Decision-making in cancer preventive therapy

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Intellectual Property and Publication Statements

I, Kelly Elizabeth Lloyd, confirm that the work submitted is my own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Study One publication (Chapter Two):

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Contributions of all authors to Study One:

Search terms were developed for the review by two information specialists (RR, NK). Another author and I screened the titles and abstracts (KEL, RJT), and two authors (RR, LHH) duplicated screening for 20% of articles. Discrepancies were resolved with a third reviewer (SGS). Another author and I (KEL, RJT) examined the articles against the inclusion criteria, and second reviewers (LHH, KEL) screened 20% of the articles. Another author and I (KEL, RJT) extracted the study data using Excel, and approximately 45% of studies were verified by second reviewers (RR, KEL). I (KEL) assessed the quality of all articles, with over 35% of articles verified by a second author (LHH). Any discrepancies were resolved with a third author (SGS). I (KEL) conducted a narrative synthesis of the data, and wrote the initial manuscript draft. All authors reviewed the manuscript, which I (KEL) revised, finalised, and submitted for publication. I (KEL) revised the manuscript following peer review at the journal Preventive Medicine, with all authors reviewing the revised manuscript before resubmission.

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L

I (KEL) developed the methodology of the paper, with contributions from my supervisors and two coauthors (SGS, RF, LHH, LZ, DGT, and MM). I recruited and interviewed all participants (KEL), with the interview recordings transcribed by The Typing Works. I (KEL) coded and analysed all transcripts. Three authors contributed to the analysis through double coding a proportion of transcripts (SMCG, ZFH, and SGS). I (KEL) wrote the original manuscript draft, which was reviewed by all co-authors. I (KEL) revised the manuscript following peer review at the journal Hereditary Cancer in Clinical Practice, with all authors reviewing the revised manuscript before re-submission.

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original draft of the full Stage 2 manuscript (KEL), which was reviewed by all co-authors. I (KEL) then finalised and submitted the full manuscript to BJGP.

Conference abstracts

Study One was accepted for a poster presentation at the Society of Behavioral Medicine Annual Meeting 2020.

Study Two was accepted as an oral presentation at the UK Society of Behavioural Medicine Annual Meeting 2022, and the Dutch/UK Clinical Genetics Societies & Cancer Genetics Group Meeting 2022.

Study Four protocol was accepted for a poster presentation at the Society of Behavioral Medicine Annual Meeting 2022.

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Thesis structure

The thesis has been structured and submitted as an alternative style of doctoral thesis which includes published material. There are a total of four studies included in the thesis. **Studies One, Two and Four** have been published/accepted by peer-reviewed journals. The protocol for **Study Four** was originally submitted and granted in-principle acceptance by the British Journal of General Practice as a Stage 1 Registered Report. The full manuscript (Stage 2 Registered Report) was subsequently accepted by the journal for publication. **Study Three** has been prepared for submission to a journal. There is an introduction chapter proceeding the manuscripts, and a discussion chapter following the presentation of the studies, to bind the manuscripts into a coherent piece of work. The four studies included in the thesis have been presented exactly as published or submitted, except in minor cases where formatting has been amended to ensure the thesis is a coherent whole (e.g. table numbers, reference formatting). As per the guidance for an alternative style of doctoral thesis, each chapter contains its own list of references. An alternative thesis style was chosen as this approach can maximise the research outputs generated from a PhD. The alternative style of thesis is also aligned with the Graduate Board at the University of Leeds, who encourage all postgraduate research students to publish and disseminate their PhD results.

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This thesis is dedicated to the memory of Richard Terry.

V

Abstract

Aspirin is increasingly recommended for cancer preventive therapy. In the United Kingdom (UK), the National Institute for Health and Care Excellence recommends (NG151) aspirin to prevent colorectal cancer in people with Lynch syndrome. Future UK guidance may recommend aspirin for those at population risk of colorectal cancer, similar to Australian guidance. In the thesis, I aimed to investigate the barriers and facilitators affecting use of aspirin for preventive therapy among people with Lynch syndrome and the UK public. I also investigated the barriers to healthcare providers recommending and prescribing aspirin. Study One is a systematic review synthesising the data on behaviour and attitudes in the context of aspirin for cancer prevention. This review found substantial scope for behavioural research into the factors affecting aspirin use. Study Two involved qualitative interviews exploring the views of people with Lynch syndrome and healthcare providers. Patients and GPs had multiple unmet informational needs in decisions concerning aspirin, which are inconsistently supported by current care pathways. Study Three was a mixed methods study recruiting the UK public aged 50 to 70. I observed mixed acceptability towards taking aspirin for colorectal cancer prevention, with concerns among participants on the necessity of the medication and the side-effects. Study Four investigated the optimal type and level of information to communicate with GPs to increase their willingness to prescribe aspirin for a hypothetical patient with Lynch syndrome. Across the factorial trial conditions, I manipulated the presence or absence of three information components: 1) national guidance; 2) trial evidence; 3) information comparing the risks and benefits of aspirin. I found no statistically significant main effects or interactions of the three components on willingness to prescribe. Overall, coordinated and multilevel strategies are warranted, addressing the needs of people with Lynch syndrome, the UK public, and GPs.

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List of abbreviations

AICR: American Institute for Cancer Research ANOVA: Analysis of variance AsCaP: Aspirin for Cancer Prevention Collaboration ASPREE: ASPirin in Reducing Events in the Elderly trial CAPP2: Colorectal Adenoma/carcinoma Prevention Programme trial CFIR: Consolidated Framework for Implementation Research CI: Confidence interval CONSORT: Consolidated Standards of Reporting Trials CRC: Colorectal cancer CVD: Cardiovascular disease FAP: Familial adenomatous polyposis GP: General practitioner LS: Lynch syndrome MEMS: Medication Event Monitoring System MMAT: Mixed Methods Appraisal Tool NHS: National Health Service NICE: National Institute for Health and Care Excellence NPT: Normalisation Process Theory NSAID: Non-steroidal anti-inflammatory drug OR: Odds ratio PPI: Proton pump inhibitor PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses **RCT: Randomised controlled trial** SD: Standard deviation

SERMs: Selective oestrogen receptor modulators

- TDF: Theoretical Domains Framework
- UK: United Kingdom
- **US: United States**
- USPSTF: US Preventive Services Taskforce
- WCRF: World Cancer Research Fund

Chapter One: Introduction

1.1 Chapter summary

This chapter provides an introduction to the use of aspirin for cancer preventive therapy, more specifically for its use in colorectal cancer prevention. An overview of the existing literature is presented discussing the effectiveness of aspirin for cancer prevention among those at population risk of cancer, and those at higher lifetime risk. The existing decision-making literature relevant to this area is also discussed, focusing on both users and healthcare providers. Several theoretical frameworks are then considered for the thesis research, to aid in exploring the determinants of behaviour in the context of aspirin for preventive therapy. The final section of this chapter outlines the aims and objectives of the thesis, and an overview of the research methods employed.

1.2 Role of behaviour in cancer prevention research

Cancer is the second leading cause of death globally (1). Incidence is rising (2); in the UK, an estimated one in two people will be diagnosed with cancer in their lifetime (3). One of the most common occurring cancers worldwide is colorectal (4), and is the fourth most common cancer in the UK (5). Over half of all colorectal cancers are diagnosed at a late stage, and it is the second highest cause of cancer death in the UK, with approximately 16,600 deaths attributed to the disease each year (5). There has been increasing focus in research on the prevention of cancer (6, 7), as approximately 38% of cancers in the UK are estimated to be preventable (8). Colorectal cancer in particular is one of the most preventable cancers (9), with 45% of cases estimated to be attributed to lifestyle factors (10).

Primary prevention can reduce cancer incidence among healthy populations and populations at increased risk of developing cancer (11), and offer a cost-effective cancer control method (12-16). There are several types of lifestyle changes which have been found to prevent primary cancers, such as diet and physical activity. A meta-analysis of cohort studies has previously found physical activity to be associated with a significant reduction of colon cancer (17). A meta-analysis of case-control and cohort studies has also observed a relationship between high intake of red meat and processed meat and a significant increase in colorectal cancer risk (18). Interventions targeting the prevention of cancer can also prevent cancer recurrence (i.e. secondary prevention) (19, 20). For example, meta-analyses have previously found evidence for the effectiveness of physical activity for breast and colorectal cancer survival (21, 22). However, there are challenges to preventing cancer through changing people's diet and physical activity, as adherence to these lifestyle programmes is often poor (23-25). In addition to these cancer preventive behaviours, there are also pharmacological

approaches to cancer prevention (26). A potential advantage of taking medication to prevent cancer is that compliance may be easier to achieve than trying to change lifestyle factors such as diet and levels of physical activity (27).

There are several prophylactic pharmacological and vaccination approaches to cancer prevention, some of which have been implemented through national cancer prevention policies. The HPV vaccine is one such approach, which has been instrumental in reducing incidence of cervical cancer (28, 29). In addition, there is also the use of daily preventive medications which can be used to reduce the risk of developing cancer. Preventive therapy, also termed chemoprevention, is the use of a natural, synthetic or biological agent to reduce the risk of a person developing a primary or secondary cancer (30). Medication to reduce the risk of developing cancer has been highly documented in breast cancer. The Selective Oestrogen Receptor Modulators (SERMs), tamoxifen, was the first United States (US) Food and Drug Administration agent for cancer risk reduction (31). Since, several medications with the aim to prevent cancer have been officially recommended by multiple countries. One form of preventive therapy that is increasingly being recommended is the non-steroidal anti-inflammatory drug (NSAID) aspirin for colorectal cancer prevention.

1.3 Aspirin – cancer preventive therapy

Aspirin's history can be traced to ancient Egypt, where the extract of salicylate-containing plants, such as willow bark, were commonly used to treat inflammation (32, 33). In the 1890s, chemist Felix Hoffman synthesised acetylsalicylic acid into a stable and usable form, which was subsequently marketed as the medical drug 'aspirin' (34). At present, aspirin is a medication available both on prescription and over-the-counter at pharmacies. In the 1950s, general practitioner Lawrence Craven first reported evidence on the effectiveness of low dose daily aspirin for preventing myocardial infarction and stroke (32). In present times, several countries have released official guidance recommending aspirin for cardiovascular disease (CVD) prevention (35-37). Following the discovery of aspirin for CVD prevention, the effectiveness of aspirin for preventing other illnesses has also been investigated. In 1988, Gabriel Kune first reported evidence supporting the use of aspirin for reducing the risk of colorectal cancer from a large case-control study (38).

Aspirin is often prescribed in the UK for CVD prevention, however the recommendations for prescribing have changed over time. While UK guidelines published between 2005 to 2008 recommended aspirin for the primary and secondary prevention of CVD, meta-analyses of trials have since found the harms of daily aspirin to outweigh the benefits among people without prior CVD (39-41). In contrast, review evidence has observed aspirin to be of substantial net benefit for secondary prevention among people with CVD (41). At present, aspirin is only recommended in the UK for the

secondary prevention of CVD (42). The history of prescribing aspirin for CVD prevention in the UK may affect perceptions of the medication for the primary prevention of cancer among both healthcare providers and patients.

The specific mechanisms of action connecting aspirin to cancer prevention are currently unknown, but several hypotheses have been suggested (43). For example, one of the main hypothesis is that aspirin's anti-cancer action is mediated through its antiplatelet function, as platelets can be involved in the mechanisms leading to the development of cancer tumours (44). Although the exact mechanisms linking aspirin to cancer prevention are not yet fully understood, the effectiveness of aspirin for primary and secondary cancer prevention has been increasingly investigated in research among the general population and those at higher risk of developing cancer (43).

1.3.1 Evidence for aspirin's effectiveness among the general public

Several observational studies have been conducted to examine the relationship between aspirin and cancer prevention. A pooled analysis of 45 observational studies, recruiting general public participants, observed regular aspirin use (vs. non-use) to be significantly associated with reduction in the risk of developing colorectal cancer (risk ratio of 0.73, 95% CI: 0.69-0.78), and several other gastric cancers (e.g. stomach, oesophageal) (45). Another pooled analysis of 423,495 people from two large cohorts examined the relationship between aspirin and prevention of several cancers (46). The study found daily aspirin use to be significantly associated with a 15% reduced risk of colorectal cancer (hazard ratio: 0.85, 95% CI: 0.80-0.89), and a moderate reduction in breast (hazard ratio: 0.96, 95% CI: 0.91–1.00) and prostate cancer (hazard ratio: 0.95, 95% CI: 0.90–1.00).

Observational studies, such as cohorts, are often used to examine the effect of a drug in a large population sample over a long time period (47). However, it can be difficult to infer causality between the exposure and outcome in observational studies (48). One reason for this is that participants are not randomised to their treatment condition, which can lead to selection bias (47, 49). Due to the design of cohort studies it is also difficult to control for any confounder variables (e.g. participant characteristics) influencing the study outcome (e.g. cancer incidence) (50). While methods can be employed to assess for causality in observational studies (51), randomised control trials (RCTs) are generally preferable to investigate causality in medical research. In an RCT, participants are randomised to their condition (intervention vs. control), which increases the confidence that any differences in the outcome are caused by the intervention (52, 53). Randomisation also helps to minimise the differences in the baseline characteristics between participant groups, which can help to control for confounders (54).

A number of RCTs have been conducted investigating the effectiveness of aspirin for CVD prevention as their primary aim, where the effects of the medication on cancer have been investigated as a secondary aim. One meta-analysis of four RCTs investigating aspirin for CVD prevention found participants who used daily low-dose (75-300mg) aspirin had a significantly reduced 20-year risk of developing colon cancer (hazard ratio of 0.76, 95% CI: 0.60–0.96) in an intention-to-treat analysis, when compared with the control groups (55). However, there was no significant relationship between aspirin and the 20-year risk of rectal cancer. Another meta-analysis across three CVD prevention RCTs observed significantly reduced risk of colorectal cancer death at 10-20 years in the aspirin groups when compared with the control groups (risk ratio of 0.51, 95% CI: 0.35–0.74, p<0.001, in an intention-to-treat analysis) (56). In addition, the meta-analysis found evidence of an association between daily aspirin (vs. no aspirin) and reduced risk of oesophagus cancer death (risk ratio of 0.36, 95% CI: 0.18–0.71, p=0.003), and stomach cancer death (risk ratio of 0.42, 95% CI: 0.23–0.79, p=0.007) at 10-20 years. However, there is greater uncertainty for these associations as the event rate of deaths from these cancers was lower than deaths from colorectal cancer, resulting in wider confidence intervals.

Utilising existing trial data to examine cancer as a secondary endpoint is an efficient approach for generating large sample data on the effect of aspirin for preventive therapy, as cancer incidence or death may not occur for many years among those at population risk. However, there are limitations to examining cancer as a secondary endpoint in CVD prevention trials. When designing a trial, the primary endpoint informs the study's design and appropriate sample size (57), while secondary endpoints are often exploratory analyses (58). Although analyses of cancer incidence and death in CVD prevention trials can generate hypotheses for future testing, exploratory analyses cannot confirm evidence for a priori hypothesis (58, 59). In addition, exploratory testing and/or analysing multiple endpoints in trials increases the risk of encountering a Type I error (60, 61), which is also known as a false positive result. By definition, observing a significant *p*-value of 0.05 refers to a 5% probability that the statistically significant result was generated by chance and that there is no real effect (i.e. a false positive result) (62). Conducting multiple exploratory analyses subsequently increases the probability of encountering a Type I error (60).

While there are potential benefits of aspirin for cancer prevention, it is important to note that there are also side-effects to its regular use. Low dose aspirin (e.g. 75-300mg) can increase the risk of several adverse outcomes such as gastrointestinal bleeding, and peptic ulcers (63, 64). In some cases, these complications can be fatal. Due to these side-effects, there is also the potential of detection bias with aspirin. A person who is taking aspirin may develop gastrointestinal bleeding, leading to the earlier diagnosis of colorectal adenomas (i.e. precursor lesion) or tumours, and in turn

improve survival rates from colorectal cancer (65). There are several factors which can increase the risk of experiencing gastrointestinal complications from aspirin. These include having a history of gastrointestinal bleeding, using aspirin at higher doses, being at older age (i.e. 70+), and Helicobacter pylori infection (64). If a person has one or more of these risk factors, they may be advised not to use aspirin, or in some cases they may be prescribed additional protective medication alongside aspirin. The overarching name for these protective medications is proton-pump inhibitor (PPI), which can be used to reduce the negative effects of aspirin. For example, trials have observed PPI medication to significantly reduce risk of gastroduodenal lesions in healthy volunteers taking 300mg daily aspirin (66, 67).

1.3.1.1 National guidance recommending aspirin for the general public

The strengths and limitations of the evidence supporting the use of aspirin for colorectal cancer prevention has been considered by several policy makers, which has led to the development of official guidance recommending aspirin for preventive therapy. In November 2017, the Cancer Council Australia released national guidance recommending the use of daily aspirin (100-300mg) for at least 2.5 years to prevent colorectal cancer among the general public aged 50 to 70 (68). Currently, there is no equivalent UK guidance recommending aspirin for cancer prevention among the general population. In the United States (US), the US Preventive Services Taskforce (USPSTF) recommended in 2016 the use of daily low-dose aspirin for colorectal cancer prevention and CVD prevention among adults aged 50 to 69 who have a 10% or greater 10-year CVD risk (69). However, in 2022, the USPSTF redacted their recommendation, concluding that the current evidence appears unclear on whether aspirin can reduce the risk of colorectal cancer incidence or mortality (70).

One study that contributed to the USPSTF's decision to remove the recommendation for using aspirin for colorectal cancer in their updated 2022 guidelines was the ASPirin in Reducing Events in the Elderly (ASPREE) trial. The ASPREE study is an RCT which recruited 19,114 people over the age of 70 in Australia and the US (71). Participants were randomised to 100mg daily aspirin or placebo. The study found those taking aspirin, vs. placebo, had a significantly increased risk of death from any cause (hazard ratio: 1.14, 95% CI: 1.01-1.29), and a significantly higher rate of cancer-related death (hazard ratio: 1.31, 95% CI: 1.10-1.56). The authors advised for the results to be interpreted with caution (71), as the findings are in contrast to previous trials conducted in this area.

Researchers have expressed concerns with the USPSTF updated 2022 guidance. Chan discussed several criticisms of the USPSTF's decision to remove the recommendation for aspirin for colorectal cancer prevention, and the limitations of the evidence from the ASPREE trial (72). One of the limitations of the trial is that participants were only followed up for 5 years, which is in contrast to

previous aspirin trials that have examined long term follow-up (e.g. 10-20 years) for the outcomes of cancer incidence and death (55, 56). Chan argues that 5 years follow-up is likely to be too short a duration for the protective effects of aspirin for colorectal cancer prevention to emerge in the ASPREE trial (72). Another limitation of the trial is that colorectal cancer death was not a prespecified primary endpoint, with the primary endpoint instead the first occurrence of death from any cause, or incident dementia, or a persistent physical disability (73).

In a subsequent ASPREE analysis study, Chan and several co-authors investigated the relationship between aspirin and incidence of cancer, and observed no significant difference between the aspirin group and the control group for all incident cancers (hazard ratio: 1.04, 95% CI: 0.95-1.14), or colorectal cancer incidence (hazard ratio: 1.02, 95% CI: 0.81 to 1.30) (74). However, there was a significant association between aspirin and an increased incidence risk of cancer that had metastasised (hazard ratio: 1.19, 95% CI: 1.00-1.43), or was at Stage 4 (hazard ratio: 1.22, 95% CI: 1.02-1.45). The authors concluded that aspirin should be used with caution in older age groups (74), and Chan has subsequently argued that starting aspirin in older age (e.g. 70) is likely too late for aspirin to have a protective effect on colorectal cancer (72).

Overall, there are a large number of observational and trial studies to support the use of aspirin for colorectal cancer prevention among those at population risk of the disease. However, there are several limitations to the data. In particular, a persistent criticism of the evidence is that trials have only investigated the relationship between aspirin and colorectal cancer as a secondary endpoint. At present, the only aspirin trials to prespecify colorectal cancer as a primary endpoint have been conducted among people at genetically higher lifetime risk of developing colorectal cancer (75).

1.3.2 Evidence for aspirin's effectiveness among people at higher risk

The use of aspirin for cancer prevention has been investigated in clinical populations, such as those at higher risk of developing cancer. Lynch syndrome is an inherited disorder caused by faulty mismatch repair genes (MLH1, MSH2, MSH6, PMS2), and increases the risk of developing multiple cancers, including colorectal, endometrial, and stomach cancer (76). One of the most common occurring cancers among people with Lynch syndrome is colorectal cancer, with people with the condition estimated to have a 10-46% lifetime risk of developing the disease, depending on the mismatch repair gene affected (77).

The discovery of Lynch syndrome dates to 1962, when Dr Henry Lynch encountered a patient at a veterans' hospital in Nebraska recovering from delirium tremens, who stated that they had a history of alcoholism because they believed they would die of cancer similar to many of their family members. Dr Lynch subsequently learnt that the patient had an extensive family history of colorectal

and endometrial cancer (labelled Family N) (78). Dr Lynch conducted an in-depth review of Family N's history to identify indicators (e.g. multiple colonic adenomas) for another colorectal cancercausing genetic condition, familial adenomatous polyposis. However, none were observed. Dr Lynch subsequently encountered another family with a history of cancer similar to Family N (Family M). In 1966, Dr Lynch published his findings discussing the hereditary cancer factors among these two families (79). Funding agencies were reluctant at first to accept an inherited genetic condition causing cancer, with environmental causes instead perceived as solely responsible for cancer (78). From approximately 1993, molecular genetics became more advanced and supported the evidence suggested from clinical genetics on hereditary cancer (80), leading to genetic causes to cancer becoming more widely accepted by funding agencies and the medical community (78). The condition was originally termed hereditary non-polyposis colorectal cancer, however the name was changed to Lynch syndrome to account for the multiple cancers patients are at increased lifetime risk of (e.g. endometrial, stomach, ovarian). At present, Lynch syndrome is estimated to account for approximately 2-4% of all colorectal cancer cases (81-83).

The first trial to prespecify colorectal cancer incidence as the primary endpoint was the Colorectal Adenoma/carcinoma Prevention Programme (CAPP2) trial. CAPP2 was an international RCT that randomly assigned 861 Lynch syndrome participants to either the intervention group (600mg daily aspirin) or control (75). The CAPP2 trial analysis published in 2011 observed that, in a per-protocol analysis, participants who completed two years of aspirin had a significantly reduced risk of developing colorectal cancer at mean 55.7 months follow-up (hazard ratio of 0.41, 95% CI: 0.19-0.86). However, there was no significant association in the intention-to-treat analysis (hazard ratio of 0.63, 95% CI: 0.35-1.13). A limitation of per-protocol analyses is that they can introduce bias and over-estimate the effects of the treatment (84), as they exclude participants who deviated from the protocol. Intention-to-treat analyses instead report the findings for the whole sample, which is beneficial for minimising biases and more accurately portrays how aspirin will be used by people in clinical practice (84).

There were also limitations to the primary endpoint analysed in the 2011 CAPP2 paper. The trial originally prespecified the primary outcome as colorectal cancer incidence, with the secondary outcomes being the development of colorectal adenomas or development of other Lynch syndrome-related cancers (75). However, at the end of the intervention the data on colorectal cancer and adenoma incidences were pooled for analysis, as the authors deemed it unlikely for aspirin to have affected the outcome of colorectal cancer within a 4-year follow-up. A key weakness of this analytic approach is that modifying prespecified primary endpoints increases the probability of encountering a Type I error (i.e. false positive result) (60, 85).

In 2020, the CAPP2 study published an additional analysis examining incidence of colorectal cancer at 10-year follow-up, with the primary endpoint solely colorectal cancer incidence. The 2020 analysis of the CAPP2 trial observed that, in the intention-to-treat analysis, participants taking aspirin daily at 600mg had a significantly reduced risk of developing colorectal cancer compared with the control group (hazard ratio of 0.65, 95% CI: 0.43-0.97) (86). The trial did not investigate the effect of aspirin on colorectal cancer mortality as the death rate among patients with Lynch syndrome participating in surveillance is low, therefore a larger powered trial would be needed. No relationship was observed between use of daily aspirin and non-colorectal Lynch syndrome cancers in either the intention-to-treat or per-protocol analyses. Overall, the trial concluded that 24 people with Lynch syndrome needed to be treated with 600mg daily aspirin to prevent one colorectal cancer case (86).

1.3.2.1 National guidance recommending aspirin for people at higher risk and future research

Following the 2011 CAPP2 publication, the National Institute for Health and Care Excellence (NICE) updated their colorectal cancer guidance (NG151) in 2020 with a recommendation to consider daily aspirin for a minimum of 2 years to prevent colorectal cancer in people with Lynch syndrome (87). The NICE committee did not recommend a dose, as one that balances the benefits and harms of aspirin remains unclear. However, they stated that 150-300mg are commonly used doses in clinical practice (87). Following the introduction of the updated guidance, NICE released a patient decision aid for people with Lynch syndrome considering aspirin for preventive therapy (88). At present, the decision aid has not been empirically tested, and the effect of the aid on patients' decision-making is unknown.

Trials are ongoing to further investigate the relationship between daily aspirin and colorectal cancer among people with Lynch syndrome. A dose non-inferiority trial (CaPP3) is currently underway to compare the effectiveness of aspirin at different doses (100mg, 300mg, or 600mg) for colorectal cancer prevention (89). The relationship between aspirin and pre-cancerous lesions among people with Lynch syndrome is also currently being investigated further. The AAS-Lynch trial is a prospective, multicentred RCT aiming to investigate whether daily aspirin at 100mg or 300mg (vs. placebo) reduces the risk of occurrence or recurrence of colorectal adenomas among people with Lynch syndrome under the age of 75 (90). As of yet, no results have been published for either trial.

Research has also investigated the effectiveness of aspirin for prevention of cancer recurrence. The Add-Aspirin trial is an ongoing RCT to examine aspirin's effectiveness in preventing recurrences of breast, colorectal, gastro-oesophageal, and prostate cancer (91). Participants are randomised in each of the four cohorts to either 100mg, 300mg of aspirin or matched placebo, with the primary outcome the specific cancer-free survival for each of the cohorts. Currently, feasibility findings have

been reported among 2,719 participants recruited and randomised at two-year follow-up, and have demonstrated that aspirin is well tolerated by the participants (92). To date, no main outcome findings have been reported.

In summary, there are both strengths and limitations to the evidence supporting the use of aspirin for colorectal cancer prevention among those at population risk and those at higher lifetime risk of the disease. Taking into consideration the evidence, policy makers have introduced guidance recommending the use of aspirin across countries, including in the UK. When introducing new guidance, it is imperative to examine the behavioural research in this area, to understand further what the facilitators and barriers are to the implementation of aspirin in clinical practice.

1.4 Decision-making in preventive therapy

There are several factors to consider when deciding on the use of aspirin for preventive therapy. The benefits of aspirin for potential colorectal cancer prevention need to be weighed against the side-effects, as even low doses can increase the risk of gastrointestinal bleeding, ulcers and, in more rare cases, haemorrhagic stroke (93, 94). When implementing aspirin for preventive therapy into clinical practice, there are likely two main decision-maker groups. These are service users (e.g. patients) who may use the medication, and their healthcare providers who may recommend or prescribe the medication. Given the potential complexity of the decision, it is important for research to examine the factors influencing the decision to use or recommend aspirin for preventive therapy, and how the medication is used in practice.

1.4.1 Decision-making among people at higher risk of cancer

In the UK, the main patient group offered the use of aspirin for colorectal cancer prevention is people with Lynch syndrome (87). However, minimal research has examined the factors influencing the use of aspirin among this group. Among the available data, studies have examined the views of people with Lynch syndrome on their general healthcare experiences. One such qualitative study interviewed participants with Lynch syndrome in Ireland, with the aim to explore participants' experiences managing their healthcare following a Lynch syndrome diagnosis (95). Several difficulties were discussed, including participants' experiences with a disjointed healthcare management pathway for Lynch syndrome, and a lack of knowledge on the condition among healthcare professionals. Another qualitative study conducted in the US observed several barriers to managing healthcare among people with Lynch syndrome, including a lack of coordinated care and knowledge among healthcare professionals (96). The views and experiences of the participants in the context of aspirin for preventive therapy were not explored.

Previous research has examined the views of people with Lynch syndrome on other cancer preventive options and lifestyle behaviours. One interview study recruited women with Lynch syndrome in Canada who had been offered prophylactic gynaecological surgery (97). Several factors were discussed as influential, with many women choosing surgery to reduce their worries about developing cancer. Barriers were also explored, such as younger women being more hesitant to undertake the procedure due to childbearing considerations (97). In the Netherlands, a qualitative study investigated the barriers and facilitators affecting adherence to the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) recommendations for cancer prevention (98). These recommendations include being physically active every day, and limiting consumption of red and processed meats. In the study, people with Lynch syndrome described several barriers to adhering to the WCRF/AICR recommendations. These barriers included participants' perceiving themselves at decreased susceptibility to colorectal cancer because they engaged in regular colonoscopies, and a feeling of not wanting a Lynch syndrome diagnosis to dominate their lifestyle choices (98). It is unknown if similar motivators and barriers are also influencing the use of aspirin for cancer prevention among this group.

There is a stronger evidence base for the factors influencing use of preventive therapy among women at higher risk of breast cancer. In 2013, NICE published clinical guidelines (CG164) with a recommendation to offer SERMs, such as tamoxifen, to women at higher risk of developing breast cancer (99). However, despite the introduction of the NICE guidance, uptake of the medication is estimated to be low. For example, a systematic review and meta-analysis observed low uptake of breast cancer preventive therapy across trials settings (25% uptake) and in clinical practice (9% uptake) (100). Prospective studies have found that women at higher breast cancer risk are more likely to initiate SERMs if they have lower concerns on its side-effects (101), report higher levels of worry about developing breast cancer (102, 103), have greater knowledge on its benefits and harms (104, 105), and express greater belief in the effectiveness of the medication (105). In addition, women who smoke, are older, with less education have been found to be less likely to adhere to breast cancer preventive therapy (106). It is currently unknown if such factors also influence the uptake of and adherence to aspirin, or if there are specific barriers applicable to this context.

Overall, research is warranted to investigate use of aspirin for preventive therapy among people with Lynch syndrome. In the UK, an investigation into use of aspirin among people with Lynch syndrome is likely to take on greater significance following the release of the 2022 NICE quality standard (QS20), which recommends that all adults with a new diagnosis of colorectal cancer are tested for Lynch syndrome (107). As 175,000 people are estimated to have Lynch syndrome in the UK but fewer than 5% are aware (108-110), it is likely that a substantially greater number of people

will be diagnosed with Lynch syndrome following the introduction of the new NICE quality standard (QS20). It is therefore imperative that the barriers to using aspirin among UK patients with Lynch syndrome are examined, to ensure patients considering the medication for preventive therapy are provided with adequate support.

