	Male	NR Weight (lb) = 140–200	Laboratory	Diet/ Supplement	Caffeine
Bonnet *et al.* 1995 [61]	USA	RCT	140	Group 1 (G1): Control = 27, Group 2 (G2): 2–4 h nap = 60, Group 3 (G3): 8 h nap = 24, Group 4 (G4): 150–300 mg Caffeine = 17, Group 5 (G5): 400 mg caffeine = 12	G1 = 20.6, G2 = 20.3, G3 = 20.3, G4 = 20.0, G5 = 19.6 (18–30)	Male	NR Weight (lb) = G1 = 160.1, G2 = 165.3, G3 = 169.7, G4 = 171.0, G5 = 150.3	Laboratory	Diet/Supplement	Caffeine
Bonnet *et al.* 1996 [62]	USA	Cross-over	12	NR	NR (18–30)	Male	NR	Laboratory	Diet/ Supplement	Caffeine
Bravo *et al.* 2013 [12]	Spain	Cross-over	35	NR	62.0 (0.82)	Male/ Female	25.5 (1.0)	Community/ free living	Diet/ Supplement	Tryptophan

Table 1 Continued

Author, Year	Country	Study design	Participants (*n*)		Age, mean (SD) (range)	Sex	BMI, mean (SD) (range)	Setting	Intervention approach	Mode
			Total	Per group [randomised controlled trial (RCT)]						
Březinová *et al.* 1972 [63]	UK	Cross-over	18	Y = 10, Older = 8	Y = 22.0 (20–30), Older = 55.0 (42–66)	Male/ Female	NR	Laboratory	Diet/Supplement	Malted milk
Březinová 1974 [64]	UK	Cross-over	6	NR	56.0 (50–63)	Male/ Female	NR Weight (kg) = 45.9–85.4	Laboratory	Diet/Supplement	Caffeine
Carrier *et al.* 2007 [65]	Canada	Cross-over	34	Night = 17, Day = 17	Night = 37.2 (3.5), Day = 39.9 (3.8)	Male/ Female	Night = 23.0 (0.7), Day = 23.6 (0.7)	Laboratory	Diet/Supplement	Caffeine
Carrier *et al.* 2009 [66]	Canada	Cross-over	24	Young (Y) = 12, Middle-aged (M-A) = 12	Y = 24.2 (3.3) (20–30), M-A = 53.8 (3.9) (45–60)	Male/ Female	NR > 28.0	Laboratory	Diet/Supplement	Caffeine
Collet *et al.* 2016 [67]	UK	Cross-over	12	NR	24.2 (1.3)	Male	23.1 (0.4)	Laboratory	Diet/Fasting	10% estimated energy requirement
Dammann *et al.* 2013 [68]	USA	Cross-over	44	NR	NR (21–50)	Male/ Female	NR	Laboratory	Diet/Supplement	Did not assess sleep, only feelings of alertness
De Valck *et al.* 2001 [69]	Belgium	Cross-over	12	NR	22.5 (1.6) (20–25)	Male/ Female	NR	Laboratory	Diet/Supplement	Caffeine
Distelberg *et al.* 2017 [70]	USA	RCT	49	Regular = 28, Control = 21	27.3 (5.7)	Male/ Female	26.1 (5.6)	Community/ free living	Diet/Supplement	Caffeine
Drake *et al.* 2003 [71]	USA	Cross-over	13	NR	27.5 (5.4) (21–35)	Male/ Female	NR (19.8–27.5)	Laboratory	Diet/Supplement	Caffeine and ethanol
Drake *et al.* 2006 [72]	USA	Cross-over	21	Low FIRST = 11, High FIRST = 10	Low FIRST = 32.6 (15.5) High FIRST = 34.2 (13.7)	Male/ Female	NR	Laboratory	Diet/ Supplement	Caffeine
Drake *et al.* 2013 [73]	USA	RCT	12	NR	29.3 (7.6)	Male/ Female	25.1 (4.9)	Community/ free living	Diet/Supplement	Caffeine
Drapeau *et al.* 2006 [74]	Canada	Cross-over	24	Y = 12, M-A = 12	Y = 23.8 (0.66) (20–30) M-A = 50.3 (1.62) (40–60)	Male/ Female	NR (>28)	Laboratory	Diet/Supplement	Caffeine
Driver *et al.* 1999 [75]	South Africa	Cross-over	7	NR	NR (20–24)	Male	23.4 (2.6)	Laboratory	Diet/Other	Temperature
Feige *et al.* 2006 [76]	Germany	Cross-over	10	NR	29.7 (7.4) (23–45)	Male/ Female	NR (20.6–24.3)	Laboratory	Diet/Other	Alcohol
Filiatrault *et al.* 2014 [77]	Canada	Cross-over	150	NR	38.8 (8.6) (20–55)	Male/ Female	33.3 (3.5) (27–42)	Community/ free living	Diet/Fasting	Calorie restriction
Garrido *et al.* 2013 [78]	Spain	Cross-over	30	Y = 10, M-A = 10, Elderly (E) = 10	NR Y = (20–30) M-A = (35–55) E = (65–85)	Male/ Female	Y = M: 24.9 (0.7) F: 23.1 (2.6) M-A = M: 24.9 (0.8) F: 23.8 (2.5) E = M: 25.0 (2.8) F: 24.8 (2.9)	Community/ free living	Diet/Supplement	Cherry

Table 1 Continued

Author, Year	Country	Study design	Participants (*n*) Total	Per group [randomised controlled trial (RCT)]	Age, mean (SD) (range)	Sex	BMI, mean (SD) (range)	Setting	Intervention approach	Mode
Hansen *et al.* 2014 [79]	USA	RCT	95	Control = 47, Intervention = 48	42.0 (21–60)	Male	NR	Community/free living	Diet/Supplement	Salmon
Harnish *et al.* 1998 [80]	USA	Cross-over	11	NR	24.4 (19–30)	Male/ Female	NR	Laboratory	Diet/Altered overall diet	High energy versus low energy
Herzog *et al.* 2012 [81]	Germany	Cross-over	14	NR	23.3 (0.5)	Male	TSD = 23.0 (0.5) LEI = 23.0 (0.5) HEI/ Sleep = 23.0 (0.5) LEI/Sleep = 23.0 (0.5)	Laboratory	Diet/Other	Sleep deprivation or not on memory (with over or under nutrition)
Hindmarch *et al.* 2000 [82]	UK	Cross-over	30	NR	27.3 (0.9) (19–36)	Male/ Female	23.4 (0.6)	Laboratory	Diet/Supplement	Caffeine
Ho *et al.* 2013 [83]	Hong Kong	RCT	10	Control = 6, Intervention = 4	Control = 21.5 (1.7) Intervention = 21.3 (1.5)	Male/ Female	NR	Community/free living	Diet/Supplement	Caffeine
Horne *et al.* 1996 [84]	UK	Cross-over	10	NR	28.0 (3.2)	Male/ Female	NR	Laboratory	Diet/Supplement	Caffeine
Howatson *et al.* 2012 [85]	UK	Cross-over	20	NR	26.6 (4.6) (18–40)	Male/ Female	24.7 (3.5)	Community/free living	Diet/Supplement	Cherry
James 1998 [86]	Australia	Cross-over	36	NR	23.0 (18–52)	Male/ Female	NR	Laboratory	Diet/Supplement	Caffeine
Jay *et al.* 2006 [87]	Australia	Cross-over	15	NR	22.0 (2.0)	Male/ Female	23.5 (4.7)	Laboratory	Diet/Supplement	Caffeine
Júdice *et al.* 2013 [88]	Portugal	Cross-over	30	NR	24.5 (4.8) (20–39)	Male	23.6 (2.5) (19.6–29.9)	Community/free living	Diet/Supplement	Caffeine
Kamimori *et al.* 2000 [89]	USA	RCT	50	Placebo = 12, Low = 13, Medium = 12, High = 13	23.6 (18–32)	Male	NR Weight (kg): Placebo = 73.8 (64.1–79.5) Low = 77.8 (54.1–95.5) Middle: 71.7 (1.4–78.2) High :72.8 (64.5–89.1)	Laboratory	Diet/Supplement	Caffeine
Karacan *et al.* 1973 [90]	USA	Pre-post	11	NR	NR (22–25)	Male	NR	Laboratory	Diet/Fasting	Fasting
Karacan *et al.* 1976 [91]	USA	Cross-over	18	NR	NR (20–30)	Male	NR Weight (kg): 75 (55–97)	Laboratory	Diet/Supplement	Caffeine
Karklin *et al.* 1994 [92]	South Africa	Pre-post	9	NR	NR (20–36)	Female	26.1 (2.8)	Community/free living	Diet/Altered overall diet	Energy restriction diet
Kelly *et al.* 1997 [93]	USA	RCT	25	Placebo = 14, Caffeine = 11	Placebo = 21.0 (4.1) Caffeine = 19.5 (1.8)	Male	NR	Laboratory	Diet/Supplement	Caffeine

Table 1 Continued

Author, Year	Country	Study design	Participants (*n*)		Age, mean (SD) (range)	Sex	BMI, mean (SD) (range)	Setting	Intervention approach	Mode
			Total	Per group [randomised controlled trial (RCT)]						
Kwan *et al.* 1986 [94]	UK	Controlled study	6	NR	NR (20–23)	Female	NR (19–24)	Community/free living	Diet/Altered overall diet	Low CHO, high fat and protein
Lacey *et al.* 1978 [95]	UK	Cross-over	9	NR	NR	Female	NR (Normal weight (sic))	Laboratory	Diet/Altered overall diet	Variation in protein %
Lagarde *et al.* 2000 [96]	France	Cross-over	24	NR	24.0 (18–38)	Male/ Female	NR Weight (kg): Male = 75 Female = 58	Laboratory	Diet/Supplement	Caffeine
Lajambe *et al.* 2005 [97]	USA	Cross-over	16	NR	NR (18–35)	Male/ Female	NR	Laboratory	Diet/Supplement	Caffeine
Landolt *et al.* 1995 [98]	Switzerland	Cross-over	9	NR	22.4 (0.4)	Male	NR	Laboratory	Diet/Supplement	Caffeine
Landolt *et al.* 1995 [99]	Switzerland	Cross-over	8	NR	23.3 (0.3)	Male	NR	Laboratory	Diet/Supplement	Caffeine
Landolt *et al.* 1996 [100]	Switzerland	Cross-over	10	NR	61.6 (0.9) (57.6–64.3)	Male	25.0 (0.6) (22.0–27.5)	Laboratory	Diet/Other	Ethanol
Landolt *et al.* 2004 [101]	Switzerland	Cross-over	12	NR	25.3 (20–30)	Male	23.7 (20.4–28.7)	Laboratory	Diet/Supplement	Caffeine
Landstrom *et al.* 2000 [102]	Sweden	Pre-post	12	Day drivers = 6, Night drivers = 6	NR (30–60)	Male	NR	Community/free living	Diet/Altered overall diet	% Fat
Landstrom *et al.* 2000 [103]	Sweden	Cross-over	10	NR	NR (18–24)	Male/ Female	NR	Laboratory	Diet/Altered nutrient	Glucose/fructose/ H_2O
Landstrom *et al.* 2001 [104]	Sweden	Cross-over	10	NR	Male = 45.0 (26–64) Female = 28.0 (23–43)	Male/ Female	Male = 26 (22–29) Female = 23 (21–25)	Laboratory	Diet/Other	Calorie density
Lieberman *et al.* 2008 [105]	USA	Cross-over	27	NR	23.6 (1.0)	Male/ Female	NR Weight (kg) = 76.2 (2.0)	Laboratory	Diet/Fasting	Very low energy diet (VLED) versus normal
Lin *et al.* 1997 [106]	USA	Cross-over	14	NR	30.0 (5.5) (25–43)	Male	NR	Laboratory	Diet/Supplement	Intravenous caffeine
Lin *et al.* 2011 [107]	Taiwan	Pre-post	24	NR	34.4 (12.9) (20–55)	Male/ Female	21.2 (2.69)	Community/free living	Diet/Supplement	Kiwifruit
Lindseth *et al.* 2013 [108]	USA	Cross-over	44	NR	20.6 (2.0	Male/ Female	24.8 (3.5) (21–28)	Community/free living	Diet/Altered overall diet	Macronutrient %
Lindseth *et al.* 2016 [109]	USA	Cross-over	36	NR	20.9 (1.9) (18–30)	Male/ Female	24.6 (4.1)	Laboratory	Diet/Altered overall diet	Macronutrient %
Lumley *et al.* 1987 [110]	USA	Cross-over	18	NR	25.6 (21–34)	Male	NR	Laboratory	Diet/Supplement	Caffeine
Martin *et al.* 2016 [111]	USA	RCT	218	Control = 75, Intervention = 143	37.9 (7.2)	Male/ Female	25.1 (1.6) (22–28)	Community/free living	Diet/Fasting	−25% total calorie restriction
Markus *et al.* 2005 [112]	Netherlands	Controlled study	28	Poor sleepers = 14, Good sleepers = 14	Poor sleepers = 22.0 (2.0) Good sleepers = 22.0 (3.0)	Male/ Female	NR (19–26)	Laboratory	Diet/Supplement	Tryptophan
Michaelson *et al.* 2003 [113]	Germany	Pre-post	13	NR	41.2 (13.4)	Male/ Female	23.9 (4.2)	Community/free living	Diet/Fasting	Fasting

Table 1 Continued

Author, Year	Country	Study design	Participants (*n*)		Age, mean (SD) (range)	Sex	BMI, mean (SD) (range)	Setting	Intervention approach	Mode
			Total	Per group [randomised controlled trial (RCT)]						
McHill *et al.* 2014 [114]	USA	RCT	30	Control = 20, Intervention = 10	21.6 (3.5) (18–33)	Male/ Female	22.5 (2.1) (18.5–27.0)	Laboratory	Diet/Supplement	Caffeine
Miller *et al.* 2014 [115]	Australia	Cross-over	6	NR	27.5 (6.9)	Male	23.1 (0.3)	Laboratory	Diet/Supplement	Caffeine
Moja *et al.* 1984 [116]	Italy	Cross-over	12	NR	NR (18–48)	Male/ Female	NR	Laboratory	Diet/Altered nutrient	Tryptophan depletion
Muehlbach *et al.* 1995 [117]	USA	RCT	30	Caffeine = 15, Placebo = 15	Caffeine = 24.7 (19–30) Placebo = 23.9 (19–30)	Male/ Female	NR Weight (kg): Caffeine = 70.9 (49.0–98.4) Placebo = 70.3 (58.5–98.9)	Laboratory	Diet/Supplement	Caffeine
Nam *et al.* 2016 [118]	USA	RCT	55	Diet = 24, Diet + Exercise = 31	54.8 (7.8) (35–65)	Male/ Female	34.4 (4.8)	Community/free living	Diet/Altered overall diet	600 kcal deficit/day, enhance glycaemic control, minimal cardiovascular disease risk
Nehme *et al.* 2014 [119]	Brazil	Cross-over	51	NR	30.8 (5.5)	Male	18.5 (25.0)	Community/free living	Diet/Altered overall diet	Macronutrient %
Newman *et al.* 2013 [120]	USA	Cross-over	15	NR	28.6 (22–40)	Male/ Female	NR (healthy according to army regulation 600–9)	Laboratory	Diet/Supplement	Caffeine
Nicholson *et al.* 1979 [121]	UK	Cross-over	6	NR	NR (20–30)	Male	NR	Laboratory	Diet/Supplement	Tryptophan
Ong *et al.* 2017 [122]	Australia	Cross-over	10	NR	26.9 (5.3)	Male	21.7 (1.9)	Community/free living	Diet/Supplement	A-LAC/tryptophan
Orr *et al.* 1997 [123]	USA	Cross-over	20	Experiment 1 = 10, Experiment 2 = 10	Experiment 1 = 22.8 (20–29) Experiment 2 = 22.5 (18–30)	Male	NR	Laboratory	Diet/Other	Altered macronutrient profile
Paech *et al.* 2016 [124]	Australia	RCT	24	Caffeine = 12, Placebo = 12	Caffeine = 22.5 (3.3) Placebo = 22.5 (2.5)	Male/ Female	Caffeine = 21.7 (1.5) Placebo = 2.3 (2.1)	Laboratory	Diet/Supplement	Caffeine
Park *et al.* 2017 [125]	Japan	Cross-over	9	NR	25.7	Male/ Female	21.8	Laboratory	Diet/Supplement	Chlorogenic acid
Penetar *et al.* 1993 [126]	USA	RCT	50	Placebo = 12, 150 mg/ 70 kg = 12 300 mg/70 kg = 12 600 mg/70 kg = 13	23.6 (18–32)	Male	NR Weight (kg): 74.6 (55–96)	Laboratory	Diet/Supplement	Caffeine
Phillips *et al.* 1975 [127]	UK	Cross-over	8	NR	NR	Male	NR	Laboratory	Diet/Altered overall diet	Altered macronutrient profile
Pontifex *et al.* 2010 [128]	Australia	Cross-over	10	NR	21.6 (2.6)	Male	NR Weight (kg) = 75.5 (4.5)	Community/free living	Diet/Supplement	Caffeine

