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Colorectal polyp outcomes after participation in the seAFOod polyp prevention trial: Evidence of rebound elevated colorectal polyp risk after short-term aspirin use

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Summary

Background: The seAFOod polyp prevention trial was a randomised, placebo-controlled, 2×2 factorial trial of aspirin 300 mg and eicosapentaenoic acid (EPA) 2000 mg daily in individuals who had a screening colonoscopy in the English Bowel Cancer Screening Programme (BCSP). Aspirin treatment was associated with a 20% reduction in colorectal polyp number at BCSP surveillance colonoscopy 12 months later. It is unclear what happens to colorectal polyp risk after short-term aspirin use.

Aim: To investigate colorectal polyp risk according to the original trial treatment allocation, up to 6 years after trial participation.

Methods: All seAFOod trial participants were scheduled for further BCSP surveillance and provided informed consent for the collection of colonoscopy outcomes. We linked BCSP colonoscopy data to trial outcomes data.

Results: In total, 507 individuals underwent one or more colonoscopies after trial participation. Individuals grouped by treatment allocation were well matched for clinical characteristics, follow-up duration and number of surveillance colonoscopies. The polyp detection rate (PDR; the number of individuals who had ≥1 colorectal polyp detected) after randomization to placebo aspirin was 71.1%. The PDR was 80.1% for individuals who had received aspirin (odds ratio [OR] 1.13 [95% confidence interval 1.02, 1.24]; $p = 0.02$). There was no difference in colorectal polyp outcomes between individuals who had been allocated to EPA compared with its placebo (OR for PDR 1.00 [0.91, 1.10]; $p = 0.92$).

Conclusion: Individuals who received aspirin in the seAFOod trial demonstrated increased colorectal polyp risk during post-trial surveillance. Rebound elevated neoplastic risk after short-term aspirin use has important implications for aspirin cessation driven by age-related bleeding risk. ISRCTN05926847.

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1 | INTRODUCTION

The seAFOod polyp prevention trial was a randomised, double-blind, placebo-controlled, 2×2 factorial trial of the colorectal cancer (CRC) chemoprevention efficacy of aspirin 300 mg daily and eicosapentaenoic acid (EPA) 2000 mg free fatty acid equivalents daily in 'high risk' patients undergoing colonoscopy surveillance in the English Bowel Cancer Screening Programme (BCSP).[1,2] Trial participants were aged 55–73 years and had been invited for screening colonoscopy on the basis of a positive faecal occult blood test or 'high risk' screening flexible sigmoidoscopy.[1,2] The trial population was predominantly (80%) male and White European, in keeping with the demographic characteristics of individuals undergoing BCSP colonoscopy.[1,2] Patients with a known genetic CRC predisposition were excluded.[1,2] The intervention period between the screening colonoscopy and the first surveillance colonoscopy was 12 months in individuals deemed 'high risk' (defined as ≥5 polyps or ≥3 polyps, if one or more polyps were ≥10 mm in size), a duration which has been associated with a similar degree of colorectal polyp risk reduction compared with a 3-year intervention period in previous aspirin polyp prevention trials.[3]

The primary finding from the seAFOod trial was that aspirin and EPA did not reduce colorectal polyp incidence, measured as the 'adenoma detection rate' (the % of individuals with one or more colorectal polyps 12 months after clearance colonoscopy) by an 'at the margins' analysis of the individual interventions.[1,2] However, aspirin use was associated with a significant reduction in overall colorectal polyp risk (measured as mean polyp number per participant).[1,2] There was also colorectal site- and polyp type (conventional adenoma or serrated polyp)-specific chemoprevention activity of aspirin and EPA; notably, randomisation to aspirin was associated with reduced risk of serrated lesions, unlike EPA treatment, which was associated with a statistically significant reduction in risk of left-sided (distal to the splenic flexure) conventional adenomas.[1,2] The seAFOod trial was not powered for a pre-specified 'inside the table' analysis of the four treatment groups, including combined aspirin and EPA therapy.[1,2] However, laboratory studies have since suggested that aspirin and EPA may have a positive interaction for CRC risk prevention via synthesis of novel oxylipins such as E-type resolvins,[4] and/or substrate diversion of EPA secondary to cyclooxygenase inhibition by aspirin.[5]

It is not known whether CRC chemoprevention agents inhibit either, or both, initiation and/or growth of tumours at the earliest stages of intestinal tumorigenesis. Inhibition of tumour initiation is hypothesised to provide prolonged benefit after cessation of a chemoprevention agent. Alternatively, tumour growth suppression alone (without inhibition of tumour initiation) is hypothesised to lead to a 'rebound' increase in colorectal polyp incidence, whereby undetectable tumours that initiated but did not grow to become macroscopically visible during chemopreventative agent use, are de-repressed and become detectable upon cessation of chemoprevention therapy. Knowledge of whether a 'rebound' increase in colorectal polyps (indicative of increased CRC risk) occurs will be critical in order to define guidelines for the duration of chemoprevention use, optimal timing of cessation of therapy and best use of accompanying colonoscopic surveillance. This is particularly important in the elderly, in whom the common practice is to stop aspirin therapy driven by increasing concern about elevated bleeding risk.[6]

seAFOod trial participants were invited by the English BCSP to undergo surveillance colonoscopy at 3 years (or earlier dictated by prior colorectal polyp findings) after the initial 'high risk' 1-year surveillance procedure (which was the seAFOod trial exit colonoscopy), with subsequent surveillance dependent on the most recent findings (Figure S1). All trial participants provided informed consent for collection and use of post-trial BCSP data up to 6 years after trial participation (covering a maximum of two 3-year surveillance cycles; Figure S1). Therefore, we obtained post-trial colonoscopy data in order to investigate colorectal polyp risk following cessation of short-term chemoprevention with aspirin and EPA.

2 | METHODS

2.1 | Bowel cancer screening programme data

English BCSP Screening System (BCSS) data were provided under approvals from the Public Health England Office for Data Release (ODR1920_199 dated 6/9/2021) and the BCSP Research Advisory Committee (BCSPRAC_285). This project was a component of the STOP-ADENOMA study, which had approval from the London and Surrey Borders Research Ethics Committee (19/LO/1655) and is registered as ISRCTN05926847.

