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GASTROINTESTINAL DISORDERS

Healthcare experiences and quality of life of adults with coeliac disease: a cross-sectional study

H. Crocker C. Jenkinson & M. Peters

Nuffield Department of Population Health, University of Oxford, Headington, Oxford, UK

Keywords
coeliac disease, cross-sectional survey, healthcare services, patient experience, quality of life.

Correspondence
H. Crocker, Nuffield Department of Population Health, University of Oxford, Old Road Campus, Headington, Oxford, OX3 7LF, UK.
Tel.: 01865 289431
E-mail: helen.crocker@ndph.ox.ac.uk

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Abstract

Background: Coeliac disease affects many aspects of quality of life and treatment can be burdensome. Access to healthcare services is necessary for the diagnosis and management of coeliac disease. The present study aimed to investigate the healthcare experiences of adults with coeliac disease and explore the relationship between experiences and quality of life.
Methods: A cross-sectional postal survey was sent to 800 members of Coeliac UK and contained questions about diagnosis, dietary advice, follow-up appointments, prescriptions, knowledge and information provision, and quality of life [Coeliac Disease Assessment Questionnaire (CDAQ)]. Descriptive statistics were calculated. A total problem score summarised the number of problems experienced with healthcare services. Multiple linear regression analyses were conducted to investigate experiential and demographic factors associated with quality of life.
Results: An average of 5.5 problems with healthcare services was reported, with females reporting significantly more problems than males (6.5 versus 5.0, $P = 0.003$). The total problem score was significantly related to the CDAQ overall index score and all CDAQ dimension scores (stigma, dietary burden, symptoms, social isolation, and worries and concerns) ($P < 0.001$). The analyses highlighted four key areas of healthcare experiences that were significantly related to quality of life: information provision, general practioners' knowledge, communication with health professionals and access to prescriptions.
Conclusions: Poorer experiences of healthcare services in coeliac disease are related to worse quality of life. Improving services in the four key areas identified may help adults with coeliac disease to achieve a better quality of life.

Introduction

Coeliac disease is a chronic autoimmune condition in which the immune response is triggered by the consumption of gluten, a protein found in wheat, barley and rye. The prevalence of coeliac disease in the UK and Europe is approximately 1% [1,2,3], with studies estimating that many more people are living with undiagnosed coeliac disease [2,4,5]. The only current treatment is a lifelong gluten-free diet [6], which can be challenging, particularly when eating outside of home and at work [7]. The burden of following a gluten-free diet is comparable to or greater than the treatment burden of chronic conditions such as hypertension and end-stage renal disease [8]. Coeliac disease can impact many aspects of quality of life, including emotional health, and daily and leisure activities [9]. Furthermore, there is a small increased risk of malignancy and mortality compared to the general population [10,11], and an increased likelihood of developing other autoimmune diseases [12]. Hence, it is important that people can access health services to diagnose and manage their condition.

In the UK, various bodies have developed guidelines for the diagnosis and management of coeliac disease, based on the best available evidence [13–17]. For example, the National Institute for Health and Care Excellence

(NICE) guidelines state that people with coeliac disease should be offered an annual review, although they do not specify which health professional should conduct this [14]. Furthermore, a Quality Standard [18] for coeliac disease sets out five key areas for healthcare improvement, including receiving dietary advice from a knowledgeable health professional. At the time of the study, people with coeliac disease were also supported with access to gluten-free foods on prescription. Prescriptions are free for those meeting eligibility criteria (e.g. 60 years or older), whereas others must pay prescription charges (currently £9 per prescription, or £104 for a 12-month prepayment certificate that covers all prescriptions received within that period). National guidelines outline the quantities and types of foods that can be prescribed [19]. However, after the present study was completed, as a result of financial pressures on the National Health Service, access to prescriptions has been restricted or stopped in some geographical areas [20].

Asking patients about their healthcare experiences provides important information that allows providers and commissioners to assess whether guidelines are followed and standards met. Patient experience data focusing on the factual aspects of the processes of care allow areas for service improvement to be identified [21,22], whereas evaluations of care can help identify problematic aspects of healthcare that are most important to patients [23], or allow the acceptability of issues, such as waiting times, to be assessed [24]. In England, the Government is committed to providing patients with a positive experience of care [25–26].

In coeliac disease, patient experience surveys have tended to focus on specific aspects of healthcare, such as follow-up [27], consultations with dietitians [28] and diagnosis [29]. As far as we are aware, no studies have explored broader experiences of healthcare services (from diagnosis to follow-up), as investigated in, for example, neurological conditions [30]. Research exploring the relationship between experiences and quality of life in coeliac disease has found significant associations between information provision and outcomes [31,32], although few studies have investigated this. The present study aimed to investigate patients' experiences of healthcare services in coeliac disease, from before diagnosis to the time of the survey, as well as explore the relationship between experiences of healthcare and quality of life.

Materials and methods

Study design

A cross-sectional postal survey of 800 members of Coeliac UK, a charity for people with coeliac disease, was conducted (September 2014). Members were eligible to participate if they were aged 18 years or older; lived in the UK; and self-reported a medical diagnosis of coeliac disease. To increase the likelihood of achieving a diverse sample, a random sample, stratified by ethnicity, age, and gender, were selected from Coeliac UK's membership database and invited to participate (for sampling strata, see Supporting information, Table S1). The number of respondents invited to participate was based on the assumption that a 30% response rate would be achieved, thus providing a sufficiently large sample on which to perform the analyses. The survey included the Coeliac Disease Patient Experience Questionnaire (developed for this study and described below) and demographic and disease-related questions (e.g. time since diagnosis, dietary adherence). The Coeliac Disease Assessment Questionnaire (CDAQ) [9,33] was also included and assesses health-related quality of life in adults with coeliac disease. It has 32 items addressing five dimensions: stigma; social isolation; symptoms; dietary burden; and worries and concerns. Dimension scores and an overall index score can be calculated (0–100), with higher scores indicating better quality of life. Ethics approval was obtained through the University of Oxford Central University Research Ethics Committee (Reference: MSD-IDREC-C1-2014-031).

The Coeliac Disease Patient Experience Questionnaire

The Coeliac Disease Patient Experience Questionnaire contains 53 questions about experiences of healthcare in relation to coeliac disease from pre- to post-diagnosis, which address diagnosis, dietary advice, follow-up appointments, prescriptions, and knowledge and information provision (for the questionnaire, see Supporting information, Appendix S1). Questionnaire items were derived from a thematic analysis of qualitative interviews with 23 adults with coeliac disease. The purpose of the interviews was two-fold: (i) to explore patients' experiences of healthcare services in relation to the diagnosis and management of coeliac disease and (ii) to understand how living with coeliac disease impacts on the health-related quality of life of adults, as reported elsewhere [9]. Interviews were conducted until data saturation was reached. Details regarding participant recruitment and characteristics have been reported previously [9]. Some minor adjustments to questions were made following a review of guidelines for the diagnosis and management of coeliac disease [13,15,17,34]. Questionnaire items were systematically assessed and refined using the Question Appraisal System (QAS-99) [35] and reviewed by experts (healthcare professionals, researchers, and Coeliac UK employees). Finally, cognitive interviews [36,37] with 12 people with coeliac disease (round 1, $n = 5$; round 2,

n = 7) were conducted to finalise the questionnaire. Two key issues identified from the cognitive interviews were the difficulty of capturing the diversity of experiences across respondents and respondents' difficulty in retrieving certain information relating to more distant events. Revisions to the questionnaire were made following each stage to address any issues identified (see Supporting information, Figure S1).

Analysis

Problem scores, missing data and summary variables

To analyse healthcare experience data, items were coded as dichotomous problem scores (i.e. 'no problem' = 0 or 'a problem' = 1) (Fig. 1), where a problem was considered by the patient to be an aspect of healthcare that could be improved upon [38]. Certain items were unsuitable for coding as problem scores because they acted as filter questions or added context to answers of other questions (e.g. 'Who was your most recent follow-up appointment with?'). Thirty-one (of 53) items were coded as problem scores.

Missing data as a result of a nonresponse were low (<4%) with the exception of two items, 'not offered a blood test to diagnose coeliac disease' (14.2%) and 'pneumococcal vaccination not offered' (10.1%) (see Supporting information, Table S2). Furthermore, 'skipped data' occurred as a result of skip patterns in the questionnaire (i.e. respondents were instructed not to complete certain questions if deemed not applicable based on previous answers) (see Supporting information, Table S2). Missing and skipped data were coded as 'no problem' based on the assumption, as adopted in other patient experience surveys [38], that (i) any problems occurring would have been reported, and (ii) if questions were not relevant, individuals could not have experienced problems with those aspects of care.

A *total problem score* was created to explore how experiences varied between respondents and investigate associations with quality of life. Not all questions were relevant to all respondents, and therefore a sum of items could result in bias in the total problem score (i.e. those receiving fewer services may achieve lower total problem scores). To minimise bias, dichotomous summary variables for dietary advice and follow-up care were created (i.e. 'no problems' = 0 or 'one or more problems' = 1), and two remaining items where missing and skipped data totalled ≥20% were excluded from the total problem score. The total problem score was the sum of problems for the remaining dichotomised items and summary variables (0–21), where a higher score indicates a greater number of problems. In summary, 29 of 31 dichotomised problem scores contributed towards the total problem score (see Table 1).

Statistical analysis

Descriptive frequencies and proportions were calculated to show respondents' overall experience of healthcare services. Proportions are presented as the 'number of people affirming an item/number of people who were asked the question'. Associations between CDAQ scores and the total problem score were assessed using Pearson's correlation coefficients.

Bivariate analyses were conducted to explore the relationship between the total problem score and gender, ethnicity, age, time since diagnosis, number of comorbidities, gluten consumption and marital status. Number of comorbidities was calculated as the sum of comorbidities that the respondent selected from a list of conditions associated with coeliac disease, plus any additional self-reported medical conditions. Chi-squared was used to explore differences in follow-up between those diagnosed for less than 10 years, and for those diagnosed for 10 years or more. Backwards stepwise multiple linear regression analyses were conducted to explore the association between quality of life (CDAQ overall index score or dimension scores) and experiences of healthcare services ('total problem score' or dichotomised experience items). Included as potential confounders were: age, years since diagnosis, number of comorbidities, gender, ethnicity, marital status and gluten consumption. Regression coefficients for significant variables are shown in tables.

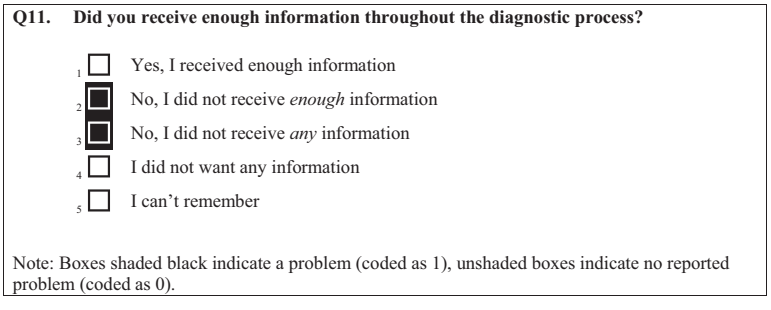

Figure 1 An example of coding experience questions as problem scores.

$P < 0.05$ (two-sided) was considered statistically significant for all analyses. Data were analysed using SPSS, version 20 (IBM Corp., Armonk, NY, USA).

Results

Characteristics of study participants

Two hundred and seventy-six (34.5%) questionnaires were returned. Eight respondents were excluded from the analysis as they had not received a medical diagnosis. The majority of respondents were female (61.9%), married (59.3%), working (55.2%), white British (84.0%) and had not purposefully consumed gluten within the past 12 months (72.0%). Respondents had a mean (SD) age of 49.5 (18.9) years and had been diagnosed for a mean (range) of 7.5 (1–50) years, of which approximately 50% were diagnosed within the past 4 years (see Supporting information, Table S3).

Descriptive statistics

Diagnosis

The majority of respondents (93.3%, $n = 250/268$) received a diagnosis of coeliac disease aged 16 years or older, with 97.6% ($n = 244/250$) experiencing symptoms prior to diagnosis. On average, respondents received their diagnosis 4.0 years (range <1–50 years) after first seeking medical advice about their symptoms, with many reporting the time to diagnose as fairly or very slow (48.0%, $n = 110/229$). The majority had (94.0%, $n = 235/250$) or were offered (1.2%, $n = 3/250$) an endoscopy to diagnose their coeliac disease, with 12.8% ($n = 32/250$) reporting waiting times as slow. Most (88.8%, $n = 222/250$) were informed of their diagnosis by a hospital doctor/consultant or their general practioner (GP), with 26.4% ($n = 66/250$) reporting their diagnosis was communicated in a somewhat unprofessional or inappropriate manner. Some felt they did not receive enough information throughout the diagnostic process (20.0%, $n = 50/250$) or at the time of diagnosis (27.6%, $n = 69/250$).

Prior to diagnosis, most respondents spoke to a GP (70.3%, $n = 161/229$) or a hospital doctor/consultant (21.8%, $n = 50/229$) the most often. One-fifth reported that they lacked confidence in this health professional (21.8%, $n = 50/229$), that they did not feel their symptoms were taken seriously (20.5%, $n = 47/229$) or that the professional did not listen carefully (16.2%, $n = 37/229$).

Dietary advice

After diagnosis, 92.4% ($n = 231/250$) had a consultation with a dietitian, although a few reported no access to a dietitian when needed (3.6%, $n = 9/250$) or that access was slow (21.6%, $n = 50/231$). The majority (82.7%, $n = 191/231$) found their initial appointment helpful. Some (17.3%, $n = 40/231$) did not receive a second dietetic appointment but would have liked one.

Follow-up appointments

More than one-half (59.3%, $n = 159/268$) reported receiving follow-up appointments, with the majority (94.3%, $n = 150/159$) seen within the past 2 years. Receipt of follow-up care was not significantly associated with time since diagnosis ($P = 0.055$). Most appointments were with a hospital doctor/consultant (46.5%, $n = 74$), GP (20.8%, $n = 33$) or dietitian (18.9%, $n = 30$). Follow-up appointments most frequently involved (i.e. more than 50% reported) blood tests (78.0%, $n = 124/159$), being weighed (69.8%, $n = 111/159$) and the discussion of symptoms (55.3%, $n = 88/159$). Few (<25%) reported a discussion around food labelling (11.3%, $n = 18/159$), an assessment of emotional well-being (17.6%, $n = 28/159$) or a review of prescriptions (21.4%, $n = 34/159$). Respondents generally found appointments helpful (84.3%, $n = 134/159$). Of those not in receipt of follow-up care, 17.2% had been diagnosed within the past year and therefore the opportunity for follow-up may not yet have arisen.

The majority (84%, $n = 225/268$) wanted follow-up appointments in the future, with those diagnosed within the past 10 years more likely to want follow-up appointments than those diagnosed for 10 years or more (88.4% compared to 77.0%, $P = 0.021$). The preferred choice was to receive annual appointments (60.4%, $n = 136/225$) with a hospital doctor or consultant (48.4%, $n = 109/225$). One-quarter were not receiving follow-up appointments when they would have liked to (25.4%, $n = 68/268$).

Prescriptions

Prescriptions for gluten-free food were obtained by 70.1% ($n = 188/268$) of respondents during the past 12 months, with the most commonly prescribed items being bread or rolls (61.6%, $n = 165$), pasta (42.9%, $n = 115$), and flour or bread mixes (41.4%, $n = 111$). Of those receiving prescriptions, 65.4% ($n = 123$) were entitled to free prescriptions. Of those who pay for their prescriptions, 47.7% ($n = 31/65$) considered the cost 'fairly' or 'very' expensive. One-third (30.2%, $n = 81/268$) felt they had not received enough information about obtaining gluten-free food on prescription, with 20.1%, ($n = 54/268$) describing the process as 'difficult'.

Knowledge and information provision

Many respondents perceived that GPs weren't always knowledgeable about coeliac disease (66.4%, $n = 178/268$) or did not have a good understanding of the condition

(42.5%, n = 114/268). Fewer people felt dietitians (19.0%, n = 51/268) or specialist hospital doctors (10.8%, n = 29/268) lacked this knowledge. In the past 12 months, 67.5% (n = 181/268) had spoken to a health professional specifically about coeliac disease, of whom 41.0% (n = 110) consulted their GP, 38.4% (n = 103) a hospital doctor/consultant and 29.1% (n = 78) a dietitian. Some (30.6%, n = 82/268) were not always able to get the information and advice needed. When information was received, 16.4% (n = 44) reported problems with its consistency.

Problem scores and their relationship to quality of life

The number of respondents reporting problems with healthcare services is shown in Table 1. Respondents reported an average of 5.5 problems [interquartile range (IQR) = 3–10; range 0–19], with females (6.5, IQR = 3–10, n = 166) reporting significantly more problems than males (5.0, IQR = 2–8, n = 97, P = 0.003). Single respondents reported significantly more problems than those who were married or in a civil partnership (P = 0.005). An increase in the total problem score was significantly associated with younger age (r_s = −0.39, P < 0.001) and a shorter time since diagnosis (r_s = −0.16, P = 0.01). No significant differences in the total problem score were found by number of comorbidities, ethnic group, and self-reported frequency of gluten consumption.

An increase in the number of problems with healthcare services were significantly related to greater stigma (r = −0.48, P < 0.001), increased dietary burden (r = −0.35, P < 0.001), more symptoms (r = −0.39, P < 0.001), greater social isolation (r = −0.48, P < 0.001), more worries and concerns (r = −0.45, P < 0.001), and worse overall quality of life (r = −0.51, P < 0.001). Mean CDAQ scores are provided in the Supporting information (see Supporting information, Table S4), with further details, such as differences between groups, available elsewhere [33].

Regression analysis

Association between total problem score and quality of life

The total problem score was significantly related to the CDAQ overall index score (P < 0.001) after adjusting for confounding factors (Table 2). The relationship between total problem score and CDAQ dimensions were all significant (P < 0.001) (see Supporting information, Table S5).

Association between individual experience items and quality of life

Healthcare experiences that were significantly related to lower CDAQ overall index scores are shown in Table 3. Healthcare experiences and demographic factors significantly associated with CDAQ dimensions are shown in Table 4. The consistency and provision of information and advice were strongly related to all dimensions. Communication with health professionals was significantly related to stigma, social isolation, and worries and concerns. Difficulty obtaining prescriptions was significantly related to dietary burden and social isolation. Respondents' perceptions of GPs' knowledge was significantly related to dietary burden. Furthermore, a lack of confidence in the health professional seen most often prior to diagnosis, usually a GP, was related to stigma.

Discussion

Asking people about their experiences of health services can provide valuable information to guide the improvement of services [39]. Furthermore, exploring the relationship between experiences of healthcare and quality of life highlights key aspects for service improvement that are most likely to result in quality of life gains. The present study aimed to identify problems with healthcare experiences of people with coeliac disease and investigate the relationship between healthcare experiences and quality of life.

This research found moderate to strong correlations between experiences of health services and quality of life, with problems found in four key areas: (i) the consistency and provision of information; (ii) perceived knowledge of GPs; (iii) communication with health professionals; and (iv) difficulties obtaining prescriptions. A strong relationship between the consistency and provision of information and quality of life is consistent with a German study [31] reporting that dissatisfaction with information provided by doctors was predictive of reduced quality of life. In the present study, quality of life was also related to the accessibility and quality of dietary advice. Although most respondents were able to see a dietitian following diagnosis, for some access was slow, an issue identified to a greater extent in a Finnish study [32]. Respondents reporting slow or no access to a dietitian reported worse quality of life. Coeliac disease requires significant dietary changes, and therefore, to maximise quality of life, it is important that people receive adequate information about the gluten-free diet, particularly at the point of diagnosis. Because dietetic service provision has been previously found to be insufficient [40], alternative methods of information provision should be explored, for example, dietitian-led group clinics [41], and web-based and mobile technologies (such as those developed for Chronic Obstructive Pulmonary Disease [42]).

Poor information provision from GPs could in part be explained by the perception of many respondents (66.4%) that GPs lack knowledge of coeliac disease. Similarly, a

Table 1 Respondents reporting problems with healthcare services (n = 268)

Healthcare experience	Respondents reporting problems		Contributed to total problem score?†
	n	%*	
Diagnosis			
Felt their diagnosis of coeliac disease was slow	110	41.0	Yes
Health professional did not always inspire confidence	105	39.2	Yes
Health professional did not always listen carefully	98	36.6	Yes
Health professional did not always take symptoms seriously	94	35.1	Yes
Did not receive enough information at time of diagnosis	69	25.7	Yes
Informed of diagnosis in a somewhat unprofessional or inappropriate manner	66	24.6	Yes
Did not receive enough information throughout diagnostic process	50	18.7	Yes
Slow wait to receive an endoscopy	32	11.9	Yes
Not offered blood test to diagnose coeliac disease	8	3.0	–
Not offered an endoscopy to diagnose coeliac disease	4	1.5	Yes
Dietary advice			
Dietary advice summary score‡	99	36.9	Yes
Slow access to see dietitian following diagnosis	50	18.7	–
Not offered second appointment with dietitian when needed	40	14.9	–
Unhelpful first dietetic appointment	36	13.4	–
No access to dietitian following diagnosis when needed	9	3.4	–
Follow-up appointments			
Pneumococcal vaccination not offered	141	52.6	Yes
Follow-up summary score‡	116	43.3	Yes
Follow-up appointments not occurring (but individual would like to have follow-up)§	68	25.4	–
Questions at follow-up appointment not always answered adequately	31	11.6	–
Unhelpful follow-up appointment	23	8.6	–
Regular follow-up is infrequent	8	3.0	–
No opportunity to ask questions at follow-up appointment	5	1.9	–
Prescriptions			
Expensive cost of prescriptions	31	11.6	–
Not given enough information about prescriptions	81	30.2	Yes
Difficulties obtaining prescriptions	54	20.1	Yes
Knowledge and information			
Felt GPs weren't always knowledgeable about coeliac disease	178	66.4	Yes
GP did not always have good understanding of coeliac disease	114	42.5	Yes
Information and advice not always available from health professional when needed	82	30.6	Yes
Not given enough information about medical test results	78	29.1	Yes
Felt dietitians lacked knowledge about coeliac disease	51	19.0	Yes
Health professionals provided inconsistent information and advice	44	16.4	Yes
Felt specialist hospital doctors lacked knowledge about coeliac disease	29	10.8	Yes

GP, general practitioner.

*Percentage of respondents reporting problems calculated as a proportion of the whole sample (n = 268).

†Indicates whether the item contributed towards the total problem score.

‡The follow-up and dietary advice summary scores are dichotomous variables where 0 = 'no problems' and 1 = 'one or more problems' based on whether problems were reported in the individual follow-up and dietary advice items.

§Two items were combined to create this dichotomised problem score.

Finnish study [32] identified a key priority for patients was the improvement of physicians' knowledge. GPs are typically the primary point of contact prior to diagnosis, and therefore a lack of knowledge may contribute to lengthy diagnostic delays [43,44]. GPs are also frequently consulted following diagnosis, including for annual review [17]. Therefore, initiatives aimed at increasing awareness and knowledge of coeliac disease among GPs are needed; for example, through training and the modification of IT systems to support GPs with diagnosis and management [45].

Difficulty obtaining prescriptions was significantly related to quality of life, specifically dietary burden and social isolation. Fewer respondents (70.1%) reported obtaining gluten-free food on prescription than a previous UK study (89%, n = 111) [27]. Almost one-third (30.2%) felt they had not been given enough information

Table 2 Multiple linear regression analysis of factors associated with Coeliac Disease Assessment Questionnaire (CDAQ) overall index score, with 'total problem score' as an independent variable

Dependent variable Independent variables	Unstandardised coefficients				
	b	SE (*b*)	β	*t*	*P*
CDAQ overall index score					
Constant	56.79				
Age	0.19	0.056	0.20	3.38	0.001
Male	6.04	1.98	0.16	3.05	0.003
No of comorbidities	−2.87	0.68	−0.23	−4.20	<0.001
Black and minority ethnicities	−6.47	2.91	−0.11	−2.23	0.027
Total problem score	−1.49	0.22	−0.37	−6.64	<0.001

Table includes significant variables only, adjusted $r^2 = 0.37$, $P < 0.001$.

Table 3 Multiple linear regression analysis of factors associated with Coeliac Disease Assessment Questionnaire (CDAQ) overall index score, with dichotomous experience items as independent variables

Dependent variable Independent variables	Unstandardised coefficients				
	b	SE (*b*)	β	*t*	*P*
CDAQ overall index score					
Constant	52.49				
Age	0.17	0.58	0.17	2.83	0.005
Male	8.01	2.06	0.21	3.90	<0.001
No of comorbidities	−2.68	0.72	−0.21	−3.73	<0.001
Years since diagnosis	0.23	0.11	0.11	2.09	0.038
Black and minority ethnicities	−7.16	2.98	−0.13	−2.40	0.017
Health professional did not listen	−6.40	2.04	−0.17	−3.14	0.002
Difficulties obtaining prescriptions	−5.71	2.44	−0.13	−2.35	0.020
Inconsistent information and advice	−7.01	2.60	−0.15	−2.70	0.008
Dietary advice score	−5.05	2.02	−0.14	−2.50	0.013

Table includes significant variables only, adjusted $r^2 = 0.37$, $P < 0.001$.

about prescriptions. People are likely to benefit from receiving clearer information about prescriptions and the prescribing process at diagnosis and follow-up. This is particularly important because prescribing policies at a local level have not always been consistent with national guidance [20], as well as with the introduction of new policies [46].

Further to the four key areas identified above, many respondents reported problems with follow-up care, such as not receiving appointments. These findings support those of another UK study [27] (62.0% received follow-up compared with 59.3% in the present study). The NICE guidelines [14] and quality standard for coeliac disease [18] both state that people should be offered an annual review, and therefore access to follow-up needs to be improved. For those receiving follow-up care, emotional well-being was rarely assessed (17.6%). Because there is a relationship between coeliac disease and mental health problems such as depression and anxiety [47–49], assessing emotional well-being as part of review appointments could help to reduce mental health problems in this population.

There are some limitations to the present study. A cross-sectional design means causality cannot be determined. However, the data appear to suggest that poorer experiences of services lead to poorer quality of life, or those with poorer quality of life are not getting the support that they need, or a combination of these factors. Either way, it follows that improving health services is likely to result in improvements to quality of life. Presenting patients' experiences as dichotomous problem scores is common with experiential data [30,38]; however, the proportions reported for questions not relevant to all respondents are likely to be conservative estimates. As such, although problem scores are a useful way of summarising patients' experiences to provide an indication of what we know to be a problem, they may be an underestimate. Furthermore, the calculation of a 'total problem score' assumes that all reported problems are equal.