1.4.2 Decision-making among the general public

While other preventive medications, such as tamoxifen, are only recommended for higher risk populations, there is potential for UK guidance to recommend aspirin for colorectal cancer prevention for the general population (45, 55, 56). It is essential to investigate decision-making for using aspirin for cancer preventive therapy among people at population risk, as the motivators and barriers to using aspirin may be different compared with people at higher risk of cancer. Previous research found evidence of moderately high acceptability towards using aspirin for cancer prevention among the public. For example, an Australian cross-sectional study presented general population participants with information on the use of aspirin for colorectal cancer prevention in four different risk communication formats, such as a bar chart and icon array. The study observed that irrespective of presentation format, there was high acceptability towards taking aspirin for the purpose of cancer prevention is currently unknown.

There may be high acceptability towards taking daily aspirin for preventive therapy among the UK public. The medication is available over-the-counter, and it is likely that a proportion of the population are already taking aspirin regularly for different reasons, including cardiovascular disease prevention (112). Research conducted in several countries has investigated rates of aspirin use among community population samples. For example, a UK survey recruited 6,322 adults in North Staffordshire with the aim to investigate prophylactic aspirin use among people with vascular issues (113). The study found that regular aspirin use was reported by 8% of participants with vascular issues, but also by 6% of people who did not report vascular issues. The specific reasons for taking aspirin regularly were not explored. An observational study in Canada investigated use of aspirin among patients in primary care practices (114). A total of 520 people were recruited, of which 26% used aspirin regularly. The authors did not report on participants' reasons for taking aspirin, however it is unlikely that many were taking aspirin for the purpose of cancer prevention as only 10% of aspirin users were aware of its cancer preventive effects (114). Overall, use of aspirin for cancer prevention among the general population is an underexplored area in research, and it is possible that a proportion of the UK public are already taking aspirin daily for this purpose.

A small number of studies have investigated decision-making in the context of aspirin for preventive therapy among those at population risk. Behavioural research in Australia has focused on the development of a decision aid to support people from the general population aged 50 to 70 considering aspirin for colorectal cancer prevention (111, 115, 116). Decision aids are tools that can inform patients of the available health-related options from an evidence-based perspective (117), and have been found to effectively support patients to arrive at decisions aligned with their values (118). In Australia, a multi-site randomised control trial is currently underway in general practices to test the efficacy of the decision aid (116). Patients attending primary care for any reason who are between the ages of 50 to 70 are invited to participate in the trial. Patients are then randomised to either the intervention or control arm, with those in the intervention arm presented with a decision aid describing risks and benefits of aspirin for colorectal cancer prevention for a person at population risk. At present, no results from this trial have been published.

Research has also been conducted to support decisions on the use of aspirin for cancer preventive therapy among the UK public, with the aim to aid in the implementation of any potential future UK guidance. In South Wales, qualitative research has developed and user-tested a prototype decision aid for aspirin among people from the general population eligible for colorectal cancer screening (119). Following the presentation of the decision aid, most participants felt that at present they would not take aspirin for preventive therapy, but they would potentially explore this option with their GP in the future. In addition, several participants who already used aspirin for a different purpose felt reassured to continue using the medication after learning of its use for colorectal cancer prevention (119). The study did not explore participants' general acceptability and attitudes towards using aspirin for colorectal cancer prevention without the presentation of a decision aid.

If future UK guidance does recommend the use of aspirin for colorectal cancer prevention for those at population risk, it is likely that many people from the public will formulate initial decisions on aspirin based on minimal information. Those who are interested in using aspirin are likely to then go on to seek further information about the medication and use tools such as a decision aid. Therefore, research should investigate the barriers to using aspirin among a wide group of participants, including those who are not interested in the medication and would not engage with a decision aid. These findings would enable an exploration of the facilitators and barriers among people from the general public who are both receptive and resistant to taking aspirin for preventive therapy.

1.4.3 Decision-making among healthcare providers

Another important group that may influence the implementation of aspirin for preventive therapy into clinical practice is healthcare providers, who are likely to advise on and prescribe the medication

for patients. Prospective studies have previously identified a positive association between healthcare provider recommendation and patients' use of breast cancer preventive therapy (102, 103). In a qualitative study conducted in Canada, several women with Lynch syndrome reported that a doctor recommendation influenced their decision to undergo prophylactic gynaecological surgery (97). Given the likely influential role of healthcare providers in patients' decision-making on aspirin, it is imperative to explore the barriers these professionals may experience when recommending or prescribing the medication for preventive therapy.

Research has identified several barriers to recommending breast cancer preventive therapy among healthcare providers. A UK survey of 928 general practitioners (GPs) investigated willingness to prescribe tamoxifen to a patient at higher risk of breast cancer (120). In the study, GPs who reported greater confidence in their knowledge of tamoxifen, and those were more aware of the NICE guidance recommending the medication were significantly more willing to prescribe tamoxifen than those unwilling (120). Several GPs were concerned about prescribing tamoxifen as it would be an off-label use of the medication, and were significantly less willing to prescribe for this reason. There are likely to be similar and different barriers healthcare providers experience when prescribing aspirin compared with breast cancer preventive therapy. Both medications are prescribed for the off-label use of cancer prevention, but there are differences in the populations (i.e. Lynch syndrome vs. higher risk of breast cancer), and the different side-effects (93, 121-123). Furthermore, healthcare providers may have varying levels of awareness and comfort in relation to these medications. While aspirin is a pain relief drug available over-the-counter, tamoxifen is a cancer-related medication only available on prescription (124).

Previous research has also investigated healthcare providers' willingness to recommend or prescribe aspirin for preventive therapy. An Australian interview study explored healthcare providers' views on the use of aspirin for colorectal cancer prevention for the general public (115). The study recruited participants across the professional groups of GPs, clinical geneticists, genetic counsellors, gastroenterologists, oncologists, and pharmacists. In the study, all participants viewed GPs as the most important healthcare provider for implementing guidance recommending aspirin for cancer prevention. Healthcare providers such as pharmacists and specialist clinicians viewed their roles instead as advocates of the guidance. Healthcare providers also described multiple barriers to the implementation of the guidance. These included uncertainties regarding the dose of aspirin to prescribe, and concerns on the side-effects of aspirin in older populations following the results of the ASPREE trial (115). A limitation of the Australian interview study is that it only explored healthcare providers' views on the use of aspirin for patients at population risk of colorectal cancer. Given that

the UK NICE guidance (NG151) recommends aspirin for people with Lynch syndrome (87), it is crucial that the views of healthcare providers on the use of aspirin for this specific population are explored.

In the UK, quantitative research has investigated healthcare providers' attitudes towards prescribing aspirin for colorectal cancer prevention for patients with Lynch syndrome (125). A UK cross-sectional survey recruited 1,007 GPs, and observed respondents were more willing to prescribe aspirin to a hypothetical patient with Lynch syndrome if they had greater awareness of the medication's cancer preventive effects (125). Dose of aspirin was also important, with only 62% of GPs willing to prescribe daily aspirin at 600mg compared with 91% at 100mg (125). While the UK study was the first to investigate healthcare providers' views towards the use of aspirin for people with Lynch syndrome, the study only quantitatively investigated GPs' attitudes. While a strength of quantitative methods is that it can statistically analyse the relationship between variables in a large dataset, qualitative studies (e.g. interviews, focus groups) can instead explore in-depth why participants experience certain barriers and motivators (126). Furthermore, qualitative research can enable participants to raise new issues that are important to them. Given the benefits of qualitative research, the methodology should be employed to explore the views of healthcare providers on the use of aspirin for preventive therapy in Lynch syndrome. The findings from this gualitative research would aid the implementation of the NICE guidance (NG151) recommending aspirin into clinical practice (87), and can inform the design of future quantitative research (127), such as intervention development (128).

1.5 Applying theory to examine the factors affecting uptake of new guidance

When examining the implementation of new guidelines into clinical practice, there is a need to understand the determinants of behaviour of the relevant actors required to make these changes (129). Theoretical frameworks have been developed to explain these determinants of behaviour (129-131). For this thesis, I considered multiple frameworks and how they might aid in the exploration of the factors influencing use of aspirin for preventive therapy among both potential users and healthcare providers. As there is existing UK NICE guidance (NG151) recommending aspirin for cancer preventive therapy (87), I specifically considered frameworks related to implementation research. There were three implementation frameworks I considered for this PhD: Normalisation Process Theory (NPT) (130); Consolidated Framework for Implementation Research (CFIR) (131); and Theoretical Domains Framework (TDF) (129).

1.5.1 Normalisation Process Theory (NPT)

The framework NPT was developed with the aim to address the gap between research and implementation of the research, by outlining the factors required for the implementation of

interventions into routine healthcare (i.e. normalisation) (130). The NPT describes four factors (i.e. domains) that can promote or inhibit the implementation of complex interventions into clinical practice (130). These are Coherence (how people make sense of an intervention); Cognitive Participation (willingness to commit to an intervention); Collective Action (the skills and ability to take on the intervention); Reflexive Monitoring (people's reflection on and evaluation of the intervention). The NPT is widely utilised in intervention research, with a systematic review observing use of the framework across multiple study types including intervention design research, feasibility trials, and qualitative process evaluations of trials (132).

One of the strengths of the NPT is that the framework recognises the importance of collaboration when implementing healthcare changes. For example, the NPT describes the interactions and collective action required between healthcare professionals, patients, service mangers, and any other relevant person that can affect implementation (130). The NPT though was developed for trialists to aid in the implementation of complex interventions into clinical practice, and may be difficult to apply to other contexts, such as examining the barriers to implementing new clinical guidance. Researchers have also discussed difficulties with applying the NPT due to the lack of accessible language to describe the domains (132, 133). Furthermore, it can be a time-consuming practice to translate the NPT domains to apply to the study's specific context and research question (133, 134).

1.5.2 Consolidated Framework for Implementation Research (CFIR)

The CFIR was the second framework considered for the thesis, which is a framework developed from several implementation theories, and aims to understand what works, where and why across multiple contexts (131). There are five main domains to the CFIR: Intervention Characteristics; Outer Setting; Inner Setting; Characteristics of the Individual; Process. The Intervention Characteristics domain refers to the characteristics of the intervention being implemented, such as the evidence strength, and intervention adaptability. Outer Setting refers to the wider external context (e.g. economic, political and social context), while Inner Setting describes the internal structural and cultural context which the implementation process will proceed through. The fourth domain is the Characteristics of Individuals, such as the knowledge, beliefs and self-efficacy of the people involved in the implementation of the intervention. The final domain is the Process, such as the active change processes required to achieve implementation of the intervention at individual level and organisational level.

An advantage of the CFIR is that the framework describes both the individual and organisational factors affecting implementation of an intervention, which I anticipated would be of relevance to a

person considering aspirin for preventive therapy. In contrast, the majority of the NPT domains focuses on the structural and environmental factors affecting implementation (130). The CFIR has also been applied to a wide breadth of research settings (135), including exploring the factors affecting implementation of breast cancer preventive therapy (136), and aspirin for colorectal cancer prevention among healthcare providers (115). However, the CFIR has been utilised much less to explore implementation problems among patients. The framework has instead predominantly focused on the barriers and facilitators affecting implementation among healthcare organisations or healthcare providers (135).

1.5.3 Theoretical Domains Framework (TDF)

The third implementation framework I considered was the TDF. The framework was developed by a collaboration of behavioural and implementation researchers, who synthesised 33 behaviour change theories highly relevant to implementation research, and clustered these theories into 14 domains (129). These domains cover both internal factors, such as a person's knowledge and their beliefs, as well as external factors such as a person's environment and the resources available to them (Table 1.1).

Table 1.1. The 14 domains in the Theoretical Domains Framework (version 2). Table adapted from	
Atkins et al. (129)	

Domains	Description of the domain
Knowledge	An awareness of the existence of something
	(e.g. clinical guidance).
Skills	A person's ability or proficiency acquired
	through skills development and practice.
Social/professional role and identity	A coherent set of behaviours and displayed
	qualities of an individual, including both
	professional and social identity.
Beliefs about capabilities	Acceptance of the truth, reality or validity
	about an ability (e.g. self-efficacy, self-esteem,
	beliefs).
Optimism	The confidence that things will happen for the
	best or that the desired goal will be attained.
	Domain includes both optimism and pessimism.

Accordance of the truth reality or validity	
Acceptance of the truth, reality, or validity	
about the outcome of a behaviour (e.g.	
outcome expectancies, consequences).	
Increasing the probability of a response by	
arranging a dependent relationship between	
the response and stimulus. Examples include	
rewards, incentives, and punishment.	
A conscious decision to perform a behaviour or	
act in a certain way.	
Mental representations of the outcomes that	
the individual wants to achieve, and includes	
factors such as action planning.	
The ability to retain information and choose between two or more alternatives (e.g. memory, decision-making).	
	Any part of the person's situation or
	environment that discourages or encourages
the development of skills, abilities, and other	
relevant behaviours. Examples include	
organisational culture, and the material	
resources available.	
The interpersonal processes and relationships	
that can cause individuals to change their thoughts, feelings, or behaviours (e.g. social	
	pressure, social support).
Includes any emotional factors affecting	
implementation such as fear, anxiety, stress,	
and happiness.	
Anything related to managing or changing an	
observed action, such as the practice of self-	

Limitations of the TDF include that the framework does not specify the relationships between the domains, which can make it difficult to determine the origin of a barrier or facilitator (137). The

framework has also been criticised for predominantly focusing on the individual factors rather than the organisational factors affecting implementation (137). For my thesis, I felt that the focus of the TDF on the individual factors affecting implementation was a strength, as I anticipated that factors such as a person's emotions and beliefs would be highly important when discussing decision-making in the context of preventive therapy.

An additional strength of the TDF is that while the framework was originally developed for understanding healthcare professional behaviour, it has since been expanded for use in patient populations (129, 138). The application of the TDF to patient research was important as I aimed to explore the determinants of behaviour among both potential aspirin users and healthcare providers. I reviewed several TDF studies to consider how the framework could be applied to my research. For example, one interview study utilised the TDF to investigate the barriers and facilitators midwives experience in relation to multiple health promotion practice behaviours (139). The authors developed their interview schedule to cover the TDF domains, and identified several domains as barriers to implementing the behaviour, such as the midwives' environmental context and resources (e.g. accessible training). In addition, the TDF has been used to investigate the determinants of patient behaviour, such as an interview study that explored the factors influencing retinal screening behaviour among patients with Type 2 diabetes (140). The authors identified several contextual and motivational factors affecting screening among patients. The study also provided suggestions for clinical practice, such as tailored support messages targeting the areas identified as amenable to change. After reviewing the previous evidence, I could envision clearly how the TDF could be applied to my PhD research across both the potential aspirin user and healthcare provider interviews.

1.5.4 Strengths of applying the TDF compared with the NPT and CFIR

There were several advantages to employing the TDF in the thesis compared with the other considered frameworks, the NPT and CFIR. In contrast to the NPT which focuses on the implementation of complex interventions, the TDF was designed for understanding and aiding in the implementation of new practices, or changing existing practices, in healthcare (129). Therefore, I judged the aims of the TDF to be more aligned to my research, which aimed to examine implementation problems in the context of existing national guidance. The majority of the NPT also focuses on the organisational and collaborative factors affecting implementation, and less on the individual factors. I considered a key strength of both the TDF and CFIR were that the framework domains described several individual factors, such as attitudes, which can affect the implementation of new practices (129, 131).

When comparing whether to apply the TDF or the CFIR to the thesis research, I felt there were three main strengths of the TDF. First, the TDF covers a wider range of individual domains than the CFIR, such as a person's emotions, optimism, and their intentions. Second, the TDF has been more consistently applied to explore determinants of behaviour among patients (138), than the CFIR (135). Third, I found the TDF easier to comprehend, as the framework describes 14 specific factors that are amenable to change and can influence behaviour. In contrast, the CFIR is less specific on the factors affecting behaviour, and instead describes an overarching typology of five general domains believed to influence implementation. To summarise, I applied the TDF to the thesis research to aid in the exploration of the factors influencing use of aspirin for preventive therapy. The main strengths of the TDF were the breadth and specificity of the 14 domains covering both internal and external factors, and the prior use of the framework to explore determinants of behaviour among both healthcare providers and patients.

1.6 Chapter summary

To summarise, there is increasing interest in the use of preventive therapy to reduce a person's risk of developing cancer. Aspirin has been investigated for its use in reducing the risk of several different cancers. Of these cancers, colorectal cancer currently has the strongest evidence base for using aspirin as preventive therapy. The medication has been used to prevent colorectal cancer among both people at higher risk of colorectal cancer and those from the general population. However, when deciding whether to use aspirin both the potential benefits and side-effects need to be considered, as even low doses can increase risk of gastrointestinal bleeding. Healthcare providers also need to consider the risks and benefits of aspirin when deciding whether to recommend or prescribe aspirin for preventive therapy. In the UK, daily aspirin is recommended by NICE (guidance NG151) for colorectal cancer prevention among people with Lynch syndrome. However, the barriers and facilitators affecting use of aspirin for preventive therapy among people with Lynch syndrome and their healthcare providers are currently unknown. There is also potential for future UK guidance to recommend aspirin for colorectal cancer prevention among those at population risk of the disease. Furthermore, it is possible that those outside of a Lynch syndrome population may already be taking daily aspirin for the purpose of cancer prevention. How aspirin is used by the UK public, and the views of those at population risk of taking aspirin for colorectal cancer prevention is currently unknown. When examining the barriers and facilitators to the implementation of new guidance into clinical practice, frameworks can be utilised to understand the determinants of behaviour. In my PhD, I will employ the TDF, which can aid in exploring both the individual and external factors which can influence behaviour in the context of new clinical guidance.

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1.7 Aims and objectives

In my thesis, I will investigate decision-making in the context of aspirin for cancer preventive therapy. In particular, I will explore the facilitators and barriers to using aspirin for cancer preventive therapy among people with Lynch syndrome and the UK general public. I will also investigate the facilitators and barriers to recommending and prescribing aspirin among the healthcare providers involved in the Lynch syndrome care pathway.

Three objectives were identified for the thesis, which were to:

- Undertake a systematic review synthesising the quantitative and qualitative data on attitudes towards aspirin for preventive therapy, and adherence behaviours among people at higher risk of cancer, the general public, and healthcare providers.
- Use qualitative interviews to explore the facilitators and barriers to using and recommending aspirin for preventive therapy among people with Lynch syndrome, the general public, and healthcare providers.
- 3) Conduct a randomised factorial trial investigating the optimal type and level of information to communicate with GPs to increase their willingness to prescribe aspirin for a patient with Lynch syndrome.

The thesis aims to address the following research questions:

- What is currently known about the factors affecting decisions to use aspirin for cancer prevention, and healthcare providers' attitudes towards implementing aspirin for this purpose in clinical practice?
- 2) What are the barriers and facilitators to taking aspirin for colorectal cancer prevention among people with Lynch syndrome, and what are the barriers and facilitators to healthcare providers recommending or prescribing aspirin for this purpose?
- 3) To what extent are the UK general population aged 50 to 70 aware of the use of aspirin for cancer prevention, and what are their views towards taking aspirin for this purpose?
- 4) What is the optimal information to communicate with GPs to increase their willingness to prescribe aspirin for colorectal cancer prevention in Lynch syndrome?

1.8 Thesis overview

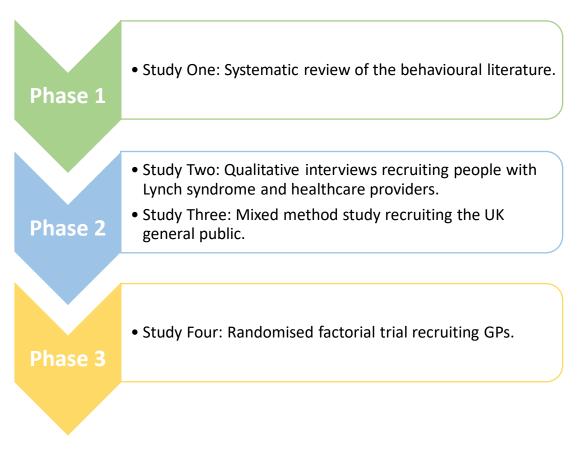
First, a review of the literature was warranted to synthesise the quantitative and qualitative behavioural evidence in the context of aspirin for cancer prevention. **Chapter Two** presents a systematic review study, which aimed to examine the data on attitudes and behaviour towards the use of aspirin for cancer prevention among the general population and those at higher cancer risk,

and healthcare providers' attitudes towards implementing aspirin in clinical practice. As aspirin has previously been investigated for preventing multiple cancers, I synthesised the evidence in the general area of aspirin for cancer prevention. Overall, the review aimed to summarise what is currently known and what the gaps are in the literature. Given the 2020 NICE guidance (NG151) (87), it was important for the thesis to investigate the factors affecting implementation of aspirin for preventive therapy for people with Lynch syndrome. **Chapter Three** presents a qualitative study which aimed to explore the facilitators and barriers to using and recommending aspirin for colorectal cancer among people with Lynch syndrome and healthcare providers.

There is also potential for future UK guidance to recommend aspirin for colorectal cancer prevention for those at population risk, similar to the Australian guidance (68). **Chapter Four** of the thesis describes a mixed methods study which aimed to explore acceptability towards taking aspirin for colorectal cancer prevention among the UK general population. The study presents the findings from a short survey recruiting participants from the public aged 50 to 70, with a qualitative exploration of the potential barriers and facilitators to taking aspirin among a sub-sample of survey respondents. If future UK guidance does recommend aspirin for colorectal cancer prevention for those at population risk, the findings from this study would aid in the implementation of this recommendation. The findings from the qualitative research presented in **Chapter Three** informed the design of the final study, which is presented in **Chapter Five**. The study is a randomised factorial trial recruiting GPs from England and Wales. The trial aimed to investigate the optimal type and level of information to communicate with GPs to increase their willingness to prescribe aspirin for preventive therapy for a hypothetical patient with Lynch syndrome. The final chapter, **Chapter Six**, discusses the findings of the whole thesis and its conclusions. An overview of the thesis structure is summarised in Figure 1.1.

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Chapter Two: Aspirin use for cancer prevention: a systematic review of public, patient and healthcare provider attitudes and adherence behaviours

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	adherence behaviours. Prev Med. 2022;154(106872).

2.1 Abstract

We undertook a systematic review to synthesise the data on attitudes and behaviour towards the use of aspirin for cancer prevention, and healthcare providers' attitudes towards implementing aspirin in practice. Searches were carried out across 12 databases (e.g. MEDLINE, EMBASE). We used the Mixed Methods Appraisal Tool to evaluate study quality, and conducted a narrative synthesis of the data. The review was pre-registered (PROSPERO: CRD42018093453). Thirty-eight studies were identified. Uptake and adherence data were all from trials. Trials recruited healthy participants, those at higher risk of cancer, and those with cancer. Four studies reported moderate to high (40.9-77.7%) uptake to an aspirin trial among people who were eligible. Most trials (18/22) reported high day-to-day adherence (\geq 80%). Three trials observed no association between gender and adherence. One trial found no association between adherence and colorectal cancer risk. Three studies reported moderate to high (43.6-76.0%) hypothetical willingness to use aspirin. Two studies found that a high proportion of healthcare providers (72.0–76.0%) perceived aspirin to be a suitable cancer prevention option. No qualitative studies were identified. The likelihood that eligible users of aspirin would participate in a trial evaluating the use of aspirin for preventive therapy was moderate to high. Among participants in a trial, day-to-day adherence was high. Further research is needed to identify uptake and adherence rates in routine care, the factors affecting aspirin use, and the barriers to implementing aspirin into clinical care.

2.2 Introduction

Cancer is the second leading cause of death globally (1), with an estimated 9.6 million cancer deaths worldwide in 2018 (2). There is increasing interest in preventive therapy as part of cancer control efforts (3). A meta-analysis of 45 observational studies found aspirin to be associated with a reduced risk of developing colorectal (relative risk: 0.73, 95% CI=0.69-0.78) and other gastrointestinal cancers (range, relative risks: 0.61-0.78) (4). Reviews have also examined the relationship between aspirin and cancer by synthesising the results of randomised controlled trials (RCTs) investigating aspirin for vascular disease prevention. These results showed that individuals taking aspirin, versus no aspirin, had a reduced 20-year risk of developing colon cancer (hazard ratio: 0.76, 95% CI=0.60-0.96) (5), and a reduced risk of colorectal cancer death at 10-20 years (hazard ratio: 0.51, 95% CI=0.35-0.74) (6). Cohort studies have observed weaker significant associations between aspirin use and risk reduction of non-gastrointestinal cancers, such as breast (hazard ratio: 0.96, 95% CI=0.91-1.00) (7), prostate (hazard ratio: 0.95, 95% CI=0.90-1.00) (7), and lung cancer (relative risk: 0.95, 95% CI=0.91–0.98) (8).

Despite many countries having national cancer screening programmes, few have implemented guidance recommending aspirin for cancer prevention. The US Preventive Services Taskforce recommends aspirin for colorectal cancer prevention among adults aged 50-69 who have ≥10% 10-year cardiovascular disease risk (9). In the UK, the National Institute for Health and Care Excellence recommends daily aspirin for people with Lynch syndrome (10), and in Australia aspirin is recommended for the public aged 50-70 (11). Guideline implementation depends on informed uptake, high adherence, and understanding the barriers to achieving these goals. However, deciding whether to use preventive therapy can be a complex choice for patients, and for their healthcare providers prescribing it. The benefits of aspirin need to be considered in relation to its side-effects, as even low doses can increase the risk of gastrointestinal bleeding, ulcers and, in more rare cases, haemorrhagic stroke (12, 13).

Studies have investigated the barriers and facilitators to using breast cancer preventive therapy. The evidence suggests the factors associated with increased uptake include having children (14), higher objective risk (15), higher cancer-related worry (16, 17), and fewer concerns about the side-effects (16, 18, 19). Women with lower educational qualifications, depression and those who are older are also less likely to adhere to the medication (15). Prospective studies have also identified a positive association between healthcare provider recommendation and patients' use of breast cancer preventive therapy (16, 17). To our knowledge, no review has examined decision-making in the context of aspirin for cancer prevention among potential users of aspirin and healthcare providers.

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We undertook a systematic review to synthesise the quantitative and qualitative data on uptake and adherence behaviours related to aspirin for cancer prevention, investigate the factors affecting decisions to use aspirin, and examine healthcare providers' attitudes towards implementing aspirin in clinical care.

2.3 Materials and Methods

2.3.1 Search strategy

We first conducted a search of the literature in March 2018, and reran the searches in February 2020. Searches were conducted in the following databases from inception to February 2020: MEDLINE; EMBASE; CINAHL; Cochrane Library (CENTRAL and Cochrane Database of Systematic Reviews); Database of Abstracts of Reviews of Effects (DARE); NHS Economic Evaluation Database; Pan Health Technology Assessment (HTA) Database; HTA Database (Wiley); PubMed; ProQuest Dissertation and Theses A&I; and Web of Science Core Collection. We also searched the International Clinical Trials Registry Platform (ICTRP) and Clinical trials.gov, and the websites of Cancer Research UK and cancer.gov for any ongoing trials. After identifying relevant conference abstracts, trials, and dissertations, we searched for the peer-reviewed articles of these studies. Search terms were developed for the concepts: aspirin, cancer and prevention by an information specialist (RR) and project team members using subject headings and free text terms (Appendix A.1). We did not apply date limits or methodological filters to the searches.

We stored and de-duplicated the records in EndNote X9, and screened them using the management software Covidence. To find additional papers, we searched the reference lists of included studies and relevant reviews. The review was pre-registered (PROSPERO number: CRD42018093453), and PRISMA guidelines for reporting were followed throughout (Appendix A.2) (20).

2.3.2 Study selection

We included both quantitative and qualitative peer-reviewed studies, which provided empirical data and recruited individuals aged 18 or over. Studies were included if they reported rates of uptake and/or adherence to aspirin (at any dose) for primary or secondary prevention (i.e. preventing recurrence) of cancer. Additionally, we included articles which reported patient, public or healthcare provider attitudes towards using aspirin for cancer prevention. We deviated from the preregistration by including quantitative studies exploring individuals' perceptions about taking aspirin for cancer prevention, instead of only qualitative data. Articles on the same trial were included if they provided additional data, such as adherence at longer follow up. We excluded articles reporting adherence on a smaller sub-sample from an included trial. As we were only interested in attitudes and behaviour data in the context of aspirin for cancer prevention, we excluded studies where aspirin was not used/prescribed for the primary purpose of cancer prevention. For example, we excluded studies using aspirin for the primary purpose of cardiovascular disease prevention/management, and case control and cohort studies if aspirin was not being used for the primary purpose of cancer prevention. Non-peer reviewed studies and reviews were also excluded. We excluded by hand non-English language studies as we did not have the resources to translate.

Screening of the titles and abstracts was completed by two authors (RJT, KEL), and two authors (RR, LHH) duplicated screening for 20% of articles. Discrepancies were resolved with a third reviewer (SGS). Two authors (RJT, KEL) screened the full text articles, and second reviewers (LHH, KEL) duplicated screening for 20% of articles. The review was managed in Covidence.

2.3.3 Data extraction

Two authors (RJT, KEL) extracted the study data using Excel, and 45% (17/38) of a random sample of articles were verified by second reviewers (RR, KEL) to ensure consistency (21). We extracted data on study characteristics; sample characteristics; aspirin dose; timing; uptake level; adherence method; adherence definitions; follow-up time; day-to-day adherence; persistence adherence; and factors associated with uptake, day-to-day adherence and/or persistence. Additionally, we extracted data reporting attitudes towards aspirin for cancer prevention.

Uptake rates were defined as the proportion of individuals who were offered aspirin and took the first dose (22). To calculate uptake to a clinical trial, we calculated the proportion of eligible participants who enrolled on the trial. The denominator was the number of eligible participants offered the trial, with ineligible participants excluded from the calculation. We classified participants who declined trial participation for unknown reasons as declining to take part. We defined day-to-day adherence as the extent to which people took the medication as prescribed (22). Data could be continuous (0-100% of medications) or categorical (proportion classified as adherent). We defined persistence as the length of time between uptake and last dose (22). Studies reporting the proportion of participants who completed the trial, without explicit reference to the medication, were excluded. We included both self-report and objective adherence measures.

