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Patient, family and carer experiences of nutritional screening: a systematic review

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Abstract

Background: Despite recommendations for nutritional risk screening of all inpatients, outpatients and care home residents, as well as work to assess clinician's experiences and the validity of tools, little attention has been paid to the experiences of patients undergoing nutritional screening. This review aims to synthesise systematically the current evidence regarding nutritional risk screening with respect to the experiences and views of patients, their families and carers.

Methods: A systematic search was performed in MEDLINE, Embase, PsychINFO, CINAHL, Web of Science and British Nursing Database (inception – July 2019); with screening terms related to malnutrition, screening tools and experience. Titles, abstracts and full-text papers were independently reviewed by two reviewers and then quality-appraised. Qualitative papers and quantitative surveys were included. A narrative review of surveys and a thematic framework synthesis of interviews were used to identify themes.

Results: Nine studies, including five qualitative interview papers, were included. Qualitative and quantitative study results were combined using a matrix chart to allow comparison. Surveyed participants reported processes of nutritional screening as acceptable. Three key themes emerged from qualitative data: (i) experience of nutritional screening; (ii) misunderstanding of malnutrition: of causes, role of screening and poor self-perception of risk; and (iii) barriers to and opportunities for change.

Conclusions: Although the screening process is acceptable, patients' misunderstanding and poor knowledge regarding causes and consequences of malnutrition result in reduced risk perception and disbelief or disregard of nutritional screening results. Findings should inform policy and clinical practice, as well as highlight the known paucity of data regarding the effectiveness of screening on clinical outcomes.

KEYWORDS
malnutrition, nutritional screening, patient experience, qualitative, quantitative, systematic review

INTRODUCTION

Screening for the risk of malnutrition is recommended by the National Institute of Health and Care Excellence (NICE) in multiple clinical care settings, including the screening of all hospital inpatients on admission, in addition to hospital outpatients and those in primary care surgeries, both at their first clinic appointment and upon clinical concern, as well as care home residents upon clinical concern.[1]

Given such extensive screening recommendations, validation of screening tools[2] and their utility and ease of use by clinical staff, including the time taken to complete screening and opinions on the methods, has been conducted.[3] However, less attention has been paid to the experiences and views of patients, their families and carers when reviewing the acceptability of the screening process. UK National Screening Committee guidance recommends that screening is simple, safe and acceptable to the target population.[4] Although NICE recommends nutritional screening, the lack of evidence regarding the benefit of screening, or most appropriate way to conduct screening is also highlighted.[1]

Arguments in favour of nutritional screening include early detection and treatment of nutritional problems associated with negative patient outcomes.[5] However, the impact and the effectiveness of nutritional interventions to manage malnutrition, as a result of heterogeneous and low-quality studies, remain unclear.[6,7] Therefore, burdens of screening must be considered alongside any potential benefits because screening may increase anxiety and distress following a positive diagnosis.[8]

This review aims to identify and summarise the available published evidence regarding nutritional screening with respect to the experiences of patients, their families and carers.

MATERIALS AND METHODS

A systematic review of the literature, including data from both quantitative and qualitative texts, was conducted in accordance with the Cochrane Handbook for Systematic Review of Interventions.[9] The study protocol was registered with the international prospective register of systematic reviews, PROSPERO (Registration No: CDR42019140859)[10] and is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[11]

Literature search

Searches were performed by AB and SG on 3 July 2019 in the databases Ovid MEDLINE(R) ALL 1946 to 2 July 2019; Embase via OVID 1974 to Week 26 2019; PsychINFO via OVID 1987 to Week 4 June 2019; CINAHL Complete via EBSCO 1937 to 2 July 2019; ISI Web of Science: Science Citation Index Expanded 1970 to 3 July 2019; and British Nursing Database via ProQuest. The search was updated on 5 June 2020. No limits on publication date or language were applied. The search combined database-specific indexed terms and textwords related to the two main concepts: Nutritional Assessment of malnutrition, or individual malnutrition screening tools, AND experience or potential harms of screening. The MEDLINE search strategy is outlined in the Supporting information (Material S1), which was translated to alternate databases as required. Forward and backward citation searching of all included studies was completed.

Inclusion and exclusion criteria

Eligible studies included participants aged 18 years or older, from any clinical setting with any diagnosis. Studies investigating nutritional screening with respect to the views or experiences of patients, their families or informal carers were included. Qualitative and quantitative studies that included surveyed responses or questions regarding views of nutritional screening were included. Studies that reviewed self-screening of nutritional status, focusing on 'ease of use', rather than experiences or opinions of screening, were excluded. Case reports, editorials, opinion pieces and papers reviewing nutritional screening for eating disorders (e.g. anorexia nervosa), were excluded.

Study selection

All citations retrieved by electronic searching were downloaded to an ENDNOTE X8 (https://endnote.com) library, with duplicates removed according to published protocol.[12] Remaining records were uploaded to COVIDENCE systematic review software.[13] Study titles and abstracts were independently screened (by AB and SG) against eligibility criteria. All potentially relevant studies were retrieved, with full texts reviewed by AB and SG. Disagreements were resolved by consensus or adjudication by a third reviewer (MJ). A custom data extraction form[10] was used, piloted, reviewed and modified before the final data extraction of included studies was completed (by AB); a random 25% was independently extracted by GM.

Quality assessment

Each study was appraised using the MIXED METHODS APPRAISAL TOOL.[14] All included papers were evaluated by AB with a random 25% being independently reviewed by GM. Disagreements were resolved by consensus. For quality assessment of studies, see the Supporting information (Material S2).

Analysis

A narrative summary with descriptions and comparisons was completed for quantitative studies, providing an initial descriptive summary and explanation of characteristics of the included studies.[15,16] A narrative approach was used to

analyse the relationship within and between studies, and assess the overall strength of the evidence.[15] Qualitative results were reported in accordance with the Enhancing Transparency in Reporting the Synthesis of Qualitative research (ENTREQ) guidance.[17] Thematic synthesis was used for the qualitative findings using Thomas and Harden methodology.[18] Combining qualitative findings allowed new and generalisable knowledge to be generated. Synthesis was performed in three stages: (i) initial data coded regarding experiences of nutritional screening (conducted by AB); (ii) descriptive themes generated, with codes grouped into categories (AB and MP); and (iii) analytical themes generated both inductively and deductively, with the investigators (AB and MP) generating themes independently, then through discussion with a third investigator (MJ). Participants quotes and the interpretations of responses by the authors of the studies were used within the qualitative synthesis. Results from qualitative and quantitative syntheses were combined and charted into a matrix to allow final comparison between studies (see Supporting information, Material S3). In view of the focussed nature of the synthesis, a theoretical framework was not used to underpin the analysis.

RESULTS

Searches returned 1164 unique articles after deduplication, with 99 studies included for full-text screening. From this, nine studies published between 2004 and 2019 were eligible for inclusion, representing 609 participants, including 83 participants from five qualitative studies (see PRISMA flow chart, Figure 1).

Design, sample size and setting

Table 1 provides a summary description of the included studies. Three studies used questionnaires,[19,20,21] one of which[21] included free-text comments. A fourth comprised researchers' opinions of patients' views.[22]

Five studies were of qualitative interviews.[23,24,25,26,27] Sample sizes ranged from 61[22] to 205[19] for quantitative studies and from 10[23] to 23[27] for qualitative studies. Four studies were conducted in outpatient settings,[19,20,21,24] three in inpatient settings[22,23,27] and two in the community.[25,26] Studies were conducted in the USA,[19,20,23] Canada,[25] Australia,[21,26] Germany,[24] Norway[27] and England.[22]

Participants

Participants with a range of medical conditions were represented, including those receiving medical or surgical treatments,[19,20,22,24,27] including anticancer treatments, such as chemotherapy and radiotherapy,[21,24,27] and free-living individuals without significant morbidity.[25,26]

FIGURE 1 PRISMA flow diagram.

TABLE 1 Study characteristics summary

	Method of data collection	Age (years)	Sample size (gender)	Diagnosis and setting	Nutrition screening tool	Recruitment
Quantitative studies						
Cawood et al. (2012) USA[19]	Questionnaire, % results	Mean 55 years, range 18–87 years,	n = 205 F = 90 M = 115	Outpatients; gastroenterology, surgical, medical, oncology, urology, and gynaecology clinics	MUST; self-screen and HCP screen	Approximately every third person in clinic; 72% consented to involvement
Cawood et al. (2018) USA[20]	Questionnaire, % results	Mean (SD) 50.4 (16.2) years	n = 100 F = 43 M = 57	Outpatients; gastroenterology, medical, oncology or surgical clinics	MUST; self-screen and HCP screen	Next available patient in clinic, HCP recruitment
Di Bella et al. (2018) Australia[21]	Questionnaire, written comments	Mean (SD) 58 (16) years	n = 160 F = 67 M = 93	Outpatients; receiving systemic supportive therapies or radiotherapy	MST; patient-led and dietitian-led	Consecutive patients
Tammam et al. (2019) England[22]	Participants questioned regarding assessment	>18 years	n = 61	Inpatient; medical, surgical and oncology wards	INSYST I & II by nurse, MUST, MNA by researcher	Convenience sample
Qualitative studies						
Callen (2004) USA[23]	Qualitative interviews, naturalistic qualitative evaluation methods of Guba and Lincoln (1981)	≥65 years, mean (SD) 74 (6.6) years, range 68–86 years	n = 10 F = 4 M = 6	Inpatients; acute services. Nutritional risk identified with DETERMINE tool	DETERMINE Level 1 screen by dietitian	Convenience sample
Kroner et al. (2012) German[24]	Qualitative interviews, Mayring, (2008) content analysis	Mean 63 years, range 37–84 years	n = 12 F = 5 M = 7	Outpatients, receiving chemotherapy	PG-SGA	Not stated
Reimer et al. (2012) Canada[25]	Qualitative interviews	>55 years	n = 22 F = 13 M = 9	Free-living in community, members of senior's association; classed as at risk by SCREEN II tool	SCREEN II	Random sample; SCREEN II via post
Hamirudin, 2016 Australia[26]	Qualitative, in-depth interviews	≥75 years	n = 17	Free-living in community; classed as 'at risk' or 'malnourished' by screening tool	MNA-SF	Opportunistic screening; GP practice
Balstad et al. (2019) Norway[27]	Structured de-briefing interviews	Mean (SD) 64.4 (11.9) years	n = 23	Inpatients n = 22, Outpatient n = 1, n = 22 receiving anti-cancer treatments	PG-SGA	Purposive sampling

DETERMINE, DETERMINE Your Nutritional Health; HCP, Health Care Professional; INSYST I & II, Imperial Nutritional Screening System I & II; MNA (Mini Nutritional Assessment); MNA-SF, Mini Nutritional Assessment Short Form; MST, Malnutrition Screening Tool; MUST, Malnutrition Universal Screening Tool; PG-SGA, Patient Generated Subjective Global Assessment; SCREEN II, Seniors in the Community – Risk Evaluation for Eating and Nutrition; M, male; F, female.

Various recruitment methods were used, including consecutive[20,21] and sequential[19] inclusion of clinic patients, and convenience[22] sampling of inpatients in quantitative studies. Qualitative studies used convenience,[23] random[25] opportunistic[26] or purposive[27] sampling. One study did not state recruitment methods.[24] No papers were identified that captured experiences of patient's families or informal carers.

Various malnutrition screening tools were used: Malnutrition Universal Screening Tool (MUST)[19,20,22]; Malnutrition Screening Tool (MST)[21]; Imperial Nutritional Screening System I and II Tools (INSYST I & II)[22]; Mini Nutritional Assessment (MNA)[22]; DETERMINE Your Nutritional Health (DETERMINE) checklist[23]; Patient Generated Subjective Global Assessment (PG-SGA)[24,27]; Seniors in the community – Risk Evaluation for Eating and Nutrition II tool (SCREEN II)[25]; and the Mini Nutritional Assessment – Short Form (MNA-SF)[26] (Table 1).

Questionnaire findings

Three studies[19,20,21] collected data regarding participant's experiences of screening using questionnaires. The fourth[22] evaluated the acceptability of the tool by asking participants their subjective opinions regarding the tool. From these, most participants reported that they were agreeable towards nutritional screening, with 99%[19] and 100%[20] of participants in two studies reporting they were happy to answer questions regarding their nutrition. Written comments[21] included three positive responses of screening as a 'good idea' and four negative comments, suggesting nutritional screening was 'unnecessary'. Requests for explanation of screening results were made.[19] Finally, the fourth study[22] where comments from participants had been noted suggested that most were comfortable with the screening process and recognised the importance of screening.

Interview findings

Three key themes emerged: (i) experience of nutritional screening; (ii) misunderstanding of malnutrition; and (iii) barriers to and opportunities for change.