Table 4 Multiple linear regression analysis of factors associated with Coeliac Disease Assessment Questionnaire (CDAQ) dimension scores, with dichotomous experience items as independent variables

Dependent variable Independent variables	Unstandardised coefficients				
	b	SE (*b*)	β	*t*	*P*
CDAQ stigma score					
Constant	40.87				
Age	0.38	0.06	0.34	6.16	<0.001
Male	6.95	2.36	0.16	2.95	0.004
No of comorbidities	−2.66	0.81	−0.18	−3.29	0.001
Informed of diagnosis unprofessionally	−7.01	2.60	−0.14	−2.70	0.008
Inconsistent information and advice	−11.83	2.97	−0.21	−3.99	<0.001
Lack of confidence in health professional	−5.83	2.33	−0.13	−2.51	0.013
CDAQ dietary burden score					
Constant	43.87				
Male	5.95	2.37	0.15	2.51	0.013
Years since diagnosis	0.41	0.13	0.19	3.27	0.001
Consumes gluten					
Never	*Reference*				
Rarely	−3.12	3.08	−0.06	−1.01	0.312
Sometimes	−7.81	3.75	−0.12	−2.08	0.038
Often or always	−20.44	7.81	−0.15	−2.62	0.009
Difficulties obtaining prescriptions	−5.56	2.78	−0.12	−2.00	0.047
Information and advice not available	−5.84	2.51	−0.14	−2.33	0.021
GPs lack knowledge of coeliac disease	−5.20	2.60	−0.13	−2.00	0.047
Dietary advice score	−4.81	2.38	−0.12	−2.02	0.045
CDAQ symptoms score					
Constant	53.89				
Age (years)	0.33	0.07	0.26	4.53	<0.001
Male	9.72	2.73	0.19	3.56	<0.001
Black and minority ethnicities	−10.72	4.15	−0.14	−2.58	0.010
Consumes gluten					
Never	*Reference*				
Rarely	−0.47	3.57	−0.01	−0.13	0.894
Sometimes	−9.91	4.31	−0.12	−2.30	0.022
Often or always	15.24	9.58	0.09	1.59	0.113
No of comorbidities	−4.86	0.94	−0.29	−5.16	<0.001
Inconsistent information and advice	−7.96	3.57	−0.12	−2.23	0.027
Dietary advice score	−8.82	2.74	−0.18	−3.22	0.001
CDAQ social isolation score					
Constant	69.44				
Age (years)	0.22	0.07	0.18	3.10	0.002
Male	5.18	2.60	0.11	1.99	0.047
No of comorbidities	−3.60	0.91	−0.22	−3.97	<0.001
Health professional did not listen	−11.21	2.61	−0.24	−4.29	<0.001
Not enough information throughout diagnosis	−8.62	3.21	−0.15	−2.69	0.008
Difficulties obtaining prescriptions	−6.65	3.15	−0.12	−2.11	0.036
Information and advice not available	−7.13	2.81	−0.14	−2.54	0.012
CDAQ worries and concerns score					
Constant	46.15				
Age (years)	0.25	0.07	0.22	3.68	<0.001
No of comorbidities	−2.44	0.85	−0.17	−2.87	0.005
Consumes gluten					
Never	*Reference*				
Rarely	7.23	3.29	0.13	2.20	0.029
Sometimes	4.89	4.02	0.07	1.22	0.224
Often or always	4.49	8.63	0.03	0.52	0.603

Table 4 Continued

Dependent variable Independent variables	Unstandardised coefficients				
	b	SE (*b*)	β	*t*	*P*
Information and advice not available	−5.63	2.81	−0.13	−2.01	0.046
Inconsistent information and advice	−6.92	3.38	−0.12	−2.05	0.042
Informed of diagnosis unprofessionally	−6.62	2.86	−0.14	−2.32	0.021
Dietary advice	−5.45	2.55	−0.13	−2.14	0.033

Table includes significant variables only.
Adjusted r^2 values - CDAQ stigma (0.34), CDAQ dietary burden (0.20), CDAQ symptoms (0.31), CDAQ social isolation (0.31), CDAQ worries and concerns (0.21), all $P < 0.001$.
GP, general practitioner.

However, certain problems may be perceived by respondents as more bothersome than others, yet this may vary between respondents. As such, a sum of problematic experiences provides a good estimate and is common practice in the literature. Survey respondents were all members of Coeliac UK and therefore it is possible that this population differs from the wider population of people with coeliac disease, although we are not aware of any evidence to support this. Finally, the survey achieved a response rate of 34.5%. Although similar to other studies [44], the results should be interpreted with caution because they may not be representative of the full population of people with coeliac disease.

This research is the most comprehensive study of patients' experiences of healthcare services in coeliac disease. The study has identified four key areas (information provision, GPs' knowledge, communication with health professionals and access to prescriptions) in which service improvements are most likely to result in quality of life gains for adults with coeliac disease.

Transparency declaration

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

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Conflict of interests, source of funding, authorship

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All authors contributed to the conception and design of the study. All authors were involved in the development of the survey. HC collected and processed the survey data. HC led the analysis of survey data, with the support of CJ and MP. HC led on drafting the manuscript with input from CJ and MP. All authors have critically reviewed and approved the final version of the manuscript submitted for publication.

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Supporting information

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

Figure S1. Number of items, and amendments made, at each stage of development of the Coeliac Disease Patient Experience Questionnaire.

Table S1. Strata used to sample Coeliac UK members for the survey.

Table S2. Number of respondents for which there is missing data as a result of a nonresponse or skip patterns.

Table S3. Characteristics of survey respondents (n = 268).

Table S4. Health-related quality of life in coeliac disease: CDAQ scores.

Table S5. Multiple linear regression analysis of factors associated with CDAQ dimension scores, with 'total problem score' as an independent variable.

Appendix S1. Experiences of healthcare services questionnaire.

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GASTROINTESTINAL DISORDERS

Short bowel syndrome and the impact on patients and their families: a qualitative study

A. M. Sowerbutts[1] C. Panter,[2] G. Dickie,[2] B. Bennett,[3] J. Ablett,[4] S. Burden[1] & S. Lal[5]

[1]Faculty of Biology, Medicine and Health and Manchester Academic Health Science Centre, University of Manchester, Manchester, UK
[2]Adelphi Values, Bollington, UK
[3]Formerly Adelphi Values, Bollington, UK
[4]St Helen's and Knowsley NHS Trust, Liverpool, UK
[5]Salford Royal NHS Foundation Trust, Manchester, UK

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short bowel syndrome, parenteral nutrition, stoma, qualitative.

Correspondence
A. M. Sowerbutts, RM5.328 Jean McFarlane Building, School of Health Sciences, University of Manchester, Oxford Rd, Manchester M13 9PL, UK.
Tel.: +44 161 306 7888
Fax: +44 161 306 7851
Email: annemarie.sowerbutts@manchester.ac.uk

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Abstract

Background: Short bowel syndrome (SBS) is a malabsorptive condition that can result in intestinal failure (SBS-IF). Many patients with SBS-IF require home parenteral nutrition (PN) for survival. However, PN has profound effects on patients and their family members. The present study aimed to understand the lived experience of SBS-IF for patients and their families.
Methods: In-depth semi-structured qualitative interviews were conducted with 15 patients with SBS-IF and five adult family members living with someone with SBS-IF. A patient-centric approach was taken, with a patient steering group providing input and guidance to develop the interview guide. Key concepts were identified using thematic analysis of interview transcripts.
Results: Patients' lives were dominated by having SBS-IF. They described physical impacts that included patient-reported signs and symptoms and physical restrictions comprising of restrictions on daily life, actives of daily living and physical functioning. In addition, they encountered emotional impacts with a plethora of negative feelings and social impacts, such as difficulties socialising and maintaining relationships. Patients coped by adapting their life around SBS-IF, having support and adopting an attitude of gratitude and acceptance. Family members were also affected and, along with patients, appreciated the respite of a night off from infusions.
Conclusions: Patients and families face many difficulties with SBS-IF. Healthcare professionals can support patients by facilitating them explore what others have found beneficial; adapting their life around PN, viewing PN with acceptance and trying to cultivate gratitude. Further research into the support required for families may be beneficial.

Introduction

Short bowel syndrome (SBS) is a malabsorptive condition caused by surgical resection of the gastrointestinal tract as a result of disease and many patients have a stoma [(1)]. SBS can cause intestinal failure (SBS-IF). These patients need to have parenteral nutrition (PN) to meet their nutritional or fluid requirements [(2)].

The prevalence of SBS-IF is difficult to establish and so a proxy measure of number of patients receiving PN is frequently reported. In Europe, this varies by country with approximately 40 per million in the UK to approximately 80 per million in Denmark [(3,4)]. However, these figures are increasing because both Denmark and the UK have reported increasing numbers of patients in recent years [(3,4)]. With this expanding patient population, it is essential that patients and family experiences are understood so that appropriate support can be offered.

Much of the available literature tends to be quantitative in nature using generic quality of life patient-reported

outcomes, which lack content validity for specific disease populations [5], or using quality of life instruments focused on PN rather than on SBS-IF [6,7]. This research indicates that patients on PN have a reduced health-related quality of life compared to matched controls [5], with psychological symptoms, as well as sexual and social dysfunction [8–10], and describe an inability to act spontaneously because daily life involves considerable planning around infusions [11].

Both family members and patients are impacted by PN, with them experiencing significant psychosocial burdens [12–15]. Families also face imposing financial restraints, including decreased employment, and, more relevant to private or insurance-based health economies, large expenses for non-reimbursed medications [13].

Qualitative research, in contrast to quantitative, allows for an in-depth exploration of a patient's and family's experience. Currently, qualitative research has explored the experiences of patients with cancer who take PN and their families [16,17], as well as the experience of patients with mixed benign conditions having PN [18,19]. Patients with cancer and family members are appreciative of the treatment because it is a life line [16], whereas those on long-term PN report impacts on functioning and overall health status [13]. However, the patients' and family members' experiences of SBS-IF involve more than just PN. The present study was to understand the patient and family experience of living with SBS-IF by taking a holistic approach. This will enable the true impact on patients and family members to be explored, adding to the overall knowledge of life on PN with SBS-IF.

Materials and methods

Study design

This was a qualitative, non-interventional interview study involving patients with SBS-IF and family members. Each participant was involved in a 1-h, face-to-face concept elicitation interview at one time-point. To provide rigour and support for a 'patient-centric approach', a separate group of patients provided input in the development of the interview guide [20]. The interviews from the present study were used in further work to create health utility scores [21].

Rigour

Rigour was introduced by having a patient steering group, comprising seven members from a support group for individuals receiving home PN, provide input into the development of the interview guide. The steering group were asked whether the questions were easy to understand, relevant to a person with SBS-IF, comprehensive (captured all relevant concepts) and appropriate. Amendments to the interview guide were made incorporating their feedback. To avoid bias, patients involved in the steering group were excluded as participants in the study sample.

Sample

Patients were recruited via physicians from one specialist intestinal failure unit. Psychological support was provided by multidisciplinary team members with patients referred to a clinical psychologist if required. Eligible patients had to be aged ≥18 years, literate, fluent in English, have a diagnosis of SBS-IF and to have received PN for at least 1 year. Eligible patients were asked whether they wanted to nominate a family member to participate in a separate interview about their experience of living with someone with SBS-IF. A purposive sampling approach was taken, with categories determined to ensure a range of clinical and demographic characteristics were captured in the study cohort (see Supporting information, Table S1).

Ethical considerations

The study was submitted for NHS ethical consideration and approved by the National Research Ethics Committee North West (Ref: 15/NW/0576) and received Research & Development approval. Eligible participants were sent written information prior to attending their routine clinic appointment and had the chance to discuss the study with a member of staff before deciding whether they wanted to take part. All participants provided their written informed consent.

Data collection

Face-to-face, semi-structured interviews were conducted by two trained interviewers in the UK with patients and family members; each interviewer conducted 10 interviews. Interviews lasted approximately 1 h, were audio recorded and were conducted using detailed semi-structured interview guides. The interviews were conducted using concept elicitation techniques such that open-ended exploratory questions were asked to facilitate spontaneous content [22–24], followed by direct, focused questions. The interviews explored symptoms of SBS-IF, the broader impact of the condition and the need for PN, as well as future outlook.

Statistical analysis

Interviews were transcribed verbatim and analysed thematically. A software package, ATLAS.TI [25], was used to

aid coding. The coding scheme was devised by discussion between the project leader and project researchers reviewing two interviews. This coding scheme was then used throughout the coding process. As an iterative analytic process, new codes were organically added throughout the coding process. Words, sentences and key phrases were identified from the transcripts and placed within the formulated codes. The themes were generated by reading through the codes and participant quotations. Quotations have been used to illustrate the themes; each quotation has been labelled with a pseudonym and, for patients, age and the number of nights on PN is included (for example, 5PN denotes 5 nights of PN).

Results

Participant sample characteristics

Seventy patients met the inclusion criteria and 37 agreed to be interviewed. From these, 15 patients were chosen to give a diverse sample that most closely matched the purposive sampling criteria. The criteria were not met in three areas because either there were no or very few patients matching the categories who had clinic appointments during the recruitment period. Five family members also took part and there was a maximum of one family member per patient. All patients were Caucasian with a mean age of 53.9 (range 32–76) years and most were living with a partner (67%). Patients had PN between 3–7 nights per week, although most were on 5–7 nights per week (73%). Overall, there was a variety of demographic and clinical characteristics (Tables 1 and 2).

Table 1 Patient and family member demographics

Description	SBS patient sample (n = 15)	Family member sample (n = 5)
Age (years)		
Mean (range)	53.9 (32–76)	53.8 (32–69)
Gender,		
Male	5	3
Female	10	2
Living status,		
Live alone	4	0
Live with husband/wife/partner	10	5
Live with parents/family or friends	1	0
Ethnicity,		
Caucasian	15	5
Highest level of education,		
GCSEs (or equivalent)	6	3
A-level (or equivalent)	2	1
Undergraduate degree	1	0
Postgraduate degree	1	0
Other	2	1
Missing data	3	0
Work status,		
Working full time	2	0
Working part-time	1	1
Full-time homemaker	1	0
Not working as a result of SBS	4	1
Retired	6	2
Other	1	1

SBS, short bowel syndrome.

Patient interviews

SBS-IF impacted on all aspects of patients' lives; these have been grouped into physical, emotional and social impacts. Patients also spoke about coping with life having SBS-IF.

Theme 1: Physical impacts

Physical impacts have been grouped into two subthemes, patient-reported signs and symptoms, and physical restrictions, which included physical restrictions on daily life, restrictions on activities of daily living and physical functioning.

Subtheme 1: Patient-reported signs and symptoms

Patients reported a variety of signs and symptoms as a result of SBS-IF, such as dehydration, tiredness and fatigue, and pain (for other signs and symptoms discussed, see Supporting information, Table S2).

Dehydration. Dehydration was a problem for patients; 'Being thirsty is horrendous ... all I want is a glass of water, but I can't have it' (Sally, 52 years, 6PN). A variety of factors triggered dehydration including eating and drinking: 'you have this dreadful thirst. Your body is telling you to drink ... and you do and then it just is that vicious circle that you just can't get out of' (Helen, 44 years, 4PN). Dehydration could be a daily occurrence; 'All the time. Every day' (Julie, 44 years, 6PN). Other patients talked about severe episodes in the past.

Tiredness and fatigue-related symptoms. Patients described tiredness and fatigue, which could leave them unable to carry out their usual activities. 'Sometimes I just can't even get up the stairs' (Dora, 47 years, 7PN). However, for some, the tiredness improved over time. One patient commented that she had it 'quite rarely now' (Helen, 44 years, 4PN).

Pain. Pain was also described by patients particularly stomach pain 'It's like someone's got your insides and knotting them up ... it's horrible, the pain. I mean really bad' (Julie, 44 years, 6PN). Others described burning pain

Table 2 Patient clinical characteristics (n = 15)

Description	
Total daily volume of PN use (ml)	
Mean (range)	2643 (2000–3500)
Time since first on PN (months)	
Mean (range)	100 (11–395)
Use of stoma bag, *n*	
Yes	11
No	4
Type of bag, *n*	*n* = 11
Colostomy	1
Ileostomy	8
Other	1
Missing data	1
Cause of SBS, *n*	
Crohns	6
Surgical complications	3
Ischaemic bowel	1
Surgical interventions for ulcerative colitis	1
Avulsion injury to mesentery	1
Radiation enteritis	1
Ischaemic gut	1
Missing data	1

PN, parenteral nutrition; SBS, short bowel syndrome.

around the stoma, associated with their stoma bag leaking. Generally, the experience of pain was variable and depended on the cause of pain; patients could have pain a few times a year, whereas others had it every week. The length of pain also varied from a few seconds to up to a whole day. 'I think the worst ones are the cramps ... even if it's only just sort of 20 seconds, it's really, really severe' (Sarah, 45 years, 6PN).

Subtheme 2: Physical restrictions

Patients could find that their life was confined as a result of their SBS-IF and the need for PN. Patients described being limited in activities or experiencing a lack of freedom. 'It impacts it a lot when ... I'm having a bad day, because I can't do nothing. And then I go on the TPN and then I'm stuck here' (Dora, 47 years, 7PN).

In addition to restrictions from disease symptoms, the patients had to be at home at a particular time to start the feed 'It's difficult because you need to ... be home at a certain time to get it' (Mark, 31 years, 3PN). The constant need for the stoma bag to be emptied was also limiting.

Patients sleep was curtailed as a result of having to pass urine as a result of the fluid from the PN and needing to empty the stoma bag 'If I am on TPN I don't sleep as well, um, one because I go to toilet a little bit more, um, from weeing ... Unfortunately my bag will leak during the night' (Frank, 35 years, 3PN).

Patients were also restricted in self-care; having a bath instead of a shower, showering every couple of days or showering cautiously. 'I tend to just have baths, so just to try and avoid that – the line getting wet ... You tend not to have any showers because of that ... it's just a risk of infection' (John, 31 years, 3PN). By contrast, one patient showered more often to maintain the sterile conditions required with PN, as she wanted to be 'extremely clean' (Sarah, 45 years, 6PN).

Patients also discussed impacts on physical functioning such as their ability to take part in exercise and their mobility being curtailed. As one patient said 'I've tried ... by walking, by like trying to get yourself like a bit stronger. I, I can't go with it ... it's too exhausting' (Julie, 44 years, 6PN).

Theme 2: Emotional impact

Patients discussed wide ranging emotional and psychological impacts such as feelings of sadness, worry and frustration.

Sadness

Patients expressed sadness due to having SBS-IF. They could feel different from other people 'It makes me feel upset that I'm not just like everybody else' (Sally, 52 years, 6PN) and not understood: 'You're feeling quite low and ... it's almost like nobody else understands what you're going through' (Helen, 45 years, 6PN). As well as sadness for themselves, patients were also sad for their spouses 'makes me feel, uh, upset really, upset for her. And when you've planned all your poor working life to do this, that, and the other' (Bill, 67 years, 5PN).

Worry

Patients commonly worried about getting a central venous catheter infection; one patient described it as 'the only thing that worries me' (Sally, 52 years, 6PN). This concern was heightened for patients responsible for the connection and disconnection of the central venous catheter from the PN and wanted to be 'always doing the right thing ... and were ... frightened of going wrong' (Joan, 70 years, 7PN). The stoma bag was another concern; 'I've just worried about my stoma leaking' (Frank, 35 years, 3PN). Patients could also be worried about being admitted to a non-specialist hospital 'nobody else understands my condition really. So it's that lack of understanding in the, the medical world' (Helen, 44 years, 4PN).

Frustration

Patients discussed feeling frustrated. This could be a result of restrictions of the PN regimen and amount of

equipment; for others, it was the symptoms of the condition or factors relating to their stoma, such as the appearance of it or the bag leaking or needing frequent emptying.

Theme 3: Social impact

Patients experienced impacts on their social relationships as a result of SBS-IF such as difficulties in socialising. This was related to their constant need for the toilet or checking the stoma bag. 'I've always got to know where a loo is and it puts me off going out for a meal' (Paul, 67 years, 5PN). Events involving food and drink were a particular problem because patients could not eat the same quantity of food as prior to their illness and had to be careful about what they ate and drank. This could lead patients to avoid such events. 'It's normal for a person to eat. That's why I avoid going out with friends ... They all sat there eating, drinking beer ... and I can't' (Julie, 44 years, 6PN).

SBS-IF impacted on patient's relationships, in particular with their partner. 'If you're having sort of sex ... I'm embarrassed by it even with him' (Sally, 52 years, 6PN). There were also impacts on other family members with patients being limited to what they could do with children and grandchildren. Friends might not understand the condition and this put strain on the friendship. 'They don't understand ... you try to explain and they don't – one of my friends just doesn't understand ... the problems I have because ... I look normal.' (Dora, 47 years, 7PN).

Patients described hiding elements of their condition from friends or family. Patients could feel embarrassed by having a stoma so did not discuss it. Other patients did not want to worry their family and wanted to be seen as normal by their friends.

Theme 4: Coping with life having short bowel syndrome with intestinal failure

The elements that helped patients cope with their condition were adapting their life around their illness, emotional attitudes, support from others and having a night off from PN.

Adaptation

Patients had adapted their life around their SBS-IF, in particular tailoring their day around the PN regimen 'Sometimes I need a bit longer in the morning to take my feed off ... I've just sort of accommodated it' (Lisa, 45 years, 5PN). They had also adapted to having the stoma bag and learnt to manage it 'It's something I've got, I've got to learn to cope with it and I just get on with it' (Mary, 66 years, 7PN).

Emotional attitudes

The attitudes that helped patients manage with their condition were gratitude and acceptance. Although the PN regimen was restrictive, patients recognised that it was keeping them alive and were grateful for it. 'I'm really, really grateful that there is such a thing as PN because I couldn't survive [without] it, literally' (Sally, 52 years, 6PN). Patients came to a place of acceptance that helped them cope with their life having SBS-IF; 'you either can work with the problem, you know, or you can be against it and it'll just make your life harder ... You have to find that happy medium' (Frank, 35 years, 3PN).

Support

Support was another element which patients cited as helping them cope with SBS-IF. Support came from various sources; friends and family, nurses or specialist hospital staff, and patient support groups. Most patients were satisfied with the support they received.

Night off from parenteral nutrition

Patients who were able to have a night off from PN discussed it as having a positive impact on their well-being. It allowed them to participate in social activities and meant that they could feel free and normal for that one night; 'It just makes me feel that that one day I can be a normal person and just get up.' (Sally, 52 years, 6PN). Although they enjoyed having a night off from PN, some patients acknowledged that it had a detrimental impact the morning or day after in that they felt tired, dehydrated or hungry.

Despite the difficulties, all patients identified that a reduction in nights on PN would make a big difference in their lives. When asked about what they would consider as an ideal treatment, a typical comment was for a reduction in the hours or nights on PN; for example, one patient said 'If I didn't have to be on it 7 nights a week ... just allow me, I suppose to feel normal' (Mary, 66 years, 7PN).

Family member interviews

SBS-IF affected both family members and patients. Family routines and activities could be affected. So, outings needed to be planned around it and could be delayed 'the biggest upset ... is that she may have to go to the toilet. She might be there for quite a while ... it does create a delay then on things' (Andrew).

There were particular impacts on holidays as a result of the amount of equipment and planning needed. One family member commented that when they went away 'literally the whole car [is] taken up with medical equipment ... anything we do has to be planned around it'

(David). This was stressful and could mean that the patient and their family did not go on holiday; 'We haven't been on holidays in a very long time ... it's mainly the [PN]' (Fiona). One family adapted by buying a motorhome and commented 'We're going away more now than we did before' (Martin).

In addition, the patients' SBS-IF could cause financial constraints as a result of family members taking time off work, which one participant described as a 'financial blow' (Martin). Another participant gave up work leading financial problems. 'I don't work anymore. I'm fulltime carer for her now ... [resulting in] mortgage arrears ... that is another massive stress' (David). There were no financial impacts reported by two participants; in one case because they were retired.

Although, it caused problems, relatives expressed gratitude for the availability of PN: 'I prefer that he didn't have to do it, but I'm delighted that it's available, because he would be dead if he didn't have it' (Michelle). Partners would get involved and try to help patients with their PN. 'I actually try and help him out ... maybe shorten the time of the preparation for him ... clean up the kitchen for him just to, to come and set up his trolley, do his med' (Fiona). However, this could sometimes cause friction between them; 'I know that if I try and go and get involved she gets agitated' (David).

Their partner having PN had psychological impacts on family members. Family members could be worried: 'I may be worried ... about his line infections and him feeling bad ... because of course it affects ... me psychologically' (Fiona). Family members could also be irritated by the constraints of PN; 'honestly in the beginning I did feel slightly ... irritated because there's things that I wanted to do that ... didn't happen' (Fiona).

Family members, as well as patients, discussed the benefit of reducing nights on PN. One participant noted that it would improve the mood of them both. Others discussed that they would be less restricted in going out and going on holiday.

Discussion

The present study aimed to understand the impact of SBS-IF on patients and family members. Patients' lives were affected by symptoms from the disease and its consequences; having a stoma and the PN regime. All aspects of patients' lives were affected by their condition; with patients reporting physical symptoms and physical restrictions, as well as effects on emotional wellbeing, their social life and relationships. Family members living with the patient also were affected in multiple ways. Patients described ways of dealing with their condition by adapting their life around the PN, adopting emotional attitudes of gratitude and acceptance, having support from others, and a night off from PN.

Previous research into patients' perspective of SBS-IF is limited; thus, the present study used qualitative methods to gain an in-depth view of the patients' perspective of SBS-IF, as well as family members living with someone with SBS-IF. Much of the literature has focused on the patient experience of PN rather than considering the effect of SBS-IF in its entirety on patients and their families [26–28]. Quantitative research using patient-reported outcome questionnaires has found that patients have diminished health-related quality of life [5,29]. The data collected from the interviews conducted in the present study illustrate why this might be the case with patients talking about a range of physical symptoms such as diarrhoea and abdominal pain, and the restrictive nature of PN, all of which have a negative impact on quality of life.

Patients' lives were limited as disease symptoms, restrictions from the PN regime and living with a stoma curtailed what they could do. Given the overwhelming nature of the disease and the constraints it imposed, patients had a plethora of negative emotions. This is unsurprising because previous research using a validated questionnaire with patients on PN has shown that belief about lack of personal control leads to emotional distress in these patients [30].

The constraints of living with SBS-IF and PN regimen curtailed patients' social lives and impacted on patients' relationships. This is keeping with other research that has demonstrated the impact of home PN on social life [18,31,32], whereas other studies report that social life is not effected [28]. It is unclear why there was discrepancy, although it does highlight the need to provide person centred care for all patients.

Both family members and patients are affected by SBS-IF and an important element of the present study was uncovering that impact. Other research using a validated questionnaire has investigated family member experience of PN [14], although the present study is the first to use qualitative interviews so that family members could freely express their views. Family members wanted to help their relative, although they could be worried about them and be irritated with impositions from PN regimen.

As well as considering the impact of SBS-IF, we investigated what helped patients cope. Patients described a number of elements, which could be classified as having a positive outlook – adapting to their situation, seeing the benefit of the PN and being thankful that it was keeping them alive. Patients also cited the support they received from others as a factor that helped them cope. Although other studies have commented on how patients coped with PN, such as trying to integrate it into daily life, they have not drawn strategies together as a coherent theme [32,33].

Another element having a positive impact on patients' on general well-being was a night off from PN because this gave them more freedom and feelings of normalcy, although they could have an increase in symptoms the following day. With the advent of treatments to improve gastrointestinal absorption, such as glucagon-like peptide (GLP)-2 and GLP-1, number of nights on PN is a potentially modifiable factor [34–36]. Patients' desire for greater freedom and normalcy was further reinforced when discussing a perfect or ideal treatment with a reduction in hours or nights on PN being the most commonly reported theme. This aligns with other research demonstrating that health-related quality of life is related to the number of nights patients receive PN [6].

Limitations and future research

The family member sample was small and further research into the impact on family members is required; in particular, exploring the adequacy of the support they receive and whether additional support is required.

Conclusions

Patients with SBS-IF and their family members were severely impacted by the condition. Healthcare professionals can help to support patients by facilitating them explore what others have found beneficial; adapting their life around PN, viewing PN with acceptance and trying to cultivate gratitude. Further research into the support required for family members may be beneficial.

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Conflicts of interest, source of funding and authorship

Unrelated to this study, SL and SB have received unrestricted research grant support from Shire/Takeda into their departments, one of which funded a study where AMS was the study researcher. JA, BB, CP and GD declare they have no conflicts of interest.

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JA, SB and SL obtained the funding and were involved in the initial conceptualisation of the study. CP and GD conducted the interviews. CP, GD, BB and AMS analysed the data. All authors interpreted the data. AMS wrote a draft of the paper. All authors reviewed, revised and edited the paper. All authors read and approved the final manuscript submitted for publication.

Transparency declaration

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

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Supporting information

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

Table S1. Sampling quotas for SBS patients and family members.

Table S2. Patient-reported signs or symptoms.

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GASTROINTESTINAL DISORDERS

Facilitators and barriers to adherence to gluten-free diet among adults with celiac disease: a systematic review

N. Abu-Janb* & M. Jaana

Health Systems Management, Telfer School of Management, University of Ottawa, Ottawa, Ontario, Canada

Keywords
barriers, coeliac, diet, facilitators, gluten, systematic review.

