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Plasma carotenoids and (poly)phenols in people living with an ileostomy: associations with dietary intake

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Individuals with an ileostomy (ileostomists) face unique physiological and dietary challenges that may impact on the bioavailability of phytochemicals, including carotenoids and (poly)phenols. In this study, we aimed to investigate habitual intake of phytochemical-rich foods and circulating concentrations of lutein, zeaxanthin, and phenolic compounds in ileostomists. In a cohort of 57 adults with an ileostomy (mean age 52.1 ± 15.0 years), habitual intake of phytochemical-rich foods and circulating concentrations of key carotenoids and phenolic compounds were markedly low. Mean intakes of fruit and vegetables (181.8 g day^{-1}), lutein (0.3 mg day^{-1}) and total (poly)phenols (524.4 mg day^{-1}) were substantially below population averages, which was reflected in low plasma concentrations of lutein (0.14 ± 0.11 μM), zeaxanthin (0.04 ± 0.04 μM) and phenolic metabolites (0.34 ± 0.15 μM). Associations between dietary intake and circulating biomarkers were generally weak, although lutein intake was moderately correlated with plasma lutein (r = 0.52, P < 0.001). Circulating phytochemicals remained consistently low irrespective of time since surgery, highlighting the combined effects of dietary restriction and loss of colonic metabolism. These findings underscore the need to explore dietary reintroduction strategies and targeted supplementation to support long-term health in ileostomists.

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1. Introduction

Globally the burden of gastrointestinal (GI) disease is rising, with 1.9 million new cases of colorectal cancer (CRC)[1] and ~375 000 new cases of inflammatory bowel disease (IBD) reported annually.[2] Approximately 20% of CRC patients and 30% of IBD patients require surgical intervention to create a stoma as part of their treatment pathway.[3,4] Consequently, approximately ~200 000 people are living with a stoma in the UK,[5] a third of which have had an ileostomy.[6] Ileostomy surgery involves externalisation of the ileum onto the abdominal wall allowing for the diversion of digested material into a disposable pouch.[7]

Post-operatively, patients will face significant physiological challenges related to surgical recovery and adaption to an altered digestive system. Initially, patients are advised to follow a low-fibre diet,[8] however restriction of higher-fibre foods, such as fruits and vegetables, often persists long-term.[9–19] Avoidance of fruit and vegetables is of particular concern, given their abundance in bioactive dietary phytochemicals, such as carotenoids and (poly)phenols, which have beneficial effects on human health, according to mounting evidence from epidemiological and clinical studies. For instance, carotenoids (lutein and zeaxanthin) have been observed to exert protective effects against certain cancers[20,21] and ameliorate age-related macular degeneration (AMD);[22–24] a systematic review and metanalysis reported dietary intake of these carotenoids reduced risk of AMD by 26%.[25] Previous systematic reviews suggest additional benefits of diets rich in (poly)phenols on the lowered incidence of gastrointestinal cancers,[26] and other chronic diseases, such as type II diabetes,[27] while recent evidence indicates that higher intakes of (poly)phenols are beneficial to cardiometabolic health;[28] a large-scale randomised intervention study (N = 21 422 adults) observed a 27% reduction in cardiovascular related deaths for participants who received a cocoa extract supplement (500 mg flavanols per day).[29]

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To exert these beneficial effects, such compounds must be bioavailable and absorbed into the circulatory system. In the case of carotenoids, *e.g.* lutein and zeaxanthin, absorption largely occurs in the small intestine through lipid dependent mechanisms.[30] In contrast, small intestinal absorbance of many (poly)phenols is limited owing to their occurrence as glycosides, esters, or complex polymers, with a relatively minor fraction (5–10%) being deconjugated and absorbed here.[31] Instead, bioavailability of (poly)phenols is largely determined by microbiota mediated reactions and subsequent colonic metabolism.[32,33]

Consequently, for individuals living without a colon (ileostomists), the impact maybe two-fold, restriction of phytochemical-rich foods post-operatively leading to reduced dietary intake, and a lack of capacity to produce colonic microbiota-mediated metabolites.

To that end, this ileostomist observation study investigates the impact of physiological changes and dietary behaviours on plasmatic levels of selected carotenoids (lutein, zeaxanthin) and microbiota-mediated phenolic metabolites.

2. Methods

2.1. Participants

Adults (aged 18–70 years) living with an ileostomy were eligible to take part. While those aged <18 or >70 years at recruitment, pregnant or taking prescribed medications that contra-indicated overnight fasting were excluded. Recruitment took place between July 2017 and October 2019. Participants were primarily recruited through the Western Health and Social Care Trust in Northern Ireland with additional participants recruited *via* local patient and community groups.

2.2. Study design

An observational study in ileostomists was conducted with the prior approval of the Office for Research Ethics Committees Northern Ireland (16/NI/0267), the University of Ulster Ethical Committee and with the informed consent of participants and in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki 2024) and registered at https://www.ClinicalTrials.gov (NCT04143139). The work presented herein focuses on secondary outcomes from that observational study including anthropometric measurements, habitual dietary intake and plasmatic quantification of a range of phenolic compounds and selected carotenoids (lutein and zeaxanthin). While other dietary carotenoids, such as α-carotene, β-carotene, lycopene and β-cryptoxanthin, also have important physiological roles, lutein and zeaxanthin were the focus of the present study as they are primarily obtained from foods that ileostomists frequently restrict (leafy vegetables, eggs) and are predominantly absorbed in the small intestine,[34] allowing assessment of diet-related status independent of colonic metabolism.

Following an overnight fast, participants attended the Human Intervention Studies Unit at Ulster University Coleraine, where they provided blood samples and returned dietary questionnaires.