Experience of nutritional screening

Comments regarding screening tool content or process were common, with data generating a theme regarding the acceptability of being screened. Participants found screening to be simple,[23,26] and possible as part of a routine assessment[25] Questions asked were acceptable, and participants did not feel they were too sensitive or intrusive.[24,26]

> 'Well it's quite simple. When you get to my age, you want things simple don't you?'[26]

However, some participants were unclear on what had been examined, or of the purpose of nutritional screening.[24] Completion of questionnaires also caused some participants distress, particularly when discussing unintentional weight loss, or negative changes to their physical condition.[27]

> 'I want to avoid this! [refers to question about weight loss]. The hardest thing is when you lose weight when you actually don't want to'[27]

Misunderstanding of 'malnutrition'

A key theme was seen regarding participants misunderstanding of the term malnutrition, with many believing that 'malnutrition' was not following a 'healthy diet', high in fruits, vegetables and wholegrains, or that being overweight precluded malnutrition.[23,24,25]

> 'I'm 280 pounds. How can I be malnourished?'[23]

This requirement to follow a 'healthy diet' was reinforced by the media (e.g. magazines), and family members, if participants had received a new medical diagnosis (e.g. cancer).[24,26] Participants had a poor understanding of malnutrition and its contributory factors; with participants reporting that their overall nutritional health was 'fair' or 'good', even if screening showed a nutritional issue to address.[23]

> 'Well I couldn't understand that. When I eat properly – I feel I eat properly – I couldn't understand why … then it showed I was malnourished'[26]

As a result of this misunderstanding, some participants reacted negatively when informed of their nutritional risk, and were disappointed or upset with screening results.[25,26] Some felt accused of having an inadequate diet,[25] or having a poor knowledge of nutrition when they believed they were well-informed.[23]

> 'I was initially kind of shocked that I scored … you know'[25]

> So in what way do you feel I … I'm not doing the right things?'[25]

This caused participants to justify their current dietary intake, and describe how they had cut down on 'bad' foods and were making an effort to consume the 'right' foods, including changing snacks to fruit, consuming wholegrain foods, or reducing red meat intakes.[23,24,25,26]

> 'Yeh well I eat loads of vegetables and so I found it ah … I am doing things right'[25]

> 'Now I eat fruit instead of chocolate'[24]

Risk perception

Further misunderstandings of malnutrition's causes and consequences were seen in participants who had lost weight. Participants saw weight loss as a positive, as a result of previously being overweight,[24] and rationalised weight loss as the result of healthy dietary changes, rather than their diagnosis. Weight loss was also seen as a normal part of ageing,[26] and was not associated with disease.[24]

> 'Yes, I noted it [weight loss], I'm better off, I was a bit too snug'[24]

However, some participants credited weight loss as a cause of physical weakness, and saw weight loss as a negative event.[24,27]

> 'I have lost a lot of weight, seven kilos, it was the end of my strength. It [weight loss] was bad and depressing'[24]

As a result of beliefs that being overweight or following a 'healthy' diet precluded malnutrition, participants did not see themselves as 'at risk'. With this, nutritional screening results were not prioritised, and advice to manage malnutrition was declined or ignored.[25,26] Participants also compared their own risk to others, feeling their risk was comparatively low; this was supported by a perceived lack of symptoms related to malnutrition.[25]

> 'I don't feel I'm as much at risk as … as the community at large. And that's what bothers me are the people out there. They're far more at risk I feel'[25]

Symptoms, such as weight loss, were seen as a normal part of ageing, or the disease process (e.g. cancer), and therefore were not seen as modifiable[24,26]

> 'Well they can't do much. It's me getting old, tired and worried and well, you know'[26]

Results of screening

Reactions to results of screening varied. On reviewing results, rather than focusing on nutritional risk, participants noted positive aspects of their current diet.[25,26] A focus on 'room for improvement' was seen; with screening results seen as affirmation of aspects of their diet they were getting 'right' rather than highlighting areas which required intervention.[23,25] Similarly, participants often dismissed results or advice, as weight loss was attributed to other perceived unrelated factors, such as cancer therapies, or a belief that their current knowledge or actions were sufficient.[24,26]

> 'I don't need it. No, we look after ourselves as far as cooking and eating is concerned. I think common sense has got a lot to do with it'[26]

Interpretation of nutritional risk was also contextualised in light of other health concerns or social situations,[23,24,25] particularly if participants felt they were eating well,[23,26] therefore dietary changes were not a priority.

> 'Well because of the issues I have with my son and his children, I didn't really take an awful lot of notice of it I'm afraid. I'm sorry, I should have but I didn't'[26]

Barriers to and opportunities for change

Barriers to change, misinformation and rejection

Several barriers to changing dietary intake emerged. Results of screening were dismissed as irrelevant, incorrect or unrequired[24,25,26] if participants felt they were eating well, or were consuming a 'healthy' diet, and resulted in participants declining information aimed at improving their nutritional status.[26]

> 'Well I couldn't understand that. When I eat properly – I feel I eat properly – I couldn't understand why … then it showed I was malnourished'[26]

Poor appetite, caused by ageing or diseases status, was as barrier to change.[23,24,25] Similarly, social circumstances and lifetime habits, such as cooking and food choices, also presented as barriers, meaning that nutritional information was not prioritised above other concerns or habits.[25,26]

Nutritional recommendations were also rejected because of participants feeling information provided was not personalised, and the methods and results of mass nutritional screening were not applicable to themselves as individuals.

> 'The recommendations were good for the average person, but like I said, I believe that I eat and watch my diet quite well'[25]

Opportunity for change

Conversely, some participants were pleased the topic of nutrition was addressed, and felt they may benefit from nutritional recommendations.[24,25,26] However, this was often seen as 'room for improvement',[23,25] rather than a requirement to change.

> 'I count on the medical profession to let me know if they see that there is something wrong. If my weight drops or whatever, then I hope they will ring bells and say "Hey!"'[25]

DISCUSSION

We provide the first systematic review and synthesis of nutritional screening with respect to the experiences of patients,

their families and carers. The results of this review suggest that participants found nutritional screening to be acceptable. Despite this, issues regarding the relevance, understanding and value of nutritional screening must be noted. Reaction to the results of screening was mixed, and included disbelief, disappointment and offence, as well as being seen by some as an opportunity for learning. Poor understanding of malnutrition, misattribution of risk and perceived barriers contributed to low prioritisation and indifference to the results and nutritional advice given.

Although the survey responses suggest nutritional screening is perceived as an acceptable process, and completion of screening tools themselves was not burdensome, analysis of qualitative papers regarding the usefulness and applicability of nutritional screening raise questions regarding the effectiveness of nutritional screenings.

The qualitative and survey responses align regarding the acceptability of the screening process; however, some participants did not understand the purpose of screening, or what was being screened for. Similarly, results showing the risk of malnutrition were met with disbelief or indifference because malnutrition and the role of screening were not well understood, and therefore not prioritised. This lack of understanding of malnutrition and its role in ageing, disease and overall health, meant that participants expressed little concern regarding a diagnosis of malnutrition risk; with perceptions of good nutrition focused on following a 'healthy' diet, rather than one appropriate for their current medical condition. Importantly, generic nutrition support advice was often rejected because participants perceived themselves to either require individualised advice (e.g. as a result of comorbidities, or not seeing themselves as one of the majority).

Common barriers to change included incorrect assumptions that weight loss and poor appetite were a normal part of ageing, or an expected part of disease. A recent systematic review[28] identifying barriers and facilitators to nutritional screening in the community, which included both patient and HCP responses, identified similar barriers, including reluctance to be screened, lack of recognition of malnutrition and its importance, and avoidance of 'unhealthy' calorie-dense foods. Moreover, our review suggested that perceptions regarding the positives of weight loss and avoidance of 'unhealthy' foods were reinforced by family and media encouragement to follow a 'healthy' diet.

Mass nutritional screening is recommended as per NICE[1]; however, its benefit has yet to be demonstrated. A Cochrane review examining the effectiveness of nutritional screening on patient outcomes and quality of care found that there was insufficient evidence in the support of screening, although no evidence of ineffectiveness was found.[29] Similarly, NICE guidance recommending nutritional screening is solely based upon expert clinical opinion, and the effectiveness of nutrition support to manage malnutrition risk is unclear because previous studies demonstrated little overall effect on mortality, and carried a high risk of bias.[1,6,30] Considerations of the cost-effectiveness and validity of methods of screening

are also required when appraising the appropriateness and viability of screening methods, and include the condition being screen for showing benefit of treatment, and the benefits weighted against possible harms cause by screening (e.g. anxiety, overdiagnosis).[4,31]

Concerns regarding the harm of screening are more often considered when discussing screening for diseases such as cancer, where the harm of testing procedures, diagnostic false-positives and anxiety caused by screening itself is more tangible.[8,30] However, the potential harm of nutritional screening, as identified by this review, includes the distress of being informed of results, particularly if participants felt they were following a 'healthy' diet, or the screening tool highlighting negative physical attributes (e.g. significant weight loss). This may cause resistance to change, or reluctance to accept advice to manage nutritional risk. With the lack of evidence regarding the role and benefit of screening, as well as the results of this review suggesting that screening results are poorly understood, questions regarding the effectiveness of nutritional screening, when the public understanding of the condition is poor, must be considered.

Implications for clinical practice, research and policy

This review identified several areas which require further considerations when implementing nutritional screening programmes. Foremost, knowledge regarding malnutrition, both its causes and consequences, must be addressed to allow informed interpretation of screening results. Primarily, misconceptions that weight loss is always a positive health outcome, and that consumption of calorie-dense foods is always 'unhealthy', must be addressed.

Education for vulnerable groups regarding the role of nutritional screening, malnutrition, and its causes and consequences, combined with a tailored approach to providing nutritional advice, may help support behaviour change, particularly in societies where key public health messages are aimed at combatting obesity.

With this, further research regarding the most appropriate and effective interventions to identify and manage malnutrition should be conducted to prevent psychological or physical distress when there is no prospect of benefit (e.g. anxiety or disbelief of results resulting in disengagement) or provision of inappropriate treatments (e.g. for patients with refractory cachexia).[32]

How to alter public health messages, aiming to encompass requirements for different nutritional needs across the lifetime, as well as between the two public health considerations of obesity and malnutrition, also requires consideration.

Strengths and limitations

The use of a mixed methods design is a main strength of this review, with both qualitative and quantitative studies being

included in the analysis. This allowed the triangulation of results and enabled a richer insight into patients' experiences of nutritional screening.

Although this review only included nine studies, the depth of information gained from the five included qualitative studies (which included 83 participants) regarding the specific topic of nutritional screening provides a robust assessment of patients' views of nutritional screening.[33] However, as a result of the limitations identified in the original articles, including some limited sample sizes, as well as a lack of diversity in research populations, caution is required when interpreting results, and further research regarding patients' experiences of nutritional screening is required.

Additionally, we did not use a theoretical framework underpinning the qualitative analysis. However because of the narrow topic and the small number of studies included, the absence of a framework is unlikely to have weakened the results.

The studies included in this review were from high income countries, where issues of obesity, its associated comorbidities and the requirement for weight loss to manage these conditions together comprise a key public health message. Therefore, the generalisability of some findings (e.g. weight loss seen as positive) may be limited to societies where obesity is considered to be a greater concern than malnutrition.

CONCLUSIONS

Misunderstanding, caused by a lack of knowledge regarding the causes and consequences of malnutrition, resulted in reduced risk perception and disbelief or the rejection of screening results. Nutritional screening can be a trigger for dietary changes, although barriers, including older age, lifetime habits, disease status and social factors, particularly family and media encouragement of 'healthy' diets, meant that nutritional problems were not prioritised, particularly when weight loss and poorer dietary intake were seen as a normal part of ageing and the disease process. This resulted in low prioritisation of screening results and associated recommendations. The effectiveness and appropriateness of nutritional screening, when results are misunderstood and risk is misattributed to disease or ageing, must be considered, particularly when the efficacy of nutritional interventions to manage malnutrition is unknown. Although the process of screening is acceptable, without addressing patient barriers, particularly a fundamental lack of knowledge regarding malnutrition, in the context of a paucity of cost-effectiveness data, the role of nutritional screening must be questioned.

CONFLICT OF INTERESTS, SOURCE OF FUNDING AND AUTHORSHIP

The authors declare that they have no conflicts of interest.

AB and MJ designed the project. AB, SG and MJ designed the protocol. AB and SG conducted the review. AB and GM performed the extraction of data. AB and MP performed the analysis. All authors revised the manuscript critically. AB and MJ had overall responsibility for the final content.

Transparency declaration

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

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REFERENCES

1. National Institute for Health and Clinical Excellence. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition (NICE Guideline CG32). London: National Collaborating Centre for Acute Care; 2006.
2. Isautier JMJ, Bosnic M, Yeung SSY, Trappenburg MC, Meskers CGM, Whittaker AC, et al. Validity of nutritional screening tools for community-dwelling older adults: a systematic review and meta-analysis. J Am Med Dir Assoc. 2019;20:1351.e1313–25.
3. Power L, Mullally D, Gibney ER, Clarke M, Visser M, Volkert D, et al. A review of the validity of malnutrition screening tools used in older adults in community and healthcare settings - a MaNuEL study. Clin Nutr ESPEN. 2018;24:1–13.
4. GOV.UK. UK National Screening Committee: Criteria for appraising the viability, effectiveness and appropriateness of a screening programme [PH England, editor]. London: GOV; 2015.
5. Guyonnet S, Rolland Y. Screening for malnutrition in older people. Clin Geriatr Med. 2015;31:429–37.
6. Muscaritoli M, Krznaric Z, Singer P, Barazzoni R, Cederholm T, Golay A, et al. Effectiveness and efficacy of nutritional therapy: a systematic review following Cochrane methodology. Clin Nutr. 2017;36:939–57.
7. Feinberg J, Nielsen EE, Korang SK, Halberg Engell K, Nielsen MS, et al. Nutrition support in hospitalised adults at nutritional risk. Cochrane Database Syst Rev. 2017;5:CD011598.
8. DeFrank JT, Barclay C, Sheridan S, Brewer NT, Gilliam M, Moon AM, et al. The psychological harms of screening: the evidence we have versus the evidence we need. J Gen Intern Med. 2015;30:242–8.
9. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [online]. The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org (accessed July 2019).
10. Bullock A, Greenley S, McKenzie G, Patterson M, Johnson MJ. Patient, family and carers experiences of nutritional screening: a systematic review CDR42019140859. 2019. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019140859 (accessed July 2019).
11. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine. 2009;6:e1000097.
12. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc. 2016;104:240–3.
13. Veritas Health Innovation. Covidence systematic review software. [online]. http://www.covidence.org (accessed July 2019).
14. Pace R, Pluye P, Bartlett G, Macaulay AC, Salsberg J, Jagosh J, et al. Testing the reliability and efficiency of the pilot Mixed Methods Appraisal Tool (MMAT) for systematic mixed studies review. Int J Nurs Stud. 2012;49:47–53.