2.3.4 Quality assessment

We used the Mixed Method Appraisal Tool (MMAT) to assess methodological quality (23). MMAT is reliable (24), and has been used in a review examining decision-making in breast cancer preventive therapy (15). For each study design (qualitative, quantitative RCTs, non-randomised quantitative

studies, quantitative descriptive studies, mixed methods studies), there was a quality checklist consisting of 5 items. All items were categorised as 'Yes', 'No', or 'Can't tell'.

RCTs received a quality assessment score ranging from 0-4, as the criterion 'Did the participants adhere to the assigned intervention?' (2.5) was removed due to adherence being a review outcome. All other study types received a score 0-5. The MMAT guidance recommended study teams agreed on an acceptable dropout rate for the criterion 'Are there complete outcome data?' (2.3, 3.3). We decided a priori that an article would qualify as 'Yes' if they reported a dropout rate of \leq 30% participants (23, 25). One author (KEL) assessed the quality of all articles, with over 35% (14/38) of a random sample of articles verified by a second author (LHH) to ensure consistency. Any discrepancies were resolved with a third author (SGS).

2.3.5 Synthesis of the evidence

To determine if a meta-analysis was appropriate we considered whether the included studies were sufficiently similar on the domains of participants (setting), intervention, comparison and outcomes (26). There was substantial heterogeneity, for example there was high variations in the doses of aspirin prescribed (intervention), assessments of adherence (outcomes), and the participant population (setting). Within subgroups, few studies used the same setting, intervention, and outcome. Therefore, we concluded that a meta-analysis was inappropriate for our review due to the high heterogeneity. Instead we conducted a narrative synthesis, with findings tabulated (27). We organised the studies into categories and synthesised the findings (27). Where possible, comparisons were made between studies on the setting (trial vs. routine care), sample population, aspirin dose/frequency, and healthcare provider population. Across the different categories, we also examined if there was a relationship between year of study, and age of the sample, on the review outcomes.

2.4 Results

We identified 17,344 papers, of which 11,258 papers remained after duplicates were removed (Figure 2.1). After screening titles and abstracts, we excluded 10,061 articles. We screened 1,197 full text articles, 37 studies met the eligibility criteria, and one study was identified by backwards citation searching. A total of 38 studies were included.

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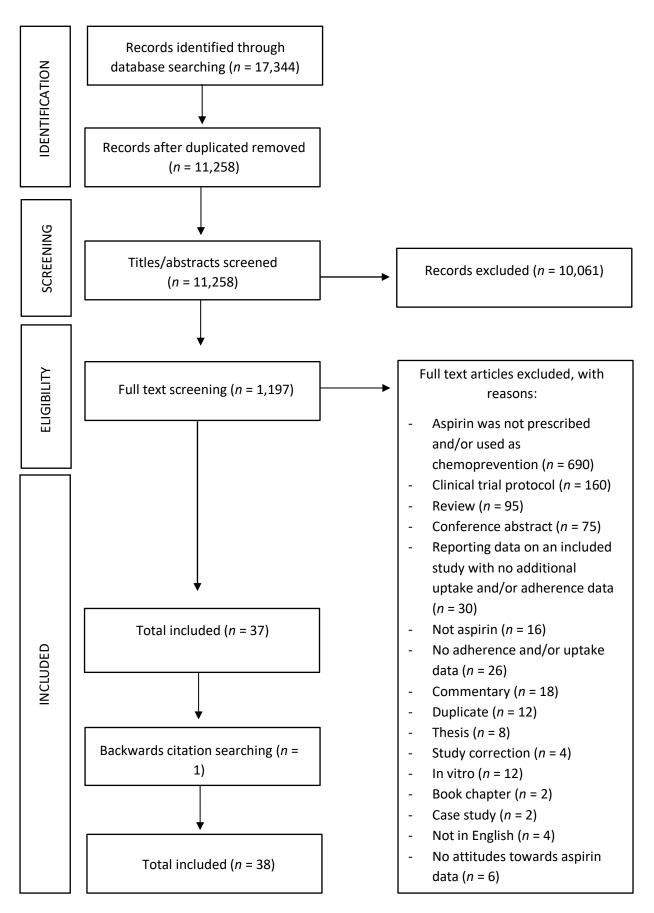


Figure 2.1. Flow diagram of search strategy

2.4.1 Uptake of aspirin

Four studies reported data on uptake of participants to an aspirin clinical trial (28-31), and all investigated aspirin for primary cancer prevention (Table 2.1). No studies were identified reporting uptake rates in routine care. All studies were RCTs (28-31), and of mixed quality with scores ranging from one (29) to four (30) on the MMAT. Three studies (75%) recruited participants at higher risk of developing cancer (28, 30, 31), and one (25%) recruited a healthy population sample (29). The dose and frequency of prescribed aspirin varied, from 100mg every alternative day (29) to 325mg administered daily (31). Rates of uptake among eligible people to an aspirin trial were moderate to high (40.9-77.7%) (28-31).

Rates of uptake to an aspirin trial did not appear to increase or decrease over time. For example, the oldest study conducted in 2000 reported an uptake rate of 61.2% (29), while two studies conducted in 2018 reported uptake rates of 40.9% (30) and 77.7% (31). A trial with a mean sample age of 65 years observed lower rates of uptake among eligible people (40.9%) (30), compared with studies with a mean sample age of 58 (65.5-77.7%) (28, 31). No studies examined the demographic, psychological or clinical factors associated with uptake. No studies compared different aspirin doses and uptake. See Appendix A.3 for the proportion of participants who enrolled onto the trial, with the dominator the number of participants offered the trial (i.e. inclusive of ineligible participants).

Study	Country	Design and quality	Population	Dose/timing	n*	Age, years	Eligible participant trial uptake ^{**}
Hull et al. 2018 (30)	UK	RCT MMAT Score: 4	Higher risk patients with colorectal adenomas	300mg/daily and/ or eicosapentaenoic acid	709	Mean: 65	40.9%
Jankowski et al. 2018 (31)	UK and Canada	RCT MMAT Score: 2	Patients with Barrett's oesophagus	300mg/daily (UK) or 325mg/daily (Canada) plus esomeprazole	2,557	Mean: 58	77.7%
Logan et al. 2008 (28)	UK	RCT MMAT Score: 3	Higher risk patients with colorectal adenomas	300mg/daily or 300mg plus folate/daily	939	Mean (range): 57.8 (27.6–74.6)	65.5%
Rexrode et al. 2000 (29)	US	RCT MMAT Score: 1	Women healthcare providers aged ≥45	100mg/alternate day plus vitamin E	39,876	45-54 (60.2%); 55- 64 (29.5%); >65 (10.3%)	61.2%

Key: RCT = Randomised controlled Trial; MMAT = Mixed Methods Appraisal Tool; n^* = number of participants enrolled at the beginning of the study; Eligible participant trial uptake** = proportion of eligible individuals who enrolled on the trial, excluding participants who were ineligible.

2.4.2 Adherence to aspirin

A total of 29 studies reported aspirin adherence data (28, 30-57), and of these 83% (24/29) were RCTs (Table 2.2) (28, 30, 31, 34, 35, 38-40, 42-57). Study quality was mixed according to the MMAT scoring, with 48% (14/29) of studies assessed as medium (3/4 or 3/5) or high (4/5 or 4/4) quality (28, 30, 32, 34, 36, 37, 40, 41, 43, 48, 49, 51, 53, 56). The sample characteristics varied, with nearly half of studies (16/29, 55%) recruiting a population at increased risk of developing cancer (28, 30-32, 42, 45-55), such as patients with colorectal adenomas. Five studies (17%) recruited participants with or who previously had cancer (36, 38, 39, 43, 56), and five (17%) studies recruited healthy populations (33-35, 41, 44). Three studies recruited mixed populations (e.g. higher risk, general public) (37, 40, 57). Most studies investigated aspirin for gastrointestinal cancer prevention, however five studies (17%) examined the relationship between aspirin and the prevention of non-gastrointestinal cancers. These were lung (34, 55), breast (34, 35, 39, 56), and prostate cancer (56).

There was high heterogeneity across the studies, with multiple definitions of day-to-day adherence, ranging from the proportion who took \geq 80% of aspirin (33, 37, 40, 41, 50, 52), and percentage of pills taken (30, 35, 42, 45-47, 53, 55). Doses of aspirin were administered from 40.5mg daily (41) to 600mg twice daily (38). Adherence measures varied, with 15 out of 29 studies (52%) using objective measures (e.g. pill count, Medication Event Monitoring System (MEMS)) (32, 35, 36, 38-40, 44-47, 50, 51, 53, 55, 57). Seven studies (24%) used self-report measures (30, 34, 43, 48, 49, 54, 56), and five studies (17%) used a combination of self-report and objective measures (28, 33, 37, 41, 42). Two studies did not report their adherence measurement (31, 52).

Day-to-day adherence estimates varied (30.0-100.0%), however 82% (18/22 studies) reported high adherence rates of aspirin (≥80.0% adherence levels) (30, 32, 35, 37, 40-42, 45-50, 52, 53, 55-57). High levels of day-to-day adherence (≥80.0%) were observed across studies using self-report measures (30, 48, 49, 56) and those using objective adherence measures (32, 35, 45-47, 50, 53, 55, 57). Four studies reported on day-to-day adherence three to four years after participants started aspirin (28, 47, 49, 53). Of these studies, three observed high adherence levels (≥80%) (47, 49, 53). One RCT reported data on healthy participants for eight years in the active trial, and for 15 years post-trial (34). At eight years, 64.0% of participants were classed as adherent (34). By 15 years, 46.0% were adherent (34). No pattern was observed between participants' age and day-to-day adherence.

There was no clear evidence of a relationship between dose and day-to-day adherence. In an RCT of high-risk participants, lower adherence was reported among those taking 650mg of aspirin (79.0% adherent), compared with those taking aspirin at 325mg (100.0% adherent) and 81mg (93.0%

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adherent) (42). Three other studies reported adherence rates across different doses of aspirin and identified few differences (47, 49, 52). We also observed no pattern between when the study was conducted (older vs. newer studies) and day-to-day adherence.

Persistence was reported by 52% (15/29) of studies (28, 31, 34, 36, 38, 39, 41-44, 49, 51, 53-55). Measurements of persistence varied from average number of months/years participants were taking the medication (31, 34, 43, 51), to increase in bleeding time (36). Short-term persistence (i.e. weeks, months) was high (83.3–100.0%) (36, 41, 42, 44, 55). The proportion of participants reporting longterm persistence (i.e. years) varied. Three RCTs, all recruiting participants with colorectal adenomas, examined persistence at three years (28, 49, 53). One RCT observed high levels of persistence, with 93.6% of participants still taking at least 50% of the medication at year three (49). In contrast, two trials reported low to moderate levels of persistence, with 38.6% and 66.8% of participants completing the three-year medication (28, 53). No pattern was observed between the year the study was conducted and persistence with aspirin. Additionally, no pattern was observed between participants' age and persistence with aspirin. For example, both a trial with a mean sample age of 31 (44), and a trial with a mean age of 66 reported high levels of persistence (≥90%) (36).

Four studies examined factors associated with day-to-day adherence. A non-randomised trial of healthy participants found self-report measures to be significantly associated with higher adherence (73.0% adherent), than the objective measure of MEMS (44.0% adherent) (33). Two RCTs and one non-randomised trial observed no association between adherence and gender (33, 45, 46). In an RCT of participants with history of colorectal adenomas, no association was found between adherence and being at higher risk of recurrence, when compared with those at lower risk (45). No other factors associated with day-to-day adherence or persistence were reported.

Study and location	Design and quality	Population	Dose/timing	n*	Age, years	Adherence measure	Day-to-day adherence definition	Persistence adherence definition	Follow-up time	Day-to-day adherence	Persistence adherence	Associations with adherence/ persistence
Barnes et al. 1999 (32)	Non- randomised	Adenomatous polyps	81mg/daily	10	Mean (range) 53.6 (47–64)	Pill count	% who took medication	-	3 months	100.0%	-	None reported
US	MMAT score: 4											
Baron et al. 2003 (49) US and Canada	RCT MMAT score: 3	Colorectal adenomas	81mg/daily or 325mg/daily	1,121	Mean (SD): 57.3 (9.9) - 57.7 (9.1)	Self-report	% who took 6-7 tablets/week	% who took ≥50% tablets in final year of trial	Approx. 3 years	81mg aspirin: 89.8% 325mg aspirin: 88.0% Placebo: 87.1%	Year 1: 97.8% Year 3: 93.6%	None reported
Benamouzig et al. 2001 (45) France	RCT MMAT score: 1	Colorectal adenomatous polyps	300mg/daily or 160mg/daily	274	Mean (SD) 57.7 (9.4)	Pill count	% of pills taken	-	16 months	84.1%	-	No association with risk (ND) ⁺ No association with gender (ND) ⁺
Benamouzig et al. 2003 (46) France	RCT MMAT score: 1			272			Mean % of pills taken	-	Approx. 1 year	Aspirin: 87.0% Placebo: 88.0%	-	No association with risk (ND) ⁺ No association with gender (ND) ⁺
Benamouzig et al. 2012 (47) France	RCT MMAT score: 2						Mean % of pills taken	-	Approx. 4 years	88.0%	-	Adherence similar between aspirin 160mg/day vs. aspirin 300mg/day vs. placebo (ND)+
Burn et al. 2008 (50) International	RCT MMAT score: 2	Lynch syndrome	300mg/twice daily plus resistant starch	937	Mean (range): 45 (25-79)	Pill count	% who took the tablets ≥80.0% of the time	-	Approx. 2 years	81.0%	-	None reported
Burn et al. 2013 (51)	RCT MMAT						% who took 1,400 (300mg) pills ≥2 years	Mean duration of treatment		Aspirin: 30.0% Placebo: 29.1%	Mean: 25.2 months	None reported

 Table 2.2. Characteristics of articles reporting adherence to aspirin for cancer prevention (n = 29)

score: 3

International

Burney et al. 1996 (33)	Non- randomised	Healthy adults	Up to 640mg/daily	64	Not reported	Self-report and MEMS	% who took ≥80.0% of the pills	-	14 days	Self-report: 73.0%	-	Self-report vs. MEMS (p = 0.002)
US	MMAT score: 2						pins			MEMS: 44.0%		No association with gender (<i>p</i> =
										Self-report and MEMS: 35.0%		0.95 <i>, p</i> = 0.78)
Cook et al. 2013 (34)	RCT MMAT	Healthy female healthcare	100mg/alternate day	39, 876	Mean: 55	Self-report	Active trial: % took ≥2/3 of aspirin	Median duration of treatment	Active trial: 8 years	Active trial: Aspirin (64.0%) Placebo (65.0%)	Median: 9 years	None reported
US	score: 3	providers	Plus vitamin E				Post-trial: % took aspirin ≥3 days per month		Post-trial: 15 years	Post-trial: Aspirin (46.0%) Placebo (43.0%)		
Duggan et al. 2014 (35) US	RCT MMAT score: 2	Post- menopausal women	325mg/daily	144	Mean (SD): 59.4 (5.4)	Pill count	% of pills taken	-	6 months	Aspirin (87.0%) Placebo (87.0%)	-	None reported
Falk et al. 2012 (52) US, Canada, Puerto Rico	RCT MMAT score: 2	Barrett's Oesophagus	81mg/daily or 325mg/daily Plus esomeprazole	122	Mean (SD): 59.7 (11.2)	Not reported	Median number of tablets taken Percentage of adherence (median)	-	28 days	27-28 tablets for aspirin and placebo (median) 100.0% (median)	-	None reported
Frommel et al. 1997 (36) US	Non- randomised <i>MMAT</i> <i>score:</i> 3	CRC	325mg/daily then 325mg/twice daily	17	Mean (SD): 65.6 (13.6)	Bleeding time	-	Increase in bleeding time at 120 days	120 days	-	94.1%	None reported
Garland et al. 2019 (55) US	RCT MMAT score: 2	High risk of lung cancer	Intermittent: 81mg/daily one week/placebo one week Continuous: 81mg/daily	54	Mean (SD): 52 (8)	Pill count	Mean % of pills taken	% who completed the intervention	12 weeks	98.0%	83.3%	None reported
Hull et al. 2018 (30) UK	RCT MMAT score: 4	Colorectal adenomas	300mg/daily and/ or eicosapentaenoic acid	709	Mean: 65	Self-report	Mean % of pills taken	-	1 year	Aspirin: 97.0% Placebo: 97.0%	-	None reported

Ishikawa et al. 2013 (48) Japan	RCT MMAT score: 3	FAP	100mg/daily	34	Mean (SD): 36.7 (13.9) – 39.7 (12.8)	Self-report	Not reported	-	10 months	Aspirin: 83.3% Placebo: 88.4%	-	None reported
Jankowski et al. 2018 (31) UK and Canada	RCT MMAT score: 2	Barrett's oesophagus	300mg/daily (UK) or 325mg/daily (Canada) Plus esomeprazole	2,557	Mean: 58 – 59	Not reported	-	% still taking aspirin at 10 years Median duration of treatment	Approx. 10 years	-	>25% still taking aspirin at 10 years Median: 8.9 years	None reported
Joharatnam- Hogan et al. 2019 (56) UK	RCT MMAT score: 3	Gastro- oesophageal, CRC, breast, prostate cancer	100mg/daily or 300mg/daily	2,719	Median: 52 – 71	Self-report	% who took 6-7 tablets/week	-	8 weeks	95.0%	-	None reported
Krishnan et al. 2001 (37) US	Non- randomised <i>MMAT</i> <i>score:</i> 4	High vs. normal risk for CRC	81mg/daily	92	Mean (SD): 36.5 (14.8) – 55.2 (13.9)	Self-report and pill counts	% who took ≥80.0% of the pills	-	28 days	100.0%	-	None reported
Liesenfeld et al. 2016 (44) US	RCT MMAT score: 2	Healthy men and women	325mg/daily	40	Mean (SD): 31 (6.2)	Salicylic acid metabolites	-	% with salicylic acid metabolites detected at study end	60 days	-	92.5%	None reported
Lipton et al. 1982 (38) US	RCT MMAT score: 1	Dukes B ₂ and CRC/rectal cancer	600mg/twice daily	66	Not described	Blood salicylate levels	-	% who had a salicylate level of ≥4 mg/dl at study end	Not described	-	83.3%	None reported
Logan et al. 2008 (28) UK	RCT MMAT score: 3	Colorectal adenomas	300mg/daily or 300mg plus folate/daily	939	Mean (range): 57.8 (27.6– 74.6)	Self-report and pill count	% who took ≥95.0% of the pills	% who completed trial medication	Approx. 3 years	Aspirin: 75.4% Placebo: 76.4%	66.8%	None reported
Pommergaard et al. 2016 (53) International	RCT MMAT score: 3	Colorectal adenomas	37.5mg aspirin with calcium carbonate/twice daily	1,107	Median (SD): 59 (8.1) – 60 (8.3)	Pill count	Median % of pills taken	% who completed 3 years of treatment	3 years	Aspirin: 99.0% Placebo: 99.0%	38.6%	None reported

	· · · · · · · · · · · · · · · · · · ·		Plus calcitriol					,				
Roop et al. 2013 (39) US	RCT MMAT score: 2	Metastatic breast cancer	325mg/daily plus clopidogrel	48	Mean: 50.7 – 58.4	Platelet- function tests	-	Inhibition of platelet- function	4 weeks	-	p<.001	None reported
Roy et al. 2017 (40) US	RCT MMAT score: 3	Colonoscopy for adenoma or CRC resected	325mg/daily	79	Mean (SD): 54 (11) – 57 (9)	Clinical assessment and pill counts	% who took ≥80.0% of the pills	-	3-months	Aspirin: 100.0% Placebo: 100.0%	-	None reported
Ruffin et al. 1997 (41) US	Non- randomised <i>MMAT</i> <i>score:</i> 3	Healthy participants	40.5mg, 81mg, 162mg, 324mg, or 648mg/daily	66	Mean (range) 27.8 (19-56)	Self-report and MEMS	% who took an extra dose on day 15	% who completed the protocol	14 days	40.5mg = 20.0% 81mg = 10.0% 162mg = 20.0% 324mg = 10.0%	98.5%	None reported
Sample et al. 2002a (42) US	RCT MMAT score: 1	Colorectal adenomas	81mg/daily or 325mg/daily or 650mg/daily	60	Mean: 58.2	Self-report, pill count; plasma salicylate levels	% of pills taken	% whose plasma salicylate levels significantly exceeded baseline	4 weeks	99.0%	93.0% (81mg); 100.0% (325mg); 79.0% (650mg)	None reported
Sample et al. 2002b (54) US	RCT MMAT score: 1			43	40-50 (10.5%); 51-60 (36.8%); 61-70 (52.6%)	Self-report	-	% taking aspirin regularly at mean 17.3 months	-	-	41.9%	None reported
Sandler et al. 2003 (43) US	RCT MMAT score: 3	CRC	325mg/daily	635	 ≤39 (1%); 40-49 (14%); 50-59 (24%); 60-69 (33%); ≥70 (28%) 	Self-report	% taking 7 pills per week	Median duration of treatment	Not reported	-	Median: 30.9 months	None reported
Sinicrope et al. 2019 (57) US	RCT MMAT score: 2	Advanced adenomas or cancer	325mg/daily plus Difluoromethylor nithine	104	Mean (SD): 62.6 (9.09)	Pill count	% who took ≥80.0% of the pills	-	1 year	98.1%	-	None reported

Key: RCT = Randomised controlled Trial; *n*^{*} = number of participants enrolled at the beginning of the study; ND= no data presented; ⁺significance testing not reported; MEMS = Medication Event Monitoring System; FAP = Familial Adenomatous Polyposis; CRC = Colorectal Cancer.

2.4.3 Attitudes towards the use of aspirin for cancer preventive therapy

2.4.3.1 High risk and general public

Five quantitative descriptive studies examined individuals' attitudes towards using aspirin for the primary prevention of cancer (58-62) (Table 2.3). All studies were of low (2/5) or medium (3/5) quality, and all were cross-sectional surveys. Three studies (60%) recruited healthy population samples (59, 60, 62), and two studies (40%) recruited patients with Barrett's oesophagus (58, 61). Four studies reported moderate to high willingness from participants to use aspirin for cancer prevention (43.6–76.0%) (58, 60-62).

Mixed results were observed for an association between participants' demographic characteristics and whether they would use aspirin for cancer prevention. A US survey examined the relationship between healthy participants' characteristics and intentions to use aspirin (59). Higher intentions were significantly associated with being male, black ethnicity, older age, history of polyps, and being a smoker (59). Another survey recruiting Barrett's oesophagus patients found higher education and younger age to be significantly associated with higher willingness to use aspirin in the univariable analysis (61). However, this association was not significant in the multivariable analysis (61). Two studies also found no evidence of a relationship between demographic factors and willingness to use aspirin (58, 62). Mixed evidence was also observed for the relationship between participants' current aspirin use and whether they would use aspirin for cancer prevention (59, 62).

Participants with increased self-efficacy, response efficacy, barriers and perceived susceptibility to developing colorectal cancer were significantly more likely to report higher intentions to use aspirin (59). Some of the barriers found to be significantly and positively associated with intentions included participants' believing their doctor would want them to take aspirin, and believing most people their age were being told to take aspirin (59). Participants who believed there was low evidence for using aspirin for cancer prevention reported significantly lower intentions (59).

No clear relationship was observed between year of study and attitudes towards aspirin. Two papers examined publics' willingness to use aspirin, with the 2019 Australian study finding higher willingness (>70%) (62), than a US-based study conducted in 2009 (43.6%) (60). However, among two US studies, one conducted in 2008 found higher willingness among patients with Barrett's oesophagus (76.0%) (61), compared with a 2015 study examining willingness among the same patient population (53.0%) (58).

2.4.3.2 Healthcare providers

Three studies reported healthcare providers' attitudes towards aspirin for cancer prevention (63-65) (Table 2.3). All studies were of medium MMAT quality (3/5). Samples consisted of

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gastroenterologists (64, 65), genetics professionals (64), colorectal surgeons (64) and general practitioners (63). Two studies reported data on healthcare providers' attitudes towards the use of aspirin for patients at higher risk of cancer (Lynch syndrome, Barrett's oesophagus) (64, 65). In both studies, a high proportion of healthcare provider respondents (72.0–76.0%) perceived aspirin to be a suitable cancer prevention option (64, 65).

A UK survey of general practitioners found willingness to prescribe aspirin was higher at lower doses, with 91.3% willing at 100mg, 81.8% willing at 300mg, and 62.3% willing at 600mg (63). General practitioners were significantly more willing to prescribe aspirin at 600mg if they had >10 years' professional experience, were aged ≥50, had greater awareness of the preventive effects of aspirin, and if they had seen a Lynch syndrome patient in clinic (range, odds ratio: 1.44 to 1.58) (63). There was evidence to suggest profession may influence willingness, with general practitioners who had a special interest in family history significantly less willing to prescribe aspirin (odds ratio: 0.41) (63). An Australian survey also found that a higher proportion of gastroenterologists (41/49, 83.7%) and genetic professionals (49/59, 83.1%) perceived aspirin to be effective for cancer prevention, than colorectal surgeons (47/73, 64.4%) (64). Across all three studies, we did not observe a pattern between year of study and healthcare providers' attitudes towards aspirin for preventive therapy (63-65).

Table 2.3. Characteristics of articles reporting public, patient and healthcare provider attitudes towards using or recommending aspirin for cancer prevention (n = 8)

Study and location	Design and quality	Population	Setting	Outcomes	n	Age, years	Attitudes towards aspirin for cancer prevention	Associations with higher attitudes (e.g. willingness, intentions)
Chen et al. 2017 (64) Australia	Cross- sectional survey MMAT score: 3	Clinicians (genetics providers; gastroenterologists; colorectal surgeons)	HCP survey	 Discuss aspirin for cancer prevention with patients with LS Recommends/ prescribes aspirin to patients with LS 	181	<50 (60.0%) ≥50 (40.0%)	76.0% thought aspirin was 'somewhat' or 'very' effective	Univariable analysis: - Professional group Multivariable analysis: - No association
Das et al. 2008 (65) UK	Cross- sectional survey MMAT score: 3	Gastroenterologists	HCP survey	Variation in practice of BO management	226	ND	72.0% thought using aspirin or COX-2 was a good option	None reported
Hur et al. 2008 (61) US	Cross- sectional survey MMAT score: 2	BO patients	Patient survey	Patient preferences for celecoxib and aspirin for cancer prevention	100	Mean (SD): 64.5 (11.3)	76.0% willing to use aspirin	Univariable analysis: - Younger age - More educational qualifications Multivariable analysis: - No association
Hur et al. 2009 (60) US	Cross- sectional survey MMAT score: 2	Healthy population	Public survey	Patient preferences for celecoxib and aspirin for cancer prevention	202	Median age group: 45–54	43.6% willing to use aspirin	Males (58.1%) more willing to take aspirin than females (31.2%)
Jensen et al. 2016 (59) US	Cross- sectional survey MMAT score: 3	Healthy population (aged 40-65)	Public survey	Intentions to use aspirin for cancer prevention on 5-point scale from strongly disagree (1) to strongly agree (5)	1000	Mean (SD): 56.65 (6.87)	Intentions to use aspirin for cancer prevention (M = 3.34, SD = 1.22)	Demographic variables: - Older - Male - Black ethnicity Clinical factors: - Did not already take aspirin - History of polyps - Smoked >100 cigarettes Psychosocial variables:

								 Increased perceived susceptibility, barriers, response and self-efficacy Reporting less Cancer Information Overload
Nguyen et al. 2019 (62) Australia	Cross- sectional survey MMAT score: 3	Healthy population (aged 50-70)	Public survey	Whether they would take aspirin for bowel cancer prevention	304	50–54 (24.7%) 55–59 (29.6%) 60–64 (21.1%) 65–70 (24.7%)	>70.0% would take aspirin	Current aspirin use No differences across demographic factors (gender, age, education, martial status), or other clinical factors (family history of CRC)
Smith et al. 2017 (63) UK	Cross- sectional survey MMAT score: 3	GPs practising in the UK	HCP survey	Willingness to prescribe LS patients aspirin at 600mg	1007	<50 (72.3%) ≥50 (27.7%)	62.3% willing to prescribe aspirin at 600mg	 ≥50 years old >10 years' experience Without special interest in family history Greater awareness of preventive effects aspirin Having seen Lynch syndrome patient in practice
Yachimski et al. 2015 (58) US	Cross- sectional survey MMAT score: 2	BO patients	Patient survey	Willingness to undergo treatment A (ablation) and/or treatment B (aspirin)	81	Mean: 60.2	53.0% willing to use aspirin (with endoscopic surveillance every 3-5 years)	No differences across demographic factors (gender, age, education, ethnicity) and clinical variables (already taking aspirin, using PPI, personal history of cancer, heart condition, and peptic ulcer)

Key: HCP = Healthcare provider; GP = General Practitioner; LS = Lynch Syndrome; BO = Barrett's Oesophagus; PPI = Proton Pump Inhibitor; CRC = Colorectal Cancer; ND = No Data.

2.4.4 Study quality

We assessed methodological quality using the MMAT (Table 2.4). Twenty-five studies were quantitative RCTs (28-31, 34, 35, 38-40, 42-57), eight were quantitative descriptive studies (58-65), and five were quantitative non-randomised studies (32, 33, 36, 37, 41). No qualitative studies were identified. Of the RCTs, one study (4%) scored 4/4 for quality (30), 36% (9/25) scored 3/4 (28, 34, 40, 43, 48, 49, 51, 53, 56), and 24% (6/25) of studies met one criterion (29, 38, 42, 45, 46, 54). Of the quantitative non-randomised studies, two studies (40%) scored 4/5 on the MMAT (32, 37), two studies (40%) scored 3/5 (36, 41), and one study (20%) scored 2/5 (33). Of the quantitative descriptive studies, 38% (3/8) scored 2/5 on the MMAT (58, 60, 61), and 63% (5/8) scored 3/5 (59, 62-65).