2.3. Dietary analysis

Habitual dietary intakes were estimated from a single 4 day food diary completed within ±14 days of sampling. Dietary intake was verbally confirmed with participants by trained researchers at the study appointment to ensure accuracy and completeness. Food diaries (n = 53) were subsequently analysed using Nutritics software (Nutritics Ltd, Swords, Ireland) to determine estimated daily intakes of carotenoids (lutein) and foods known to be rich in phytochemicals (namely lutein, zeaxanthin and (poly)phenols). The comprehensive online database, Phenol-Explorer (https://phenol-explorer.eu/), was used to develop an in-house database to estimate dietary intake of (poly)phenols. Raw food items reported in the 4 day food diaries with known (poly)phenol content were matched with the appropriate food listed on Phenol-Explorer. For dishes and processed foods containing multiple ingredients, each ingredient was matched to the appropriate food on Phenol-Explorer, considering the proportion contained within the consumed dish or food item using values from standard recipes available on Nutritics (dishes) or on retailer websites (processed foods). Whilst detailed information regarding cooking methods (*e.g.* temperature) were not collected, changes during processing and/or food preparation were accounted for by applying a process yield factor according to data available on Phenol-Explorer, which are derived from experimentally measured retention factors for common culinary treatments such as boiling, steaming, frying and baking.[35] Where no appropriate yield factor was available, a multiplier of 1 was applied. Intakes of individual (poly)phenolic compounds were estimated by multiplying food or beverage consumption by their (poly)phenol content per 100 g. For all classes of compound considered, total (poly)phenol intake was calculated as the sum of all quantified phenolics derived by chromatography without hydrolysis, or by chromatography after hydrolysis if the former was unavailable.

2.4. Biological sample collection and analysis

Fasting blood samples were collected by venipuncture into EDTA-containing tubes. All EDTA blood samples were kept chilled/on ice before processing. Plasma samples were prepared by centrifugation at 3000 rpm for 15 min at 4 °C and within 15 min of collection. Once prepared, plasma samples were aliquoted and immediately frozen at −80 °C. All samples were kept frozen at Ulster University according to Human Tissue Act (HTA) standards until further analysis.

2.4.1. Analysis of carotenoids in plasma samples. Prior to analysis, plasma samples were defrosted, vortexed, and 200 μL aliquots mixed with 200 μL of ethanol and 400 μL of hexane : dichloromethane (50 : 50, v/v) containing 0.1 g L^{-1} BHT. The mixture was vortexed and ultrasonicated for 10 min. The organic phase was collected, and the pellet was reextracted with 400 μL of hexane : dichloromethane mixture. Organic phases were pooled, vortexed, and reduced to dryness *in vacuo*

using a Speedvac concentrator (Thermo Fisher Scientific Inc. San José, CA) and resuspended in 200 μL of dichloromethane.

Extracted plasma samples were analysed for lutein and zeaxanthin using a Dionex Ultimate 3000 RS HPLC system (ThermoFisherScientific, San Jose, CA) equipped with a photodiode array detector and a YMC Carotenoid HPLC column (C30, 5 μm, 250 mm × 4.6 mm). The elution conditions consisted of two mobile phases: methanol/water (96 : 4 v/v, phase A) and methyl *tert*-butyl ether (phase B). The elution gradient was: 0 min, 95% phase A; 10 min, 90% phase A; 40 min, 55% phase A; 45 min, 25% phase A; 50 min, 100% phase B; and 57 min, 95% phase A. The flow rate was0.75 mL min^{-1}, and chromatograms were monitored at 450 and 285 nm. HPLC grade lutein and zeaxanthin were used as standards for identification and quantification. Identification of carotenoids was carried out by comparison of the HPLC retention times with reference standards. Lutein and zeaxanthin were quantified using seven-pointed calibration curves that were linear (correlation coefficients ≥0.99) within the working range: 0.125–12.5 mg L^{-1}.

2.4.2. Analysis of phenolic compounds in plasma. Prior to analysis, plasma samples were defrosted, vortexed, and 400 μL aliquots were mixed with 1 mL of 2% formic acid in acetonitrile. The mixture was vortexed and ultrasonicated for 10 min. After centrifugation at 1800*g* for 10 min, supernatants were reduced to dryness *in vacuo* using a Speedvac concentrator (Thermo Fisher Scientific Inc. San Jose, CA) and resuspended in 100 μL of methanol : water : formic acid (50 : 50 : 0.1, v/v/v), centrifuged at 1800*g* for 10 min, and 5 μL aliquots of the supernatant were analysed by UHPLC-HRMS. (Poly) phenols and their metabolites were analysed using a Dionex Ultimate 3000RS UHPLC system (Thermo Fisher Scientific, San José, CA, USA). Chromatographic separation was performed at 40 °C using a Zorbax SB-C18 RRHD column (100 × 2.1 mm i.d., 1.8 μm) (Agilent, Madrid, Spain) equipped with a guard pre-column of the same material. The flow rate was 0.2 mL min^{-1}. The mobile phases consisted of 0.1% aqueous formic acid (A) and 0.1% formic acid in acetonitrile (B). The 26 min gradient was as follows: 0–2 min, 3% B; 2–20 min, linear increase to 65% B; 20–21 min, increase to 80% B; 21–27 min, 80% B; followed by 10 min of re-equilibration at 3% B.

The UHPLC column was coupled to an Exactive Orbitrap mass spectrometer fitted with a heated electrospray ionization (HESI) probe (Thermo Fisher Scientific), and operated in negative ionization mode scanning from 100 to 1000 *m*/*z*. Capillary and the heater temperatures were set to 300 °C and 150 °C, respectively. Sheath and auxiliary gas flow rate were 20 units, sweep gas was 3 units, and the spray voltage was 4.00 kV. Xcalibur (3.0 software) was used for data acquisition and processing.

Compounds were identified by comparing the exact mass and the retention time with available authentic standards (MSI level 1). In the absence of standards, compounds were putatively identified based on accurate mass measurement (mass error < 5 ppm) and expected chromatographic behaviour. Putative annotations were supported by comparison with databases containing HRMS spectral information, including Phenol-Explorer (https://phenolexplorer.eu/), Phytohub (https://phytohub.eu/) and Metlin (https://metlin.scripps.edu/landing_page.php?pgcontent=mainPage). Identifications were categorized according to the Metabolic Standards Initiative (MSI) levels[36] as follows: level 1, confirmed identification using authentic standards; level 2, putatively annotated compounds based on accurate mass and database comparison.