15. Sutton A, Clowes M, Preston L, Booth A. Meeting the review family: exploring review types and associated information retrieval requirements. Health Info Libr J. 2019;36:202–22.

16. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination; 2008.

17. Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012;12:181.

18. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol. 2008;8:45.

19. Cawood AL, Elia M, Sharp SK, Stratton RJ. Malnutrition self-screening by using MUST in hospital outpatients: validity, reliability, and ease of use. Am J Clin Nutr. 2012;96:1000–7.

20. Cawood AL, Walters ER, Sharp SKE, Elia M, Stratton RJ. 'Self-screening' for malnutrition with an electronic version of the Malnutrition Universal Screening Tool ('MUST') in hospital outpatients: concurrent validity, preference and ease of use. Br J Nutr. 2018;120:528–36.

21. Di Bella A, Blake C, Young A, Pelecanos A, Brown T. Reliability of patient-led screening with the malnutrition screening tool: agreement between patient and health care professional scores in the cancer care ambulatory setting. J Acad Nutr Diet. 2018;118:1065–71.

22. Tammam JD, Gardner L, Hickson M. Validity, reliability and acceptability of the Imperial Nutritional Screening System (INSYST): a tool that does not require the body mass index. J Hum Nutr Diet. 2009;22:536–44.

23. Callen B. Understanding nutritional health in older adults. A pilot study. J Gerontol Nurs. 2004;30:36–43.

24. Kroner A, Stoll H, Spichiger E. Malnutrition and weight loss - nurse assessment of nutritional status and counselling: experiences of patients with newly diagnosed or relapsed cancer. Pflege. 2012;25:85–95.

25. Reimer H, Keller H, Tindale J. Learning you are "at risk": seniors' experiences of nutrition risk screening. Eur J Ageing. 2012;9:81–9.

26. Hamirudin AH, Charlton K, Walton K, Bonney A, Albert G, Hodgkins A, et al. Implementation of nutrition screening for older adults in general practice: patient perspectives indicate acceptability. J Aging Res Clin Pract. 2016;5:7–13.

27. Balstad TR, Bye A, Jenssen CR, Solheim TS, Thoresen L, Sand K. Patient interpretation of the Patient-Generated Subjective Global Assessment (PG-SGA) Short Form. Patient Prefer Adherence. 2019;13:1391–400.

28. Harris PS, Payne L, Morrison L, Green SM, Ghio D, Hallett C, et al. Barriers and facilitators to screening and treating malnutrition in older adults living in the community: a mixed-methods synthesis. BMC Fam Pract. 2019;20:100.

29. Omidvari AH, Vali Y, Murray SM, Wonderling D, Rashidian A. Nutritional screening for improving professional practice for patient outcomes in hospital and primary care settings. Cochrane Database Syst Rev. 2013;Cd005539.

30. Woolf SH, Harris R. The harms of screening: new attention to an old concern. JAMA. 2012;307:565–6.

31. Shickle D, Chadwick R. The ethics of screening: is 'screeningitis' an incurable disease? J Med Ethics. 1994;20:12–8.

32. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12:489–95.

33. Guest G, Bunce A, Johnson L. How many interviews are enough? Field methods. Field Method. 2006;18:59–82.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Body mass index mediates the effect of the DASH diet on hypertension: Common metabolites underlying the association

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Abstract

Background: The Dietary Approaches to Stop Hypertension (DASH) diet is beneficial in reducing blood pressure; however, this may be a consequence of concurrent weight reduction. In the present study, we investigated whether body mass index (BMI) mediates the association between the DASH diet and hypertension and investigate common metabolic pathways.

Methods: We included 2424 females from the cross-sectional TwinsUK cohort, with blood pressure, BMI and dietary intake measured within 1.01 (SD = 0.68) years and serum metabolomics profiling (591 metabolites). We constructed a mediation model to test the mediation effects of BMI on the total effect of the DASH diet on hypertension. To identify a metabolite panel associated with the DASH diet and BMI, we built random forest models for each trait, and selected the common metabolic contributors using five-fold cross-validation error.

Results: We found that BMI fully mediates the association between the DASH diet and hypertension, explaining 39.1% of the variance in hypertension. We then identified a panel of six common metabolites predicting both the DASH diet and BMI with opposing effects. Interestingly, at the univariate level, the metabolites were also associated with hypertension in the same direction as BMI. The strongest feature, 1-nonadecanoyl-GPC (19:0), was positively associated with the DASH diet (β [SE] = 0.65 [0.12]) and negatively with BMI (β [SE] = −1.34 [0.12]) and hypertension (odds ratio = 0.71, 95% confidence interval = 0.6–0.84).

Conclusions: We highlight the role of BMI in the mechanisms by which the DASH diet influences hypertension and also highlight common metabolic pathways. Further studies should investigate the underlying molecular mechanisms to increase our understanding of the beneficial ways of treating hypertension.

KEYWORDS
BMI, DASH, hypertension, mediation, metabolomics

Key points

- Adherence to the DASH diet can reduce blood pressure; however, this may be a consequence of concurrent weight reduction.

INTRODUCTION

Hypertension is a highly prevalent and modifiable risk factor for cardiovascular morbidity and mortality worldwide.[1] The risk factors for hypertension are multifactorial and include both genetic predisposition and environmental or lifestyle factors, including diet, alcohol use and sedentary behaviour.[1,2]

Previous studies not only identified individual nutrients, such as sodium and potassium, but also alcohol, saturated fat, riboflavin, tryptophan, biotin and carbohydrate intakes to be associated with differences in blood pressure (BP).[3–8] However, foods are consumed, not individual nutrients and the combinations of foods, each with their own matrices of nutrient compositions,[9] may also have an effect on human health, including cardiovascular disease outcomes,[8] through nutrient–nutrient interactions.[8,10]

The Dietary Approaches to Stop Hypertension (DASH) diet was designed to combine the effects of numerous foods and nutrients, previously shown to be beneficial for BP reduction.[11,12] The DASH diet is rich in fruits, vegetables, whole grains, fish, nuts and low-fat dairy products, at the same time as limiting the intake of red meats and full-fat dairy products.[11,13] Following a number of successful clinical trials, several countries, including the USA and many European nations, have promoted the DASH diet as an effective nutritional approach for preventing hypertension.[11,14–17]

In addition to hypertension, population-based studies have reported that adhering to the DASH diet reduces BP,[5,18] cardiovascular events,[19] cancer[20] and obesity.[21,22]

Obesity is a major risk factor for hypertension, cardiorenal and cardiometabolic disorders.[23,24] A linear dose–response meta-analysis reported a 16% increased risk of hypertension per one unit increase in body mass index (BMI) and a 49% increased risk per five unit increase.[23] Moreover, in a recent systematic review of 17 randomised controlled trials (RCTs), Saneei et al.[5] reported the DASH diet to be negatively associated with BP; however, the results suggested that the beneficial BP-reducing effects of the DASH diet may have occurred as a result of its weight-reducing impact.[5]

In the present study, we aimed to investigate the mediatory effect of BMI in the relationship between the DASH diet and hypertension and to further explore the metabolic pathways by which diet may act with respect to reducing BMI in a large population-based cohort.

METHODS

A flowchart of the study design is presented in Figure 1.

Study subjects were adults enrolled in the TwinsUK registry, comprising a national register of adult twins recruited as volunteers without selecting for any particular disease or traits, as described in greater detail elsewhere.[25] Briefly, TwinsUK is the largest cohort of community-dwelling adult twins in the UK, which was initially developed to investigate the heritability and genetics of disease prevalence in women. The cohort now comprises over 14,000 predominantly female twins and is representative of the British general population. Here, we analysed data from 2424 females, with BP, antihypertensive drug use, BMI, age, and dietary intake measured within a 3-year period (mean [SD] = 1.01 [0.68]) (Figure 1).
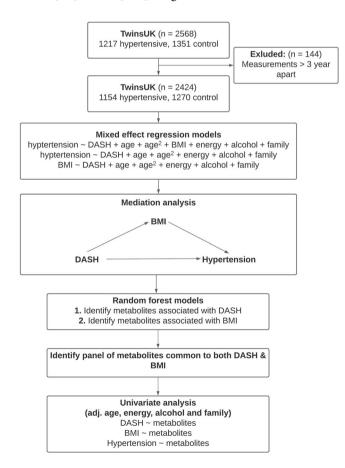

FIGURE 1 Flowchart of the study design. BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension

Phenotypes

BP was measured by a trained nurse as previously described.[6] Briefly, triplicate measurements (interval of 1 min) were performed with the patient in the sitting position and the mean of the second and third recorded.

Hypertension was defined based on the subject's BP level or use of BP-lowering drugs. The individual was classified as a hypertensive case if systolic BP (SBP) > 130 mmHg OR diastolic BP (DBP) > 90 mmHg,[26] OR using BP-lowering drugs at the time of BP measurement; otherwise, the subject was classified as a normotensive control.

Dietary intake was estimated by a 131-item paper-based food frequency questionnaire (FFQ), modified from the European Prospective Investigation into Diet and Cancer (EPIC) FFQ, as described previously.[27,28] The FFQ has been validated against urinary biomarkers and plasma ascorbic acid levels in the EPIC Norfolk cohort.[29] FFQs were processed using FETA software, an open-source, cross-platform tool designed to process dietary data from the EPIC FFQ, in accordance with their guidelines (https://www.epic-norfolk.org.uk/for-researchers/feta-download). The default nutritional database of FETA is based on *McCance and Widdowson's The Composition of Foods*.[30] Individuals were excluded if they answered fewer than 10 food items or for those where the ratio between the FFQ derived total energy intake and the individual's estimated basal metabolic rate (Harris–Benedict equation) was outside of the mean ratio (2 SD).[31] From the processed FFQs, intakes of specific food components comprising the DASH score (discussed below) were localised into quintiles. Alcohol intake (g day^{-1}) was categorised (0: <5 g day^{-1}; 1: 5–15 g day^{-1}; 2: >15 g day^{-1}).

The DASH index, a score developed by Fung et al.,[32] which assesses eight foods and components pertinent to the DASH diet, positively scoring higher intakes of (i) vegetables, (ii) fruit and fruit juice, (iii) nuts, legumes and tofu, (iv) whole grain cereals, (v) low-fat dairy and negatively scoring higher intakes of (i) red and processed meats, (ii) sugar-sweetened beverages (iii) sodium, was calculated (further details on scoring are provided elsewhere[28]; see also the Supporting information, Table S1). DASH scores can range from 8 to 40 and, in the present study, scores ranged from 11 to 37, with a higher score suggesting a dietary pattern more aligned with the DASH diet.

Circulating serum levels of 591 metabolites were quantified using liquid and gas chromatography coupled with untargeted mass spectrometry by Metabolon, Inc., as previously described.[33] Metabolite concentrations were then inverse normalised to counteract abnormal distribution and missing values were imputed using the minimum run-day measures.[33]

Ethical approval

Twins provided their informed written consent and the study was approved by St Thomas' Hospital Research Ethics Committee (REC Ref: EC04/015).

Statistical analysis

Statistical analysis was performed using R, version 4.0.2.[34]

Continuous variables were standardised using the z-scoring scale to improve model convergence. We used binomial generalised mixed models (R package "lme4"[35]) to investigate associations between the DASH diet and hypertension after adjusting for age, age^2, BMI, energy and alcohol intakes, and family relatedness, whereas linear mixed effect models (R package "lme4"[35]) were employed to explore the effect of the DASH diet on BMI (Figure 1). We then constructed a mediation analysis as implemented in the R package "mediation"[36] to test the mediation effects of BMI (indirect effect) on the total effect of the DASH diet on hypertension adjusting for age, age^2, energy and alcohol intakes, and family structure. We constructed a mediation model to quantify both the direct effect of the DASH diet on hypertension and the indirect (mediated) effects noted above. The variance accounted for (VAF) score, which represents the ratio of indirect-to-total effect and determines the proportion of the variance explained by the mediation process, was further used to determine the significance of mediation effect[36] (Figure 1).

Because the effect of the DASH diet on reducing BP is complemented by sodium intake, in a dose-dependent manner,[4] we conducted a sensitivity analysis by additionally adjusting for sodium intake (mg day^{-1}) in the models outlined above.