All participants in the seAFOod polyp prevention trial provided specific, written informed consent to allow access to post-trial BCSS data.[1,2] Endoscopy surveillance data on procedures that occurred in the BCSP for a maximum of 6 years after the seAFOod trial exit colonoscopy (which was the first 'high risk' BCSP surveillance colonoscopy at 12 months after screening) were obtained, where linkage was possible (Figure S1). The first trial exit colonoscopy was in November 2012 and the last trial exit colonoscopy was in June 2017.

The BSCP data extraction date was 7 October 2021. BCSS data were linked to the seAFOod trial database using date of birth, sex and hospital site, as well as dates of the screening and first surveillance colonoscopy. No other data on seAFOod trial participants were available after the trial finished, including subsequent use of aspirin and/or omega-3 polyunsaturated fatty acid supplements. Participants were not told their treatment allocation after the trial had completed and the Plain English Summary of the trial described the null primary outcome of the trial without any recommendation for future CRC chemoprevention.

2.2 | Data collection

Data were obtained at individual-, test (each endoscopic procedure)-, BCSP episode (which can include one or more endoscopic procedures as a single administrative clinical episode)- and polyp-level. For each post-trial surveillance colonoscopy, the time elapsed since the first

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surveillance colonoscopy and extent of examination (complete or incomplete colonoscopy) were noted, as well as the number of separate procedures per individual. Endoscopic procedures occurring within 6 months of the date of the trial exit colonoscopy were assumed to be part of the same episode of BCSP care as the surveillance colonoscopy at 12 months after screening and were discounted.

Colorectal cancer detection during BCSP colonoscopic surveillance was stipulated as a key outcome. Colorectal polyp analysis was stratified according to total number of polyps, polyp type (adenoma or serrated-hyperplastic), polyp size (histological size as per BCSP guidelines), polyp location (proximal [right-sided]—proximal to splenic flexure; distal [left-sided]—at and distal to splenic flexure), and on the basis of 'advanced' features (defined as ≥10 mm by histology size, and/or high-grade dysplasia and/or any villous architectural component), in keeping with criteria used in the seAFOod trial.[1,2] Although the terminology and classification of serrated and hyperplastic polyps have changed since the start of the seAFOod trial in 2011, with the acceptance that diminutive (≤5 mm) rectal hyperplastic polyps can be ignored for the purposes of risk stratification for future surveillance,[7] we continued to report a combined serrated-hyperplastic polyp category in order to facilitate comparison with the original seAFOod trial results.[1,2]

Colorectal polyp incidence was reported as the 'polyp detection rate' (PDR; calculated as the % of individuals with one or more colorectal polyps detected during the total surveillance period). The colorectal polyp number, size in millimetres (the mean value of the maximum dimension of all polyps detected per individual, measured histologically [or endoscopically if the complete polyp could not be assessed]) and 'burden' (defined as the sum of the individual polyp diameters) were reported as the mean value per person (for example, mean polyp number per person [MPP]).

In addition, the BCSP classification of colonoscopic outcome (normal, abnormal [but no polyp], one or more polyps [sub-classified as 'high-risk' {≥5 polyps or ≥3 polyps if one or more are ≥10 mm in size}, 'intermediate-risk' {3–4 subcentimetre polyps}, 'low-risk' {1–2 subcentimetre polyps}]), which was in use during the seAFOod trial, was used to report findings at procedural and BCSP episode level.[8] Since the seAFOod trial finished, updated British Society of Gastroenterology (BSG) Guidelines on colonoscopic surveillance after polypectomy have been adopted by the BSCP since mid-2020.[7] Current risk stratification now consists of a single 'high-risk' category (≥5 polyps or ≥2 polyps if one or more are ≥10 mm in size) for 3-year surveillance, as opposed to other findings that do not warrant further colonoscopic surveillance. Therefore, data were also analysed at test and episode level according to the new BCSP classification, to ensure that the results reflected current BCSP practice and current US Multi-Society Task Force on CRC guidelines on colonoscopic surveillance.[9]

The baseline characteristics (age, sex, body mass index [BMI], smoking status) of seAFOod trial participants that had post-trial BCSP surveillance data (included in this analysis) versus trial participants that did not have any linked endoscopic BCSP surveillance data after the seAFOod trial were compared.

2.3 | Statistical analysis

2.3.1 | Post-trial surveillance colonoscopy outcomes

The primary outcome for the post-trial analysis was stipulated as total colorectal polyps by an 'at the margins' analysis, consistent with the primary analysis of the seAFOod trial,[1,2] by comparing data from those randomised to aspirin versus no aspirin, and individuals randomised to EPA versus no EPA.

Colorectal polyp data are reported as the % value for each PDR outcome, as well as the mean and 95% confidence interval (CI) values for colorectal polyp number (MPP). Secondary colorectal polyp size and burden data are also reported as mean and 95% CI values. The Student's *t*-test or one-way analysis of variance was used for univariate comparison of continuous participant characteristics and follow-up duration across two or more groups, as appropriate. A chi-squared test was used to compare sex ratios across treatment groups. Treatment group differences in PDR were tested by logistic regression. Data are reported as the odds ratio (OR) and 95% CI. A negative-binomial regression model was used to compare colorectal polyp number (and polyp burden) outcomes based on the skewed distribution of individual colorectal polyp frequencies that was apparent at the trial exit colonoscopy (Figure S2).[1,2] The incidence rate ratio (IRR) and 95% CI values for groups based on prior seAFOod trial treatment allocation are reported for comparison with the respective placebo group. The mean colorectal polyp size per person was compared across previous trial treatment allocation by linear regression and reported as the mean size difference and 95% CI. All models were adjusted for age and sex and also included BCSP research site as a random effect. Statistical significance for all analyses was assumed at $p \leq 0.05$.

In addition to the main analysis of cumulative post-trial colorectal polyp outcomes, which included BCSP surveillance data from colonoscopies for up to 6 years after the trial exit colonoscopy (Figure S1), we also performed a sensitivity analysis of total colorectal polyp outcomes at a single point in time after seAFOod trial participation. This was restricted to individuals who had 3-year surveillance colonoscopy outcomes only (using a 2.5- to 3.5-year post-trial window), excluding individuals who had undergone any post-trial procedure prior to this.