Table 1 Continued

Author, Year	Country	Study design	Participants (*n*)		Age, mean (SD) (range)	Sex	BMI, mean (SD) (range)	Setting	Intervention approach	Mode
			Total	Per group [randomised controlled trial (RCT)]						
Porter *et al.* 1981 [129]	UK	Cross-over	6	NR	NR Young adults	Male	NR Within + 5 kg of ideal body weight (IBW)	Laboratory	Diet/Altered overall diet	Altered macronutrient profile
Reyner *et al.* 2000 [130]	UK	Cross-over	16	Study 1 = 8, Study 2 = 8	23.0 (2.0)	Male/ Female	NR Normal weight for height	Laboratory	Diet/Supplement	Caffeine
Reyner *et al.* 2002 [131]	UK	Cross-over	12	NR	24.0 (2.0)	Male/ Female	NR Normal weight for height	Laboratory	Diet/Supplement	Caffeine
Reyner *et al.* 2012 [132]	UK	Cross-over	12	NR	21.0 (19–25)	Male	23.0 (20–27)	Laboratory	Diet/Other	Did not assess sleep, only feelings of alertness
Robillard *et al.* 2015 [133]	Canada	Cross-over	47	Y = 22, M-A = 25	Y = 23.5 (1.9) M-A = 51.7 (11.5)	Male/ Female	Y: 200 mg = 23.3 (2.4) 400 mg = 22.4 (2.0) M-A: 200 mg = 24.5 (3.1) 400 mg = 25.7 (2.1)	Laboratory	Diet/Supplement	Caffeine
Rohsenow *et al.* 2014 [134]	USA	RCT	64	Caffeinated beer = 28, Placebo beer = 36	Caffeinated beer = 22.8 (2.3) Placebo beer = 23.3 (2.1)	Male/ Female	NR	Laboratory	Diet/Supplement	Caffeine
Rosenthal *et al.* 1991 [135]	USA	RCT	36	NR	NR (19–35)	Male	NR	Laboratory	Diet/Supplement	Caffeine
Saito *et al.* 2017 [136]	Japan	RCT	119	29–30 per group (four groups)	NR (20–84)	Male/ Female	NR	Community/free living	Diet/Supplement	Zinc or Zn and astaxanthin
Shilo *et al.* 2002 [137]	Israel	Cross-over	6	NR	32.0 (12.0)	Male/ Female	NR	Community/free living	Diet/Supplement	Caffeine
Smith *et al.* 1993 [138]	UK	Controlled study	48	12 per group (four groups)	20.3	Male/ Female	NR Weight (kg) = 67.7	Laboratory	Diet/Other	Food/caffeine; no food/caffeine; caffeine/no food; no caffeine/food
Spaeth *et al.* 2017 [139]	USA	Pre-post	46	NR	33.9 (9.1) (21–50)	Male/ Female	24.5 (3.6)	Laboratory	Diet/Other	Body composition and sleep characteristics
Unno *et al.* 2017 [140]	Japan	Cross-over	20	NR	51.3 (6.7)	Male/ Female	NR	Community/free living	Diet/Supplement	Low caffeine green tea
Van Dongen *et al.* 2001 [141]	USA	RCT	28	Placebo = 13, Caffeine = 15	29.0 (21–47)	Male	NR	Laboratory	Diet/Supplement	Caffeine and napping
Verhoef *et al.* 2013 [142]	Netherlands	Pre-post	98	NR	NR (20–50)	Male/ Female	31.9 (3.2) (28–35)	Community/free living	Diet/Fasting	8wk

Table 1 Continued

Author, Year	Country	Study design	Participants (*n*)		Age, mean (SD) (range)	Sex	BMI, mean (SD) (range)	Setting	Intervention approach	Mode
			Total	Per group [randomised controlled trial (RCT)]						
VLED + 10 months maintenance										
Voderhozler *et al.* 1998 [143]	Germany	Cross-over	12	NR	34.0 (3.0) (23–55)	Male/ Female	NR	Laboratory	Diet/Altered nutrient	Tryptophan depletion
Walsh *et al.* 1990 [144]	USA	Cross-over	16	Study A = 10, Study B = 6	Study A = 30.3 (21–37) Study B = 31.5 (23–47)	Male/ Female	NR	Laboratory	Diet/Supplement	Caffeine
Wells *et al.* 1997 [145]	UK	Cross-over	18	NR	25.5 (21–38)	Male/ Female	23.7	Laboratory	Diet/Altered overall diet	Altered macronutrient profile
Wells *et al.* 1998 [146]	UK	Cross-over	9	NR	NR (19–27)	Male/ Female	23.4	Laboratory	Diet/Altered overall diet	Altered macronutrient profile
Wells *et al.* 1998 [147]	UK	Cross-over	16	Group 1 = 8, Group 2 = 8	27 (0.9)	Male/ Female	23.4 (0.32)	Laboratory	Diet/Altered overall diet	Altered macronutrient profile
Wyatt *et al.* 1970 [148]	USA	Cross-over	15	Study 1 = 5, Study 2 = 7, Study 3 = 3	NR Study 1 = (18–21) Study 2 = (45–68) Study 3 = NR	Male/ Female	NR	Laboratory	Diet/Supplement	Tryptophan
Wyatt *et al.* 2004 [149]	USA	Controlled	16	Caffeine = 8, Placebo = 8	NR (18–30)	Male	NR	Laboratory	Diet/Supplement	Caffeine
Yajima *et al.* 2014 [150]	Japan	Cross-over	10	NR	24.6 (0.7)	Male	Weight (kg) = 67.6 (2.3)	Laboratory	Diet/Altered overall diet	High fat versus high CHO
Yamadera *et al.* 2007 [151]	Japan	Cross-over	11	NR	40.5 (10.1)	Male/ Female	NR	Laboratory	Diet/Supplement	Glycine
Yamamura *et al.* 2009 [152]	Japan	Cross-over	30	Placebo first (FM2) = 15, Intervention first (FM1) = 14	FM1 = 72.1 (5.7) FM2 = 70.6 (5.7)	Male/ Female	NR	Community/free living	Diet/Supplement	*Lactobacillus helveticus*
Zammit *et al.* 1992 [153]	USA	Cross-over	12	NR	22.3 (2.8) (19–28)	Male	NR Weight (kg): 76.3 (10.5) (61.2–95.7)	Laboratory	Diet/Other	HE/LE CHO meal
Zammit *et al.* 1995 [154]	USA	Controlled	21	Control = 9, Food = 12	NR (18–30)	Male	NR Within + 15% of IBW	Laboratory	Diet/Other	HE/LE/fasting

Table 1 Continued

Author, Year	Country	Study design	Participants (*n*)		Age, mean (SD) (range)	Sex	BMI, mean (SD) (range)	Setting	Intervention approach	Mode
			Total	Per group [randomised controlled trial (RCT)]						
Zhou *et al.* 2016 [155]	USA	Cross-over	S1 = 14, S2 = 44	S1: Intervention SL = 9, Intervention BP = 5, S2: Intervention NP = 23, Intervention HP = 21	S1 = 56.0 (3.0) S2 = 52.0 (1.0)	Male/ Female	S1 = 30.9 (0.6) S2 = 31.4 (0.5)	Community/ free living	Diet/Altered nutrient	Protein
Zwyghuizen-Doorenbos *et al.* 1990 [156]	USA	RCT	24	NR	NR (21–36)	Male	NR	Laboratory	Diet/ Supplement	Caffeine
Sleep interventions										
Benedict *et al.* 2011 [157]	Germany	Cross-over	14	14	22.6 (0.8)	Male	23.9 (0.5)	Laboratory	Sleep (restricted duration)	Individual (face to face)
Bosy-Westphal *et al.* 2008 [158]	Germany	Cross-over	14	14	27.5 (5.3)	Female	25.8 (5.8)	Community/ free living	Sleep (restricted duration)	Individual (face to face)
Brondel *et al.* 2011 [159]	France	Cross-over	12	12	22.0 (3.0)	Male	22.3 (1.83) (19–24.6)	Laboratory	Sleep (restricted duration)	Individual (face to face)
Broussard *et al.* 2016 [19]	USA	Cross-over	19	NR	23.5 (0.7)	Male	23.1 (0.4v	Laboratory	Sleep (restricted duration)	Individual (face to face)
Cain *et al.* 2015 [160]	Australia	Cross-over	16	16	20.1 (1.4)	Male/ Female	20–25	Laboratory	Sleep (restricted duration)	Group based (face to face)
Calvin *et al.* 2013 [161]	USA	RCT	17	Study = 8 Control = 9	Study = 24.1 (4.5) Control = 25.4 (4.7)	Male/ Female	Study = 22.9 (1.8) Control = 22.4 (2.5)	Laboratory	Sleep (restricted duration)	Individual (face to face)
Dennis *et al.* 2016 [162]	USA	Cross-over	66	A = 34, B = 32	34.4 (9.0)	Male/ Female	24.4 (3.2)	Laboratory	Sleep (restricted duration)	Group based (face to face)
Fang *et al.* 2015 [163]	USA	Cross-over	46	Study = 34, Control = 12	Study = 34.7 (7.9), Control = 33.5 (9.3)	Male/ Female	Study = 24.8 (2.8), Control = 24.4 (3.6)	Laboratory	Sleep (restricted duration)	Individual (face to face)
Hart *et al.* 2015 [164]	USA	Cross-over	12	12	NR (25–55)	Female	NR (25–40)	Laboratory	Sleep (restricted and extended duration)	Group based (face to face)
Markwald *et al.* 2013 [165]	USA	Cross-over	16	16	22.4 (4.8)	Male/ Female	22.9 (2.4)	Laboratory	Sleep (restricted and extended duration)	Group based (face to face)
McNeil *et al.* 2016 [166]	Canada	Cross-over	18	18	23.0 (4) (18–33)	Male/ Female	22.7 (2.7) (19–30)	Laboratory	Sleep (restricted duration)	Individual (face to face)
Nedeltcheva *et al.* 2009 [167]	USA	Cross-over	11	11	39.0 (5) (34–49)	Male/ Female	26.5 (1.5)	Laboratory	Sleep (restricted duration)	Individual (face to face)
Nedeltcheva *et al.* 2010 [168]	USA	Cross-over	10	10	41.0 (5.0)	Male/ Female	27.4 (2.0)	Laboratory	Sleep (restricted duration)	Individual (face to face)
Romney *et al.* 2016 [169]	USA	Cross-over	44	Normal weight = 22, Obese = 22	29.8 (0.7)	Female	Normal weight = 22.0 (1.6), Obese = 37.0 (5.7)	Community/ free living	Sleep (restricted duration)	Individual (face to face)
Schmid *et al.* 2009 [170]	Germany	Cross-over	15	15	27.1 (1.3) (20–40)	Male	22.9 (0.3)	Laboratory	Sleep (restricted duration)	Individual (face to face)

Table 1 Continued

Author, Year	Country	Study design	Participants (*n*)		Age, mean (SD) (range)	Sex	BMI, mean (SD) (range)	Setting	Intervention approach	Mode
			Total	Per group [randomised controlled trial (RCT)]						
Spaeth *et al.* 2013 [171]	USA	RCT	225	Restricted sleep (RS) = 198, Control = 27	RS = 31.3 (7.9), Control = 31.9 (8.4)	Male/ Female	RS = 24.8 (3.3), Control = 25 (3.1)	Laboratory	Sleep (restricted duration)	Group based (face to face)
Spaeth *et al.* 2014 [172]	USA	Pre-Post	44	44	32.7 (8.7)	Male/ Female	25.2 (3.5)	Laboratory	Sleep (restricted duration)	Individual (face to face)
St-Onge *et al.* 2011 [173]	USA	Cross-over	27	Male = 14, Female = 13	Male = 36.6 (5.6) Female = 33.9 (4.3)	Male/ Female	Male = 24.1 (1.1), Female = 23 (1.1)	Laboratory	Sleep (restricted duration)	Individual (face to face)
Tajiri *et al.* 2018 [174]	Japan	Cross-over	16	16	21.6 (0.5) nn	Female	Short sleep = 20.4 (2.1), Control = 20.4 (2.0)	Community/ free living	Sleep (restricted and extended duration)	Individual (face to face)
Wells *et al.* 2006 [175]	USA	Pre-Post	50	Male = 22, Female = 28	Male = 19.6 (1.3), Female = 19 (0.9)	Male/ Female	Male = 23.3 (2.5), Female = 21.6 (2.7)	Community/ free living	Sleep (restricted duration)	Individual (face to face)

BP, beef and pork; CHO, carbohydrate; FM1, fermented milk first; FM2, fermented milk second; HEI, high energy intake; HE/LE, high energy/low energy; HP, high protein; LEI, low energy intake; M-A, middle aged; NP, normal protein; NR, not reported; SL, soy and legume; TSD, total sleep deprivation.

Types of dietary interventions

Of the 109 dietary interventions, the majority involved the provision of a supplement to participants (n = 66; 60.55%). Of the supplement studies, caffeine was the most frequently investigated in n = 49 studies, with tryptophan investigated in n = 5 studies. Other dietary interventions in descending order were the altering of overall diet (n = 16; 14.7%) with n = 13 of those studies modifying/manipulating the macronutrient profiles of diet such as fat, protein or carbohydrate. Fasting or energy restriction was reported in n = 9 studies with altering of nutrient/s (n = 7; 6.4%) with tryptophan depletion being most common (n = 3 studies). An additional 11 (10.1%) interventions were considered 'Other' because the intervention did not fit uniquely into one of the other aforementioned categories and often used a combination of the previously mentioned categories. As shown in Figure 2 dietary interventions investigating supplements and altered overall diet have shown to be of consistent interest over time however in contrast studies investigating energy restriction/fasting have only shown to be of more research interest since the year 2000 and similar studies investigating single nutrients have also shown to have increased in popularity in recent years.

Types of sleep outcomes measured

Of the sleep outcomes assessed, the majority of studies reported at least two sleep outcomes (n = 91 studies) with 39 studies reporting three outcomes. The most commonly reported outcome was sleep efficiency (n = 80 studies) followed by sleep duration (n = 66), with sleep hygiene reported in 52 and sleepiness reported in 36 studies.