We further explored potential metabolic pathways underlying the DASH diet and obesity by running random forest (RF) models. For each metabolite, we calculated residuals by running linear regressions adjusting for age and family. We then split the dataset (80:20), with 80% going into a training set and the other 20% becoming a test set. Hyperparameters were tuned using the adaptive resampling search and the optimum number of features calculated using five-fold cross-validation and selected by node purity. We then identified a metabolite panel common to both traits by selecting common features (between BMI and the DASH diet). To further understand and interpret the effects of the metabolites in our model, SHAP (SHapley Additive exPlanation)[37] values were used to visualise the inner workings. Mixed effect models were further employed to investigate the univariate associations between the identified metabolites and BMI, the DASH diet and hypertension when adjusting for age, energy and alcohol intakes, family (random effect) and multiple testing (false discovery rate [FDR]).

RESULTS

The demographic characteristics of the study populations are presented in Table 1. Here, we investigated the relationship between adherence to a DASH diet and hypertension in 2424 females from the TwinsUK cohort, of whom 1154 were hypertensive cases and 1270 were

TABLE 1 Descriptive characteristics of the study population ($n = 2424$)

Hypertension status	All			Normotensive controls			Hypertensive cases		
N	2424			1270			1154		
Females, N (%)	2424 (100%)			1270 (100%)			1154 (100%)		
Age (years), mean (SD)	58.23 (10.04)			54.43 (9.56)			62.41 (8.83)		
BMI (kg m^{-2}), mean (SD)	26.52 (4.81)			25.34 (4.25)			27.82 (5.06)		
SBP (mmHg), mean (SD)	127.68 (17.07)			115.66 (8.89)			140.9 (13.84)		
DBP (mmHg), mean (SD)	77.27 (9.7)			72.68 (7.25)			82.33 (9.54)		
DASH score, mean (SD)	24.18 (4.22)			24.21 (4.34)			24.13 (4.08)		
Energy intake (kcal), mean (SD)	1856.66 (513.05)			1848.03 (515.6)			1866.16 (510.27)		
Alcohol intake (g day^{-1}), N (%)	<5	5–15	>15	<5	5–15	>15	<5	5–15	>15
	1180 (48.68%)	816 (33.66)	428 (17.66)	586 (46.14)	453 (35.67)	231 (18.19)	594 (51.47)	363 (31.46)	197 (17.07)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.
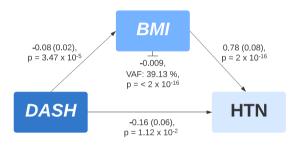

FIGURE 2 Mediation analysis of the association between the Dietary Approaches to Stop Hypertension (DASH) diet and hypertension (HTN). Path coefficients are denoted beside each path and indirect effect and variance accounted for (VAF) score is denoted below the mediator (body mass index [BMI])

normotensive controls. Overall, our sample was composed of middle-aged females with an mean (SD age of 58.2 (10) years and a mean (SD) BMI of 26.5 (4.8) kg m^{-2} (Table 1).

We find that closer adherence to the DASH diet is associated to a lower prevalence of hypertension (odds ratio [OR] = 0.85, 95% confidence interval [CI] = 0.76–0.97; $p = 1.12 \times 10^{-2}$) after adjusting for all the confounders (Figure 2). However, when further adjusting for BMI the association between the DASH diet and hypertension was no longer significant (OR = 0.91, 95% CI = 0.81–1.03; $p = 0.15$). We therefore conducted a formal mediation analysis to determine the indirect effect of BMI on the effect between the DASH diet and hypertension. The analysis found that BMI fully mediates the negative association between DASH and hypertension (VAF = 39.13%, $p < 2 \times 10^{-16}$). Because studies have reported that one of the main effects of DASH on hypertension is attributed to the low amount of sodium content,[4] we ran a sensitivity analysis additionally adjusting for sodium intake (mg day^{-1}). The results remained the same.

Next, we utilised a machine learning approach to identify common metabolic pathways underlying both the DASH diet and BMI. For both the DASH diet and BMI, we ran RF models on the 591 age-adjusted metabolite residuals. The RF BMI model identified 37 metabolic features for BMI, whereas the RF DASH diet model also identified 37 features for DASH. Six of the identified set of features were overlapping (Figure 3a; see also Supporting information, Table S2). The "common" metabolites panel jointly explained 18.45% of the variance in BMI and 5.38% of the variance in the DASH diet after adjusting for family. Among the metabolites identified, the lipid 1-nonadecanoyl-GPC (19:0) and the amino acids hydrocinnamate and proline were the most important contributors to the phenotypes' variance (Figure 3a; see also Supporting information, Figures S1 and S2). The other three common features were 1-palmitoleoyl-2-oleoyl-glycerol (16:1/18:1), dihydroorotate and N6-carbamoylthreonyladenosine (see Supporting information, Figures S1 and S2 and Table S2). We further tested the univariate effect of each metabolite on both the DASH diet and BMI by running linear mixed model for each metabolite adjusting for age, energy and alcohol intakes and family, and the results were in line with the RF findings.
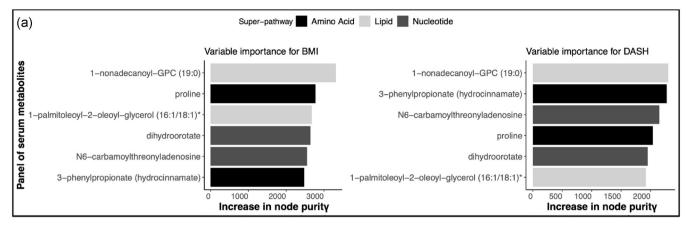
Indeed, all six metabolites were associated (FDR < 0.1) with DASH and BMI with opposing effects (Figure 3b). The association between 1-palmitoleoyl-2-oleoyl-glycerol and DASH was borderline significant. Circulating hydrocinnamate and 1-nonadecanoyl-GPC (19:0) levels were positively associated with the DASH diet and negatively associated with BMI (Figure 3b). Proline, dihydroorotate, 1-palmitoleoyl-2-oleoyl-glycerol (16:1/18:1) and N6-carbamoylthreonyladenosine were negatively associated with the DASH diet and positively associated with BMI (Figure 3b).

Age, energy and alcohol intakes and family adjusted residuals of the metabolites were also associated (FDR < 0.05) with an increased risk of hypertension, with OR values ranging from 1.55 (95% CI = 1.30–1.86) for
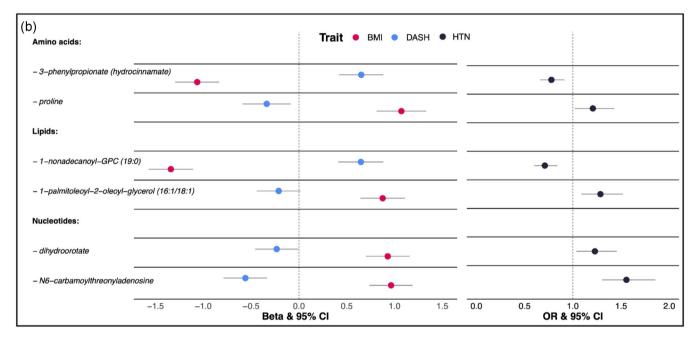
FIGURE 3 (a) Increase in node purity for the six overlapping metabolites from the DASH diet and BMI random forest models, (b) Univariate correlations between each metabolite in the common metabolite panel, the DASH diet, BMI and hypertension. Metabolites are grouped by super pathway. Points represent coefficients for BMI and DASH diet analyses, and odds ratios (OR) for hypertension, whereas error bars represent 95% confidence intervals (CI) after adjusting for age, energy and alcohol intakes and family relatedness. BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; HTN, hypertension

N6-carbamoylthreonyladenosine to 1.21 (95% CI = 1.02–1.43) for proline (Figure 3b). 1-Nonadecanoyl-GPC (19:0) and hydrocinnamate were associated with a lower risk of hypertension, with OR values of 0.71 (95% CI = 0.60–0.84) and 0.78 (95% CI = 0.66–0.91), respectively. When further adjusting for BMI and the DASH diet, the results remain consistent, although the effects were attenuated (see Supporting information, Table S3).

DISCUSSION

In this large community-based study, we observed for the first time, that the effect of the DASH diet on hypertension may be fully mediated by BMI after adjusting for age, age^2, energy and alcohol intakes, and family. Using RF models, we then identified a panel of six common molecular markers underlying both the DASH diet and BMI, resulting in opposing effects upon both traits (Figure 3b). Furthermore, the four metabolites negatively associated with the DASH diet and positively associated with BMI were also positively associated with hypertension, whereas the two metabolites positively associated with the DASH diet and negatively associated with BMI were also negatively associated with hypertension (Figure 3b). When further adjusting for BMI and the DASH diet, the results remained consistent, although the effects were attenuated supporting the mediatory role of BMI in the DASH diet–hypertension association.

RCTs have reported that the combination of eight food/nutrient components targeted by the DASH diet is more effective in reducing BP than a diet high in fruits and vegetables or the standard Western diet.[4,11,38] Additionally, restricting sodium intake (150–50 mmol), one of DASH

diet's components, resulted in greater BP reductions (SBP: −3 [95% CI = −1.7 to −4.3], $p = 0.001$).[4] The DASH diet has also been shown to reduce more body weight compared to a population's habitual diet (e.g., the Western diet).[21] Although the positive effect of the DASH diet upon bodyweight has been suggested as a potential mechanism as a result of its beneficial effects on hypertension,[21,39] for the first time, we show that this not only contributes to the effect, but also fully mediates it.

When looking for a panel of common metabolites underlying both the DASH diet and BMI, we found that the strongest common metabolic features to be 1-nonadecanoyl-GPC (19:0), 3-phenylpropionate (hydrocinnamate) and proline. Interestingly, all of these metabolites have been previously associated with BMI/obesity related traits.[40,41]

1-Nonadecanoyl-GPC (19:0)

Out of the six common metabolites identified, the lipid 1-nonadecanoyl-GPC (19:0) was the most important contributor with respect to both BMI and the DASH diet prediction (Figure 3; see also Supporting information, Figures S1 and S2). 1-nonadecanoyl-GPC (19:0) is a lysolipid derived from nonadecanoic acid and has been previously reported to have a significant negative effect on longitudinal BMI.[40] Consistent with this, we report a negative association with BMI and hypertension and a positive association with the DASH diet.

3-Phenylpropionate (hydrocinnamate)

The microbial metabolite 3-phenylpropionate (hydrocinnamate) was one of the most influential DASH positive features (see Supporting information, Figure S2) with a significant negative association with both BMI and hypertension (Figure 3b). Hydrocinnamate is a phenolic compound with a recognised antioxidant capacity.[42] Derivatives of this compound are known to have agonistic effects on peroxisome proliferator-activated receptors with antidiabetic and lipid-lowering activity.[42] We have previously reported hydrocinnamate to be negatively associated with weight change, as well as positively associated with healthy eating behaviours (e.g., higher consumption of apples and pears and lower consumption of fried fish and savoury pies)[42] and higher gut microbiome diversity.[43] This is the first report of a negative association between hydrocinnamate and hypertension. Interestingly, the beta-adrenergic blocker, Esmolol, used for short-term control of ventricular and heart rate, contains hydrocinnamate.[44]

Proline

Previous studies have found circulating proline levels to be positively associated with obesity.[45] Consistent with previous results, we observed a positive association between proline and BMI and hypertension and a negative association with the DASH diet (Figure 3b). Proline is a proteinogenic amino acid and its unique features contribute to the role it plays in protein structures and functions.[46] In a longitudinal study of over 4000 subjects (median follow-up of 3.1 years), Teymoori et al.[47] reported a 45% increased risk of hypertension relating to dietary proline intake (highest versus lowest tertile).[47]

The nucleotides *N6-carbamoylthreonyladenosine* and *Dihydroorate* and the lipid *1-Palmitoleoyl-2-oleoyl-glycerol* have also been previously associated with BMI,[40] obesity and metabolic risk.[41] However, their association with diet is novel.

Although the present study benefits from a relatively large dataset with measures collected within a biologically meaningful timeframe, it should be interpreted in the context of the certain limitations. First, our sample was composed solely of middle-aged (58 years), mostly overweight (26.52 kg m^{-2}) females. Second, our data are cross-sectional, preventing any inferences of causative effects without further clinical feeding studies. Third, dietary intake was measured using FFQs. Although those FFQs have been validated, as for any self-reported retrospective questionnaire, they also have numerous limitations.[9]

In conclusion, the present study provides novel insights into the relationship between the DASH diet, hypertension and BMI. Moreover, we have highlighted the presence of a common metabolic pathways between DASH diet score, BMI and hypertension. Although our observations require replication and testing, these findings extend our knowledge of the molecular mechanisms at play and may have implications for global public health providing future dietary recommendations for the prevention of hypertension.

CONFLICT OF INTERESTS

TDS is a co-founder of Zoe Global Ltd. SEB and AMV are consultants for Zoe Global Ltd. The remaining authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

CM and MM conceived and designed the experiment; PL and AN ran the analysis; PL and CM wrote the original manuscript; OM, PC, SEB, AMV, RG and TDS contributed methods/materials/analysis tools. All authors revised the manuscript 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 STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

DATA AVAILABILITY STATEMENT

The data used in the present study are held by the Department of Twin Research at King's College London. The data can be released to bona fide researchers using our normal procedures overseen by the Wellcome Trust and its guidelines as part of our core funding (https://twinsuk.ac.uk/resources-for-researchers/access-our-data).