2.3.2 | seAFOod trial colonoscopy outcomes

We repeated the 'at the margins' analysis of total colorectal polyp number from the seAFOod trial in the subgroup of trial participants that had post-trial colonoscopy data, in order to confirm the original trial treatment effect of aspirin on total colorectal polyp risk in the current study cohort. The same Poisson regression model included in the original final trial analysis, adjusted for the BCSP research site as a random effect and for repeat colonoscopy at trial baseline, was used.[1,2] A separate negative-binomial model

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was also used based on the distribution of individual colorectal polyp frequencies that was apparent at the trial exit colonoscopy (Figure S2).[1,2]

In addition, we performed *post hoc* 'inside the table' analysis of seAFOod trial colorectal polyp outcomes, comparing the four individual treatment groups (placebo aspirin and placebo EPA [placebo]; active aspirin and placebo EPA [aspirin]; placebo aspirin and active EPA [EPA]; active aspirin and active EPA [aspirin and EPA]), on the basis that the total number of colorectal polyps detected at the seAFOod trial exit colonoscopy in the group receiving both aspirin and EPA together was noticeably less than in the groups who received either agent alone, or placebo only.[1,2] Using the original seAFOod trial outcomes data and the same regression model used in the primary trial analysis, we generated the IRR and 95% CI for the group that received combined treatment compared with the other three groups.[1,2] An interaction between aspirin and EPA was analysed by comparing individuals allocated to active EPA with those who received placebo EPA, using a Poisson regression model,[1,2] which also included age, sex, BMI, smoking status, alcohol intake, baseline red blood cell % EPA level and randomisation to aspirin as co-variables, with statistical significance reported as the Wald test for interaction. Evidence of an interaction between aspirin and EPA prompted a secondary comparison of the post-trial surveillance colonoscopy outcomes across the four treatment groups, in addition to the primary analysis according to factorial margins.

2.4 | Patient and public involvement

A patient and public representative was a member of the STOP-ADENOMA study group and supported the application to the Public Health England Office for Data Release for access to the BCSP data, by writing a General Data Protection Regulation Privacy Notice in conjunction with the co-investigators.

3 | RESULTS

3.1 | The post-trial study population and BCSP procedures

Five hundred and seven individuals, who had been randomised to the seAFOod trial, had undergone one or more colonoscopies in the English BCSP, which were more than 6 months after, and less than 6 years after, trial participation (Figure 1A). No BCSS data were available for 200 participants for several reasons (Figure 1A). Only 71 individuals were invited for BCSP colonoscopy but did not attend, a number which is likely to have been increased by the ongoing COVID-19 pandemic (Figure 1A).

The 507 individuals, for whom post-trial surveillance colonoscopy data were available, were distributed equally across the four seAFOod trial treatment groups (placebo 127 [72.2% of the original trial treatment group]; aspirin 128 [72.7%]; EPA 129 [72.5%]; aspirin + EPA 123 [69.5%]) and displayed similar demographic and clinical characteristics to the overall seAFOod trial population, which was predominantly male with excess body weight (Table S1).[1,2]

We confirmed that the post-trial surveillance study population of 507 individuals displayed a similar on-trial treatment effect size for aspirin and EPA as the published primary analysis of the full seAFOod trial population.[1,2] The IRR (95% CI) for aspirin treatment versus no aspirin was 0.77 (0.66, 0.91), and 0.93 (0.79, 1.09) for EPA versus no EPA, for total colorectal polyps, thereby confirming the chemoprevention activity of aspirin in the seAFOod trial sub-population, for which post-trial data were available. The corresponding IRR (95% CI) values from the negative binomial model were 0.78 (0.61, 0.99) and 0.91 (0.71, 1.17) for aspirin and EPA, respectively.

The study population underwent 602 colonoscopies in 574 separate BCSP episodes with the majority (76.6%) of procedures corresponding to the expected 3-year surveillance colonoscopy window (2.5–3.5 years after the first surveillance [trial exit] colonoscopy) for individuals without 'high risk' findings (Figure 1B and Figure S1). Four hundred and thirty (84.8%) individuals in the study population underwent only one colonoscopy during the follow-up period. Ninety-six per cent ($n=551$) of BCSP episodes during the study period consisted of only one colonoscopy (Figure S3).

Colonoscopy was reported as complete with insertion to the caecum in 588 (97.7%) of 602 procedures (Figure S4). Diagnostic outcomes according to the BCSP classification recorded in the BCSS at individual colonoscopy and episode level are reported in Figure S4. We also re-classified surveillance outcomes according to the current risk stratification used by the English BCSP surveillance pathway.[8] Overall, 96 (16.0%) of 602 procedures were classified as 'high-risk' (≥5 polyps, or ≥2 polyps if one or more are ≥10 mm in size) and 359 (59.6%) procedures found at least one colorectal polyp but did not fulfil current 'high-risk' criteria. Findings were similar at episode level with 90 (15.7%) of 574 BCSP episodes that occurred during the post-trial follow-up period being classified as 'high risk'.

In total, 1298 'polyps' were recorded, of which 936 (72.1%) were adenomas and 273 (21.0%) were serrated-hyperplastic polyps (Table 1). Current BCSP guidance is clear that diminutive (≤5 mm) rectal, hyperplastic-looking polyps are not recorded,[7] but practice was more variable during the seAFOod trial and the follow-up period encompassed by this study. Therefore, a small number ($n=15$) of diminutive rectal hyperplastic polyps were recorded in the BCSS and are included in the analysis (Table 1). Overall, 750 (57.8%) polyps were located proximal to the splenic flexure as opposed to 548 (42.2%) polyps at or distal to the splenic flexure. There were 77 'advanced' adenomatous polyps in 54 individuals, 40 of which were ≥10 mm in size. Thirty-eight 'advanced' polyps exhibited ≥25% villous architecture and three lesions displayed high-grade dysplasia. No CRCs were detected during post-trial colonoscopic surveillance of the 507 individuals who were originally deemed 'high risk' at screening colonoscopy.