(Poly)phenolic compounds were quantified by targeting the exact theoretical mass of the molecular ion, using standard curves within a concentration range of 0.01–100 ng μL^{-1} with a total of 12 calibration levels. A linear response was obtained for all available standards, as checked by linear regression analysis (R^2 > 0.9824). Limits of detection (range: 9–8193 nmol L^{-1}), limits of quantification (range: 27–24 582 nmol L^{-1}), the specificity (measured as the mass accuracy predicted compared with the observed mass error) less than 5 ppm in all compounds, the precision of the assay (as the coefficient of intra-assay variation, range 0.1–14.8%) and the recovery of the phenolic compounds (ranged from 81 to 116%) in plasma were considered acceptable for accurate quantification of metabolites. The analytical protocol was fully validated for sensitivity, specificity, response linearity, precision, accuracy, as well as matrix effect as described previously.[37]

2.5. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics Version 30.0.0.0 (172). All data were checked for normality using the Shapiro Wilk test. Non-normally distributed data were log transformed and reassessed for normality. Demographic variables and dietary intake data are presented as mean in Table 1 as mean ± standard deviation. Partial correlation (controlling for age and BMI) was used to explore relationships between time since surgery, dietary intake (carbohydrate, fibre, phytochemical rich foods [fruit and vegetables, leafy vegetables, berries, eggs, coffee and tea], lutein and (poly)phenols) with circulating levels (lutein, zeaxanthin and phenolic compounds). One-way ANOVA or Non-parametric ANOVA (Kruskal-Wallis) were conducted to establish differences for time elapsed since ileostomy surgery (0–3 years, 4–10 years and >10 years) *versus* dietary intake of phytochemicals and phytochemical-rich foods, and circulating levels. Bonferroni adjustment for multiple comparisons was performed to identify key differences between groups. Two-tailed *P* values lower than 0.05 were considered statistically significant.

3. Results

3.1 Participant characteristics

Sixty-five participants were screened for eligibility, of whom 61 were invited to take part as they met the inclusion criteria. Four participants were lost to follow up, resulting in a final sample of *N* = 57 who provided informed consent and took part in the study. Participants (mean age 52.1 ± 15.0 years) had

Table 1 Descriptive characteristics of study participants (N = 57)

Characteristic	Mean ± sd or n (%)
Sex	
Male	25 (43.9)
Female	32 (56.1)
Age (years)	52.1 ± 15.0
Weight (kg)	77.7 ± 19.8
BMI (kg m^{-2})	27.8 ± 6.7
Time since surgery[a] (years)	7.4 ± 23.6
Pre-existing condition resulting in ileostomy (%)	
Ulcerative colitis	34 (59.6)
Crohn's disease	12 (21.1)
Colorectal cancer	5 (8.8)
Other	6 (10.5)
Phytochemical-rich foods[b] (g day^{-1})	
Fruit and vegetables (total)	181.8 ± 153.4
Leafy vegetables	8.9 ± 17.1
Berries	9.6 ± 20.7
Eggs and egg dishes	18.9 ± 25.6
Coffee and tea(s)	689.1 ± 511.4
Energy[b] (kcal)	**2098.5 ± 621.6**
Macronutrients[b] (g day^{-1})	
Fat	82.8 ± 29.3
Protein	85.7 ± 24.3
Carbohydrate	243.2 ± 103.2
Fibre	18.4 ± 5.8
Compound[b] (mg day^{-1})	
Lutein	0.3 ± 0.9
Total (poly)phenols	524.4 ± 266.7
Flavonoids	117.9 ± 80.3
Stilbenes	0.4 ± 0.7
Phenolic acids	189.9 ± 92.0
Lignans	29.2 ± 25.5
Other (poly)phenols[c]	187.0 ± 113.8

Data presented as mean ± standard deviation, or n (%) for categorical data. (Poly)phenol intake calculated using in-house database. BMI, body mass index. [a] Data missing for 2 participants. [b] Data missing for 4 participants. [c] Main dietary sources of other (poly)phenols are cereals, oils, caffeinated and alcoholic beverages.

their ileostomy formed 7.4 ± 23.6 (range: 0–49) years prior to taking part in the study, with inflammatory bowel disease as the predominant reason for surgery (80.7%). CONSORT diagram depicting participant flow is presented in Fig. 1 and the characteristics of the participants who completed the study are presented in Table 1.

3.2. Dietary intake

Food diaries were completed by n = 53 participants, and their dietary data are summarised in Table 1. The estimated daily energy intake was 2098.5 ± 621.6 kcal day^{-1}: with macronutrient contributions to total energy of 36% from fat, 16% from protein, and 44% from carbohydrates. Mean total daily consumption of fruit and vegetables was 181.8 ± 153.4 g, or ~2 portions per day. Twenty-three participants (43%) reported leafy vegetable(s) consumption which comprised only a small proportion of their total fruit and vegetable intake, with a mean daily intake 8.9 ± 17.1 g day^{-1}. Similarly, berries accounted for 9.6 ± 20.7 g of daily fruit and vegetable intake and were reported for only 18 participants (34%). Other dietary sources of carotenoids, such as eggs and egg-based dishes (intake reported by 59% of participants, mean intake 18.9 ± 25.6 g day^{-1}), contributed to an overall lutein intake of 0.3 ± 0.9 mg day^{-1}. Total (poly)phenol intake was 524.4 ± 266.7 mg day^{-1}; phenolic acids were the largest contributors to this intake (mean 189.9 ± 92.0 mg day^{-1}), followed by "other" (poly)phenols (187.0 ± 113.8 mg day^{-1}) and flavonoids (117.9 ± 80.3 mg day^{-1}). Contribution to total (poly)phenol intake by (poly)phenol subclass for individual participants is outlined in Fig. 2.

3.3. Circulating lutein, zeaxanthin and phenolic compounds

Plasma concentrations of lutein and zeaxanthin in the ileostomists were 0.14 ± 0.11 μM and 0.04 ± 0.04 μM, respectively. Twenty phenolic compounds were identified and quantified, with a total concentration of 0.34 μM, primarily phenylpropanoic acids (0.17 μM across 6 compounds) and hippuric acids

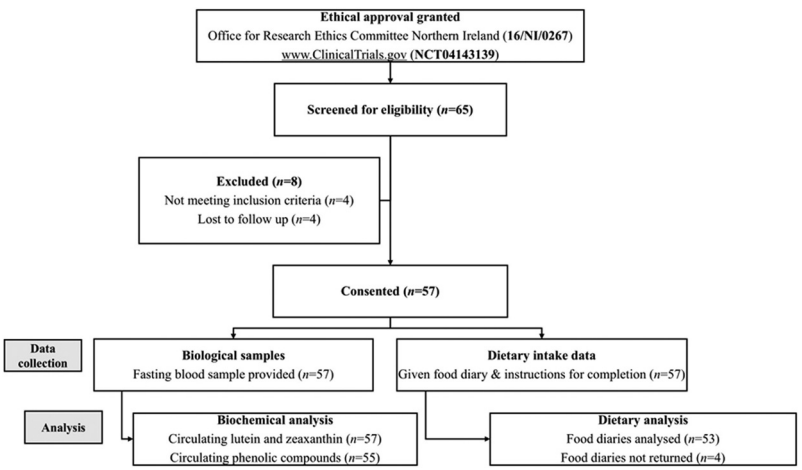

Fig. 1 CONSORT diagram.