ETHICAL APPROVAL

Twins provided their informed written consent and the study was approved by the St Thomas' Hospital Research Ethics Committee (REC Ref: EC04/015).

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PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/jhn.12956

REFERENCES

1. Kjeldsen SE. Hypertension and cardiovascular risk: general aspects. Pharmacol Res. 2018;129:95–9.
2. Louca P, Menni C, Padmanabhan S. Genomic determinants of hypertension with a focus on metabolomics and the gut microbiome. Am J Hypertens. 2020;33:473–81.
3. Blumenthal JA, Babyak MA, Hinderliter A, Watkins LL, Craighead L, Lin PH, et al. Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. Arch Intern Med. 2010;170:126–35.
4. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001;344:3–10.
5. Saneei P, Salehi-Abargouei A, Esmaillzadeh A, Azadbakht L. Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials. Nutr Metab Cardiovasc Dis. 2014;24:1253–61.
6. Louca P, Mompeo O, Leeming ER, Berry SE, Mangino M, Spector TD, et al. Dietary influence on systolic and diastolic blood pressure in the TwinsUK cohort. Nutrients. 2020;12.
7. Bazzano LA, Green T, Harrison TN, Reynolds K. Dietary approaches to prevent hypertension. Curr Hypertens Rep. 2013;15:694–702.
8. Barabási A-L, Menichetti G, Loscalzo J. The unmapped chemical complexity of our diet. Nature Food. 2020;1:33–7.
9. Leeming ER, Louca P, Gibson R, Menni C, Spector TD, Le Roy CI. The complexities of the diet-microbiome relationship: advances and perspectives. Genome Med. 2021;13:10.
10. Aljuraiban GS, Gibson R, Oude Griep LM, Okuda N, Steffen LM, Van Horn L, et al. Perspective: the application of a priori diet quality scores to cardiovascular disease risk-a critical evaluation of current scoring systems. Adv Nutr. 2020;11:10–24.
11. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med. 1997;336:1117–24.
12. Song Y, Lobene AJ, Wang Y, Hill Gallant KM. The DASH diet and cardiometabolic health and chronic kidney disease: a narrative review of the evidence in East Asian countries. Nutrients. 2021;13:984.
13. Sacks FM, Moore TJ, Appel LJ, Obarzanek E, Cutler JA, Vollmer WM, et al. A dietary approach to prevent hypertension: a review of the Dietary Approaches to Stop Hypertension (DASH) study. Clin Cardiol. 1999;22:6–10.
14. Chiu S, Bergeron N, Williams PT, Bray GA, Sutherland B, Krauss RM. Comparison of the DASH (Dietary Approaches to Stop Hypertension) diet and a higher-fat DASH diet on blood pressure and lipids and lipoproteins: a randomized controlled trial 1–3. Am J Clin Nutr. 2016;103:341–347.
15. Jones N, Forouhi NG, Khaw K-T, Wareham NJ, Monsivais P. Accordance to the Dietary Approaches to Stop Hypertension diet pattern and cardiovascular disease in a British, population-based cohort. Eur J Epidemiol. 2018;33:235–44.
16. Filippou CD, Tsioufis CP, Thomopoulos CG, Mihas CC, Dimitriadis KS, Sotiropoulou LI, et al. Dietary approaches to stop hypertension (DASH) diet and blood pressure reduction in adults with and without hypertension: a systematic review and meta-analysis of randomized controlled trials. Adv Nutr. 2020;11:1150–60.
17. Chiavaroli L, Viguiliouk E, Nishi SK, Blanco Mejia S, Rahelić D, Kahleová H, et al. DASH dietary pattern and cardiometabolic outcomes: an umbrella review of systematic reviews and meta-analyses. Nutrients. 2019;11:338.
18. Mompeo O, Berry SE, Spector TD, et al. Differential associations between a priori diet quality scores and markers of cardiovascular health in women: cross-sectional analyses from TwinsUK. Br J Nutr. 2020;1–11.
19. Salehi-Abargouei A, Maghsoudi Z, Shirani F, Azadbakht L. Effects of Dietary Approaches to Stop Hypertension (DASH)-style diet on fatal or nonfatal cardiovascular diseases—incidence: a systematic review and meta-analysis on observational prospective studies. Nutrition. 2013;29:611–8.
20. Jones-Mclean E, Hu J, Greene-Finestone LS, de Groh M. A DASH dietary pattern and the risk of colorectal cancer in Canadian adults. Health Promot Chronic Dis Prev Can. 2015;35:12–20.
21. Soltani S, Shirani F, Chitsazi MJ, Salehi-Abargouei A. The effect of Dietary Approaches to Stop Hypertension (DASH) diet on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. Obes Rev. 2016;17:442–54.

22. Wang T, Heianza Y, Sun D, Huang T, Ma W, Rimm EB, et al. Improving adherence to healthy dietary patterns, genetic risk, and long term weight gain: gene-diet interaction analysis in two prospective cohort studies. BMJ. 2018;360:k693.

23. Jayedi A, Rashidy-Pour A, Khorshidi M, Shab-Bidar S. Body mass index, abdominal adiposity, weight gain and risk of developing hypertension: a systematic review and dose–response meta-analysis of more than 2.3 million participants. Obes Rev. 2018;19:654–67.

24. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension. Circ Res. 2015;116:991–1006.

25. Verdi S, Abbasian G, Bowyer R, Lachance G, Yarand D, Christofidou P, et al. TwinsUK: the UK adult twin registry update. Twin Res Hum Genet. 2019;22:523–9.

26. Carey RM, Whelton PK. Evidence for the universal blood pressure goal of <130/80 mmHg is strong. Hypertension. 2020;76:1384–90.

27. Bingham SA, Welch AA, Mctaggart A, Mulligan AA, Runswick SA, Luben R, et al. Nutritional methods in the European Prospective Investigation of Cancer in Norfolk. Public Health Nutr. 2001;4: 847–58.

28. Mompeo O, Gibson R, Christofidou P, Spector TD, Menni C, Mangino M. Genetic and environmental influences of dietary indices in a UK female twin cohort. Twin Res Hum Genet. 2020;23:330–7.

29. Bingham SA, Gill C, Welch A, Cassidy A, Runswick SA, Oakes S, et al. Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. Int J Epidemiol. 1997;26(Suppl 1):S137–51.

30. Holland B, Welch AA, Unwin ID, Buss DH, Paul AA, Southgate DAT. McCance and Widdowson's the composition of foods. 5th ed., Cambridge: Royal Society of Chemistry; 1991.

31. Frankenfield DC, Muth ER, Rowe WA. The Harris-Benedict studies of human basal metabolism: history and limitations. J Am Diet Assoc. 1998;98:439–45.

32. Fung TT, Chiuve SE, Mccullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. Arch Intern Med. 2008;168:713–20.

33. Long T, Hicks M, Yu HC, Biggs WH, Kirkness EF, Menni C, et al. Whole-genome sequencing identifies common-to-rare variants associated with human blood metabolites. Nat Genet. 2017;49: 568–78.

34. R Core Team. R: A language and environment for statistical computing. 3.6.3 ed. (2020). Vienna, Austria: R Foundation for Statistical Computing.

35. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw. 2015;67:48.

36. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. mediation: R package for causal mediation analysis. J Stat Softw. 2014;59:38.

37. Lundberg SM, Erion G, Chen H, DeGrave A, Prutkin JM, Nair B, et al. From local explanations to global understanding with explainable AI for trees. Nat Mach Intell. 2020;2:56–67.

38. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER, et al. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids results of the OmniHeart randomized trial. JAMA. 2005;294:2455–64.

39. Lopes HF, Martin KL, Nashar K, Morrow JD, Goodfriend TL, Egan BM. DASH diet lowers blood pressure and lipid-induced oxidative stress in obesity. Hypertension. 2003;41:422–30.

40. Cirulli ET, Guo L, Leon Swisher C, Shah N, Huang L, Napier LA, et al. Profound perturbation of the metabolome in obesity is associated with health risk. Cell Metab. 2019;29:488-500.e2-500.

41. Perng W, Rifas-Shiman SL, Sordillo J, Hivert MF, Oken E. Metabolomic profiles of overweight/obesity phenotypes during adolescence: a cross-sectional study in project viva. Obesity. 2020;28: 379–87.

42. Menni C, Migaud M, Kastenmüller G, Pallister T, Zierer J, Peters A, et al. Metabolomic profiling of long-term weight change: role of oxidative stress and urate levels in weight gain. Obesity. 2017;25: 1618–24.

43. Menni C, Zhu J, Le Roy CI, Mompeo O, Young K, Rebholz CM, et al. Serum metabolites reflecting gut microbiome alpha diversity predict type 2 diabetes. Gut Microbes. 2020;11:1632–42.

44. National Center for Biotechnology Information. (2021) PubChem Compound Summary for CID 59768, Esmolol. PubChem.

45. Wahl S, Yu Z, Kleber M, Singmann P, Holzapfel C, He Y, et al. Childhood obesity is associated with changes in the serum metabolite profile. Obes Facts. 2012;5:660–70.

46. Morgan AA, Rubenstein E. Proline: the distribution, frequency, positioning, and common functional roles of proline and polyproline sequences in the human proteome. PLoS One. 2013;8:e53785.

47. Teymoori F, Asghari G, Farhadnejad H, Nazarzadeh M, Atifeh M, Mirmiran P, et al. Various proline food sources and blood pressure: substitution analysis. Int J Food Sci Nutr. 2020;71:332–40.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Louca P, Nogal A, Mompeo O, Christofidou P, Gibson R, Spector TD, et al. Body mass index mediates the effect of the DASH diet on hypertension: common metabolites underlying the association. J Hum Nutr Diet. 2022;35:214–222.
https://doi.org/10.1111/jhn.12956

Exploring changes in dietary intake, physical activity and body weight during chemotherapy in women with breast cancer: A Mixed-Methods Study

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Abstract

Background: The present study aimed (i) to assess changes in dietary intake (DI), physical activity (PA) and body weight (BW) in breast cancer patients during chemotherapy; (ii) to describe how women explained, experienced and dealt with these potential changes; and (iii) to eventually develop lifestyle intervention strategies tailored to the women's personal needs during chemotherapy.

Methods: A longitudinal parallel mixed-method design was used with quantitative assessment of changes in dietary intake (24-h recall, Appetite, Hunger, Sensory Perception questionnaire), physical activity (Short Questionnaire to Assess Health-enhancing physical activity, Multidimensional Fatigue Inventory) and BW (dual-energy X-ray absorptiometry), in addition to qualitative interviews with 25 women about these potential changes during chemotherapy.

Results: Most women who perceived eating less healthily with low energy intake (EI) and being less active before diagnosis continued to do so during chemotherapy, according to quantitative measurements. They struggled to maintain sufficient energy intake. Despite a lower than average reported EI, they unexpectedly gained weight and explained that fatigue made them even more inactive during chemotherapy. Active women usually managed to stay active because exercise was very important to them and made them feel good, although they also suffered from the side-effects of chemotherapy. They found more ways to deal with taste, smell and appetite problems than women with a lower energy intake.

Conclusions: The combination of the quantitative and qualitative data provided more insight into the changes in dietary intake, physical activity and BW during chemotherapy. The women's explanations showed why some women remain active and others need support to deal with changes in lifestyle factors such as healthy nutrition and fatigue.

KEYWORDS
body weight, breast cancer, dietary intake, mixed methods, perceptions, physical activity

INTRODUCTION

For breast cancer patients, the side-effects of chemotherapy include unfavourable changes in body composition (i.e. increase in fat mass and loss of muscle mass) and weight changes.[1] A meta-analysis shows that body weight (BW) during chemotherapy increases with a mean of 2.7 kg (95% confidence interval = 2.0–3.3).[1] These changes may have a profound negative influence on quality of life and self-esteem in breast cancer survivors, and may increase the risk of several co-morbidities, such as cardiovascular disease, diabetes mellitus and breast cancer recurrence.[2,3]

Changes in lifestyle factors such as dietary intake (DI) and physical activity (PA) may influence changes in BW and body composition during chemotherapy.[4–7] DI during chemotherapy may be influenced by increased appetite and intake of energy-dense comfort foods, which were found to be more common among women who gained weight during treatment.[8] A decline in subjective taste perception and appetite is associated with weight loss.[5,9,10] Lower intake of foods and drinks may be the result of experiencing a dry mouth, nausea, difficulty chewing, lack of energy as a result of fatigue and lower taste and smell perception.[11] An earlier study reported that DI in patients with breast cancer just before start of chemotherapy was similar to a comparison group of women without breast cancer (2070 kcal day^{-1}). However, during chemotherapy, the average EI of patients was 214 kcal day^{-1} lower than in the comparison group.[12]

When breast cancer patients become more physically active during therapy (e.g. because of a training intervention), they experience increased wellbeing, restored energy levels and a sense of purpose and control over their disease.[13] However, the side effects of the treatment often compel women to reduce their daily activities.[14] Their decision to reduce PA is often a result of fatigue, the need to conserve energy,[15] difficulty staying focused because of 'chemo brain' (cancer-therapy-associated cognitive change),[16] fear, possible injury, lack of time as a result of taking care of children and lack of motivation.[15]

Patients reported unanticipated weight gain during chemotherapy as a major concern. They experienced gaps in information on weight management and needed better information on dietary and lifestyle changes during and after chemotherapy, so that life can continue as normally as possible during this period.[5,17,18] More knowledge about how individual women experience and respond to quantitative changes in DI, PA and BW can enrich and clarify evidence from quantitative measurements.[19] This knowledge can be used to develop lifestyle intervention strategies and advice, tailored to the women's personal needs during chemotherapy.