			Yes		No	Ca	annot tell
	n	n	%	n	%	n	%
2. Quantitative randomized controlled trials	25						
2.1. Is randomization appropriately performed?		6	24	0	0	19	76
2.2. Are the groups comparable at baseline?		20	80	2	8	3	12
2.3. Are there complete outcome data?		19	76	4	16	2	8
2.4. Are outcome assessors blinded to the intervention provided?		10	40	4	16	11	44
3. Quantitative non-randomized studies	5						
3.1. Are the participants' representative of the target population?		4	80	1	20	0	0
3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?		5	100	0	0	0	0
3.3. Are there complete outcome data?		4	80	1	20	0	0
3.4. Are the confounders accounted for in the design and analysis?		0	0	1	20	4	80
3.5 During the study period, is the intervention administered (or exposure occurred) as intended?		3	60	1	20	1	20
4. Quantitative descriptive studies	8						
4.1. Is the sampling strategy relevant to address the research question?		4	50	3	38	1	13
4.2. Is the sample representative of the target population?		1	13	5	63	2	25
4.3. Are the measurements appropriate?		5	63	2	25	1	13
4.4. Is the risk of nonresponse bias low?		4	50	1	13	3	38
4.5. Is the statistical analysis appropriate to answer the research question?		7	88	0	0	1	13

Table 2.4. Mixed Methods Appraisal Tool assessment for the 38 included studies

2.5 Discussion

In this systematic review investigating attitudes and behaviour towards aspirin for preventive therapy, we found moderate to high levels of uptake to an aspirin clinical trial among people who were eligible to participate. A large proportion of participants in trials reported high levels of adherence on a day-to-day basis. At short-term follow up, most people were still taking aspirin for cancer prevention. However, there was mixed evidence observed for long-term persistence with aspirin. Given that aspirin is recommended to be taken regularly for several years for a cancer preventive benefit (9, 10), persistence among users of aspirin should be investigated further.

In contrast to the more extensive behavioural research conducted in breast cancer preventive therapy (14-19), minimal research has examined the factors associated with use of aspirin for cancer prevention. In our review, we only identified four studies reporting any factors associated with adherence, and none with uptake. Additionally, no qualitative studies were identified. Several studies investigated willingness or intention to use aspirin, which was found to be moderately high among members of the public and those at higher cancer risk. The demographic, clinical and psychological factors associated with willingness and intentions were also investigated, but evidence was either limited or conflicting.

While observational studies were eligible, we only identified trials reporting uptake and adherence data, which presents generalisability issues. Trial participants may be more motivated to use aspirin than those in routine care, and frequent follow-ups may have increased adherence rates. Previous research has also observed that people at lower socioeconomic status (66) and those from an ethnic minority group (67) are less likely to participate in cancer trials. Furthermore, the decision to participate in a trial would not have been just a consideration of aspirin, but also other agents being simultaneously investigated. The four trials reporting uptake data were also evaluating esomeprazole, vitamin E, folate, and eicosapentaenoic acid alongside aspirin. Members of the public may be less familiar with these agents, which may have negatively affected their decision to participate in the trial.

In our review, we identified studies conducted across multiple decades (1982 to 2019). However, official guidance recommending the use of aspirin for colorectal cancer prevention has only recently been introduced (2016 onwards) (9-11). While we did not find an increase over time in trial uptake and adherence, future trials may observe higher rates of uptake and adherence as official guidance becomes more widely known among the public and healthcare providers. Furthermore, in the future we may observe an increasing trend in positive attitudes towards aspirin for preventive therapy.

Despite searching for studies using aspirin for secondary cancer prevention, most articles investigated aspirin for primary prevention. Our review findings should be applied with caution to a secondary prevention context. Patients who have previously had cancer may have different motivations for taking aspirin than those offered aspirin for primary prevention. Healthcare providers may also have less positive views towards aspirin for secondary cancer prevention, as a lower number of secondary prevention trials have been conducted compared with primary prevention (68). However, there is a large ongoing trial in the adjuvant setting (Add-Aspirin trial), which will provide further evidence on the effects of regular aspirin use in patients with nonmetastatic breast, colorectal, gastro-oesophageal, and prostate cancer (69).

Relevant studies have been published following our search cut-off date that contribute further to our knowledge in this topic area. Similar to our review findings, the ASPIRED trial, investigating aspirin for colorectal cancer prevention, found that most participants reported high levels of day-today adherence to aspirin at dose of 81mg (79% reported 95-100% adherence) and 325mg (91% reported 95-100% adherence) (70). Furthermore, a recent qualitative study was published exploring healthcare professionals' views on the Australian guidance recommending aspirin for colorectal cancer prevention for the public (71).

2.5.1 Directions for future research

Overall, we found that the likelihood that eligible users of aspirin would participate in a trial that requires randomisation to aspirin for cancer prevention was between 40.9-77.7%. Researchers developing a trial in this area should take these findings into consideration when planning and designing their study. While clinical guidelines in the US, Australia and the UK recommend aspirin for colorectal cancer prevention (9-11), it is currently unknown if people initiate and adhere to aspirin in routine care. To date, only studies reporting data on intentions and willingness to use aspirin have been published. As intentions do not always translate into behaviour (72), further research should investigate how people form a decision to initiate and adhere to aspirin for preventive therapy, and the support they may need.

Despite searching for studies investigating aspirin for any cancer prevention, the vast majority of identified studies focused on gastrointestinal cancer risk reduction. As the evidence base is stronger for gastrointestinal cancer prevention, we may expect lower rates of uptake, adherence and acceptability for other cancers (e.g. breast, lung, prostate). Research should investigate further rates of uptake and adherence of, and attitudes towards, aspirin for the prevention of non-gastrointestinal cancers.

Previous research has found higher uptake of breast cancer preventive therapy among women with fewer concerns about its side-effects (18, 19). While there are several reported side-effects to using aspirin (12, 13), it is currently unknown the relationship between participants' side-effects, perceived or experienced, in relation to aspirin and their rates of uptake and adherence. We recommend that future research should investigate the relationship between these factors further.

The recent Australian qualitative study reported that healthcare providers viewed primary care physicians as having the most important role in the implementation of guidance recommending aspirin for cancer prevention (71). We recommend that future research aiming to examine decision-making in the context of aspirin for cancer prevention should focus on the primary care setting. In our review, we found moderately high levels of willingness among general practitioners to prescribe aspirin to patients with Lynch syndrome. Factors that may be influencing willingness include the aspirin dose, professional background, and awareness of the cancer preventive benefits of aspirin.

The review had limitations. Due to time and resource constraints, the literature was limited to English language articles, and second reviewers only duplicated screening, data extraction, and quality assessment for a proportion of articles (20-45%). Our review excluded studies that did not use or prescribe aspirin for the primary purpose of cancer prevention, such as the ASPREE trial which had fatal and non-fatal cancer as a secondary endpoint (73). However, in clinical practice consideration to use aspirin is likely to factor in both its use as a form of cancer preventive therapy and other outcomes, such as cardiovascular disease prevention. Uptake rates to a clinical trial were also strongly affected by the approach used to calculate uptake. For example, as reported in Appendix A.3, when we calculated rates of uptake to a trial with the denominator all people who were approached about the trial, including those who were ineligible to participate, uptake rates were much lower. More standardised and transparent reporting of uptake data is warranted to compare across cohorts.

2.5.2 Conclusions

Overall, we found that most people who were eligible and offered participation in an aspirin trial accepted. The majority of participants also reported a good level of adherence on a day-to-day basis. We found high levels of short-term aspirin persistence, but evidence was mixed for long-term persistence. No studies examined uptake and adherence in routine care, and minimal research investigated the factors associated with using aspirin. Overall, we found that there is substantial scope for research into the barriers and facilitators to implementing aspirin for preventive therapy into clinical care.

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Chapter Three: Barriers and facilitators to using aspirin for preventive therapy: a qualitative study exploring the views and experiences of people with Lynch syndrome and healthcare providers

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3.1 Abstract

Background: The National Institute for Health and Care Excellence (NG151) recommends considering daily aspirin for people with Lynch syndrome to reduce colorectal cancer risk. However, deciding whether to initiate aspirin could be a complex decision for patients and their healthcare providers, as both the potential benefits and harms need to be considered.

Methods: We conducted semi-structured interviews to explore the barriers and facilitators to using aspirin for preventive therapy. We recruited 15 people with Lynch syndrome, and 23 healthcare providers across multiple professions in primary, and specialist care (e.g. clinical genetics) in the United Kingdom. Interview schedules were informed by the Theoretical Domains Framework.

Results: There were three themes: 1) Considering potential harms and benefits; 2) Healthcare pathway; 3) Patients' level of interest in aspirin. All healthcare providers, across primary and specialist care, viewed general practitioners (GPs) as being responsible for prescribing and overseeing the use of aspirin. However, GPs were unfamiliar with aspirin for preventive therapy, and concerned about prescribing at higher doses (300-600mg). To support decision-making, GPs wanted clarification from specialist clinicians on the evidence and dose to prescribe. Not all participants with Lynch syndrome received information on aspirin from their healthcare provider, and several were unsure who to discuss aspirin with. GPs were more inclined to prescribe aspirin for patients with expressed preferences for the medication, however several patients were uncertain and wanted further guidance.

Conclusions: Coordinated and multilevel strategies are needed, addressing the needs of both GPs and people with Lynch syndrome, to ensure consistent implementation of national guidance on aspirin for preventive therapy.

3.2 Introduction

Lynch syndrome is an inherited disorder caused by faulty mismatch repair genes (MLH1, MSH2, MSH6, PMS2) (1). People with Lynch syndrome have an increased risk of developing a spectrum of cancers, including colorectal cancer (2, 3), with studies estimating a 10-46% lifetime risk of colorectal cancer, depending on gender and the mismatch repair gene affected (2, 4). Aspirin has been investigated as a potential preventive therapy agent for colorectal cancer. The CAPP2 trial found participants with Lynch syndrome randomised to receive aspirin at 600mg daily (vs. placebo) for at least 2 years had a reduced risk of developing colorectal cancer at 10 year follow-up (hazard ratio of 0.65 in intention-to-treat analysis) (5). A dose non-inferiority trial (CaPP3) is currently underway to compare the effectiveness of aspirin at different doses (100mg, 300mg, or 600mg) for colorectal cancer prevention. At present, the evidence for a preventive effect of aspirin on non-colorectal Lynch syndrome cancers is weak (5). In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) updated their colorectal cancer guideline (NG151) in 2020 with a recommendation to consider daily aspirin to reduce the risk of colorectal cancer in people with Lynch syndrome (6). The guidance does not stipulate a dose, but 150-300mg is commonly used in practice (6).

Deciding whether to initiate preventive therapy can be a complex choice for patients. In the area of breast cancer prevention, women at higher risk of breast cancer express reluctance to initiate preventive therapy using tamoxifen due to concerns regarding side-effects (7-10), and perceived lack of control over their cancer risk (8). The facilitators and barriers patients experience when considering the use of aspirin for preventive therapy have been less explored (11). People with Lynch syndrome need to consider both the risks and benefits of aspirin for cancer prevention. While there are demonstrable benefits, even low doses of aspirin can increase the risk of gastrointestinal ulceration and bleeding (12), with these risks increasing substantially after the age of 70 (13). At present, the NICE guidance NG151 does not specify an age limit for the long term use of aspirin among people with Lynch syndrome. However, it does stipulate that aspirin may not be suitable for particular cases, such as people with a history of peptic ulcers (6).

It is also important to consider the perspectives of healthcare providers when implementing clinical guidance. At present, the NICE guidance does not specify a recommended healthcare prescriber (6). Previously, the introduction of cancer preventive therapy within specialist care has led to uncertainties with regard to prescribing responsibilities (14). An Australian interview study explored healthcare providers' (e.g. specialists, pharmacists, general practitioners (GPs)) views on the use of aspirin for colorectal cancer prevention in the general public (15). Healthcare providers described multiple barriers to recommending aspirin, including confusion over which dose to prescribe and

concerns about side-effects, especially in older populations (15). In addition, GPs were viewed as the most important healthcare provider for implementing the Australian guidance recommending aspirin. Qualitative research exploring the views of healthcare providers on the use of aspirin for cancer prevention in a Lynch syndrome population has not yet been undertaken (11). However, a cross-sectional survey of UK GPs observed respondents were more willing to prescribe aspirin to a person with Lynch syndrome if they had greater awareness of its cancer preventive effects (16). Furthermore, the dose of aspirin influenced willingness to prescribe, with only 62% of GPs willing to prescribe daily aspirin at 600mg compared with 91% at 100mg (16).

Here, we conducted qualitative interviews to explore the perceived or experienced barriers and facilitators to using aspirin for preventive therapy among people with Lynch syndrome. We also explored the perceived or experienced barriers and facilitators to prescribing or recommending aspirin among healthcare providers involved in the Lynch syndrome healthcare pathway, including perspectives on the NICE guidance (NG151).

3.3 Method

3.3.1 Design

We conducted semi-structured one-to-one interviews with participants. The study was preregistered (<u>https://osf.io/3efg7</u>).

3.3.2 Participants and recruitment

We recruited both people with Lynch syndrome and healthcare providers, with recruitment organised by one author (KEL) and supported by co-authors. Across both participant groups, people based in the UK and over the age of 18 were recruited. We advertised the study through the charity Lynch Syndrome UK, aiming to recruit both people with Lynch syndrome who use and do not use aspirin for prevention. People who had not been diagnosed with Lynch syndrome were excluded. To recruit healthcare providers, we used snowball sampling, and advertised the study through social media (e.g. Twitter) and relevant professional organisations. We recruited healthcare providers involved in the Lynch syndrome healthcare pathway, including GPs, community pharmacists, genetic counsellors, nurse practitioners, and specialist clinicians. Specialist clinicians included those in the roles of clinical geneticist, consultant in cancer genetics, gastroenterologist, and gynaecologist. Healthcare providers were excluded if their clinical roles did not appear to include potential discussions with people with Lynch syndrome about aspirin. All participants received a £25 Amazon voucher.

One author (KEL) recruited participants in both groups until data saturation had been reached, and followed an established method to assess this (17). Initially a minimum sample size of 10 was sought

in each participant group before looking for evidence of data saturation (17). After 10 interviews had been conducted, data saturation was assessed. Data saturation was judged to have been achieved for each group once three further consecutive interviews had been conducted which yielded no new themes. For example, recruitment would cease after interview 13, if interviews with participants 11, 12, and 13 resulted in no new themes.

3.3.3 Interview schedule

At the beginning of all interviews, the NICE guidance (NG151) recommending aspirin for colorectal cancer to people with Lynch syndrome was described. We presented participants with basic information on aspirin for two main reasons. Firstly, to create a more realistic clinical scenario where participants would consider using or recommending aspirin in relation to existing information, such as official guidance, dose and duration. Secondly, we did not want the interviews to be perceived by participants as a test of their prior knowledge on the use of aspirin for preventive therapy.

A semi-structured interview approach was employed, with improvised follow up questions guided by participants' responses, and with flexibility to the order of the questions asked. The interview schedule covered the 14 domains in the Theoretical Domains Framework (TDF; version 2) (Appendices B.1 and B.2) (18). The TDF is a theoretical framework derived from multiple behaviour change theories. The framework identifies several factors (i.e. domains) that could influence behaviour when implementing new clinical practices, such as a person's knowledge, skills, beliefs, environment and the resources available to them (18). This framework was chosen as it has previously been used to explore influences on healthcare provider and patient behaviour when implementing evidence-based recommendations (18-20). The draft interview schedule was reviewed by a patient representative to assess for comprehension before finalising (MM).

In the healthcare provider interviews, we also presented participants with clinical vignettes, with the aim to explore the potential barriers to recommending aspirin among healthcare providers who may not have experience in this area. We developed realistic scenarios where the participant may encounter a patient with Lynch syndrome enquiring the use of aspirin for colorectal cancer prevention. The scenarios were reviewed by a primary care clinician before finalising (RF). We explored healthcare providers' initial thoughts and likely responses to these scenarios.

3.3.4 Data collection and analysis

One author (KEL) conducted all interviews, over video or telephone, from November 2020 to November 2021. KEL is a behavioural scientist with academic training in qualitative research methods. She had not previously undertaken qualitative interviews, but was supported by a team of experienced investigators who met with her regularly throughout the recruitment period. Interviews were audio-recorded, transcribed verbatim, and anonymised. All participants were given pseudonymised initials.

Our two-stage analysis involved coding the transcripts inductively using reflexive thematic analysis (21, 22), and mapping the extracted themes onto the TDF (18). We mapped our themes onto the TDF as this framework can aid in specifying the beliefs and attitudes that are amenable to change (18). In turn, this can inform strategies to implement aspirin for preventive therapy into clinical practice. In addition, we employed the TDF flexibly alongside an inductive analysis approach, which can help to identify themes and factors unrelated to the TDF (23). One author (KEL) coded all transcripts, while three additional authors (SGS, SMCG, ZFH) double-coded a proportion of transcripts. All four authors discussed the findings and reached consensus on the final themes. One author (KEL) mapped the themes onto the TDF, which was reviewed by all authors. Transcripts were managed in NVivo (version 12) and Microsoft Word.

3.4 Results

We interviewed 15 people with Lynch syndrome (Table 3.1), and 23 healthcare providers across multiple disciplines (Table 3.2). Interview duration ranged from 22 to 60 minutes. Findings were organised into three overarching themes, which were mapped onto the TDF (Table 3.3).

	n
Age	
18-30	0
31-40	1
41-50	5
51-60	5
61-70	4
Gender	
Male	2
Female	13
Ethnicity	
White British	13
White British and Irish	1
White European	1
Country in UK	·

England	12		
Scotland	2		
Missing data	1		
Year of Lynch syndrome diagnosis			
1990-2000	2		
2001-2011	0		
2012-2021	13		
Previously diagnosed with cancer			
Yes	9		
No	6		
Using aspirin for preventive therapy			
Yes	9		
No	6		

	n	
Age		
18-30	6	
31-40	7	
41-50	4	
51-60	3	
61-70	2	
Missing data	1	
Gender		
Male	7	
Female	16	
Ethnicity		
White British	16	
White European	2	
British Asian/ Asian	3	
Black Caribbean	1	
Missing data	1	
Country in UK	·	
England	20	
Wales	3	
Profession	·	
General practitioner	9	
Community pharmacist	4	
Specialists	·	
Genetic counsellor / nurse practitioner	5	
Specialist clinicians	5	
Number of years in profession		
0-10	14	
11-20	3	
21-30	4	
31-40	2	
Previously encountered patient with Lynch syndrome		

Table 3.2. Description of the healthcare providers interviewed (n = 23)

Yes	13	
No	10	
If yes, approximately often do you encounter a patient with Lynch syndrome		
Daily	3	
Weekly	3	
Monthly	3	
Once or twice a year	4	

Themes Potential facilitators to the use of aspirin for		Potential barriers to the use of aspirin for preventive	Main TDF domain(s)	
	preventive therapy	therapy		
Considering	Confidence in the evidence supporting aspirin for	Concerns about using daily aspirin at higher doses (300-	Beliefs about consequences	
potential harms and	colorectal cancer prevention.	600mg).		
benefits	National guidance (i.e. NICE) recommending aspirin	Lack of strong evidence to support an appropriate dose of		
	for preventive therapy.	aspirin which balances the benefits and harms.		
	Low concerns about using aspirin as it is a pharmacy			
	drug.			
Healthcare pathway	Agreement among GPs and specialists on the	Most GPs are unfamiliar with evidence supporting the use	Social/professional role and	
	appropriate healthcare pathway for patients to	of aspirin for colorectal cancer prevention.	identity	
	acquire a prescription for aspirin.	Lack of clarity on the appropriate treatment pathway for	Environmental context and	
		aspirin among people with Lynch syndrome.	resources	
		Specialist clinicians in genetics may be an underutilised	Knowledge	
		resource among GPs.		
		Some people with Lynch syndrome may be reluctant to		
		approach their GP to discuss aspirin.		
Patients' level of	Patients having a high level of knowledge on the	Patients who are uncertain whether to use aspirin and	Knowledge	
interest in aspirin	risks and benefits of aspirin.	require further support.	Environmental context and	
	Patients' expressed preference to use aspirin.		resources	

Table 3.3. The themes, and corresponding facilitators, barriers, and domains within the Theoretical Domains Framework (TDF; version 2)

Note. Table adapted from Burgess et al. (24).

3.4.1 Considering potential harms and benefits

3.4.1.1 Consideration of benefits

Participants considered the benefits of aspirin and the evidence supporting this recommendation in their decision-making. Participants with Lynch syndrome typically had high confidence in the evidence supporting the use of aspirin for preventive therapy. Among healthcare providers, confidence in the evidence varied. Specialists were positive about using aspirin, while GPs and community pharmacists tended to be more sceptical.

"I think it's amazing that there is a drug that is so cheap and with lots of safety data and been used for 100 years that has a demonstrable and significant effect on cancer prevalence in Lynch syndrome." (S.D., specialist clinician, 0-10 years' experience)

"So the answer is, at the moment, for me the jury's still out and it sounds like it is from the latest studies as well." (H.H., GP, 31-40 years' experience)

Although GPs were unaware prior to the interview of the NICE guideline NG151, this organisational body was considered to be a trustworthy source. Learning of the NICE recommendation appeared to increase several GPs' confidence in the effectiveness of aspirin for preventive therapy and their comfort prescribing aspirin for this purpose.

"You know, and I'm kind of thinking if someone came in, I'd kind of think god, if it's in NICE guidelines I'd kind of very much believe it." (T.Y., GP, 0-10 years' experience)

3.4.1.2 Consideration of harms

Several participants with Lynch syndrome and healthcare providers discussed aspirin's adverse effects as an important barrier to using or recommending aspirin. In considering dose, participants with Lynch syndrome were more worried about using higher doses of aspirin, such as 300mg or 600mg, because of potential harms.

"There's no way I would take that 300, oh my god, no, if I was having as many problems with 150." (L.O., participant with Lynch syndrome)

Among healthcare providers, GPs and community pharmacists in particular expressed concerns about patients using aspirin at higher doses, due to the increased risk of side-effects such as gastrointestinal bleeding.

"I think I'd be less hesitant if it was a lower dose medication such as 75 or 150mg, I'm clinically comfortable with. You know, 600mg doses is not something I'm used to prescribing,

[...] So I'd be worried about their bleeding risk, especially if they were elderly and frail." (F.F., GP, 0-10 years' experience)

"You know, my thoughts would be that 600mg would be quite a significant risk to patients at risk of GI issues." (B.K., community pharmacist, 0-10 years' experience)

Across both groups, not all participants considered the risks of aspirin to be a prominent factor in their decision-making, partly because aspirin is a well-known medication that can be purchased from pharmacies without a prescription.

"People sort of take aspirin a bit like, you know, paracetamol. So, so many millions of people have taken it that it seems that the side-effects that you might possibly get would be minimal." (Z.B., participant with Lynch syndrome)

"I think anything that a patient can happily buy over-the-counter, whatever reason, sits a little bit happier with GPs." (F.P., GP, 0-10 years' experience)

Most GPs discussed prescribing proton pump inhibitors (PPI) alongside aspirin for patients at higher risk of gastrointestinal ulcers and bleeding (25), which in turn lowered their concerns regarding the harms.

"I think we rarely actually see GI bleeds and things, I think we've got better at prescribing [...] like Omeprazole [a PPI] you know something that's going to reduce acid and things alongside." (T.Y., GP, 0-10 years' experience)

3.4.1.3 Consideration of the harms vs. benefits

Most participants with Lynch syndrome felt that the potential benefits of aspirin for colorectal cancer prevention outweighed their concerns about aspirin's side-effects. This was generally supported by healthcare providers.

"My father's had two cases of bowel cancer, and the second one it nearly killed him, I don't want that, I don't want bowel cancer. So yeah, for me I'll take [aspirin] to reduce that." (A.D., participant with Lynch syndrome)

"Obviously there are potential side-effects and risks but if those can be ruled out, the benefits of taking it are huge, particularly for the kind of sub-group of patients that we deal with." (M.C., genetic counsellor/nurse practitioner, 11-20 years' experience)

However, some patients explained how they made difficult trade-offs when deciding to take aspirin.

"I'm not particularly happy about taking aspirin [...] it could trash your stomach, it could trash other parts of your body. But if it reduces your risk of cancer you feel there's a gun to your head in a sense." (L.O., participant with Lynch syndrome)

The lack of strong evidence to support an appropriate dose of aspirin which balances the benefits and harms, and the absence of a recommended dose by NICE for this reason (6), was a concern among several healthcare providers and participants with Lynch syndrome. Among participants who did not use aspirin, some felt that at present the risks outweighed the benefits for them.

"I find those discussions about dosing quite tricky [...] we have a rough guidance of the dosing but we don't really know exactly what that's going to do and whether we need to change that in the future once the CaPP3 dose comes out." (A.P., specialist clinician, 0-10 years' experience)

"The benefits have had to outweigh the risks, but at the moment not until somebody tells me exactly how much I should be taking, I'm not going to start on [aspirin]." (R.R., participant with Lynch syndrome)

3.4.2 Healthcare pathway

3.4.2.1 Perceptions of the ideal healthcare pathway

Healthcare providers across professional groups viewed specialists as patients' main source of information regarding aspirin for preventive therapy; they were perceived as having the requisite expertise in this topic area. Healthcare providers agreed GPs were responsible for prescribing aspirin, as they will have access to patients' medical histories to check for potential contraindications.

"I think [aspirin] would probably be kind of started in conjunction with specialist advice but then we would carry on prescribing it long-term." (K.M., GP, 0-10 years' experience)

"I'm primarily focusing on information giving in that appointment [with the patient] and it's important if you are going to start a new medication that you do that in conjunction with your GP." (A.P., specialist clinician, 0-10 years' experience)

However, GPs were mostly unfamiliar with the evidence for using aspirin for colorectal cancer prevention, and required further support from specialist clinicians before prescribing. GPs wanted clarity on the appropriate dose to prescribe, the supporting evidence, the referring clinician's opinion on this evidence, and a clear recommendation to prescribe. "Well I would want to know what the recommended dose and timescale was and it would also be helpful to know a bit more about how much it reduces the risk and about what the risk reduction actually is." (Z.E., GP, 11-20 years' experience)

"So as long as it said please prescribe, if it said please consider prescribing then again it's a more complicated scenario, [...] It depends on what the wording is from the geneticist." (G.H., GP, 21-30 years' experience)

Specialists, across areas such as genetics and gastroenterology, agreed their role included supporting GPs who were considering prescribing aspirin for a patient with Lynch syndrome.

"I see lots of patients with Lynch, so I feel it's a decision in the sense that we're better placed to make and I feel it's only fair that I could give the GP as much guidance as I can in that." (O.I., specialist clinician, 0-10 years' experience)

3.4.2.2 Healthcare pathway in practice

In reality, pathways to treatment were inconsistent. Despite specialists accepting their role as information providers, not all participants with Lynch syndrome were told about aspirin in a healthcare setting. Some participants first learnt about aspirin through other sources, such as the charity Lynch Syndrome UK.

"Yeah, I have actually [been told about aspirin], not through the hospital that I'm under, or like my GPs or anything, mainly [...] from joining the [Lynch Syndrome UK] side." (B.H., participant with Lynch syndrome)

Although clinical geneticists viewed their role as providing information on aspirin, not all GPs made use of this source. Instead, several GPs were more likely to approach the patient's colorectal cancer team for discussions.

"Well you've even also got local sources, so we get access to individual colorectal teams, for instance. [...] We might occasionally use genetics but I haven't used a geneticist for yonks really, so I couldn't say hand on heart that I would use them straightaway." (H.H., GP, 31-40 years' experience).

Several participants with Lynch syndrome found the pathway unclear. They were unsure which type of healthcare provider they should approach to discuss aspirin further with, and where they should acquire the medication from.

"I mean, my first instinct would just be go to the pharmacy and buy it but I don't know what the dose is that you get there [...] so I guess I'd try just to buy it first but if it wasn't the right dose I guess I'd go to maybe the GP and get it prescribed." (Z.B., participant with Lynch syndrome)

Not all participants with Lynch syndrome were aware of the option for aspirin on prescription, and instead purchased aspirin from the pharmacy. In contrast, community pharmacists felt it was not their role to sell higher doses of aspirin (>75mg) for preventive therapy to patients without a prescription. The lack of licence for this indication was a particular issue for this group.

"I couldn't imagine it getting to the point where we'd be [...] selling aspirin over the counter for that indication, [...] it would be off-label use." (B.K., community pharmacist, 0-10 years' experience)

Equally, several participants with Lynch syndrome were recommended by a specialist clinician to approach their GP for aspirin on prescription and had obtained the medication through this route.

"My GP actually prescribed the aspirin and they never sort of questioned it, [...] they just said, 'oh well if it's been recommended by the geneticist, fine we'll do it'." (T.R., participant with Lynch syndrome)

However, not all participants were comfortable approaching their GP to discuss aspirin, due to previous negative experiences with GPs who were unfamiliar with Lynch syndrome.

"I find that the GPs aren't very clued up about Lynch syndrome. [...] So no, I don't find going to the GPs very useful, unfortunately." (Z.B., participant with Lynch syndrome)

3.4.3 Patients' level of interest in aspirin

There was a strong interest in using aspirin among participants with Lynch syndrome currently using the medication. These participants typically considered aspirin a high priority, and were motivated to research the use of aspirin for preventive therapy and the recommended dose.

"So I gathered all the information, read all the information, had a look around, went onto the [Lynch Syndrome UK] site [...] so I did a lot of research into it, and basically sort of discovered really that I should be on about 300mgs aspirin a day." (A.D., participant with Lynch syndrome)

Using aspirin for preventive therapy appeared to be a lower priority among participants who did not use the medication, especially when compared with other life and family priorities. Furthermore, other preventive options for Lynch syndrome seemed to be considered higher priorities, or more effective options, such as surgery and surveillance. "I wasn't actually given any other [information from GP surgery] than 'oh well there's not a lot of research that shows it's kind of very beneficial' [...] I mean, I could've like researched and everything in the meantime but as I say, life gets in the way." (K.J., participant with Lynch syndrome)

"Well I suppose I'm not so worried about my bowel cancer coming back because I would just have the lot removed, [...] and I think it would be picked up before it could do me any damage." (H.A., participant with Lynch syndrome)

A patient's strong interest in aspirin was an important factor for GPs. Several GPs described feeling more inclined to prescribe aspirin, especially higher doses, for patients who were already keen to use the medication and appeared knowledgeable on the subject.

"If the patient really wanted to start it, they've done the research, they understand the risks and benefits then yeah, I probably would feel comfortable [prescribing aspirin]." (M.V., GP, 0-10 years' experience)

The tendency to be more willing to prescribe aspirin for patients who have already decided to use the medication may be problematic, as several participants with Lynch syndrome were uncertain and wanted further guidance. In particular, some participants wanted a clear recommendation to use aspirin from their healthcare provider, based on such factors as their medical history.

"I want somebody to tell me you know, yes this would be ideal for you, or to say no, because you've got this, [...] rather than it just be my decision." (R.R., participant with Lynch syndrome)

The relationship between patients' prior preferences for aspirin and acquiring a prescription is further illustrated by two individuals. Participant A.D., who wanted to use aspirin at 300mg, described how they encountered recurrent barriers before they acquired a prescription at this dose.

"[GP] rang up and said, "Yes, you can have it on prescription," and went and had a look at it, and basically it was for 75mgs, and so I went back to see him and I said, "This really isn't, you know, enough," [...] And then finally after probably a good couple of months going backwards and forwards he agreed that I could take 300mgs of aspirin a day." (A.D., participant with Lynch syndrome)

Participant K.J., who was more uncertain, encountered resistance from their GP surgery and subsequently did not initiate aspirin.