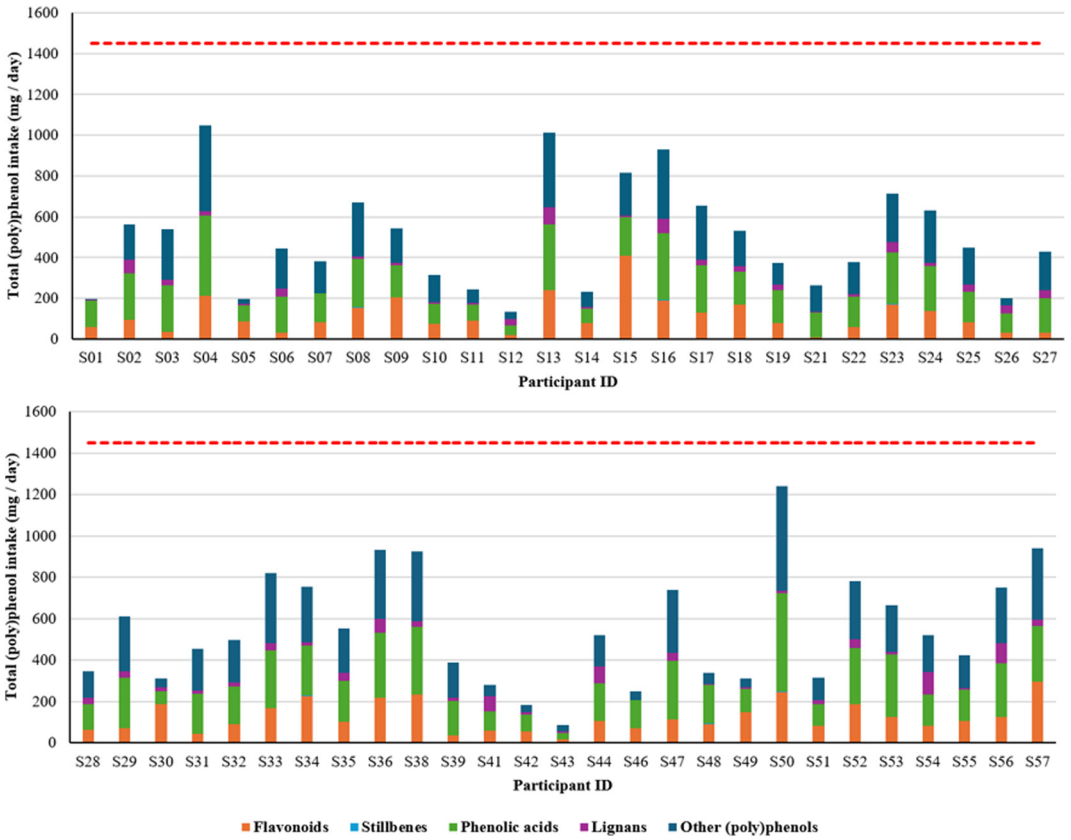

Fig. 2 Total (poly)phenol intake for individual participants. Data missing for n = 4 participants. Dashed line indicates total (poly)phenol intake in UK adults reported in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.[38]

(0.09 μM across 2 compounds). Benzoic acids (8 compounds) and phenylacetic acids (2 compounds) represented a smaller fraction of the circulating profile, totalling 0.08 μM. While two cinnamic acids were detected, their contribution to total plasma concentrations was negligible (<0.001 μM) (Table 2). Individual variability in these concentrations is illustrated in Fig. 3 and 4.

3.4. Correlation between dietary intake of phytochemical rich foods and circulating lutein, zeaxanthin and phenolic compounds

Partial correlation analysis (Table 3) revealed that total (poly)phenol intake was significantly correlated with intake of fruit and vegetables (r = 0.29, P = 0.044) coffee and tea (r = 0.73, P < 0.001). Total lutein intake was strongly associated with circulating lutein (r = 0.52, P < 0.001), yet no significant correlations were reported between dietary intake of carotenoid-rich (*i.e.* leafy vegetables, eggs) or (poly)phenol-rich (*i.e.* fruit and vegetables, berries, coffee and tea(s)) foods and circulating carotenoid concentrations. No significant correlations were observed between total metabolite concentrations and intake of phytochemical rich foods or total (poly)phenols.

Considering the proportion of participants classed as non-consumers of leafy vegetables (57%), berries (66%) and eggs (41%), exploratory subgroup analyses comparing consumers *versus* non-consumers of these phytochemical-rich foods were conducted. The findings were consistent with the overall weak associations observed between dietary intake and circulating compounds; no further meaningful differences for diet-biomarker associations were observed.

To establish whether the intake of phytochemical-rich foods/(poly)phenols and circulating concentration of carotenoids and metabolites changed with respect to time since stoma surgery, ileostomists were grouped according to post-operative duration (0–3, 4–10, >10 years) (Table 4). Fruit and vegetable intake was not significantly different across the three groups, indicating persistent dietary restriction. A similar pattern was evident for coffee and tea consumption as with fruit and vegetable intake. No group differences were observed for intake of lutein and other foods rich in phytochemicals (*i.e.* leafy vegetables, berries, eggs), however significant differences were observed in total (poly)phenol intake (P = 0.015), flavonoids (P = 0.029), phenolic acids (P = 0.018) and other (poly)phenols (P = 0.016). Bonferroni *post hoc* tests revealed that participants 0–3 years post-surgery had significantly lower intakes of total (poly)phenols compared to those in the 4–10 and >10 year groups (P = 0.047 and P = 0.030 respectively). Flavonoid intake was significantly greater in those 4–10 years

Table 2 Plasma carotenoids (n = 57) and (poly)phenols (n = 55) of ileostomists compared to adults with an intact colon