Sleep interventions reporting dietary outcomes

Study designs

For sleep interventions, the majority of studies were of a cross-over design (n = 13; 65%) where the same individuals were exposed to a variety of variations of the intervention with nine specifically describing the allocation to the intervention being randomised. Four (20%) studies were RCTs where different populations were allocated to different interventions and three (15%) studies were pre-post studies with exposure to one type of intervention only.

Settings and geographical locations

For sleep interventions, the majority of participants were recruited from a free-living setting (n = 13; 65%). Other recruitment settings included clinical laboratories (n = 4; 20%), a community/free-living setting (n = 2; 10%), and a clinic setting (n = 1; 5%). More than half of the sleep

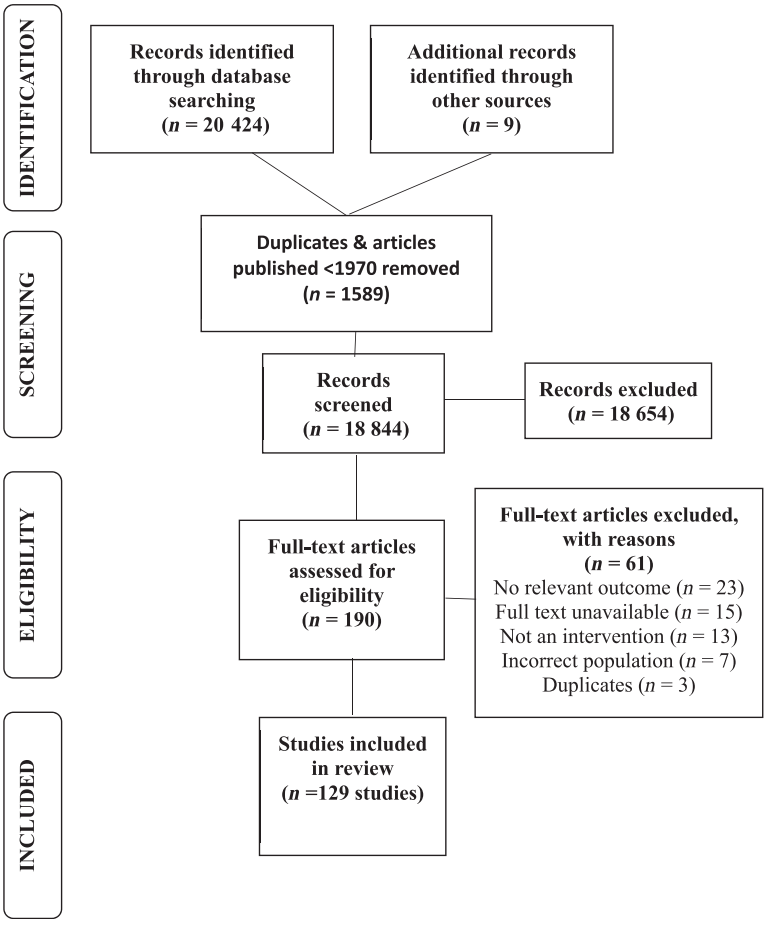

Figure 1 Flow diagram of article identification and inclusion in the scoping review.

interventions took place in a laboratory setting (n = 12; 60%) with only four (20%) carried out in a free-living setting and four (20%) interventions carried out in a mixed laboratory/free-living setting. Of the studies were carried out in the USA (n = 13; 65%), followed by Germany (n = 3; 15%) with the remaining studies performed in France (n = 1; 5%), UK (n = 1; 5%), Canada (n = 1; 5%) and Japan (n = 1; 5%).

Participant characteristics

The average number of total participants across sleep studies was 35 (range 10–225). The age range of

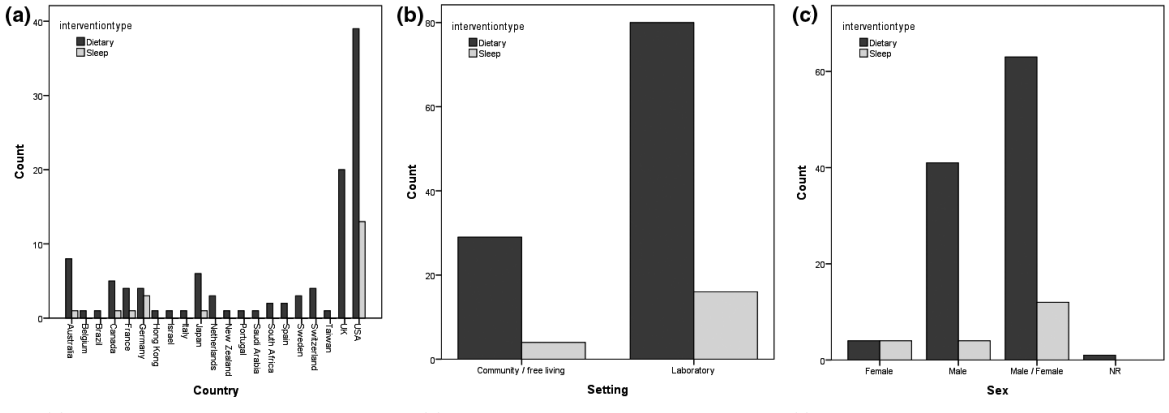

Figure 2 (a) Diet and sleep interventions by country. (b) Diet and sleep interventions by setting. (c) Diet and sleep interventions by sex.

participants derived from reported values was 18–55 years. In most sleep studies, participants were mixed sexes (n = 12, 60%). In four (20%) studies, participants were exclusively male and, in four (20%) studies, participants were exclusively female. All but two studies reported on the BMI of participants, with the BMI range of participants derived from reported values being 19–40 kg m^{-2}. Of the reported mean values of BMI for study participants, n = 3 studies were reported above the healthy weight range (BMI >25).

Types of sleep interventions

All of the 20 sleep interventions imposed a sleep restriction on study participants by reducing total sleep duration to under 5.5 h per night. Sleep was partially restricted (n = 17; 85%) or total sleep deprivation (n = 3; 15%) was used as the intervention. Differing sleep timings were assessed in addition to restricted sleep duration (n = 1 study). No other aspects of sleep health were modified in any of the interventions (e.g. quality) and no interventions assessed the effect of extending sleep duration or promoting sleep hygiene practices.

Types of dietary outcomes measured

The most commonly reported dietary outcomes reported were energy intake (n = 20; 100%) and macronutrient intake (carbohydrate, fat, protein) (n = 16; 80%). Other nutrient intake, saturated fat, sugar, fibre (n = 2 studies) and sodium (n = 1 study) was also reported, as was intake of types of foods (n = 1 study). None of the studies reported overall diet quality or dietary patterns.

Intervention delivery methods

Sleep interventions were predominantly delivered individually (n = 15; 75%) with four (20%) interventions delivered in a group format, with all interventions delivered face-to-face (n = 20; 100%).

Discussion

This scoping review set out to determine the extent and nature of the evidence with respect to both sides of the relationship between dietary intakes and sleep health outcomes. By undertaking a scoping review in this area of research, it was found that the majority of published research has investigated the effect of dietary interventions on sleep outcomes (n = 109), with far fewer studies (n = 20) investigating sleep interventions on dietary outcomes.

Not surprisingly, most dietary studies investigated the effect of caffeine on sleep. This likely reflects the well-documented sleep inhibiting effects that caffeine can have on sleep. Reviews investigating the effects of caffeine show its consumption increases sleep latency, reduces total sleep time, efficiency and worsened reports of sleep quality [28]. Caffeine can have these effects by working on the adenosine receptors [29], increasing the time taken to get to sleep, with the effects known to be most pronounced in the 30 min after consumption, which is why recommendations often include not having directly before bed; however, the effect is variable between individuals [30]. Caffeine consumption can take many forms, including most commonly from coffee, tea and cola-based drinks, but is increasingly now available from energy drinks and energy shots, especially as consumed by young adults [31]. In such drinks, caffeine is consumed in higher quantities and is often consumed in addition to alcohol, and is also often mixed with other additives that may also have a compounding effects on sleep because both alcohol and caffeine have negative effects [31].

Surprisingly few interventions (n = 3) reported on alcohol intake in the review or focused on this aspect of diet in the intervention. Alcohol intake has been associated a variety of indicators of sleep health, including sleep quality, sleep latency and sleep disturbance but less often daytime sleepiness [16]. This effect has been shown to be more pronounced in females compared to males; however, few studies have explored this [16,32,33]. The influence of alcohol on sleep has been shown to be dose dependent [32,33]. Alcohol may have these effects because it is a known depressant, and its consumption can reduce sleep latency, potentially by short-term changes in adenosine, and disrupt sleep in the later part of the night. Moderate and higher consumption reduces the proportion of REM sleep can also disrupt the sleep cycle [34]. REM sleep is the type of sleep known to be restorative [35]. Interestingly, alcohol intake close to bedtime is known to reduce sleep latency times, although adversely influence sleep by reducing the depth of sleep [36]. Fewer studies (n = 5) were identified that investigated sleep-promoting nutrients such as tryptophan. Tryptophan is often found in higher quantities in core foods such as eggs, legumes, potatoes, bananas and salmon. This means studies aiming to investigate a whole of dietary approach will likely increase dietary consumption of tryptophan; however, a whole dietary approach was only investigated in 16 studies.

The field of dietary intake and approaches has evolved over time from a nutrient approach to overall dietary quality/foods and, progressively, to eating behaviours [37] although there were few studies (n = 16) examining how overall diet influences sleep or sleep influences overall dietary quality is an area for future research. The current review has focused on dietary intake and not eating behaviours; however, eating behaviours are increasingly recognised as being important, including regular meal times,

snacking night time eating and addictive eating behaviours. Eating behaviours warrant future investigation because they have been previously shown to be associated with poorer quality sleep [38]. Addictive eating behaviours present overlap with night-time eating and poorer sleep quality [38].

Given the current review is a scoping review, details on the outcomes of each study were not extracted and so it is not possible to examine the influence of diet behaviours on sleep or ways in which diet may be modified to influence sleep. A future systematic review detailing these outcomes is warranted because, given the increased recognition of this field of research, dietary recommendations would be beneficial.

Most dietary interventions used a face-to-face approach and focused on delivery at an individual level. Given the scope of reported sleep issues internationally with large proportions of adults and increasingly reported in children with parents acting as proxy reporters [39], if future studies demonstrate the efficacy of diet modifications to improve sleep, some consideration may be required for a scaled up delivery of dietary interventions to improve sleep outcomes both for community-based and clinical settings. Telehealth and the use of technology, either in the delivery or the assessment and provision of dietary feedback using wearables or image-based methods, could be of high use in population groups with sleep issues because it has shown promise with respect to improving dietary outcomes [40].

The only manipulated component of sleep health in the included studies was sleep duration. Sleep is multicomponent in nature and overall sleep health includes sleep duration, efficiency/quality, timing and daytime function [25]. This limits the implications of current findings because it is currently unexplored regarding which dimension of sleep has the most impact and whether these dimensions are additive or not in their effect on dietary outcomes. It is possible to reduce the efficiency of sleep (e.g. creating disruptions) and alter the timing of sleep under experimental conditions to examine how modifying these components of sleep health may influence diet. Given that the components of sleep health are inter-related and also that many adults report poor sleep, examining the broader influence of sleep health on diet will improve understanding of this. No studies examined the influence of improved sleep health on diet, which is an important area to address given the focus on improving sleep at the population. It is possible to manipulate the other dimensions of sleep health and they can be assessed using existing self-report instruments [41], accelerometry [42], or using overall measures of sleep health [43,44]. The other dimensions of sleep may not have been explored for a variety of reasons, including that the publications in this review range in publication date from 1975 onwards and, during this time, other components of sleep were not yet ascertained, in addition to some settings not being feasible to measure (i.e. laboratory versus community setting). Many adults report indicators of poor sleep in addition to sleep duration (i.e. poor sleep quality/efficiency) and there is evidence from cross-sectional research that these components of sleep health are predictors of higher BMI, cardiometabolic disorders [3,45–47]. Associations have been found between lower sleep efficiency and higher energy intake, as well as late sleep timing and higher energy intake, which may explain how higher BMI is linked to poor sleep health. It is therefore important that indicators of sleep health in addition to sleep duration are examined in intervention studies to clarify the causal links between sleep health and dietary intake and adverse health conditions.

The majority of sleep studies were carried out in laboratory-based environments. This is not surprising given that a controlled environment is often required because reduced sleep in individuals can effect fatigue and impact on the safety of regular activities such as driving performance. The advantages of laboratory-based settings include the controlled environment and the fact that compliance can be more easily measured objectively compared to free-living where this would be often based on self-report measures. Other advantages include the laboratory setting allowing greater control with respect to manipulating participant sleep and monitoring of any adverse events. The disadvantages of laboratory-based settings in the context of sleep and diet include that different sleeping arrangements likely exist, the different foods and beverages available are not likely to reflect habitual intake, which can limit the generalisability of study findings, and there is a need to better understand how sleep and diet interact to influence each other in more ecologically valid settings. Qualitative research not captured in this review may also be valuable to better understand the impact of dietary and sleep behaviours. A previous qualitative analysis of young adults ($n = 57$) found that individuals were willing to change sleep behaviour to improve waking function, advance sleep onset and optimised sleep periods [48]. Importantly, in this previous study, barriers were also identified for this population group, which included time demands, technology use, difficulty switching off, and unpredictable habits [48]. These would be key considerations to getting individuals involved and motivated for interventions to improve sleep.

The identified gaps in research include more studies assessing sleep interventions and assessing and reporting on dietary outcomes, given that there were disproportionately less studies. Using study designs in community populations that make use of longer-term follow-up

(>3 months) would be useful to assess the impact of longer-term sleep issues on diet. Although, for dietary interventions, there is a gap with respect to exploring a broader dietary approach, such as diet quality rather than supplemental studies, in addition to using study designs such as RCTs that allow for direct comparisons between dietary approaches. Other components of sleep health such as quality, timing and hygiene are important to consider in research and clinical environments to assist in the development of a new understanding in this area of research.

The limitations to the review include that the review was limited to studies that were published in the English language. The review was limited to search several online databases only; however, these were considered to comprise and index the majority journals that would be likely to publish health-related research. This scoping review has several strengths, namely a comprehensive search strategy being implemented across multiple databases. Also, a detailed data extraction process relative to other published scoping reviews provided comprehensive information about the included studies. Although the included studies were limited to English language papers only, it has been found that English language publications in public health are over-represented, with 96.5% of 210 433 public health publications in Europe being reported in English [49]. Thus, it is likely that only a small minority of studies would have been missed.

In conclusion, the relationship between sleep and diet has been investigated in adults; however, this has not been comprehensive and remains disproportionate, with far more studies investigating dietary interventions on sleep outcomes. Considering the health implications associated with both sleep and diet, more research is warranted in this area.

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All authors developed the search and contributed to the data screening, extraction and drafting the manuscript. All authors have critically reviewed the manuscript and have approved the final version 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 PRISMA 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. Full Medline search strategy.

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WEIGHT LOSS AND WEIGHT MAINTENANCE

The association between chronotype, food craving and weight gain in pregnant women

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Keywords
chronotype, eveningness, food craving, pregnancy, weight gain.

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The present study investigated the association between chronotype, food craving and weight gain in pregnant women. The evening chronotype was associated with the food craving trait. Pregnant women who tend to eveningness are more likely to gain weight in the early gestational period.