"When I then contacted my GP surgery to get a prescription for that I was kind of put off getting it, probably thinking about it now due to their lack of knowledge." (K.J., participant with Lynch syndrome)

3.5 Discussion

In this interview study, both people with Lynch syndrome and their GPs were found to have a range of unmet informational needs around the use of aspirin for preventive therapy, which are inconsistently supported by current treatment pathways. GPs were seen by all healthcare providers, across primary and specialist care, as the main prescribers of aspirin. However, GPs were unfamiliar with the use of aspirin for colorectal cancer prevention, and wanted clarification from specialists on the evidence and dose to prescribe. Furthermore, there were varying levels of support for people with Lynch syndrome considering aspirin. For example, not all participants with Lynch syndrome received information on aspirin from their healthcare provider, and several were unsure who to discuss aspirin with.

Our findings are consistent with previous healthcare provider research conducted in Australia (15) and the UK (16), which identified several barriers to prescribing aspirin among GPs. These barriers included low awareness of the national guidance recommending aspirin for cancer prevention, and concerns regarding the side-effects of aspirin at higher doses. In our study, we compared and contrasted perspectives of both patients and healthcare providers to develop a more complete understanding of areas for improvement than if we had focused on one group. For example, our study adds further to the literature by demonstrating that patients with Lynch syndrome also have concerns about using aspirin at higher doses, which may subsequently affect whether they initiate preventive therapy.

Our results indicate that a shared decision-making approach could be valuable for patients who are uncertain on whether to initiate aspirin and want further guidance from their GP, with the aim for both parties to reach consensus and agreement on the decision (26). Where clinical evidence is uncertain, recommended approaches to promoting shared decision-making include tailoring information to the needs of the patient, and utilising decision support technology (e.g. decision aids) (27). However, any such shared decision-making approaches need to be adaptable to the realities of clinical practice. For example, a UK study found that primary care consultations covered an average of 2.5 problems in just under 12 minutes (28). Furthermore, our findings highlight that GPs alone may not have the knowledge and resources to fully support a patient considering aspirin for preventive therapy.

Our work suggests that initiatives to support shared decision-making are unlikely to bring about significant change in isolation. We found the TDF useful in understanding further how the identified barriers and facilitators to the use of aspirin for preventive therapy could inform future implementation strategies (18). The four main TDF domains we identified were: the 'Social/professional role and identity' of the healthcare providers; 'Environmental context and resources'; 'Beliefs about consequences' of using aspirin; and existing 'Knowledge' regarding the use of aspirin for preventive therapy.

The integration of aspirin for cancer prevention into clinical practice is likely to depend on clearly defined and consistently applied healthcare professional roles. Our findings suggest that specialists, such as clinical geneticists, are the main providers of information on aspirin, whilst GPs are the main prescribers. However, poorly defined care pathways may result in environmental context barriers, such as some patients with Lynch syndrome being unaware of the option to use aspirin for preventive therapy. There is a need for a coherent strategy, developed in collaboration with specialist and primary care, to ensure consistent and equitable support for people with Lynch syndrome and their GPs. Such a strategy should recognise that successful change will depend upon coordinated efforts across different levels of healthcare systems (29), with national guidance underpinned by clear local healthcare pathways and defined roles. In addition, such pathways should specify who is responsible for the assessment, counselling, and treatment of people with Lynch syndrome, as well as specifying how aspirin is prescribed and recorded in patient records.

Both patients and healthcare professionals may benefit from support for relatively complex decisions. Existing resources, such as the NICE patient decision aid for people with Lynch syndrome considering aspirin (30), should be consistently utilised in the healthcare pathway. Decision aids can improve patient knowledge of treatment options and reduce feelings of uncertainty around decisions (31). In addition, future research could develop and evaluate interventions to support GPs when advising patients with Lynch syndrome on aspirin for colorectal cancer prevention. These interventions could target the beliefs and attitudes among GPs that we have identified are amenable to change.

Our study had several limitations. We recruited most healthcare providers through snowball sampling and Twitter, which could have resulted in an unrepresentative sample of participants who are particularly research active. In addition, we recruited all participants with Lynch syndrome through the charity Lynch Syndrome UK. As several participants with Lynch syndrome first became aware of aspirin through Lynch Syndrome UK, there may be different levels of awareness and interest in aspirin among a wider population of people with Lynch syndrome. Our sample of

participants with Lynch syndrome mostly consisted of white women. In order to address potential health inequalities, further research should aim to understand the barriers and facilitators to using aspirin across all socio-demographic groups. Across all interviews we provided participants with information on aspirin from NICE guidance NG151. However, there is potential that some of the barriers and facilitators explored by participants may have been different without this prior information. Furthermore, in some cases participants may have been more inclined to respond positively regarding the use of aspirin for colorectal cancer due to the presence of the interviewer.

3.5.1 Conclusions

GPs and patients with Lynch syndrome have multiple unmet informational needs in decisions concerning aspirin use, which are inconsistently supported by current care pathways. The implementation of national guidance therefore needs to be underpinned by clearly defined local roles and accessible information to support shared decision-making. Future research could include the development and evaluation of interventions to support GPs advising people with Lynch syndrome on aspirin for cancer prevention.

Declarations

Ethical approval and consent to participate: Ethical approval was awarded by the University of Leeds School of Medicine Research Ethics Committee (MREC 19-091). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in this study.

Consent for publication: Consent forms provided to participants included information regarding publication of the study results.

Availability of data and material: Public access to the interview schedules, and restricted access to a subset of anonymised interview transcripts is available from University of Leeds Research Data Repository: <u>https://doi.org/10.5518/1097</u>. Anonymised transcripts have only been uploaded to the repository for participants who consented to this procedure and for transcripts that could be reasonably anonymised.

Competing interests: Robbie Foy is a member of the NICE Implementation Strategy Group. All other authors have no competing interests to declare that are relevant to the content of this article.

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Chapter Four: Acceptability of aspirin for cancer preventive therapy: a mixed methods study exploring the views of the UK general population

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4.1 Abstract

Background: Australian guidance recommends aspirin for colorectal cancer prevention among people aged 50-70 at population risk. The medication could be offered more widely in the future in the UK and other countries. To ensure the views of the general population are considered in future guidance, we explored public perceptions of aspirin for preventive therapy.

Methods: We recruited 400 UK respondents aged 50-70 through a market research company to a survey investigating current aspirin use, and awareness of aspirin for cancer prevention. We used purposeful sampling to recruit and conduct semi-structured interviews with 20 survey respondents, with the aim to explore participants' acceptability towards aspirin for preventive therapy. We analysed the interview data using reflexive thematic analysis, and mapped the themes onto the Theoretical Domains Framework.

Results: In the survey, 19.0% (76/400) of respondents were aware that aspirin can be used to prevent cancer, and 1.0% (4/400) had taken aspirin for cancer preventive therapy. Across the interviews, there were three themes: 1) Perceived necessity of aspirin; 2) Concerns about side-effects; 3) Preferred information sources. Several participants considered themselves at low risk of cancer and would only start aspirin if at higher risk. Participants who reported a higher perceived necessity for taking aspirin often had a personal or family history of cancer. Concerns regarding aspirin's side-effects were common.

Conclusion: Among the general population, those with a personal or family history of cancer may be more receptive towards taking aspirin for preventive therapy, and could be an appropriate group to target in future policies. Many had concerns about aspirin's side-effects, highlighting the need to support informed decisions on the medication.

4.2 Introduction

Colorectal cancer is one of the most common occurring cancers worldwide, with an estimated two million cases and nearly one million deaths from the disease globally in 2020 (1). There is increasing interest in the pharmacological prevention of cancer (2), including aspirin to prevent colorectal cancer (3). A pooled analysis of 423,495 people from two cohort studies found daily aspirin use to be associated with a 15% reduced risk of colorectal cancer (hazard ratio: 0.85, 95% CI=0.80-0.89) (4). Furthermore, a meta-analysis of four randomised controlled trials investigating aspirin for vascular disease prevention have observed aspirin to be associated with reduction of colon cancer incidence (hazard ratio: 0.76, 95% CI=0.60-0.96) (5). Studies have also investigated use of aspirin for preventing other cancers, however the evidence is more limited (6).

Aspirin is often recommended for people at higher risk of developing colorectal cancer. Australian national guidance (7), and the United Kingdom (UK) National Institute for Health and Care Excellence (guidance NG151) recommends aspirin for colorectal cancer prevention for people with Lynch syndrome (8). The guidance does not state a recommended dose, but 150-300mg is commonly used in practice. In some cases, aspirin is recommended to prevent colorectal cancer for those at age-specific population risk of the disease. Australian guidance recommends considering 100-300mg daily aspirin for those in the general population aged 50 to 70 to prevent colorectal cancer (7). There is no current equivalent national guidance for the public in the UK and United States (US).

Decisions on whether to use aspirin involve consideration of potential benefits and side-effects, such as an increased risk of gastrointestinal bleeding (9). For individuals at population risk of colorectal cancer, regular aspirin use between 75mg to 325mg appears to have a favourable benefit-harm profile (6), although the risk of side-effects increases substantially after age 70 (6, 10, 11). Current use and acceptability of aspirin for colorectal cancer prevention among the UK public is unknown (12), but previous research has explored the views of people with Lynch syndrome on aspirin (13). It is likely that a proportion of the public regularly use aspirin for multiple purposes (14), such as cardiovascular disease risk reduction (15). Australian cross-sectional research has observed moderately high acceptance (>70%) for using aspirin regularly for colorectal cancer prevention among the general population (16). The study did not explore participants' motivators and barriers towards the use of aspirin. The majority of research examining barriers to using preventive therapy has focused on breast cancer prevention medication among women at higher risk of the disease. Barriers to use include concerns about the side-effects (17-20), and perceptions of the medication as a 'cancer drug' (17). Less is known about barriers to and facilitators of aspirin for colorectal cancer prevention among people at population risk (12).

The potential impact of using aspirin for cancer prevention in the wider population will depend on acceptability as well as effectiveness, and an understanding of the barriers to implementation. Public perceptions of aspirin for cancer preventive therapy should be explored to inform both clinical guideline development (21), and support informed decision-making (22). In this study, we recruited people from the UK public to investigate their aspirin use and associated knowledge. In addition, we explored the potential facilitators and barriers towards taking aspirin for colorectal cancer prevention among a sub-sample of survey respondents.

4.3 Methods

4.3.1 Design

We carried out a mixed methods study. We conducted an online survey to recruit people from the UK general population to an interview study. The survey also provided a useful opportunity to collect data on participants' prior use of aspirin and their knowledge on the use of aspirin for cancer prevention. Following the survey, we conducted semi-structured one-to-one interviews with a sub-sample of survey participants to explore their perceptions of aspirin for colorectal cancer prevention. We pre-registered the methods and analysis plan (<u>https://osf.io/3efg7</u>), and were granted ethical approval by University of Leeds School of Medicine Research Ethics Committee (MREC19-091).

4.3.2 Participants and recruitment

We hosted the online survey on Qualtrics, and recruitment was advertised through a market research company (Dynata). We recruited people from the UK public between the ages of 50 to 70, as the benefits of prophylactic aspirin use are estimated to be greater than the risks of side-effects within this age range (6). At the end of the survey, we asked respondents for contact details if they wished to take part in a follow-up interview. All interviewees received £25 from Dynata. One author (KEL) recruited participants until data saturation was considered to have been achieved, following an established method (23). After 10 interviews, we assessed for data saturation and stopped recruitment once three subsequent interviews had been conducted and no new themes were identified (23). For example, recruitment would stop after participant 13, if no new themes were observed from participants 11, 12, and 13.

4.3.3 Survey measures

4.3.3.1 Aspirin use

We asked participants whether they had ever taken aspirin. Those who answered yes were asked if they took aspirin regularly (i.e. most days or every day) and their reasons for taking aspirin, such as for pain relief, cancer prevention, or cardiovascular disease prevention (Appendix C.1).

4.3.3.2 Knowledge

We asked participants if they were aware prior to the survey that aspirin can be used to reduce the risk of developing certain cancers. We also asked whether a healthcare provider had previously discussed with them about taking aspirin to prevent colorectal and other cancers.

4.3.3.3 Characteristics of the sample

We collected data on participant characteristics, including any previous cancer diagnoses, gender, age, ethnicity, and highest educational or professional qualification obtained.

4.3.4 Interview schedule

We developed the interview schedule based on the Theoretical Domains Framework (TDF; version 2) (24), which is a framework derived from multiple behaviour change theories (Appendix C.2). Each of the 14 framework domains describes a factor that could influence individual behaviour when implementing new clinical practices. The TDF domains cover both internal factors, such as a person's knowledge and emotions, and external factors, such as social influences and available resources.

We conducted semi-structured interviews with flexibility to the order of questions, and improvised follow-up questions. At the beginning of all interviews, participants were informed that aspirin is currently only recommended in the UK for people at higher risk of colorectal cancer due to a genetic syndrome, but that there is potential for wider recommended use in the future. A patient representative (MM) reviewed the draft interview schedule to ensure the questions were comprehensible to the public.

4.3.5 Data collection and analysis

One author (KEL) analysed the survey data in R Studio (R version 4.2.1), with findings presented in proportions and frequencies. One author (KEL), with previous experience in collecting and analysing qualitative data, conducted all interviews by video call or telephone. Interviews took place from July to August 2022. Interviews were audio-recorded, transcribed verbatim, and anonymised using pseudonymised initials to replace participants' names.

The interview data was analysed in two stages, which has been recommended for the TDF to optimise its use in qualitative research (25), and can identify themes not captured by a theoretical framework (25, 26). The interview transcripts were coded and analysed using reflexive thematic analysis (27, 28). The developed themes were then mapped onto the TDF domains (24). During analysis, we found the Necessity-Concerns Framework to be an additional useful framework for guiding our analytic process (29). The framework specifies that people consider their treatment necessity beliefs against the concerns when making decisions on medication (30, 31). One author

(KEL) coded and analysed all transcripts, and two authors (SGS, SMCG) double coded a proportion of interviews. Themes were discussed and finalised collaboratively among the three authors. One author (KEL) mapped the themes onto the domains in the TDF (version 2), which was reviewed by co-authors. All transcripts were managed in NVivo (version 1.6.1) and Microsoft Word.

4.4 Results

4.4.1 Survey findings

Four hundred people participated in the survey (Table 4.1). The mean age of the sample was 60.8 years (SD=5.7). Most of the sample were men (213; 53.3%), educated below degree level (251; 62.8%), and were white British or Irish (371; 92.8%). Seventy-six (19.0%) were aware prior to the survey that aspirin can be used to reduce the risk of developing certain cancers, and 15 (3.8%) had previously discussed aspirin for this purpose with a healthcare professional.

Most participants (216; 54.0%) had taken aspirin at least once. Among the 216 previous aspirin users, most had taken it for pain relief (150; 69.4%). Fewer had taken aspirin for prevention of cardiovascular disease (61; 28.2%) and cancer (4; 1.9%). One person (0.5%) had taken aspirin as part of a trial. Among the 216 previous aspirin users, 59 (27.3%) reported using aspirin regularly, defined as most days or every day. Most of the 59 regular aspirin users took the medication for cardiovascular disease prevention (45; 76.3%), 11 (18.6%) for pain relief, and a minority (3; 5.1%) for cancer prevention.

Table 4.1. Characteristics of the survey respondents, recruited from the UK general population (n =
400)

	n (%)			
Age				
50-55	88 (22.0%)			
56-60	106 (26.5%)			
61-65	103 (25.8%)			
66-70	103 (25.8%)			
Gender				
Women	186 (46.5%)			
Men	213 (53.3%)			
Another identity	1 (0.3%)			
Ethnicity				
White British or Irish	371 (92.8%)			

White Gypsy or Irish Traveller	1 (0.3%)
Any other White background	12 (3.0%)
Asian or Asian British	9 (2.3%)
Mixed White and Asian	1 (0.3%)
Arab or Arab British	2 (0.5%)
Black/ African/ Caribbean background / mixed	2 (0.5%)
background	
Any other ethnic background / mixed	2 (0.5%)
background	
Education	1
Degree level and above	149 (37.3%)
Below degree level	251 (62.8%)
Previously diagnosed with cancer	
Yes	46 (11.5%)
No	354 (88.5%)
Among those 'Yes' to cancer (<i>n</i> =46), which cance	er (s)
Prostate	11 (23.9%)
Breast	10 (21.7%)
Skin	6 (13.0%)
Colorectal	5 (10.9%)
Other cancers	14 (30.4%)
	1

Note: Proportions may not compute to 100% due to rounding.

4.4.2 Interview findings

Two hundred and two (50.5%) survey respondents expressed an interest in a follow-up interview. We periodically invited participants by email to be interviewed until data saturation was deemed to have been reached. We aimed to recruit participants from different demographic groups (e.g. gender), and a balance of current and never aspirin users. In batches of 5-10 invites, we invited 53 survey respondents to be interviewed, and 20 (37.7%) responded and were interviewed (Table 4.2). Interview duration ranged between 15 to 30 minutes. We identified three overarching themes, and interview findings were mapped onto the TDF (Table 4.3).

	n (%)			
Age				
50-55	3 (15.0%)			
56-60	7 (35.0%)			
61-65	5 (25.0%)			
66-70	5 (25.0%)			
Gender				
Women	12 (60.0%)			
Men	8 (40.0%)			
Ethnicity				
White British or Irish	17 (85.0%)			
Asian or Asian British	3 (15.0%)			
Country in the UK				
England	18 (90.0%)			
Scotland	1 (5.0%)			
Northern Ireland	1 (5.0%)			
Previously diagnosed with cancer				
Yes	6 (30.0%)			
No	14 (70.0%)			

Table 4.2. Characteristics of the general public interview respondents (n = 20)

Note: Proportions may not compute to 100% due to rounding.

Themes	Potential facilitators to the use of aspirin for	Potential barriers to the use of aspirin for preventive	Main TDF domain(s)
	preventive therapy	therapy	
Perceived necessity	Those who perceive themselves at higher risk of	Those who perceive themselves at lower risk of cancer	Beliefs about consequences
of aspirin	cancer because they have a personal or family	because they do not have a personal or family history of	
	history of the disease.	the disease.	
Concerns about side-	Low concerns regarding the side-effects of aspirin	High concerns about using daily aspirin because of the	Beliefs about consequences
effects	because it is well-known over-the-counter	side-effects, such as increased risk of gastrointestinal	
	medication for pain relief.	bleeding.	
		Concerns about taking aspirin daily at doses above 75mg.	
Preferred	Wanting information on aspirin to come from	Current lack of a recommendation to support the use of	Environmental context and
information sources	trusted online sources of information, such as the	aspirin for colorectal cancer prevention among the UK	resources
	NHS and UK cancer charities (e.g. Cancer Research	general public.	
	υк).		
	Wanting information on aspirin to come from a		
	medical professional.		

Note. Table adapted from Burgess et al. (32).

4.4.2.1 Perceived necessity of aspirin

4.4.2.1.1 Did not perceive a necessity for aspirin

Participants' beliefs varied about the perceived necessity of taking aspirin for colorectal cancer prevention. Several people perceived themselves to be at low risk of the disease, typically because they had no family history or personal history of cancer. Often, these participants described how they would only consider using aspirin for cancer prevention if a medical doctor assessed them to be at higher risk, or if they were diagnosed with colorectal cancer.

"If someone said to me I was high risk and aspirin was the, was a possible option, I would take it." (J.J., 56 years old, woman).

"Yeah, well I think probably if I have had bowel cancer and I was in recovery [...] then I probably would take [aspirin]." (W.G., 69 years old, man).

Several participants were averse to using daily medication in general, unless deemed highly necessary for their health.

"I would only take [medication] if it was really necessary." (A.G., 69 years old, woman).

"On the whole I don't like taking pills, [...]. Unless there was very definite proof that not taking [aspirin] would lead to bowel cancer." (W.G., 69 years old, man).

A few participants perceived other lifestyle changes, such as diet, as more effective and necessary than taking medication to prevent cancer.

"I think [colorectal cancer] can be broadly governed by diet, fibre, etc." (E.Y., 60 years old, man).

4.4.2.1.2 Perceived a necessity for aspirin

A number of participants discussed having previously been diagnosed with cancer (e.g., breast, colorectal, prostate), which in turn increased their interest in using aspirin, and their feelings on the importance of cancer prevention.

"If I saw the GP yesterday [...] 'oh would you like to take aspirin as a preventative for bowel cancer?' I would say yes, particularly now that I've been diagnosed with, with breast cancer." (I.N., 64 years old, woman).

Several participants appeared more inclined to use aspirin because friends or family members had been diagnosed with cancer. Out of three interviewees who currently used or had previously used aspirin for cancer prevention, all had started because of a family history of cancer.

"A few years ago I heard an article on [a public service radio station] and there was two eminent doctors, and they were talking about the possibility that aspirin prevented not just bowel cancer but other cancers. [...] That triggered me to start taking it, my father died of cancer and my sister also died of cancer." (H.B., 69 years old, man).

4.4.2.2 Concerns about side-effects

4.4.2.2.1 Expressed high concerns about aspirin

Many participants expressed concerns about the side-effects of daily aspirin use, such as increased risk of gastrointestinal bleeding. In a Lynch syndrome population, aspirin is often prescribed in clinical practice at a daily dose of 150-300mg (8). However, several participants expressed feeling more comfortable using a lower dose of aspirin (e.g. 75mg), due to concerns about the side-effects.

"Because [150-300mg] seems to be a lot. [...], but 75mg, a small dose, I would feel comfortable with that." (S.S., 70 years old, woman).

Several participants' concerns regarding aspirin appeared to be related to the perceived harm of taking any long-term medication. These participants felt that taking daily medication would make them go from *"being a healthy person to a potentially unhealthy person"* (*R.C., 58 years old, man*). Most participants wanted further information on the side-effects of aspirin before they would consider initiating the medication. Participants often wanted to know if the benefits of aspirin for preventive therapy substantially outweighed the side-effects.

"I probably would like to know more about what effects it would have on my body, what damage it could do to my heart, or other organs." (K.H., 60 years old, woman).

4.4.2.2.2 Did not have concerns about aspirin

Despite widespread concerns about aspirin, these views were not universally held among participants. Aspirin was a familiar drug to many, which lowered several people's concerns about the side-effects.

"Because it's been well known to me that [aspirin] can help prevent heart problems and that's kind of been around for decades [...] So I think knowing that and not hearing of anything happening to anybody then that's very reassuring for me." (R.L., 57 years old, woman).

Some participants expressed low concerns about aspirin because of their own or family members previous experiences using the medication without encountering side-effects.

"No, no I don't [have concerns about the side-effects], because you know whenever I've taken it, [...] I don't take them every day but my mother had no side-effects whatsoever." (I.N., 64 years old, woman).

4.4.2.3 Preferred information sources

Participants discussed their preferred source of information on the use of aspirin for colorectal cancer prevention. Many participants wanted the information on aspirin to come from trusted online sources, such as the National Health Service (NHS) and UK cancer charities (e.g. Cancer Research UK).

"Cancer Research would probably be, or Macmillan, it would be a trusted website that [...] I would look at." (K.H., 60 years old, woman).

Other important information sources discussed were medical professionals. Several participants wanted the information on aspirin for cancer prevention to come from their GP, while others preferred speaking to a cancer specialist. In most cases, participants felt that they would not initiate aspirin for preventive therapy without a doctor's recommendation.

"Well certainly I think I would first and primarily go to the GP." (A.N., 68 years old, woman).

"Maybe not a GP but somebody who was specialised in that area, maybe a gastroenterologist [...] I wouldn't automatically [take aspirin] because I wouldn't have enough information to warrant what else it could do to me." (K.H., 60 years old, woman).

Several people expressed positive views towards speaking to a pharmacist about aspirin, often because they had previously had positive experiences consulting their pharmacists on other medical issues. However, not all were comfortable with this approach, and only wanted to speak with a medical doctor about aspirin.

"Well I think my doctor is the trustworthy cause, but also my pharmacy is really good." (A.G., 69 years old, woman).

"I've always gone to GP, I've never discussed anything with a pharmacist ever [...] I mean they're giving a lot of powers to the pharmacist, but I don't feel comfortable talking to a pharmacist." (L.L., 62 years old, man).

Official UK guidance recommending aspirin for cancer prevention for the general public was an important factor to some participants. However, this was only mentioned by a small number of people as a potential barrier to using aspirin.

"I'd be happy if [aspirin] was recommended though, but I'd wait till it was recommended, I wouldn't jump on things too quickly." (F.L., 52 years old, man).

4.5 Discussion

In this UK study exploring the views of the general population, we observed low current use of aspirin for preventive therapy among survey respondents, and varying levels of potential acceptance across the interviews with non-aspirin users. Among those interviewed, people who had a personal or family history of cancer were more receptive to taking aspirin. Those who considered themselves at lower risk of colorectal cancer, or cancer in general, were more resistant towards the medication. When examining the potential for future guidance to recommend aspirin outside of a Lynch syndrome population, the publics' perceptions towards taking aspirin for cancer prevention should be considered.

Most survey respondents had some experience taking aspirin, often for pain relief. People's perceptions of aspirin as a well-known pharmacy drug may support its use for preventive therapy, as several participants interviewed held positive views towards aspirin for this reason. However, many had concerns about aspirin's side-effects, highlighting the need to support informed choice about taking medication. Awareness of aspirin for cancer prevention among survey respondents was low, and only a small percentage took aspirin for preventive therapy. The interview findings suggest an important motivator to taking aspirin among those at population risk was a family history of cancer.

We considered our qualitative findings in relation to the 14 domains in the TDF, and identified two main domains (24). These domains were the 'Beliefs about the consequences' of using aspirin, and the potential 'Environmental context and resources' which would aid in implementing aspirin for the public. Participants' beliefs about the perceived necessity for taking aspirin and concerns about the side-effects were particularly important, and relate to the Necessity-Concerns Framework (29). Previous evidence has found those who report low necessity for a medication and high concerns on the side-effects are less likely to initiate and adhere to a range of different medications (33-36).

Similarly, a UK prospective study found women at higher risk of breast cancer with low concerns about side-effects were significantly more likely to initiate preventive medication (37). However, in that context there was no relationship with necessity.

4.5.1 Implications for research and practice

While the interview findings suggest a relationship between perceived cancer risk and uptake of aspirin, a large population survey is warranted to investigate these potentially motivating factors further. Although minimal previous research has been conducted in this area (12), surveys in the US and Australia have observed mixed findings on a relationship between cancer risk and interest in aspirin for colorectal cancer prevention (16, 38). Interventions aiming to support informed uptake of aspirin for preventive therapy should consider targeting people's beliefs regarding the side-effects and benefits of taking the medication. There is also scope for research to explore the relationship between the Necessity-Concerns Framework and adherence to aspirin.

Guidance recommending aspirin for preventive therapy among the public should consider how the information is communicated, as several participants wanted the advice to come from a healthcare professional. People who have previously had cancer or a precursor to cancer may be particularly receptive to taking aspirin for preventive therapy. There is trial and observational evidence supporting the use of aspirin among people with colorectal adenomas (39-45), and this may be an appropriate group for policy makers to target if the harm-benefit profile is deemed sufficient. While the evidence for using aspirin for secondary cancer prevention is less developed (46), the ongoing Add-Aspirin trial is investigating the effectiveness of regular aspirin for patients with non-metastatic colorectal, breast, gastro-oesophageal, and prostate cancer (47, 48). Our findings suggest such groups may be particularly receptive to receiving a recommendation to use aspirin for preventive therapy, however further research in this area is warranted.

4.5.2 Limitations

The study had several limitations. As we recruited a moderate sample size of 400 respondents to the survey, it is difficult to generalise these findings to the wider UK public aged 50 to 70. In some cases, weighting approaches can be employed with the aim to weight participants' responses to represent the target population (49). However, we concluded that weighting was inappropriate for our survey as several demographic (e.g. ethnicity) categories contained little to no data, which can lead to over or underrepresenting responses for these population groups (50). Self-selection to the survey and interviews may have also resulted in recruiting people with stronger views on the topic than those in the general population (51).

For the interviews, most participants were white, with only three people recruited from an Asian background. Further research is warranted to explore the views of people from different ethnic minority groups on the use of aspirin for cancer preventive therapy. There are likely to be specific barriers among some ethnic minority groups. For example, research has observed South Asian respondents to view cancer as a taboo subject (52, 53), and have discussed the stigma attached to taking long-term medications (54-56), which could prevent uptake of cancer preventive therapy.

4.5.3 Conclusions

People from the general population with personal or family history of cancer were more receptive towards aspirin for colorectal cancer prevention, and could be an appropriate group to target in future policies. Several had concerns about the side-effects of aspirin, highlighting the need to support informed decisions on the medication. Guidance and advice recommending aspirin should be communicated from sources deemed trustworthy by the public, such as healthcare professionals.

Declarations

Ethical approval and consent to participate: Ethical approval was awarded by the University of Leeds School of Medicine Research Ethics Committee (MREC 19-091). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in this study.

Competing interests: Robbie Foy is a member of the NICE Implementation Strategy Group. All other authors have no competing interests to declare that are relevant to the content of this article.

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Chapter Five: A factorial randomised trial investigating factors influencing general practitioners' willingness to prescribe aspirin for cancer preventive therapy in Lynch syndrome: a registered report

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5.1 Abstract

Background: The National Institute for Health and Care Excellence (NICE) recommends aspirin for colorectal cancer prevention for people with Lynch syndrome. Strategies to change practice should be informed by understanding the factors influencing prescribing.

Aim: To investigate the optimal type and level of information to communicate with GPs to increase willingness to prescribe aspirin.

Design and setting: We recruited GPs in England and Wales (n=672) to an online survey with a 2^3 factorial design. GPs were randomised to one of eight vignettes describing a hypothetical patient with Lynch syndrome recommended to take aspirin by a clinical geneticist.

Method: Across the vignettes, we manipulated the presence or absence of three types of information: 1) existence of NICE guidance; 2) results from the CAPP2 trial; 3) information comparing risks/benefits of aspirin. We estimated the main effects and all interactions on the primary (willingness to prescribe) and secondary outcomes (comfort discussing aspirin).

Results: There were no statistically significant main effects or interactions of the three information components on willingness to prescribe aspirin or comfort discussing harms and benefits. In total, 80.4% (540/672) of GPs were willing to prescribe, with 19.7% (132/672) unwilling. GPs with prior awareness of aspirin for preventive therapy were more comfortable discussing the medication than those unaware (p=0.031).