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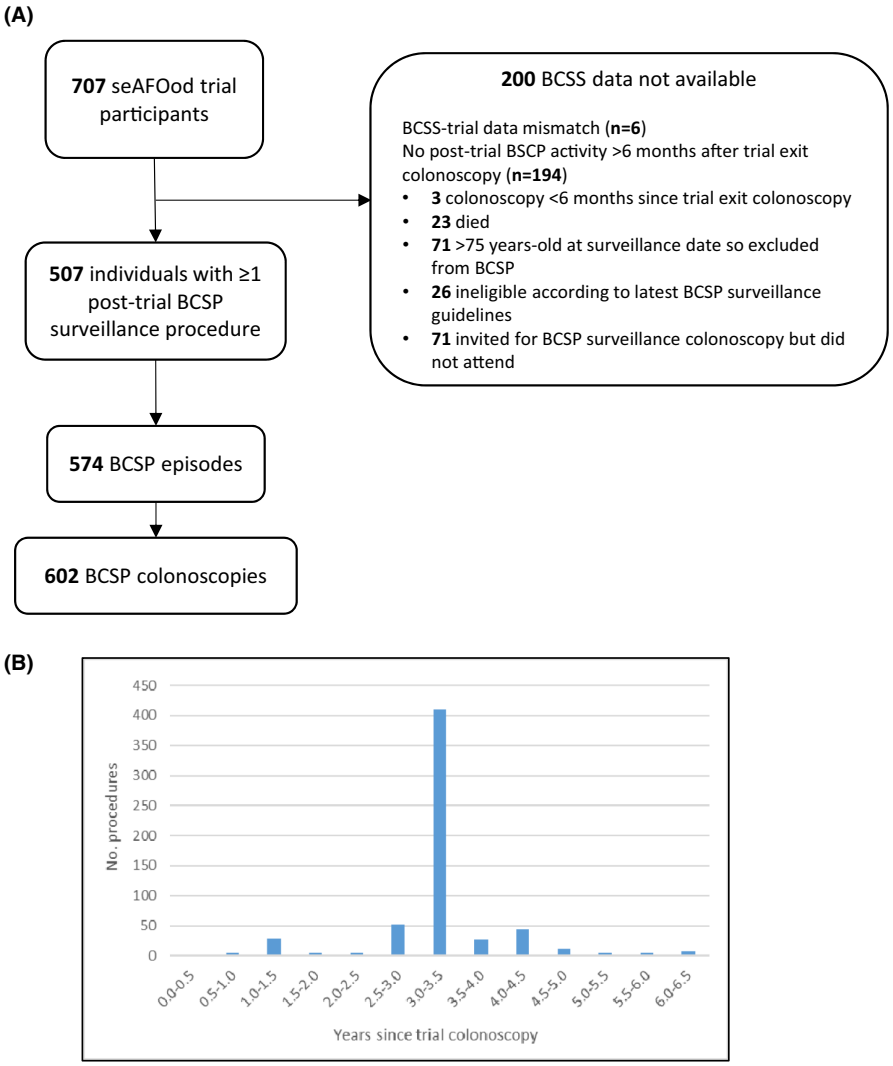


FIGURE 1 Post-trial colonoscopy surveillance of seAFOod trial participants. (A) Linkage of the 707 seAFOod trial participants who provided trial data to post-trial BCSP colonoscopy surveillance episodes. The reasons why no BCSS data were available for 200 participants are listed. Ninety-seven participants were not invited for surveillance colonoscopy as per BCSP guidelines. (B) Duration between the seAFOod trial exit colonoscopy (first surveillance colonoscopy) and subsequent post-trial surveillance colonoscopies (Figure S1). BCSP, Bowel Cancer Screening Programme; BCSS, Bowel Cancer Screening System.

3.2 | The effect of seAFOod trial interventions on post-trial colorectal polyp outcomes

Respective active versus placebo intervention groups were well-matched for the duration of post-trial follow-up and the number of surveillance procedures that had been performed per person (Table 2). The PDR after being randomised to placebo aspirin was 71.1%. By contrast, the PDR was 80.1% for individuals who had received active aspirin for 1 year during the seAFOod trial (OR 1.13 [1.02, 1.24]; $p=0.02$). A similar increase in PDR in the group that had received aspirin, as opposed to its placebo, was observed for conventional adenomas (69.3% vs. 59.4%; OR 1.16 [1.03, 1.32]; $p=0.02$), but not for serrated-hyperplastic polyps (31.5% vs. 27.7%; OR 1.10 [0.84, 1.44]; $p=0.47$).

In addition, the number of colorectal polyps detected during colonoscopic surveillance was higher in those who had received aspirin during trial participation (MPP 2.7) compared with the group who received placebo aspirin (MPP 2.5), but the difference was not statistically significant (IRR for total colorectal polyps 1.11 [0.90, 1,36]; $p=0.32$: Table 2).

By contrast, prior aspirin users did not demonstrate the altered risk of advanced colorectal polyps during post-trial follow-up compared with individuals previously allocated to placebo aspirin (IRR 1.04 [0.63, 1.71]; Table 2).

There was no difference in PDR (OR for total colorectal polyps 1.00 [0.91, 1.10]; $p=0.92$) or the number of colorectal polyps (IRR 1.10 [0.90, 1.36]; $p=0.35$) detected during post-trial BSCP surveillance between individuals, who had received either active or placebo EPA during the seAFOod trial (Table 2).

Secondary analysis of colorectal polyp size demonstrated that individuals, who were allocated to aspirin treatment during the seAFOod trial, also had larger colorectal polyps detected during post-trial BCSP surveillance than those who received placebo aspirin (Table S2). This was evident for total colorectal polyps (size difference +0.48 mm [+0.09, +0.86]; $p=0.02$) and was most marked for serrated-hyperplastic polyps (size difference +1.09 mm [+0.29, +1.89]; $p=0.01$). However, no significant difference was observed in colorectal polyp size, who did or did not previously receive EPA (size difference for total colorectal polyps +0.10 mm [−0.28, 0.49]; $p=0.60$; Table S2).

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TABLE 1 Histological type and location of colorectal polyps removed during colonoscopic surveillance after seAFOod trial participation.

Polyp histology			Polyp location		
	n	%		*n*	%
Adenoma	936	72.1	Rectum	117	9.0
Serrated-hyperplastic	273	21.0	Sigmoid colon	225	17.3
Serrated[a]	40		Descending colon	119	9.2
Hyperplastic ≥10 mm	9		Splenic flexure	87	6.7
Hyperplastic <10 mm[b]	224		Transverse colon	299	23.0
Inflammatory polyp	13	1.0	Hepatic flexure	50	3.9
Lymphoid aggregate	4	0.3	Ascending colon	269	20.7
Histology not available	72	5.5	Caecum	132	10.2
Total	1298	100	Total	1298	100

[a]36 sessile serrated lesions, one sessile serrated adenoma and three traditional serrated adenomas.
[b]15 rectal hyperplastic polyps ≤5 mm.