Abstract

Background: This cross-sectional study investigated the association between chronotype, food craving and weight gain in pregnant women.
Methods: In total, 245 pregnant women attending the public health service in Brazil were included. Chronotype was derived from the time of mid-sleep time on free days, with a further correction for calculated sleep debt, and higher scores on this variable indicate a tendency to eveningness. A Food Craving Questionnaire Trait and State assessment was performed, and weight gain was calculated. Generalised linear models were used to determine the association between the variables under analysis.
Results: Evening types presented higher anticipation of relief from negative states and feelings as a result of eating as a usual behaviour compared to morning ($P = 0.013$) and non-evening types ($P = 0.028$); less intense desire to eat as a sporadic behaviour compared to morning ($P = 0.012$) and non-evening types ($P = 0.009$); and less anticipation of positive reinforcement that may result from eating as a sporadic behaviour than non-evening types ($P = 0.022$). We also found a significant association between chronotype score and anticipation of relief from negative states and feelings as a result of eating ($P = 0.004$); anticipation of positive reinforcement that may result from eating ($P = 0.013$) as a usual behaviour; weight gain during the early gestational period ($P = 0.024$); and intense desire to eat ($P = 0.045$) as a sporadic behaviour.
Conclusions: We conclude that evening chronotype was associated with the food craving trait. Pregnant women who tend to eveningness are more likely to gain weight in the early gestational period.

Introduction

Excessive weight gain during pregnancy is associated with adverse conditions, such as hypertension and pre-eclampsia [(1)], gestational diabetes [(2)] and a higher frequency of emergency caesarean delivery [(3)]. It is already known that these conditions could be a result of previously having been overweight or obese or an excessive gestational weight gain during pregnancy, or a combination of both [(4,5)]. From this perspective, a multidisciplinary approach to pregnancy should focus on controlling the different risk factors for excessive weight gain, such as an inappropriate eating behaviour, which is very common in pregnant women [(6–8)].

Food craving is one of several factors influencing the feeding behaviour during pregnancy [(9)]. This multidimensional experience is defined as an intense desire to eat a specific food that is difficult to resist [(10)], which may vary in different levels of intensity and frequency [(11)], and which is strongly intensified during the gestational period [(12–15)]. The aetiology of food craving is not clear, although the decrease in sensitivity of taste during the gestational period may influence the food choices, prioritising more palatable food [(16)]. Moreover, aspects related

to the individual preference to perform activities at certain times of the day [17], or chronotype, have been studied as an important influence on food craving [18]. However, studies in this area are scarce and are conducted with restricted groups. For example, in pregnant women who are very prone to problems associated with food consumption [19,20], this subject remains unexplored.

Therefore, the present study aimed to investigate the association between chronotype and weight gain in the early gestational period, which reflects the maternal body fat [21] and may induce adverse conditions to mother and child [22], and food craving. We hypothesised that evening types, such as those who have a preference to perform their activities at later times of the day, may present a higher weight gain in the early gestational period and a higher food craving than morning and non-evening types.

Materials and methods

Participants and ethics

The study comprised a cross-sectional study conducted with 245 pregnant women attending the prenatal clinics in the public health service in the city of Uberlandia, Minas Gerais, Brazil. In total, 271 pregnant women were invited to participate when they were waiting for prenatal consultation in the waiting room. Before the invitation, a brief explanation of the research and procedures was given. Pregnant women were recruited according to the following eligibility criteria: older than 18 years and not being shift worker or using illegal substances. Pregnant who tested positive for human immunodeficiency virus or with a disease such as toxoplasmosis, syphilis, varicella, rubella and cytomegalovirus were excluded from the study. Twenty-six participants were excluded because they did not provide all of the necessary information ($n = 24$) or because they presented twin pregnancy ($n = 2$). The pregnant women with metabolic diseases such as diabetes ($n = 6$), hypothyroidism ($n = 21$) and hyperthyroidism ($n = 1$) were not exclude from the study. Accordingly, the final sample was 245 pregnant women in the three gestational trimesters (Figure 1). Assessments were conducted between October 2016 and September 2017.

The sample size required was determined using G*POWER, version 3.1.9.2 (http://www.gpower.hhu.de). The calculation of the sample size was based on a F test linear multiple regression with an effect size of 0.15, an alpha level of 0.05 and a test power of 95%. Given these specifications, a total of 119 women was needed for the final analysis. Considering a 20% adjustment for possible losses, a minimum of 143 women was required.

All of the methods were carried out in accordance with relevant guidelines and regulations. This study was approved by the Ethics Committee of the Federal University of Uberlandia (CAAE: 43473015.4.0000.5152/2015).

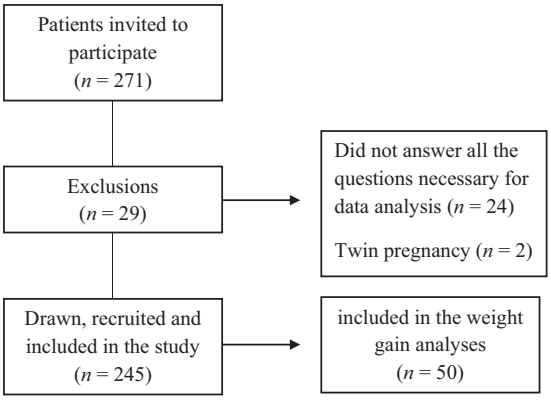

Figure 1 Study flowchart.

Evaluations

Preliminary questionnaire

An initial questionnaire was applied by the researchers to evaluate age, occupation, level of education, previous pregnancy and gestational age. Women who were 0–13 weeks pregnant were grouped in the first trimester, those who were 14–26 weeks pregnant were grouped in the second trimester and women who were 27–40/41 weeks pregnant were grouped in the third trimester [23]. We considered the early gestational period as the first 50% of the total gestational period and those women with gestational age ≤20 weeks were considered as pregnant in the early gestational period. Data regarding vomiting, nausea, heartburn, food desire, physical activity and sleep pattern were also self-reported in this evaluation.

Anthropometric variables

Height and current weight were measured and the body mass index (BMI) was calculated. The pre-pregnancy weight was obtained from the pregnant woman's medical record and the pre-pregnancy BMI (kg m^{-2}) was calculated and classified according to the BMI classification by the World Health Organization [24]. The current BMI was classified according to gestational week suggested by Atalah *et al.* [25]. Weight gain in the early gestational period was calculated as the difference between current weight, measured between 12 and 20 weeks of gestation and pre-pregnancy weight, and we excluded all of the pregnant women up to 12 weeks of gestation because our sample showed many negative values in this period, which could compromise the analyses. The weight gain analyses were adjusted for nausea, vomiting, gestational week and pre-gestational BMI.

Sleep patterns

Pregnant women were asked to report their usual bedtimes and waking times on weekdays and weekends, as described previously by Gontijo *et al.* [26]. Chronotype was assessed via mid-sleep time (MSFsc) on free days with correction for calculated sleep debt, which was assessed as the difference between average sleep duration on the weekends and the average sleep on weekdays [27]. Those women with MSFsc chronotype ≤03.59 h were classified as morning type, pregnant women with MSFsc chronotype between 04.00 h and 04.59 h were classified as intermediate type, and women with MSFsc chronotype ≥05.00 h were classified as evening type [28]. Morning and intermediate types were grouped in non-evening types to establish a new category for the statistical analyses [29].

To assess the sleep duration, the average of self-reported sleep duration, which considers weekdays and weekends, was computed using: [(Reported current weekday sleep duration × 5) + (Reported current weekend sleep duration × 2)]/7 [30]. An average sleep time ≥7 h was rated as adequate [31].

Sleep quality was assessed via a self-reported sleep quality scale, which ranges from 0 to 10, with 0 being very poor and 10 being very good.

Food craving

Food craving was assessed via the Food Craving Questionnaire Trait (FCQ-T) and by the Food Craving Questionnaire State (FCQ-S) validated for the Brazilian population [32]. The FCQ-T consists of 39 statements grouped according to categories that cause food craving and was developed to access aspects of the intense desire for food over time and in various situations, considering them as a usual (trait) behaviour of the respondent. Items are scored on a six-point scale from never/not applicable (1) to always (6). Thus, sum scores can range between 39 and 243, with higher scores indicating more frequent and intense food cravings. The FCQ-T is grouped into the subscales: (i) intentions and plans to consume food; (ii) anticipation of positive reinforcement that may result from eating; (iii) anticipation of relief from negative states and feeling as a result of eating; (iv) lack of control over eating; (v) thoughts and preoccupations with food; (vi) craving as a physiological state; (vii) emotions that may be experienced before or during food craving or eating; (viii) cues that may trigger food craving; and (ix) guilt from craving and/or for given into them [33].

The FCQ-S is composed of 15 statements and is an instrument sensitive to changes in contextual, psychological and physiological states in response to specific situations (e.g., stressful events or food deprivation), considering the intense desire for food as a sporadic behaviour of the respondent. Higher scores in this questionnaire are associated with increased food deprivation, negative experiences related to eating and increased susceptibility to triggers that lead to eating. The FCQ-S contains 15 items to form five subscales: (i) an intense desire to eat; (ii) anticipation of positive reinforcement that may result from eating; (iii) anticipation of relief from negative states and feelings as a result of eating; (iv) lack of control over eating; and (v) craving as a physiological state [33].

Statistical analysis

First, the Shapiro–Wilk normality test was performed. Descriptive statistics were used to summarise participant sociodemographics, lifestyle, anthropometrics, chronobiology data and sleep patterns. Kruskal–Wallis and chi-squared tests were performed to analyse the differences between the groups in scale and categoric data, respectively. Bonferroni post-hoc tests were used to assess which group differed significantly from the others.

Generalised linear models (GLM) were used to determine the association of chronotype (independent variable) with food craving and weight gain in the early gestational period (dependent variables). Individual tests were conducted for each food craving subscale for both trait and state questionnaire and for weight gain, using gamma or linear distributions. The best model was chosen based on the smaller Akaike information criterion resulting from the analysis. All of the statistical tests were adjusted for the confounder variables that are described where appropriate.

Statistical analyses were performed using SPSS, 20.0 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Results

Descriptive data of pregnant women according to the chronotype are presented in Table 1. On average, evening types were younger (24 years) than morning (27 years) and intermediate (26 years) types and went to sleep and woke up later than morning and intermediate types both on weekdays and weekends ($P < 0.05$). Morning types had, at least, one previous pregnancy more than evening and intermediate types ($P = 0.025$) (Table 1).

GLM analysis with food craving subscales and chronotype, adjusted for confounding variables, are shown in Tables 2 and 3. Evening types had higher anticipation of relief from negative states and feelings as a result of eating as a usual behaviour compared to morning types ($P = 0.013$) and non-evening types ($P = 0.028$) (Table 2).

Table 1 Descriptive data of pregnant women according to the chronotype (n = 245)

	All Median (interquartile range) or Prevalence (n = 245)	Evening types Median (interquartile range) or Prevalence (n = 58)	Morning types Median (interquartile range) or Prevalence (n = 121)	Intermediate types Median (interquartile range) or Prevalence (n = 57)	P*
Age (years)	27 (19–35)	24 (16–32)[a]	27 (19–35)[b]	26 (18–34)[b]	**0.040**
Education level					
Primary incomplete/complete	10.1 (25)	10.4 (6)	11.6 (14)	8.8 (5)	0.197
Secondary incomplete/ complete	50.9 (125)	62.0 (36)	49.6 (60)	50.9 (29)	
Higher Incomplete/complete	31.7 (78)	24.2 (14)	33.9 (41)	40.3 (23)	
Previous pregnancy	58.2 (139)	50.9 (29)[a]	67.5 (79)[b]	49.1 (28)[c]	**0.025**
Gestational age (week)	25 (4–40)	28 (4–40)	25 (5–40)	25 (6–40)	0.799
Gestational trimester					
First trimester	24 (58)	22.8 (13)	23.3 (28)	26.8 (15)	0.804
Second trimester	28.5 (69)	24.6 (14)	28.3 (34)	32.1 (18)	
Third trimester	47.5 (115)	52.6 (30)	48.3 (58)	41.1 (23)	
Early gestational period	20.4 (50)	22.0 (11)	48.0 (24)	30.0 (15)	0.070
Vomiting	39.7 (95)	47.4 (27)	39.3 (46)	28.1 (16)	0.103
Nausea	50.6 (121)	52.6 (30)	49.1 (57)	45.6 (26)	0.755
Heartburn	62.9 (154)	70.7 (41)	62.8 (76)	54.4 (31)	0.195
Food desire	33.7 (82)	43.1 (25)	31.7 (38)	30.4 (17)	0.252
Physical activity–yes	16.9 (40)	15.5 (9)	20.3 (24)	11.1 (6)	0.308
Anthropometric data					
BMI pre-pregnancy (kg m^{-2})	24.6 (19.2–30.4)	24.7 (18.9–30.5)	24.4 (18.6–30.2)	23.8 (18–29.6)	0.104
Underweight	5.6 (13)	8.8 (5)	1.8 (5)	10.9 (6)	0.222
Normal	47.4 (110)	42.1 (24)	51.8 (58)	45.5 (25)	
Overweight	28.9 (67)	26.3 (15)	28.6 (32)	30.9 (17)	
Obese	18.1 (42)	22.8 (13)	17.9 (20)	12.7 (7)	
Current BMI (kg m^{-2})	27.3 (20.4–34.2)	28.6 (21.7–35.5)	28.8 (21.9–35.7)	26.3 (19.4–33.2)	0.100
Underweight	8.1 (20)	10.3 (6)	4.1 (5)	15.8 (9)	0.360
Normal	36.7 (90)	34.5 (20)	38.0 (46)	42.1 (24)	
Overweight	25.7 (63)	25.9 (15)	26.4 (32)	28.1 (16)	
Obese	20.8 (51)	25.9 (15)	23.1 (28)	14.0 (8)	
Weight gain in early gestational period	3.5 (0–6.2)	4 (1.5–7.5)	3 (1–5.0)	4 (0–8)	0.098
Sleep patterns					
Week sleep time (h)	23.00 (21.00–01.00)	24.15 (22.15–02.15)[a]	23.00 (21.00–01.00)[b]	24.00 (22.00–02.00)[c]	**<0.001**
Week awake time (h)	07.00 (05.00–09.00)	09.30 (07.30–11.30)[a]	06.00 (04.00–08.00)[b]	08.00 (06.00–10.00)[c]	**<0.001**
Weekend sleep time (h)	24.00 (22.00–02.00)	02.00 (24.00–04.00)[a]	23.00 (21.00–01.00)[b]	24.00 (22.00–02.00)[c]	**<0.001**
Weekend awake time (h)	09.00 (07.00–11.00)	10.00 (08.00–12.00)[a]	08.00 (06.00–10.00)[b]	09.00 (08.00–11.00)[c]	**<0.001**
Mean sleep duration (h)	08.00 (06.00–10.00)	09.00 (07.00–11.00)	09.00 (06.00–11.00)	08.00 (06.00–10.00)	0.581
Sleep duration >7 h	85.7 (203)	79.3 (46)	87.6 (106)	87.7 (50)	0.294
Sleep quality					
Poor <4	9.7 (23)	17.5 (10)	5 (6)	12.5 (7)	0.091
Medium 4–6	40.3 (96)	36.8 (21)	45 (54)	35.7 (20)	
Good >6	50.0 (119)	45.6 (26)	50 (60)	51.8 (29)	

Bold values indicate an statistical significance ($P < 0.05$). Values are presented as the median (interquartile range) for data not distributed normally or as a percentage (n) for frequency data.

*Kruskal–Wallis tests were used for linear variables with not normal distribution. Variables with significant values in the Kruskal–Wallis test were tested by post-hoc test via Bonferroni's method. For frequency variables (previous pregnancy, gestational trimester, vomiting, nausea, heartburn, food desire, physical activity, body mass index (BMI) categories, sleep time >7 h and sleep quality), Pearson's chi-squared test was used.