Compound	Plasma concentrations (μM)
Cinnamic acids	
3′-Methoxycinnamic acid-4′-glucuronide	n.d.
4′-Methoxycinnamic acid-3′-glucuronide	n.d.
Phenylpropanoic acids	
3-(3′-Hydroxyphenyl)propanoic acid-4′-*O*-glucuronide	n.d.
3-(4′-Hydroxyphenyl)propanoic acid-3-*O*-glucuronide	n.d.
3-Hydroxy-3-(3′-hydroxy-4′-methoxyphenyl)propanoic acid	0.14 ± 0.08
(Phenyl)propanoic acid-sulfate	n.d.
3-(4′-Hydroxyphenyl)propanoic acid	0.03 ± 0.01
3-(4′-Hydroxyphenyl)propanoic acid-3′-sulfate	n.d.
Benzoic acids	
Benzoic acid-4-sulfate	n.d.
3-Methoxy-4-hydroxybenzoic acid/3-hydroxy-4-methoxybenzoic acid	0.04 ± 0.03
Methoxybenzoic acid sulfate	n.d.
3-Hydroxy-4-methoxybenzoic acid-5-sulfate	n.d.
2-Hydroxybenzene-1-sulfate	n.d.
Hydroxy-methyl-benzene-sulfate 1	n.d.
Dihydroxy-benzene-sulfate	n.d.
Hippuric acids	
3′-Methylhippuric acid	0.03 ± 0.01
Hippuric acid	0.06 ± 0.04
Phenyl acetic acids	
Hydroxyphenylacetic acid-sulfate	0.01 ± 0.01
2-Hydroxy-2-(4′-hydroxy-3′-methoxyphenyl)acetic acid	0.03 ± 0.02
Total circulating phenolic compounds	0.34 ± 0.15
Lutein	0.14 ± 0.11
Zeaxanthin	0.04 ± 0.04

Data presented as mean ± SD. n.d., not detected.

post-op, compared to those 0–3 years after surgery. Additionally, the intake of phenolic acids and other (poly)phenols was significantly lower in the 0–3 years post-op, compared with those living with their ileostomy for >10 years (P = 0.021 and P = 0.022 respectively). Although there is some evidence of improved (poly)phenol intake as post-op duration increases, estimated consumption remains well below average intake (Fig. 2). No other significant differences were observed between groups, including circulating levels of carotenoids and phenolic metabolites, which remained consistently low regardless of time since surgery.

4. Discussion

To date, this is the first study to assess the dietary intake of phytochemical-rich foods and circulating carotenoids and phenolic compounds in people living with an ileostomy following a habitual diet. Overall, participants reported low consumption of fruits and vegetables, which was reflected in total (poly)phenol intake. Further, participants exhibited diminished plasma concentrations of lutein, zeaxanthin and phenolic compounds, indicative of the significant changes to the digestive tract and/or dietary behaviours resulting from ileostomy surgery. Correlations between dietary intake and circulating carotenoids and phenolics were generally weak or low, however small positive associations were observed between lutein intake and circulating lutein. Whilst no change to intake of fruits and vegetables, and other phytochemical rich foods, were observed when grouped by years since ileostomy surgery, total (poly)phenol intake was significantly greater in those who had their ileostomy for 4–10 and >10 years, compared to those 0–3 years post-operative. This was not reflected in plasma metabolite concentrations which were similar for participants at varying post-op durations.

In the UK, fruit and vegetable intake remains consistently below public health recommendations. Data from the National Diet and Nutrition Survey (NDNS) indicates that adults aged 19–64 years consume an average 3.3 portions per day.[39] This remains a public health concern given the extensive evidence linking fruit and vegetable-rich diets to a reduced risk of chronic diseases, including cardiovascular disease and certain cancers.[40–43] For adults living with an ileostomy, who actively and intentionally avoid fruits and vegetables to mitigate stoma-related symptoms,[9–19] the implications could be even more severe. Although reasons for long-term dietary restriction were not collected in this cohort, recent evidence suggests these behaviours are largely driven by mitigation of ileostomy-related symptoms (*i.e.* stomal blockages, increased output), resulting in fruit and vegetable intakes of approximately 2.7 portions per day.[17] Similar intakes were observed for this NI based cohort, where habitual daily consumption of fruit and vegetables was equivalent to 2.3 portions per day. More specifically, green leafy vegetables – a valuable source of lutein[44] – tends to be avoided by ileostomists[15] as evidenced in this study with over half of the cohort classed as non-consumers.

Dietary restriction in ileostomists is often not limited to just fruits and vegetables, with other carotenoid-rich foods also commonly avoided by this group. For example, consumption of eggs is frequently limited to reduce unpleasant odours from stoma output.[45] Which is reflected in the low mean daily intake of eggs and egg dishes (18.9 ± 25.6 g day^{-1}) in this group of NI ileostomists, whose intake is notably lower than NDNS data which suggests UK males and females consume an average of 54 g and 46 g of eggs and egg dishes per day, respectively.[46] Eggs are rich in both lutein and zeaxanthin,[47] unlike most plant sources which lack the latter,[44] and so are a valuable dietary source of carotenoids. Whilst there are no formal recommendations for lutein intake, 5–10 mg day^{-1} has been suggested as a target to protect eye health.[48] Estimated lutein intakes in the present cohort were 0.3 ± 0.9 mg day^{-1}; well below the suggested target levels, and habitual intakes reported in other populations, which range from 0.74 mg day^{-1} in Spanish populations,[49] to 1.59 mg day^{-1} in UK adults.[50]

Whilst habitual lutein intake in the current study was low, this was correlated with circulating levels, likely a result of