We also calculated the cumulative colorectal polyp burden, combining colorectal polyp number and size as a readout of overall neoplastic recurrence (Table S2). Consistent with the colorectal polyp number and size data, the total colorectal polyp and serrated-hyperplastic polyp burden in individuals, who had been randomised to aspirin during the seAFOod trial, was larger than those who had received placebo aspirin, with statistical significance for the increase in serrated-hyperplastic polyp burden (IRR 1.28 [1.04, 1.59]; $p=0.02$; Table S2).

Although the groups that were defined by the prior trial intervention were well-matched for clinical characteristics, length of post-trial surveillance and the number of surveillance procedures per individual (Table 2), the complex relationship between colorectal polyp detection and subsequent BCSP risk stratification, thus driving the number and timing of colonoscopies, and hence chance of colorectal polyp detection, could potentially introduce bias. Therefore, we also performed a sensitivity analysis of total colorectal polyp outcomes that was restricted to the three-year surveillance colonoscopy. In 444 seAFOod trial participants, who had 3-year surveillance colonoscopy data only (in which 885 colorectal polyps were reported), total colorectal polyp analysis confirmed the findings of the main analysis (Figure S2 and Table S3). There was a higher PDR (75.0%) in individuals that had been allocated to active aspirin in the seAFOod trial compared with those allocated to placebo aspirin (PDR 67.7%, or 1.10 [0.98, 1.24], which just failed to reach statistical significance; $p=0.11$; Table S3). However, the number of total colorectal polyps was higher in individuals previously allocated to aspirin as opposed to placebo aspirin (IRR 1.25 [1.00, 1.58]; $p=0.05$; Table S3).

3.3 | Evidence for an interaction between aspirin and EPA for reduction in total colorectal polyp risk

In addition to the pre-specified analysis of colorectal polyp outcomes in the seAFOod trial, we noted that the number of colorectal polyps detected in individuals who had been randomised to both aspirin and EPA was lower than the other three treatment groups.[1,2] Using data from all seAFOod trial participants ($n=707$), direct comparison of the group that received combined treatment with the groups that received either a single agent or placebo only demonstrated that there was a significantly lower risk of any colorectal polyp (25%–35%) in individuals who had received both aspirin and EPA compared with the other trial groups (Table 3). Further analysis stratified for randomisation to active EPA or placebo EPA, demonstrated a significant interaction with allocation to active aspirin compared with placebo aspirin (IRR for EPA vs no EPA 0.60 [0.43–0.85] in aspirin users compared with 1.04 [0.75–1.44] in those receiving placebo aspirin [$p_{int}=0.01$]; Table 4).

In view of the unexpected interaction between aspirin and EPA for the reduction in colorectal polyp risk, analysis of the post-trial colonoscopy data was also performed 'inside the table' across all four treatment groups (Table S4).[1,2] Results mirrored the 'at the margins' analysis of the individual interventions shown in Table 2 with an increase in PDR for total colorectal polyps and distal colorectal polyps in the treatment combinations that included active aspirin compared with the group that received placebo aspirin and placebo EPA only (Table S4). A similar relationship with previous single-agent aspirin use was also observed for increased distal colorectal polyp number (Table S4). Prior use of EPA alone was associated with an increased PDR for distal colorectal polyps (OR 1.31 [1.00, 1.70]; $p=0.05$), reflecting a reciprocal relationship with the decrease in risk of distal colorectal polyps linked to EPA use during the seAFOod trial.[1,2] Previous treatment with EPA alone was also associated with increased serrated-hyperplastic polyp number during follow-up (IRR 1.62 [1.05, 2.50]; $p=0.03$). Furthermore, analysis of total colorectal polyp size demonstrated that those individuals, who had been randomised to a combination of aspirin and EPA treatment during the seAFOod trial, had larger colorectal polyps (mean size difference +0.56 [+0.02, +1.11]; $p=0.04$) that was explained by the increased size of serrated-hyperplastic polyps (mean size

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TABLE 2 Comparison of colorectal polyp outcomes during post-trial colonoscopic surveillance between individuals who received either active intervention or its respective placebo in the 2×2 factorial seAFOod trial.