Correspondence
M. Jaana, Health Systems Management, Telfer School of Management, University of Ottawa, 55 Laurier Avenue East, Ottawa, ON K1N 6N5, Canada.
Tel.: (613) 562-5800 (Ext. 3400)
E-mail: jaana@telfer.uottawa.ca

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Abstract

Background: Coeliac disease (CD) is a chronic, autoimmune disease that prevents individuals from processing gluten, leading to adverse health effects. People with CD should adhere to a gluten-free diet (GFD); however, adherence rates are well below optimal in adults with CD, ranging between 42% and 91%. To date, limited evidence is available on the nature and magnitude of factors that affect adherence to GFD. The present study aimed to develop a systematic review that critically appraises and synthesises evidence on facilitators and barriers that affect adherence to GFD among adults with CD.
Methods: Four databases were searched (Ovid Medline, CINAHL, PsychInfo and Embase) using variant keywords to identify empirical studies meeting the inclusion/exclusion criteria. A coding scheme was developed to extract relevant information from each article.
Results: Forty articles were included. Grounded in the bioecological theory of development, we synthesised the facilitators and barriers in the literature into a social ecological model with multiple levels: system, community, organisational, interpersonal and individual. The studies varied by design and level of evidence; only one randomised trial was identified. The most significant facilitators include (% of studies): increased education (22.5%); increased knowledge of a GFD (20%); increased intention/self-regulatory efficacy (17.5%); and coeliac association membership (12.5%). The most significant barriers include: lower knowledge of CD (35%); restaurant/supermarket shopping (30%); poor patient education from practitioner (17.5%); and low intention/motivation to adhere to a GFD (17.5%).
Conclusions: Improving knowledge of a GFD, becoming a member of a coeliac association, and improving practitioners' abilities to educate patients on CD will create opportunities for improved adherence to GFD among adults with CD.

Introduction

Coeliac disease (CD) is a chronic, autoimmune disease that negatively impacts an individual's digestive system. Approximately 1% of the population worldwide live with CD [(1)]. For individuals who have CD, there is an environmental trigger that leads to adverse health outcomes, known as gluten. Gluten is a storage protein found in many grains, including wheat, barley, rye, oats and triticale [(2)]. When an individual is exposed to gluten, the gluten will customarily transfer through the individual's digestive system until it reaches the small intestine. At this point, the gluten particles are recognised as foreign invaders, leading to the release of immune cells that attempt to destroy the gluten particles [(3)]. As a result, the lining of the small intestine also gets damaged, causing possible villous atrophy responsible for many complications, including significant levels of nutrient malabsorption, leading to comorbidities [(4)]. Although the majority of individuals living with CD will display classic

symptoms, such as diarrhoea, malabsorption and abdomen discomfort, some individuals can show atypical symptoms or even no symptoms at all [5].

Because there is no known cure for CD, stringent adherence to a gluten-free diet (GFD) is necessary to prevent adverse health effects [6,7]. Despite this, prior research has shown that the adherence to a proper diet is not always maintained, with dietary compliance ranging from 42% to 91% [8,9]. The low adherence rates may compromise the health and well-being of individuals living with CD, leading to comorbidities such as anemia, severe malabsorption and various forms of malignancies [10]. Hence, it is important to obtain a better understanding of the factors that can influence the ability of a person with CD to adhere to a GFD.

To date, although some studies have investigated various factors that may enhance, and/or limit an individual's ability to adhere to a GFD, limited knowledge is available on the existing evidence in this area, which may inform future research, practice and policy changes. Grounded in the Bio-Ecological Theory of Development (BETD) and the Social Ecological Model (SEM), the present study contributes to this area and reports the results of a systematic review of the literature that identifies, critically appraises and synthesises existing evidence on the facilitators and barriers to adherence to GFD among adults living with CD.

Bio-ecological theory of development/social ecological model

The BETD originated from Urie Bronfenbrenner [11], progressing from his original ecological systems theory. The theory's main underpinnings dictate that, to understand human development and decision-making, one needs to explore the entire ecological system that encompasses their life.

Derived from the BETD is the SEM, which incorporates the different components of the former into a visual that describes the development of individuals as they go through their lives, faced with both facilitators and barriers at the different ecological layers that encompass their lives. In the context of this systematic review, the SEM is used to help explain the factors that are present in peoples' lives, which impact their adherence to a GFD. Several facilitators and barriers impact their ability to cope with their diagnosis. These facilitators and barriers are expected to exist at various ecological levels. The relationship among these categories will help portray the experience of an adult with CD attempting to adhere to a GFD.

Materials and methods

Following the PRISMA guidelines [12], a systematic review was conducted that synthesises existing evidence on the facilitators and barriers for adherence to GFD among adults with CD. Four major databases were searched (November 2017): Ovid Medline (http://ovidsp.ovid.com), CINAHL (http://www.ebscohost.com/nursing/products/cinahl-databases/the-cinahl-database), PsychInfo (https://www.apa.org/pubs/databases/psycinfo) and Embase (https://www.embase.com/) (for a detailed search example, see Appendix A). These databases were used to identify empirical studies that met the inclusion/exclusion criteria (Table 1), which allowed a wide range of potential studies to be identified, helping guarantee a saturated search. The search strategy keywords included: coeliac, adherence, gluten-free, gluten, treatment, coeliac, maintenance, compliance, barrier(s), facilitator(s), factor(s) and impacts. Reference lists of the retrieved articles were further hand-searched.

Search strategy

Figure 1 presents the steps used in the search and screening process of articles. A coding scheme was developed to extract relevant information from the included empirical studies, including:

- Country of origin
- Age range and mean of participants
- Population sample including subsequent groups

Table 1 Inclusion/exclusion criteria

Term	Inclusion criteria	Exclusion criteria
Date of articles	Published until 15 November 2017	–
Age of participants	Adult population	Children studies
Study design and reporting	Empirical studies that report on facilitators and barriers	Non-empirical studies (e.g. opinion papers, policy papers, review)
Participant population Condition	Studies that solely focus on patients with CD	Studies where comorbid disorders are present that influences adherence to a GFD
Language	English studies	Non-English studies

- Design of the study
- Barriers identified
- Facilitators identified
- Barriers influencing adherence to GFD
- Facilitators influencing adherence to GFD
- Summary of results
- Potential types of bias presented

Data extraction and analysis

The facilitators and barriers reported in each study were classified according to the SEM. Hence, the facilitators/barriers are presented according to the nature of each factor: Individual factors, Interpersonal factors, organisational factors, community factors and system-level factors.

For all of the included articles, a critical appraisal was conducted to assess the strength and rigour of the study. Depending on the design of the study, a specific checklist was used to assess the quality of each particular study. Based on these validated checklists, the quality of evidence and degree of recommendation of the article was evaluated [13]. The investigator was responsible for coding all of the included articles. To ensure reliability, five were randomly selected and also coded by another investigator. The coding between the two researchers has high inter-rater reliability, with 85% agreement.

Following recommended guidelines [14], a systematic narrative synthesis was conducted; the results and specific characteristics are reported and summarised for each of the included studies. As per the PRISMA guidelines [15], all of the information was compared across each of the included studies, as well as within each study. The reported facilitators/barriers were placed into different ecological layers. These ecological layers are described in the sections below.

Results

Table 2 presents a general overview of the studies included in this review. Nineteen studies were conducted in Europe, 15 in North America, five in Australia and one in Asia. The studies were conducted from 1992 to 2017. The strength of evidence of each study is based on the JBI levels of evidence (LOE) tool, which assesses the quality of the study based on its design [15]. It includes

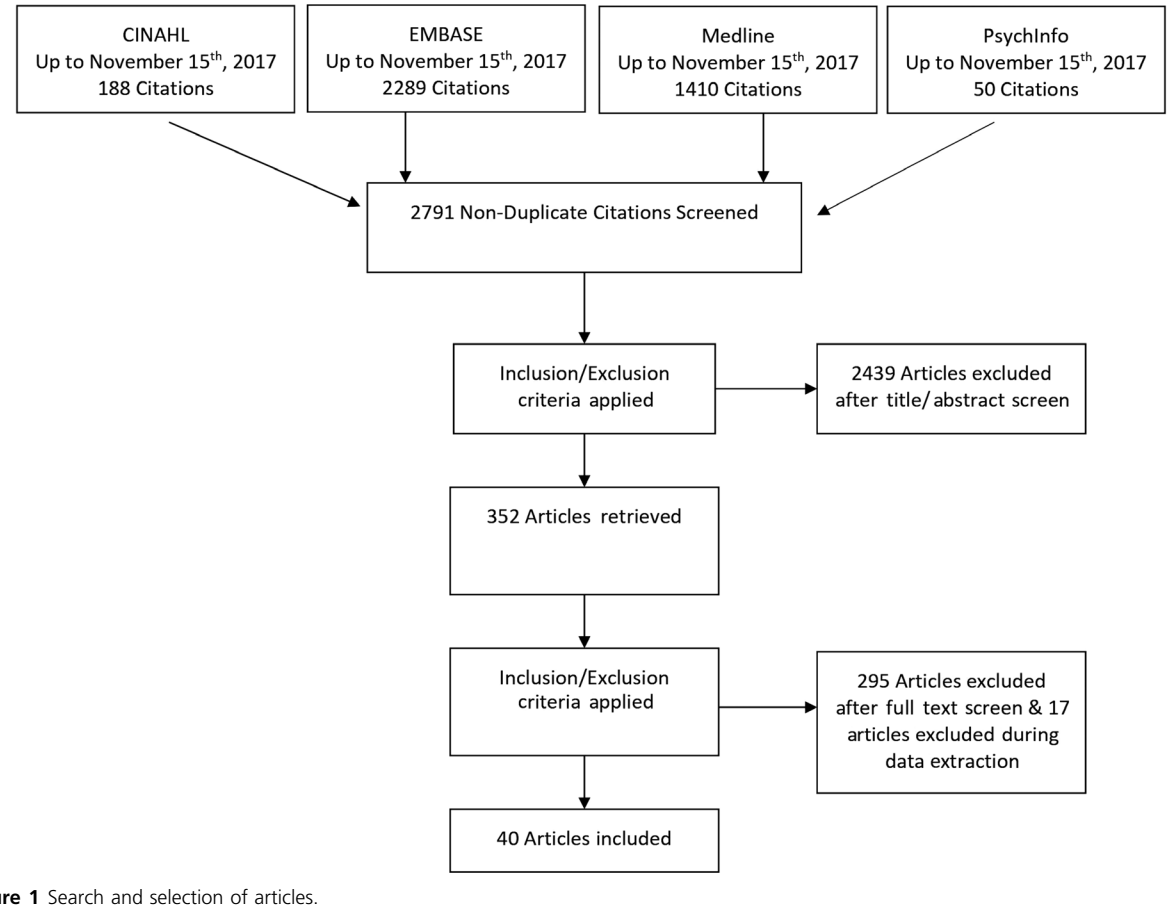

Figure 1 Search and selection of articles.

five levels, with multiple sublevels, including 1.a [systematic review (SR) of Randomised controlled trials (RCT)], 1.b (SR of RCT and lower studies), 1.c (RCT), 1.d (Pseudo RCT), 2.a (SR of quasi-experimental studies), 2.b (SR of quasi-experimental and lower studies), 2.c (quasi-experimental prospectively controlled study), 2.d (pre-test/post-test control group), 3.a (SR of cohort studies), 3.b (SR of cohort and lower studies), 3.c (cohort with control group), 3.d (case-controlled), 3.e (observational study without control), 4.a (SR of descriptive studies), 4.b (cross-sectional), 4.c (case series), 4.d (case study), 5.a (SR of expert opinion), 5.b (expert consensus) and 5.c (single expert opinion). The LOE of the studies included in this systematic review ranged from 1.c to 4.c, with 1.c−3.d referring to a high level of evidence compared to 3.e–4.c. The majority of the studies had observational/analytic designs, including case–control, cohort, and analytical cross-sectional studies. Only one randomised controlled trial was found and included in the review; 10 studies had nonrandomised control groups and six studies were descriptive in nature. The sample sizes ranged from 30 participants to 5912 participants. As a result of the nature of CD, purposive sampling was used in the majority of the studies.

Synthesis of facilitators and barriers

Tables 3 and 4 summarise the studies that reported evidence on each facilitator and barrier that impacted GFD adherence in adults with CD. Taking into consideration the magnitude of the significance, the LOE, and the quality of each study, which takes into consideration participant selection, data collection/analysis and study biases, the facilitators and barriers with the most supporting evidence at each ecological layer were identified.

The *individual layer* represents factors that influence dietary adherence based on personal characteristics, irrespective of individuals' surrounding relationships and environment. The *interpersonal layer* represents factors that influence dietary adherence based on individuals' direct relationships in their lives. The *organisational layer* includes rules, regulations and influences from one's surrounding environment on adherence to a GFD. The *community layer* refers to factors that are based on individuals' influences by their relationships with their surrounding society and social institutions. It also includes any cultural influence on dietary adherence. This layer also includes environmental boundaries. Last, the *system's layer* represents factors that impact dietary adherence that originate from a macro, policy level [16].

Figure 2 synthesises and illustrates the results of this systematic review using a social ecological model that organises the various facilitators and barriers into ecological layers and displays relationships that exist across many layers in an individual's life, and specifically within the health system [17]. When an individual is diagnosed with CD, they are faced with many facilitators and barriers that impact their ability to adhere to a GFD. This model reports what area of one's life each facilitator and barrier fits into, highlighting where improvements can be made to make positive changes. Beyond the individual layer, the interpersonal layer includes factors that correspond to the relationships that exist in an adult's everyday life. As we move externally, the organisational structure includes the interactions adults make in their environment and how those end up influencing GFD adherence. The community layer is past the organisational level, and relates to society's impact on an adult with CD; it includes geographical variables and cultural differences. Last, the final layer, which is most distant from the individual, is the systems layer. This layer encompasses laws and policies that may impact an adult with CD. Although this layer is the most distant, it also has the most substantial impact because the structure of this layer has an impact on every other layer of an individual's life [10].

Individual facilitators/barriers

At the individual layer, four main factors were reported in the literature that related to adherence to a GFD by adults with CD: Education level/income, health status, knowledge, and intention/motivation. The LOE of these studies ranged from 1.c to 4.b.

First, individuals with a high level of education/income were significantly associated with having higher GFD adherence levels [18,19]. These individuals were more aware of the negative health impacts of non-adherence and were less likely to be impacted by the high costs associated with GF foods.

Second, an adult's overall health and their adherence levels to a GFD were shown to be correlated [18,20,21]. Adults' perspectives on their health influenced their adherence level to a GFD. This emphasises the importance of facilitating constant patient-practitioner communication to ensure patients are knowledgeable about their health status.

Third, understanding how the consumption of gluten can have adverse health risks to someone with CD was linked to a higher ability to adhere to a GFD [22]. If the severity of CD is not known, someone may not be willing to put in the effort to follow a GFD [23–28]. Being educated on an illness allows individuals to be able to make a more informed decision on how seriously they take their treatment protocol.

Fourth, adults who had positive intentions when starting out with a GFD were shown to have an increased

Table 2 Overview of the studies included in the systematic review

Study	Year	Country	Study design	Participants/sample Size	Age of participants	Level of evidence
Twist & Hackett [46]	1992	UK	Case–control	Group 1: 46 Group 2: 46	14–40	3.d
Lamontagne *et al*. [37]	2001	Canada	Analytical, cross-sectional	230	Mean = 49.6	3.e
Ciacci, Iavarone, Siniscalchi, Romano & Rosa [23]	2002	Italy	Case–control	Group 1:25 Group 2: 114	Mean = 29.62	3.d
Ciacci *et al*. [51]	2003	Italy	Analytical, cross-sectional	581	Mean = 31.47	3.e
Hogberg, Grodzinsky & Stenhammar [52]	2003	Sweden	Case–control	Group 1: 15 Group 2: 14	Mean = 26	3.d
Butterworth *et al*. [45]	2004	UK	Prospective, cohort	Group 1: 66 Group 2: 21	Mean Group 1: 46.3 Mean Group 2: 28.95	3.c
Zarkadas *et al*. [41]	2006	UK	Descriptive, cross-sectional	2681	Mean = 56	4.b
Hauser, Stallmach, Caspary & Stein [20]	2007	Germany	Analytical, cross-sectional	522	Mean = 46.3	3.e
Hopman, Koopman, Wit & Mearin [53]	2009	Netherlands	Case–control	Group 1: 33 Group 2: 8 Group 3: 12	Mean Group 1: 57 Mean Group 2: 26 Mean Group 3: 30	3.d
Smith [42]	2009	USA	Descriptive, cross-sectional	156	Mean = 51.5	4.b
Barratt, Leeds & Sanders [18]	2011	UK	Case–control	Group 1: 348 Group 2: 225	18+	3.d
Black & Orfila [24]	2011	UK	Descriptive, cross-sectional	146	18-70	4.b
Sainsbury & Mullan [38]	2011	Australia	Analytical, cross-sectional	265	Mean = 45.1	3.e
Biagi *et al*. [36]	2012	Italy	Retrospective, cohort	141	Mean = 34	3.c
Casella *et al*. [54]	2012	Italy	Prospective, cohort	Group 1: 1166 Group 2: 59	Group 1: 18-64 Group 2: 65+	3.c
Ford, Howard & Oyebode [22]	2012	UK	Analytical, cross-sectional	274	19-85	3.e
Lee, Ng, Diamond, Ciaccio & Green [43]	2012	USA	Case–control	Group 1: 1179 Group 2:1743	18+	3.d
Ukkola *et al*. [25]	2012	Finland	Prospective, cohort	698	Median = 50	3.c
Hall, Rubin & Charnock [19]	2013	UK	Analytical, cross-sectional	287	Mean = 56.17	3.e
Mahadev *et al*. [55]	2013	USA	Analytical, cross-sectional	413	18+	3.e
Sainsbury, Mullan & Sharpe [56]	2013	Australia	Analytical, cross-sectional	390	Mean = 44.2	3.e
Sainsbury, Mullan & Sharpe [29]	2013	Australia	Randomised Control Trial	Experimental: 101 Control: 88	Mean = 46.5	1.c
Verrill, Zhang & Kane [39]	2013	USA	Analytical, cross-sectional	1583	18-98	3.e
Zarkadas *et al*. [49]	2013	Canada	Analytical, cross-sectional	5912	18+	3.e
Dowd *et al*. [34]	2014	Canada	Descriptive, cross-sectional	203	Mean = 42.13	4.b
Rose & Howard [44]	2014	UK	Descriptive, grounded theory	130	Mean = 52.7	4.c
Shah *et al*. [35]	2014	USA	Analytical, cross-sectional	341	Mean = 51.14	3.e

Table 2 Continued

Study	Year	Country	Study design	Participants/sample Size	Age of participants	Level of evidence
Casellas *et al*. [21]	2015	Spain	Analytical, cross-sectional	366	Mean = 40	3.e
Ferster, Obuchowicz, Jarecka, Pietrzak & Karczewska [47]	2015	Poland	Descriptive, cross-sectional	30	19–71	4.b
Kothe, Sainsbury, Smith & Mullan [30]	2015	Australia	Analytical, cross-sectional	228	Mean: 45.2	3.e
Rajpoot *et al*. [26]	2015	India	Prospective, cohort	Group 1: 54 Group 2: 92	Mean = 28.9	3.c
Sainsbury, Mullan & Sharpe [57]	2015	Australia	Case–control	Group 1: 88 Group 2: 101	Mean = 46.5	3.d
Villafuerte-Galvez *et al*. [31]	2015	USA	Analytical, cross-sectional	355	Mean = 53.6	3.e
Dowd, Jung, Chen & Beauchamp [32]	2016	Canada	Prospective, cohort	212	Mean = 42.08	3.c
Silvester, Weiten, Graff, Walker & Duerksen [27]	2016	Canada	Analytical, cross-sectional	82	18+	3.e
Silvester, Weiten, Graff, Walker & Duerksen [40]	2016	Canada	Analytical, cross-sectional	222	18+	3.e
Ramirez-Cervantes, Romero-Lopez, Nunez-Alvarez & Uscanga-Dominguez [28]	2016	Mexico	Analytical, cross-sectional	56	Mean = 59.4	3.e
Dowd & Jung [33]	2017	Canada	Prospective, cohort	200	Mean = 44.02	3.c
Hughey *et al*. [50]	2017	USA	Analytical, cross-sectional	1832	19–65	3.e
Muhammad, Reeves, Ishaq, Mayberry & Jeanes [48]	2017	UK	Analytical, cross-sectional	375	Mean = 48	3.e

likelihood in following a GFD correctly [22,29–33]. Studies also showed that those who had poor intention/ a poor level of self-efficacy were also found to have a lower likelihood of following a GFD [19,22,28]. The belief an individual had, as to whether a GFD would improve their CD outcomes impacted adherence levels. Individuals considered that a GFD will improve CD outcomes correlated to an increase in GFD adherence [31] and individuals considering that a GFD will not improve CD outcomes correlated to them being less likely to follow a GFD [19,23,34,35]. Individuals who were less careful with maintaining precautions, such as informing their cooks about their allergies, were less likely to adhere to a GFD [36].

Interpersonal facilitators/barriers

At the interpersonal layer, four main factors were related to adherence to a GFD by adults with CD: social fear, confidence in practitioner, social activities and embarrassment. The LOE of these studies ranged from 3.c to 4.c.

It is human nature to act differently when in the presence of others. It is common for people with CD to engage in behaviour that can influence their adherence to a GFD. Studies included in this review highlighted a significant correlation between low levels of adherence to a GFD and the social fear of having CD [18,23].

Confidence in the practitioner impacted GFD adherence. If an individual was not confident in their treatment advice provided by their specialist, they were less likely to adhere to a GFD [37]. In addition, individuals with CD reported that it is easier to follow a GFD when they had a high level of support from family and friends [38–40]. Having increased support from surrounding relationships lowers the risk of isolation and allows individuals to adhere to their health needs without feeling alienated.

Last, several studies discussed that participating in social activities played a negative role in relation to diet adherence. Specifically, people reported that participating in social activities, including dining outside of the home and spending time with friends had a negative impact on their ability to maintain a GFD [24,41–43]. Reasons included overly trusting others with food preparation [38] and the overall ignorance of others in understanding the severity of CD [44]. It is common for an individual with CD to feel isolated and different from those around them. The need for inclusivity causes individuals to neglect their illness and risk adverse health outcomes.

Table 3 Facilitators to gluten-free diet (GFD) adherence

Study	Individual facilitators	Interpersonal facilitators	Organisational facilitators	Community facilitators	Systems facilitators
Twist & Hackett [46]	–	–	–	–	–
Lamontagne *et al.* [37]	Older age increased a person's ability to maintain a GFD ($P < 0.05$)	Having a high level confidence in gastroenterologists and dieticians was correlated with a higher adherence to a GFD ($P < 0.005$)	Having a high level of satisfaction with GF products was correlated with improved GFD scores ($P < 0.01$)	–	Having improved communication with specialists was correlated with a higher adherence to a GFD ($P < 0.005$)
Ciacci, Iavarone, Siniscalchi, Romano & Rosa (2002) [23]	A longer time on a GFD was correlated with a higher adherence level to a GFD ($P = 0.0025$)	–	–	–	A longer time on a GFD was correlated with a higher adherence level to a GFD ($P = 0.0025$)
Ciacci *et al.* (2003) [51]	A higher education level was associated with an increase GFD adherence ($P = 0.0001$) If an individual was diagnosed later in life (after 20), there was a correlation with a higher level of GFD adherence ($P = 0.0001$) Women were statistically more likely to be adherent to a GFD ($P = 0.0025$)	–	–	–	–
Hogberg, Grodzinsky & Stenhammar [52]	A significant relationship found between being diagnosed before the age of 4 years and having improved GFD adherence ($P = 0.021$)	–	–	–	
Butterworth *et al.* [45]	–	–	Membership in a coeliac society was correlated with an increase in GFD adherence. OR (95% CI) 2.94 (1.72–5.26) for Caucasians Having a better understanding of food labelling was correlated with an increase in GFD adherence [OR (95% CI) 2.13 (1.08–4.17)]. Affordability of GF products was correlated with an increase in GFD adherence OR (95% CI) [Caucasian: 1.82 (1.12–2.86)]	–	Obtaining GF products by prescription was correlated to increased adherence to a GFD OR (95% CI): Caucasian: 2.0 (1.04–3.85) A GFD was shown to improve as more GF products were prescribed. OR (95% CI): Caucasian: 1.89 (1.08–3.33) Detailed explanation post-diagnosis was correlated with better adherence to a GFD OR (95% CI) 2.04 (1.16–3.57) Regular follow-up with a practitioner or dietician showed a correlation with increased dietary adherence OR (95% CI): Caucasian: 2.22 (1.12–4.35)

Table 3 Continued

Study	Individual facilitators	Interpersonal facilitators	Organisational facilitators	Community facilitators	Systems facilitators
Zarkadas *et al.* (2006) [41]	Descriptive data highlighted that individuals were better able to adhere to a GFD if they were diagnosed earlier in life	–	Individuals in this study stated that having better access to GF foods in supermarkets, as well as restaurants, and understanding food labels increase their ability to maintain dietary adherence	–	Individuals in this study shared what would improve their ability to adhere to a GFD. Factors included: Early diagnosis, better food labelling, and increased follow-up for dietary counselling
Hauser, Stallmach, Caspary & Stein [20]	–	–	–	–	–
Hopman, Koopman, Wit & Mearin [53]	–	–	–	–	–
Smith [42]	–	–	–	–	–
Barratt, Leeds & Sanders [18]	Individuals who were from an Affluent background had better adherence to a GFD [$P = 0.0077$: OR = 0.33 95% CI (0.15–0.75)]	–	–	–	–
Black & Orfila [24]	–	–	–	–	–
Sainsbury & Mullan (2011) [38]	Through a qualitative process, participants shared factors that increased their ability adhere to a GFD. These factors included: Increased knowledge of ingredients/ label reading, being prepared and organised, the desire to minimise CD symptoms and feel physically better	Participants shared factors that increased their ability to maintain a GFD including: Support from friends and the confidence to ask food-handlers questions about contamination	Support from coeliac associations was mentioned through interviews as a facilitator to adhering to a GFD. Clear labelling of foods was a common response by participants as a facilitator to adhering to a GFD	–	Clear labelling of foods was a common response by participants as a facilitator to adhering to a GFD
Biagi *et al.* [36]	–	–	–	–	–
Casella *et al.* [54]	–	–	–	–	–
Ford, Howard & Oyebode [22]	A higher rating of self-efficacy was correlated with increased adherence to a GFD ($P = 0.04$); There was a correlation between Older age and increased adherence to a GFD ($P = 0.002$); If an individual viewed the consequences of Ingesting gluten as more severe, there was a correlation with increased adherence to a GFD ($P = 0.009$); The belief in the cyclical nature of CD was correlated with an increase in GFD adherence ($P = 0.02$)	–	–	–	–
Lee, Ng, Diamond, Ciaccio & Green [43]	–	–	–	–	–
Ukkola *et al.* [25]	–	–	–	–	–

Table 3 Continued

Study	Individual facilitators	Interpersonal facilitators	Organisational facilitators	Community facilitators	Systems facilitators
Hall, Rubin & Charnock [19]	If an individual was diagnosed as an adult, there was a correlation with an increased level of GFD adherence ($P < 0.05$) There was a correlation between having a higher education and an increased adherence level ($P = 0.047$) If an individual was older they were more likely to have a higher level of GFD adherence ($P < 0.001$)	–	Being a member of a coeliac society was correlated with an increase in GFD adherence ($P < 0.001$)	–	Regular follow-up with practitioner was shown to be correlated with an increase in GFD adherence ($P < 0.01$) A correlation was shown with time of diagnosis. A longer time since diagnosis was correlated with an increase in GFD adherence ($P = 0.019$) A correlation also showed a relationship with being diagnosed as an adult and increased GFD adherence ($P < 0.05$) A correlation was present between receiving prescription GF foods and better adhering to a GFD ($P < 0.01$)
Mahadev *et al.* [55]	–	–	–	–	–
Sainsbury, Mullan & Sharpe (2013) [56]	Having higher intention to maintain a GFD was correlated with an increased likelihood of maintaining a GFD ($P < 0.01$) Having an increased level of knowledge on CD and a GFD was correlated with an increased level of adherence to a GFD ($P < 0.01$) If an individual had a high Perceived behavioural control level, they were more likely to also be following a GFD at a higher level of adherence ($P < 0.001$) This study also highlighted that being female was linked to better adherence to a GFD ($P < 0.05$)	–	–	–	–