Conclusion: It is unlikely that providing information on clinical guidance, trial results and information comparing benefits and harms will increase aspirin prescribing for Lynch Syndrome in primary care. Alternative multilevel strategies to support informed prescribing may be warranted.

5.2 Introduction

Lynch syndrome is an inherited condition that increases the risk of developing several cancers, including colorectal cancer (1). Aspirin has been investigated as a preventive therapy for colorectal cancer (2). The CAPP2 trial observed a reduced risk of colorectal cancer among people with Lynch syndrome randomised to 600mg aspirin versus placebo at 10 years (hazard ratio: 0.65, 95% CI=0.43-0.97) (3). In 2020, the National Institute for Health and Care Excellence (NICE) NG151 guideline for colorectal cancer management recommended to consider daily aspirin to reduce colorectal cancer risk in people with Lynch syndrome (4). NICE did not recommend a dose, but 150-300mg are commonly used in practice (4).

Aspirin prescribing is likely to occur in primary care, but general practitioners (GPs) may be reluctant to do so (5). Ideally, strategies to change clinical practice should be informed by an understanding of the barriers to prescribing behaviour (6). An Australian interview study identified several barriers amongst healthcare professionals to aspirin prescribing for colorectal cancer prevention for the public, including concerns about side-effects, limited awareness of the national guidance, and uncertainties about the strength of evidence (7). In addition, a large UK survey found GPs who were more aware of aspirin's cancer preventive benefits were more willing to prescribe the medication to a patient with Lynch syndrome (5). In the present study, we evaluated the relative effects of these different, potentially modifiable influences on decisions to prescribe aspirin for patients with Lynch syndrome in light of the new NICE guidance.

We investigated the optimal type and level of information to communicate with GPs to increase their willingness to prescribe aspirin to a patient with Lynch syndrome. We presented GPs with one of eight versions of a patient vignette, manipulating the presence or absence of three types of information on the effectiveness of aspirin for colorectal cancer prevention: existence of NICE guidance [NG151] (4); results from the CAPP2 trial (3); and information comparing the risks and benefits of aspirin (8). We hypothesised main effects of each manipulation on willingness to prescribe aspirin, and comfort with discussing aspirin. As exploratory research, we investigated twoway and three-way interactions between these main factors on the outcomes, and examined barriers and facilitators to prescribing aspirin among GPs.

5.3 Methods

5.3.1 Setting and participants

We recruited GPs in England and Wales to a cross-sectional online survey. A market research company (M3 Global Research) advertised the survey to their network of over 240,000 GPs. We excluded GPs not currently practising, and those outside England and Wales. GPs from Scotland and

Northern Ireland were excluded. We preregistered the stage one registered report on Open Science Framework (<u>https://doi.org/10.17605/OSF.IO/B5SFH</u>). We followed CONSORT reporting guidelines (Appendix D.1) (9).

5.3.2 Experimental design

We used a 2³ factorial trial design, with participants randomised evenly across the eight conditions (i.e. minimisation) by the survey platform Qualtrics. All vignettes described a hypothetical scenario where a clinical geneticist recommends that the GP prescribes aspirin to a patient with Lynch syndrome (Appendix D.2). Three factors were manipulated to form the eight conditions (Table 5.1). These factors were selected and designed using our interview data with UK healthcare providers and people with Lynch syndrome (preregistered: <u>https://osf.io/3efg7</u>), the Theoretical Domains Framework (10), existing evidence (5, 7, 11), and expert opinion from healthcare professionals and a patient representative. The three factors were:

- 1) NICE guidance [NG151] recommending aspirin for people with Lynch syndrome (4) (vs. no information);
- 2) Results from the CAPP2 trial investigating the effectiveness of aspirin for people with Lynch syndrome (3) (vs. no information);
- 3) Information comparing the risks and benefits of aspirin (8) (vs. no information).

Participant blinding was not possible, but we only informed participants about the three factors across the vignettes after survey completion.

Table 5.1. Description of the eight experimental conditions (i.e. vignettes) in the study, and the
three factors across the conditions.

Experimental	NICE guidance [NG151]	CAPP2 trial results	Risks/ benefit
condition			information
1	Yes	Yes	Yes
2	Yes	Yes	No
3	Yes	No	Yes
4	Yes	No	No
5	No	Yes	Yes
6	No	Yes	No
7	No	No	Yes
8	No	No	No

5.3.3 Measures

5.3.3.1 Participant characteristics

Participants self-reported their gender, status in practice, number of years qualified, and their specialism (Appendix D.3).

5.3.3.2 Willingness to prescribe

We asked GPs how willing they would be to prescribe aspirin to this patient with Lynch syndrome (11). Response options ranged from 'not at all willing' to 'definitely willing'.

5.3.3.3 Comfort discussing aspirin

GPs were asked how comfortable they would feel discussing the benefits and harms of aspirin with this patient (11). Response options ranged from 'very uncomfortable' to 'very comfortable'.

5.3.3.4 Barriers and facilitators to prescribing

We asked participants how much they agree or disagree that 14 factors affected their willingness to prescribe. The factors were based on a similar survey (11), with additional items included relevant to Lynch syndrome and aspirin. Example factors included the dose of aspirin being prescribed (5), and the patient's age (7).

5.3.3.5 Previous experience

Participants were asked questions on their professional experience, such as if they have ever prescribed aspirin for colorectal cancer prevention to a patient with Lynch syndrome.

5.3.3.6 Awareness

We asked participants if they were aware, before taking the survey, that aspirin can be used to reduce the risk of colorectal cancer, how they first became aware of this, and if they were aware of the NICE guidance [NG151] (4).

5.3.4 Sample size calculation

We calculated the smallest expected main effect size (12). A UK survey of GPs found willingness to prescribe aspirin to patients with Lynch syndrome was as low as 62% (5). After considering effect size data from reviews of interventions targeting prescribing behaviour (13, 14), we determined the smallest expected effect size is a 10% absolute increase in willingness to prescribe aspirin. We calculated an increase of willingness from 62% to 72% as an odds ratio of 1.58 (~Cohen's D of 0.25). With this effect size, power of 90%, *alpha*=0.05, and an equal number of participants per condition,

the required sample size was 672 participants. The sample size calculation is available as an R Script here: <u>https://osf.io/mgxc4/</u>.

5.3.5 Analysis

We described the data using proportions and frequencies. The primary outcome was willingness to prescribe, and the secondary outcome was comfort discussing the harms and benefits of aspirin. We used an ANOVA to estimate the main effects and all interactions on the primary and secondary outcomes. We used effect coding (-1, 1) to enable interpretation of the main and interaction effects simultaneously (15).

The outcomes of willingness and comfort were also be dichotomised at mid-point. We conducted multivariable logistic regression models assessing the relationship between GPs' characteristics, awareness, and previous experience on willingness to prescribe (willing vs. unwilling), and comfort discussing aspirin (comfortable vs. uncomfortable). We also reported the proportion of GPs who agreed that each of the 14 factors influenced their willingness to prescribe.

To minimise missing data, participants were required to answer all survey questions, unless a question was not applicable due to a previous answer. We used RStudio (version 4.1.2) for the analysis, with p<0.05 statistically significant. The dataset and analysis scripts were made available on the Research Data Leeds Repository (https://doi.org/10.5518/1184).

5.4 Results

Out of 2,200 GPs approached, 867 (39.4%) started the survey. After excluding 195 ineligible participants, 672 GPs were included (CONSORT Flow Diagram; Appendix D.4). Recruitment was open between March to April 2022. Table 5.2 summarises participant characteristics, which were comparable across the eight conditions (Appendix D.5).

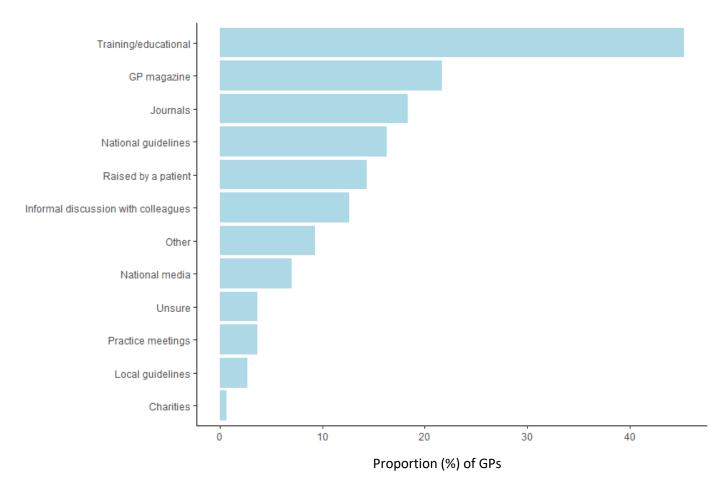
	n (%)
Country	
England	651 (96.9%)
Wales	21 (3.1%)
Gender	
Female	373 (55.5%)
Male	290 (43.2%)
Non-binary	1 (0.15%)
Another identity	1 (0.15%)
Prefer not to say	7 (1.0%)
GP status	
Salaried/locum GP	389 (57.9%)
GP partner	233 (34.7%)
GP specialist trainee	44 (6.6%)
GP retainers	3 (0.5%)
Other	3 (0.5%)
Years qualified	
0-4 years	24 (3.6%)
5-9 years	151 (22.5%)
10-14 years	174 (25.9%)
15-19 years	143 (21.3%)
20+ years	180 (26.8%)
Specialism	
Cancer	37 (5.5%)
Family history	28 (4.2%)
Genetics	4 (0.6%)
Preventive medicine	87 (13.0%)
Other	132 (19.6%)
N/A - no speciality	384 (57.1%)

Table 5.2. Demographic and professional characteristics of the GP sample (n = 672)

5.4.1 Awareness of aspirin for colorectal cancer prevention

Nearly half (300/672, 44.6%) of GPs reported prior awareness of aspirin for colorectal cancer prevention in people with Lynch syndrome, while 17.4% (117/672) were aware of NICE guidance NG151 recommending aspirin. GPs who were aware of aspirin for Lynch syndrome selected all applicable information sources which made them first aware of using the medication for preventive therapy. The most common sources of information were training days/educational meetings (136/300, 45.3%), GP magazines (65/300, 21.7%), academic journals (55/300, 18.3%), and national guidelines (49/300, 16.3%) (Figure 5.1). Prior awareness of the NICE guidance was comparable across the eight conditions (Appendix D.5).

Figure 5.1. Proportion of GPs (%) who learnt about the use of aspirin for colorectal cancer prevention in people with Lynch syndrome from the following information sources (n = 300)



5.4.2 Previous professional experience

In total, 46.3% (311/672) of GPs reported previously consulting a patient with Lynch syndrome, while 16.7% (112/672) were unsure. A smaller proportion of GPs recalled having discussed aspirin for prevention (61/672, 9.1% had discussed; 28/672, 4.2% were unsure), or prescribing aspirin to a patient with Lynch syndrome (73/672, 10.9% had prescribed; 40/672, 6.0% were unsure).

5.4.3 Willingness to prescribe aspirin

Most (390/672, 58.0%) GPs were 'probably willing' to prescribe aspirin for the hypothetical patient with Lynch syndrome, while 22.3% (150/672) were 'definitely willing' to prescribe. In total, 19.7% of GPs were unwilling to prescribe (112/672, 16.7% probably not willing; 20/672, 3.0% not at all willing). Willingness to prescribe among GPs was comparable across the three information components (NICE guidance; CAPP2 results; risk and benefit information) (Table 5.3). There were no significant main effects or interactions of these three components on willingness to prescribe aspirin (Appendix D.6).

Table 5.3. Willingness to prescribe aspirin among GPs presented with each of the three information components (n = 672)

Willingness	Total <i>n</i>	NICE guidance	CAPP2 results	Risks/ benefits
		n (%)	n (%)	n (%)
Definitely willing	150	80 (53.3%)	72 (48.0%)	74 (49.3%)
Probably willing	390	188 (48.2%)	194 (49.7%)	196 (50.3%)
Probably not	112	52 (46.4%)	59 (52.7%)	59 (52.7%)
willing				
Not at all willing	20	15 (75.0%)	11 (55.0%)	8 (40.0%)

In the multivariable logistic regression model, GPs who were unsure whether they had previously prescribed aspirin for colorectal cancer prevention were significantly more willing to prescribe aspirin than those who had not prescribed, however confidence intervals were wide (OR=5.67, p=0.032, 95% CI=1.37–34.71). Furthermore, there was no significant relationship between GPs who recalled previously prescribing aspirin and willingness to prescribe (p=0.183). No other factors were associated with willingness to prescribe (Table 5.4).

	Willing to prescrib		
	n (%)	OR (95% CI)	<i>p</i> value
Country			
England	524 (80.5%)	1.17 (0.37-3.18)	0.771
Wales	16 (76.2%)	Ref	Ref
Gender			
Female	297 (79.6%)	Ref	Ref
Male	238 (82.1%)	0.94 (0.61-1.46)	0.793
Another identity [*]	0 (0.0%)	-	0.994
Non-binary [*]	1 (100.0%)	-	0.996
Prefer not to say	4 (57.1%)	0.27 (0.05-1.48)	0.105
GP status			
Salaried/locum GP	307 (78.9%)	1.00 (0.62-1.58)	0.988
GP partner	193 (82.8%)	Ref	Ref
GP retainers [*]	3 (100.0%)	-	0.991
GP specialist trainee	34 (77.3%)	1.22 (0.51-3.1)	0.667
Other [*]	3 (100.0%)	-	0.992
Years qualified			
0-4 years	20 (83.3%)	Ref	Ref
5-9 years	114 (75.5%)	0.47 (0.13-1.39)	0.205
10-14 years	133 (76.4%)	0.52 (0.14-1.51)	0.263
15-19 years	114 (79.7%)	0.61 (0.16-1.83)	0.409
20+ years	159 (88.3%)	1.04 (0.27-3.23)	0.952
Specialism			
Cancer	34 (91.9%)	1.75 (0.56-7.67)	0.387
Family history	21 (75.0%)	0.58 (0.23-1.59)	0.256
Genetics [*]	4 (100.0%)	-	0.989
Preventive medicine	69 (79.3%)	0.72 (0.39-1.38)	0.312
Other	104 (78.8%)	0.74 (0.44-1.26)	0.258

Table 5.4. GPs' willingness to prescribe aspirin by participant characteristics, previous experience, and awareness (n = 672)

N/A – no speciality	308 (80.2%)	Ref	Ref
Previous experience			
Consulted a patient with Lynch syndrome			
Consulted - yes	261 (83.9%)	1.57 (0.99-2.5)	0.055
Consulted - unsure	90 (80.4%)	1.23 (0.69-2.27)	0.497
Consulted - no	189 (75.9%)	Ref	Ref
Discussed aspirin with a patient with			
Lynch syndrome			
Discussed aspirin - yes	57 (93.4%)	0.81 (0.21-3.57)	0.763
Discussed aspirin - unsure	23 (82.1%)	0.37 (0.10-1.53)	0.153
Discussed aspirin - no	460 (78.9%)	Ref	Ref
Prescribed aspirin to a patient with Lynch			
syndrome			
Prescribed aspirin - yes	68 (93.2%)	2.34 (0.72-9.05)	0.183
Prescribed aspirin - unsure	37 (92.5%)	5.67 (1.37-34.71)	0.032
Prescribed aspirin - no	435 (77.8%)	Ref	Ref
Awareness			
Prior awareness of aspirin in Lynch			
syndrome population			
Yes	261 (87.0%)	1.49 (0.91-2.49)	0.118
No	279 (75.0%)	Ref	Ref
Prior awareness of NICE guidance NG151			
Yes	107 (91.5%)	1.74 (0.80-4.07)	0.177
No	433 (78.0%)	Ref	Ref

*OR (95% CI) not reported due to insufficient cases.

5.4.4 Discussing the harms and benefits of aspirin

Most GPs felt comfortable discussing aspirin harms and benefits with the hypothetical patient (361/672, 53.7% quite comfortable; 150/672, 22.3% very comfortable), while 24.0% were uncomfortable with these discussions (130/672, 19.4% quite uncomfortable; 31/672, 4.6% very uncomfortable). GPs' comfort discussing aspirin harms and benefits was comparable across the three components (NICE guidance; CAPP2 results; risk and benefit information; Appendix D.7). There was no statistically significant main effects or interactions of the components on comfort discussing aspirin (Appendix D.6).

In the multivariable logistic regression model, GPs who reported awareness of aspirin for colorectal cancer prevention in people with Lynch syndrome were more comfortable discussing benefits and harms than those who were unaware prior to the survey (OR=1.68, 95% CI=1.06–2.72, p=0.031). GPs who were unsure whether they had previously prescribed aspirin were more comfortable discussing harms and benefits than those who had not prescribed aspirin (OR=6.30, p=0.019, 95% CI=1.61-36.67). However, confidence intervals were wide, and GPs who recalled previously prescribing aspirin were not more comfortable discussing the medication (p=0.823). No other factors were significantly associated with comfort discussing aspirin (Appendix D.8).

5.4.5 Factors influencing willingness to prescribe

Among GPs willing to prescribe aspirin, the factors participants agreed were important in their decision were the benefits of aspirin (527/540, 97.6%), the geneticist recommendation to prescribe (492/540, 91.1%), patient interest in using aspirin (491/540, 90.9%), and patient awareness of aspirin harms and benefits (519/540, 96.1%; Table 5.5). Those GPs unwilling to prescribe felt the most important factors influencing their decision were the harms of aspirin (121/132, 91.7%), benefits (113/132, 85.6%), dose being asked to prescribe (112/132, 84.8%), and prescribing off label (110/132, 83.3%).

A higher proportion of those unwilling to prescribe aspirin wanted to speak to a colorectal cancer specialist (96/132, 72.7%) before prescribing than those who were willing (224/540, 41.5%). The patient's interest in aspirin factored less into the decision-making of those unwilling (86/132, 65.2%), than those willing (491/540, 90.9%). In an open text box, participants were able to write additional factors that influenced their decision. Among unwilling GPs, 12.1% (16/132) suggested that the clinical geneticist should make the first prescription, and 7.6% (10/132) that patients should buy aspirin from the pharmacy instead (Appendix D.9).

Table 5.5. The proportion of GPs (%) who agreed that each of the 14 factors influenced their
willingness to prescribe (n = 672)

	Willing, n (%)	Unwilling, n (%)
Benefits of aspirin	527 (97.6%)	113 (85.6%)
Harms of aspirin	472 (87.4%)	121 (91.7%)
Dose of aspirin asked to prescribe	455 (84.3%)	112 (84.8%)
Prescribing aspirin off-label	369 (68.3%)	110 (83.3%)
Geneticist recommendation to	492 (91.1%)	93 (70.5%)
prescribe		
Patients' interest in using aspirin	491 (90.9%)	86 (65.2%)
Patients' awareness of the harms	519 (96.1%)	104 (78.8%)
and benefits of aspirin		
Wanting to speak to specialist in	235 (43.5%)	86 (65.2%)
genetics before prescribing		
Wanting to speak to specialist in	224 (41.5%)	96 (72.7%)
colorectal cancer before prescribing		
Wanting to speak with another GP	227 (42.0%)	74 (56.1%)
before prescribing		
Patients' age	375 (69.4%)	78 (59.1%)
Confidence in aspirin in general	478 (88.5%)	92 (69.7%)
Confidence in aspirin as a form of	451 (83.5%)	104 (78.8%)
preventive therapy		
Prescribing budget in your practice	132 (24.4%)	28 (21.2%)

5.5 Discussion

5.5.1 Summary

In this online factorial experiment, we found highlighting the clinical guidance, summarising trial evidence, or giving information on aspirin's benefits and harms did not increase GPs' willingness to prescribe aspirin for colorectal cancer prevention. Reassuringly, most GPs participating in our experiment were willing to prescribe aspirin for a hypothetical patient with Lynch syndrome. However, a fifth of GPs were unwilling. Most GPs who were unwilling described several barriers that behavioural interventions are unlikely to affect, such as the harms of aspirin and prescribing offlabel. Alternative strategies targeting multiple levels of prescribing behaviours may be warranted, including targeted support for GPs unwilling to prescribe.

5.5.2 Strengths and limitations

Our study design enabled us to test three different intervention components in a more efficient approach than if we had conducted individual experiments (16). However, we highlight several limitations. First, whilst the clinical vignette described a hypothetical patient with Lynch syndrome, the specific patient characteristics which may affect GPs' willingness to prescribe, such as patient age and other medication use, are likely to vary widely among the Lynch syndrome population. Our study only measured GPs' hypothetical willingness to prescribe aspirin; prescribing behaviour may be different in clinical practice. Our sample of GPs was also derived via a market research company and may not be typical of the wider GP community. Finally, we may have encountered a ceiling effect of willingness to prescribe aspirin for preventive therapy, beyond which it becomes difficult to influence the outcome.

5.5.3 Comparison with existing literature

We found GPs' levels of willingness to prescribe aspirin for colorectal cancer prevention to a patient with Lynch syndrome were comparable to a previous cross-sectional UK survey (5). We also observed barriers to prescribing aspirin which were consistent with previous research conducted in breast cancer prevention. In our study, several GPs unwilling to prescribe reported a preference for the clinical geneticist to initiate the prescription. Similarly, in breast cancer research, GPs have been observed to be more willing to prescribe preventive medicine to a hypothetical patient at higher risk of cancer if a clinical geneticist makes the first prescription (11). There are several potential barriers which may prevent aspirin from being initiated in specialist care. Previous UK and Australian research into breast cancer preventive therapy has observed a resistance among hospital-based clinicians to prescribe preventive medicines, given unfamiliarity with prescribing and side-effect management (17, 18), and lack of access to patients' medical history (17). An Australian study also found that specialist clinicians typically viewed GPs as the main prescribers of aspirin for cancer prevention, while perceiving their own roles as more advisory (7).

5.5.4 Implications for research and practice

Multilevel strategies, targeting both patients and healthcare professionals, could be utilised to support prescribing of aspirin for preventive therapy. Our findings suggest one approach to supporting GPs' discussions with patients on the benefits and harms of aspirin for preventive therapy is increasing awareness on using aspirin for this purpose through formal training, educational events, and GP magazines. There may also be scope to change GPs' knowledge and

behaviour through patient-mediated interventions (19), as patients were identified as an important information source by many GPs. One approach to increasing patients' knowledge is decision aids. This approach has been successful for breast cancer preventive therapy whereby tailored web-based decision aids have been observed to increase patients' knowledge and to support decision-making (20, 21). Similar educational tools may also be effective for some patients with Lynch syndrome considering aspirin. In 2020, NICE released a decision aid for people with Lynch syndrome considering aspirin for preventive therapy (8), however its effectiveness on patients' decisionmaking is unknown.

We found evidence to suggest that individual guidance and advice from specialist clinicians, especially in colorectal cancer, may help increase the prescribing of aspirin among unwilling GPs. Local pathways setting out roles and responsibilities of GPs, pharmacists, and specialist clinicians are warranted, and should be clearly described in GP training materials that discuss the use of aspirin for colorectal cancer prevention. Furthermore, these training and educational materials should clarify the role of GPs when asked to prescribe off-label medication, as well as highlighting the importance of ensuring medications obtained over-the-counter are recorded on patients' medical records. **Funding:** This work is fully funded by the Aspirin for Cancer Prevention AsCaP Group CRUK Grant Code: **A24991,** Senior Executive Board Prof. J Burn, Prof. A.T Chan, Prof. J Cuzick, Dr. B Nedjai, Prof. Ruth Langley. KEL is supported by an Economic and Social Research Council studentship [grant number ES/P000745/1]. This report is independent research supported by the National Institute for Health Research NIHR Advanced Fellowship, Dr Samuel Smith, [grant number NIHR300588]. SGS also acknowledges funding support from a Yorkshire Cancer Research University Academic Fellowship. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethical approval: Ethical approval was awarded by the University of Leeds School of Medicine Research Ethics Committee (MREC 20-075). The study was conducted in accordance with the Declaration of Helsinki.

Competing interests: Robbie Foy is a member of the NICE Implementation Strategy Group. All other authors declare no conflicts of interest.

Data availability: The dataset and analysis scripts generated during the study are publicly available in the Research Data Leeds Repository, (<u>https://doi.org/10.5518/1184</u>).

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Chapter Six: Discussion and conclusions

6.1 Chapter summary

In the Discussion chapter, I summarise the main findings across the four studies in the thesis. First, I discuss how conducting the systematic review identified an important gap in the literature, which the subsequent studies aimed to address. The qualitative research is summarised, after which I discuss how these findings led to the development of the factorial trial. Finally, I discuss the strengths and limitations of these methods, consider directions for future research, and implications of the findings for clinical practice.

6.2 Summary of findings and contribution to the literature

The aim of the thesis was to investigate decision-making in the context of aspirin for cancer preventive therapy, and the barriers and facilitators influencing use of the medication. Aspirin is often recommended as a form of preventive therapy for people with Lynch syndrome, and in some cases for those at population risk. However, prior to this PhD, little was known regarding stakeholders' attitudes towards the use of aspirin for cancer prevention, and the potential barriers to implementation. In the thesis, I explored the views of three main stakeholder groups: people with Lynch syndrome, the general public and healthcare providers. I conducted four studies in total. Study One involved a systematic review synthesising the existing research, with the aim to identify important gaps in the literature. I then conducted qualitative interviews exploring the factors influencing implementation of aspirin (Studies Two and Three), which were then experimentally tested in Study Four.

For Study One, I conducted a systematic review, synthesising the quantitative and qualitative data on attitudes and behaviour (i.e. uptake, day-to-day adherence, persistence) in the context of aspirin for cancer prevention among the public and those at higher cancer risk. I also synthesised the data on healthcare providers' attitudes towards implementing aspirin in clinical practice. The review involved a comprehensive search of the literature, covering 12 databases and several clinical trial repositories. In total, I included 38 studies in the review, and only identified clinical trials reporting data on uptake and adherence to aspirin for cancer prevention. Participants typically reported moderate to high uptake to an aspirin trial, and high day-to-day adherence. There was mixed evidence for long-term persistence with aspirin. Only a small number of studies investigated the factors (e.g. gender, cancer risk) influencing day-to-day aspirin adherence, all of which found no significant association. No studies investigated the factors associated with aspirin uptake. Four studies observed moderate to high hypothetical willingness to use aspirin among patients and the public. Two studies found a high proportion of healthcare providers considered aspirin to be a suitable cancer prevention option, and one study found moderate to high willingness to prescribe aspirin among GPs.

The review identified several important gaps in the literature. Minimal research had investigated the factors influencing use of, or willingness to use, aspirin for cancer prevention, and the views of healthcare providers on aspirin. At the time the review was conducted, no qualitative studies were identified, and minimal behavioural research had been conducted outside of a trial setting. Overall, I found substantial scope for behavioural research into the barriers and facilitators to implementing aspirin into clinical practice. I also identified a need to conduct qualitative research to understand the perspectives and lived experiences of the potential users of aspirin, and the healthcare providers involved in recommending or prescribing aspirin.

In Study Two, I employed one-to-one interviews to explore in-depth the factors affecting use of aspirin for preventive therapy, recruiting both people with Lynch syndrome and relevant healthcare providers. I used a mixed methods design in Study Three, recruiting people from the UK public aged 50 to 70 to a short survey on aspirin, and then conducting semi-structured interviews with a sub-sample of respondents. The aim of Study Three was to explore the public's potential motivators and barriers to taking aspirin for preventive therapy. Across Studies Two and Three, I focused the topic of the interviews on the use of aspirin for reducing the risk of colorectal cancer, as official guidance in the UK (1), Australia (2) and the US (3) has recommended aspirin for this purpose. Overall, I identified several barriers and facilitators to using, or interest in using, aspirin for preventing colorectal cancer. A number of barriers and motivators to recommending or prescribing aspirin among healthcare providers were also observed. The main findings from these studies are summarised below. In several places, I compare the findings from this thesis to the literature in breast cancer prevention medication, as the large majority of behavioural research in the area of cancer preventive therapy has focused on factors influencing use of tamoxifen (4-7).

6.2.1 Facilitators and barriers to aspirin use – Studies Two and Three

6.2.1.1 Perceptions of aspirin

In Study Three, I observed that over half of the public survey respondents had some experience with taking aspirin, with the majority taking the medication for pain relief. The general public's prior use of aspirin as a pain relief drug may facilitate the adoption of the medication for cancer prevention. In the interviews, a number of public participants, those with Lynch syndrome, and healthcare providers were positive about the use of aspirin for preventive therapy. These participants typically felt reassured to take or recommend aspirin because it is a well-known over-the-counter medication.

Aspirin was also perceived as a medication with minimal side-effects because it is commonly used for pain relief. Several public participants had low concerns with taking aspirin daily because they had seen family members use the medication for CVD prevention and experience no side-effects. The finding of positive perceptions towards aspirin because it is a pain-relief medication contrasts with the literature examining the barriers to using breast cancer preventive therapy. Previous research has found that some women at higher risk of breast cancer are reluctant to initiate tamoxifen because it is viewed as a cancer treatment medication (7, 8). Findings from the thesis suggest that perceptions of aspirin as a pain relief drug available over-the-counter may support its implementation for cancer prevention in clinical practice.

6.2.1.2 Concerns about the side-effects

Public respondents, people with Lynch syndrome, healthcare providers were variously aware of the side-effects of aspirin, and several had concerns about taking aspirin daily, such as increased risk of gastrointestinal bleeding. In particular, there were concerns about taking aspirin at 300-600mg daily because the dose is much higher than typical recommendations for CVD prevention (e.g. 75mg daily (9)). A few participants from the public and with Lynch syndrome were resistant to taking a daily dose of aspirin above 75-100mg. Most GPs described feeling more comfortable prescribing aspirin at a lower dose, such as 75-150mg, which they had more clinical experience in prescribing and managing. These findings are consistent with a previous UK cross-sectional study that found GPs were more willing (91%) to prescribe aspirin for colorectal cancer prevention at 100mg/daily, than 300mg (82% willingness) or 600mg (62% willingness) (10).

There is a need for further support on the side-effects for those considering aspirin for preventive therapy, which in turn will aid informed choice on the medication. It is important to note however that research to support people considering the use of aspirin for preventive therapy at higher doses may become obsolete in the future. This is because there is an ongoing CaPP3 dose non-inferiority trial comparing the effectiveness of aspirin at 100mg, 300mg, or 600mg for colorectal cancer prevention among people with Lynch syndrome (ClinicalTrials.gov ID: NCT02497820). At present, no findings have been published, but there is potential that 100mg daily aspirin will become the standard recommended dose if found to be non-inferior to 600mg.