Group characteristics	No aspirin ($n=256$)	Aspirin ($n=251$)	p	No EPA ($n=255$)	EPA ($n=252$)	p
Age (years)[a]	65 (64, 65)	64 (64, 65)	0.76	64 (64, 65)	64 (64, 65)	0.58
Sex (male [%]:female)	200 (78):56	204 (81):47	0.38	202 (79):53	202 (80):50	0.79
Duration of post-trial follow-up (days)[a]	1188 (1160, 1217)	1218 (1186, 1250)	0.17	1216 (1186, 1246)	1189 (1158, 1220)	0.22
Number of colonoscopies per person[a]	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)	0.86	1.2 (1.1, 1.3)	1.2 (1.1, 1.2)	0.35
PDR	**% (no. with ≥1 polyp)**	**% (no. with ≥1 polyp)**	**OR (95% CI) p value[b]**	**% (no. with ≥1 polyp)**	**% (no. with ≥1 polyp)**	**OR (95% CI) p value[b]**
Total colorectal polyp	**71.1 (182)**	**80.1 (201)**	**1.13 (1.02, 1.24) $p=0.02$**	75.3 (192)	75.8 (191)	1.00 (0.91, 1.10) $p=0.92$
Advanced polyp	10.5 (27)	10.8 (27)	1.04 (0.63, 1.71) $p=0.89$	9.8 (25)	11.5 (29)	1.16 (0.70, 1.92) $p=0.57$
Adenoma	**59.4 (152)**	**69.3 (174)**	**1.16 (1.03, 1.32) $p=0.02$**	65.5 (167)	63.1 (159)	0.96 (0.85, 1.09) $p=0.53$
Serrated-hyperplastic	27.7 (71)	31.5 (79)	1.10 (0.84, 1.44) $p=0.47$	27.1 (69)	32.1 (81)	1.19 (0.91, 1.55) $p=0.21$
Distal polyp	46.5 (119)	54.2 (136)	1.15 (0.97, 1.37) $p=0.11$	48.6 (124)	52.0 (131)	1.04 (0.88, 1.24) $p=0.63$
Proximal polyp	57.8 (148)	60.2 (151)	1.03 (0.89, 1.19) $p=0.67$	59.2 (151)	58.7 (148)	1.00 (0.87, 1.15) $p=1.00$
Colorectal polyp number	**MPP (mean [95% CI])**	**MPP (mean [95% CI])**	**IRR (95% CI) p value[c]**	**MPP (mean [95% CI])**	**MPP (mean [95% CI])**	**IRR (95% CI) p value[c]**
Total colorectal polyp	2.5 (1.9, 3.0)	2.7 (2.3, 3.1)	1.11 (0.90, 1.36) $p=0.32$	2.4 (2.0, 2.9)	2.7 (2.2, 3.2)	1.10 (0.90, 1.36) $p=0.35$
Advanced polyp	0.17 (0.10, 0.25)	0.13 (0.08–0.19)	0.77 (0.47, 1.25) $p=0.29$	0.14 (0.07, 0.20)	0.17 (0.10, 0.23)	1.21 (0.75, 1.96) $p=0.47$
Adenoma	1.8 (1.3, 2.2)	1.9 (1.6, 2.3)	1.15 (0.92, 1.43) $p=0.22$	1.8 (1.4, 2.2)	1.9 (1.5, 2.3)	1.05 (0.84, 1.30) $p=0.84$
Serrated-hyperplastic	0.51 (0.34, 0.67)	0.57 (0.38, 0.76)	1.13 (0.84, 1.51) $p=0.44$	0.49 (0.32, 0.66)	0.59 (0.41, 0.77)	1.20 (0.89, 1.62) $p=0.23$
Distal polyp	1.0 (0.8, 1.2)	1.1 (0.9, 1.4)	1.13 (0.89, 1.44) $p=0.32$	1.0 (0.8, 1.2)	1.2 (0.9, 1.4)	1.18 (0.92, 1.50) $p=0.19$
Proximal polyp	1.4 (1.0, 1.8)	1.5 (1.3, 1.8)	1.08 (0.86, 1.36) $p=0.50$	1.4 (1.1, 1.8)	1.5 (1.2, 1.9)	1.05 (0.84, 1.32) $p=0.54$

Note: Data per person are cumulative counts during the total surveillance period for each individual.

Abbreviations: IRR, incidence risk ratio; MPP, mean polyp number per person; OR, odds ratio; PDR, polyp detection rate.

[a]Data are expressed as the mean value and 95% confidence interval (CI).

[b]Statistical significance between groups originally allocated placebo or active interventions was tested by logistic regression adjusted for age and sex.

[c]Statistical significance between groups originally allocated placebo or active interventions was tested by negative binomial regression adjusted for age and sex. Statistically significant findings are highlighted in bold text.

difference + 1.44 [+0.29, +2.60]; $p=0.01$) during post-trial surveillance (Table S2). Use of the colorectal polyp burden endpoint amplified the relationship between prior EPA or aspirin use and increased serrated-hyperplastic polyp recurrence (Table S2).

'Inside the table' analysis of the post-trial colonoscopy outcomes restricted to 3-year procedures confirmed that the increased PDR compared with previous placebo users was explained by the group that had received both aspirin and EPA 3 years' earlier (OR 1.20 [1.01, 1.42]; $p=0.04$), rather than the those who received either agent alone (aspirin only OR 1.15 [0.96, 1.37] and EPA only OR 1.12 [0.94, 1.35]; both $p>0.1$). The total colorectal polyp number per person in those previously allocated to combination of aspirin and EPA was also higher than those that had been allocated to placebo (MPP 2.28 [1.82, 2.74] vs. 1.68 [1.18, 2.17]; IRR 1.40 [1.01, 1.93], $p=0.04$), unlike the groups that had received aspirin (1.22 [0.88, 1.70]; $p=0.24$), or EPA (1.09 [0.78, 1.52]; $p=0.63$), alone, compared with those who received placebos only.

4 | DISCUSSION

This pre-specified analysis of colorectal polyp risk during routine colonoscopic surveillance in the English BCSP, following participation in the seAFOod polyp prevention trial, has demonstrated that those individuals who originally received aspirin in the seAFOod trial (which was associated with *decreased* colorectal polyp risk as measured by colorectal polyp number[1,2]) actually had *increased* cumulative (total and adenomatous) colorectal polyp risk during post-trial surveillance compared with those previously allocated to placebo aspirin.

These data support the hypothesis that short-term aspirin use inhibits colorectal tumour growth, but not initiation, leading to derepression of polyp growth upon treatment cessation, reflected as 'rebound' increased colorectal polyp risk during subsequent colonoscopic surveillance. This relationship was restricted to aspirin, which had chemopreventative efficacy against adenomatous and serrated

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TABLE 3 Comparison of total colorectal polyp number in individuals who received combined aspirin and EPA treatment in the seAFOod trial with participants who received either agent alone or placebos only.

	Incidence risk ratio (95% CI) for the active aspirin and active EPA group[a]
Placebos only	0.70 (0.57, 0.86)
Placebo aspirin and active EPA	0.65 (0.53, 0.80)
Active aspirin and placebo EPA	0.75 (0.61, 0.93)

[a]Adjusted by BCSP site as a random effect and for repeat colonoscopy at baseline in the seAFOod trial [see ref. 1, 2].

polyps in the seAFOod trial (which was also confirmed in the post-trial surveillance population),[1,2] whereas allocation to active EPA in the seAFOod trial (which was not linked to reduced risk of total colorectal polyps) was not associated with altered colorectal polyp risk during post-trial follow-up, according to factorial trial margins. 'Inside the table' treatment group analysis of colorectal polyp findings during post-trial surveillance also reflected individual agent chemopreventative efficacy during the seAFOod trial, with prior EPA use, which was associated with reduced on-trial distal colorectal polyp risk,[1,2] being associated with increased distal colorectal polyp risk during post-trial surveillance.