Table 3 Continued

Study	Individual facilitators	Interpersonal facilitators	Organisational facilitators	Community facilitators	Systems facilitators
Sainsbury, Mullan & Sharpe (2013) [29]	This RCT concluded that Completing the Intervention was linked with an improvement in following a GFD ($P < 0.001$) For those specifically who had low GFD adherence levels prior to the intervention, they were more likely to follow a GFD following the intervention ($P = 0.014$)	–	–	–	This RCT concluded that Completing the Intervention linked to improvement in following a GFD ($P < 0.001$) For those specifically who had low GFD adherence levels prior to the intervention, they were more likely to follow a GFD after the intervention ($P = 0.014$)
Verrill, Zhang & Kane [39]	This study also found a correlation between being Female and having an improved level of GFD adherence ($P = 0.013$) High self-rated health was also linked to an improved level of GFD adherence ($P < 0.0001$)	This study found that having Support from family and friends was correlated to improved adherence levels to a GFD ($P < 0.0001$)	–	–	–
Zarkadas *et al*. (2013) [49]	If an individual was following a GFD for longer period of time, they were less likely to make a mistake ($P < 0.001$) If an individual had a high level of strategy to maintain a GFD, they were correlated with better following a GFD ($P < 0.001$) Participants noted other reasons that lead them to being extremely careful with following a GFD: Preventing long-term complications; Immediate reactions; knowledge of GFD.	–	–	–	A correlation was shown between being on a GFD for longer period and better being able to adhere to that GFD ($P < 0.001$) Participants shared that having a higher knowledge level on CD and a GFD post-diagnosis increased their ability to maintain a GFD
Dowd *et al*. (2014) [34]	A recent diagnosis decreased likelihood of purposeful gluten consumption ($P = 0.002$), and having a diagnosis further in the past decreased accidental gluten consumption ($P = 0.001$) Participants listed the following as facilitators: Pain as a result of CD, Hitting rock bottom, and the need to gain or lose weight	–	–	–	–

Table 3 Continued

Study	Individual facilitators	Interpersonal facilitators	Organisational facilitators	Community facilitators	Systems facilitators
Rose & Howard [44]	–	–	–	Through narratives given by individual's with CD, having access to the Coeliac Community improved their ability to adhere to a GFD	–
Shah *et al.* [35]	–	–	–	–	–
Casellas *et al.* [21]	This study showed that there is a correlation between an increased Quality of Life score based on a validated questionnaire and an increase in GFD adherence ($P < 0.05$)	This study showed that there is a correlation between an increased Quality of Life score based on a validated questionnaire and an increase in GFD adherence ($P < 0.05$)	This study showed that there is a correlation between an increased Quality of Life score based on a validated questionnaire and an increase in GFD adherence ($P < 0.05$)	There is a correlation between an increased Quality of Life score based on a validated questionnaire and an increase in GFD adherence ($P < 0.05$)	This study showed that there is a correlation between an increased Quality of Life score based on a validated questionnaire and an increase in GFD adherence ($P < 0.05$)
Ferster, Obuchowicz, Jarecka, Pietrzak & Karczewska [47]	–	–	–	–	–
Kothe, Sainsbury, Smith & Mullan [30]	Having an improved attitude towards a GFD was correlated with higher adherence ($P = 0.029$) Having a higher Perceived behavioural control level was also correlated to higher adherence to a GFD ($P < 0.001$) Higher intention to maintain a GFD (when Perceived behavioural control is low and habit is high) was a third factor that was correlated to maintaining a GFD ($P < 0.001$)	–	–	–	–
Rajpoot *et al.* [26]	–	Having a Counselling relationship improved an individual's ability to maintain a GFD ($P = 0.014$)	–	–	–
Sainsbury, Mullan & Sharpe (2015) [57]	This study (follow-up to RCT) showed that if individuals rated a portion of the intervention as interesting, it was more likely to improve the adherence level to a GFD ($P < 0.05$)	–	–	–	–

Table 3 Continued

Study	Individual facilitators	Interpersonal facilitators	Organisational facilitators	Community facilitators	Systems facilitators
Villafuerte-Galvez *et al.* [31]	If an individual Perceived the effectiveness of GFD as high, there was a correlation with a higher GFD adherence ($P < 0.0001$) If an individual had a high level of Knowledge of GFD and CD, there was a correlation to being better able to follow a GFD ($P < 0.0001$) If individuals had a high Self-effectiveness score at following GFD, they were correlated to better follow a GFD ($P < 0.0001$)	–	–	–	If an individual had a high level of Knowledge of GFD and CD, there was a correlation to being better able to follow a GFD ($P < 0.0001$)
Dowd, Jung, Chen & Beauchamp (2016) [32]	This study highlighted that having greater symptom severity increased GFD adherence ($P < 0.05$) If an individual viewed CD as having a lower perceived cost, GFD adherence was increased ($P < 0.05$) If an individual had a High self-regulatory efficacy level based on a validated questionnaire, GFD adherence was shown to be higher ($P < 0.001$) If an individual had increased plans to eat GFD, their adherence was higher ($P < 0.001$) If an individual had Greater knowledge of CD and a GFD, their adherence rates were higher ($P < 0.001$) If individuals had Positive intentions with their GFD, their adherence was higher ($P < 0.001$)	–	–	–	If an individual had Greater knowledge of CD and a GFD, their adherence rates were higher ($P < 0.001$)
Silvester, Weiten, Graff, Walker & Duerksen (2016) [27]	–	–	–	This study found a correlation between having a Patient-advocacy group and better adhering to a GFD ($P < 0.005$)	–

Table 3 Continued

Study	Individual facilitators	Interpersonal facilitators	Organisational facilitators	Community facilitators	Systems facilitators
Silvester, Weiten, Graff, Walker & Duerksen (2016) [40]	Participants shared that having access to Internet-based advice on CD and a GFD, as well as Magazines, increased their ability to maintain a GFD.	Participants shared that knowing another person on GFD increased their ability to follow a GFD.	It was stated that being a member of the Canadian Celiac Association allowed adherence to be improved; This was also mentioned for local CD groups.	Participants shared that having access to complementary medicine professionals such as naturopaths increased their ability to adhere to their GFD	Participants clearly articulated the importance of having access to practitioners when help was needed. This includes: Access to Family doctor/specialist, Dieticians and Complementary medicine professionals. Having this open communication was stated to improve the participant's ability to maintain a GFD.
Ramirez-Cervantes, Romero-Lopez, Nunez-Alvarez & Uscanga-Dominguez [28]	–	–	–	–	–
Dowd & Jung (2017) [33]	If an individual had a higher level of Self-compassion based on a validated questionnaire, their adherence levels were higher ($P < 0.01$ GFD) If an individual had a higher level of self-regulatory efficacy based on a validated questionnaire, their adherence levels were higher ($P < 0.001$)	–	–	–	–
Hughey *et al.* [50]	–	–	–	–	Visiting a health care practitioner in the last 5 years was correlated with an increase in an individual's ability to maintain a GFD ($P = 3.6 * 10^{-4}$)
Muhammad, Reeves, Ishaq, Mayberry & Jeanes [48]	This study found that being of an older age increased the ability to adhere to a GFD, slightly ($P = 0.03$)	–	This study found that being a member of the UK Celiac Society was correlated with an increase in GFD adherence ($P < 0.001$)	–	This study found a correlation between a General practitioner prescribing GF foods and an individual's ability to maintain a GFD ($P < 0.001$)

Organisational facilitators/barriers

At the organisational layer, four main factors related to adherence to a GFD by an adult with CD: Membership in a coeliac association, availability of GF foods in restaurants/supermarkets, clear labelling, and affordability. The LOE of these studies ranged from 3.c to 4.c.

Membership in a coeliac association was considered as a facilitator to adherence to GFD in several studies. Membership allowed for exposure to others with CD, improved the lives of many people with CD, and as a result, improved GFD adherence [19,27,38,45].

Furthermore, the presence of GF foods in restaurants/supermarkets play an important role in enabling access to GF products. Studies showed correlations between the inability to find GF products in stores and restaurants to a lower likelihood of following a GFD [23–26,34,42–44,46]. Even in situations where there are GF options, participants shared that the poor taste of the items impacted adherence levels to a GFD [36,43]. Without access to sufficient food items, consumption of products containing gluten is more likely to occur. Availability of GF foods is linked to societies' awareness of CD. In societies where CD is not prevalent or well known, availability of products will unlikely be sufficient. Many individuals in multiple studies reported that dining establishments were unable to provide a safe experience for them correctly and, as a result, they made a mistake on their GFD [18]. These mistakes include the risk of cross-contamination [34,47]. Overall, lack of patient education can translate to the individual's ability to follow a GFD when choosing food in restaurants and supermarkets. Using available tools to get others to understand the severity of CD and to find suitable food options can impact their ability to properly follow a GFD. It is also important to note that the studies that highlighted the lack of availability of gluten-free food are older, and therefore not as relevant in today's context.

Gluten is found in multiple, hidden ingredients. Hence, clear food labelling can act as an important facilitator to GFD adherence [38,45]. Although gluten and its derivatives must be disclosed on packaged labels in North America, clear food labelling is not a requirement in all countries/regions. If allergens are explicitly listed, individuals will know to avoid certain products. Individuals with CD can instantly identify a product as being safe to consume if there is a GF claim on the product.

Finally, GF foods are often more expensive than non-GF foods. Studies showed that the inability to afford GF foods was linked to lower adherence to a GFD [34,42,43,45].

Community facilitators/barriers

At the community layer, two main factors were related to adherence to a GFD by adults with CD: general society awareness and culture. The LOE of these studies ranged from 3.c to 4.c.

General society awareness was discussed in some studies, which showed a significant correlation between society's general knowledge of what gluten and CD are, as well as an adult's ability to maintain a GFD [19,32]. In more CD-friendly communities, individuals were able to find better options on foods to eat and to communicate their dietary restrictions. Improved society awareness translates to improved knowledge of employees at restaurants and other food establishments. There is also an increased chance that peers will be more knowledgeable about CD as a result of them being a part of a CD-friendly society. This translates to better support from peers to those with CD [19,32].

Another important discussed factor was culture, with individuals reporting that cultural factors lowered their likelihood to follow a GFD [26,28,46]. Being of South-Asian background was shown to significantly be correlated to a lower likelihood of following a GFD [45,48]. Individuals also reported relatives forcing them to eat foods containing gluten, not understanding how harmful they can be [46].

System facilitators/barriers

At the system layer, three main factors were related to adherence to a GFD by adults with CD: physician–patient knowledge, poor communication post-diagnosis and finances. The LOE of these studies ranged from 1.c to 4.b.

Physician–patient knowledge communication/follow-up was considered as an important barrier is multiple studies in the literature, and was significantly correlated with lower adherence to a GFD [25–27,35,43]. The most prominent system-level barrier found in the systematic review was the lack of knowledge that individuals recently diagnosed with CD had with their disease and the composition of a GFD. Although this is also an individual barrier, this is rather a systematic issue. At a system level, this lack of knowledge stems from patient-practitioner communication, which may inadequately equip individuals with CD with the educational tools and resources. Several studies showed that providing recently diagnosed patients with detailed descriptions of what CD was and what a GFD entailed, correlated to them being more likely to be able to accurately follow a GFD [31,34,37,45,49]. These studies' findings emphasise that there need to be proper communication channels open with a patient once they are diagnosed, to ensure that they entirely are aware of the extent of their disease and that they know how to handle their diet correctly.

Table 4 Barriers to gluten-free diet (GFD) adherence

Study	Individual barriers	Interpersonal barriers	Organisational barriers	Community barriers	Systems barriers
Twist & Hackett [46]	–	Participants shared that relatives forcing foods limited their ability to adhere to a GFD	Participants shared that the lack of availability of GF products lowered their ability to adhere to a GFD	Participants shared that relatives forcing foods limited their ability to adhere to a GFD (cultural impact)	Participants shared that their dietary adherence was lowered as a result of doctors being unwilling to prescribe GF products, as well as having problems with the large chemist responsible for prescriptions
Lamontagne *et al.* [37]	This study shows a correlation between worrying over planning and cooking GF meals and a lower ability to follow a GFD ($P < 0.005$)	–	–	This study showed a correlation between living in a large region of residence and having a lower ability to adhere to a GFD ($P < 0.02$)	–
Ciacci, Iavarone, Siniscalchi, Romano & Rosa (2002) [23]	A correlation was shown between a patient with CD reporting being angry and them having a lower ability to follow a GFD ($P = 0.0005$)	–	–	–	–
Ciacci *et al.* (2003) [51]	Individuals reported that having anger towards CD, not wanting to be different than others and believing the occasional consumption of gluten was okay lowered their ability to adhere to a GFD	Embarrassment of CD was shown to have a strong correlation to being unable to adhere to a GFD ($P = 0.0001$)	Participants showed that dining at restaurants lowered their adherence levels to a GFD	–	–
Hogberg, Grodzinsky & Stenhammar [52]	–	–	–	–	This study presented showed a significant relationship between being diagnosed after the age of 4 and having lower GFD adherence levels ($P = 0.021$)
Butterworth *et al.* [45]	–	–	–	The study highlighted that being of a South Asian background, lowered the ability to follow a GFD ($P = 0.04$)	–
Zarkadas *et al.* (2006) [41]	–	This study highlights that participants find that dining outside home limited their ability to maintain a GFD	This study highlights that participants find that dining outside home limited their ability to maintain a GFD	–	This study highlights that patients find Hospital stays lower their GFD adherence

Table 4 Continued

Study	Individual barriers	Interpersonal barriers	Organisational barriers	Community barriers	Systems barriers
Hauser, Stallmach, Caspary & Stein [20]	This study showed a correlation between a Reduced Health related quality of life score and having a lower likelihood to follow a GFD ($P = 0.01$)	This study showed a correlation between a Reduced Health related quality of life score and having a lower likelihood to follow a GFD ($P = 0.01$)	This study showed a correlation between a Reduced Health related quality of life score and having a lower likelihood to follow a GFD ($P = 0.01$)	This study showed a correlation between a Reduced Health related quality of life score and having a lower likelihood to follow a GFD ($P = 0.01$)	This study showed a correlation between a Reduced Health related quality of life score and having a lower likelihood to follow a GFD ($P = 0.01$)
Hopman, Koopman, Wit & Mearin [53]	This study reported that individuals were less likely to follow a GFD when they had no symptoms when ingesting gluten, as well as if they were diagnosed with CD at a younger age	–	–	–	This study reported that GFD adherence was negatively impacted by poor medical advice (statements that CD was cured)
Smith [42]	Participants shared reasons as to why they did not adhere to a GFD. This included the dislike of the taste of GF foods	Participants found that problems outside the home, including social events/potluck dinners contributed to non-adherence to a GFD	Participants in this study shared that dining at restaurants and the high cost of GF foods impacted their ability to adhere to a GFD	Participants shared that whenever they traveled, their ability to adhere to a GFD was lowered.	–
Barratt, Leeds & Sanders [18]	Reductions in QOL paired with risk of anxiety and depression were correlated with a lower level of GFD adherence ($p < 0.001$)	Individuals reported that eating out, personal relationships, home environment, and socialising lowered their ability to adhere to a GFD	Individuals reported that eating out and an individual's workplace environment lowered their ability to adhere to a GFD	Individuals reported that traveling lowered their ability to adhere to a GFD	–
Black & Orfila [24]	Individuals reported that a lack of care, as well as lacking knowledge of GF options lowered their ability to follow a GFD;	Individuals reported that dining of outside home lowered their ability to adhere to a GFD	Individuals reported that specifically, dining at restaurants lowered their ability to adhere to a GFD	–	–
Sainsbury & Mullan (2011) [38]	Participants shared that overly trusting non-coeliac individuals with their food preparation lowered an individual's ability to follow a GFD	–	–	–	–

Table 4 Continued

Study	Individual barriers	Interpersonal barriers	Organisational barriers	Community barriers	Systems barriers
Biagi *et al.* [36]	A questionnaire that asked specific questions about an individual with CD was linked to not adhering to a GFD. The questions included: 1. Not informing cook about allergy, 2. Not checking labels. 3. Eat packaged food not certified by Celiac Association, 4. Desire to taste gluten-containing food. ($P = 0.001$)	–	–	–	–
Casella *et al.* [54]	–	–	–	–	–
Ford, Howard & Oyebode [22]	This study reported a correlation between having a Low self-efficacy rating and lower adherence to a GFD ($P = 0.04$)	–	–	–	–
Lee, Ng, Diamond, Ciaccio & Green [43]	Individuals in the study stated that finding a GFD Difficult to follow, and finding GF foods Tasteless lowered their adherence to a GFD	Several interpersonal factors limited participant's ability to maintain a GFD. These included: Social activities, spending time with friends, and being uncomfortable in social settings	Dining at Restaurants and finding a GFD too expensive were highlighted as barriers to a GFD. A correlation was also shown between finding a GFD too restrictive and low adherence to a GFD ($P = 0.01$)		Participants in this study reported that their dietary adherence was lowered as a result of not learning about CD from physicians
Ukkola *et al.* [25]	Lack of knowledge on GF foods was highlighted by participants that lowered their likelihood of following a GFD	–	Participants helped highlight that the poor labelling of GF products and difficulties in identifying GF food when dining out lowered their ability to adhere to a GFD	–	At a systems level, Lack of knowledge of CD and a GFD, as well as poor labelling of GF products decrease the ability to adhere to a GFD

Table 4 Continued

Study	Individual barriers	Interpersonal barriers	Organisational barriers	Community barriers	Systems barriers
Hall, Rubin & Charnock [19]	This study shows a correlation between people who believe they have a Perceived tolerance to gluten and lower GFD adherence ($P < 0.001$) Another correlation was found between having a Low Self-efficacy score and having a lower adherence level to a GFD ($P < 0.01$) A third correlation was shown between an individual having low intention with following a GFD, and actively following a GFD ($P < 0.001$)	–	–	–	–
Mahadev *et al.* [55]	–	–	–	–	–
Sainsbury, Mullan & Sharpe (2013) [56]	This study showed a correlation between depression and a lower ability to adhere to a GFD ($P < 0.01$) If an individual was at-risk for an eating risk disorder, a correlation showed they were also less likely to adhere to a GFD ($P < 0.05$)	–	–	–	–
Sainsbury, Mullan & Sharpe (2013) [29]	–	–	–	–	–
Verrill, Zhang & Kane [39]	This study showed that a greater consumption of packaged, processed foods was associated with participants being less likely to adhere to a GFD	–	This study showed that a greater consumption of packaged, processed foods was associated with participants being less likely to adhere to a GFD	–	–
Zarkadas *et al.* (2013) [49]	–	–	–	–	–

Table 4 Continued

Study	Individual barriers	Interpersonal barriers	Organisational barriers	Community barriers	Systems barriers
Dowd *et al*. (2014) [34]	Individuals who had a belief in being less sensitive, the desire to taste gluten-containing foods, the desire to travel, and being exposed to alcohol, reported having a lower adherence level to a GFD	–	This study highlighted organisational factors that limited adherence to a GFD. These include: Dining at restaurants, GF foods being too expensive and cross-contamination risks	The study highlighted that travelling lowered individual's ability to adhere to a GFD	–
Rose & Howard [44]	This study shared participants views that those who did not have visible symptoms, were less likely to adhere to a GFD.	Participants found that the ignorance of others limited their ability to maintain a GFD	Participants shared that the Ignorance of others and the lack of GF options impacted their ability to maintain a GFD	–	–
Shah *et al*. [35]	This study displayed several correlations that were linked with lower adherence to a GFD These included: Having an income less than $200,000 ($P = 0.047$), being unemployed ($P = 0.05$), having increased severity of CD symptoms ($P < 0.001$), having a lower perceived importance of treatment ($P < 0.001$) And having a greater treatment burden score ($P < 0.001$)	–	–	–	Having a lower perceived importance of treatment was correlated with a lower level of adherence to a GFD ($P < 0.001$)
Casellas *et al*. [21]	–	–	–	–	–
Ferster, Obuchowicz, Jarecka, Pietrzak & Karczewska [47]	–	–	This study showed various factors that participants found limited their ability to adhere to a GFD. These include: Inadequate food labelling, and cross-contamination risks from mass catering establishments	This study highlighted that travelling (both within the country and international) were linked as factors that lowered the ability for an adult with CD to adhere to a GFD	This study highlighted that Inadequate food labelling, having no governmental reimbursement plan and having limited access to nutritionist's advice lowered their ability to adhere to a GFD
Kothe, Sainsbury, Smith & Mullan [30]	–	–	–	–	–

Table 4 Continued

Study	Individual barriers	Interpersonal barriers	Organisational barriers	Community barriers	Systems barriers
Rajpoot *et al.* [26]	Individuals in this study reported that their lack of understanding of gluten and CD, and issues with their regular eating habits, lowered their ability to follow a GFD	–	Individuals in this study reported that the lack of availability of GF products and high costs of GF foods lowered their ability to adhere to a GFD	Participants stated that travelling, set eating habits, as well as social/cultural factors negatively impacted their ability to adhere to a GFD	Individuals in this study reported that their lack of understanding of gluten and CD initiating from poor communication with physicians lowered their ability to adhere to a GFD
Sainsbury, Mullan & Sharpe (2015) [57]	–	–	–	–	–
Villafuerte-Galvez *et al.* [31]	–	–	This study showed a clear link between participants finding the Cost of a GFD being high and their likelihood of not following a GFD ($P < 0.0001$)	–	–
Dowd, Jung, Chen & Beauchamp (2016) [32]	–	–	–	–	–
Silvester, Weiten, Graff, Walker & Duerksen (2016) [27]	This study showed a clear link between the lack of knowledge of gluten-containing foods and not being able to adhere to a GFD. Every single participant was unaware of all gluten-containing products	–	–	–	This study showed a clear link between the lack of knowledge of gluten-containing foods and not being able to adhere to a GFD. Every single participant was unaware of all gluten-containing products
Silvester, Weiten, Graff, Walker & Duerksen (2016) [40]	–	–	–	–	–
Ramirez-Cervantes, Romero-Lopez, Nunez-Alvarez & Uscanga-Dominguez [28]	This study explained that participants low intention with following a strict diet and having lower knowledge on CD decreased their ability to follow a GFD	–	–	This study showed that cultural differences decreased participants' abilities to adhere to a GFD	–
Dowd & Jung (2017) [33]	–	–	–	–	–
Hughey *et al.* [50]	–	–	–	–	–

Table 4 Continued

Study	Individual barriers	Interpersonal barriers	Organisational barriers	Community barriers	Systems barriers
Muhammad, Reeves, Ishaq, Mayberry & Jeanes [48]	The study reported a decrease in ability to follow a GFD for south Asian patients compared to Caucasian patients. A correlation was found between an individual finding unpleasant taste when it comes to GF foods and their adherence to a GFD ($P = 0.028$)	–	This study reported that poor food labelling was correlated with a lower ability to adhere to a GFD ($P < 0.001$)	The study reported a decrease in ability to follow a GFD for south Asian patients compared to Caucasian patients.	This study reported that poor food labelling was correlated with a lower ability to adhere to a GFD ($P < 0.001$).

This systematic review found that many individuals are left to manage their disease on their own without support. This lack of communication continues post-diagnosis. Studies have shown that when adults with CD are looking for aid from a practitioner, they are not always readily available, leading to lower adherence rates to a GFD [47]. Many studies also reported on the benefit of consistent follow-up with practitioners, post-diagnosis [19,41,45,50]. Specifically, correlations existed that showed that, when individuals had constant follow-up appointments with their physicians, they were more likely to continue adhering to a strict GFD [19,41,45,50].

Last, finance can impact multiple layers in an adult's life. Hence, lack of financial reimbursement to support individuals with CD acts as a barrier, at the system level, to adhering to a GFD. While certain individuals had access to reimbursement plans to help offset the high costs of GF foods, it was reported that the lack of adequate reimbursement provided by the government lowered their ability to follow a GFD [46-47]. Studies reported correlations between the supply of prescription foods, and an improved ability to maintain a GFD [19,48]. Individuals who receive these subsidies do not need to worry about finding safe foods.

Discussion

Systematic reviews provide the highest level of evidence on a particular topic. This systematic review critically appraised and synthesised evidence from primary studies, which investigated the facilitators and barriers that influence dietary adherence for adults with CD. Several empirical studies in the literature have analysed the factors that influence an individual's adherence to a GFD. However, limited information was available to date on the evidence on the impacts that these factors may have in relation to GFD adherence. In light of the adverse events that may result from poor adherence to GFD, and the potential social and financial impacts at the individual and system level, it is of utmost importance to understand what changes and improvements can be made to facilitate GFD adherence. Hence, the results of this review present relevant information that can inform changes at the policy and practice levels. To provide practical solutions to policymakers in the healthcare system regarding the lives of adults with CD, a clear understanding of their day-to-day lifestyle is needed. Fully understanding the lifestyle of adults with CD can potentially improve dietary adherence, and as a result, improve the health of individuals with CD.

At the individual level, *knowledge of CD/GFD* was the most significant factor identified in the literature. It was reported in eight studies as a facilitator, and 14 studies

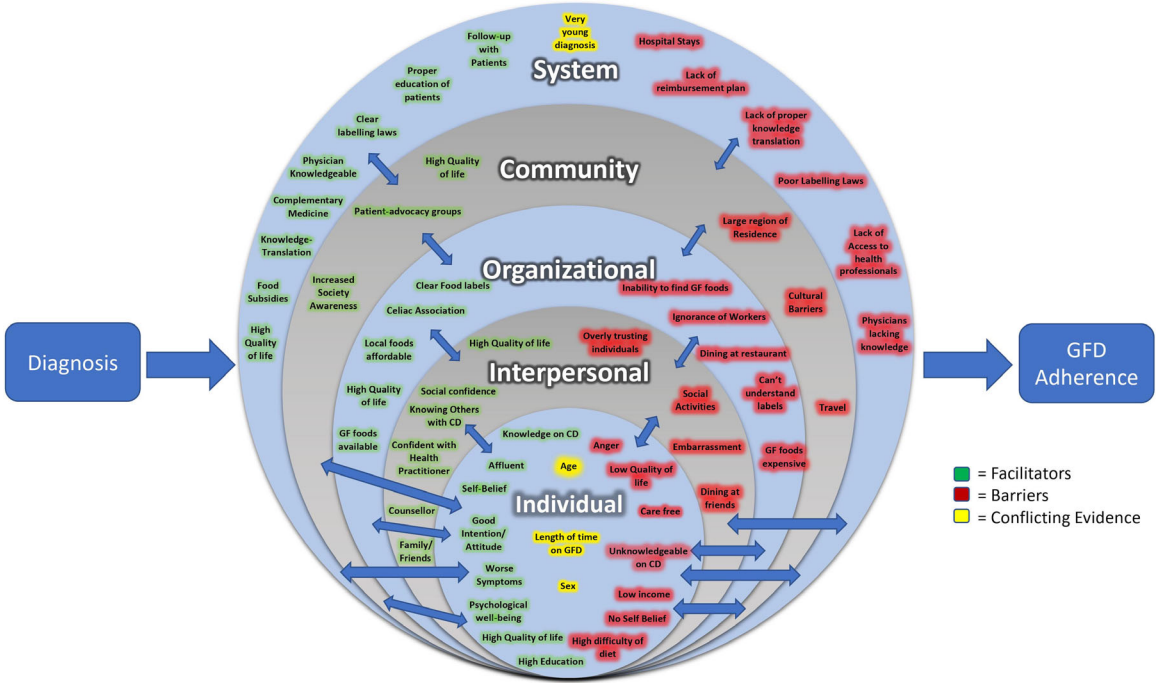

Figure 2 Social ecological model. CD, coeliac diet; GFD, gluten-free diet..

indicated lack of knowledge of CD/GFD as a barrier. The designs of the studies varied greatly; some studies had strong designs, and others presented the results of descriptive studies that employed rigorous methodologies.

At the interpersonal level, *social support* was the most significant facilitator reported in four studies. All of these studies had analytical designs. On the other hand, the most significant barrier presented at the interpersonal level was *social fear*. Although other interpersonal barriers such as *social activities* were discussed by a higher number of studies, as compared to *social fear*, the strength of the designs and methodologies that reported significant effect of social fear was higher, which is an indication of its significance.