6.2.1.3 Objective and perceived cancer risk

Across Studies Two and Three, there appeared to be a relationship between cancer risk and interest in aspirin for colorectal cancer prevention. People with Lynch syndrome generally had higher interest in taking aspirin than respondents from the general population. One important motivator to taking aspirin was their increased lifetime risk of developing colorectal cancer. Among those with Lynch syndrome, worries about developing colorectal cancer typically outweighed their concerns regarding aspirin's side-effects. Similarly, many healthcare providers felt that the benefits of aspirin outweighed the risks among populations at genetically higher risk of colorectal cancer. The thesis findings suggest that objective cancer risk may be an important motivator to taking aspirin for preventive therapy.

In Study One, I identified no studies examining the relationship between objective cancer risk and uptake of aspirin. Objective measures of cancer risk and interest in preventive therapy has been investigated in breast cancer research. A UK study recruiting women at increased breast cancer risk observed a relationship between higher objective estimates of non-BRCA-associated risk and tamoxifen uptake (8). A US study also examined the association between objective measures of breast cancer risk and uptake of tamoxifen, which found mixed evidence (11). The study found that while estimated objective risk was not associated with uptake, participants with a history of lobular carcinoma in situ or atypical hyperplasia, risk indicators of invasive breast cancer, were more likely to accept preventive therapy. Further research is needed to assess whether there is a relationship between objective colorectal cancer risk and uptake of aspirin for preventive therapy. In turn, this research would help to identify areas of support for people considering the medication for cancer prevention.

In Study Three, I identified evidence of a relationship between perceived risk and interest in aspirin. People from the general population were more receptive to taking aspirin for colorectal cancer prevention if they perceived themselves at higher risk of developing any type of cancer, such as having a personal or family history of the disease. The finding of an apparent relationship between perceived risk and interest in aspirin is consistent with some research conducted in breast cancer prevention examining comparative risk (5, 12), however evidence is mixed (4). For example, a US prospective study recruiting women at increased breast cancer risk asked participants to rate on a Likert scale what their risk of getting breast cancer is compared with other women their age (5). The study observed women with higher estimates of comparative risk were significantly more likely to enrol in a tamoxifen trial at follow-up. In contrast, an Italian retrospective study found no association between comparative perceived risk and enrolment to a tamoxifen trial (13). It is important to understand further whether perceived cancer risk could affect uptake of aspirin, particularly as people's perceived risk of cancer can be an inaccurate assessment of their objective lifetime risk (14, 15).

Feelings-of-risk is another measurement of perceived risk, and may correlate more strongly with behaviour than comparative risk. Researchers have hypothesised that people are more likely to evaluate health options using emotional reactions to risk, rather than cognitive assessments such as perceived absolute and comparative risk (16). A study has previously investigated the relationship between three measurements of perceived risk (i.e. absolute perceived risk; comparative risk; feelings-of-risk) on intentions to engage in colorectal cancer screening. For feelings-of-risk, participants were asked to rate on a Likert scale the item 'If I don't get screened, I would feel very vulnerable to getting colon cancer sometime in my life' (17). The study concluded that feelings-ofrisk was the best predictor of colorectal cancer screening intentions, when compared with absolute and comparative risk. However, the relationship between perceived risk and uptake of colorectal cancer screening was not investigated, and behaviour in practice may be different to intentions (18, 19).

As Studies Two and Three were qualitative explorations, the thesis findings of an apparent association between objective and perceived cancer risk and interest in aspirin should be interpreted with caution. Quantitative research is needed to establish if there is a relationship between cancer risk and interest in taking aspirin, and which aspects of objective and perceived risk are most important. At present, minimal quantitative research has investigated the relationship between cancer risk and interest in aspirin for cancer preventive therapy, with mixed evidence observed. One cross-sectional survey conducted in the US recruited 1,000 participants from the general population, and observed those with a history of polyps (objective risk), and those reporting increased perceived susceptibility to developing colorectal cancer had higher intentions to use aspirin (20). However, there was no relationship between intentions to use aspirin and having a personal or family history of cancer. Similarly, an Australian cross-sectional survey recruiting over 300 participants from the general public found no relationship between family history of cancer and willingness to take aspirin for colorectal cancer prevention (21). A large population survey is warranted to understand further if, and which aspects of, objective and perceived cancer risk influence interest in taking, or uptake of, aspirin for preventive therapy. The findings from this investigation could help to provide more targeted support being directed to people considering aspirin for cancer preventive therapy.

6.2.1.4 Trustworthy sources of information

Another important factor that could influence the uptake of aspirin for preventive therapy is the source communicating the information to potential users. Several public respondents and participants with Lynch syndrome viewed healthcare professionals as a trustworthy and credible source of information on aspirin. Many participants felt they would only take the medication in

conjunction with a doctor's recommendation. These findings are consistent with the literature in breast cancer research, which has observed a relationship between healthcare provider recommendation and uptake of preventive therapy (5, 6). The thesis research also explored the most important information sources among healthcare providers. Specialist clinicians viewed their role as the main information providers to both patients and GPs, as they had expert knowledge on the use of aspirin for colorectal cancer prevention. GPs agreed they would seek advice from a specialist clinician before prescribing aspirin for preventive therapy.

In the thesis, national guidance was recognised as a crucial source of information on aspirin among healthcare providers. Most GPs felt reassured to prescribe aspirin for colorectal cancer prevention after learning of NICE guidance NG151 (1), as this organisation was perceived to be trustworthy. My findings are consistent with an Australian interview study, which found several GPs were comfortable prescribing aspirin because of the national guidance recommending the medication for colorectal cancer prevention (22). In Study Three, national guidance was also discussed as a barrier to taking aspirin among some public respondents, with a small number stating they would only initiate aspirin if there was UK guidance for those at population risk. Overall, the qualitative findings on participants' perceptions of the trustworthy information sources that could influence their decision on aspirin should be interpreted with caution, as behaviour in practice may be different (18). Quantitative research is needed to investigate further whether these factors influence decisionmaking in the context of aspirin for preventive therapy.

6.2.1.5 Inconsistent healthcare support

While healthcare providers' views on recommending aspirin for colorectal cancer prevention had previously been explored in an Australian interview study (22), there was a lack of research examining the barriers among potential users of the medication. In Study Two, I contrasted perspectives of both patients with Lynch syndrome and healthcare providers, which provided novel data highlighting inconsistencies in the care pathway for aspirin. For example, although several participants with Lynch syndrome purchased, or would purchase, aspirin from the pharmacy, community pharmacists were typically against selling aspirin for cancer prevention to those without a prescription. I also found that while healthcare providers agreed on the appropriate care pathway for aspirin (e.g. GPs prescribe), participants with Lynch syndrome experienced mixed levels of support. For example, not all participants were made aware of the option to use preventive therapy from a medical professional, and several did not know who to approach to discuss aspirin further with.

The finding of inconsistent healthcare support for people with Lynch syndrome is similar to several qualitative studies conducted in the UK (23), Ireland (24), and the US (25, 26). For example, one UK interview study recruited women with Lynch syndrome to discuss their general healthcare experiences (23). Participants described receiving inconsistent care, such as varied access to surveillance, and a lack of knowledge on the condition among many healthcare professionals. Similarly, an interview study conducted in Ireland found many participants with Lynch syndrome described a lack of coordinated medical care, and feeling unsupported by healthcare professionals following a diagnosis. Participants also felt there was poor knowledge on the condition among both oncology specialists and GPs. The findings from the thesis and previous literature demonstrates the essential need for coordinated and consistent care for people with Lynch syndrome, which in turn will support patients considering aspirin for preventive therapy.

6.2.2 Experimental testing of the factors influencing aspirin prescribing – Study Four

The qualitative investigation in the thesis led to the development of Study Four, where I conducted a randomised factorial trial recruiting GPs from England and Wales. To guide the development of the intervention, I utilised the Theoretical Domains Framework (TDF) in the qualitative phase of the PhD (27). First, I developed the interview topic guides in Studies Two and Three to cover the 14 domains in the TDF (27). After analysing the transcripts using reflexive thematic analysis (28), I mapped the developed themes onto the TDF (29). Across both interview studies, an important TDF domain was the 'Environmental context and resources' influencing implementation of aspirin, such as information sources. Often, participants with Lynch syndrome and public respondents wanted a recommendation from their doctor to take aspirin, however in some cases GPs were perceived as a barrier to taking aspirin. For example, a small number of people with Lynch syndrome described encountering some resistance from primary care when enquiring about aspirin for preventive therapy, and subsequently did not initiate the medication (Study Two). In the final PhD study, I aimed to investigate whether presenting GPs with certain information would increase their willingness to prescribe aspirin for a hypothetical patient with Lynch syndrome. In turn, I anticipated these findings would aid in the design of a prototype information resource to support GPs considering prescribing aspirin for a patient.

When choosing the informational factors to target in the intervention, I considered the findings from the interview study with healthcare providers. Study Two identified two important TDF domains that could influence GPs' willingness to prescribe aspirin. These were 'Beliefs about the consequences' of using aspirin (e.g. benefits, side-effects), and 'Knowledge' on the use of the medication for colorectal cancer prevention (27). GPs were concerned about the side-effects of aspirin, and were unfamiliar

with the evidence and national guidance supporting its use for colorectal cancer prevention in a Lynch syndrome population (Study Two). Similarly, an Australian qualitative study recruiting healthcare providers (e.g. GPs) identified several barriers to prescribing aspirin for colorectal cancer prevention for the public, including lack of awareness of the national guidance, side-effect concerns, and uncertainties about the strength of the evidence (22). After consideration of the evidence in this area, I decided to target, in Study Four, GPs lack of awareness of the national guidance (Factor One), their unfamiliarity with the trial evidence in this area (Factor Two), and their concerns about aspirin's side-effects compared with the benefits (Factor Three). When deciding on the intervention materials, I considered the available information resources that a specialist clinician could provide to a GP. In Study Four, I manipulated the presence or absence of three types of information: 1) existence of the NICE national guidance (1) (Factor One); 2) the CAPP2 trial results providing evidence for aspirin in a Lynch syndrome population (30) (Factor Two); 3) information comparing aspirin's benefits and risks from the NICE patient decision aid (31) (Factor Three).

In total, 672 GPs were recruited and randomised across eight experimental conditions in Study Four. Despite qualitative evidence from Study Two to support these factors, I found no statistically significant main effects or interactions in Study Four for the three information components (national guidance; trial evidence; risk/benefit information) on GPs' willingness to prescribe aspirin for a hypothetical patient with Lynch syndrome. Furthermore, there were no significant main effects or interactions of the three information components on GPs' comfort discussing the harms and benefits of aspirin. I also examined the relationship between GPs' characteristics (e.g. gender, years qualified), prior awareness of aspirin for cancer prevention, and previous clinical experience on the outcomes of willingness to prescribe, and comfort discussing aspirin. While I did not observe evidence of these factors influencing GPs' willingness to prescribe, those with prior awareness of aspirin for preventive therapy were significantly more comfortable discussing the benefits and harms. The findings from Study Four contrast with results from a previous UK survey, which recruited over 1,000 GPs to investigate willingness to prescribe aspirin for colorectal cancer prevention in Lynch syndrome at 600mg (10). In the survey, GPs were more willing to prescribe aspirin at 600mg if they had more professional experience, were aware prior of aspirin's cancer preventive effects, and had previously seen a patient with Lynch syndrome in practice (10). However, in Study Four GPs were told that commonly used doses in clinical practice are 150-300mg, which may have resulted in the different findings across the two studies.

As an exploratory analysis in Study Four, GPs rated 14 potential factors they believed influenced their willingness to prescribe aspirin for the patient. These factors included the patient's age, the

benefits of aspirin, the harms, and the patient's interest in using aspirin. Among GPs unwilling to prescribe, the most commonly endorsed barriers were a reluctance to prescribe aspirin for preventive therapy because it is an off-label use of the medication, the dose of aspirin asked to prescribe, and concerns about the harms of aspirin irrespective of its benefits. While these findings provide novel evidence of the potential barriers to prescribing aspirin, these untested exploratory findings should be interpreted with caution. As observed in Studies Two and Four, the factors suggested to influence GPs' prescribing behaviour may not result in behaviour change when experimentally manipulated. These potential barriers to prescribing should be investigated further through hypothesis-testing research (32), which is an approach that minimises the probability of a false positive result (i.e. Type I error) (33, 34).

Both the findings from Study Two and Study Four highlighted the importance of the TDF domain 'Professional role/identity' to support the implementation of aspirin for preventive therapy. In Study Two, healthcare providers agreed that GPs should prescribe and oversee the use of aspirin for preventive therapy. I concluded from this study that clearly defined and consistently applied healthcare provider roles in the care pathway for aspirin will likely in turn support patients considering the medication for cancer prevention. However, not all GPs may agree that their role includes the prescribing of aspirin for cancer prevention. In Study Four, I found that several GPs reported in an open text box that they were unwilling to prescribe aspirin as they did not perceive it to be within the scope of their role. A number of these GPs wanted the clinical geneticist to issue the first prescription. However, it is unlikely that a clinical geneticist would prescribe aspirin, and were reluctant to prescribe the medication as they did not have access to patients' medical records to examine for contraindications. These findings are consistent with UK and Australian research, which has observed similar barriers to prescribing breast cancer preventive therapy among hospital-based clinicians (35, 36).

In contrast to breast cancer preventive medication which patients can only obtain with a prescription, aspirin is an over-the-counter medication. In Study Four, I found several GPs were unwilling to prescribe aspirin due to its availability from pharmacies. It is unlikely though that community pharmacists will, to their knowledge, sell aspirin for colorectal cancer prevention. I previously identified a reluctance among community pharmacists to sell aspirin at a daily dose greater than 75mg for those without a doctor's prescription (Study Two). The main barriers to pharmacists selling higher aspirin doses were the harms of the medication and its off-label use for colorectal cancer prevention. Off-label use of medications is widespread (37, 38). However, there

are also legitimate concerns that need to be considered, such as the potential toxicity risks (39, 40), and concerns about litigation, as several major fraud lawsuits and settlements have resulted from pharmaceutical companies promoting off-label medications (41-43).

Overall, the thesis findings suggest an important barrier to the implementation of aspirin for preventive therapy is a lack of clarity regarding healthcare providers' roles in the care pathway for aspirin. In turn, this could inadvertently act as a barrier to taking aspirin among patients with Lynch syndrome. Coordinated and multilevel strategies are warranted, addressing the needs of GPs and people with Lynch syndrome, to ensure consistent implementation of national guidance on aspirin for preventive therapy. These coordinated strategies would also facilitate the implementation of any future guidance recommending aspirin for colorectal cancer prevention outside of the Lynch syndrome population.

6.3 Strengths and limitations of the methods

In this thesis, I employed a wide range of methods to explore and investigate the factors influencing decision-making in the context of aspirin for cancer prevention. These methods included a systematic review of the literature to identify important gaps; qualitative interviews to gain new perspectives on the barriers and facilitators affecting use of aspirin; and a randomised factorial trial to investigate further the factors influencing GPs' willingness to prescribe aspirin. There are both strengths and limitations to these methods, which I have summarised below.

6.3.1 Resource constraints in the systematic review

In Study One, I excluded non-English language articles as I did not have the financial resources for an external company to translate the identified articles. Limiting the language of the included articles in the review may introduce bias, as non-English language studies in the topic area may produce substantially different findings than English language studies (44). However, research has previously found no evidence to suggest that limiting reviews to English articles significantly changes the review findings (45, 46). For example, one study assessed a random sample of 59 Cochrane systematic reviews and found that excluding non-English language studies had minimal effect on the review conclusions (45).

Another important limitation to Study One was that second reviewers only duplicated screening, data extraction, and quality assessment for a proportion of articles (20-45%), due to the resource and time constraints. In contrast, guidance for increasing the quality of a systematic review recommends the use of two independent reviewers for duplicating all screening and data extraction of the identified studies (47-49). Alternative approaches can be used though when there are

resource constraints (47). For example, the AMSTAR-2 guidance, a critical appraisal tool for systematic reviews, advises that a second reviewer can also check agreement on a sample of studies when conducting screening and data extraction (50). Systematic review guidance is more mixed on whether a second reviewer should independently review the quality of the included articles (47, 50, 51). For example, while the Cochrane guidance recommends risk of bias assessments to be completed independently by two people (51), the AMSTAR-2 guidance does not provide a recommendation for the use of a second reviewer for checking study quality (50). To improve the quality of my systematic review whilst balancing the resource constraints, second reviewers screened, extracted data, and assessed quality for a proportion of articles, and findings were discussed to achieve consensus. However, the use of two independent reviewers to screen all articles in the review would have provided greater confidence that no relevant studies were missed (47).

6.3.2 Recruitment and sample representativeness

6.3.2.1 Sampling methods

I used different approaches to recruitment throughout the thesis. When designing Study Two, I considered recruiting participants with Lynch syndrome through the NHS, such as genetics clinics. However, recruiting participants from clinics would have likely been a time-consuming approach resulting in a low sample size, as it is estimated that fewer than 5% of those with Lynch syndrome are aware they have the condition (52-54). Instead, I recruited participants through the charity Lynch Syndrome UK, which has a large membership of over 2,000 people with Lynch syndrome. While advertising the study through Lynch Syndrome UK was an efficient approach to recruitment, there were also limitations. As the charity focuses on patient information, members may be more aware and positive towards the use of aspirin than the wider Lynch syndrome population. To mitigate this limitation, I recruited a relatively balanced number of people who did and did not use aspirin for colorectal cancer prevention. In total, 40% of the Lynch syndrome sample did not use aspirin, which provided the opportunity to explore the views of those who were unaware of aspirin for preventive therapy, and those who were aware and had chosen not to take the medication.

On reflection, I believe there would have been benefits to recruiting people with Lynch syndrome to Study Two through multiple routes, such as clinics and charities. By recruiting participants through both avenues, I could have compared levels of awareness and barriers to taking aspirin among members and non-members of Lynch Syndrome UK. To recruit a high number of participants with Lynch syndrome from an NHS clinic, I could have advertised recruitment to the study at a specialised clinic. For example, the Lynch Syndrome Clinic at St Mark's National Bowel Hospital in London.

However, there would have also been challenges carrying out this approach in Study Two. For example, recruiting participants through specialist NHS clinics would have been a resource intensive approach by asking NHS staff to aid in recruitment, and would have been difficult to have achieved during the COVID-19 pandemic.

In Study Two, I used snowball sampling to recruit healthcare providers, which is an approach that can help to efficiently recruit a niche target population (55). However, an important limitation is representativeness, with snowball sampling more likely to produce a homogenous sample with similar socio-demographic characteristics (56). To minimise the impact of this limitation, I also recruited healthcare providers through social media and relevant professional organisations, such as the UK Cancer Genetics Group. Overall, in Study Two I recruited healthcare providers across a range of ages and professions. There was also high variation in whether participants had previous clinical experience in the topic area, with 57% of the 23 healthcare providers having encountered a patient with Lynch syndrome in practice. By interviewing healthcare providers with varying levels of clinical experience, I was able to explore a wide range of barriers to recommending aspirin for preventive therapy.

Another approach I employed in the thesis was utilising market research companies to recruit participants from the general population (Study Three), and GPs (Study Four). Advertising studies through market research companies helps to recruit large samples of participants efficiently (57), which is particularly valuable for survey research. For Study Three, I employed the market research company, Dynata, to recruit participants through multiple online survey platforms, such as Valued Opinions and e-Rewards. Given the wide reach of Dynata, I anticipated that recruiting public participants through a market research company would result in a more representative sample than if I had advertised through avenues such as social media. However, recruiting participants through market research companies and social media suffers from the same limitation of self-selection bias. Participants selecting themselves for a study does not adhere to the principles of random sampling (58, 59), and could result in an unrepresentative sample (57). For example, participants may have been more positive towards the use of aspirin for colorectal cancer prevention than the target population because participants self-selected to the study based on their interests. The thesis findings should therefore be generalised to the target population with caution.

6.3.2.2 Representativeness of survey samples

In Studies Three and Four, I recruited participants through an online survey, which is a low-cost method for quickly recruiting large sample sizes compared with mailing paper-based surveys (60). There are also limitations, as this approach can result in overrepresenting certain demographic

groups due to factors such as internet access, such as higher education, younger age, and white ethnicity (61, 62). However, internet access is likely less of a limitation to sample representativeness than previously documented. Current estimated internet use among the UK general population is high, even among older populations. In Study Three, I aimed to recruit participants from the UK public between 50 and 70 years of age. In 2020, 96% of people in the UK were estimated to have access to the internet (63), and 95% of people aged 55 to 64 were estimated to have used the internet within the last three months (64). Recent estimates of internet use in the UK has also been found to be broadly similar across socio-demographic groups, such as ethnicity and geographical location (65).

To examine further whether conducting an online survey led to recruiting an unrepresentative sample in Study Three, I compared the survey demographic data with the latest UK population statistics. Overall, I found that the general population survey sample was somewhat comparable to the UK population. I recruited 47% women to the general public aspirin survey, while the Office for National Statistics (ONS) estimates that in 2021 a total of 51% of the UK population were women (66). I also recruited 37% public respondents to the survey who were educated to degree level or above, which is comparable to the ONS in 2020 that estimated that approximately 39% of people aged 50 to 64 in the UK were educated to at least bachelor's degree or equivalent (e.g. NVQ4) (67). Some demographic groups though were underrecruited. In the survey, I recruited only 4% of public participants from an ethnic minority background (including Gypsy/Irish traveller), however the ONS estimated that in 2020 people from ethnic minority backgrounds comprise of 15% of the UK population (68). The limitations of recruiting underrepresented groups in this thesis are discussed in the next section.

When recruiting the general population to a quantitative survey, there are statistical techniques that can be employed to increase the representativeness of the sample. Statistical weighting procedures can be applied with the aim to weight the responses to match the target population and account for non-responders (69). However, when the number of participants recruited in several demographic groups is small, this can lead to the survey estimates over or underrepresenting the target population (70). As I recruited a moderately sized sample of 400 respondents to Study Three, resulting in a small number of participants in certain demographic groups (e.g. ethnicity), it was decided that weighted approaches would not be appropriate. It is difficult therefore to generalise the findings from Study Three on public participants' aspirin use and associated knowledge to the wider UK population.

6.3.3 Underrepresented groups

In the Lynch syndrome interviews (Study Two), white women were overrepresented in the sample. Only two men were recruited to the study, and no participants from an ethnic minority group were interviewed. There are widespread issues with recruiting men and ethnic minority groups to health behaviour research (71), and cancer studies (72-74), which may have affected recruitment to Study Two. Following this experience, I made a concentrated effort to recruit men and people from ethnic minority groups to the general public interviews (Study Three). I examined participants' survey data on prior use of aspirin, gender, and ethnicity with the aim to recruit an interview sample balanced across these characteristics. In total, 40% of the interview sample were male, but only three participants were from an Asian background (Study Three). To achieve meaningful data on the different barriers experienced towards aspirin for preventive therapy across ethnic groups, research recruiting a larger sample of ethnic minority participants is needed.

In the PhD, I could have also employed more intensive effort to recruit other underrepresented groups in research, such as other genders (e.g. non-binary) (75). It would have also been beneficial to recruit participants with lower levels of education or health literacy (76), as the thesis findings suggest that inequalities may be affecting patients considering aspirin for preventive therapy. In Study Two, several GPs felt more inclined to prescribe aspirin for patients with expressed preferences for the medication. However, GPs could inadvertently act as a barrier to aspirin initiation among patients who are uncertain. In turn, this could exacerbate existing health inequalities if participants from certain socio-demographic groups, such as those with lower education, are more likely to be uncertain on aspirin. For example, a previous study I am a co-author on observed women at higher risk of breast cancer who were educated to at least degree level were more likely to recognise the benefit and harms of tamoxifen, than women with lower education (77). While there was not a statistically significant difference, a higher proportion of women who recognised the harms and benefits of tamoxifen went on to initiate the medication (28%; 12/43), compared with those who did not recall this information (12%; 25/205). It is unknown if similar inequalities are affecting people with Lynch syndrome considering aspirin, and is warranted for research to further explore.

6.3.4 Hypothetical willingness

Throughout the thesis, I have investigated both experienced and hypothetical barriers to use of aspirin for preventive therapy. As there is official NICE guidance (NG151) recommending aspirin for people with Lynch syndrome (1), I was able to explore several participants' experienced motivators and barriers to taking or recommending aspirin for preventive therapy (Study Two). Several

participants did not have experience in this area, where I instead explored their hypothetical willingness to use, recommend, or prescribe aspirin (Studies Two and Three). Similarly, in Study Four, I presented GPs with an imagined scenario describing a patient with Lynch syndrome interested in taking aspirin for colorectal cancer prevention, and measured GPs' hypothetical willingness to prescribe. I investigated GPs' willingness to prescribe rather than intentions, as aspirin's side-effects may be greater than the benefits for some patients with Lynch syndrome, for example those aged 70 and above (78). While intentions focuses on plans to engage in the behaviour in the future, behavioural willingness reflects whether a person would be willing to perform a potentially risky behaviour (e.g. aspirin prescribing) in particular circumstances (79).

A limitation of measuring hypothetical willingness is that behaviour in practice may be different. Intentions to perform a behaviour often do not translate into action (18, 19). Similarly, gaps between willingness and behaviour have also been observed (80, 81). Therefore, the findings from Study Four investigating GPs' willingness to prescribe aspirin should be interpreted with caution, as actual behaviour in practice may be different. Methods can be employed to study doctors' and patients' behaviour in clinical practice, such as routinely collected prescribing behaviour (82, 83), and direct observation studies conducted in clinics (84-86). There are difficulties though with measuring behaviour in the context of aspirin for cancer prevention. Firstly, there is no UK guidance recommending aspirin for preventive therapy among the general population, therefore participants' hypothetical willingness to take aspirin was the most suitable outcome to explore in Study Three. Secondly, although NICE guidance (NG151) recommends aspirin for the Lynch syndrome population (1), most GPs will not encounter a patient with this condition in clinic. For example, in Study Four, less than half of GPs (46%; 311/672) had ever consulted a patient with Lynch syndrome, and only 9% (61/672) recalled previously discussing aspirin for preventive therapy with a patient. Finally, the NICE guidance recommending aspirin (NG151) was only released in 2020 (1); it will likely take time for the guidance to be widely adopted in clinical practice.

6.3.5 Theoretical framework

Utilising theoretical theories and framework in health research is valuable for explaining the psychological and structural factors influencing behaviour (87), and for guiding the development of behavioural change interventions (88). For the thesis, I employed the TDF in the qualitative research (27), which aided in the design and development of an intervention trial (Study Four). However, a limitation of the framework in the thesis was that the TDF was relatively ineffective for explaining the qualitative findings generated from interviews with the UK public (Study Three). While the TDF covers a wide range of 14 factors potentially affecting behaviour in the context of clinical guidance, a

limitation of the framework is the breadth and lack of depth of the domains. The findings from the general public study instead mapped clearly onto the Necessity-Concerns Framework (89).

The Necessity-Concerns Framework specifies two main constructs. These are the beliefs regarding the necessity of the medication for maintaining health, and concerns regarding the side-effects of taking the medication long-term (89). The framework has been designed to be flexibly applied to all contexts, with previous evidence observing a relationship between medication necessity and concerns influencing adherence to (90-92), and uptake of (92, 93), a range of different medications. In Study Three, applying the Necessity-Concerns Framework alongside the TDF enabled a more indepth exploration of participants' beliefs towards aspirin. The main barriers to taking aspirin were public respondents' beliefs about the necessity of the medication and concerns on the long-term effects. While the TDF was useful in the thesis for explaining the factors affecting implementation of existing guidance recommending aspirin for preventive therapy, the Necessity-Concerns Framework was more appropriate for exploring hypothetical willingness to use aspirin. In Study Three, I observed benefits to applying both frameworks to the interview findings, as this approach identified an additional theme not captured by the Necessity-Concerns Framework. The third theme described public participants' preferred information sources on the use of aspirin for preventive therapy, which relates to the TDF domain 'Environmental context and resources' (27). By utilising two frameworks in Study Three, I developed a more complete understanding of the barriers to taking aspirin among the general population.

6.3.6 Factorial trial

In Study Four, I recruited GPs to a factorial randomised trial to investigate the effects of the three informational components (NICE guidance; CAPP2 results; risk/benefit information) on willingness to prescribe aspirin. Factorial trials are an efficient approach that can test multiple main effects and interactions simultaneously, which can result in acceptable statistical power with fewer participants than needed for a standard RCT (94). To demonstrate this, I calculated and compared the sample size calculation at 80% statistical power for a factorial trial (i.e. Study Four) against the sample size calculation required for conducting three separate randomised experiments, using the MOST package in R (95). To achieve 80% power in Study Four, a total of 504 GP participants needed to be recruited, resulting in 63 participants in each of the eight experimental conditions. If I had carried out three separate experiments to test the effects of the three informational components on willingness to prescribe, I would have needed to recruit an estimated 1,500 GPs for 80% statistical power. By conducting a factorial trial in Study Four, I was able to efficiently provide evidence that

presenting GPs with the three informational components did not increase willingness to prescribe aspirin for preventive therapy.

6.3.7 Registered Report

I conducted Study Four as a Registered Report, which is a publication format increasingly offered by journals. Publishing research as a Registered Report involves two submission stages (96). First, I submitted the paper protocol (i.e. Stage 1 Registered Report) to the British Journal of General Practice for the first stage of peer-review. At this stage, the manuscript was reviewed and granted in-principle acceptance based on the quality of the introduction, research question/hypothesis, and methodological design. Following in-principle acceptance, I publicly registered the protocol online (https://doi.org/10.17605/OSF.IO/B5SFH), after which data collection commenced. Once recruitment and analysis were complete, I submitted the full manuscript (i.e. Stage 2 Registered Report) to the journal for the second stage of peer-review. At this point, the reviewers assessed if the Stage 2 manuscript adhered to the protocol, and if any deviations were transparent and appropriately justified. The presentation of the results and discussion sections of the paper were also assessed. The full manuscript was then accepted for publication by the journal.

Publishing a study as a Registered Report has several important benefits. Firstly, peer-reviewers provide suggestions for improvement to the study methodology and analysis plan at a crucial stage where changes can be implemented as data collection has not yet commenced (97, 98). Secondly, a sample size calculation is required for the Stage 1 submission (98, 99), which ensures the target sample size is large enough to sufficiently investigate the research question, while being costeffective by not over-recruiting (100). As Registered Reports are accepted after evaluating the methodological quality of the protocol, the full manuscript cannot be rejected based on the results of the study (96). Therefore, there is less incentive for researchers to undertake questionable research practices in order to produce statistically significant results and increase the chance of the study being published (99), such as HARKing (Hypothesising After Results are Known) (101), phacking (misusing statistical tests to generate a significant result) (102), and selective reporting of results (99). Previous research has investigated the benefits of Registered Reports, and found studies published through this format were significantly more likely to report null findings than those published through the traditional publication route (61% null findings in Registered Reports vs. 5-20% in traditional literature) (103). By publishing Study Four as a Registered Report, I enhanced the methodological quality of the study, and increased the transparency and trustworthiness of the findings.