The effect size (a 10%–15% increase in PDR and MPP in those allocated aspirin, as opposed to placebo during the seAFOod trial) is clinically meaningful based on a similar effect size for colorectal polyp risk reduction in aspirin polyp prevention trials that is coupled with observational data on CRC risk reduction,[3,10,11] as well as PDR differences reported for endoscopic interventions that improve colorectal polyp detection, which have been adopted into clinical practice.[12]

Secondary colorectal polyp size and polyp burden analyses concurred with the PDR outcomes in that trial allocation to aspirin was associated with larger colorectal polyps, including serrated lesions. In general, serrated-hyperplastic polyps detected during surveillance were larger than adenomatous polyps. This observation might be explained by a faster growth rate and/or higher colonoscopy miss rate for serrated lesions,[13] which could also underlie the prominent relationship between previous aspirin or EPA treatment and larger serrated-hyperplastic polyps. There was an excess of proximal colorectal polyps during second and subsequent rounds of surveillance of this 'high-risk' cohort of screened individuals, which is consistent with a left-to-right shift reported in other surveillance colonoscopy cohort studies.[14]

Increased colorectal adenomatous polyp risk after treatment cessation has previously been reported in three randomised polyp prevention trials of coxib selective cyclooxygenase (COX)-2 inhibitors (APPROVe, PreSAP and APC), which each included an unscheduled 1-2-year off-treatment follow-up period following premature termination of Investigative Medicinal Product use due to cardiovascular safety concerns.[15–17] In the APPROVe and PreSAP trials, the increased risk of any colorectal adenoma in prior coxib users reached

TABLE 4 Interaction between EPA use and clinical factors, baseline EPA status, aspirin use and repeat colonoscopy at baseline during the seAFOod trial.

	IRR (EPA vs no EPA)	*p* for interaction[a]
Increasing year of age	1.01 (0.98–1.04)	0.65
Sex		
Female	1.20 (0.77–1.85)	0.42
Male	1.04 (0.58–1.86)	
Baseline EPA level (%)[b]		
Low (<0.46%)	0.98 (0.70–1.38)	0.78
High (≥0.46%)	0.91 (0.65–1.28)	
BMI		
Normal (<25 kg/m^2)	1.31 (0.72–2.39)	0.88
Overweight (25–29.9 kg/m^2)	1.18 (0.69–2.01)	
Obese (≥30 kg/m^2)	1.25 (0.73–2.12)	
Smoking		
Never smoked	0.93 (0.62–1.38)	0.27
Ex-smoker	1.14 (0.79–1.66)	
Current	1.07 (0.60–1.90)	
Units of alcohol per week		
None	1.04 (0.56–1.95)	0.78
1–7	1.17 (0.69–1.96)	
8–21	1.33 (0.79–2.24)	
22+	0.92 (0.51–1.66)	
Aspirin allocation		
Active	0.60 (0.43–0.85)	0.01
Placebo	1.04 (0.75–1.44)	
Repeat colonoscopy in trial		
No	0.89 (0.68–1.15)	0.78
Yes	1.01 (0.62–1.65)	

[a]Wald test for interaction.

[b]Red blood cell % EPA (of total fatty acids) level was dichotomised using the mean baseline EPA level (0.46%).[2]

statistical significance compared with those previously allocated placebo, with a relative risk of any colorectal adenoma of 1.21 and 1.48, respectively.[15,16]

However, post-trial colonoscopy outcomes analysis after the Aspirin/Folate Polyp Prevention Study (AFPPS) did not reveal increased colorectal adenoma risk in individuals, who had been randomised to either 81 or 325 mg aspirin for 3 years compared with those allocated placebo and who underwent repeat colonoscopy approximately 4 years later (PDR 39.6% [either aspirin dose] vs. 39.9%; relative risk 1.00 [95% CI 0.80–1.24]).[18] No colorectal polyp number outcomes were reported in the AFPPS follow-up study.[18] The seAFOod trial recruited a 'high risk' cohort with greater colorectal polyp multiplicity at trial entry and post-trial colonoscopic surveillance continued in a quality-assured national programme (that is reflected in the much higher PDR [70%–80%] during follow-up in the BCSP compared with the AFPPS follow-up study),

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which could explain the discrepancy in results between the two studies.[1,2]

Overall, the yield of advanced neoplasia was low, with no CRCs detected during the entire surveillance period. Advanced colorectal polyp detection during post-trial surveillance was similar in individuals who had received aspirin, as opposed to placebo aspirin, during the seAFOod trial. This is consistent with the observation from post-treatment follow-up of the APPROVe trial that prior use of the selective COX-2 inhibitor rofecoxib was associated with increased risk of any colorectal adenoma, but not advanced adenomatous polyps.[15] A valid hypothesis is that advanced colorectal polyps detected during short-term post-trial follow-up represent more established lesions (probably missed at an earlier colonoscopy) that are less amenable to growth repression by aspirin and subsequent de-repression upon treatment cessation.

Our study does not address whether a 'rebound' increase in colorectal polyp risk after cessation of short-term aspirin treatment would manifest as a subsequent increase in CRC incidence. Based on a latent period of at least 8–10 years between randomisation to aspirin and reduced CRC risk (compatible with current understanding of the slow natural history of malignant progression from adenomatous polyps) observed during post-trial follow-up of multiple primary and secondary placebo-controlled vascular prevention trials,[10,11] the number of individuals followed-up for sufficient time (>20 years) to observe a possible 'rebound' increase in CRC incidence in these studies is limited.[10,11] Median 10-year observational follow-up of the Women's Health Study (WHS) of 100 mg alternate-day aspirin versus placebo, used for 10 years, demonstrated that aspirin use was associated with reduced CRC risk (hazard ratio 0.58 [95% CI 0.42, 0.80]) with a latency of 10 years.[19] However, additional WHS follow-up from 17.5 to 26 years is reported to demonstrate no significant difference in CRC incidence between the group that was originally randomised to aspirin use for 10 years and those allocated placebo (odds ratio 1.16 [95% CI 0.78, 1.72]) suggesting that the aspirin group might have had an excess of CRC events during later follow-up.[20] A study of the relationship between the timing or dose of aspirin and CRC risk in the Nurses' Health Study and Health Professionals Follow-Up Study identified a group of individuals with a 'high' duration and dose of prior aspirin use, who had subsequently become 'low' aspirin users (≤5 years or <1.5 tablets per week) during prolonged (>20 years) 'real-life' use of aspirin.[21] However, this subcohort accounted for only 201 CRC cases and the study did not specifically identify a group that stopped aspirin, highlighting the difficulty of studying CRC risk after aspirin use, even in a large prospective cohort study.[21]