At the organisational/environmental level, *membership in a coeliac association* was the most significant facilitator, reported by five studies, which varied in the rigor of their study designs. On the other hand, *restaurant dining and supermarket shopping* were the most significant reported barriers, with twelve studies presenting evidence on their impacts on adherence to GFD. Despite the variation in the LOE in this group of twelve studies, it is worth noting that several of these studies were conducted in Canada, and presented very rigorous methodologies.

At the community level, *high society awareness* was the most significant facilitator, which was reported in three studies, despite the limitations of their study weak designs. Cultural factors were the most significant barriers at the community level, with five studies (analytical and descriptive) referring to them as important barriers to adhering to a GFD. From our analysis, it was clear that the study of and reporting on facilitators and barriers at the community level was very limited.

Last, at the systems level, *patient education/ physician–patient communication* was the most significant factor reported. Ten studies reported that improved patient education from physician to patient was a facilitator to GFD adherence and seven studies reported that poor patient education/lack of physician–patient communication was a barrier to GFD adherence. These studies varied in their designs and LOE, with one randomised clinical trial and remaining descriptive studies; several studies were presenting findings in the Canadian context.

Overall, the relatively low LOE in the empirical studies found in the literature calls for more carefully designed studies that employ more rigorous methodologies. It is important to also acknowledge the limitations associated with this review. In the coding and data extraction from the empirical studies, there was reliance on the information presented by the authors of the included studies, which may have not always been complete or detailed. Furthermore, we had to make an assumption that the diagnosis of CD for the individuals in the studies was conducted through a valid process; either a serological test or an upper-intestinal endoscopy.

Understanding the existing barriers to GFD adherence is the first step towards planning interventions that may provide decision-makers with knowledge on where to

target aid and future research, and practitioners with examples of how to improve adherence. In this systematic review, we organised the facilitators and barriers to GFD adherence among adults with CD into a SEM that helps portray a clear picture of what an adult with CD faces following diagnosis. Targeted, future research on specific facilitators and barriers highlighted in this systematic review is recommended to provide additional evidence and support. Examples include, amongst others, conducting an empirical study that examines the impact of implementing a program that increases patient education; evaluating healthcare providers' extent of knowledge of CD and the impact of improving the knowledge levels of CD/GFD on the GFD adherence rates among adults with CD; assessing the impact of financial compensation and label-laws at the system level. We call for system-level interventions addressing the main factors identified in this review to address the challenges faced by adults with CD, improve their health and alleviate the pressure on the health system. Facilitators and barriers presented in this systematic review also potentially impact individuals who are facing dietary restrictions as a result of other chronic illnesses in their lives. Hence, the importance and necessity of understanding these factors to support the care of individuals living with these conditions and enabling a better quality of life for them.

Transparency declaration

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

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Conflict of interests, source of funding, and authorship

The authors declare that they have no conflicts of interest.
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All of the authors made substantial contributions to the conception and design of the study, or acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be submitted. In particular, Nicholas Abu-Janb developed the concept for the systematic review, drafted the initial article, oversaw all data collection and analysis, developed the initial interpretation of the findings, and approved the final version submitted for publication. Mirou Jaana revised the initial article, refined the coding scheme, analysed the data and refined the interpretation, and approved the final version submitted for publication.

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Appendix A

Search Strategy

1 Coeliac Disease/
2 coeliac disease.tw,kw.
3 cooeliac disease.tw,kw.
4 coeliac.tw,kw.
5 cooeliac.tw,kw.
6 gluten sensitive entero*.tw,kw.
7 1 or 2 or 3 or 4 or 5 or 6
8 Patient Compliance/
9 patient compliance.tw,kw.
10 adher*.tw,kw.
11 nonadher*.tw,kw.
12 maint*.tw,kw.
13 compliance.tw,kw.
14 noncompliance.tw,kw.
15 coopera*.tw,kw.
16 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 17. Diet, Gluten-Free/
17 gluten free diet.tw,kw.
18 Diet/
19 treatment.tw,kw.
20 gluten.tw,kw.
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Perceived dietary salt intake and the risk of primary liver cancer: a population-based prospective study

M. Sun,[1,2,*] H. Cui,[1,2,*] M. Liang,[1,2] W. Wang,[2] Y. Wang,[2] X. Liu,[2] S. Liu[2] & L. Cao[2]

[1]Department of Graduate School, North China University of Science and Technology, Tangshan, Hebei, China
[2]Department of Hepatobiliary Surgery, Kailuan General Hospital Affiliated to North China University of Science and Technology, Tangshan, Hebei, China

Keywords
incidence, perceived salt intake, primary liver cancer, prospective cohort, risk.

Correspondence
Siqing Liu and Liying Cao, Department of Hepatobiliary Surgery, Kailuan General Hospital Affiliated to North China University of Science and Technology, Tangshan, Hebei 063000, China.
E-mails: siqingliu@163.com; caoliying@kailuan.com.cn

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Abstract

Background: Although a high-salt diet is associated with high risk of chronic diseases such as hypertension, stroke and cardiovascular disease, little is known about the relationship between a high-salt diet and the risk of primary liver cancer (PLC). Consequently, we prospectively assessed the association of high perceived salt intake with the risk of PLC in the Kailuan Study.

Methods: In total, 97 006 participants who were healthy adults or free living adults at the baseline (2006) were included in the present study. The data of perceived salt intake were collected via questionnaire and classified into three categories: <6 g day^{-1} for low salt intake, 6–10 g day^{-1} for intermediate salt intake, >10 g day^{-1} for high-salt intake. PLC including hepatocellular carcinoma and intrahepatic cholangiocarcinoma (excluding liver metastasis), and was confirmed by review of medical records. We used a Cox proportional hazards model to analyse the association between high perceived salt diet and the risk of PLC after adjusting for possible confounders, including age, gender, body mass index, high sensitivity-C-reactive protein, low-density lipoprotein-cholesterol, total cholesterol, triglycerides, alanine aminotransferase, HbsAg positive, cirrhosis, fatty liver, hypertension, diabetes, drinking status, smoking status and physical exercise.

Results: During the follow-up period of 1 113 816 person-years, 397 PLC events were diagnosed. After adjusting for most potential confounders, subjects in intermediate salt intake and high salt intake had a multivariable hazard ratio and 95% confidence interval of 1.49 (0.97–2.29) and 1.98 (1.22–3.22) (P for trend = 0.0042), respectively, compared to low salt intake.

Conclusions: A higher perceived salt intake was associated with a higher risk of PLC.

Introduction

Worldwide, primary liver cancer (PLC) is a heavy burden of disease that affects human public health. Based on the latest data of the International Agency for Research on Cancer in 2018, primary liver cancer has become the sixth most common cancer and the fourth leading cause of cancer death worldwide [(1)]. Over the past decade, the age-standardised incidence of PLC had increased from 8.1 per 100 000 person-years [(2)] to 13.9 per 100 000 person-years [(1)] worldwide. The incidence of PLC is the highest in Asia and Africa, at approximately 85%. Furthermore, the incidence of PLC registries in China has been reported at over 50% [(3–5)]. To the best of our knowledge, ageing [(6)], male [(7)], obesity [(8)], fasting blood glucose [(9)], hepatitis B virus and hepatitis C virus infection [(10)] are well-established risk factors for the development of PLC, and research on other potential risk factors for PLC is still in progress.

High salt consumption has become a common phenomenon in the modern world, especially in Asia

(Central Asia, Asia Pacific High Income and East Asia) [19]. Previous studies have confirmed that high-salt diet plays a significant role in the pathogenesis of many chronic diseases (such as hypertension, stroke and cardiovascular disease) [11–13]. Recently, a case–control study from France showed that high sodium intake is a risk factor for hepatocellular carcinoma (HCC) [14]. In addition, Ma *et al.* [15] found that low sodium diet is associated with decreased risk of HCC but non-significant based on the Heath professionals Follow-up Study (HPFS) and the Nurses' Heath Study (NHS) from America. In our previous studies, although it had been indicated that high salt intake is associated with nonalcoholic fatty liver [16], the relationship between high salt intake and the risk of PLC had not been explored further and remains unclear. So far, few studies have reported the relationship between high salt intake and the risk of PLC. Therefore, based on the Kailuan Study (Trial registration number: ChiCTR-TNRC-11001489), the present study aims to analyse the relationship between high perceived salt intake and the risk of primary liver cancer.

Materials and methods

Study design and participants

As reported elsewhere [17,18], the Kailuan Study is a prospective cohort study based on Kailuan community population, and is owned and managed by Kailuan Group in Tangshan city, Hebei Province, north of China. From 2006 onward, the Kailuan Group has invited working (≥ 18 years old) and retired staffs (mainly referring to former staff from Kailuan Group) to participate in the physical examination every two years, which is carried out in 11 hospitals affiliated to Kailuan Group. Between July 2006 and October 2007, a total of 101 510 participants attended the first physical examination. All participants were administered questionnaires and underwent clinical and laboratory examination, and these data provided an opportunity to research the risk factors for chronic diseases.

In the present study, we excluded 378 participants who had liver cancer and a history of malignant tumors before the first health examination, and also excluded 4126 subjects with missing information of perceived salt intake. Finally, a total of 97 006 individuals included in the current analyses (Fig. 1).

Ethical approval

The study was approved by Ethics Committee of Kailuan General Hospital, and it was in compliance with the Declaration of Helsinki. Informed consent was obtained from the participants.

Assessment of perceived salt intake

The information of perceived salt intake is mainly obtained by self-report, as previously described [12,16]. Briefly, perceived salt intake was assessed by asking participants in the face-to-face questionnaire survey to rate their habitual daily salt intake as low, medium or high, which was estimated approximately (Appendix 1). According to the salt consumption of the participants, we divided them into three levels: low salt intake, intermediate salt intake and high salt intake. <6 g day^{-1} (<2400 mg day^{-1} sodium intake) for low salt intake, 6–10 g day^{-1} (2400–4000 mg day^{-1} sodium intake) for intermediate salt intake, and >10 g day^{-1} (>4000 mg day^{-1} sodium intake) for high salt intake. Low salt intake (<6 g day^{-1}) is greater than the salt intake (<5 g day^{-1}) recommended by the World Health Organization [19], although this classification is more in line with Chinese salt consumption habits. Likewise, the Committee on Medical Aspects of Food and Nutrition Policy (COMA) in the UK recommended that salt intake was 6 g day^{-1}, which would be of demonstrable benefit to the population.

In 2012, we collected random spot urine samples from 231 participants with hypertension, without use of any antihypertensives, based on the Kailuan Study. The average 24-h urinary sodium excretion of the low salt intake group and the high salt intake group were 3745 mg day^{-1} and 3958 mg day^{-1}, respectively ($P < 0.001$), after adjustment for age, sex and blood pressure. This showed that a higher perceived salt intake was significantly associated with higher estimated 24-h urinary sodium excretion [20].

Definition and ascertainment of primary liver cancer

During the period from the first physical examination of participants to 31 December 2018, subjects which diagnosed as hepatocellular carcinoma or intrahepatic cholangiocarcinoma were defined as PLC (excluding liver metastasis). Follow-up began at the first physical examination, and ended at occurrence of cancer, death or on 31 December 2018, whichever event came first. The information of PLC was collected by self-reported questionnaires and clinical examinations. In addition, medical records from the Tangshan medical insurance system and death certificates from Kailuan social security system were checked yearly to obtain PLC information that may have been missed. This part of information is collected by professionally trained staff and CANREG 4.0 software provided by the International Agency for Research on Cancer of the World Health Organization (IARC/WHO) is used to input and logically verify new cases of PLC. According to

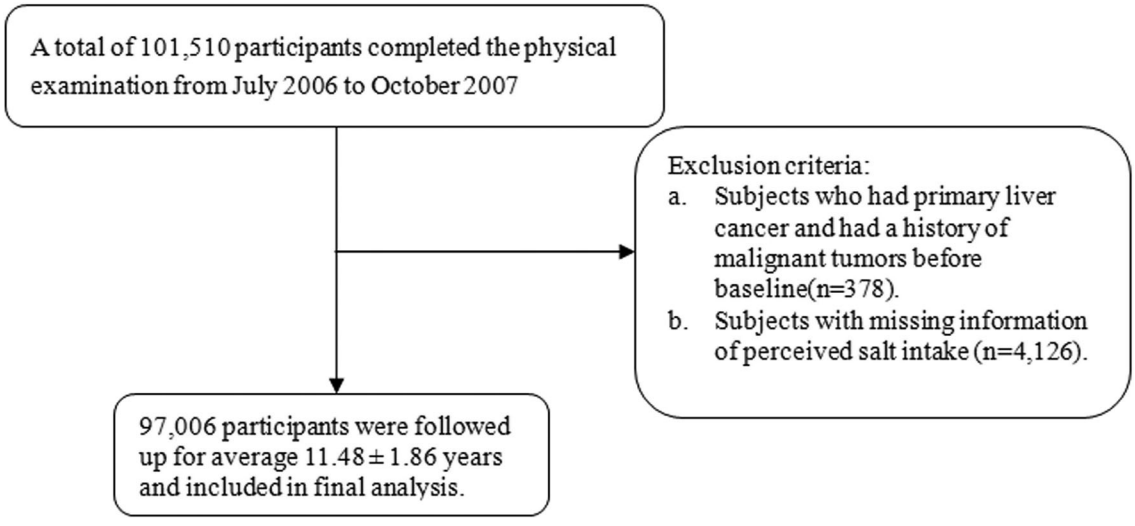


Figure 1 Flow chart of participant screening.

the International Classification of Diseases, Tenth Revision (ICD-10), PLC is defined as C22 [21].

Assessment of other relevant variables

In 2006, our questionnaire included about 83 items and they were all open questions. The content of the questionnaire includes: age, gender, smoking habits, drinking status, physical activity, past medical history (eg, hypertension, diabetes mellitus, malignant tumors, etc.), etc [22,23]. On the day of physical examination, trained medical and nursing personnel assisted the participants with completing the questionnaires together via face-to-face interviews to ensure the authenticity and accuracy of the results. Height and weight were measured by professionally trained staff. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m^2). Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, or using antihypertensive medication. Diabetes was defined as fasting blood glucose (FBG) $\geq$ 7.0 mmol L^{-1} or the use of oral hypoglycemic agent. Smoking was defined as having smoked at least one cigarette per day on average for at least 1 year. Drinking status was defined as having taken 100 mL day^{-1} (alcohol contents > 50%) of a hard liquor for more than 1 year. Physical activity was defined as taking exercise more than four times a week, each time lasting at least 30 min [24]. Fatty liver on ultrasound (US) scanning was diagnosed according to the criteria: diffuse increase of the hepatic echogenicity with evident contrast between the liver and kidney; diffuse increase of the hepatic echogenicity with blurring of the intrahepatic vessels and the diaphragm; or brightness of the hepatic echogenicity with poor penetration of the posterior hepatic segments, with the intrahepatic vessels or the diaphragm being invisible [25,26]. Cirrhosis of the liver was diagnosed according to the criteria: surface nodularity of the liver detected by US; coarsening and nodularity of the liver parenchyma with ascites, splenomegaly, or evident collateral circulation shown on US, or coarsening and nodularity of the liver parenchyma with medical history of variceal haemorrhage [25,26].

High-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), total cholesterol (TC), fasting blood glucose (FBG), high-sensitivity C-reactive protein (hs-CRP) and alanine aminotransferase (ALT) were determined by automatic biochemical analyser (Hitachi 747; Hitachi, Tokyo, Japan). The enzyme-linked immunosorbent assay for HbsAg (Shanghai Kehua Bio-Engineering, Shanghai, China) was applied to detect HbsAg quantitatively. All of the plasma samples were analysed at the central laboratory at Kailuan General Hospital.

Statistical analysis

Quantitative data with normal distribution were expressed as the mean (SD) and one-way analysis of variance was used for multiple comparison between groups. The measurement data with skewed distribution were reported as the median (interquartile range) and the nonparametric Kruskal–Wallis test of variance was used for multiple comparison between groups. Categorical variables were reported as a percentage and compared using the chi-squared test. Incidence rates were calculated by dividing the number of events by person-years of follow-up in each group. The life table method was used to calculate the cumulative incidence of PLC in each group, and a

log-rank test was used to compare the difference of cumulative incidence among each group. A Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for perceived salt intake and the PLC. Three multivariable Cox proportional hazard models were constructed as: (i) Model 1: a univariate analysis; (ii) Model 2: adjusted for age, gender; and (iii) Model 3: further adjusted for BMI, hs-CRP, LDL-C, TC, TG, ALT, HbsAg(+), liver cirrhosis, fatty liver, hypertension, diabetes, drinking, smoking and physical exercise. We also conducted a sensitivity analysis and a subgroup analysis, respectively. In the sensitivity analysis, the participants who occurred PLC within 1 year after entry to the cohort and the lipid-lowering agent users were further excluded, separately. Subgroup analysis was conducted stratified by these potential confounders including age, diabetes, hypertension, BMI, HBsAg status, cirrhosis and fatty liver. Data management and all analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC, USA). $P < 0.05$ (two-sided) was considered statistically significant.

Results

The mean (SD) age of 97 006 participants was 51.44 (12.48) years; 77 323 (79.71%) were male and 19 683 (20.29%) were female. Table 1 shows the baseline characteristics of participants by different perceived salt intake groups. Excluding being HBsAg positive and cirrhosis, there were statistically significant differences in sex (male), age, BMI, HDL-C, LDL-C, FBG, hs-CRP, TG, TC, ALT, fatty liver, hypertension, diabetes, drinking, smoking and physical exercise among the subjects in different perceived salt intake groups ($P < 0.05$).

The incidence and risk for primary liver cancer with different perceived salt intake

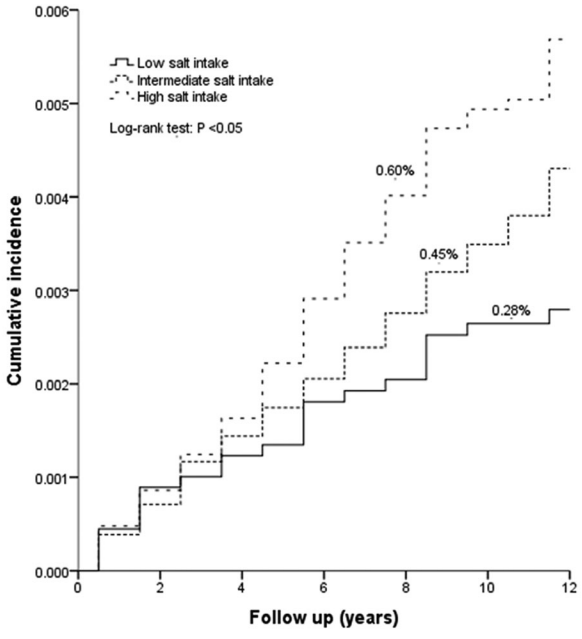
During the follow-up period of 1 113 816 person-years [mean (SD) 11.48 (1.86) years], 397 patients were diagnosed PLC, with an incidence of 0.36 per 1000 person-years. The follow-up rate of PLC was approximately 100%. The incidence of low salt intake, intermediate salt intake and high salt intake for PLC was 0.18 per 1000 person-years, 0.32 per 1000 person-years and 0.43 per 1000 person-years, respectively. The total cumulative incidence was 0.45%. The cumulative incidence of PLC in each group was 0.28%, 0.45%, 0.60%, respectively. A significant difference of the cumulative incidence was revealed between each group ($\chi^2 = 9.04$, $P < 0.05$) by log-rank test (Fig. 2).

In the univariate Cox proportional hazards model, compared with the low salt intake group, the HR and 95% CI for the intermediate salt intake group and high salt intake group for PLC were 1.53 (1.01–2.31) and

Table 1 Baseline characteristics of the participants by different salt diet

Variables	Low salt intake* (n = 8989)	Intermediate salt intake* (n = 77 532)	High salt intake* (n = 10 485)	F/χ^2	P
Male, n (%)	7163 (79.69%)	61 024 (78.71%)	9136 (87.13%)	$\chi^2 = 405.43$	<0.0001
Age, year	52.21 (12.95)	51.38 (12.41)	51.23 (12.53)	$F = 19.47$	<0.0001
BMI (kg m^{-2})	24.84 (3.41)	25.02 (3.50)	25.40 (3.54)	$F = 69.93$	<0.0001
HDL-C (mmol L^{-1})	1.52 (0.39)	1.56 (0.40)	1.50 (0.38)	$F = 123.38$	<0.0001
LDL-C (mmol L^{-1})	2.52 (0.91)	2.32 (0.87)	2.55 (0.86)	$F = 495.24$	<0.0001
FBG (mmol L^{-1})	5.48 (1.66)	5.47 (1.68)	5.56 (1.71)	$F = 10.92$	<0.0001
hs-CRP (mg L^{-1})	0.80 (0.30–1.93)	0.79 (0.30–2.09)	0.87 (0.36–2.06)	$\chi^2 = 34.81$	<0.0001
TG (mmol L^{-1})	1.25 (0.87–1.90)	1.27 (0.90–1.92)	1.32 (0.89–2.01)	$\chi^2 = 29.03$	<0.0001
TC (mmol L^{-1})	4.98 (1.20)	4.94 (1.15)	5.02 (1.16)	$F = 27.11$	<0.0001
ALT (U L^{-1})	17.00 (12.00–25.00)	18.00 (13.00–24.40)	18.00 (13.00–26.00)	$F = 30.35$	<0.0001
HBsAg Positive, n (%)	250 (2.78)	2134 (2.75)	298 (2.84)	$\chi^2 = 0.29$	0.8665
Cirrhosis, n (%)	29 (0.32)	264 (0.34)	36 (0.34)	$\chi^2 = 0.08$	0.9597
Fatty liver, n (%)	2668 (29.83)	24 387 (31.59)	3629 (34.89)	$\chi^2 = 63.35$	<0.0001
Hypertension, n (%)	3906 (43.45)	34 052 (43.92)	4856 (46.31)	$\chi^2 = 23.34$	<0.0001
Diabetes, n (%)	871 (9.69)	6900 (8.90)	1012 (9.65)	$\chi^2 = 11.21$	0.0037
Drinking status, n (%)	2083 (23.17)	11 940 (15.40)	3351 (31.96)	$\chi^2 = 1909.30$	<0.0001
Smoking status, n (%)	3553 (39.53)	20 771 (26.79)	5624 (53.64)	$\chi^2 = 3467.22$	<0.0001
Physical exercise, n (%)	2713 (30.18)	9631 (12.42)	2790 (26.61)	$\chi^2 = 3011.38$	<0.0001

ALT, alanine aminotransferase; BMI, body mass index; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; hs-CRP, hypersensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol.
*Low salt intake, <6 g day^{-1} (<2400 mg day^{-1} sodium intake); Intermediate salt intake, 6–10 g day^{-1} (2400–4000 mg day^{-1} sodium intake); High salt intake, >10 g day^{-1} (>4000 mg day^{-1} sodium intake).



Number at Risk (cases)							
High salt intake	10451 (9)	10343 (8)	10164 (13)	9925 (11)	9687 (9)	7796 (6)	3007 (1)
Intermediate salt intake	77307 (55)	76523 (56)	75198 (46)	73619 (52)	71935 (53)	56049 (50)	20516 (4)
Low salt intake	8954 (8)	8848 (3)	8690 (5)	8486 (2)	8276 (5)	6768 (1)	2684 (0)

Figure 2 The cumulative incidence curves of primary liver cancer with three different perceived salt intake. Low salt intake, <6 g day^{-1} (<2400 mg day^{-1} sodium intake); Intermediate salt intake, 6–10 g day^{-1} (2400–4000 mg day^{-1} sodium intake); High salt intake, >10 g day^{-1} (>4000 mg day^{-1} sodium intake).

2.03 (1.26–3.28), respectively (P for trend = 0.0026). After adjustment of gender and age, compared with the low salt intake group, the adjusted HR (95% CI) for PLC were 1.58 (1.04–2.39) and 2.00 (1.24–3.23) in the intermediate salt intake group and high salt intake group, respectively (P for trend = 0.0041). Compared with the low salt intake group, the risk of PLC still exists in the high salt group; the multivariable HR (95% CI) is 1.98 (1.22–3.22) (P for trend = 0.0042), after adjustment for gender, age, BMI, hs-CRP, LDL-C, TC, TG, ALT, HBsAg status, cirrhosis, fatty liver, hypertension, diabetes, drinking status, smoking status and physical exercise (Table 2).

Table 2 The hazard ratio (HR) and 95% confidence interval (CI) of perceived salt intake for the risk of primary liver cancer

	Total	Low salt intake*	Intermediate salt intake*	High salt intake*	*P* for trend
Person-year (cases)	1 113 816 (397)	103 154 (24)	890 198 (316)	120 464 (57)	
Incidence, per 1000 person-years	0.36	0.18	0.32	0.43	
Model 1		Ref.	1.53 (1.01–2.31)	2.03 (1.26–3.28)	0.0026
Model 2		Ref.	1.58 (1.04–2.39)	2.00 (1.24–3.23)	0.0041
Model 3		Ref.	1.49 (0.97–2.29)	1.98 (1.22–3.22)	0.0042
Sensitivity analysis					
Excluding participants who were diagnosed with PLC within the first year after entry to the cohort					
Adjusted HR†		Ref.	1.72 (1.06–2.78)	2.36 (1.38–4.04)	0.0011
Excluding lipid-lowering agent users					
Adjusted HR†		Ref.	1.52 (0.98–2.36)	2.01 (1.23–3.31)	0.0042

HR, hazard ratio; CI, confidence interval; PLC, primary liver cancer; Ref, reference.

*Low salt intake, <6 g day^{-1} (<2400 mg day^{-1} sodium intake); Intermediate salt intake, 6–10 g day^{-1} (2400–4000 mg day^{-1} sodium intake); High salt intake, >10 g day^{-1} (>4000 mg day^{-1} sodium intake). Model 1: Univariate analysis. Model 2: Adjusted for age, gender. Model 3: Further adjusted for body mass index (kg m^{-2}), hypersensitive C-reactive protein (mg L^{-1}), low-density lipoprotein cholesterol (mmol L^{-1}), total cholesterol (mmol L^{-1}), triglyceride (mmol L^{-1}), alanine aminotransferase (U L^{-1}), HBsAg (negative/positive), cirrhosis, fatty liver, hypertension, diabetes, drinking status, smoking status and physical exercise (Yes/No for each categorical variable) based on Model 2.

†The adjusted components for HR were the same as those for Model 3.

Sensitivity analysis

After excluding 40 participants who were diagnosed with PLC within the first year after entry to the cohort and excluding 941 lipid-lowering agent users, respectively. The adjusted HR (95% CI) of high salt intake group for PLC was 2.36 (1.38–4.04) and 2.01 (1.23–3.31), respectively, after adjustment for gender, age, BMI, hs-CRP, LDL-C, TC, TG, ALT, HBsAg status, cirrhosis, fatty liver, hypertension, diabetes, drinking status, smoking status and physical exercise (Table 2).

Subgroup analyses showed that there was a significant association between high salt intake and the risk of PLC, especially in subjects aged <60 years, in subjects without diabetes, in subjects with hypertension, in subjects with a BMI < 25, in subjects who were HBsAg positive, or in subjects without cirrhosis or without fatty liver, stratified by age, diabetes, hypertension, BMI, HBsAg status, cirrhosis and fatty liver, respectively (see Supporting information, Fig. S1).

Discussion

Based on the Kailuan study cohort, we found that high salt intake was associated with an increased risk of PLC with a mean (SD) follow-up period of 11.48 (1.86) years.

One of our important findings is that high salt intake was positively associated with the risk of primary liver cancer. After adjusting for potential confounding factors, we observed that the risk of PLC caused by high salt intake was 1.98-fold higher (HR = 1.98; 95% CI = 1.22–3.22) than low salt intake. Meanwhile, Rizk *et al.* [14] found that high sodium intake was associated with the risk of HCC (OR = 2.00; 95% CI: 1.14–3.53) based on the French multicenter CiRCE case–control study ('Cirrhosis and Risk of Hepatocellular Carcinoma in the East'). Additionally, other results from the HPFS (Health Professionals Follow-Up Study) cohort and the NHS (Nurses' Health Study) cohort suggested that a low sodium intake was associated with a non-statistically significant lower risk of HCC (HR = 0.99; 95% CI = 0.89–1.09) based on score models [15]. To our knowledge, this is the first prospective cohort study to directly analyse the relationship between salt intake and the risk of PLC. This reminds us that, in the prevention stage of PLC, obesity, diabetes, hepatitis, liver cirrhosis and other known risk factors of primary liver cancer should be well controlled. Moreover, we should also recognise the importance of salt diet for the risk of PLC.