The superscript letters indicate the difference between the groups: 'a' is different of 'b' and 'c'; 'b' is different of 'c'.

In addition, evening types had less intense desire to eat as a sporadic behaviour compared to morning types (P = 0.012) and non-evening types (P = 0.009) (Table 3). Evening types had less anticipation of positive reinforcement that may result from eating as a sporadic behaviour than non-evening types (P = 0.022) (Table 3).

We found a positive association between chronotype score and anticipation of relief from negative states and feelings as a result of eating ($P = 0.004$) and anticipation of positive reinforcement that may result from eating ($P = 0.013$) as a usual behaviour. A negative association between chronotype score and intense desire to eat ($P = 0.045$) as a sporadic behaviour (Figure 2) was found. We did not find significant association between chronotype score and other food craving subscales.

A positive association between chronotype score and weight gain in pregnant woman during the early gestational period ($P = 0.024$) was also found and is shown in Figure 2.

Discussion

The present study investigated the association between chronotype and food craving in pregnant women as a momentary state and as a frequent behaviour, as well as

Table 2 Subscales of Food Craving Questionnaire trait according to chronotype ($n = 245$)

	Evening versus morning types*				Evening versus non-evening types*		
Dependent Variable	Evening types, mean (SD)	Morning types, mean (SD)	β	*P* value (95% CI)	Non-evening types, mean (SD)†	β	*P* value (95% CI)
FCQ-T Total	88.41 (30.0)	84.32 (28.0)	0.06	0.550 −0.165–0.048	85.03 (28.9)	0.05	0.333 −0.051–0.150
Subscale 1 FCQ-T Intentions and plans to consume food	7.14 (3.4)	6.64 (3.0)	0.078	0.282 −0.064–0.220	6.94 (3.0)	0.032	0.648 −0.104–0.167
Subscale 2 FCQ-T Anticipation of positive reinforcement that may result from eating	14.4 (5.6)	12.98 (5.2)	0.132	**0.041** 0.005–0.259	13.29 (5.2)	0.101	0.102 −0.020–0.221
Subscale 3 FCQ-T Anticipation of relief from negative states and feelings as a result of eating	7.95 (3.4)	6.83 (3.1)	0.180	**0.013** 0.038–0.321	7.02 (3.2)	0.150	**0.028** 0.016–0.284
Subscale 4 FCQ-T Lack of control overeating	11.86 (5.5)	11.74 (5.1)	0.364	0.680 −1.363–−2.091	11.71 (5.2)	0.033	0.607 −0.094–0.161
Subscale 5 FCQ-T Thoughts and preoccupations with food	12.02 (5.2)	11.69 (4.7)	0.035	0.595 −0.094–0.164	11.08 (5.2)	0.023	0.712 −0.099–−0.145
Subscale 6 FCQ-T Craving as a physiologic state	10.71 (3.7)	10.83 (3.9)	−0.020	0.749 −0.142–0.102	10.82 (4.2)	−0.013	0.819 −0.129–0.102
Subscale 7 FCQ-T Emotions that may be experienced before or during food craving or eating	8.41 (4.4)	7.77 (4.1)	0.085	0.281 −0.069–0.239	7.6 (4.1)	0.110	0.141 −0.036–0.256
Subscale 8 FCQ-T Cues that may trigger food craving	10.34 (4.0)	10.22 (4.1)	0.010	0.869 −0.113–0.134	10.3 (4.0)	0.002	0.968 −0.114–0.119
Subscale 9 FCQ-T Guilt from craving and/or for given into them	5.6 (2.9)	5.64 (2.9)	0.007	0.921 −0.139–0.154	5.55 (2.7)	0.026	0.713 −0.113–0.165

Bold values indicate an statistical significance ($P < 0.05$). Generalised linear model adjusted for age, gestational trimester, sleep quality, sleep time and nausea.

FCQ-T, Food Craving Questionnaire Trait.

*Evening types was used as reference category.

†Morning and intermediate types.

Table 3 Subscales of Food Craving Questionnaire state according to chronotype (n = 245)

Dependent variable	Evening versus morning types*				Evening versus non-evening types*		
	Evening types, mean (SD)	Morning types, mean (SD)	β	P value (95% CI)	Non-evening types, mean (SD)†	β	P value (95% CI)
FCQ-S Total	33.57 (11.6)	35.97 (10.6)	−0.059	0.308 −0.038–0.175	36.1 (11.0)	−0.076	0.139 −0177–0.025
Subscale 1 FCQ-S Intense desire to eat	5.86 (2.5)	6.91 (2.9)	−0.188	**0.012** −0.335–−0.042	6.88 (3.0)	−0.184	**0.009** −0.323–−0.045
Subscale 2 FCQ-S Anticipation of positive reinforcement that may result from eating	6.41 (2.5)	7.22 (2.9)	−0.129	0.066 −0.266–−0.008	7.35 (3.0)	−0.152	**0.022** −0.282–−0.022
Subscale 3 FCQ-S Anticipation of relief from negative states and feelings as a result of eating	6.48 (2.4)	6.91 (2.5)	−0.307	0.486 −1.170–−0.556	6.96 (2.6)	−0.053	0.401 −0.175–0.070
Subscale 4 FCQ-S Lack of control over eating	5.55 (1.9)	6.06 (2.4)	−0.091	0.168 −0.221–−0.038	6.10 (2.4)	−0.096	0.123 −0.219–0.026
Subscale 5 FCQ-S Craving as a physiologic state	8.45 (2.7)	8.87 (2.9)	−0.046	0.436 −0.161–−0.069	8.9 (2.9)	−0.051	0.364 −0.160–0.059

Bold values indicate an statistical significance ($P < 0.05$). Generalised linear model adjusted for age, gestational trimester, sleep quality, sleep time, nausea and time since the last meal.
FCQ-S, Food Craving Questionnaire State.
*Evening types was used as reference category.
†Morning and intermediate types.

the association between chronotype and weight gain in the early gestational period. Our results showed that evening types had higher food cravings as a frequent behaviour for some subscales compared to morning and non-evening types, as well as less food cravings as a momentary state for some subscales compared to both morning and non-evening types. Our results also show that greater chronotype score, which is indicative of eveningness, was associated with food cravings as a usual behaviour and weight gain during the early gestational period, whereas lower chronotype score, indicative of morningness, was associated with food cravings as a sporadic behaviour. Taken together, the results of the present study partially confirm our initial hypothesis that evening types may present more food cravings as a repetitive/constant action and have a higher weight gain in the early gestational period.

Our results showed that evening cronotype was associated with some food craving subscales that have been previously associated with other evening type attributes, such

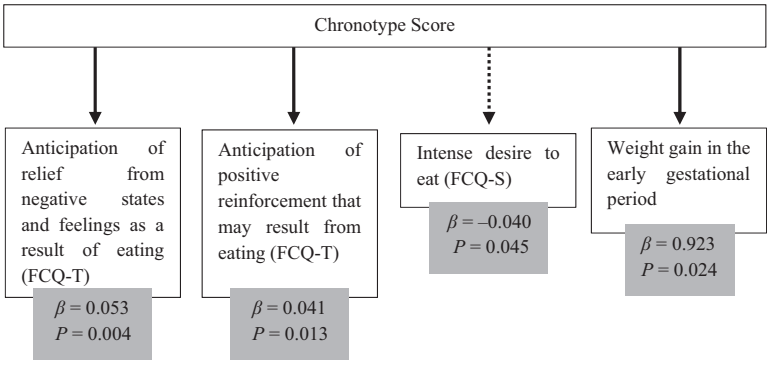

Figure 2 Associations between chronotype and food craving subscales and weight gain. Solid line indicates a positive association. The dotted line indicates a negative association. A generalised linear model was performed. Food craving subscales (n = 245) analysis were adjusted for age, gestational trimester, sleep quality, sleep time and nausea. Weight gain analysis in the early gestational period (n = 50; between 12 and 20 weeks of gestation) was adjusted for nausea, vomiting, gestational week and pre-gestational body mass index. FCQ-T, Food Craving Questionnaire Trait; FCQ-S, Food Craving Questionnaire State.

as eating at later times of the day [34,35]. The habit of eating later at night is associated with eating disorders, stronger emotional eating tendencies and more frequent food cravings [34]. In addition, researchers have already shown that food cravings are closely related to emotional aspects, including emotional eating [36], which is similar for eveningness. Vera *et al.* [37] found a relationship between eveningness and emotional eating ($P = 0.046$) in a study involving 2126 volunteers, suggesting greater emotional influence on evening types feeding behaviour [mean (SD) = 12.4 (0.19)] than morning types [11.85 (0.19)]. Moreover, previous studies had shown that evening types are more prone to psychological problems, including eating disorders than morning types [38,39]. In this way, evening types are more susceptible to eating in response to negative emotions and may try to cope with the negative affects that they experience by eating [36].

A study conducted with 1323 university students found a strong association between eveningness and impulsivity [40], which is an important characteristic that significantly contributes to food addiction [40]. Furthermore, in a study involving 616 participants investigating the relationship between food addiction and food craving, Meule and Kübler [41] found a strong correlation between these two variables. In their study, food addiction symptoms predicted food craving in all subscales of the Food Craving Questionnaire Trait, which is an indicative of usual behaviour [41]. These previous studies support and help to explain our results indicating that evening types have more food cravings, especially with respect to anticipation of relief from negative states and feelings as a result of eating, such as 'Satisfying my food craving would make me feel less grouchy and irritable', as an usual behaviour than morning and non-evening types ($\beta = 0.180$; $P = 0.013$). In this sense, eveningness appears to have a strong association with food craving as an usual behaviour, particularly related to emotional aspects.

In the present study, we also identified less food cravings as a momentary state of an intense desire to eat, such as 'I have an urge for one or more specific foods', in evening types compared to non-evening ($\beta = -0.184$ $P = 0.009$) and morning types ($\beta = -0.188$ $P = 0.012$) and to anticipation of positive reinforcement that may result from eating ($\beta = -0.152$ $P = 0.022$), such as 'Eating one or more specific foods would make things seem just perfect', in pregnant evening types compared to pregnant non-evening types. In other words, morning and non-evening types have food cravings as changes in contextual, psychological and physiological states in response to specific situations, such as stressful events or food deprivation, considered as a sporadic behaviour. We could explain this result with respect to previous research that found morning types to be more stable and regular in their lifestyle regarding event timing [42,43] and therefore they 'suffer' more with temporary and unexpected changes that expose them to a momentary stressful situation. Moreover, morningness is negatively correlated with risk-taking behaviour (i.e. it means impulsiveness, sensation seeking and novelty seeking) in aspects related to health [44] and changes in routine of morning types may be interpreted as a risk-taking behaviour and thus reflect on the mechanism of food craving control.

The present study analysed the weight gain in the early gestational period, between 12 and 20 weeks of gestation, with 50 pregnant women and found a strong positive association with chronotype score. The weight gain recommendation during the early gestational period ranges from 4 to 7 kg according to pre-gestational BMI [21], and weight gain higher than this recommendation can result in numerous damage for both the mother and child [45], especially when it occurs during the early gestational period. Gaillard *et al.* [22] showed that, regardless of maternal pre-gestational weight and total pregnancy weight gain, a high weight gain in the early gestational period was associated with higher values for BMI, body fat, infant abdominal fat and higher systolic blood pressure values in childhood ($P < 0.05$). The results of the present study suggest that eveningness can be one of the factors leading to higher weight gain in pregnancy. In non-pregnant women, a higher weight and BMI have been associated with worse health indicators in evening people [46], such as metabolic syndrome [47] and more risk of heart disease [47], as well as worse feeding behaviour [48].

We emphasise that the significant associations between chronotype and food craving in the present study were related only to some subscales of the FCQ-S and FCQ-T. Although subscales are highly inter-correlated [18,33], our results may indicate a situational circumstance in which food cravings occur [33]. In addition, the only data from the literature so far that have investigated the relationship between food craving (by FCQ-T and FCQ-S) and chronotype also only found associations in two isolated food craving subscales: intense desire to eat (FCQ-S) and guilt from food craving and/or for given into then (FCQ-T) [18]. Future studies are needed to confirm the results found in the present study, whereas the relation between chronotype and food craving is remains poorly explored.

There are some limitations to the present study. The experimental design of this exploratory study was cross-sectional, which limits its ability to establish causal relationships, although we performed analyses that removed the effects of possible confounding factors. Also, some evaluations were performed using questionnaires that are subjective and dependent on the memory and motivation of the pregnant women. Despite these limitations, we

expect that the results of the present study can improve the understanding of the association between eating behaviour and chronobiological variables during pregnancy. However, the need for further studies on this subject is evident. Randomised clinical trials should be conducted to confirm the effect of the chronotype on pregnant women's food craving. In addition, cohort studies should explore pregnancy outcomes in populations of different chronotypes. Lastly, interventions that test the effects of chronotherapeutic interventions according to chronotype on pregnancy weight gain should be performed.

We conclude that evening chronotype was associated with the food craving trait, which means a usual and constant food craving experience for anticipation of relief from negative states and feelings as a result of eating and anticipation of positive reinforcement that may result from eating. Also, pregnant women who tend to eveningness are more likely to gain weight in the early gestational period.

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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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YCPM, CAC and CAG designed the study. GPT, LCTB, WMF and CAG collected the data. GPT analysed the data. GPT drafted the manuscript. CAC and YCPM revised the manuscript. All authors provided feedback 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 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 and registered in the Ethics Committee of the Federal University of Uberlandia (CAAE: 43473015.4.0000.5152/2015) have been explained.

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CLINICAL NUTRITION

Measuring nutrition-related outcomes in a cohort of multi-trauma patients following intensive care unit discharge

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Abstract

Background: Functional recovery is an important outcome for those who survive critical illness. The present study aimed to assess nutrition provision and nutrition-related outcomes in a multi-trauma cohort following intensive care unit (ICU) discharge.
Methods: The present study investigated a prospective cohort of patients discharged from an ICU, who had been admitted because of major trauma and required mechanical ventilation for at least 48 h. Nutrition-related outcomes, including body weight, quadriceps muscle layer thickness (QMLT), handgrip strength and subjective global assessment, were recorded on ICU discharge, days 5–7 post-ICU discharge and then weekly until hospital discharge. Nutrition intake was recorded for 5 days post-ICU discharge. Unless otherwise stated, data are presented as the mean (SD).
Results: Twenty-eight patients [75% males, 55 (22.5) years] were included. Intake met 64% (28%) of estimated energy and 72% (32%) of protein requirements over the 5 days post-ICU discharge, which was similar to over the ICU admission. From ICU admission to hospital discharge, the mean reduction in weight was 4.2 kg (95% confidence interval = 2.2–6.3, $P < 0.001$) and after ICU discharge, the mean reduction in weight and QMLT was 2.6 kg (95% confidence interval = 1.0–4.2, $P = 0.004$) and 0.23 cm (95% confidence interval = 0.06–0.4, $P = 0.01$), respectively.
Conclusions: Patients received less energy and protein than estimated requirements after ICU discharge. Weight loss and reduction in QMLT also occurred during this period.

Introduction

Functional ability and health-related quality of life are important outcomes for those who survive critical illness [(1–3)]. An intensive care unit (ICU) admission can lead to rapid reductions in muscle mass and substantial muscle weakness [(1,4,5)] and changes in body composition have been associated with prolonged hospital admissions, reductions in post-hospital discharge functional recovery and diminished health-related quality of life [(1,4–7)].