A consistent methodological weakness of post-trial observational follow-up studies, which is shared by our study, is the absence of data on post-trial aspirin usage. At the end of the seAFOod trial, participants were not informed of their treatment allocation and the Plain English Summary of the trial results, which was available online and on request, did not recommend aspirin and/or EPA use. Therefore, one would not expect widespread aspirin use in previous seAFOod trial participants (clinically indicated aspirin use was an exclusion criterion) or that post-trial aspirin use would be unbalanced across the randomised seAFOod trial treatment groups. Moreover, any bias related to post-trial aspirin use would be expected to reduce the 'rebound' effect size compared with the placebo arm based on the reduction in colorectal polyp number associated with current aspirin use.[1,2]

Another important observation is that combination treatment with aspirin and EPA was associated with significantly lower colorectal polyp recurrence in the seAFOod trial compared with either agent alone. This was apparent in the primary report of the seAFOod trial,[1,2] but an 'inside the table' analysis of the seAFOod trial data was not pre-specified based on the understanding of the mechanism(s) of action of aspirin and EPA, at the time, which focused on inhibition of COX by both agents, as well as observation that there was no interaction between the two agents when anti-platelet (COX-1-dependent) activity is measured.[22] The pharmacological basis of an interaction between aspirin and EPA for colorectal polyp prevention remains unclear. It has been suggested that EPA can be metabolised to a trihydroxy derivative 5,12,18-trihydroxy-EPA (also known as resolving [Rv] E1) by a *trans*-cellular pathway involving aspirin-acetylated COX-2.[4] E-type resolvins have inflammation-resolving activity in in vitro and preclinical studies, associated with inhibition of nuclear factor kappa B, which is hypothesised to mediate the additive anti-cancer activity of the combination of aspirin and EPA.[23] RvE1 and its precursor oxylipin 18*R*-hydroxy-EPA have been detected in multiple different human sample types and clinical disease settings.[24] However, RvE1 was not detected (above a limit of detection of 20 pg/mL) in plasma and rectal mucosal samples from seAFOod trial participants.[25] Although combination of aspirin and EPA treatment were associated with reduced colorectal polyp risk, compared with either agent alone, during the seAFOod trial, we did not observe a larger 'rebound' increase in colorectal polyp risk during post-trial surveillance compared with individuals that had received aspirin alone. The relationship between on-treatment chemoprevention and size of the post-treatment increase in colorectal polyp risk will be dependent on the balance between inhibition of tumour (polyp) initiation versus polyp growth suppression for any given agent(s). This will require further investigation during future polyp prevention trial follow-up and improved understanding of the mechanism(s) of action of aspirin.

This study has several strengths including detailed colorectal polyp outcomes data from a national quality-assured colonoscopy surveillance programme generating a large number of incident colorectal polyps during follow-up. We acknowledge that colorectal polyp nomenclature, as well as risk stratification for colonoscopic surveillance based on colorectal polyp characteristics, has changed during the time encompassed by the seAFOod trial and the post-trial surveillance period, up to the present day.[7,26] Changes include a clearer distinction between serrated and hyperplastic polyps,[26] with the exclusion of diminutive rectal hyperplastic polyps from the BCSP risk stratification algorithm.[7] However, we continued to describe colorectal polyp outcomes according to the terminology and

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reporting tools employed by the BCSP at the time, in order to allow direct comparison between on-trial and post-trial colorectal polyp outcomes.

Study limitations include the lack of data on post-trial aspirin and omega-3 polyunsaturated fatty acid use, absence of data on incident co-morbidities and other drug use, as well as a relatively short post-trial follow-up period, which encompassed only one 'intermediate risk' 3-year colonoscopy for the majority of trial participants. Unfortunately, seAFOod trial participants were not asked to provide consent for future contact at trial entry so we have been unable to contact individuals to enquire about concurrent drug use and permission to access BCSP records at the end of the pre-determined 6-year follow-up period.

Despite the fact that the post-trial surveillance groups, which were defined by randomised trial treatment allocation, were well-matched for post-trial follow-up duration and the number of surveillance colonoscopies per person, we acknowledge that the complex relationship between colorectal polyp outcomes and the timing and frequency of colonoscopy according to the BCSP surveillance algorithm could introduce bias. However, the secondary analysis was restricted to colonoscopy outcomes at a single time-point 3 years after the seAFOod trial exit colonoscopy confirmed the findings of the main analysis of cumulative colorectal polyp outcomes during follow-up.

We suggest that future biomarker-driven CRC chemoprevention trials include prospective post-intervention follow-up to corroborate our findings that a short-term intervention (aspirin ± EPA), which is associated with reduced on-treatment colorectal polyp risk, is subsequently linked to 'rebound' increased colorectal polyp incidence when the intervention is stopped. A 'rebound' increase in colorectal polyp risk (and possible increased CRC risk, albeit after a much longer latent period) after short-term aspirin use should be considered as part of the ongoing debate about how best to harness the undoubted cancer-preventative properties of aspirin whilst minimising risk in a precision manner,[27] one approach to which is to stop aspirin use in line with age-dependent elevated risk of bleeding.

AUTHOR CONTRIBUTIONS

Amy Downing: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Hayley Fenton:** Data curation (equal); formal analysis (equal); writing – review and editing (equal). **Claire Nickerson:** Data curation (equal); writing – review and editing (equal). **Paul M. Loadman:** Funding acquisition (equal); investigation (equal); writing – review and editing (equal). **Elizabeth A. Williams:** Funding acquisition (equal); investigation (equal); writing – review and editing (equal). **Colin J. Rees:** Conceptualization (equal); funding acquisition (equal); writing – review and editing (equal). **Louise C. Brown:** Formal analysis (equal); funding acquisition (equal); methodology (equal); writing – review and editing (equal). **Eva J. A. Morris:** Conceptualization (equal); data curation (equal); funding acquisition (equal); investigation (equal); methodology (equal); resources (equal); writing – review and editing (equal). **Mark A. Hull:** Conceptualization (lead); data curation (equal); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (equal); project administration (lead); resources (equal); supervision (equal); validation (lead); visualization (equal); writing – original draft (lead); writing – review and editing (lead).

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SUPPORTING INFORMATION

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

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