Tran *et al.* [27] found that taking lipid-lowering agent was associated with the risk of liver cancer. Therefore, to further eliminate the interference of potential confounders on the results, sensitivity analysis and subgroup analysis were conducted, respectively. After excluding lipid-lowering agent users, it was found that this result did not change. The well-accepted view is chronic liver diseases (hepatitis, cirrhosis, fatty liver, etc.) were strongly associated with the risk of primary liver cancer [28]. To avoid the influence of chronic liver diseases on the results of the study, subgroup analyses were conducted. Similarly, after adjusting for potential confounding factors, it was found that the significant association between high-salt diet and the risk of PLC still existed in subjects with age <60 years, without diabetes, with hypertension, with BMI <25, being HBsAg positive, without cirrhosis and without fatty liver, respectively.

The underlying mechanisms by which high salt intake increased the risk of liver cancer remain uncertain. High salt intake may play an important aetiological role in obesity [29], insulin resistance and nonalcoholic fatty liver disease [15], which were important predisposing factors for liver cancer [30,31]. Dmitrieva *et al.* [32] considered that high sodium chloride (NaCl) was assumed to be genotoxic as high sodium chloride (NaCl) exposure could damage DNA and impair its repair, thus inducing the growth of tumor cells. Additionally, macrophages, which are an important part of inflammation, play a pivotal role in tumor microenvironment, whereas high salt intake was recently reported to worsen autoimmune diseases via specific activation of macrophages, as well as pro-inflammatory cytokines. It is also closely related to the occurrence and development of tumor cells [33,34]. Indeed, high-salt diets also include the consumption of processed foods such as ham and pickled vegetables, etc., which are rich in sodium nitrite ($NaNO_2$). It had been reported that hepatotoxicity induced by $NaNO_2$ was associated with mitochondrial injury and oxidative stress in rat isolated hepatocytes, this further promoting the occurrence and development of liver cancer [35].

The present study has several strengths. The most important strength is that this is a large-scale community-based prospective cohort study, with a good number of primary liver cancer cases. Second, the information of PLC was obtained from comprehensive health system, including medical records, death certificates and health insurance in Tangshan, China, with an approximately 100% follow-up rate and reduced recall bias. Until 2018, a total of 474 subjects were diagnosed with PLC in the Kailuan community population. Moreover, our study fully considered the influence of potential factors, including age, gender, BMI, hs-CRP, LDL-C, TC, TG, hypertension, diabetes, drinking status, smoking status and physical exercise, especially ALT, HBsAg status, cirrhosis and fatty liver.

Certainly, several limitations should also be noted. First, the most important limitation is that the information of salt diet in this study is obtained via self-report, which is not as representative as 24-h urinary sodium excretion for estimating daily salt intake. However, the positive correlation between high perceived salt intake and 24-h urinary sodium excretion has been confirmed in previous studies [12,20]. Second, the present study lacked detailed information on dietary intake and did not adjust for potential dietary confounding factors (such as total energy, total fat intake, etc.). The participants with high salt intake habits may consume more processed foods and none of these have been controlled for. The discovered relationship between high salt intake and the risk of developing PLC could also be affected by dietary pattern. Third, the follow-up time of the study was relatively short, and case numbers of PLC were relatively small, especially in the subgroup analysis. Fourth, using one time point to define the dietary salt intake could be a defect. This is because the habits of dietary salt intake may change over time. Thus, it is necessary to build a time-varying covariate model to make up this deficiency in future work. Finally, the subtype of PLC included hepatocellular carcinoma and intrahepatic cholangiocarcinoma. We did not further explore the relationship between these and salt intake, respectively.

In conclusion, the results of the present study show that a high salt intake was positively associated with the risk of PLC. A high salt intake is related not only to cardiovascular and cerebrovascular diseases [12,13], but also to the development of PLC. Therefore, advocating a low salt diet was advantageous for decreasing the risk of chronic diseases, and providing new directions and ideas for the prevention and control of PLC in the future.

Transparency declaration

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

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
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MS and SL conceived and designed the work. WW, YW and XL performed the data acquisition. MS, HC and YW analysed the data. MS and ML wrote the paper. MS, SL and LC reviewed the manuscript. All authors have critically reviewed the manuscript and approved the final version submitted for publication.

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Appendix 1

Information about dietary salt intake from baseline questionnaire; Kailuan Study 2006–2007.

How about your regular salt consumption in a regular day?	
☐ light taste	[low salt intake, <6 g day^{-1} (<2400 mg day^{-1} sodium intake)]
☐ medium taste	[intermediate salt intake, 6 to 10 g day^{-1} (2400–4000 mg day^{-1} sodium intake)]
☐ heavy salty taste	[high salt intake, >10 g day^{-1} (>4000 mg day^{-1} sodium intake)]

The cut-offs of the three different salt intakes are based on the population in northern China and were estimated approximately according to a standard salt spoon.

Supporting information

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

Figure S1. The adjusted hazard ratios (HR) and 95% confidence interval (CI) of perceived salt intake for the risk of primary liver cancer (PLC), stratified by (A) age, diabetes, hypertension and body mass index (BMI) and (B) HBsAg status, cirrhosis and fatty liver. The subgroup analyses were adjusted for age, BMI, hypersensitive C-reactive protein, low-density lipoprotein cholesterol, total cholesterol, triglyceride, alanine aminotransferase, HBsAg positive, cirrhosis, fatty liver, hypertension, diabetes, drinking status, smoking status and physical exercise. Ref, reference.

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Beliefs about inevitable decline among home-living older adults at risk of malnutrition: a qualitative study

L. Payne[1] P. Harris,[1] D. Ghio,[2] J. Slodkowska-Barabasz,[1] M. Sutcliffe,[3] J. Kelly,[2] M. Stroud,[4] P. Little,[2] L. Yardley[1,5] & L. Morrison[1,2]

[1]Centre for Clinical and Community Applications of Health Psychology, University of Southampton, Southampton, UK
[2]School of Primary Care, Population Sciences and Medical Education, Aldermoor Health Centre, University of Southampton, Southampton, UK
[3]Dietetics Department, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[4]Department of Gastroenterology, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[5]School of Psychological Science, University of Bristol, Bristol, UK

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eating patterns, intervention development, malnutrition, older adults, person-based approach, qualitative research.

Correspondence
L. Payne, Centre for Clinical and Community Applications of Health Psychology, University of Southampton, 44/3065, Highfield, Southampton, SO17 1BJ, UK.
Tel.: +44 023 8059 9732
E-mail: e.a.payne@soton.ac.uk

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Abstract

Background: Approximately 14% of free-living adults aged ≥65 years are at risk of malnutrition. Malnutrition screen and treat interventions in primary care are few, show mixed results, and the advice given is not always accepted and followed. We need to better understand the experiences and contexts of older adults when aiming to develop interventions that are engaging, optimally persuasive and relevant.
Methods: Using the Person-based Approach, we carried out 23 semi-structured interviews with purposively selected adults ≥65 years with chronic health or social conditions associated with malnutrition risk. Thematic analysis informed the development of key principles to guide planned intervention development.
Results: We found that individuals' beliefs about an inevitable decline in appetite and eating in older age compound the many and varied physical and physiological barriers that they experience. Also, we found that expectations of decline in appetite and physical ability may encourage resignation, reduce self-efficacy to overcome barriers, and reduce motivation to address weight loss and/or recognise it as an issue that needs to be addressed. Fear of loss of independence may also reduce the likelihood of asking general practitioners for advice.
Conclusions: The key findings identified include a sense of resignation, multiple different barriers to eating and a need for independence, each underpinned by the expectation of a decline in older adulthood. Interventions need to address misperceptions about the inevitability of decline, highlight how and why diet recommendations are somewhat different from recommendations for the general population, and suggest easy ways to increase food intake that address common barriers.

Introduction

Malnutrition in older adulthood is a global issue, although contextual differences between countries will impact on how malnutrition can best be addressed in each country. In the UK, 1.3 million (11%) of adults aged ≥65 years are considered to be malnourished, rising to 18% for those receiving home or day care [(1–3)]. Global Leadership Initiative on Malnutrition (GLIM) diagnostic criteria for malnutrition include: non-volitional weight loss, low body mass or muscle strength; plus reduced food intake or assimilation, disease burden or inflammation [(4)]. Malnutrition risk, measured by, for example, the Malnutrition Universal Screening Tool (MUST) [(5)] or

Mini-Nutritional Assessment (MNA) [6], is associated with frailty, sarcopenia, falls [7–9], general practioner (GP) consultations, hospitalisation [10] and reduced quality of life [11]. Malnutrition among older adults in the UK was associated with excess costs of £10 billion in 2011–2012, mostly for institutional care or hospitalisation, and so early identification of risk, and treatment for free-living adults might produce significant savings [3]. Screening and treating malnutrition risk in primary care may also improve health and quality of life for patients [12,13], although it is unclear how best to do this, or how to engage older adults who may not consider themselves to be 'at risk'.

Additionally, consensus is lacking about which malnutrition risk factors can be usefully targeted. More than 120 potential causes of malnutrition have been identified, which individually may be unrelated to malnutrition risk [14], but which interact to increase risk, although the mechanisms are little understood [15]. Nevertheless, deteriorating health, widowhood and retirement can influence changes in food choices and ways of acquiring and preparing food [16–19]. Changes in such habits can lead to a deterioration in diet quality and quantity accompanied by reduced personal control, exclusion at social events, and changed roles and responsibilities [16–19]. A range of physical and psychosocial factors can undermine motivation to improve eating habits [20] by promoting unhelpful beliefs and fears. A mixed-methods review identified that patients had reservations about screening and discussing diet [21], and that difficulty chewing, swallowing, shopping or preparing food are barriers to nutritional self-care [21]. Psychosocial barriers included not considering nutrition important, not recognising personal risk, avoiding 'unhealthy' energy-dense food and loneliness [21], being told to gain weight and not believing that recommendations will work [22].

In previous intervention studies, barriers were addressed through eating pattern advice, such as recommending small portions, energy-rich food, daily snacks and care pathways (e.g. dental referral for chewing problems) [21], although participants did not always follow the advice given. Psychosocial barriers or beliefs about personal risk were rarely addressed [21]; for example, patients can be surprised, offended or unconcerned when told they are 'at risk' [23]. Previous studies were constrained by small sample size, variable quality and conflicting findings. Few took place in the UK, reducing confidence about applicability to UK settings.

Qualitative methods inform intervention design through the in-depth exploration of individuals' experiences, habits, needs, values and beliefs [24]. Previous qualitative studies highlight the engagement of older adults in nutritional self-care. For example, men with health conditions or recent bereavement were motivated to develop cooking skills or ate simple meals [25,26]. However, those living alone remained 'at risk' despite self-care knowledge, willingness and ability [27], perhaps through apathy or unmet support needs [28]. Luncheon club participants ate more with friends than with strangers or at home, highlighting the importance of social eating [29]. These studies capture possible explanations for a lack of adoption of eating advice to address malnutrition risk, such as apathy toward cooking and eating alone, although they do not explain how this apathy is developed or maintained through specific beliefs around eating in older adulthood. To design sufficiently engaging and optimally effective behavioural interventions aiming to address malnutrition risk, we need to better understand the role of such psychosocial factors with respect to the eating behaviour of older adults, how they vary between individuals and how best to address psychosocial barriers. More qualitative work is therefore needed to explore the beliefs and experiences of older adults with respect to eating and low appetite, aiming to help understand how support for overcoming barriers can be provided in a way that is relevant for older adults and that also addresses their diverse specific needs and circumstances.

In summary, free-living older adults need support to address malnutrition risk. Barriers to engagement include: reservations about screening and discussing diet, physical barriers to nutritional self-care, and psychosocial barriers including considering nutrition unimportant, not recognising risk, avoiding energy-dense food, loneliness, aversion to being told to gain weight and not believing recommendations will work. Psychosocial barriers are not commonly addressed in previous intervention studies and there is limited evidence explaining how problematic beliefs about malnutrition risk and eating develop and are maintained. Clarifying these issues will inform engaging and persuasive interventions to supplement evidence-based screening and care pathways.

In the present study, we used the Person-based Approach (PBA) to clarify issues around eating and appetite in a varied sample of older adults with a range of health or social conditions associated with malnutrition risk. The PBA systematically applies qualitative research, integrating user perspectives when developing behaviour change interventions in healthcare [24,30], ensuring they are appropriate, engaging, likely to be useful and used. The study findings will inform the development of an intervention to identify and treat malnutrition or malnutrition risk; specifically, a self-management package that is delivered in primary care and supported by healthcare professionals. We propose that the intervention is guided by four principles, from current evidence: (i) raise awareness of older adults' nutrition needs; (ii) motivate

engagement in diet and lifestyle change; (iii) promote self-efficacy for lifestyle change; and (iv) support and promote autonomy, empowering healthy choices. We will refine the guiding principles, based on the findings of our study.

Research aim

We aimed to explore how older adults, with health or social conditions associated with risk of malnutrition, experience psychosocial factors relevant to appetite and eating behaviour. The purpose of the study was to inform an intervention comprising a screen and treat policy, incorporating a self-management package, delivered in primary care.

Materials and methods

This qualitative study is part of a larger project using the Person-based Approach, which involves using qualitative interviews to capture participants' experiences and beliefs [24], as well as variation in individuals' personal contexts [31]. This approach is ideal for exploratory work to inform the development of healthcare interventions. The team that collected and analysed the data are experienced in applying qualitative methods to inform intervention development. We carried out face-to-face semi-structured interviews in participants' homes. Interviews took 20–90 min, with most taking 1 h or more. We obtained approval from the National Health Service (Ref: 207060) ethics committee before data collection. Experienced qualitative researchers (DG, JSB, LP and PH) carried out the interviews after receiving training to ensure ethical and safe good practice. The study is reported following COREQ criteria [32].

Participants

Participants were free-living adults aged ≥65 years, with one or more health or social conditions associated with malnutrition risk. Such individuals might in practice be offered malnutrition screening tests in healthcare settings:

- Chronic health conditions [e.g. chronic obstructive pulmonary disease, cerebrovascular disease; cardiac failure; chronic kidney disease (stage IIIb/IV/V); liver disorders; Parkinson's disease; current depression], OR
- Hospital stay in the previous 6 months, OR
- Living alone

Participants were identified via general practice database searches in Wessex, England, or by snowballing after sharing study details through word-of-mouth. Those interested in participating completed a reply slip after receiving a participant information sheet and consent form. Researchers telephoned to confirm that candidates were happy to participate and arranged interviews. Consent forms were signed at the start of interviews. A carer or spouse was present in five interviews. Recruitment stopped once a range of views were given and data saturation was reached. Interviews took place between November 2016 and July 2017.

Twenty-three participants took part: 16 from a pool of 60 identified via database searches, and seven by word-of-mouth. The general practice sample was purposive, including men and women of different ages. Participant characteristics are summarised in Table 1. All lived in their own homes, with two of these being in warden-assisted flats. The snowball sample consisted only of women. Most participants were aged 75–84 years, most lived alone, three had recent hospital stays and three were bereaved. Families helped one-third of participants with their shopping or cooking. Most participants rated their health in the past week as good to excellent but qualified this as 'for my age' or 'considering' their health conditions.

Topic guide

The topic guide was based on evidence and evidence gaps, including findings from a mixed-methods review [21] and previous qualitative research, as discussed in the Introduction. There were seven key questions, each with 'probing' questions that interviewers could use to prompt further detail about topics of interest, if needed. Participants were asked to describe their appetite and eating patterns and related topics, including any concerns or needs around shopping, food preparation or eating, and experiences of oral nutritional supplements (ONS) (see Supporting information, Appendix S1). The topic guide evolved between interviews, ensuring questions were relevant and understood by participants. For example, a question about participants' freezer contents was added to elicit food choices and psychosocial factors, such as how choices reflect nutritional self-care and beliefs about energy-dense food.

Data analysis

Interviews were transcribed verbatim by a professional transcriber. Inductive thematic analysis was conducted in accordance with Braun and Clarke [33]. Transcripts were coded line-by-line by two researchers independently (LP + PH, LP + LM). All coders discussed which codes best captured participants' experiences. LP compiled the researchers' decisions in a coding manual of mutually exclusive codes. Codes were applied to further transcripts (LP, LM and PH) and iteratively adjusted by consensus.

Table 1 Characteristics of the interview participants

	General practice *n* (%)	Snowballing *n* (%)
Age range (years)		
65–74	3 (13)	1 (4)
75–84	7 (30)	5 (22)
85–94	5 (22)	1 (4)
Missing data	1 (4)	0
Gender: female/male	9/7 (39/30)	7/0 (30/0)
Health conditions (self-report)		
Arthritis, bursitis, joint pain	5	4
Asthma	2	0
Bone disorders	1	0
Cancer (not currently in treatment)	2	0
Chronic kidney disease	2	0
COPD	2	0
Chronic gastrointestinal disorders (Crohn's disease, Diverticulitis)	2	0
Depression	1	4
Epilepsy	2	0
Eye conditions (cataracts, macular degeneration, eye membranes)	1	1
Heart valves (leaky or replaced)	2	1
Hip and knee replacements	1	2
High blood pressure	4	2
Infections needing hospital stay in last year (sepsis, pneumonia)	4	0
Leg ulcers	0	1
Stoma	1	0
Stroke	1	0
Missing data (number of participants)	1	1
Self-rated health in last week		
1–3 = Poor to very poor	1 (4)	1 (4)
4 = Average	5 (22)	2 (9)
5–7 = Good to excellent	10 (43)	4 (17)
Sheltered accommodation	2 (9)	0
Living alone	7 (30)	7 (30)
Recent hospital (last 6 months)	2 (9)	2 (9)
Bereavement in last year	2 (9)	1 (4)
Help to shop or cook	6 (36)	2 (9)

Self-rated health was participants' response to the question, 'How would you rate your overall health during the past week? On a score of 1–7, where 1 is very poor and 7 is very good'. COPD, chronic obstructive pulmonary disease.

Related codes were grouped into themes (Table 2); for example, the codes 'Desire to eat', 'Competing priorities' and 'Bereavement' were grouped as 'Perceptions about appetite and eating experiences'. Data were collated in a spreadsheet and analysed systematically retrieving excerpts for each code and looking for shared and disparate experiences within codes (LP).

The analysis was scrutinised and elaborated (LP and LM). This included (i) considering the range of experiences of appetite and eating in their everyday lives that participants described; (ii) describing how barriers and facilitators around eating were experienced; (iii) identifying support needs; and (iv) examining values and beliefs expressed about eating activities. We then considered what would be the key implications of the findings for intervention design.

Results

Themes

Seven themes were identified (Table 2). There was striking variation in participants' experiences, but participants also experienced common challenges and beliefs. Participants talked extensively about psychosocial aspects of their eating experiences and behaviours, in relation to their physical challenges, perceptions, beliefs, social context, self-regulation, psychological responses to unintended weight loss and perceptions about nutritional supplements. The results presented focus primarily on these psychosocial aspects, supporting our aim to identify and make sense of barriers, facilitators, values and beliefs around eating in older adulthood.

Physical and physiological aspects

Many participants offered physical or physiological explanations for not eating as much as they used to, including illness, immobility, pain, medication, reduced activity, or difficulty chewing, swallowing or digesting certain foods. They described how any of these physical difficulties could present physical and psychological challenges to shopping or preparing food or making what they considered to be 'good' food choices. For example, pain was described as making it difficult to stand in the kitchen to prepare food, as well as reducing motivation to eat. Some participants described their appetite as 'good', 'normally good', 'fine', 'healthy' or 'ok', whereas many described it as 'not that good' or reported noticing their appetite deteriorate. Loss of appetite and losing enjoyment for eating were attributed to changing taste perceptions, nausea, medication, feeling full or anticipating indigestion.

> 'A lot of things that were normal for me now I find too sweet, cakes and chocolates and biscuits and things like that … Taste does seem to have changed since I had pneumonia … But that could be drugs that they put into me …' (P223, male, 86 years)

Perceptions about appetite and eating experiences

Some participants described their perceptions about challenges they experienced around appetite and eating. Most

Table 2 Themes and codes

Physical and physiological aspects	Perceptions about appetite and eating experiences	Beliefs around eating	Support needs
Physical challenges	Desire to eat	'Normal' ageing	Needing tangible support
Overcoming immobility	Trying to eat	Good and bad food	Having support
Chewing, swallowing and digesting	Fatigue	Quantity of food	Wanting support with changing eating habits
Medication effects	Competing priorities	Link between eating and health	Unhelpful support
	Bereavement	Conflicting messages	Influence of source of advice on change
	Cooking experiences	Social comparison	Eating with others
	Weight concerns		

Regulation and self-regulation	Psychological responses to unintended weight loss	Perceptions of oral nutritional supplements
Patterns of eating	Sense of loss	ONS as a strategy
Others influencing choices	Seeing the need for change	Emotional response
Using external cues	Ups and downs	
Strategies for eating without desire	Resignation	
Planning	What can be done?	
Easy food		

ONS, oral nutritional supplements.

described reduced desire for food making them less inclined to eat substantial meals but, for some, 'desire' for certain foods was distinguished from 'feeling hungry', which was perceived as a need for food. Some participants perceived appetite or weight loss positively for health reasons or because they valued thinness, whereas others reported efforts to regain weight following challenging experiences, such as illness or hospitalisation, and some of these were successful. Preparing food, cooking and eating were described as a chore by several participants, who stated that they sometimes or often could not be bothered to cook or eat. Although others did not specify that they 'could not be bothered', they reported prioritising other activities above eating, missing meals to look after grandchildren or continuing with activities such as gardening, and stated that hunger soon passed. A few participants described losing a spouse as the point at which they struggled to eat, and reported not being bothered to cook, not fancying food or feeling too lonely to eat.

> 'We just keep going, by the time I get to two o'clock, the idea of food has worn off, and I won't think of it, although by the time we, if we come back here, by four o'clock or half past four, then seeing the little nibbles I start to pick, then it might reawaken the appetite, but I can easily slide through it . . .' (P53, female, 65 years)

> 'And since I lost him I suppose it [my appetite] just went down. I can't, I think to myself, oh I can't be bothered, not for one' (P111, female, 79 years)

Beliefs around eating

Participants frequently expressed an understanding that eating is important to stay fit and healthy. However, participants described often skipping meals, eating two or fewer meals a day or eating small amounts, which was then perceived as confirmation of the belief that they needed less food. Many stated that appetite and quantity of food consumed are expected to decline with age, and this perceived inevitable decline was attributed to reduced activity and mobility after retirement.

> 'I will usually always have breakfast, but sometimes at lunch I don't feel hungry, then in the evening I don't feel hungry and a couple of times I've sort of just had cereal before I've gone to bed because I think I'm going to wake up hungry' (P393, female, 83 years)

Several participants favoured balanced diets, but some emphasised their adherence to 'healthy' diets by describing fruit, vegetables, skimmed milk and cereals they ate, or stating that they avoided ready meals. A few adhered to restrictive diets, believing them to be healthy and protective against weight gain and some avoided dairy products, for health reasons. Two participants expressed awareness of eating high-energy foods to regain weight or prevent excessive weight loss, although another disagreed with their GP's recommendation to eat high-energy foods. Some participants were reluctant to admit to making food preparation or eating easier by having ready meals or snacking, if they believed that these strategies were unhealthy. Where

these strategies were used, participants emphasized their selection of 'healthy' versions.

> 'It seems terrible to say this but it's easier not to eat than it is to prepare, that's why it's easy to snack. When you get a bit older um its ... I'll just have this (Yeah) I'll have some toast, I won't have a meal or we'll have a ready meal' (P33, male, 75 years)

Support needs

Participants living alone or with challenges around shopping, preparing food and eating often had tangible support from family or support organisations and were grateful for this. However, some expressed regret that relying on others sometimes meant getting help at the wrong time, or that their preferences were not always considered. Social eating occasions with friends or family at home, in pubs or restaurants were experienced in various ways. Some participants reported eating more or richer food than usual with others, including with strangers in a café. However, those with little appetite or difficulty eating certain foods described social eating as uncomfortable, either physically or if they felt embarrassed or pressured to eat certain foods. A few participants reported forcing themselves to eat what they felt they should and sometimes giving in to coercion from family members. Resentment or sadness then seemed evident, and participants expressed more contentment when families encouraged choice.

P: 'She said, 'Now you eat, Mum, what you wants. Don't force anything down you, just eat what you wants', and that's what I've been doing'

I: 'Yeah. And how is that going?'

P: 'Alright, yeah. Yeah, it's going alright' (P111, female, 79 years)

Some participants expressed a desire for help to change their habits, if unsure how much to eat or how to gain weight. A few had received advice from doctors but did not always follow it if they found it difficult or did not understand or accept the rationale for recommendations. One participant stated that the personable approach of a new doctor made them confident to ask for advice, but others were deterred from seeking help based on prior, unsuccessful experiences.

I: 'And how did you feel about that advice, to put cream in instead of milk?'

P: 'Well I wouldn't say I agreed with her really ... because I think all you're going to do is put a big tummy and not going to build the muscle back up at all ...' (P393, female, 83 years)

Regulation and self-regulation

Participants described varied eating self-regulation, with some following set patterns most mornings, lunchtimes and evenings, whereas others reported eating when hungry or often skipping meals. Some outlined experiences from childhood or habits developed when working that they believed had influenced their current eating patterns, including two who described experiencing anorexia when younger. Some participants reported keeping the eating patterns that they had at work, which could mean continuing to have a large meal at lunchtime or in the evening, or prioritising other activities and grabbing a bite when they had an opportunity. Others described enjoying changing to eating more casually or more regularly after retirement, unrestrained by work routines. Participants with less regular eating patterns generally described their spouses' influence as beneficial; for example, if the spouse cooked or preferred to eat regularly. However, there were examples of potentially negative influences, such as participants following their spouse's prescribed diet for convenience, although their health problems differed.

> 'Well I mean we've sort of got ourselves in a discipline of not eating between meals, umm and so we don't eat between meals. If we feel hungry, we wait until the next meal' (P143, male, 74 years)

Participants outlined strategies for eating without desire, including eating at set times, creating a conducive atmosphere, or grazing throughout the day on 'easy' food including soup, rice pudding or treats. External cues were described as having positive or negative effects: seeing, smelling or tasting food could increase desire, remind one to eat, or be off-putting. Some participants favoured planning, including pre-ordering meat, planning the week's meals, stocking easy-to-cook food and freezing food portions, whereas others stated that they did not plan because, living alone, they could suit themselves. A few participants talked about low mood affecting whether they would carry out plans. Both planners and non-planners sometimes missed meals, although some non-planners described difficulty deciding what to eat if appealing options were unavailable.

> 'I'll just suddenly find, well I wouldn't mind such and such a thing, and then I'll go round the cupboard and just see if something appeals to me ... and I don't really, you know I don't really fancy something, or I haven't planned for anything' (P333, female, 88 years)

Psychological responses to unintended weight loss

Participants often expressed negative feelings about appetite or weight loss or loss of enjoyment around eating, and many considered these changes to be inevitable as they got older. Some expressed a desire to change their eating habits, however difficult it was to eat more, more frequently or regularly, although others accepted a decreasing desire to eat and described avoiding social activities that involved eating. A few participants stated they tried to eat well but had not gained weight and did not know what else to try, and this was tinged with sadness and resignation. A few also expressed dissatisfaction and resignation about other aspects of their lives, such as loneliness, living somewhere they disliked, or mood fluctuations, which they suggested could influence the desire to eat. One participant made a link between eating well and positive mood.

> 'There are ups and downs, and if it's one of your down moments, then you do something, like stop eating, when really and truly you should be eating more to get you up out of that down beat' (P593, female, 92 years)

Perceptions of oral nutritional supplements

A few participants had experienced ONS, prescribed for themselves or their spouse, or had tried over-the-counter supplements. Some participants liked some ONS flavours, or mentioned strategies to make ONS more palatable but, overall, ONS were disliked and avoided as a result of their texture, a sensation of being too full or difficulty in digesting the milk used to mix them, which was perceived as appetite-reducing. Participants also alluded to ONS reminding them of their spouse's terminal decline.