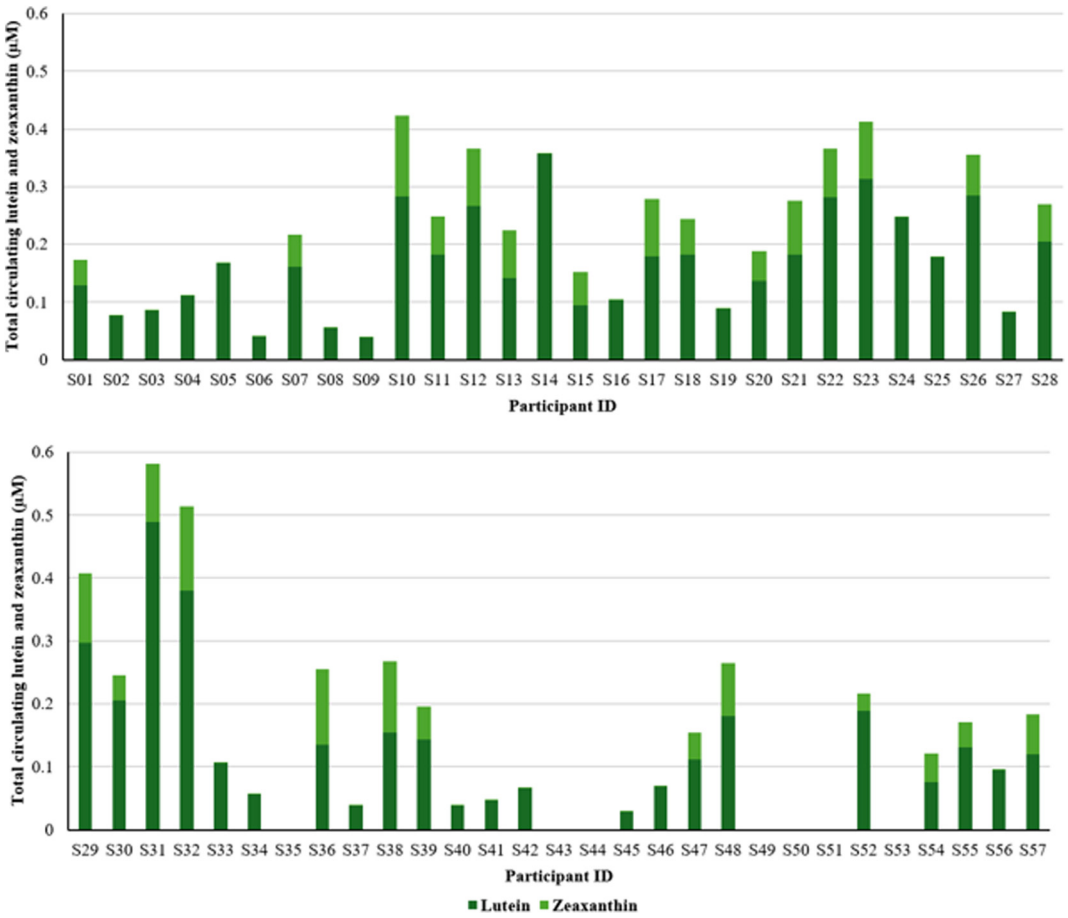

Fig. 3 Circulating lutein and zeaxanthin for individual ileostomist participants.

lutein's high accessibility in the small intestine (80%).[34] However, intakes of carotenoid-rich foods in the current study population were not significantly correlated with circulating levels. The current study included a relatively small sample, which likely impacted the statistical power of these tests; the high proportion of participants being non-consumers of lutein rich foods (*i.e.* leafy vegetables, eggs) further limits this power which could provide an explanation for the weak diet-biomarker associations observed. Nevertheless, plasma lutein and zeaxanthin concentrations in the current study (0.14 ± 0.11 μM and 0.04 ± 0.04 μM respectively) were notably lower when compared to mean baseline values observed in adults with an intact colon in western populations (*i.e.* Ireland, United States, Canada), which range from 0.19–0.41 μM and 0.05–0.19 μM respectively.[51–57] This disparity is likely a result of persistent dietary restriction of carotenoid-rich foods. Small-scale, non-randomised interventions have demonstrated the benefits of individualised dietary advice in supporting dietary reintroduction in the early post-operative period.[58–62] However, considering the long-term dietary restriction evidenced in this and other ileostomy cohorts,[19] tailored dietary support to improve intake of carotenoid and other phytochemical-rich foods, warrant consideration as strategies to support long-term eye health and overall nutritional status in this population. Such interventions must consider common barriers to dietary-reintroduction – including fear of stoma-related symptoms[17] and limited access to dietetic support[63] – and may need to be complemented with targeted supplementation where adequate intakes cannot be achieved through diet alone.

Habitual dietary intake of (poly)phenols was highly variable within ileostomist participants, with estimated intakes of 524.4 ± 266.7 mg day^{-1} (ranging from 84.7–1238.5 mg day^{-1}). This is consistent with population-level distributions reported in adults with an intact colon, despite absolute intakes being substantially lower. For example, total (poly)phenol intakes from NDNS data range from 634 mg day^{-1} (adults aged 19–34 years) to >1000 mg day^{-1} (adults aged >50 years).[64] Estimations from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort suggest total (poly)phenol intakes in UK adults may be higher, at approximately 1450 mg day^{-1} (median value, 5th–95th percentile; 662–2309 mg day^{-1}),[38] and intake of US adults following a typical western diet has been estimated as 1666 mg day^{-1}.[65] Variation in pre-