Nutrition has been identified as a potential modifiable factor that may aid in the preservation of skeletal muscle during critical illness and help restore muscle lost in the recovery phase [(8–10)]. However, the amount, type and phase of critical illness or recovery on which nutrition support will have greatest impact all remain unknown [(8–10)]. Various nutritional interventions have been administered within the ICU with the objective of attenuating muscle loss and functional weakness, although the impact has been inconsistent [(7,11,12)]. This may be a result of the

interventions chosen being of limited or no benefit, the duration of period provided by the nutrition intervention not being ideal for the substrate to be utilised, the period of the ICU admission being too brief to obtain a benefit, or the studies conducted to date not having been sufficiently powered to detect a difference [8]. It has been suggested that nutritional interventions administered after the acute phase of critical illness may have greater impact [8,13–15]. However, quantifying nutritional intake and nutrition-related outcomes after ICU discharge is likely to be more challenging because of a variety of factors, including equipment and personnel availability, challenges in accurately quantifying volitional ingested nutrient intake, and less predictable timing of discharge from hospital [16–18].

One cohort of patients that may benefit from a nutritional intervention post-ICU discharge comprises those admitted as a result of of severe traumatic injuries. After a traumatic injury, patients can have elevated energy expenditure and increased protein catabolism [19,20], which is likely to continue post-ICU and throughout recovery [20,21]. Despite patients with traumatic injury frequently being prescribed more energy and protein than non-trauma patients in ICU [22], substantial cumulative nutritional deficits have been observed during ICU for this cohort [16,22].

There are limited data available reporting nutrition intake and nutrition-related outcomes after ICU discharge. The primary aim of the present study was to determine the feasibility of repeatedly assessing nutrition intake and measuring nutrition-related outcomes (weight, nutritional status, muscle mass and strength) in a cohort of patients with traumatic injury following ICU discharge. The secondary aims were to (i) compare nutrition intake post-ICU discharge to nutrition intake when in the ICU; (ii) to determine whether post-ICU discharge there were any differences between those receiving only oral intake compared to any artificial nutrition support; and (iii) to explore the relationships between nutritional intake and nutrition-related outcomes.

Materials and methods

This cohort study was conducted in one of the two trauma referral centres that receive all major adult trauma for the state of Victoria (population approximately 6.3 million). Between July to September 2018, all patients admitted to the ICU as a result of a traumatic injury and who were ≥18 years old and mechanically ventilated for at least 48 h were screened for eligibility. Recruitment occurred on the day of discharge from the ICU. Patients were excluded if, on discharge to the ward, they had impaired neurology (defined as the best motor score of abnormal flexion or worse) or bilateral upper arm injury, or the goal of treatment was altered to include a focus on palliative care. Reporting of the present study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [23]. This project was approved by the Melbourne Health Human Research Ethics Committee (QA2018048). Eligible patients, or their responsible person (if they were unable to comprehend written information), were provided with written information regarding the study and they were given the opportunity to opt out from inclusion in the study.

Data were collected from ICU discharge and censored 26 days after ICU discharge or on hospital discharge, whichever came first (Figure 1). Baseline demographic data and patient characteristics were collected from the ICU admission. Routine care in this ICU includes assessement by an ICU dietitian for all patients who are mechanically ventilated for ≥48 h and are receiving nutritional therapy. Protein and energy requirements were

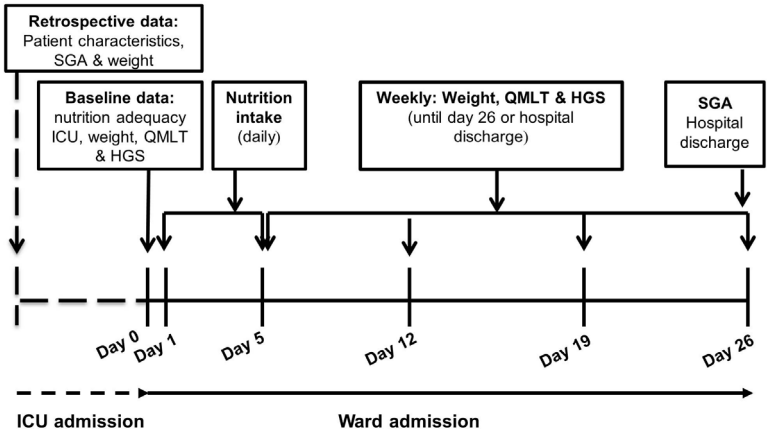

Figure 1 Outcome measurement procedure. HGS, handgrip strength; QMLT, quadriceps muscle layer thickness; SGA, Subjective Global Assessment.

based on the dietitians' assessment in the ICU and post-ICU discharge. Estimated nutritional requirements were calculated using actual body weight for patients below or within the ideal body weight (IBW) range [body mass index (BMI) 18.5–25 kg m^{-2} and for those aged ≥ 65 years BMI 22–27 kg m^{-2}] [24]. For overweight participants, IBW was used and, for obese participants with a BMI greater than 30 kg m^{-2}, an obesity adjusted weight was used [IBW + 25% (actual body weight − IBW)] [24].

Nutrition intake over the ICU admission was retrospectively determined from fluid balance charts through daily analysis of enteral and parenteral nutrition delivery. Energy provided from other sources (e.g. intravenous propofol and glucose as part of fluid therapy) was not included and discarded gastric residual volumes were not subtracted from energy provision.

Ward nutrition intake was collected for 5 days post-ICU discharge. Diet orders, nutrition consumed and mode of nutrition delivery were recorded daily. For patients receiving artificial nutrition, fluid balance charts were reviewed to determine protein and energy intakes. For patients with volitional intake, the proportion of each component of the meal consumed (using visual estimates of 0%, 25%, 50%, 75% or 100%) was recorded in the MOBILE INTAKE™ data application in the hospitals electronic menu management system (CBORD™; The CBORD group, New York, NY, USA). If a meal period could not be assessed by a dietitian, food record charts, completed by nursing staff and including visual estimates of meals consumed, or patient-reported intake were used to estimate the food intake. The hospital menu management system CBORD™ was used to analyse protein and energy intake using the 2011–2013 AUStralian Food and NUTrient (AUSNUT) database (https://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/ausnutdatafiles/Pages/foodnutrient.aspx).

The ward (5 days) and ICU energy and protein adequacy was calculated in the same way. Daily intake was compared with dietitian estimated requirements, and averaged over the study period. The ICU adequacy excluded the day of ICU admission and discharge if it was less than 12 h.

Nutrition-related outcomes including weight and muscle mass and strength were recorded at baseline (within 48 h of discharge from the ICU), days 5–7 post-ICU discharge and then weekly thereafter.

Weight on admission to ICU was recorded using bed scales (Hill-Rom®; Hill-Rom, Inc., Indiana, USA) for the majority of patients. If it was not physically possible to weigh the patient on admission, family reports were used for the admission weight. Post-ICU weight was measured using standing scales (model 876; Seca, Hamburg, Germany), chair scales (BW1122; Colonial, Melbourne, Australia) or hoist scales (Maxi Move L8038; Ajor, Malmö, Sweden), depending on the patient's injury type and mobility. Weight change was calculated as the difference in weight from ICU admission to ICU discharge and to hospital discharge.

Muscle mass was assessed using an ultrasound to measure quadriceps muscle layer thickness (QMLT). QMLT measurements were performed using a portable ultrasound machine (S-ICU; Sonosite, Bothell, WA, USA) with a multiple-frequency transducer (13–6 MHz, 6 cm) using the technique described previously [7,16,25]. Measurements were taken with the patient lying supine with leg relaxed and in extension and the bedhead elevated at approximately 30°. QMLT was measured unilaterally (on the right side unless contraindicated as a result of injury or impairment) at two points: the midpoint between the anterior superior iliac spine and the upper pole of the patella and at the point two thirds between the anterior superior iliac spine and the top of the patella. A still image was taken with minimal pressure and then again with maximal pressure applied. The measurements were taken twice for each point and then the four measurements were averaged to obtain the final QMLT measurement. A third measurement was taken if there was a difference of >10% between the first two measurements, and the measurement with greater than a 10% difference was discarded.

A trained dietitian used handgrip dynamometry (Commander Echo Dynamometer; JTECH Medical, Midvale, UT, USA) to assess upper limb muscle strength bilaterally [26]. Patients were assessed in a seated position, in a chair where possible or sitting at least at 45° in bed, with their forearm in flexion at 90° and wrist in extension, supported by the arm of the chair or a pillow. Patients were asked to perform a maximal voluntary isometric contraction and maintain the contraction for 3–5 s. Three consecutive isometric contractions with 30-60 s of rest in between test were completed and the highest measurement was recorded.

The Subjective Global Assessment (SGA), was used to assess nutritional status [27]. Patients were categorised as well nourished (Score A), with mild to moderately malnutrition (Score B) or severely malnourished (Score C). As part of usual care at the study institution, the SGA is completed by ICU dietitians on initial assessment (within 48 h of admission). This score was then retrospectively extracted from the notes of eligible patients. The SGA was subsequently repeated at hospital discharge by the trained research dietitian.

Feasibility was determined though retention of study participants for at least 5 days post-ICU. Feasibility was predefined as >75% of eligible participants completing 5 days of intake data and having ≥1 repeat measure recorded.

Statistical analysis

Continuous and interval data were reported as the mean (SD) and/or median interquartile range as appropriate. Proportions were used to summarise ratios, and malnutrition was compared over time with McNemar's test accompanied by a 95% confidence interval (CI). Initial univariable exploration of differences in continuous measures over time used the construction of trajectory plots, followed by paired *t*-tests. Changes in QMLT over time were explored using a population-averaged multivariable linear model with a generalised estimating equation approach, an exchangeable working correlation structure and robust standard error estimates accounting for clustering within individual subjects. Independent variables included baseline QMLT, protein adequacy, BMI, presence of traumatic brain injury, age ≥65 years and the patient's ICU admission. $P < 0.05$ (two-sided) was considered statistically significant, with no adjustment for multiple testing. Data analysis was carried out using the SPSS, version 23.0 (IBM Corp., Armonk,, NY, USA) and STATA, version 15.1 (StataCorp, College Station, TX, USA).

Results

During the 4-month study period, 67 patients were screened for inclusion, 32 (47%) met all inclusion and no exclusion criteria, and 28 (42%) patients agreed to participate (Figure 2). Study participant characteristics are described (Table 1).

During ICU admission, participants received a mean of 62% (17%) and 63% (19%) of estimated energy and protein requirements. At ICU discharge 19 (68%) participants were receiving exclusive oral intake, five (18%) participants were on a combination of oral diet and enteral nutrition (EN) via a feeding tube, three (11%) participants were receiving exclusive EN via a feeding tube, and one (4%) patient was receiving a combination of EN and parenteral nutrition (PN).

Over the 5 days post-ICU discharge that nutritional intake was observed, there was a total of 120 days (85% of all days) of data available, with all missing data being a result of patient discharge from hospital (Table 2). Daily mean energy and protein intake was 1478 (651) kcal and 75 (37) g, which equated to 64% (28%) and 72% (32%) of estimated energy and protein requirements (Figure 3). There were no statistical group differences in either energy (−3%; 95% CI = −15 to 10; $P = 0.66$) or protein adequacy (−10%; 95% CI = −25 to 5; $P = 0.19$) between ICU admission and post-ICU periods.

Patients receiving solely oral intake consumed less energy and protein compared to patients receiving any artificial nutrition support (oral diet plus EN, EN alone or EN plus PN); the mean energy and protein intakes were 1298 (640) kcal and 68 (39) g and 1857 (524) kcal and 89 (30) g, respectively. The between group difference was statistically significant for daily energy (mean difference 558 kcal; 95% CI = 53–1062; $P = 0.03$) but not protein (mean difference 22 g; 95% CI = −8 to 51; $P = 0.15$. Compared with dietitian prescriptions, patients on any artificial nutrition received a mean adequacy of 87% (14%) of energy and 87% (17%) of protein compared to those on oral diets who consumed a mean adequacy of 54% (26%) of energy and 65% (36%) of protein.

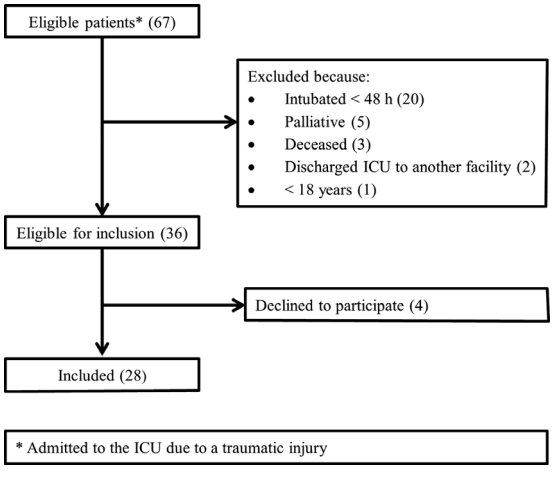

Figure 2 Consort diagram. *Eligible patients, were those admitted to the intensive care unit as a result of a traumatic injury. ICU, intensive care unit.

Table 1 Patient characteristics

Patient characteristics (n = 28)	Value
Age (years), mean (SD)	50 (22.5)
Males, *n* (%)	21 (75)
Length of stay, mean (SD)	
ICU	10.6 (6.7)
Ward	10.9 (9.2)
Total hospital	21.6 (11.8)
Mechanical ventilation (days), median (IQR)	6.0 (3.0–9.5)
Injury, *n* (%)	
Multi-trauma	16 (57)
Multi-trauma with TBI	12 (43)
APACHE II score, mean (SD)	15 (6)
APACHE III score, mean (SD)	111 (55)
Body mass index (kg m^{-2}), median (IQR)	26 (25–32)
Body weight ICU admission (kg), mean (SD)	86 (23)
Malnourished – SGA B/C, *n* (%)	3 (11)

APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; IQR, interquartile range; SGA, Subjective Global Assessment; TBI, traumatic brain injury.

Table 2 Feasibility of outcome measures

	Baseline* *n* (%)	Day 5 post-ICU discharge *n* (%)	At least ≥ 1 time point	Met feasibility criteria (Yes/No)
Weight	25 (89)	13 (46)	15 (54)	No
QMLT	27 (97)	18 (64)	18 (64)	No
Handgrip Strength	17 (61)	12 (43)	14 (50)	No
Subjective Global Assessment†	28 (100)	NA	28 (100)	Yes
Intake (days)‡	NA	120 (85)	NA	Yes

ICU, intensive care unit; NA, not available; QMLT, quadriceps muscle layer thickness.
*Baseline: within 48 h of ICU discharge.
†Subjective Global Assessment completed at baseline and hospital discharge.
‡Intake days: number of days intake data was recorded for the first 5 days post-ICU discharge.

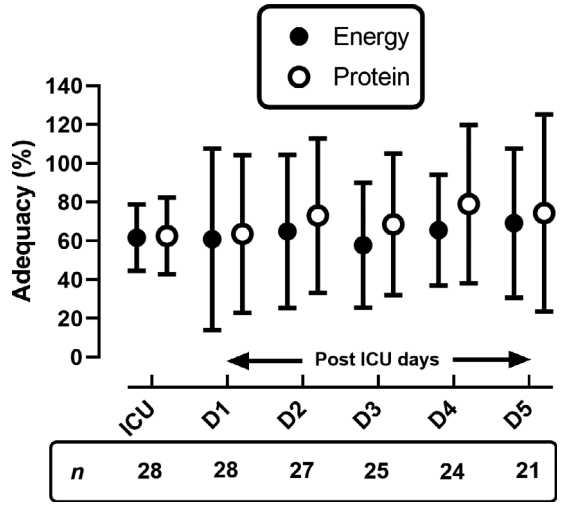

Figure 3 Mean daily energy and protein adequacy for intensive care unit (ICU) admission and the first 5 days post-ICU discharge. *Error bars indicate the mean (SD); *n*, number of participants included at each time point.