> 'I don't know what you can do to get your appetite back unless you're saying we try and make myself drink a protein drink each day – we did have that – I still got some in the cupboard' (P001, female, 83 years)

Discussion

Participants offered multiple reasons, and shared their perceptions and beliefs, when explaining why they did not eat as much as they used to, and many described reduced enjoyment or desire around eating. They outlined how shopping, cooking and eating habits changed in the face of physical challenges; for example, relying on others for shopping, making simple food, or eating less when experiencing pain. Participants believed that certain foods were needed for health and fitness, although most expected appetite to decline with age. Support needs were generally met in this sample, although the quality of support, particularly encouragement and personal choice, was most valued. Participants' eating patterns were varied, with some keeping regular mealtimes, whereas others ate when they felt like it. Participants expressed sadness about unintended weight loss and reduced enjoyment of eating.

Sense of resignation

Our findings confirm that older adults have little awareness of malnutrition risk factors and tend to attribute reduced appetite and food intake to normal ageing rather than risk-taking behaviour. Expanding on the study by Reimer *et al* [23], we found that some people deny their risk, whereas others are acutely aware that weight loss can have serious health consequences. Recently bereaved participants expressed fear about their reduced appetite and weight loss after caring for someone who became frail and died, perhaps worrying that they are also in decline [34]. Behaviour change interventions need to increase understanding of risk, although strategies to address risk and provide reassurance that one can stay well are also needed.

We found a widely expressed belief that reduced appetite and food intake are normal in ageing, as noted previously [35]. This is important because ageing-related stereotype beliefs may reduce the confidence of individuals to carry out health-promoting behaviours [36]. Novel to the present study, participants with long-term eating difficulties, pain, inactivity or reliant on others for everyday needs expressed their resignation to a reduced appetite and reduced eating alongside physical decline and deteriorating quality of life. Resignation was frequently expressed as no longer being 'bothered' to cook or eat as effortfully as they had previously. Those with recent weight loss, such as during bereavement or hospitalisation, appeared to be motivated, through fear or hope, to find solutions, although they also seemed to have a sense of resignation when experiencing the pain of loss. There appeared to be a trajectory towards resignation that started with age-related beliefs, reinforced by experiencing decline and reduced choices. Interventions need to address beliefs about inevitable decline, highlighting how eating can prevent decline and encourage self-efficacy.

Diverse experiences, significant common barriers

Our findings revealed that many lacked the confidence to change their eating habits, and overcome barriers, as identified in previous studies [37,38]. Misperceptions about ready meals, frozen vegetables and snacks being

'unhealthy' were common, perhaps reflecting long-held beliefs or guilt about choosing easy options over home cooking [39]. Interventions need to address misperceptions, normalise easy cooking options, share participants' successful strategies and provide food suggestions, aiming to support users' confidence.

Difficulty with self-regulation (i.e. eating few meals, skipping meals, eating only when hungry) was also common, particularly, but not exclusively, for those who lived alone. This is congruent with research suggesting that sensations of hunger and feeling full are related to self-regulation [40]. Demonstrating beneficial habits and using visual cues and reminders to trigger hunger and eating can support self-regulation of eating [41,42] and could also be included in interventions.

Novel to the present study, these significant common barriers were experienced despite striking variation in participants' eating experiences and behaviours. Uncertainty about how much or what to eat to stay well or prevent further weight loss appeared to hinder beneficial food choices. Extending previous research [43], reduced taste perceptions, expecting a reduced appetite, distracting activities, negative emotions and loneliness appeared to over-ride the body's need for food and the subsequent sensation of hunger. Lack of hunger was commonly seen as a sign that food was not needed. Novel in research with older adults, some participants distinguished between hunger and the desire for food items and were more likely to eat as a result of desire than hunger. Interventions could therefore encourage eating desired foods.

Some available ONS flavours were liked, contradicting previous research [44], although dislike of ONS textures and the finding that ONS would be avoided except as a last resort concurred with previous research [45]. A new finding was that participants may be averse to ONS if they associate ONS use with distress about a spouse's terminal illness. Interventions need to address how to package the message that ONS can help prevent unplanned weight loss and encourage speedier recovery from infections. Interventions can also offer suggestions to make ONS more appealing and easier to drink, including suggestions given by participants. In the future, enriched food products may provide a more acceptable alternative to ONS [45], although the way they are presented to users will also be important.

Difficulties maintaining independence

In the present study, many participants ate less than they used to, concurring with previous research [27,46–49]. Some participants appeared to have an almost obsessive adherence to eating behaviours that they felt would keep them healthy and independent; for example, emphasising the amount of fruit, skimmed milk and breakfast cereals they ate, or how little they ate. This concurs with the study by Winter *et al.* [35] who found that food choices were influenced by a desire for independence, although strict diets could compromise nutrition, undermining independence. We also concur with Maitre *et al.* [50] who found that malnutrition risk is associated with food 'pickiness', both of which increase alongside growing dependence on others for food-related activities. It is important to convey older adults' dietary needs in interventions, while also emphasising how meeting these needs can support independence. Participants also reported sometimes eating more or richer food than usual when eating with friends and family, concurring with Burke *et al.* [29], whose luncheon club attendees ate more among familiar people. Interventions would do well to offer strategies for lone eating and encourage social eating.

Extending previous research, accumulating impacts from health conditions and life events, underpinned by age-related beliefs, made shopping, cooking and eating harder, resulting in it being difficult to maintain independence. Participants remained independent if sharing eating-related tasks with a partner but, once alone, some struggled to sustain the range of behaviours required for self-care. Declining independence impacted further on their ability to shop, cook and eat, contradicting research reporting that men living alone with chronic health conditions, or who were bereaved, adapted to providing for themselves [25,26].

Key implications for intervention design

Prior to the present study, we proposed that intervention development would be guided by four principles, from current evidence: (i) raise awareness of older adults' nutrition needs; (ii) motivate engagement in diet/lifestyle change; (iii) promote self-efficacy for lifestyle change; and (iv) support and promote autonomy, empowering healthy choices. The findings of the present study allow refinement of these principles. We clarified that appropriate intervention targets are: (i) improving risk awareness; (ii) promoting self-efficacy to manage malnutrition risk; (iii) promoting self-efficacy to overcome barriers to eating and making long-term changes, particularly resignation to age-related decline; and (iv) promoting support from healthcare professionals that offers choice and encouragement and harnesses personal reasons for lifestyle change. Self-efficacy and motivation for lifestyle change are thus combined, being closely linked and underpinned by resignation to age-related decline. Participants' unmet needs and desire for support with respect to tackling eating difficulties encourage us to address this need despite previous research suggesting that older adults are unlikely to make changes [51].

Strengths and limitations

The strengths of the present study include the findings from interviews with a range of free-living older adults with different malnutrition risk factors, adding to previous research about psychosocial aspects of eating among this population. In particular, this includes an expectation of decline that contributes to a sense of resignation to multiple different barriers to eating, and difficulty maintaining independence. The resulting understanding of participants' experiences will inform the development of interventions to encourage eating that meets the needs of such older adults.

The included individuals were currently struggling to shop, prepare food and/or eat, or anticipated such challenges in the near future. Some appeared undernourished, although we used no objective measure of malnutrition risk. We also included individuals who were currently eating regularly, some of whom had experience of unintended weight loss from which they had recovered, giving useful insights. The present study could be improved by including more men, or those with a wider range of conditions known to increase malnutrition risk.

Conclusions

The key findings are that: (i) sense of resignation; (ii) diverse experiences and common significant barriers; and (iii) difficulties in maintaining independence underpin the experience of eating and appetite among older adults at risk of malnutrition. There appears to be a trajectory of increasing resignation in the face of common beliefs, values and barriers to eating among older adults with health and/or social conditions known to increase malnutrition risk. Diverse multiple barriers to eating were found, which may be underpinned by common beliefs and misperceptions. Beliefs, values and barriers can also conspire to undermine older adults' aim to remain independent.

Interventions need to counteract commonly held beliefs and misperceptions about the process of inevitable decline in appetite and eating needs during ageing in older adulthood, outline facilitators that have worked for others, and persuade participants that some currently unpopular behaviours (e.g. ONS) can support wellbeing and independence.

Unanswered questions and future research

Future intervention development studies would do well to incorporate the findings of the present study and implement and test ways of addressing the key barriers identified. The study team has carried out such an investigation and aims to publish the results shortly. The mooted mechanisms identified in the present study (e.g. raising risk awareness, promoting self-efficacy), also need to be tested, and the study team is carrying out a randomised controlled trial in which these will be investigated. It will be important to assess whether behavioural techniques included in interventions address patients' psychological needs and issues (resignation, independence) and influence behavioural and clinical outcomes. It would also be useful to identify which food-related strategies work best to enable continued independence for older adults.

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 COREQ guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Conflicts of interest, source of funding and authorship

The authors declare that they have no conflicts of interest.
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LP and JK obtained ethical approval. JK, LP and DG recruited participants. DG, JSB, LP and PH carried out interviews. LP, PH and LM coded the data. LP analysed the data and drafted the paper. All authors read and commented on the draft manuscript and provided clinical, nutritional or psychological expertise during the analysis of the findings.

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Supporting information

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

Appendix S1. Eat well feel well: a study about people's appetite and eating patterns. Topic guide.

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MALNUTRITION

Skin autofluorescence and malnutrition as predictors of mortality in persons receiving dialysis: a prospective cohort study

Daniela Viramontes Hörner[1] Nicholas M. Selby[1,2] & Maarten W. Taal[1,2]

[1]Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, Centre for Kidney Research and Innovation, University of Nottingham, Royal Derby Hospital, Derby, UK
[2]Department of Renal Medicine, University Hospitals of Derby and Burton NHS Foundation Trust, Royal Derby Hospital, Derby, UK

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advanced glycation end-products, dialysis, malnutrition, mortality, skin autofluorescence.

Correspondence
Daniela Viramontes Hörner, Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, Royal Derby Hospital, Uttoxeter Road, Derby DE22 3NE, UK.
Tel.: +44 01332 788262
E-mail: mszdv@nottingham.ac.uk

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Abstract

Background: Skin autofluorescence (SAF), which is a measure of accumulation of advanced glycation end-products (AGE), and malnutrition are each associated with higher mortality in dialysis populations, although no studies have investigated these potentially related associations together. We simultaneously assessed SAF and malnutrition as risk factors for mortality in persons receiving dialysis.
Methods: SAF was measured in 120 haemodialysis and 31 peritoneal dialysis patients using an AGE Reader (DiagnOptics, Groningen, The Netherlands). Dietary AGE, energy, protein and fat intake, handgrip strength, anthropometry, biochemistry and Subjective Global Assessment were also evaluated. Time to event was days from baseline to death, kidney transplantation or 30 September 2018.
Results: Median observation time was 576 days, during which 33 (21.9%) patients died. Those who died had higher baseline SAF levels [3.8 ± 1.0 versus 3.3 ± 0.8 arbitrary units (AU); $P = 0.001$] and were more likely to be malnourished (58% versus 31%; $P = 0.006$). Malnourished persons who died had higher SAF values than those who died but were well-nourished (4.2 ± 1.1 versus 3.3 ± 0.7 AU; $P = 0.007$). Survival was significantly better in participants with baseline SAF below the median and in those well-nourished than those with baseline SAF above the median and in those malnourished, respectively. Multivariable analysis identified SAF [hazards ratio (HR) = 1.44; 95% confidence interval (CI) = 1.05–1.97; $P = 0.02$], malnutrition (HR = 2.35; 95% CI = 1.16–4.78; $P = 0.02$) and chronological age (HR = 1.60; 95% CI = 1.10–2.33; $P = 0.01$) as independent predictors of mortality.
Conclusions: Although higher SAF and malnutrition are potentially interrelated, they were both independently associated with increased mortality in this population. Interventions to improve outcomes by reducing SAF through correction of malnutrition or dietary AGE restriction require testing in prospective studies.

Introduction

Dialysis is a life-prolonging therapy for persons with end-stage kidney disease (ESKD), although it is associated with a high mortality rate in large part due to increased cardiovascular disease [1,2]. Malnutrition, systemic inflammation and oxidative stress have been proposed as non-traditional cardiovascular risk factors that contribute to

the increased cardiovascular mortality risk observed in the ESKD population [3], although the manner in which these factors interact and their relative importance remains to be elucidated.

Advanced glycation end-products (AGEs) are uremic toxins that accumulate in persons receiving dialysis as a result of reduced renal clearance and increased formation [4,5]. Endogenous sources of AGEs include oxidative and carbonyl stress, as well as hyperglycaemia [4]. AGEs can also be formed exogenously, either by cigarette smoking or through the ingestion of foods cooked under dry heat and high temperatures (e.g. grilling, roasting, frying) [6]. Taking advantage of the fluorescence properties of some AGEs, the accumulation of these toxins in the skin can be assessed non-invasively using skin autofluorescence (SAF), which has proven to be an independent predictor of all-cause and cardiovascular mortality in the dialysis population [7–9]; however, the mechanisms underlying this association are not completely understood.

AGEs are markers of oxidative stress, which is linked with systemic inflammation. Oxidative and inflammatory processes act synergistically with respect to promoting protein catabolism, muscle wasting and reduced hepatic albumin synthesis, which together lead to the development of malnutrition in the setting of ESKD [10,11]. Malnutrition, an independent predictor of mortality in the dialysis population [12–15], exacerbates the deleterious effects of systemic inflammation and oxidative stress by increasing the susceptibility to infections and cardiovascular disease risk [16,17]. It therefore appears reasonable to suggest that a vicious cycle between inflammation, oxidative stress and malnutrition may contribute to the poor survival rates observed in persons on dialysis [18]. Malnutrition and SAF have previously been reported in separate studies to independently predict worse survival on dialysis but, to our knowledge, no studies have simultaneously investigated the association of SAF and malnutrition with mortality. This is particularly important because it has been previously reported that higher SAF and several markers of malnutrition are independently associated in persons on haemodialysis (HD) [19], raising the possibility that the association between higher SAF and poorer survival may be explained by an association with malnutrition, which was not assessed in previous studies [7,9]. We therefore aimed to investigate the prognostic significance of SAF and malnutrition when evaluated together in persons receiving dialysis.

Materials and methods

Study population

This was a single centre prospective observational study conducted in the Department of Renal Medicine, Royal Derby Hospital. Persons receiving HD and performing peritoneal dialysis (PD) who were ≥18 years of age and had an expected survival more than 1 year were eligible. We enrolled 120 HD and 31 PD patients from September 2016 to August 2017. Participants on HD were dialysed three or four times per week for 3–4 h using high-flux polysulphone, polyarylethersulfone or polyvinylpyrrolidone dialyzers. Persons performing PD dialysed using lactate/bicarbonate-buffered 1.36% and 3.86% glucose (Physioneal; Baxter Healthcare Corporation, Deerfield, IL, USA), 7.5% icodextrin (Extraneal; Baxter Healthcare Corporation) and/or 1.1% aminoacid-containing solutions (Nutrineal; Baxter Healthcare Corporation). The exclusion criteria used were: pregnancy or intending pregnancy, breastfeeding and having dark skin colour. Written informed consent was obtained from all patients. The study was approved by the local Research Ethics Committee (East Midlands – Nottingham 1. REC reference: 16/EM/0243).

Data collection

Electronic medical records were used to collect participant characteristics, including: age, sex, ethnicity, dialysis vintage (i.e. time subsequent to first dialysis treatment), dialysis adequacy, blood results, presence of diabetes (defined by clinical diagnosis) and obesity [defined as having a body mass index (BMI), ≥30 kg m^{-2}] [20], as well as history of cardiovascular disease. Information regarding educational level, occupation and smoking status was obtained from direct interview.

Dates and causes of death were obtained from electronic medical records. Causes of death were classified into specific groups [21]: cardiovascular, infection, malignancy, treatment withdrawal and other cause of death. The classification was performed independently by two consultant nephrologists (NMS and MWT) and any disagreements were resolved by discussion. Survival time was defined as the number of days between the baseline assessment and the date of death, censoring as a result of kidney transplantation or 30 September 2018.

Skin autofluorescence measurement

SAF was measured using a validated Autofluorescence Reader, version 2.4.3 (AGE Reader; DiagnOptics, Groningen, The Netherlands) as described in more detail elsewhere [7,19]. In brief, the AGE Reader directs an ultraviolet excitation light (intensity 300–420 nm) through an illumination window of approximately 1 cm^2 on a skin area (free of visible vessels, scars, tattoos or any other skin irregularities) of the volar surface of the forearm at approximately 10 cm below the elbow. The AGE Reader then measures

the amount of emitted light that is reflected back from the skin (intensity 300–600 nm) using a spectrometer (AVS-USB2000; Avantes Inc., Eerbeek, The Netherlands) and a 200-μm glass fibre. SAF is calculated by dividing the average emitted light intensity in the range between 420–600 nm by the average excitation light intensity in the range between 300–420 nm, and expressed as arbitrary units (AU). Three SAF readings were conducted on the nonfistula arm or the dominant arm if this did not have a fistula, and within the first hour of HD treatment. The mean value of three SAF readings was used for statistical analyses. SAF readings may be affected by dark skin colour and pigmentation as a result of a higher proportion of the excitation light being absorbed. The AGE Reader has not yet been validated in persons with darker skin colour and skin reflectivity <6% (i.e. Fitzpatrick skin colour types 5–6) [22]. Consequently, SAF might not be reliable in this population and persons with dark skin were therefore excluded. It has been previously reported that SAF readings have good reproducibility and repeatability (i.e. coefficient of variation of 7–8%) [23].

Nutritional assessments

Information regarding energy, protein and fat intake was obtained from three 24-h dietary recalls. Participants were asked to recall all foods and drinks they had the day before. Dietary recalls were analysed with DIETPLAN, version 7 (Forestfield Software Limited, Broadbridge Heath, UK) to calculate the average energy, protein and fat intake. Average daily intake of energy and protein was then calculated (kJ and g, respectively) and expressed per kg of ideal body weight. Dietary AGE intake (reported in kilounits per day) was estimated with a food frequency questionnaire previously validated in persons with diabetes [24]. For further analysis, dietary AGE intake was corrected for total average energy intake and for post-dialysis body weight.

Anthropometric measurements were conducted in line with international standard methods of assessment [25]. Post-dialysis weight and height were measured to calculate BMI (kg m^{-2}), whereas measurement of mid-arm circumference (MAC) and triceps skinfold thickness (TSF) (both in cm) was conducted to calculate mid-arm muscle circumference (MAMC) using the equation: MAMC (cm^2) = MAC – (3.14 × TSF). Handgrip strength (HGS) measurement was conducted within the first hour of HD treatment or during PD clinic visits using the Takei 5401 handgrip digital dynamometer (Takei Scientific Instruments Co., Ltd, Tokyo, Japan). HGS was measured in the nonfistula arm or the dominant arm if this did not have a fistula as described elsewhere [19].

The seven-point scale Subjective Global Assessment (SGA) [26] was performed to evaluate the nutritional status. Based on the ratings of six individual core components (i.e. history of weight loss, dietary intake, gastrointestinal symptoms, functional status, metabolic stress and subjective physical examination of loss of subcutaneous fat and muscle mass, and presence of oedema), nutritional status can be classified into normal nutritional status (scores of 6 or 7), mild-moderate malnutrition (scores of 3–5) or severe malnutrition (scores of 1 or 2). For statistical analysis, participants were placed in two groups: well-nourished (SGA scores 6–7) or malnourished (SGA scores 1–5).

Statistical analysis

All statistical analyses were performed using SPSS, version 24.0 (IBM Corp., Armonk, NY, USA). Data are expressed as the mean (SD), median [interquartile range (IQR)], percentages or hazard ratios [HR, 95% confidence interval (CI)], as appropriate. Missing data were omitted: C-reactive protein (CRP), $n = 7$; HGS, $n = 6$; MAC, MAMC and TSF, $n = 1$. Comparisons of continuous variables between two independent groups were performed using Student's t test or a Mann–Whitney U test, whereas intergroup comparisons for categorical variables were conducted with a chi-squared test or Fisher's exact test. Kaplan–Meier survival curves were computed according to baseline SAF levels above or below the median value and nutritional status at baseline.

Cox proportional hazards models were used to investigate the prognostic value of SAF and malnutrition for predicting mortality. As a result of the limited number of events (deaths), only the three variables of greatest interest that were associated with mortality in the univariable analyses were included in the model. A product term (i.e. two-way interaction term) was included in the regression model to test for an interaction between SAF and malnutrition. $P < 0.05$ was considered statistically significant.

Sample size determination with mortality as the primary outcome showed that with a sample size of 150 participants split in two groups (group 1: SAF below the median, $n = 75$; group 2: SAF above the median, $n = 75$), the analysis would have more than 80% power to detect a HR of 2.7, assuming that the total number of events (i.e. deaths) achieved was 34 and the average probability of the event was 0.1 in group 1 and 0.35 in group 2 (NQUERY ADVANCED, version 8.0; Statistical Solutions Limited, Boston, MA, USA).

RESULTS

Baseline participant characteristics

The demographic, clinical, biochemical and nutritional characteristics of 120 HD and 31 PD participants are

shown in Table 1. The mean (SD) age of the whole cohort was 64 (14) years. Sixty-four percent of the population were male and 88% were of white ethnicity. Mean (SD) SAF was high at 3.4 (0.9) AU compared to the reference value of 2.5 (0.6) AU for the age group of 60–70 years [27]. Participants had low calorie and protein intake compared to the estimated nutritional requirements for persons receiving dialysis [28].

SGA identified 56 participants (37%) as malnourished and 95 as well-nourished (63%). SAF was significantly higher in malnourished participants compared to those who were well-nourished. Serum albumin, total dietary AGE, energy, protein and fat intake, HGS, and all anthropometric variables were significantly lower in malnourished participants compared to those with a well-nourished status. Dietary AGE intake corrected for post-dialysis body weight and for total energy intake was not significantly different between malnourished and well-nourished participants. Females, current smokers and those who were unemployed were more likely to be malnourished than males, nonsmokers and employed participants, respectively. Coronary heart disease was more evident in malnourished participants (Table 1).

Follow-up results

Median observation time was 576 days (IQR = 395–684 days) during which 33 (21.9%) participants died and 22 (14.6%) received a kidney transplant. The most common cause of death was infection (33.3%) followed by cardiovascular (30.3%), treatment withdrawal (15.1%), other cause of death (12.1%) and cancer (9.2%).

Table 2 shows baseline participant characteristics according to survival status. Participants who died had

Table 1 Baseline participant characteristics by nutritional status classification

Variable	Overall (*n* = 151)	Malnourished (*n* = 56)	Well-nourished (*n* = 95)	*P* value†
Age (years)	64 (14)	62 (16)	65 (13)	0.5
Female, *n* (%)	54 (36)	30 (54)	24 (25)	<0.0001
White ethnicity, *n* (%)	133 (88)	47 (84)	86 (91)	0.2
Educational qualifications, *n* (%)	85 (56)	28 (50)	57 (60)	0.2
Unemployed, *n* (%)	114 (76)	48 (86)	66 (70)	0.03
Current smoking, *n* (%)	23 (15)	16 (29)	7 (7)	<0.0001
Diabetes, *n* (%)	62 (41)	21 (38)	41 (43)	0.5
Coronary heart disease, *n* (%)	60 (40)	29 (52)	31 (33)	0.02
Peripheral vascular disease, *n* (%)	11 (7)	5 (9)	6 (6)	0.6
Obesity, *n* (%)	55 (36)	11 (20)	44 (46)	0.001
Dialysis vintage (months)	29 (10–69)	31 (11–61)	26 (10–67)	0.4
Dialysis adequacy (Kt V^{-1})*	1.45 (0.59)	1.54 (0.62)	1.40 (0.56)	0.1
Serum albumin (g L^{-1})	31.5 (4.6)	30.1 (5.4)	32.4 (3.8)	0.02
C reactive protein (mg L^{-1})	8 (4 to 17)	9 (3 to 23)	8 (4 to 14)	0.6
Total cholesterol (mmol L^{-1})	4.1 (1.2)	4.2 (1.3)	4.1 (1.1)	0.9
Serum creatinine (μmol L^{-1})	646 (214)	607 (211)	669 (214)	0.06
Serum phosphate (mmol L^{-1})	1.56 (0.51)	1.64 (0.56)	1.51 (0.47)	0.2
Serum potassium (mmol L^{-1})	4.6 (0.7)	4.5 (0.7)	4.7 (0.7)	0.2
Skin autofluorescence (AU)	3.4 (0.9)	3.6 (1.0)	3.2 (0.7)	0.009
Dietary AGE intake (kU day^{-1})	14545 (781)	12763 (6580)	15595 (8315)	0.02
Dietary AGE intake/body weight (kU kg^{-1})	168 (120–237)	168 (122–237)	168 (115–237)	1.0
Dietary AGE intake/energy intake (kU kJ^{-1})	2.2 (1.7–3.1)	2.3 (1.7–3.4)	2.2 (1.7–3.1)	0.6
Energy intake (kJ kg^{-1} day^{-1})‡	87.5 (31.8)	77.9 (31.8)	92.9 (30.6)	0.001
Protein intake (g kg^{-1} day^{-1})	0.88 (0.29)	0.79 (0.32)	0.94 (0.25)	<0.0001
Fat intake (g day^{-1})	57.9 (29.7)	47.9 (24.2)	63.8 (31.2)	<0.0001
Post-dialysis weight (kg)	79.3 (20.8)	69.7 (17.8)	85.0 (20.4)	<0.0001
Body mass index (kg m^{-2})	27.7 (6.3)	25.1 (5.1)	29.2 (6.4)	<0.0001
Handgrip strength (kg)	23.0 (11.5)	19.1 (10.9)	25.1 (11.3)	0.001
Mid-arm muscle circumference (cm^2)	25.6 (3.7)	23.9 (3.6)	26.6 (3.5)	<0.0001
Triceps skinfold thickness (mm)	17.2 (7.2)	15.1 (6.3)	18.4 (7.5)	0.02

Data are expressed as the mean (SD), median (interquartile range) or percentages, as appropriate
AGE, advanced glycation end-product; AU, arbitrary units; kU, kilounits.
*Kt V^{-1} is weekly in peritoneal dialysis and per session in haemodialysis;
†Malnourished versus Well-nourished.
‡kcal kg^{-1} day^{-1}: overall, 20.9 (7.6); malnourished, 18.6 (7.6); well-nourished, 22.2 (7.3).

Table 2 Comparison of baseline participant characteristics between survivors and non-survivors

Variable	Non-survivors (n = 33)	Survivors (n = 118)	P value*
Age (years)	69 (12)	62 (14)	0.004
Female, n (%)	13 (39)	41 (35)	0.6
Educational qualifications, n (%)	20 (61)	46 (39)	0.03
Unemployed, n (%)	30 (91)	84 (71)	0.02
Current smoking, n (%)	6 (18)	17 (14)	0.6
Diabetes, n (%)	15 (46)	47 (40)	0.6
Coronary heart disease, n (%)	17 (52)	43 (36)	0.1
Malnutrition, n (%)	19 (58)	37 (31)	0.006
Dialysis vintage (months)	43 (20–71)	25 (8–68)	0.1
Serum albumin (g L^{-1})	29.5 (6.1)	32.1 (3.9)	0.02
C reactive protein (mg L^{-1})	11 (5 to 29)	7 (3 to 14)	0.04
Total cholesterol (mmol L^{-1})	4.0 (1.2)	4.1 (1.2)	0.6
Serum creatinine (μmol L^{-1})	657 (206)	643 (217)	0.8
Skin autofluorescence (AU)	3.8 (1.0)	3.3 (0.8)	0.002
Dietary AGE intake (kU day^{-1})	13381 (7032)	14870 (8019)	0.4
Energy intake (kJ kg^{-1} day^{-1})†	75.4 (26.0)	90.8 (32.7)	0.01
Protein intake (g kg^{-1} day^{-1})	0.75 (0.25)	0.92 (0.29)	0.003
Fat intake (g day^{-1})	48.6 (24.7)	60.5 (30.6)	0.02
Body mass index (kg m^{-2})	28.3 (6.5)	27.5 (6.2)	0.6
Handgrip strength (kg)	18.6 (10.7)	24.1 (11.5)	0.008
Mid-arm muscle circumference (cm^2)	25.7 (4.5)	25.6 (3.5)	0.7
Triceps skinfold thickness (mm)	18.5 (6.7)	16.9 (7.4)	0.2

Data are expressed as the mean (SD), median (interquartile range) or percentages, as appropriate.