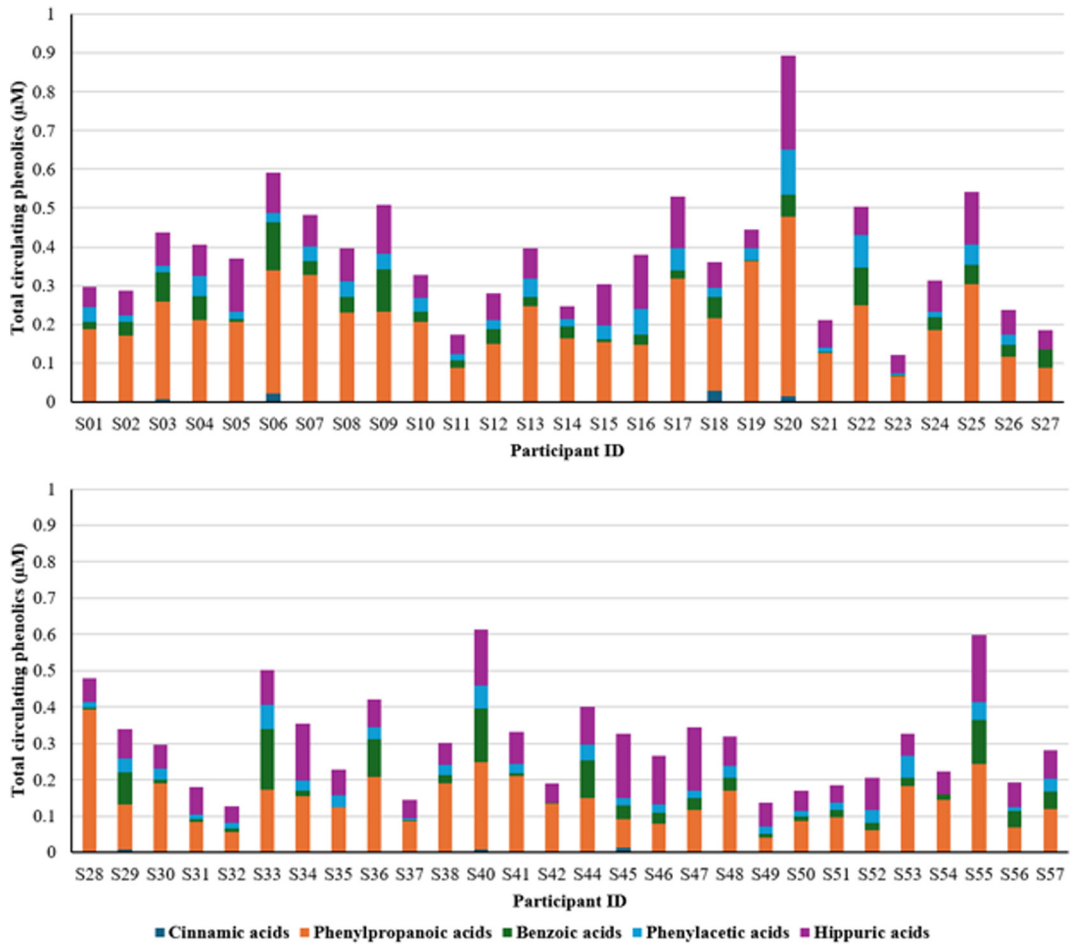

Fig. 4 Circulating phenolic compounds for individual ileostomist participants. Data missing for n = 2 participants.

vious reports of (poly)phenol intake in adults with an intact colon are likely owing to differences in dietary assessment methods and databases used, nevertheless (poly)phenol consumption amongst ileostomists is substantially lower (~two thirds less) in comparison to the general population. The primary contributors to total (poly)phenol intake in ileostomists were phenolic acids (36% of total (poly)phenol intake), consistent with other cohorts.[38,65] Contribution from flavonoids was approximately 23%, in alignment with a US study where intake from this subclass made up 23% of total (poly) phenol intake.[65] However, a greater proportion of flavonoid intake was observed in UK populations (approximately 40%)[38,64] likely reflective of dietary restriction of foods rich in these compounds, including berries and other fruits and vegetables. Whilst (poly)phenol intake was significantly higher in those living with an ileostomy for longer, fruit and vegetable consumption remained unchanged. Consumption of undefined, or other, (poly)phenols, which are largely found in cereals, oils, caffeinated and alcoholic beverages[66,67] also made up a significant proportion of total (poly)phenol intake (36%). Intake from this subclass was increased in those who had their ileostomy for a greater period. This indicates that improvements in total (poly)phenol intake over time were driven by beverages, such as coffee and tea, and cereal foods rather than a return to fruit and vegetable rich dietary patterns.

Alongside dietary intake of (poly)phenols, plasma phenolic compounds, including phenolic acids and their microbial-derived metabolites, were low in ileostomists with substantial inter-individual variability (0.34 ± 0.15 μM). This heterogeneity likely reflects variation in small intestinal transit time, which may influence the extent of (poly)phenol absorption and exposure to residual microbial metabolism. To contextualise these unusually low concentrations, secondary analysis from the EPIC cohort (n = 1618) demonstrates that free-living adults of similar age (56.8 years) and BMI (26 kg m^{-2}) with an intact colon had circulating levels of phenolic acids (benzoic acids, phenylacetic acids, phenylpropanoic acids, cinnamic acids) exceeding 1.8 μM – more than five-fold greater than those observed in the current ileostomist cohort.[68] Hippuric acids were not reported here, which made up ~27% of circulating phenolic concentrations in ileostomy participants in the

Table 3 Correlations for dietary intakes and circulating compounds, controlling for age and BMI

	Fruit and veg	Leafy veg	Berries	Eggs	Coffee and tea	Lutein	Total (poly)phenols	Lutein	Zeaxanthin	Total (poly)phenols	Cinnamic acids	Phenylpropanoic acids	Benzoic acids	Phenylacetic \ acids	Hippuric acids
Estimated daily intakes															
Fruit and veg	1.00														
Leafy veg	0.27	1.00													
Berries	**0.39**[b]	0.18	1.00												
Eggs	0.24	0.17	−0.05	1.00											
Coffee and tea	0.07	0.04	−0.05	0.25	1.00										
Lutein	0.09	0.26	0.00	0.12	0.07	1.00									
Total (poly)phenols	**0.29**[a]	0.10	0.28	0.13	**0.73**[b]	−0.05	1.00								
Circulating levels															
Lutein	0.03	0.08	0.08	0.04	−0.02	**0.52**[b]	−0.17	1.00							
Zeaxanthin	0.05	−0.07	0.26	0.08	0.21	0.21	0.08	**0.64**[b]	1.00						
Total (poly)phenols	−0.01	0.01	0.08	0.08	0.01	−0.22	0.02	−0.11	−0.06	1.00					
Cinnamic acids	−0.02	−0.08	−0.18	0.28	0.05	−0.12	−0.10	0.00	0.00	0.28	1.00				
Phenylpropanoic acids	−0.03	0.04	0.10	−0.02	−0.03	−0.17	−0.04	−0.06	−0.02	**0.08**[b]	0.21	1.00			
Benzoic acids	0.14	−0.08	0.02	0.21	0.09	−0.19	0.02	−0.06	−0.03	**0.60**[b]	**0.33**[a]	0.27	1.00		
Phenylacetic acids	−0.01	0.03	0.19	−0.08	0.12	−0.19	0.14	−0.06	0.05	**0.65**[b]	0.01	**0.47**[b]	**0.42**[a]	1.00	
Hippuric acids	−0.11	0.00	−0.03	0.11	−0.09	−0.10	−0.43	−0.16	−0.15	**0.53**[b]	0.00	0.25	0.23	**0.30**[a]	1.00

[a] Correlation is significant at the 0.05 level (2-tailed). [b] Correlation is significant at the 0.01 level (2 tailed).