Nutritional intake data and the measurement of nutritional status using the SGA were both found to be feasible outcomes measures; however, the other nutrition-related outcome measures (weight, QMLT and handgrip strength) were not found to be feasible in this cohort (Table 2).

The proportion of participants observed to be malnourished increased from ICU admission to hospital discharge; however, this was not found to be statistically significant [3/28 (11%) versus 7/28 (25%), change 14%; 95% CI = −2 to 31; $P = 0.13$]. Of the participants who had weight measured at ICU admission and ICU discharge ($n = 25$), there was a significant reduction in weight [mean reduction 2.3 kg (95% CI = 0.5–4.2; $P = 0.02$), with a mean percentage loss of weight over this period of 3.9% (4.6%). From ICU admission to hospital discharge, the mean reduction in weight was 4.2 kg (95% CI = 2.2–6.3; $P < 0.001$), with a significant loss of weight also observed over the first 5 days post-ICU (Table 3).

QMLT was measured on more than one occasion post-ICU discharge in 18/28 patients (64%) (Table 2). There was a significant reduction in mean QMLT (no pressure) over ward admission by 0.23 cm (95% CI = 0.06–0.40; $P = 0.01$) (Table 3) and the mean percentage reduction was 7.2% (13%). The change in QMLT (no pressure) for individuals over time is shown in the Supporting information (Figure S1). Mean change in QMLT over time was associated with greater baseline QMLT and a greater number of days post-ICU discharge (Table 4). There was no significant association found between change in QMLT and age, BMI, severity of illness on admission to the ICU, presence of a traumatic brain injury or ward protein adequacy. There was a significant improvement in handgrip strength from baseline to day 5 post-ICU discharge in the group of participants ($n = 10$) who had two measurements completed (Table 3).

Discussion

In this single-centre cohort study of patients with a traumatic injury who were discharged from an ICU, patients received less energy and protein than it was estimated that they required. Energy and protein provision and nutritional adequacy on the ward were similar to that provided during the ICU admission; however, patients receiving artificial nutrition support post-ICU discharge had improvements in energy and protein provision. It was also observed that, after ICU discharge, a significant reduction in weight and QMLT occurred. According to the predefined criteria, missing data limited feasibility for several nutrition-related outcomes.

The results obtained in the present study are similar to those of several studies conducted in the ICU, with patients receiving approximately 60% of their nutritional targets [28–31]. Although few studies have reported nutritional adequacy after ICU discharge, in a single-centre study of 37 patients with traumatic brain injury by Chapple *et al.* [18], patients received similar nutritional adequacy in ICU and after ICU discharge. However, greater

Table 3 Change in nutrition-related outcomes from ICU discharge to day 5 post-ICU discharge

	n	Baseline* Mean (SD)	Day 5 post-ICU discharge, mean (SD)	Mean difference (95% CI)	*P*-value
Body weight (kg)	13	83.6 (16.1)	81.0 (16.2)	−2.6 (−0.98 to −4.2)	0.004
Handgrip strength (kg)	10	27.9 (9.5)	30.1 (11.1)	2.3 (0.22 to 4.3)	0.034
QMLT no pressure (cm)	18	2.8 (0.8)	2.6 (0.8)	−0.23 (−0.06 to −0.40)	0.01

CI, confidence interval; ICU, intensive care unit; QMLT, quadriceps muscle layer thickness.
*Baseline: within 48 hours of ICU discharge.

Table 4 Effect estimates from multivariable linear model assessing change in QMLT from baseline to hospital discharge

Variable	Coefficient of effect*	95% CI	*P*-value
QMLT Baseline (cm)	0.88	0.79 to 0.96	<0.001
ICU protein adequacy, per 10%	−0.04	−0.07 to 0.002	0.06
Number of days post-ICU discharge	−0.04	−0.05 to −0.02	<0.001
BMI ≥ 30 kg m^{-2}	0.07	−0.08 to 0.2	0.37
Presence of a traumatic brain injury	0.05	−0.05 to 0.15	0.31
Age ≥65 years	−0.02	−0.13 to 0.0.9	0.69
APACHE II score on admission, per 5 points	0.02	−0.04 to 0.07	0.59

APACHE, acute physiology and chronic health evaluation; BMI, body mass index; CI, confidence interval; ICU, intensive care unit; QMLT, quadriceps muscle layer thickness.
*All reported effect estimates are adjusted for all other variables within a multivariable linear model, using a generalised estimating equation approach (refer to statistical analysis methods for details).

energy and protein provision were observed in both settings than in the present study, with patient recieving a mean of 81% (35%) of energy and 77% (35%) of protein requirements after ICU discharge. These differences could be related to the different patient cohorts and the proportion of patients with traumatic brain injury who require artificial nutrition after ICU discharge rather than consuming oral intake. In the present study, patients who received any artificial nutrition had significant increases in energy but not protein adequacy in the post-ICU period compared to those receiving oral intake alone. These results are similar to those observed by Chapple *et al.* [18] who described less intake in patients who were reliant solely on oral diet. Additionally, Peterson *et al.* [32] examined oral nutrition intake via multi-pass 24 h food recall for 7 days post-extubation in a single-centre cohort of 50 critically ill patients; it was observed that mean energy and protein intake never exceeded 55% of daily requirements [32]. These results demonstrate that nutritional inadequacy persists in the cohort of patients after traumatic injury, and that patients receiving oral intake alone are possibly at greatest risk of nutritional inadequacy in the ICU and the post-ICU period. This may be a result of the early withdrawal of artificial nutrition support or because hospital systems do not support achieving nutritional adequacy during periods of volitional oral intake [33]. Further research is warranted to understand why nutritional inadequacy persists after ICU discharge and how to improve nutritional adequacy throughout the entire hospital admission [34].

In the present study, nutrition-related outcome data for weight, QMLT and handgrip strength were not recorded in sufficient numbers to meet the predefined feasibility criteria. Patient factors, including delirium, agitation and post-traumatic amnesia; hospital factors, including appropriate equipment availability, multiple procedures and scans; early discharge; and research resource allocation all contributed to missing data. It has been reported that the prevalence of cognitive impairment after a traumatic brain injury is up to 70% [35], and this may affect capacity to complete some of the outcome measures. Therefore, outcome measures that do not require participation, volitional movements and cooperation, such as QMLT, are probably more feasible in this population, rather than handgrip strength and functional capacity and quality of life [36]. Although the frequency of QMLT measurements did not achieve the predefined feasibility criteria, it was successfully measured in 64% of participants and, of the missing data, five (14%) participants were discharged prior to the first repeat measure time point (day 5 post-ICU). These results are similar to those reported previously by Chapple *et al.* [16,25] in studies measuring QMLT weekly post-ICU in 79% of a traumatic brain injury cohort. The evidence from these two centres therefore supports the concept that QMLT is perhaps the most feasible variable for repeated measurement

in this population when attempting to evaluate the impact of nutritional therapies on body composition.

It remains unclear what, if any, impact energy and protein provision in the ICU or following ICU admission have on patient-centred and nutrition-related outcomes [8]. In the present study, there was a significant reduction in weight and QMLT over the study period; however, there was no evidence to suggest that greater protein provision was associated with attenuation of QMLT loss. Similarly, a previous multi-centre observational study (UK MUSCLE) reported that greater loss of quadriceps muscle was associated with greater protein delivery in ICU [5]. However, in contrast to this observed association, other cohort studies [37,38], as well as a recent randomised control trial by our group, report that greater protein delivery is associated with attenuation of muscle loss in ICU [7]. These conflicting results highlight the issues involved when interpreting associations in observational studies of critically ill cohorts, particularly because the severity of illness is a confounder that may not be adequately accounted for. Although muscle thickness and body composition outcomes are only surrogate physiological outcomes for outcomes that are important to patients, Chapple *et al.* [16] reported that greater QMLT at hospital discharge was associated with significant improvements in self-related quality of life 3 months after hospital discharge. Further research is required to evaluate the impact of nutritional therapies on functional outcomes post-discharge from hospital [8,34].

This is the first study to evaluate the feasibility of measuring nutrition-related outcomes and nutritional intake in patients with multiple injuries following trauma after ICU discharge. Nutritional intake was measured using meal observations and an electronic menu management system and nutritional outcomes such as muscle mass, muscle strength and nutritional status were recorded. However, there are several limitations, including the study comprising a single-centre study, with a relatively small number of patients being investigated. Moreover, the size of the cohort was not sufficient to determine whether nutrition-related outcomes were affected by nutritional adequacy and, as a result of the observational nature, causality cannot be established for any associations observed. Data collection was limited to weekdays and acute hospital admission. Increasing the resource allocation and study timeframes in future interventional studies may increase the sample size and data completeness and consideration should be given to include outcome data form admissions to rehabilitation facilities. It was also not within the scope of the present study to examine the feasibility of measuring nutrition-related outcomes post-hospital discharge. With recovery from acute illness, patient participation in outcome measures may increase and therefore increase their utility.

Conclusions

Mean energy and protein intake were below the estimated requirements and were similar during the ICU admission and after ICU discharge; however, patients receiving artificial nutrition support received greater amounts of energy. Within the limitation of missing data, weight loss and reductions in QMLT were observed after ICU discharge. A greater change in QMLT was associated with a greater baseline QMLT and length of ward admission. The most appropriate outcome measures for investigating associations between nutrition provision and recovery remain unclear and warrant further investigation. Well-designed and adequately powered randomised clinical trials are required to determine the effect of greater nutrition provision on nutrition-related outcomes in patients discharged from an ICU after major trauma.

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Conflict of interests, source of funding and authorship

K. Fetterplace has received conference, travel grants and/or honoraria from Baxter, Fresenius Kabi, Nutrica and Nestle Health Science (not related to this study). A. M. Deane and his institution have received honoraria or project grant funding from Baxter, Fresenius Kabi, GSK, Medtronic and Takeda (not related to this study). The other authors declare that they have no conflicts of interest.

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KW, KF and AMD contributed equally to the conception and design of the research. ESG, RJ and CMM contributed to the design of the research. KW, MC and KF contributed to the acquisition of the data. KW, KF and JJP contributed to the analysis and the interpretation of the data. KW, KF and AMD drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final 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[1] 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. This project was approved by the Melbourne Health Human Research Ethics Committee (QA2018048).

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Supporting information

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

Figure S1. Quadriceps muscle layer thickness measurements over time post-ICU discharge.

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CLINICAL NUTRITION

Metabolic bone diseases in intestinal failure

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Keywords
fracture, home parenteral nutrition, intestinal failure, metabolic bone disease, osteomalacia, osteoporosis.

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Abstract

Metabolic bone diseases are a group of conditions that are common complications in patients with intestinal failure. These may occur as a result of the underlying condition, leading to intestinal failure, particularly inflammatory conditions such as Crohn's disease and their associated treatments including corticosteroids. Malabsorption, as a result of a loss of enterocyte mass or gut function, of many nutrients, including vitamin D, may further compound metabolic bone problems, and there has been historical contamination of parenteral nutrition with aluminium that has prevented normal bone metabolism contributing to osteoporosis. This review looks at the diagnosis and current management of bone health in patients with intestinal failure.

Introduction

Intestinal failure (IF) is the loss of gut function such that a person cannot survive without intravenous water, electrolytes, micronutrients (vitamins and minerals) and macronutrients (carbohydrates, lipids and protein) [(1)]. Typical causes of IF are wide ranging and frequently are caused by complications following intra-abdominal surgery (21–25%) [(2–4)]. Other common causes include mesenteric vascular catastrophes (15–16%), mucosal disease such as Crohn's disease (CD) (28–34%) and intestinal dysmotility following previous surgery or from a myo-/neuropathic gut (7–15%) or cancer (5–29%) [(2–4)]. These underlying aetiological processes result in a number of ways to subclassify IF: type 1 and type 2 IF are acute conditions, with the former lasting less than 28 days and latter lasting more than 28 days with more metabolic instability. Type 3 IF occurs when the patient is metabolically stable and goes home on parenteral nutrition (PN); it can be reversible or irreversible.

Second, pathophysiological separation can occur to differentiate between short bowel syndrome (SBS) [with end jejunostomy (38.6%), with a jejuno-colic anastomosis (19.9%) and jejuno-ileal anastomosis with ileocaecal valve and whole colon *in situ* (5.9%)], mechanical obstruction (4.4%), dysmotility (17.5%) or mucosal disease (6.8%) [(5)]. Alternative methods of classifying IF include volume of stomal losses and volumes of intravenous support needed, such as number of nights on parenteral nutrition (PN) compared to volume required [(1)].

The provision of PN to provide supplemental or total nutrition as home PN (HPN) allows many patients to have a reasonable quality [(6)] and quantity of life [(3)]. Unfortunately, IF is associated with complications [(7)]. These mainly occur as a result of PN administration:

- Venous thromboses that may cause loss of venous access
- Catheter-related blood stream infections (CRBSI) that may lead to devastating infections such as fungal endophthalmitis, endocarditis or osteomyelitis [(7,8)]

• IF associated liver disease (IFALD) that lead to hepatic fibrosis and cirrhosis [9]

Other complications of IF include:

• Renal dysfunction as a result of chronic dehydration [10]
• Renal oxalate stones as a result of calcium/oxalate competition for fatty acids
• Metabolic bone disease (MBD) [10]

Life-threatening complications, especially loss of venous access, recurrent or fungal CRBSI and IFALD are indications for considering intestinal transplantation [11,12].

Metabolic bone disease

Definition

Metabolic bone disease is defined as alteration in skeletal homeostasis that results in defective bone density (e.g. osteoporosis, osteopetrosis and Paget's) and bone mineralisation (e.g. Rickets, osteomalacia and renal osteodystrophy) [13]. These may be a result of alterations in serum calcium and phosphate because of changes in circulating vitamin D or parathyroid hormone (PTH) levels affecting mineral deposition, leading to changes in calcium or phosphate concentrations in hydroxyapatite, or a result of changes in bone turnover or growth [14]. The commonest conditions observed in IF patients include osteoporosis and rarely osteomalacia. Osteoporosis has been reported as occurring in 57–88% of adult patients with IF with both osteopaenia and osteoporosis increasing with age, as in the general population [15–18]. In children with IF, osteopaenia occurs in 45% [19] and osteoporosis in 16–25% taking into account growth restriction [20]. On the other hand, in both adults and children, osteomalacia is less common, with no reported incidence associated with IF but the prevalence in 16 individuals on home PN undergoing bone biopsy yielded a diagnosis of osteomalacia in 12 (75%) [21].

Diagnosis

The diagnosis is a clinical one often taking into account mechanism of fracture, history of bone (Paget's or osteomalacia) or muscle pain (osteomalacia) and radiographical findings. Typical radiographical changes of osteoporosis include general loss of bone mass and fractures in common osteoporotic sites [14]. Wide growth plates and frayed metaphyses were consistent with rickets in children, whereas osteomalacia may present with radiographic evidence of Looser zones. Radiographic changes in hyperparathyroidism consist of hand subperiosteal resorption, while, vitamin C deficiency causes subperiosteal haemorrhage as a result of collagen defects [14].