The aim of this mixed-methods study was the quantitative assessment of changes in dietary intake, physical activity and BW in breast cancer patients during chemotherapy, in addition to a qualitative description how women explain, experience and deal with these potential changes.

MATERIALS AND METHODS

Design

This study is part of the COBRA study (Change Of Body composition in BReast cancer: All-in assessment).[19,20] We conducted a mixed-methods study among breast cancer patients, using semi-structured interviews, questionnaires and measurements on DI, PA and BW (Figure 1).

We expected the perspectives of patients in the qualitative part to complement the quantitative part, which is based on validated questionnaires and other quantitative measurements.[21] In addition, the approach was enriched by the use of triangulation to enhance the reliability and credibility of the findings.[22,23] We did not aim to make generalising statements about an entire population, but rather contextual (i.e. within this group of 25 women) statements that reflect the spectrum of individual experiences related to the objective individual measurements.[24]

Participants were contacted for measurements and in-depth interviews at three time points (Table 1): at enrollment into the study after diagnosis, before the start of chemotherapy (T1); between the third and fourth cycle of chemotherapy (T2); and 6 weeks after the last cycle of chemotherapy (T3).

The Medical Ethics Committee of Wageningen University approved the COBRA study (ABR NL40666.081.12). All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Study sample

We selected 25 participants from the total COBRA-study cohort ($n = 181$). All women underwent surgery and chemotherapy for breast cancer, in variable order. Via purposive sampling,[25,26] we selected a heterogeneous group of respondents representing the following characteristics: age (young versus older), type of chemotherapy (adjuvant and neo-adjuvant), body mass index (BMI) (>25 and <25 kg m^{-2}), menopausal status (pre and post), and patients treated in different hospitals.

Data collection

Quantitative data collection

From the Appetite, Hunger, Sensory Perception (AHSP) questionnaire,[27] a 29-question self-assessment tool answered on a five-point Likert scale (Table 1), we used three categories: taste (eight items, score range 8–40), smell (six items, range
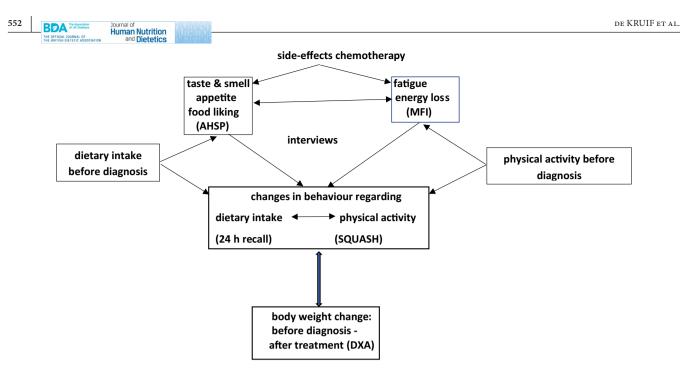
FIGURE 1 Conceptual behavioural model of women with breast cancer treated with chemotherapy and possible changes in dietary intake, physical activity and body weight. AHSP, Appetite Hunger Feelings and Sensory Perception questionnaire; SQUASH, Short Questionnaire to Assess Health-enhancing physical activity; MFI, Multidimensional Fatigue Inventory; DXA, dual-energy X-ray absorptiometry

TABLE 1 Overview of timing and type of quantitative and qualitative measurements among 25 women with breast cancer

_n_ = 25	T1 after diagnosis, pre chemotherapy	T2 mid-way chemotherapy	T3 6 weeks post chemotherapy
Quantitative measurements			
Taste, smell and appetite[a]	x	X[f]	x
Energy intake[b]		x[g]	
Physical activity[c]	x		x
Fatigue[d]	x		x
Body weight[e]	x		x
Qualitative measurements			
Self-reported body weight		x	
Perceptions of women on potential changes in dietary intake, physical activity and body weight[h]	x	x	x

[a]AHSP: Appetite Hunger Feelings and Sensory Perception questionnaire.
[b]24-h dietary recall.
[c]SQUASH: Dutch Short Questionnaire to Assess Health-enhancing physical activity.
[d]MFI: Multidimensional Fatigue Inventory.
[e]DXA: dual-energy X-ray absorptiometry.
[f]Assessed on same days as 24-h dietary recalls.
[g]Based on two 24-h dietary recalls on randomly chosen days during chemotherapy.
[h]Interviews.

6–30) and appetite (six items, range 6–30). Higher scores indicate a more positive self-judgement on taste, smell and appetite. Trained dietitians conducted two 24-h dietary recalls by telephone on randomly chosen days at T2, using a standardised protocol. The intake of total energy (kcal) was calculated in the computation module of Compl-eat™ using the Dutch Food Composition Table 2013.[28] BW was assessed with

a dual-energy X-ray absorptiometry (DXA) scan at T1 and T3. The Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) was used to assess PA.[29] Reported activities were subdivided into three intensity categories (min day^{-1}): light [1.6–2.9 metabolic equivalent of tasks (MET)], moderate (3–5.9 METs), vigorous (≥6 METs). One MET is the energy expenditure at rest. We then calculated adherence to the

2017 Dutch Physical Activity guideline,[30] which recommends a minimum of 150 min of moderate to vigorous activity per week. The Multidimensional Fatigue Inventory (MFI-20) is a self-reporting tool consisting of twenty propositions on five dimensions of fatigue (general fatigue, physical fatigue, reduction in activity, reduction in motivation and cognitive fatigue) and its consequences.[31-33]

Qualitative data collection

The semi-structured interviews were based on an interview guide that included topics such as side-effects of chemotherapy (focus on smell and taste), experiences and explanations of changes in DI, PA and BW, as well as perceptions on dealing with these changes.[26] The interviews were conducted at the participant's home. Oral permission for audiotaping was obtained before each interview.

Data analysis

Quantitative data

We first dichotomised the women based on EI at T2, PA and BW at baseline (T1) and T3. All intake parameters were complete for 117 participants of the total COBRA population ($n = 181$).

We compared EI during chemotherapy (T2) with the mean (SD) EI of 1779 (55.7) kcal day^{-1} of the total COBRA population of $n = 117$ persons during chemotherapy (12) and created two groups: above (high) or below (low) that averaged energy intake. For PA at T1 and T3, we applied the Dutch Physical Activity Guideline[30]; performance below the guideline at T3 compared to T1 was classified as inactive and above the guideline at T3 compared to T1 was classified as active. For changes in BW, we calculated the changes in kg between T1 and T3 measured by DXA.

In addition, we compared taste, smell and appetite with the mean scores of the total COBRA population[12]: for taste [mean (SD) 22.0 (0.57)], smell [mean (SD) 20.6 (0.42)] and appetite [mean (SD) 18.7 (0.50)]; above (high) or below (low) mean scores. For fatigue at T1 and T3, we calculated the MFI, and compared the values with the mean scores of a reference group of cancer survivors; above (high) or below (low) the mean scores. BMI was classified such that <25 kg m^{-2} was considered low and BMI ≥ 25 kg m^{-2} was considered high.

Qualitative data

All audiotaped interviews were transcribed verbatim and a synopsis was written for each respondent. To identify, analyse and describe patterns in respondents' individual experiences, athematic analysis[34,35] was carried out during which, after close reading and coding of the transcribed interviews, we formulated subthemes and eventually overarching themes.

Interview data were managed with MAXQDA (VERBI Software, Marburg, Germany).[36] All subthemes and themes were described in a mind map: one for each individual. In this way, we identified the essence of each theme, searched for relations through constant comparison across cases, looked for deviant cases, and analysed variation within and between cases.

Combining quantitative and qualitative data

All mind maps included individual results of the quantitative measurements (AHSP, BW, 24 h dietary recall, SQUASH and MFI) to find characteristics that further differentiate the themes. Subsequently, we gathered the relevant (sub) themes and quantitative measurements necessary to answer the research question. Finally, all the data were fit into the overarching story emerging from the data, aiming to gain insight into differences and similarities between the women regarding the findings from the quantitative and qualitative analyses.

RESULTS

Twenty-five women from the COBRA study were included in the present study (Table 2).

Quantitative results

Dietary intake

The average reported EI of the 25 women during chemotherapy of 1761 kcal (range 1182–3102 kcal) was similar to the average reported EI of all women in the total COBRA study of 1779 (55.7) kcal.[12] Women ($n = 11$) with an EI above average (mean 2165 kcal; range 1783–3102 kcal) were almost equally distributed between a lower BMI ($n = 6$) and a higher BMI ($n = 5$), just like women ($n = 14$) with an EI below average (mean 1442 kcal; range 1182–1738 kcal) were equally distributed between a higher BMI ($n = 7$) and a lower BMI ($n = 7$). Women with an EI above average were approximately as active (60% versus 54% met PA recommendation) and as fatigued (70% versus 77%) as women with an EI below average during chemotherapy. Those with a higher EI less often gained BW (64% versus 79%). Scores on appetite, taste and smell were low for most women, regardless of their EI. Women with lower EI during chemotherapy more often had a lower taste score (91%) than women with a higher EI (70%) (Table 3).

Physical activity

All women were moderately intensely physically active for ≥150 min per week at T1. At T3, approximately half of the women (13/23) were physically active for more than

TABLE 2 Baseline characteristics of the participants

Characteristics	n = 25
Age in years, mean (range)	50.4 (25–67)
Body mass index (kg m^{-2}) at T1 pre-chemotherapy, mean (range)	Mean 24.9 (19.3–32.4)
Menopausal status at T1, n (%)[a]	
Premenopausal	10 (40%)
Perimenopausal	3 (12%)
Postmenopausal	12 (48%)
Treatment chemotherapy, n (%)	
Adjuvant	17 (68%)
Neoadjuvant	8 (32%)
Type of chemotherapy, n (%)[b]	
FEC/docetaxel	9 (36%)
TAC	14 (56%)
ACPT[c]	2 (8%)
Received radiotherapy, n (%)	18 (72%)
Received hormonal therapy, n (%)	22 (88%)

[a]Patients with uterine extirpation (n = 3).

[b]FEC: F – fluorouracil (5 FU), E – epirubicin, C – cyclophosphamide. Docetaxel: also called Taxotere (Sanofi Mature IP, Paris, France). TAC: T – docetaxel (also called Taxotere), A – doxorubicin (also called Adriamycin), C – cyclophosphamide. ACPT: A – adriamycin (doxorubicin), C – cyclophosphamide P = paclitaxel, T = docetaxel.

[c]These patients also received immunotherapy (trastuzumab) in combination with chemotherapy.

150 min per week. Active women during chemotherapy (women who were active at T1 and stayed active at T3) (n = 13) more often had a lower BMI (69%) before treatment than inactive women (women who were active at T1 and below guideline PA at T3) (n = 10) (30%). They were more likely to have an EI above average (60% vs. 40%). The majority gained BW (62%), although inactive women were more likely to gain BW (90%). Active women during chemotherapy were less fatigued (54% versus 100%) and less often showed appetite problems (100% versus 58%) and smell problems (100% versus 50%) compared to inactive women (Table 3).

Body weight

Women had a mean baseline (T1) BMI of 24.9 kg m^{-2} (19.3–32.4). Their average BW at T1 was 71.4 kg (range 54.0–93.1 kg), the average difference in BW between T1 and T3 was 0.8 kg (range −6.5 to +4.5 kg). The majority of women (72%, n = 18) showed an increase in BW between T1 and T3: mean +1.9 kg (range 0.1–4.5); 28% (n = 7) showed a decrease in BW: mean −2.1 kg (range −0.2 to −6.5 kg). Women who gained weight were less likely to have an EI above average (39%) than women who lost weight (57%). Women with weight gain were less likely to meet the PA recommendation during chemotherapy (47% vs. 83%) and more often had a low BMI at baseline (61% vs. 29%). Women who gained weight and women who lost weight both showed high levels of fatigue (76% vs. 67%), appetite problems (76% vs. 80%) and taste problems (82% vs. 80%). Women with weight gain

reported less smell problems (88% vs. 100%) than women with weight loss (Table 3).

Qualitative results

Dietary intake

Most women with an EI above average reported they perceived their diet was healthy before diagnosis and were able to maintain their diet despite chemotherapy-related complaints (Table 4). Most women with low EI indicated they did not always eat healthily and were less aware of what healthy eating was before the diagnosis. These women continued to struggle during chemotherapy. Sometimes eating was such a problem that they were happy when they could eat at all, healthily or not:

> … happy when it went down, no matter what it was. Preferred sausage rolls to bread, baked potatoes and fries were tasty, no more fight against candy.
> [woman with low EI, BMI high, PA low, fatigue high, BW increased, Taste (T), Smell (S) and Appetite (A) low]

Some women struggled because of extremely bad taste, especially during the last three courses with Docetaxel, and could not eat at all.