current study; therefore the disparity in circulating phenolic compounds between ileostomists and adults with an intact colon presented is likely greater. However, a previous ADME study reported that hippuric acid levels remained unchanged in ileostomists 0–24 h following ingestion of mango purée.[69,70] Taken together, this indicates that these metabolites are not truly reflective of (poly)phenol intake and could, in part, explain the lack of correlations between dietary (poly)phenol intake and plasma levels. This is line with previous work highlighting the limitations of correlation analyses when applied to complex and metabolically diverse phenolic biomarkers.[71] Moreover, the metabolite profile in ileostomists was sparse, with many conjugated compounds undetectable. In contrast, adults with an intact colon exhibit a more diverse range of metabolites, even when following a (poly)phenol restriction diet.[69] This is consistent with previous untargeted metabolic analyses which displayed significant differences in the plasma metabolic profiles in patients with a temporary ileostomy, following ileostomy reversal and restoration of colonic metabolism,[72] pointing towards persistent dysregulation of gut microbiota in ileostomists, independent of dietary intake. Similarly, profiling of phenolic metabolites after controlled dietary (poly)phenol intake in adults with and without a colon demonstrated many microbial-derived metabolites were reduced or altered in the absence of colon fermentation.[69] This is further supported by previous studies, which report an absence of γ-valerolactones in the plasma of ileostomy participants following ingestion of cocoa flavan-3-ols,[73] and correlations between dietary intake of flavan-3-ols and plasma γ-valerolactones in older adults with an intact colon highlighting the dependence of these metabolites on colonic microbial metabolism.[73] Taken together, this indicates that the low circulating levels of phenolic compounds in ileostomists is not solely a function of dietary intake and are likely to persist over time. This aligns with observations from the present study, where there were limited correlations between intake of (poly)phenols, (poly)phenol-rich foods and circulating levels, and circulating compounds remained consistently low when participants were grouped by post-operative duration, regardless of dietary intake.

This observation study has some limitations. Most notably, the clinical relevance of the observed plasma concentrations in ileostomists should be interpreted with caution due to the absence of a matched control group (*i.e.* adults with an intact colon). Secondly, habitual intake was estimated from a single 4 day food diary, which does not fully capture long-term dietary patterns. Additionally, the study design did not allow for consideration of the timing of food consumption relative to blood sampling. This is an important limitation as the temporal proximity of intake can influence circulating levels of compounds with short elimination half-lives. Despite these constraints, this work represents the first comprehensive investigation of the relationship between phytochemical intake and circulating carotenoids and phenolic compounds in adults living with an ileostomy.

Table 4 Differences in dietary intake of phytochemical rich foods, lutein and (poly)phenols with time elapsed since ileostomy surgery

	0–3 years (n = 18)	4–10 years (n = 19)	>10 years (n = 18)	X^2 (df)	p
Variables					
Dietary intake[a]					
Fruit and vegetables (g day^{-1})	71.3 ± 62.4	61.1 ± 53.1	160.4 ± 182.6	3.47 (2)	0.178
Leafy vegetables (g day^{-1})	12.7 ± 25.3	7.0 ± 11.7	6.8 ± 10.1	0.25 (2)	0.178
Berries (g day^{-1})	5.7 ± 14.3	14.3 ± 28.5	9.1 ± 17.4	1.49 (2)	0.474
Eggs (g day^{-1})	23.7 ± 33.4	15.0 ± 15.4	17.9 ± 24.8	0.29 (2)	0.866
Coffee and tea (ml day^{-1})	480.7 ± 431.2	814.6 ± 627.7	779.1 ± 415.0	4.96 (2)	0.084
Lutein (mg day^{-1})	0.5 ± 1.5	0.2 ± 0.2	0.2 ± 0.2	0.21 (2)	0.900
Total (poly)phenols	372.9 ± 186.2	619.5 ± 334.8	585.9 ± 200.5	8.38 (2)	0.015
Flavonoids	83.1 ± 55.3	156.2 ± 100.6	116.5 ± 66.6	7.10 (2)	0.029
Stilbenes	0.3 ± 0.5	0.4 ± 0.9	0.4 ± 0.7	0.82 (2)	0.665
Phenolic acids	139.5 ± 64.4	215.3 ± 119.4	216.2 ± 65.1	8.05 (2)	0.018
Lignans	27.2 ± 27.3	30.7 ± 29.6	29.7 ± 20.3	0.76 (2)	0.684
Other (poly)phenols[c]	122.8 ± 84.9	216.5 ± 147.2	223.1 ± 73.4	8.32 (2)	0.016
Plasma concentrations					
Total phenolic compounds[b] (μM)	0.30 ± 0.13	0.32 ± 0.09	0.37 ± 0.15	3.47 (2)	0.176
Lutein[d] (μM)	0.13 ± 0.14	0.15 ± 0.08	0.15 ± 0.10	1.19 (2)	0.551
Zeaxanthin[d] (μM)	0.04 ± 0.05	0.03 ± 0.04	0.05 ± 0.05	1.92 (2)	0.383

Data presented as mean ± SD. (Poly)phenol intake calculated using in-house database. [a] Data missing for n = 6 participants, n = 51 included in analysis. [b] Data missing for n = 4 participants, n = 53 included in analysis. [c] Main dietary sources of other (poly)phenols are cereals, oils, caffeinated and alcoholic beverages. [d] Data missing for n = 2 participants, n = 55 included in analysis.

5. Conclusions

Ileostomists exhibit markedly reduced circulating carotenoids and phenolic compounds, likely driven by both dietary restriction and loss of colonic metabolism. While positive associations were observed between lutein intake and circulating lutein, overall diet – plasma concentration correlations remained weak, reflecting limited consumption of phytochemical-rich foods and the absence of colonic fermentation. Intake of (poly)phenols was improved in those who had their ileostomy for longer, however fruit and vegetable intake and circulating levels remained consistently low. These results underscore the dual impact of physiological and behavioural factors on phytochemical status, highlighting the need for future interventional studies to investigate whether graded reintroduction of fruits, vegetables and other phytochemical-rich foods is feasible and tolerable, and to assess the potential role of targeted supplementation in supporting long-term health in this population.

Author contributions

C. G. designed the study; K. P., M. S., R. L., G. O. and C. G. conducted study; G. P. C. and S. C. J. performed the analysis of lutein, zeaxanthin and phenolic compounds in plasma; N. M. and B. O. M. performed dietary and statistical analysis; N. M. wrote the original manuscript, and all authors contributed to reviewing and editing the final draft.

Conflicts of interest

The authors confirm there are no conflicts of interest to declare.

Data availability

Anonymised data supporting the findings of this study are available from the corresponding author upon reasonable request. Restrictions apply to the availability of these data to protect participant confidentiality and in accordance with ethical approval conditions.

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