AGE, advanced glycation end-product; AU, arbitrary units; kU, kilo-units.

*Nonsurvivors versus Survivors.

†kcal kg^{-1} day^{-1}: non-survivors, 18.0 (6.2); survivors, 21.7 (7.8).

significantly higher baseline SAF and CRP levels compared to those who did not die. Nonsurvivors were more likely to be malnourished in comparison to survivors. Participants who died also had significantly lower serum albumin, HGS, and energy, protein and fat intake compared to those who did not die. Older age, lack of educational qualifications and unemployment were more evident among nonsurvivors than in survivors.

Participants who died and were malnourished (n = 19) had significantly higher SAF levels and lower serum albumin, serum creatinine, total dietary AGE, energy, protein and fat intake, BMI, HGS, MAMC, and TSF compared to those who died but were well-nourished (n = 14) (see Supporting information, Table S1). No significant differences were observed in dietary AGE intake corrected for body weight and for total energy intake between survivors and nonsurvivors, nor between those who died and were malnourished and those who died but were well-nourished.

Kaplan–Meier analysis showed that survival was significantly better in those participants with a baseline SAF level below the median value of 3.3 AU and in those who were well-nourished at baseline in comparison to those with baseline SAF level above the median value and in those malnourished at baseline, respectively (Figures 1 and 2). Univariable analysis identified malnutrition, no educational qualifications, higher SAF, chronological age and lower serum albumin, HGS, and energy, protein and fat intake as significant determinants of higher mortality, although total dietary AGE intake, as well as AGE intake corrected for body weight and for total energy intake, were not. Multivariable Cox proportional hazards analysis identified SAF (HR = 1.44; 95% CI = 1.05–1.97 per SD; P = 0.02), malnutrition (HR = 2.35; 95% CI = 1.16−4.78; P = 0.02) and chronological age (HR = 1.60; 95% CI = 1.10–2.33 per SD; P = 0.01) as independent predictors of mortality (Table 3). Inclusion of a product term in the model showed no interaction between SAF and malnutrition.

Discussion

In this prospective observational study, we found that higher SAF and malnutrition were both significant and independent predictors of increased mortality in persons receiving dialysis. We also identified that several markers of malnutrition such as serum albumin, HGS, and energy, protein and fat intake were important determinants of higher mortality, and that SAF was significantly increased among those dialysis patients who died and were malnourished.

The association between SAF and increased mortality in persons receiving dialysis has been investigated previously in several studies. In one of the first prospective studies carried out in this area [7], higher SAF was independently associated with a four-fold increased mortality risk over 3 years, with cardiovascular disease being the main cause of death. We observed a 44% higher risk of all-cause mortality for each SD increase in SAF. Similarly, Mukai *et al.* [8] reported that each one SD increase in SAF was independently associated with a 56% higher risk of death. Several other observational studies have also reported that increased SAF independently predicts higher rates of all-cause and cardiovascular mortality in persons

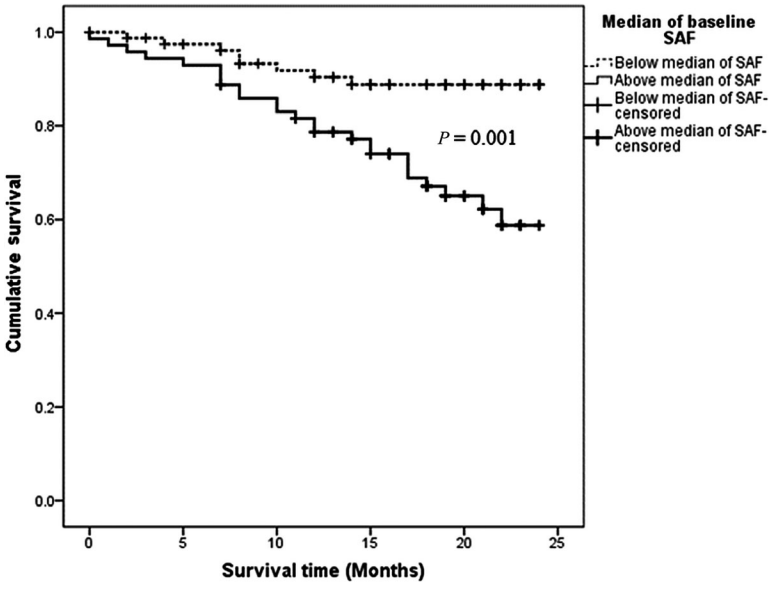

Figure 1 Kaplan–Meier plot of survival according to baseline skin autofluorescence (SAF) above or below the median value.

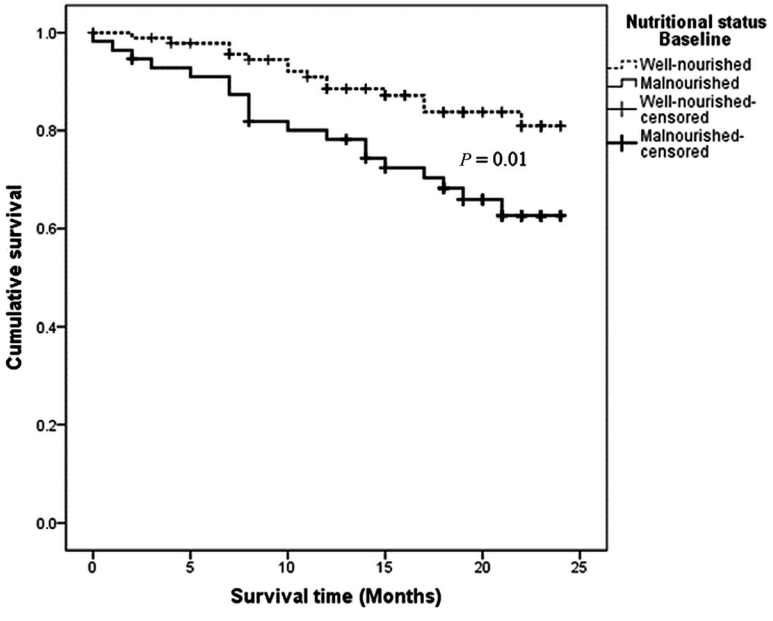

Figure 2 Kaplan–Meier plot of survival according to nutritional status at baseline.

receiving dialysis [9,29–32]. Multiple mechanisms may explain the association between increased SAF and mortality. AGEs cross-link proteins of the extracellular matrix (e.g. collagen and elastin), altering their structural and functional properties, which translates into increased arterial stiffness and endothelial dysfunction [33], both of which contribute to the pathogenesis of cardiovascular disease. In addition, AGEs exacerbate vascular tissue damage by binding to specific AGE receptors that induce oxidative stress and systemic inflammation [34]. Systemic inflammation in turn promotes endothelial dysfunction and vascular calcification [35]. Oxidative stress, alongside inflammation, also causes endothelial dysfunction, which leads to the development and progression of atherosclerosis [10,36–38]. Additionally, the association may be explained, at least in part, by an association between increased SAF and malnutrition [19], which is a well-described risk factor for reduced survival on dialysis, although, unfortunately none of the aforementioned prospective studies included an assessment of nutritional

Table 3 Cox proportional hazards analysis showing predictors of overall mortality in persons receiving dialysis

	Univariable analysis		Multivariable analysis	
Predictor	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	1.53 (1.04–2.24)	0.03	1.60 (1.10–2.33)	0.01
Sex (Female versus Male)	1.18 (0.59–2.37)	0.7		
Educational qualifications (No versus Yes)	2.09 (1.04–4.12)	0.04		
Current smoking (Yes versus No)	1.15 (0.48–2.79)	0.8		
Diabetes (Yes versus No)	1.12 (0.57–2.23)	0.7		
Coronary heart disease (Yes versus No)	1.59 (0.80–3.15)	0.2		
Nutritional status (Malnourished versus Well-nourished)	2.30 (1.15–4.59)	0.02	2.35 (1.16–4.78)	0.02
Dialysis vintage (months)	1.00 (0.99–1.00)	0.7		
Serum albumin (g L^{-1})	0.89 (0.84–0.96)	0.001		
C reactive protein (mg L^{-1})	1.01 (1.00–1.03)	0.06		
Total cholesterol (mmol L^{-1})	0.92 (0.67–1.25)	0.6		
Serum creatinine (μmol L^{-1})	1.00 (0.99–1.00)	0.6		
Skin autofluorescence (AU)	1.55 (1.16–2.07)	0.003	1.44 (1.05–1.97)	0.02
Dietary AGE intake (kU day^{-1})	1.00 (1.00–1.00)	0.4		
Dietary AGE intake/body weight (kU kg^{-1})	1.00 (0.99–1.00)	0.2		
Dietary AGE intake/energy intake (kU kJ^{-1})	1.01 (0.98–1.06)	0.3		
Energy intake (kJ kg^{-1} day^{-1})	0.93 (0.88–0.99)	0.02		
Protein intake (g kg^{-1} day^{-1})	0.16 (0.04–0.61)	0.008		
Fat intake (g day^{-1})	0.98 (0.97–0.99)	0.03		
Body mass index (kg m^{-2})	1.02 (0.97–1.07)	0.5		
Handgrip strength (kg)	0.96 (0.92–0.99)	0.04		
Mid-arm muscle circumference (cm^2)	1.01 (0.92–1.11)	0.8		
Triceps skinfold thickness (mm)	1.03 (0.98–1.07)	0.2		

AGE, advanced glycation end-product; AU, arbitrary units; CI, confidence interval; kU, kilounits; HR, hazards ratio.

status. We have now filled this knowledge gap by showing that SAF and malnutrition are independent predictors of higher mortality on dialysis. Thus, elevated SAF does not appear to be simply a surrogate marker of malnutrition.

Malnutrition is one of the major and most prevalent complications in persons receiving dialysis[39,40]. In the present study, we found that malnutrition, as assessed by the seven-point scale SGA, was a significant and independent determinant of increased mortality. Several prospective studies have also reported that malnutrition, as evaluated by the original and modified versions of the SGA, is independently and strongly associated with overall and cardiovascular mortality in the dialysis population [12–15]. This association might be partially explained by interactions between multiple risk factors related to malnutrition that are also associated with increased mortality, including inadequate dietary intake [41–44], presence of cardiovascular disease [2], metabolic acidosis [45] and, most importantly, systemic inflammation [46] and oxidative stress [36]. Although the accuracy of the seven-point scale SGA to assess nutritional status relies on the dietitian's experience and training to interpret the data collected [40], it continues to be the recommended nutritional assessment tool by national and international nutrition guidelines in the dialysis population [28,47].

It has been reported previously in a cross-sectional analysis that SAF was significantly higher among malnourished persons on HD and that markers of malnutrition such as lower serum albumin, lower protein intake and lower HGS, as well as longer dialysis vintage, presence of diabetes and history of smoking, were independent determinants of increased SAF [19]. The present study extends these observations by showing that higher SAF and malnutrition were independent risk factors for higher mortality, although no interaction was found on statistical testing. Additionally, SAF was significantly higher in nonsurvivors who were malnourished compared to those who died but were well-nourished. Furthermore, lower serum albumin, HGS, and energy, protein and fat intake were significant determinants of higher mortality in univariable analyses. The association between higher SAF and malnutrition may be explained by overlapping mechanisms that likely contribute to both. AGEs are rapidly formed during oxidative stress. Oxidative stress in turn promotes systemic inflammation and vice versa. Chronic inflammation and oxidative stress together induce a number of mechanisms including increased muscle proteolysis, decreased appetite and hypoalbuminemia, which ultimately lead to the development of malnutrition [10,11,48]. Malnutrition may also contribute to AGE

formation through its interaction with oxidative and inflammatory processes. Thus, a vicious cycle likely exists between chronic inflammation, oxidative stress and malnutrition to explain the association between SAF, malnutrition and increased mortality.

Our findings highlight the importance of dietetic monitoring and support to help patients cope with the nutritional challenges associated with ESKD [39]. Malnutrition should be detected early by means of comprehensive screening and assessment using different objective and subjective nutritional markers [40], followed by implementation of an individualised dietetic intervention to treat it. One recent proof of principle study has reported that an improvement of nutritional intake and markers of nutritional status was associated with the stabilisation of SAF levels in malnourished persons receiving dialysis [49]. On the other hand, restriction of dietary AGE intake has been found to reduce serum AGE levels in some patient groups [50,51] but risks provoking or exacerbating malnutrition in patients requiring dialysis [19,52] and would therefore require close dietetic supervision. Large prospective trials are now warranted to investigate the role of dietary interventions with respect to reducing SAF and improving outcomes in persons receiving dialysis.

There are some limitations that need to be considered when interpreting our findings. First, we included subjects from a single centre and the sample size was relatively small, which prevented us from including more variables in the multivariable Cox proportional hazards model, and may have resulted in a failure to detect weaker associations between some baseline variables and outcomes. Second, the follow-up period was relatively short, and a longer observation period may have revealed more evidence of interaction between higher SAF, malnutrition and mortality. Third, we limited our analysis to consideration of baseline variables, whereas a larger study would have allowed inclusion of change in SAF and change in nutritional status as time-varying factors. Nevertheless, unlike previous cohorts, the present study is the first to prospectively and simultaneously assess SAF and malnutrition as risk factors for increased mortality. The observational design of the present study did not allow us to assess causality; however, our results suggest that the risk of death is considerably higher among those subjects with increased SAF and malnutrition. Finally, valid SAF readings cannot be obtained when the skin reflectivity is lower than 6% [22]; therefore, persons with dark skin colour (i.e. Fitzpatrick skin colour types 5–6), who have an ultraviolet reflectance of less than 6%, were excluded from the study, and our findings may be applicable only to persons with Fitzpatrick skin types 1–4.

In conclusion, although higher SAF and malnutrition are potentially inter-related, we have found that they were independently associated with increased mortality in this dialysis population. Our observations strengthen the role of SAF as an independent risk factor in the dialysis population and suggest that interventions to reduce SAF may result in improved survival, although this should now be tested in prospective trials. Such interventions may include correction of malnutrition and dietary AGE restriction, although care should be taken in the latter case to avoid exacerbating malnutrition.

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 (East Midlands – Nottingham 1. REC reference: 16/EM/0243) and that any discrepancies from the study as planned have been explained.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest. The results presented in this paper have not been published previously in whole or part, except in abstract form.
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DVH designed and conducted the study, analysed the data and wrote the manuscript. MWT assisted with the study design, the interpretation of the data and the writing of the manuscript. NMS assisted with the interpretation of data and the writing of the manuscript. All authors approved the final version of the manuscript submitted for publication.

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Supporting information

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

Table S1. Comparison of nonsurvivor characteristics according to nutritional status at baseline.

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TECHNOLOGY

Portable gluten sensors: qualitative assessments by adults and adolescents with coeliac disease

R. L. Wolf[1] A. Vipperman-Cohen,[1] P. H. R. Green,[2] A. R. Lee,[2] N. R. Reilly,[2] P. Zybert[1] & B. Lebwohl[2,3]

[1]Department of Health & Behavior Studies, Program in Nutrition, Teachers College, Columbia University, New York, NY, USA
[2]Department of Medicine, Celiac Disease Center, Columbia University Irving Medical Center, Harkness Pavilion, New York, NY, USA
[3]Department of Epidemiology, Mailman School of Public Health, Columbia University Irving Medical Center, New York, NY, USA

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adolescents, adults, coeliac disease, portable gluten sensor, qualitative, technology.

Correspondence
R. L. Wolf, Teachers College, Columbia University, 525 West 120th Street, Box 137, New York, NY 10027, USA.
Tel.: +1 212 678 3912
Fax: +1 212 678 8259
E-mail: wolf@tc.columbia.edu

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Abstract

Background: Portable gluten sensors are now commercially available to the public, although there is genuine uncertainty within the medical community over whether they should be used for coeliac disease management. The present study described qualitatively the experience of using a portable gluten sensor for 15 adults and 15 adolescents with coeliac disease participating in a 3-month pilot clinical trial.
Methods: Participants were 30 individuals, aged 13–70 years, with biopsy-confirmed coeliac disease on a gluten-free diet. All received a portable gluten sensor and were randomised to low, medium, and high numbers of single-use capsules. Open-ended questions addressed likes and dislikes using the portable gluten sensor after 3 months. Major themes were identified and described.
Results: Participants liked that the portable gluten sensor provided extra assurance to check foods presented as gluten-free, the convenient size and portability, the added sense of control, and overall peace-of-mind. Participants disliked having attention drawn to them when using the sensor and feeling as if they were deterring others from eating. Participants also disliked the physical difficulty associated with using the capsules, questionable accuracy and the inability to test fermented foods. Adults were more enthusiastic about the sensor than adolescents.
Conclusions: Positive and negative experiences may be expected when using commercially available portable gluten sensors to help manage coeliac disease. As future versions of this and other gluten sensors become available, it will be important to investigate the relationship between users' experience with the sensors and long-term outcomes such as mucosal healing and quality of life.

Introduction

Although the focal point for coeliac disease (CeD) treatment is adherence to a strict gluten-free (GF) diet, inadvertent gluten exposures are commonly reported [(1)]. Portable gluten sensors are now commercially available, although there is genuine uncertainty within the medical community over whether they should be used for coeliac disease management. One such sensor is Nima [(2)]. Nima uses antibody-based chemistry to quickly indicate 'gluten found' or 'no gluten found' in pea-sized samples of food. Levels < 20 ppm are considered GF by the US Food and Drug Administration [(3)], although Nima frequently detects gluten at lower concentrations [(4,5)]. Although data are emerging regarding the performance of portable gluten sensors, little is known about patient responses to real-time access to the data provided. A correlation between strict gluten-free diet management and diminished quality of life, including anxiety and depression, has been highlighted. More specifically, we have documented that adults reporting greater vigilance to a gluten-free diet to have lower quality of life scores compared to their less

vigilant counterparts [6]. Although portable gluten sensors have the potential to reduce unintentional gluten exposure, anxiety when eating out, and concern about cross-contact, we were concerned that the technology could be a source of frustration when unexpected gluten is detected and/or may trigger extreme vigilance and stress. We previously reported quantitative data on potential beneficial effects of using Nima on quality of life and depression for adults and adolescents with CeD participating in a 3-month clinical trial [7]. The present study covers the qualitative data from those same study participants, which were collected at the same time.

To provide context for the present study, we summarise some results of the quantitative report [7]. At follow-up, adults had statistically and clinically significant improvements in Overall and Limitations CeD-specific quality of life (CD-QOL) and depression scores (CESD); teenagers exhibited no changes. The benefits of using Nima acknowledged by almost all of the adults and teenagers (i.e. approximately 90%) included ease of use, helpfulness in following a GF diet and giving peace of mind. Not a major barrier for either group, however, more teenagers than adults agreed that using Nima made them anxious (43% versus 0.0%, $\chi^2 = 5.7$, d.f. = 1, $P = 0.02$). The vast majority of participants would recommend the device to others with CeD and planned to continue using it. Six participants (20%), all randomised to the lower use groups, desired more capsules. However, for adults in the 'moderate use' and 'heavy use' groups, as well as for adolescents in all three groups, the majority (60 adults, 100% adolescents) desired fewer. The portable gluten sensor did not encourage hypervigilance but, instead, selective testing once or twice per week in specific situations.

Materials and methods

Fifteen adults and 15 adolescents with biopsy-confirmed CeD were recruited from a New York City (NYC) CeD referral centre. All participants received a Nima sensor and were randomised to receive low, medium or high numbers of single-use capsules. Participants received either 24 capsules per month (72 in all 'heavy use'); 12 capsules per month (36 in all, 'moderate use'); or 6 capsules per month (18 in all, 'light use'). Group assignment was based on two iterations (one for adults and one for teens) of randomisation of 15 into three groups of five, as accomplished using a table of random digits by the statistician. Our goal in offering different 'doses' was two-fold: to get a handle on typical desired usage and to allow some participants sufficient room for the possibility of hypervigilance as evidenced by testing 'everything'. Two instructional handouts were provided and reviewed. The handouts described how to run a test, what can and cannot be accurately tested, and how to pair Nima with the Nima app to log one's history of tests (note that the sensor can be operated without being paired with the app). No recommendations for what, where or when to test were offered. The 3-month follow-up included open-ended questions on the benefits, barriers and limitations using Nima: Overall, what did you like most about Nima? Overall, what didn't you like about Nima?, Do you think Nima can improve the management of CeD for yourself? For others? And how? Spontaneous responses were noted and probed, as appropriate. Themes were identified via researcher consensus [8] and are described. Additional study details and quantitative results have been reported previously [7]. The study was approved (12/28/17) by the Institutional Review Boards at the Columbia University Medical Center and at Teachers College Columbia University and registered with ClinicalTrials.gov (NCT03321214).

Results

For adults, the median age was 34 years with a median CeD diagnosis 2.2 years previously. Two-thirds were female and most self-described as non-Hispanic white and college-educated. For adolescents, the median age was 16 years with a median CeD diagnosis 6.7 years previously. Nine (60%) were female, all self-described as non-Hispanic white. All participants were from the NYC metropolitan area. One adolescent was lost to follow-up and all adults completed the study. Table 1 summarises the main themes that emerged from the open-ended questions and includes illustrative quotes. Themes are listed in order of decreasing overall prevalence.

Participants liked that Nima provided added assurance that foods being presented as GF by family or friends, restaurants, cafeterias, or packaged product labels were, indeed, GF. Participants used Nima to '*double check*' foods they already believed to be GF. The convenient size and portability of the sensor, appreciated by most participants, allowed for Nima to be used in situations of uncertainty such as when traveling. For some, this translated to feeling less limited in trying foods and/or restaurants.

Participants disliked having attention drawn to them when using Nima or feeling as if they were deterring others from eating. Participants also disliked the physical difficulty associated with closing the capsules, a major drawback mentioned by the majority of participants. For adolescents, especially, this struggle was embarrassing and discouraged them from wanting to use the sensor around friends. Now, the manufacturer offers a small wrench to close capsules, an option not available at the time of the study. Some participants had concerns about Nima's accuracy and reliability. A lack of trust was often related to inconsistent results after multiple tests of the same

Table 1 Main themes and illustrative quotes based on open-ended questions concerning what participants most liked and disliked about Nima

Liked	Disliked
• Extra assurance to check foods presented as gluten-free a Prepared by family or friends b From restaurants or when travelling c From school lunch* d Made in a shared facility or uncertified *Quote: 'Was able to have Wendy's hot food out with friends instead of my PB&J from home because I felt safe after testing – in the past I never would have risked it'*	• Social difficulties a Three-minute wait for result (too long) b Noise during testing c Not wanting to draw attention or deter others from eating d Unsure what to do if sample tested positive for gluten while in restaurant e Guilt of not testing favorite places for fear of possibly having to eliminate† f Remembering to carry/use it* *Quote: 'I wasn't sure what to do if I got a wheat symbol in a restaurant. Re-order? Wait for a whole other meal to be cooked? Leave?'*
• Convenient size and/or portability a Being able carry in a pocket or purse b Can test inconspicuously *Quote: 'Fits into a backpack easily – am heading off to college in fall – capsules will be small and easy to carry'*	• Physical difficulties a Difficulty closing capsules‡ b Inserting appropriate-sized food sample *Quote: 'Couldn't bring to a party and do a test myself because the capsules were too hard to close. Could only use with my dad around'*
• Overall peace of mind a Added comfort, confidence b Added sense of control *Quote: 'If concerned, I had the device as a way to double check or triple check'*	• Questionable accuracy or reliability a Inconsistent repeated tests/didn't trust b Overly sensitive or not sensitive enough† c Only testing a sample of a whole dish† *Quote: 'Tested a packet of cheese sauce twice and got two different results – felt unreliable and frustrating'*
• Nima App benefits a Crowd-sourcing nature and reviews *Quote: 'Liked having other people's tests; used for eliminating places rather than places that said they were OK'*	• Nima App difficulties a Too few reviews to be helpful b loss of connectivity† *Quote: 'Searching for other peoples' tests was cumbersome'*
• Feeling less limited a By trying foods and/or restaurants they normally wouldn't b By adding back foods previously avoided *Quote: 'In the past, I would have been more hesitant, worried I might get sick. Now, I can test, get a smile, and feel relief/happy to eat the food'.*	• Cost of capsules *Quote: '$6 per capsule is too much'*
• Immediacy of testing *Quote: 'Liked that you could tell right away whether food had gluten in it – there's no other way to get instant results'*	• Inability to test fermented foods or meds† *Quote: 'If we go for Japanese or Thai, I wouldn't be able to test for gluten-free soy sauce'*
• Extra caution restaurants seemed to take when sensor was being used† *Quote: 'Can put it on the table and restaurants notice and think their reputation is on the line, so they are extra careful'*	

*Theme mentioned only by adolescents.
†Theme mentioned only by adults.
‡Nima now includes a wrench to close capsules. This wrench was not available during the study period.

meal. Some reported that the sensor was too sensitive for their personal needs. Some had difficulties with the mobile app. Others disliked the inability to test fermentable foods such as soy sauce, barley malt and beer.

Discussion

Long-term adherence to a strict GF diet is currently the only treatment for CeD. Avoidance of and contact with gluten can be a constant concern [9-11], particularly when eating outside the home. Nima is one of three currently available home or personal gluten detection kits [12]. A recent study of crowd-sourced data from Nima testing found that approximately one-third of restaurant foods that claimed to be GF contained detectable levels of gluten [13].

Our earlier report related to the present study confirmed a predominance of user satisfaction with Nima as indicated by an intention to continue using the device

and willingness to recommend it to others with CeD [7]. This was the case among both adults and adolescents. The present study is the first to qualitatively describe the experiences of adults and adolescents with CeD as they used such a sensor.

Our prior work has described the psychological impact of CeD treatment, and that dietary hypervigilance may be detrimental to quality of life [6]. However, we found that, in this pilot study, the use of Nima did not appear to foster hypervigilance but rather gave peace of mind to users [7]. The manufacturer intends Nima to be used in conjunction with asking questions about meals and food preparation, and not to use Nima as the sole source of information [14]. Our results suggest Nima was being used as intended. The sensitivity of the sensor beyond FDA standards appeared to be concerning to our study participants, potentially rendering the sensor too restrictive for some.

The present study has limitations. It was conducted at a single CeD referral centre, the sample size was small, the follow-up was brief and the population was demographically homogenous. Additionally, we only studied a sensor from a single manufacturer. Because comments by the study participants were sensor-specific, these data may not be generalisable to other portable gluten sensors.

Our findings suggest that both positive and negative experiences may be expected among patients using portable gluten sensors to help manage their CeD. Determining who might benefit from gluten sensors and in what settings is still unknown and should be investigated further. As future versions of this and other gluten sensors become available, it will be important to investigate the relationship between user experience with the sensors and clinical outcomes, such as mucosal healing, as well as the effects of use on long-term quality of life.

Transparency declaration

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

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Conflict of interests, source of funding, authorship

RW, AVC, NR and PZ declare that they have no conflicts to disclose. AL is on the Medical Advisory Boards for Dr Schar Foods and the University of Monash Low FODMAP Diet. BL serves as a consultant for Takeda, Innovate and Anokion. PG is a consultant to Janssen/J&J, Innovate, ImmunogenX. Speakers bureau – Abbvie. BL and PG are both unpaid members of Nima's Scientific Advisory Board.

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RW, BL and PG conceived and designed the study. AL and NR helped to facilitate study enrollment and implementation. PZ managed and analysed the data. AVC collected data and assisted with the thematic analysis of the qualitative data. All authors (RW, AVC, PG, AL, NR, PZ and BL) reviewed and commented on multiple drafts of the manuscript and all played a key role in the interpretation of study results. All authors have approved the final version of the manuscript submitted for publication.

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CORRIGENDUM

In Nishioka et al. [1], under the heading 'Reference standard', the following equation was incorrect (it should be a – before 6.19, not a +):

eCER = 879.89 + 12.51 × body weight (kg) + 6.19 × age + 34.51(if black) − 379.42(if female)

The correct equation is:

eCER = 879.89 + 12.51 × body weight (kg) − 6.19 × age + 34.51(if black) − 379.42(if female)

The authors apologize for any inconvenience this may have caused.

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