Some women with higher intake were matter-of-fact about their eating problems:

TABLE 3 Assessment of changes in dietary intake, physical activity and body weight during chemotherapy

	Energy intake[a] (kcal)		Physical activity[b] (min week⁻¹) T3[f]		Body weight[d] difference (kg) T1–T3	
	≥1780 $n=11$	<1780 $n=14$	≥150 $n=13$	<150 $n=10$	Increase $n=18$	Decrease $n=7$
Energy intake[a] (kcal)						
≥1780 $n=11$			6 (46%)	4 (40%)	7 (39%)	4 (57%)
<1780 $n=14$			7 (54%)	6 (60%)	11 (61%)	3 (43%)
Physical activity[b] (min week⁻¹) T3[f]						
≥150 $n=13$	7 (54%)	6 (46%)			8 (47%)	5 (83%)
<150 $n=10$	4 (40%)	6 (60%)			9 (53%)	1 (17%)
Body weight[d] difference (kg) T1–T3						
Increase $n=18$	7 (64%)	11 (79%)	8 (62%)	9 (90%)		
Decrease $n=7$	4 (36%)	3 (21%)	5 (38%)	1 (10%)		
BMI T1						
≥25 kg m⁻² $n=12$	5 (45%)	7 (50%)	4 (31%)	7 (70%)	7 (39%)	5 (71%)
<25 kg m⁻² $n=13$	6 (55%)	7 (50%)	9 (69%)	3 (30%)	11 (61%)	2 (29%)
Fatigue[c] T3[f]						
High $n=17$	7 (70%)	7 (54%)	7 (54%)	10 (100%)	13 (76%)	4 (67%)
Low $n=6$	3 (30%)	6 (46%)	6 (46%)	-	4 (24%)	2 (33%)
Appetite[e] (6–30) T2[f]						
Normal/high $n=5$	2 (20%)	3 (25%)	5 (42%)	-	4 (24%)	1 (20%)
Low $n=17$	8 (80%)	9 (75%)	7 (58%)	10 (100%)	13 (76%)	4 (80%)
Taste[e] (8–40) T2[f]						
Normal/high $n=4$	3 (30%)	2 (17%)	2 (17%)	2 (22%)	3 (19%)	1 (20%)
Low $n=17$	7 (70%)	10 (83%)	10 (83%)	7 (78%)	13 (82%)	4 (80%)
Smell[e] (6–30) T2[f]						
Normal/high $n=2$	1 (10%)	1 (8%)	2 (100%)	-	2 (12%)	-
Low $n=20$	9 (90%)	11 (92%)	10 (50%)	10 (100%)	15 (88%)	5 (100%)

[a] 24-h dietary recall, above or below mean 1779 kcal ± 55.7 kcal in the total COBRA population for patients with breast cancer.
[b] Short Questionnaire to Assess Health-enhancing physical activity above or below 150 min at least moderately intense physical activity.
[c] Multidimensional Fatigue Inventory: above or under below mean scores of reference group of cancer survivors.
[d] Dual-energy X-ray absorptiometry scan, difference body weight (kg) T1–T3.
[e] Appetite Hunger Feelings and Sensory Perception questionnaire: above or below mean scores of total Cobra population (mean appetite 18.7; mean taste 22.0; mean smell 23.3). Higher scores indicate more positive self-judgement on the questionnaire categories.
[f] Missing values: for two women on physical activity and fatigue, as well as taste, smell and appetite.

TABLE 4 Overview of the most important experiences during chemotherapy, according to women's dietary intake, physical activity and change in body weight

	Before chemotherapy	Changes during chemotherapy	Explaining changes	Dealing with changes
Dietary intake				
Above average	• Quite healthy diet • BMI at T1: equally distributed between lower (≤ 25 kg m^{-2}) and higher (>25 kg m^{-2})	• Able to maintain their diet despite chemotherapy-related complaints, and appetite, taste and smell problems • Gained body weight	• Suffering from side-effects chemotherapy, but a healthy diet is very important • Chemotherapy is temporary, just keep eating as normally as possible	• Functional eating and more, smaller portions • Easy-to-manage healthy diet taking less effort to prepare • Use of dietary supplements
Below average	• Less healthy • BMI at T1: equally distributed between lower and higher BMI	• Intake: quantity takes precedence over healthy choices • Insufficient energy intake results in hospital admissions • Gain more body weight • More intake problems during Docetaxel • More problems with taste and structure of food	• No clear expectations/no preparation for side-effects of chemotherapy • Advice on a 'normal diet' not in line with desire to do more themselves with healthy food and supplements. Need for more information.	• Functional eating • Improvement of eating habits with less success than women with intake above average.
Physical activity				
According to guideline	• Active • BMI at T1 often lower	• Able to remain active • Gained body weight	• Valued being active greatly and tried to keep active as much as possible	• Struggled hard to maintain activity level for health reasons despite fatigue • Adjusting their pace • Made choices to spend time on physical activity, not on increasing the number of hours of workOR • Found it easy to remain active because limited experienced side-effects of chemotherapy
Below guideline	• Inactive • BMI at T1 often higher	• Felt overwhelmed by fatigue and often unable to be active • Gained more body weight	• Never liked to be activeAND/OR • Too tired (fatigue, neuropathy, bone pain)	• Overwhelmed by fatigue and experienced no possibilities to change
Body weight				
Gain	• BMI at T1 lower	• Unexpected weight gain • Some gained less weight by intentionally eating less but remained inactive	• Desire to lose weight • Constant good appetite, difficult to stop eating	• Being less active • Intake mainly tasty (high-energy) foods • Could not stop eating
Loss	• BMI at T1 higher	• Great difficulty eating • Do anything not to lose weight • Sometimes happy to lose weight	• Focus more on diet than on being physically active	• Could not eat enough to avoid weight lossOR • Intentional weight loss

Abbreviations: BMI, body mass index; T1, before the start of chemotherapy.

The chemo is temporary, I wasn't looking for a solution; just keep eating as normally as possible, even if it's not tasty …

[woman with high EI, BMI high, PA not available (NA), fatigue NA, BW decreased, T, S, A: NA]

Women with lower intake indicated that they first needed to experience what it was like to be treated with chemotherapy. They found it difficult when health care professionals (HCPs) recommended 'a normal diet' during chemotherapy, because they assumed that a normal diet was not good enough and they longed to do more:

I was searching for supplements, vitamins yes or no, no grapefruit, but orange? What is or isn't healthy to eat now?
(woman with low EI, BMI high, PA low, fatigue high, BW increased, T, S and A low)

Women with higher EI looked for creative solutions to be able to continue their intake, such as adding herbs, ketchup, salt for better taste; sucking ice cubes to avoid a metallic taste; eating yoghurt instead of bread; eating fruits such as grated apple because it went down easier. They mainly cooked easy-to-prepare meals, such as oatmeal in the morning and ready-to-eat meals in the evening. They more often ate smaller portions throughout the day. Some women reported that they perceived eating more healthily than before diagnosis and added various healthy alternatives and supplements to their diet.

Women with lower EI also tried to change their eating habits to accommodate a damaged and dry mouth, no appetite and loss of taste, although their aversion to almost every food was hard to overcome. They continued to struggle because they realised that it was necessary and called it functional eating:

I eat because I know I have to, but it's not going well and I certainly don't enjoy it
(woman with low EI, BMI high, PA low, fatigue high, BW increased, T, S and A low)

Physical activity

Some women meeting the PA recommendation during chemotherapy who engaged in intensive sports before diagnosis tried to maintain this as much as possible during chemotherapy, although it was not always easy:

Yesterday I walked 20 kilometres, I really like that […] But it took me half an hour longer because I had diarrhoea every two hours. There I was, sitting with my roll of toilet paper and body cream, with my head in the bushes …
(woman with PA high, BMI low, EI normal,

fatigue high, BW increased, T and S low, and A normal)

They explained that keeping fit was very important to them:

I need to keep in shape; I could have worked a bit more but then I couldn't go cycling; cycling just takes precedence …
(woman with PA high, BMI low, EI normal, fatigue low, BW decreased, T, S and A low)

Other women remained physically active mainly because the hospital offered exercise training for cancer patients. This was mainly experienced as meaningful contact with fellow patients aimed at recognition and sharing, not as PA.

Although active women were also tired, they did not want to give into it. They tried to keep cycling and walking as much as possible, they continued to work, but for fewer hours and they adjusted their pace (e.g. in household activities).

Most women who were inactive during chemotherapy indicated that before diagnosis PA was not their first priority and they usually did not like it. During chemotherapy, they experienced side-effects such as neuropathy and bone pain and their fatigue prevented activity:

Well, when I was very tired, I got up in the morning … Hoping the day would be over as soon as possible … so I could go back to bed … I just didn't know how to get through the day …
(woman with PA low, BMI high, EI low, fatigue high, BW increased, T, S and A low)

Some of them experienced even minimal PA as an almost insurmountable threshold and felt unable to change this:

At a certain point all your energy simply goes into learning to deal with the complaints you have
(woman with PA low, BMI high, PA low, fatigue high, EI low, BW increased, T, S and A low)

Some hesitated joining activities in a group because of their hair loss and the deterioration of their breasts after surgery. They related their appearance to their female identity.

Body weight

Most women noticed unexpected weight gain during chemotherapy:

I was not allowed to exercise during the last cycles of chemotherapy because of my lungs [radiation effect], so gradually another kilo is added
(woman with weight gain, BMI high; EI low; PA normal, fatigue low, T and S low, A normal)

To their surprise, some women who were expecting weight gain based on information from HCPs, actually lost weight.

Some women attributed their weight gain mainly to eating tasty (high-energy) foods, or not being able to stop eating. Others related it to decreased PA, not to changes in their diet.

Especially women with a lower BMI at diagnosis intentionally gained weight to be able to get through chemotherapy.

Other women, most of them with a higher BMI at diagnosis, were happy to lose some weight:

> They said with this chemo you don't lose weight but you gain weight; I've lost three kilos, I'm happy … I felt I was 10 kilos too heavy
> (Woman with weight loss, BMI high, low EI, PA normal, fatigue high, A, T and S NA)

Most women focused on their diet, and how to deal with it, rather than on physical activity:

> I did more with yoghurt and stuff and with fruit and vegetables, lettuce, I'd be able to control it a little more … I started fitness, stopped again … that's not my thing
> (woman with weight loss, BMI low, EI low, PA low, fatigue high, T and S low and A normal)

DISCUSSION

In this mixed-methods study, we aimed to assess changes in dietary intake, physical activity and BW in breast cancer patients during chemotherapy. We divided women into two groups for each lifestyle factor based on quantitative data: EI above and below the average, above and below the PA recommendation, and BW increase and decrease during chemotherapy. Through interviews, we determined how women experienced, explained and tried to deal with these changes. These results are complementary and explanatory to the quantitative measurements.

Our study is concordant with the recently published study by Da Costa Marinho et al.[37] who observed a negative impact of chemotherapy on meal enjoyment and taste changes in breast cancer patients receiving chemotherapy. In addition, BW and BMI increased slightly, as described by Bernhardson et al.[38] Almost all women in the present study experienced this negative impact independent of DI, PA or changes in BW. It appears that changes in DI, PA and BW also partly depend on how women deal with them.

We found that most women suffered taste (17/25), smell (20/25) and appetite (17/25) problems, regardless of their intake. The majority of interviewed women indicated having many problems with the taste and structure of food, and struggled to find solutions. All women aimed for sufficient DI through functional eating, which is synonymous with 'eating for the sake of eating' and in line with the studies of Bernhardson et al.[38] and Kwok et al.[5] It is not exactly clear why women with a higher EI were more successful at finding creative solutions to maintain their EI at sufficient levels than women with a lower intake. Women with a lower EI reported needing information about a healthy diet and whether or not to take supplements. Moreover, they needed information on alternatives for food intake to meet their dietary requirements.[39]

Although the majority of women were physically active during chemotherapy (15/25), only a few felt more fit during chemotherapy. The review by Abdin et al.[40] suggests that PA interventions for women with breast cancer have positive results, such as feeling better. However, women in our study who participated in such a programme experienced it mainly as an opportunity for peer-to-peer contact and only secondly as an opportunity to be physically active. Especially, the inactive women indicated, in line with Henry et al.,[41] that the impact of fatigue and neuropathy affected their ability to exercise. Women who were generally more active before chemotherapy greatly valued being active and tried to stay as active as possible, for example by adjusting their pace. Their baseline BMI was relatively lower and despite more taste problems they had a higher EI than inactive women, possibly because they were more creative in finding ways to continue eating. The level of PA during chemotherapy showed less fatigue (54%) for active women and more fatigue (100%) for inactive women. This is in line with the findings of Carayol et al.[42] who assessed the effect of an exercise-diet intervention during chemotherapy on cancer-related fatigue. Fatigue was significantly improved by exercising, and BMI was significantly lower, although they found no significant effect on nutritional intake and physical activity.[43]

Some of the women were reluctant to continue their training routine because of visible side-effects of chemotherapy, such as needing a wig because of hair loss. For them, this aspect was linked to their female identity. Courneya et al.[43] and Browall et al.[44] reported this aspect as one of the treatment-related barriers to PA. The information need for PA was less clear, probably because PA was not deemed as important as their diet.