With the advent in 1988 of dual-energy X-ray absorptiometry (DEXA) scans assessing bone mineral density on the femoral neck and spine [22,23], the diagnoses of osteoporosis and osteopaenia could be made with better accuracy and a lower radiation dose. However, it cannot differentiate between osteoporosis and osteomalacia on the basis of bone mineral density (BMD) alone. Osteopaenia has been defined by the International Society of Clinical Densitometry as a *T*-score −0.1 - −2.5 and osteoporosis as a *T*-score <−2.5 using a normative reference database of Caucasian women for all adults, irrespective of race or gender [24]. Children, on the other hand, require a clinical diagnosis of either a vertebral compression fracture or a *Z*-score < 2 and either two long bone fractures by the age of 10 years or three long bone fractures by the age of 19 years [25,26]. DEXA scans have been used widely by many groups to determine the BMD for their patients with IF, whether paediatric or adults [19,24,27–32] such that current IF guidelines now suggest annual DEXA scanning in adults and children [33,34]. Osteopaenia occurs in 45% children (ideal weight for height adjusted *Z*-score <−2.0) on PN [19], whereas 52% of adults have been found to demonstrate an 'abnormal' DEXA on commencement of HPN [30]. An older study followed 10 HPN-dependent adults (7 : 3 male : female, 19–66 years) for 0–67 months (mean 24) and found that four out of 10 had spinal osteoporosis on radiographs [35].

Following on from DEXA, the FRAX® tool was developed in 2008 from the World Health Organization Collaborative Centre for Metabolic Bone Diseases based in the University of Sheffield, UK [36]. This simple tool uses age, gender and body mass index with seven simple risk factor questions and femoral neck *T*-score to calculate a 10-year major osteoporotic fracture risk and hip fracture risk.

By contrast, osteomalacia is a qualitative not quantitative defect in mineralisation and can be frequently diagnosed on clinical history (painful bones and muscles with fractures) and serum biochemistry investigations. The role of these investigations is to determine the cause of osteomalacia and to differentiate between vitamin D deficiency and phosphate wasting conditions such as renal phosphate wasting, renal tubular acidosis (proximal, type 2) or skeletal fluorosis. Often the diagnosis is challenging and often delayed [37–39] and so the gold standard method of diagnosis is through bone biopsy. In a study, 16 adults followed for 7–89 months on PN found that 12 of 16 had osteomalacia on bone biopsy [21].

Aetiology of metabolic bone disease in intestinal failure

MBD in IF may occur, as can be observed in Table 1, because of the underlying condition that caused IF (e.g.

inflammatory conditions such as CD) and the IF or PN itself [9]. A Japanese study [40] of 388 patients with inflammatory bowel disease (IBD) without IF, aged 20–50 years, found that 78 of 388 (20%) had osteopenia [17% ulcerative colitis (UC), 24% CD) and 17 (4%) had osteoporosis (3.4% UC, 5.8% CD); risk factors for developing MBD included male gender, low body mass index (BMI) and steroid use. Following intestinal surgery, such as gastrectomy, bone metabolism is altered, with one group observing reduced hand bone calcium content [41], suggesting an interaction between gut function/hormonal changes and bone metabolism. It is therefore unsurprising that MBD can occur in patients with IF occurring as a result of surgical injury. In particular, SBS is associated with malabsorption of calcium, phosphate and vitamin D, which are key to bone health.

How does intestinal failure change bone metabolism?

It is unclear whether, and to what degree, MBD can improve over time with PN, although what is clear is that MBD early on in the natural history of IF will be a result of the underlying condition (e.g. CD with previous steroid use). For example, a study on 75 adult patients receiving HPN (35 with an underlying diagnosis of CD), reported worse BMD at the start of the study period in CD patients compared to patients without CD, suggesting that the underlying condition leading to IF impacts more on BMD than IF itself. However, a 1% loss per year ($P < 0.005$) was also found in the entire cohort, although, importantly, this rate was not significantly different from the rate of BMD decline of age- and gender-matched controls. This suggests that being on HPN may attenuate any BMD decline that could otherwise have been observed [24].

In children, correction of the underlying deficit, whether inadequate provision of macro/micronutrients or control of inflammation, allows normal hormonal factors to facilitate growth and therefore increase in BMD. This was observed in a study of 31 HPN-dependent children, who had a median of 6 years between the first and last DEXA scan; during that time, total bone mineral content increased by a mena (SD) of 0.1 (0.04) per year, whereas the risk of having low bone mass reduced with an odds ratio of 0.9 per year of HPN (95% confidence interval = 0.02–0.99, $P = 0.018$)[19]. However, this is not the experience of another study, where a multivariate analysis found an association between longer duration of PN and a reduction of BMD [32]. In both studies, vitamin D supplementation made no difference to BMD. However, a small case series of six children benefited from bisphosphonate treatment [42] suggesting that a larger trial of newer agents in paediatric IF should be considered.

Vitamin D

Vitamin D is a vital part of bone metabolism and exerts its effect by increasing calcium absorption from the gut, which is then deposited in the bone [43]. In patients with IF, where calcium absorption may be less, adequate calcium intake can be ensured via PN.

However, initial studies had somewhat perplexing findings regarding Vitamin D, and perhaps best explained by the lack of intestinal or PN calcium availability. For example, Klein *et al.* [44] found osteomalacia in 11 patients on PN for more than three months duration despite normal phosphate, 25(OH) vitamin D and PTH levels, perhaps implying pre-existent osteomalacia, some other component toxicity (e.g. aluminium) or inability to convert 25(OH) vitamin D to 1,25 (OH) vitamin D. In another study during the same year, 10/16 patients on PN had hypercalciuria and negative calcium balance, with three patients with the severest form having their vitamin D removed from PN, resulting in normalisation of calcium balance in two out of three of them [21]. A later study investigating 11 PN patients found excessive unmineralised bone tissue on bone biopsy despite a normal phosphate and vitamin D (25-hydroxyl-vitamin D) level, with three of 11 reporting bone pain and fractures. It was found that removal of the vitamin D from PN resulted in an improved histological assessment as demonstrated by a decrease in osteoid bone and an increase in tetracycline uptake, whereas pain reduced and fractures healed in the three symptomatic patients [45]. There are a number of possible explanations for this, including out current understandomg that this may have been all related to aluminium toxicity or the form of vitamin D assessed, which was 25(OH)-vitamin D. In retrospective paediatric studies, vitamin D deficiency was observed in 41–64% [31,32], hyperparathyroidism (PTH >55 pg mL^{-1}) was surprisingly common (25%) [32], 20% complained of bone pain [32], pathological fractures were observed in 10–29%[31,32] osteopaenia occurred in 34% [31] and BMD was significantly lower compared to controls [46].

It is clear that factors other than vitamin D will play a part in BMD; indeed, a more recent study of 51 HPN-dependent adult patients, 81% had reduced DEXA measurements despite 35% displaying normal vitamin D levels [30]. In preterm neonates, which are a very different group of patients with their bones in a different developmental stage to adults, Bridges *et al.* [47] evaluated the role of novel lipid emulsions on bone health. The findings obtained suggest that such PN does not provide sufficient calcium, phosphorus, docosahexaenoic acid or arachidonic acid, which are important modulators of bone cell differentiation, bone lengthening and matrix

deposition. This may account for some of the changes seen in adults.

Ingestion of elements that interfere with bone metabolism
Accumulation of aluminium in both tissues and bone has been known subsequent to the early 1980s and, on investigation, was attributed to the casein protein in the PN with a switch to amino acid formulation reduced aluminium levels [48]. Further work to address the role aluminium played in MBD found that, on converting patients from casein containing PN to amino acid containing PN, there was greater bone formation, greater osteoid area and both the bone surface stainable aluminium and total bone aluminium were lower [49]. These data suggest that plasma and bone surface aluminium inhibit bone formation and that reducing aluminium consumption via a change in PN formulation to amino acids improves BMD [49]. In the USA, the Food and Drug Administration (FDA) proposed to limit the level of aluminium permissible within PN in 2001 with commencement of the rule in 2003 [50].

Other heavy metals are also known to influence BMD. A study of 31 adults, primarily with IF as result of SBS, assessed their BMD and serum fluoride levels. The researchers found that 102/120 fluoride dosages were above the upper limit of normal intake. The mean daily supply was 8 mg (US upper adequate intake 3.1–3.8 mg per day). Notably, BMD was lower in the spine and this correlated with fluoride intake. Two patients had symptoms of fluorosis with calcaneum fissures, interosseous calcifications or femoral neck osteoporosis. It was suggest that the high intakes of fluoride originate not only from the PN, but also significantly from mineral water and tea consumed [29]. These do not constitute appropriate isotonic fluids that are currently recommended for oral adjuncts to aid hydration status in IF [51].

Is small intestinal bacterial overgrowth implicated?
Following intestinal surgery, the small bowel can become affected by bacterial overgrowth as a result of a change in motility. This is a common problem for patients with IF [51,52] but small intestinal bacterial overgrowth (SIBO) in patients without IF is also associated with a reduction in BMD compared to healthy controls [28]. It was suggested the SIBO had an impact on BMD as a result of the accumulation of D-lactate [28] that results in acidosis [53].

SIBO and other intestinal malabsorptive conditions are associated with deficiencies in fat-soluble vitamins, including vitamin K. It is unclear why this occurs, although it may be a result of changes in serum unconjugated bile acids, which was the focus of a novel method of diagnosing SIBO in a pilot paediatric study [54]. Unfortunately, however, despite antibiotic treatment, there were no changes in serum unconjugated bile acid levels. A retrospective study from the Canadian HPN registry found that the 78/189 (41.1%) individuals who had 10-mg weekly vitamin K intravenously in addition to normal PN also had a trend towards a better hip DEXA *T*-score ($P = 0.063$) [55]. In addition, a recent comprehensive review of the role of vitamin K in bone health [56] suggests that there are two main pathways involved: first the osteocalcin or bone Gla protein (BGP), which is produced by osteoblasts under influence of vitamin D, is activated by vitamin K and enables incorporation of calcium ions into hydroxyapatite crystals [56,57]. Second, there is some suggestion that vitamin K may be the ligand for steroid and xenobiotic receptor (SXR) that promotes bone formation and prevents bone resorption [56,58].

Hypercalciuria
A number of studies describe hypercalciuria occurring in the early phase of MBD. In early studies, ten of 16 patients on PN for 7–89 months developed hypercalciuria and negative calcium balance [21]; 11 of 11 on PN for more than 3 months developed hypercalciuria, three of 11 patients had hypercalciuria associated with severe bone and pain fractures [45]; seven adults for more than 7 months PN all had hypercalciuria and six of seven had negative calcium balance [59]. The underlying cause of this was poorly understood. An early rat model of IF demonstrated significantly increased excretion of calcium in the urine, although not phosphorus or magnesium, in animals undergoing small bowel resection [60]. An alternative explanation relates to acidosis exacerbating urinary calcium loss [61] particularly in those receiving high levels of protein in PN [62].

What about parenteral iron?
There is growing evidence that parenteral iron causes hypophosphataemia that can last for up to 6 months following administration. This was observed in a retrospective study in 22% of patients treated with iron sucrose and 51% in those treated with ferric-carboxymaltose [63]. The likely underlying pathogenesis may be as a result of renal phosphate wastage [64]. The resulting hypophosphataemia can result in hypophosphataemic osteomalacia, and so switching to another form of parenteral iron may be necessary and ensuring adequate parenteral phosphate is used to keep levels within the normal range [64].

Surveillance for and treatment of metabolic bone disease

Surveillance for MBD is part of the current guidelines for practitioners caring for patients with IF, regardless of whether they are adults [33] or children [65,66]. Simple measures to increase vitamin D and calcium levels

improve bone health [33], although there are a paucity of high-quality data avaiable in IF patients regarding the effect [67,68]. High-dose calcium was also demonstrated to off-set the toxic effect of aluminium on bone in a case report, with reduced bone pain, increased serum calcium, abolished aluminium deposits in trabecula and increased bone density on biopsy [69]. Maximising vitamin K would appear sensible, even though there are no clear data to recommend this [55].

Oral bisphosphonates are effective in patients with IF where there is sufficient enteric absorption, which may not always be possible in patients with IF such that intravenous preparations are required (e.g. zoledronate). The first paediatric study looked at six children on PN for at least 3 years with evidence of osteoporosis. Two cycles of intravenous pamidronate 30 mg m^{-2} monthly were given for 6 months and a significant improvement was found at both 6 and 12 months following treatment and, by follow-up at 108 months, none out of six patients had become osteoporotic again, nor were there any osteoporotic associated fractures [42]. Alternative treatment strategies include denosumab, a monoclonal antibody that targets osteoclast activity and, in one study of 15 patients with 1 year of treatment, this demonstrated a marked improvement in DEXA results [70]. In the case report of a woman with SBS and renal impairment, who was treated with teriparatide (a subcutaneous PTH analogue) the normalisation of BMD was reported in 18 months [71]. Tangpricha *et al.* [72] randomised subcutaneous growth hormone (GH) or placebo in adults with SBS on PN. There was a high incidence of vitamin D deficiency (78–79%) in both control and GH treated subjects. Markers of bone turnover were assessed and it was found that only osteocalcin increased significantly (62%; $P < 0.05$) at 12 weeks and DEXA scans (baseline and at 24 weeks) found no change in BMD at the spine or hip, although there was a slight reduction at the femoral neck in the control group compared to the GH group.

There is much excitement within the IF community about the role that incretin gut hormones, in particular glucagon-like peptide (GLP)-2, have on gut function to improve the absorption of nutrients through elongation of the mucosal villi [73,74]. A recent review of gut hormones and bone health has brought together data on GLP-2 and other incretin hormones, such as GLP-1, glucose-dependent insulinogenic peptide and protein YY, and their effect on the reduction of bone resorption and increase bone formation [75].

Conclusions

Bone health is vital for the well-being of patients with intestinal failure. With DEXA, non-invasive monitoring of the commonest MBD, namely osteoporosis, is not only possible, but also easily accessible and relatively cheap. The aetiology of MBD is multifactorial and includes vitamin D deficiency, the underlying aetiology for intestinal failure and the collateral damage caused by inadvertent ingestion of elements (e.g. aluminium or fluoride) that impact on bone health. Teams caring for patients with IF should be mindful to try population strategies aiming to prevent deterioration in bone health by minimising both

Table 1 The aetiology of metabolic bone disease in intestinal failure

Metabolic bone disease	Aetiology in intestinal failure	Cause	Treatment
Osteoporosis	Low vitamin D	Malabsorption as a result of short bowel or gut inflammation or lack of sun exposure	High oral dose, and consider intramuscular dosing
	Underlying inflammatory condition	Inflammatory burden of disease	Control inflammatory bowel disease with appropriate medication, treat abdominal inflammation using Sepsis-Nutrition-Anatomy-Plan (SNAP) protocol
	Low calcium absorption	Malabsorption as a result of short bowel or low vitamin D status	Replace vitamin D and add oral calcium or calcium in parenteral nutrition
	Aluminium toxicity	Casein protein in parenteral nutrition	Change formulation to modern amino acid formulation
	Fluoride toxicity	High levels in tea and certain bottled water	Use recognised isotonic drinks that give Na >90 mmol e.g. double-strength dioralyte or St Mark's solution, or Lucozade Sport (Lucozade Ribena Suntory Limited, Uxbridge, UK) 500 mL with ½ teaspoon salt
Osteomalacia	Low vitamin D	Malabsorption as a result of short bowel or gut inflammation or lack of sun exposure	High oral dose, and consider intramuscular dosing
	Hypophosphataemia	Inadequate phosphate intake, excessive oral calcium intake or parenteral iron	Increase parenteral phosphate intake and switch to iron sucrose to provide parenteral iron

medication that has a negative impact, such as corticosteroids, and elements in oral rehydration solutions and PN, at the same time as optimising vitamin D status and general nutritional status, as well as paying attention to normal risks factors for developing MBD, such as smoking and alcohol.

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

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