Women with weight gain had a lower EI during chemotherapy and were more inactive and tired than women who lost weight. By contrast to expectations, 61% of women with weight gain have an EI below average. Women themselves attributed their weight gain to being less active than usual. On average, women gained 0.8 kg BW between T1 and T3 during chemotherapy, similar to the weight change reported in the COBRA study.[20] Before chemotherapy, a large part of the women focused on losing a few kilos, and half of them had a BMI ≥ 25 kg m^{-2} at the start of the study. In line with the studies by Klok et al.[5] and de Kruif et al.,[45] they experienced little support from HCPs to lose weight during chemotherapy. They experienced unintentional changes in BW as concerning, possibly because it undermined their feelings of control, as found in earlier studies.[5] Compared to women with a baseline BMI ≥ 25 kg m^{-2} (7/12; 58%), women with BMI < 25 kg m^{-2} (11/13; 85%) had an above average EI approximately as often and were more likely to be active,

although they more often gained BW. On average, women with low BMI had a slightly higher intake (mean 1789 kcal, range 1182–3102 kcal) than women with high BMI (mean 1712 kcal, range 1289–2588 kcal).

Strengths and limitations

The major strength of the present study is the mixed-methods design. The combined results provide more insight into how women themselves explained and dealt with the changes in EI, PA and BW. Because this is the first study to undertake these types of analyses, the results can be considered a first step towards understanding similarities and differences between women associated with specific changes in BW and weight-related lifestyle factors.

We selected the 25 women from the COBRA population by purposive sampling,[46] based on characteristics that are important according to literature rather than on the COBRA population itself. As a result, these 25 women are expected to adequately reflect the general population of women with breast cancer treated with chemotherapy. That may explain why we found a lower score on appetite, taste and smell and a slightly lower score on EI than in the COBRA study.[12]

It is a well-known problem that energy intake is difficult to assess. The limitation in our research is that we had no information about the basic energy needs of women. The energy needs of people are determined by their basal metabolic rate and physical exercise. We could report only on the latter. We therefore repeated the analyses on the basis of kcal kg^{-1} BW. Three women were classified differently, although this did not materially change the results. Also, misclassification of EI could affect the findings because people with a higher BMI are more prone to under-reporting and people with a lower BMI are more prone to over-reporting.[47]

We divided women into two groups for EI, PA and BW at baseline (T1) and T3: above or below the Dutch PA guideline and averages for EI, taste, smell and appetite of the COBRA population. To our knowledge, no general cut-off points have been or can be determined for measurements of EI (EI depends on a woman's need), nor for taste, smell, appetite and fatigue for women with breast cancer aiming to dichotomise them into lower versus higher. The use of the guideline for PA and the mean scores of the entire COBRA cohort for EI, taste, smell and appetite and fatigue were necessarily arbitrary and may have influenced our results and conclusions.

Another limitation of the present study is our focus on physical lifestyle factors. In addition to these physical factors, psychological and social-environmental factors, including socio-economic status, education and knowledge of nutrition and lifestyle, are also expected to influence lifestyle and how women experience and deal with changes in BW and weight-related lifestyle. We need further research into these factors to develop tailored dietary advice and PA strategies,

which can be implemented to provide high-quality health care to breast cancer patients during chemotherapy.

CONCLUSIONS

The unique combination of quantitative and qualitative data has provided good insight into how women themselves explain and deal with the changes in dietary intake, physical activity and BW during chemotherapy. Women with a lower reported healthy intake and physical activity before diagnosis struggled more with sufficient and healthy dietary intake during chemotherapy than other women. They were overwhelmed by fatigue, barely saw possibilities of being active and experienced more unexpected weight gain. They need support to find ways to do more with respect to EI, PA and BW changes. To support them with respect to being active during chemotherapy, women with a low intake needed help especially with their eating habits, and inactive women needed help to deal with fatigue.

CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTION
JK, MW, MdB and MV contributed to the conception and design of the study. JK, MB, RW and EK were responsible for the data collection. JK, MW, MK, IS, MdB, JV and MV were responsible for the analysis and interpretation of data. All authors contributed to the and to the writing and revision of the paper. All authors critically reviewed the manuscript and approved the final version submitted for publication.

TRANSPARENCY DECLARATION
The authors affirm that this manuscript is an honest, accurate and transparent account of the study being reported. The authors affirm that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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REFERENCES
1. Berg van den MMGA, Winkels RM, Kruif de JTCM, van Laarhoven HW, Visser M, de Vries JH, et al. Weight change during chemotherapy in breast cancer patients: a meta-analysis. BMC Cancer. 2017;17:259. https://doi.org/10.1186/s12885-017-3242-4
2. Makari-Judson G, Braun B, Joseph Jerry D, Mertens WC. Weight gain following breast cancer diagnosis: implication and proposed mechanisms. World JClin Oncol. 2014;5:272–82.

3. Vance V, Mourtzakis M, McCargar L, Hanning R. Weight gain in breast cancer survivors: prevalence, pattern and health consequences. Obes Rev. 2011;12:282–94.

4. McInnes JA, Knobf MT. Weight gain and quality of life in women treated with adjuvant chemotherapy for early-stage breast cancer. Oncol Nurs Forum. 2001;28:675–84.

5. Kwok A, Palermo C, Boltong A. Dietary experiences and support needs of women who gain weight following chemotherapy for breast cancer. Support Care Cancer. 2015;23(6):1561–8.

6. Demark-Wahnefried W, Peterson BL, Winer EP, Marks L, Aziz N, Marcom PK, et al. Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol. 2001;9:2381–9.

7. Demark-Wahnefried W, Rimer BK, Winer EP. Weight gain in women diagnosed with breast cancer. J Am Diet Assoc. 1997;97:519–26.

8. Vance V, Campbell S, Mccargar L, Mourtzakis M, Hanning R. The voice of experience: diet and weight change in women with breast cancer associate with psychosocial and treatment-related challenges. Can J Diet Pract Res. 2017;78(2):74–80.

9. Bernhardson BM, Tishelman C, Rutqvist LE. Chemosensory changes experienced by patients undergoing cancer chemotherapy: a qualitative interview study. J Pain Symptom Manage. 2007;4:403–12.

10. Boltong A, Keast R. The influence of chemotherapy on taste perception and food hedonics: a systematic review. Cancer Treat Rev. 2012;38:152–63.

11. Pekmezi DW, Demark-Wahnefried W. Updated evidence in support of diet and exercise interventions in cancer survivors. Acta Oncol. 2011;50(2):167–78.

12. de Vries YC, van den Berg MMGA, de Vries JHM, Boesveldt S, de Kruif JThCM, et al. Differences in dietary intake during chemotherapy in breast cancer patients compared to women without cancer. Support Care Cancer. 2017;8:2581–91.

13. Ingram C, Wessel J, Courneya KS. Women's perceptions of home-based exercise performed during adjuvant chemotherapy for breast cancer. Eur J Oncol Nurs. 2010;14:238–43. https://doi.org/10.1016/j.ejon.2010.01.027.

14. Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. J Clin Oncol. 2002;20:1128–43.

15. Brunet J, Taran S, Burke S, Sabiston CM. A qualitative exploration of barriers and motivators to physical activity participation in women treated for breast cancer. Disabil Rehabil. 2013;35:2038–45.

16. Selamat MH, Loh SY, Mackenzie L, Vardy J. Chemo brain experienced by breast cancer survivors: a meta-ethnography study investigating research and care implications. PLoS One. 2014;9(9):e108002. https://doi.org/10.1371/journal.pone.0108002.

17. Macmillan Cancer Support. Two million reasons. The cancer survivorship agenda: why people need to support people living with or beyond cancer. Macmillan Cancer Support. 2008;MAC11578. Two million reasons - Nwlcn.nhs.uk.

18. Harrison JD, Young JM, Price MA, Butow PN, Solomon MJ. What are the unmet supportive care needs of people with cancer? A systematic review. Support Care Cancer. 2009;17:1117–28.

19. Kruif JThCM, Visser M, van den Berg MMGA, Derks MJM, de Boer MR, van Laarhoven HWM, et al. A longitudinal mixed methods study on changes in body weight, body composition, and lifestyle in breast cancer patients during chemotherapy and in a comparison group of women without cancer: study protocol. BMC Cancer. 2019;19:7.

20. van den Berg MMGA, Kok DE, Visser M, de Vries JHM, de Kruif JTHCM, de Vries Y, et al. Changes in body composition during and after adjuvant or neo-adjuvant chemotherapy in women with breast cancer stage I-IIIB compared with changes over a similar timeframe in women without cancer. Support Care Cancer. 2019;28:1685–93. https://doi.org/10.1007/s00520-019-04951-6.

21. Tashakkori A, Teddlie C. Handbook of mixed methods in social & behavioural research. Thousands Oaks: Sage; 2003.

22. Pilnick A, Swift JA. Qualitative research in nutrition and dietetics: assessing quality. J Hum Nutr Dietet. 2011;24:209–14.

23. Ostlund U, Kidd L, Wengstrom Y, Rowa-Dewar N. Combining qualitative and quantitative research within mixed method research designs: a methodological review. Int J Nurs Stud. 2011;48:369–83.

24. Swift JA, Tischler V. Qualitative research in nutrition and dietetics: getting started. J Hum Nutr Dietet. 2010;23:229–566.

25. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. Adm Policy Ment Health. 2015;42:533–44.

26. Draper A, Swift JA. Qualitative research in nutrition and dietetics: data collection issues. J Hum Nutr Dietet. 2011;24:3–12.

27. Mathey MFAM, de Jong N, de Groot CPGM. Assessing appetite in Dutch elderly with the appetite, hunger and sensory perception (AHSP) questionnaire. J Nutr Health Aging. 2001;1:22–8.

28. RIVM. NEVO-tabel. Nederlands: Voedingsstoffenbestand Bilthoven; 2013.

29. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56:1163–9.

30. Health Council of the Netherlands. Dutch physical activity guidelines 2017. The Hague: Health Council of the Netherlands; 2017. Publication no. 2018/08e. https://www.gezondheidsraad.nl/sites/default/files/grpublication/physical_activity_guidelines_2017_0.pdf. Accessed 27 July 2019.

31. Smets EM, Garssen B, Bonke B, DE Haes JC. The multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995;39:315–25.

32. Meek PM, Nail LM, Barsevick A, Schwartz AL, Stephen S, Whitmer K, et al. Psychometric testing of fatigue instruments for use with cancer patients. Nurs. Res. 2000;49:181–90.

33. Schwarz R, Krauss O, Hinz A. Fatigue in the general population. Onkologie. 2003;26:140–4. https://doi.org/10.1159/000069834.

34. Fade SA, Swift JA. Qualitative research in nutrition and dietetics: data analysis issues. J Hum Nutr Dietet. 2011;24:108–14.

35. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3:77–101.

36. MAXQDA. Software for qualitative data analysis. Berlin, Germany: VERBI Software - Consult - Sozialforschung GmbH; (1989–2015).

37. Da Costa ME, Dias Custódio ID, Borges Ferreira I, Crispim CA, Paiva CE, Maia YCP. Impact of chemotherapy on perceptions related to food intake in women with breast cancer: a prospective study. PLoS One. 2017;12:1–14. https://doi.org/10.1371/journal.pone.0187573.

38. Bernhardson BM, Olson K, Baracos VE, Wismer WV. Reframing eating during chemotherapy in cancer patients with chemosensory alterations. Eur J Oncol Nurs. 2012;16:483–90.

39. Bernhardson BM, Tishelman C, Rutqvist LE. Self-reported taste and smell changes during cancer chemotherapy. Support Care Cancer. 2008;16:275–83.

40. Abdin S, Lavallée JF, Faulkner J, Husted M. A systematic review of the effectiveness of physical activity interventions in adults with breast cancer by physical activity type and mode of participation. Psychooncology. 2019;28:1381–93.

41. Henry DH, Viswanathan HN, Elkin EP, Traina S, Wade S, Cella D. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. Support Care Cancer. 2008;16:791–801.

42. Carayol M, Ninot G, Senesse P, Bleuse JP, Gourgou S, Sancho-Garnier H, et al. Short- and long-term impact of adapted physical activity and diet counseling during adjuvant breast cancer therapy: the "APAD1" randomized controlled trial. BMC Cancer. 2019;19:737.

43. Courneya KS, Segal RJ, Gelmon K, Reid RD, Mackey JR, Friedenreich CM, et al. Predictors of supervised exercise adherence during breast cancer chemotherapy. Med Sci Sports Exerc. 2008;40:1180–7.

44. Browall M, Mijwel S, Rundqvist H, Wengström Y. Physical activity during and after adjuvant treatment for breast cancer: an integrative review of women's experiences. Integr Cancer Ther. 2018;1:16–30.

45. de Kruif JThCM, Scholtens MB, van der Rijt J, de Boer MR, van den Berg MMGA, de Vries YC, et al. Perceptions of Dutch health care professionals on weight gain during chemotherapy in women with breast cancer. Support Care Cancer. 2019;27(2):601–7.

46. Kemper EA, Stringfield S, Teddlie C. Mixed methods sampling strategies in social science research. Tjashakkori A, Teddlie C, editors. In: Handbook of mixed methods in social & behavioural research. Thousand Oaks: Sage Publications; 2003.

47. Trijsburg L, Geelen A, Hollman PCH, Hulshof PJM, Feskens EJM, van't Veer P, et al. BMI was found to be a consistent determinant related to misreporting of energy, protein and potassium intake using self-report and duplicate portion methods. Public Health Nutr. 2017;4:598–607.