6.4 Implications of findings

6.4.1 Implications for practice

Overall, there is a need for clarity on the roles of the healthcare providers involved in the care pathway for patients acquiring aspirin for preventive therapy. At present, the NICE guidance (NG151) recommending aspirin for people with Lynch syndrome does not specify the healthcare providers responsible for implementing the guidance (1). The findings from the thesis have consistently demonstrated a need for a coherent strategy across primary and specialist care to support the use of aspirin. Such a strategy should recognise the importance of a multilevel approach, targeting the individuals, groups and wider organisational systems, in order to successfully implement new practices (104). In particular, the strategy should specify the roles and responsibilities of GPs, pharmacists, and specialist clinicians in the care pathway for aspirin for preventive therapy. Information on the care pathway for aspirin should also be effectively and consistently communicated to patients with Lynch syndrome, which in turn will support those considering the medication.

In Study Three, I observed higher acceptability towards taking daily aspirin for colorectal cancer prevention among those in the general population who perceive themselves at increased cancer risk, due to a personal or family history of cancer. There is potential that the UK may recommend aspirin for colorectal cancer prevention for those in the general population aged 50 to 70, similar to the Australian national guidance (2). However, given the recently redacted US guidance recommending aspirin for this purpose among the general public (105), it is also possible that UK guidance will not endorse the medication for those at population risk. If the harm-benefit profile is deemed sufficient, future UK guidance may recommend aspirin for those at higher risk of cancer outside of the Lynch syndrome population.

Clinical trials and observational studies have previously found evidence to support the use of aspirin for preventing recurrent colorectal adneomas (106-112). Therefore, aspirin may become more widely recommended in the future for patients with adenomas. The strength of the evidence is mixed though. For example, the multicentred seAFOod Polyp Prevention trial recruited 709 participants who previously had colorectal adenomas. Participants were randomised to receive either aspirin, omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA), or placebo (113). The trial concluded that aspirin did not reduce colorectal adenoma risk at one year follow up, which was measured as the proportion of participants with at least one adenoma. There was a significant relationship though between aspirin use and the secondary outcome of reducing mean total number of adenomas per participant.

In addition to patients with adenomas, there is also potential that aspirin could be recommended in the future to prevent recurrence of different cancer types. The evidence base is more limited for aspirin's use for secondary cancer prevention (114), however there is an ongoing trial (Add-Aspirin) aiming to investigate the effectiveness of regular aspirin use for patients who have previously had cancer, which includes non-metastatic colorectal, breast, gastro-oesophageal, and prostate cancer (115, 116). If the trial concludes that aspirin is effective for preventing cancer recurrence, the medication may be recommended for cancer patients in the future. Overall, for aspirin to be effective for preventing precursors or recurrence of cancer, there needs to be sufficient acceptability and uptake of the medication among these target groups. The findings from Study Three provides important evidence on acceptability towards taking aspirin for preventive therapy among those with a personal or family history of cancer, outside of the Lynch syndrome population.

6.4.2 Directions for future research

In the thesis, I have identified several important gaps in the literature for future research to address. In the systematic review (Study One), I identified no evidence reporting data on adherence to aspirin for cancer prevention outside of a clinical trial setting. Across the trial studies, adherence to aspirin in the short-term was high, but there was mixed evidence for persistence in the long-term. When interviewing users of aspirin in Studies Two and Three, I did not identify any salient themes concerning adherence to aspirin. However, as this is an underexplored area, further quantitative research is needed to investigate long-term adherence to aspirin for colorectal cancer prevention in routine care. Persistence to aspirin for colorectal cancer prevention is essential as the medication is recommended to be taken daily for at least 2 years among people with Lynch syndrome (NICE guidance NG151) (1), and for 2.5 years for the Australian public aged 50 to 70 (2).

In Study Two, several participants with Lynch syndrome expressed uncertainty on whether to take aspirin for preventive therapy, and felt there was a lack of support from their healthcare provider with the decision. While a NICE patient decision aid has been developed to support people with Lynch syndrome considering aspirin for colorectal cancer prevention (31), the findings from Study Two suggest that the aid is inconsistently applied in practice. The effect of the NICE decision aid on patients' decision-making is also currently unknown, as the tool has not been experimentally tested. Future research is warranted to evaluate and potentially adapt this patient support tool for people with Lynch syndrome deciding on aspirin for colorectal cancer prevention. There is strong evidence to support the use of decision aids in effectively aiding patients with decisions on treatment options. For example, a meta-analysis of RCTs previously found cancer-related decision aids to increase patients' knowledge on the treatment options, without increasing anxiety (117). Furthermore, a

Cochrane systematic review observed decision aids to effectively improve patients' knowledge and reduce their feelings of uncertainty around health decisions (118).

In Study Four, providing GPs with information on the official NICE guidance, trial evidence, and information comparing aspirin's benefits and harms did not influence willingness to prescribe the medication. Among GPs unwilling to prescribe, several untested barriers were reported that future research could address. Other components that could be tested in a future randomised trial include providing information on the role of GPs in the care pathway for aspirin for cancer prevention, and their role in prescribing off-label and over-the-counter medications. If these components are observed to influence GPs' willingness to prescribe aspirin for preventive therapy, this could lead to the development of support tools for GPs. These tools could include a prototype information resource that specialist clinicians could provide to GPs, or training and educational materials. Whether materials such as these would change GPs' clinical practice behaviour is unclear, and would be difficult to measure as the vast majority of GPs will most likely never encounter a patient with Lynch syndrome enquiring about aspirin for cancer prevention. Previous evidence has observed modest evidence of an effect of educational materials on improving outcomes among GPs. For example, a systematic review of educational interventions designed for GPs in Australia reviewed the findings of 13 studies across multiple settings (e.g. diabetes, cancer diagnosis), nine of which reported improvement in at least one outcome: knowledge, skills or change in clinical behaviour (119). However, the review also observed low recruitment and retention of GPs to these educational interventions, and results were inconsistent across the studies.

There is a need for future research to investigate the barriers to taking aspirin for preventive therapy among those of lower education and socio-economic status (SES). Previous UK research has observed people of lower SES are less likely to participate in colorectal cancer screening than those at higher SES (120). Furthermore, people with lower levels of numeracy have been found to report lower intentions to participate in colorectal cancer screening than those with higher numeracy (121). It is unknown if similar inequalities are affecting uptake of aspirin for colorectal cancer prevention, and should be investigated further. Similarly, future research should examine the barriers to taking aspirin among ethnic minority groups. Several UK studies have examined the barriers to participating in cancer services among South Asian communities. These barriers have included low awareness of cancer services, cancer fatalism, language barriers, and cancer being a taboo topic (122-124). Similar barriers may also be affecting uptake of aspirin among people from ethnic minority groups. To investigate the views of ethnic minority participants on the use of aspirin for preventive therapy, more intensive recruitment efforts could be employed. For example, recruitment techniques that

have been recommended to reach South Asian participants includes working with relevant places of worship, and finding solutions to language barriers (e.g. linguistically matched researchers or interpreters) (125).

6.5 Conclusions

In summary, this thesis contributes novel evidence on the barriers and facilitators to implementing aspirin for preventive therapy into UK clinical practice. Across the thesis research, there were consistent concerns among participants on the use of aspirin. People with Lynch syndrome, public respondents, and healthcare providers expressed worries on the side-effects of taking aspirin long-term and at higher doses. Public respondents also had unique concerns regarding the necessity of the medication for colorectal cancer prevention given their population risk of the disease. People with Lynch syndrome reported receiving inconsistent healthcare support when considering aspirin for preventive therapy, and a proportion of GPs were reluctant to prescribe the medication. Clarification is warranted on the roles and responsibilities of the healthcare providers involved in the care pathway for aspirin. Overall, coordinated and multilevel strategies are needed to support patients and their GPs when considering the use of aspirin for cancer preventive therapy.

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Appendix A: Study One supplementary materials

Appendix A.1: Search strategies for systematic review

In March 2018, we searched for studies examining the use of aspirin to prevent the development of cancer. We updated and re-ran the searches in February 2020. The following databases and websites were searched:

Database	Date Searched	Searcher
Cancer.gov	24/2/20	NK
Cancer Research UK	24/2/20	NK
CINAHL (EBSCO) 1981- present	20/2/20	NK
ClinicalTrials.gov (U.S. NIH)	20/2/20	NK
Cochrane Central Register of Controlled Trials (Wiley): Issue 2 of 12, February 2020	20/2/20	NK
Cochrane Database of Systematic Reviews (Wiley): Issue 2 of 12, February 2020	20/2/20	NK
Database of Abstracts of Reviews of Effects (Wiley) : Issue 2 of 4, April 2015	27/3/18	RR
CRD HTA database only all available dates (using Pan Canadian interface)	20/2/20	NK
Dissertations & Theses A&I (Proquest) 1743 – present	20/2/20	NK
Embase Classic+Embase (Ovid) 1947 to 2020 February 19	20/2/20	NK
Health Technology Assessment Database (Wiley): Issue 4 of 4, October 2016	27/3/18	RR
International Clinical Trials Registry Platform (WHO)	20/2/20	NK
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to February 19, 2020	20/2/20	NK
NHS Economic Evaluation Database (Wiley): Issue 2 of 4, April 2015	27/3/18	RR
PubMed (NLM) 1946 – present	27/3/18	RR
 Web of science core collection: Science Citation Index Expanded (SCI-EXPANDED)1900-present Social Sciences Citation Index (SSCI)1900-present Arts & Humanities Citation Index (A&HCI)1975-present Conference Proceedings Citation Index- Science (CPCI-S)1990-present Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH)1990-present 	20/2/20	NK

Emerging Sources Citation Index (ESCI)2015-present	
Total records: 17,344 After duplicated records were removed by EndNote and Covidence: 11,258 (1662 unique in 2020 update)	

Cancer.gov

https://www.cancer.gov/about-cancer/treatment/clinical-trials/search

Date searched: 24/2/20

Aspirin selected 1/13 (2 were unique and 1 was not relevant) Acetylsalicylic Acid 0/1 (0 unique)

Cancer Research UK

http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial

Date searched: 24/2/20

Aspirin 0/1 unique hits Acetylsalicylic Acid 0/0

CINAHL (EBSCO) 1981- present

Thursday, February 20, 2020 10:48:29 AM

- # Query Results
- S11 S7 AND S10 945

S10 S8 OR S9 16,134

S9 TX (Aspirin* or "2-(Acetyloxy)benzoic Acid*" or "Acetylsalicylic Acid*" or Acetysal* or Acylpyrin* or Aloxiprimum* or Colfarit* or Dispril* or Easprin* or Ecotrin* or Endosprin* or Magnecyl* or Micristin* or Polopirin* or Polopiryna* or Solprin* or Solupsan* or Zorprin* or R16CO5Y76E or 50-78-2 or 200-064-1) 16,134

- S8 (MH "Aspirin") 10,608
- S7 S3 AND S6 82,381
- S6 S4 OR S5 845,708
- S5 TX (chemoprevent* or Chemoprophyl*) 5,535
- S4 TX (prevent* or Prophyla*) 844,419

S3 ((TX (adenocarcinoma* or adenosarcoma* or angiosarcoma* or astrocytoma* or blastoma* or cancer* or carcino* or Cholangiocarcinoma* or Craniopharyngioma* or chondrosarcoma* or Ependymoma* or Fibrosarcoma* or Glioblastoma* or glioma* or Hemangioendothelioma* or

Hepatoblastoma* or Hodgkin* or Leiomyosarcoma* or leuk#emia or Liposarcoma* or "Lynch Syndrome#" or lymphoma* or malignan* or Medulloblastoma* or melanoma* or Meningioma* or Mesenchymous* or Mesothelioma* or metast* or microcytic* or "Mycosis) AND (S1 OR S2)) AND (S1 OR S2) 555,949

S2 TX (adenocarcinoma* or adenosarcoma* or angiosarcoma* or astrocytoma* or blastoma* or cancer* or carcino* or Cholangiocarcinoma* or Craniopharyngioma* or chondrosarcoma* or Ependymoma* or Fibrosarcoma* or Glioblastoma* or glioma* or Hemangioendothelioma* or Hepatoblastoma* or Hodgkin* or Leiomyosarcoma* or leuk#emia or Liposarcoma* or "Lynch Syndrome#" or lymphoma* or malignan* or Medulloblastoma* or melanoma* or Meningioma* or Mesenchymous* or Mesothelioma* or metast* or microcytic* or "Mycosis 539,423

S1 (MH "Neoplasms+") 494,850

ClinicalTrials.gov (U.S. NIH)

Date searched: 20/2/20

condition or disease: adenocarcinoma OR adenosarcoma OR angiosarcoma OR astrocytoma OR blastoma OR cancer OR carcinoma OR Cholangiocarcinoma OR Craniopharyngioma OR chondrosarcoma

AND

other terms: Aspirin OR benzoic Acid OR Acetylsalicylic Acid OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin **178**

condition or disease: Fibrosarcoma OR Glioblastoma OR glioma OR Hemangioendothelioma OR Hepatoblastoma OR Hodgkin OR Leiomyosarcoma OR leukemia OR leukaemia OR Liposarcoma OR Lynch Syndrome OR lymphoma

AND

other terms : Aspirin OR benzoic Acid OR Acetylsalicylic Acid OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin **10**

condition or disease: malignancy OR Malignancies OR Medulloblastoma OR melanoma OR Meningioma OR Mesenchymous OR Mesothelioma OR metastasis OR metaplasia OR Metaneoplasia OR microcytic* OR Mycosis Fungoides

AND

other terms : Aspirin OR benzoic Acid OR Acetylsalicylic Acid OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin **216**

condition or disease: Myelodysplastic OR myeloma OR neoplasia OR Neoplasm OR nephroblastoma OR Neuroblastoma OR Non-Hodgkin OR Oligodendroglioma OR oncology OR Oncogenic OR

Osteosarcoma OR Pancreatoblastoma

AND

other terms : Aspirin OR benzoic Acid OR Acetylsalicylic Acid OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin **177**

condition or disease: Paget OR Pheochromocytoma OR Pineoblastoma OR retinoblastoma OR Rhabdomyosarcoma OR sarcoma OR teratoma OR tumor OR tumour OR Thymoma

AND

other terms : Aspirin OR benzoic Acid OR Acetylsalicylic Acid OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin **177 (same as above – double checked)**

Cochrane Library

Date searched: 20/2/20

#1 MeSH descriptor: [Neoplasms] explode all trees and with qualifier(s): [prevention & control -PC] 4038

#2 MeSH descriptor: [Neoplasms] explode all trees 77072

#3 (adenocarcinoma* or adenosarcoma* or angiosarcoma* or astrocytoma* or blastoma* or cancer* or carcino* or Cholangiocarcinoma* or Craniopharyngioma* or chondrosarcoma* or Ependymoma* or Fibrosarcoma* or Glioblastoma* or glioma* or Hemangioendothelioma* or Hepatoblastoma* or Hodgkin* or Leiomyosarcoma* or leuk?emia or Liposarcoma* or "Lynch Syndrome?" or lymphoma* or malignan* or Medulloblastoma* or melanoma* or Meningioma* or Mesenchymous* or Mesothelioma* or metast* or microcytic* or "Mycosis Fungoides" or Myelodysplastic* or myeloma* or neoplas* or nephroblastoma* or Neuroblastoma* or Non-Hodgkin* or Oligodendroglioma* or oncolog* or Osteosarcoma* or Rhabdomyosarcoma* or sarcoma* or teratoma* or tumo?r* or Thymoma*):ti,ab,kw (Word variations have been searched) 235637

- #4 #2 or #3 238958
- #5 MeSH descriptor: [Primary Prevention] explode all trees 3985
- #6 MeSH descriptor: [Secondary Prevention] explode all trees 3069
- #7 MeSH descriptor: [Chemoprevention] explode all trees 1614
- #8 (prevent* or Prophyla*):ti,ab,kw (Word variations have been searched) 235695
- #9 (chemoprevent* or Chemoprophyl*):ti,ab,kw 3026
- #10 #5 or #6 or #7 or #8 or #9 237553
- #11 (#4 and #10) 34282
- #12 #11 or #1 34282

#13 MeSH descriptor: [Aspirin] explode all trees 5764

#14 (Aspirin* or "2-(Acetyloxy)benzoic Acid*" or "Acetylsalicylic Acid*" or Acetysal* or Acylpyrin* or Aloxiprimum* or Colfarit* or Dispril* or Easprin* or Ecotrin* or Endosprin* or Magnecyl* or Micristin* or Polopirin* or Polopiryna* or Solprin* or Solupsan* or Zorprin* or R16CO5Y76E or "50-78-2" or "200-064-1"):ti,ab,kw 16423

#15 #13 or #14 16423

#16 #12 AND #15 679

Cochrane Database of Systematic Reviews: Issue 2 of 12, February 2020 (6)

Cochrane Central Register of Controlled Trials: Issue 2 of 12, February 2020 (669)

Did not download editorial (1)

CRD HTA database all available dates

Date searched: 20/2/20

1 MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES 11971

2 (adenocarcinoma* or adenosarcoma* or angiosarcoma* or astrocytoma* or blastoma* or cancer* or carcino* or Cholangiocarcinoma* or Craniopharyngioma* or chondrosarcoma* or Ependymoma* or Fibrosarcoma* or Glioblastoma* or glioma* or Hemangioendothelioma* or Hepatoblastoma* or Hodgkin* or Leiomyosarcoma* or leuk?emia or Liposarcoma* or "Lynch Syndrome?" or lymphoma* or malignan* or Medulloblastoma* or melanoma* or Meningioma* or Mesenchymous* or Mesothelioma* or metast* or microcytic* or "Mycosis Fungoides" or Myelodysplastic* or myeloma* or neoplas* or nephroblastoma* or Neuroblastoma* or Non-Hodgkin* or Oligodendroglioma* or oncolog* or Osteosarcoma* or Pancreatoblastoma* or Paget* or Pheochromocytoma* or Pineoblastoma* or retinoblastoma* or Rhabdomyosarcoma* or sarcoma* or teratoma* or tumo?r* or Thymoma*) IN HTA 3690

- 3 #1 OR #2 12884
- 4 MeSH DESCRIPTOR Primary Prevention EXPLODE ALL TREES 914
- 5 MeSH DESCRIPTOR Secondary Prevention EXPLODE ALL TREES 441
- 6 (prevent* or Prophyla*) IN HTA 2119
- 7 MeSH DESCRIPTOR Chemoprevention EXPLODE ALL TREES 382
- 8 (chemoprevent* or Chemoprophyl*) IN HTA 15
- 9 #4 OR #5 OR #6 OR #7 OR #8 3712
- 10 #3 AND #9 537
- 11 MeSH DESCRIPTOR Aspirin EXPLODE ALL TREES 387
- 12 (Aspirin*) IN HTA 77
- 13 (Acetylsalicylic Acid*) IN HTA 13

14 (Acetysal* or Acylpyrin* or Aloxiprimum* or Colfarit* or Dispril* or Easprin* or Ecotrin* or Endosprin* or Magnecyl* or Micristin* or Polopirin* or Polopiryna* or Solprin* or Solupsan* or Zorprin*) IN HTA 1

15 #11 OR #12 OR #13 OR #14 440

16 #10 AND #15 17

Database of Abstracts of Reviews of Effects (Wiley): Issue 2 of 4, April 2015

Date searched: 27/3/18 See Cochrane strategy Number retrieved = 22

Dissertations & Theses A&I (Proquest) 1743 – present

Date searched: 20/2/20

ti((adenocarcinoma* or adenosarcoma* or angiosarcoma* or astrocytoma* or blastoma* or cancer* or carcino* or Cholangiocarcinoma* or Craniopharyngioma* or chondrosarcoma* or Ependymoma* or Fibrosarcoma* or Glioblastoma* or glioma* or Hemangioendothelioma* or Hepatoblastoma* or Hodgkin* or Leiomyosarcoma* or leuk?emia or Liposarcoma* or "Lynch Syndrome?" or lymphoma* or malignan* or Medulloblastoma* or melanoma* or Meningioma* or Mesenchymous* or Mesothelioma* or metast* or microcytic* or "Mycosis Fungoides" or Myelodysplastic* or myeloma* or neoplas* or nephroblastoma* or Neuroblastoma* or Non-Hodgkin* or Oligodendroglioma* or oncolog* or Osteosarcoma* or Pancreatoblastoma* or Paget* or Pheochromocytoma* or Pineoblastoma* or retinoblastoma* or Rhabdomyosarcoma* or sarcoma* or teratoma* or tumo?r* or Thymoma*) AND (Aspirin* or "2-(Acetyloxy)benzoic Acid*" or "Acetylsalicylic Acid*" or Acetysal* or Acylpyrin* or Aloxiprimum* or Colfarit* or Dispril* or Easprin* or Ecotrin* or Endosprin* or Magnecyl* or Micristin* or Polopirin* or Polopiryna* or Solprin* or Solupsan* or Zorprin* or R16CO5Y76E or 50-78-2 or 200-064-1)) OR ab((adenocarcinoma* or adenosarcoma* or angiosarcoma* or astrocytoma* or blastoma* or cancer* or carcino* or Cholangiocarcinoma* or Craniopharyngioma* or chondrosarcoma* or Ependymoma* or Fibrosarcoma* or Glioblastoma* or glioma* or Hemangioendothelioma* or Hepatoblastoma* or Hodgkin* or Leiomyosarcoma* or leuk?emia or Liposarcoma* or "Lynch Syndrome?" or lymphoma* or malignan* or Medulloblastoma* or melanoma* or Meningioma* or Mesenchymous* or Mesothelioma* or metast* or microcytic* or "Mycosis Fungoides" or Myelodysplastic* or myeloma* or neoplas* or nephroblastoma* or Neuroblastoma* or Non-Hodgkin* or Oligodendroglioma* or oncolog* or Osteosarcoma* or Pancreatoblastoma* or Paget* or Pheochromocytoma* or Pineoblastoma* or retinoblastoma* or Rhabdomyosarcoma* or sarcoma* or teratoma* or tumo?r* or Thymoma*) AND (Aspirin* or "2-(Acetyloxy)benzoic Acid*" or "Acetylsalicylic Acid*" or Acetysal* or Acylpyrin* or Aloxiprimum* or Colfarit* or Dispril* or Easprin* or Ecotrin* or Endosprin* or Magnecyl* or Micristin* or Polopirin* or Polopiryna* or Solprin* or Solupsan* or Zorprin* or R16CO5Y76E or 50-78-2 or 200-064-1)) 234

Embase Classic+Embase (Ovid) 1947 to 2020 February 19

Date searched: 20/2/20

- 1 cancer prevention/ (41624)
- 2 exp Neoplasm/pc (77020)
- 3 exp *Neoplasm/ (3535622)

4 (adenocarcinoma* or adenosarcoma* or angiosarcoma* or astrocytoma* or blastoma* or cancer* or carcino* or Cholangiocarcinoma* or Craniopharyngioma* or chondrosarcoma* or Ependymoma* or Fibrosarcoma* or Glioblastoma* or glioma* or Hemangioendothelioma* or Hepatoblastoma* or Hodgkin* or Leiomyosarcoma* or leuk?emia or Liposarcoma* or "Lynch Syndrome?" or lymphoma* or malignan* or Medulloblastoma* or melanoma* or Meningioma* or Mesenchymous* or Mesothelioma* or metast* or microcytic* or "Mycosis Fungoides" or Myelodysplastic* or myeloma* or neoplas* or nephroblastoma* or Neuroblastoma* or Non-Hodgkin* or Oligodendroglioma* or oncolog* or Osteosarcoma* or Pancreatoblastoma* or Paget* or Pheochromocytoma* or Pineoblastoma* or retinoblastoma* or Rhabdomyosarcoma* or sarcoma* or teratoma* or tumo?r* or Thymoma*).tw,kw. (5299129)

- 5 or/3-4 (5699829)
- 6 primary prevention/ (40026)
- 7 secondary prevention/ (27909)
- 8 prevention study/ (3816)
- 9 (prevent* or Prophyla*).tw,kw. (2082238)
- 10 chemoprophylaxis/ (25231)
- 11 (chemoprevent* or Chemoprophyl*).tw,kw. (35882)
- 12 or/6-11 (2124291)
- 13 and/5,12 (364501)
- 14 or/1-2,13 (413454)
- 15 *acetylsalicylic acid/ (60304)

16 (Aspirin* or "2-(Acetyloxy)benzoic Acid*" or "Acetylsalicylic Acid*" or Acetysal* or Acylpyrin* or Aloxiprimum* or Colfarit* or Dispril* or Easprin* or Ecotrin* or Endosprin* or Magnecyl* or Micristin* or Polopirin* or Polopiryna* or Solprin* or Solupsan* or Zorprin* or R16CO5Y76E or 50-78-2 or 200-064-1).tw,kw,rn. (223440)

- 17 or/15-16 (223490)
- 18 and/14,17 (7602)

Date searched: 27/3/18

See Cochrane strategy

Number retrieved = 6

International Clinical Trials Registry Platform (WHO)

Date searched: 20/2/20

Condition: adenocarcinoma OR adenosarcoma OR angiosarcoma OR astrocytoma OR blastoma OR cancer OR carcinoma OR Cholangiocarcinoma OR Craniopharyngioma OR chondrosarcoma

AND

Intervention: Aspirin OR benzoic Acid OR Acetylsalicylic Acid OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin **288 records (for 160 trials)**

Condition: Fibrosarcoma OR Glioblastoma OR glioma OR Hemangioendothelioma OR Hepatoblastoma OR Hodgkin OR Leiomyosarcoma OR leukemia OR leukaemia OR Liposarcoma OR Lynch Syndrome OR lymphoma

AND

Intervention: Aspirin OR benzoic Acid OR Acetylsalicylic Acid OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin **273 (for 127 trials)**

Condition: malignancy OR Malignancies OR Medulloblastoma OR melanoma OR Meningioma OR Mesenchymous OR Mesothelioma OR metastasis OR metaplasia OR Metaneoplasia OR microcytic* OR Mycosis Fungoides

AND

Intervention: Aspirin OR benzoic Acid OR Acetylsalicylic Acid OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin **284 (for 152 trials)**

Condition: Myelodysplastic OR myeloma OR neoplasia OR Neoplasm OR nephroblastoma OR Neuroblastoma OR Non-Hodgkin OR Oligodendroglioma OR oncology OR Oncogenic OR Osteosarcoma OR Pancreatoblastoma

AND

Intervention: Aspirin OR benzoic Acid OR Acetylsalicylic Acid OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin **140 (for 90 trials)**

Condition: Paget OR Pheochromocytoma OR Pineoblastoma OR retinoblastoma OR Rhabdomyosarcoma OR sarcoma OR teratoma OR tumor OR tumour OR Thymoma

AND

Intervention: Aspirin OR benzoic Acid OR Acetylsalicylic Acid OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin **356 (for 227 trials)**

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to February 19, 2020>

Date searched: 20/2/20

- 1 exp Neoplasm/pc (94259)
- 2 exp Neoplasm/ (3285261)

3 (adenocarcinoma* or adenosarcoma* or angiosarcoma* or astrocytoma* or blastoma* or cancer* or carcino* or Cholangiocarcinoma* or Craniopharyngioma* or chondrosarcoma* or Ependymoma* or Fibrosarcoma* or Glioblastoma* or glioma* or Hemangioendothelioma* or Hepatoblastoma* or Hodgkin* or Leiomyosarcoma* or leuk?emia or Liposarcoma* or "Lynch Syndrome?" or lymphoma* or malignan* or Medulloblastoma* or melanoma* or Meningioma* or Mesenchymous* or Mesothelioma* or metast* or microcytic* or "Mycosis Fungoides" or Myelodysplastic* or myeloma* or neoplas* or nephroblastoma* or Neuroblastoma* or Non-Hodgkin* or Oligodendroglioma* or oncolog* or Osteosarcoma* or Pancreatoblastoma* or Paget* or Pheochromocytoma* or Pineoblastoma* or retinoblastoma* or Rhabdomyosarcoma* or sarcoma* or teratoma* or tumo?r* or Thymoma*).tw,kw. (3775592)

- 4 or/2-3 (4420303)
- 5 Primary Prevention/ (18118)
- 6 Secondary Prevention/ (19882)
- 7 (prevent* or Prophyla*).tw,kw. (1492889)
- 8 Chemoprevention/ (5870)
- 9 (chemoprevent* or Chemoprophyl*).tw,kw. (27070)
- 10 or/5-9 (1525518)
- 11 and/4,10 (251231)
- 12 or/1,11 (307565)
- 13 exp Aspirin/ (44354)

14 (Aspirin* or "2-(Acetyloxy)benzoic Acid*" or "Acetylsalicylic Acid*" or Acetysal* or Acylpyrin* or Aloxiprimum* or Colfarit* or Dispril* or Easprin* or Ecotrin* or Endosprin* or Magnecyl* or Micristin* or Polopirin* or Polopiryna* or Solprin* or Solupsan* or Zorprin* or R16CO5Y76E or 50-78-2 or 200-064-1).tw,kw,rn. (69938)

15 or/13-14 (69938)

16 and/12,15 (2970)

NHS Economic Evaluation Database (Wiley): Issue 2 of 4, April 2015

Date searched: 27/3/18

See Cochrane strategy

Number retrieved = 11

PubMed (NLM) 1946 - present

Date searched: 27/3/18

Number retrieved = 1,055

Search ((("Aspirin"[Mesh]) OR (((((Aspirin*[Title/Abstract] OR "2-(Acetyloxy)benzoic Acid*"[Title/Abstract] OR "Acetylsalicylic Acid*"[Title/Abstract] OR Acetysal*[Title/Abstract] OR Acylpyrin*[Title/Abstract] OR Aloxiprimum*[Title/Abstract] OR Colfarit*[Title/Abstract] OR Dispril*[Title/Abstract] OR Easprin*[Title/Abstract] OR Ecotrin*[Title/Abstract] OR Endosprin*[Title/Abstract] OR Magnecyl*[Title/Abstract] OR Micristin*[Title/Abstract] OR Polopirin*[Title/Abstract] OR Polopiryna*[Title/Abstract] OR Solprin*[Title/Abstract] OR Solupsan*[Title/Abstract] OR Zorprin*[Title/Abstract] OR R16C05Y76E[Title/Abstract] OR 50-78-2[Title/Abstract] OR 200-064-1)[Title/Abstract])) OR ((Aspirin*[Other Term] OR "2-(Acetyloxy)benzoic Acid*"[Other Term] OR "Acetylsalicylic Acid*"[Other Term] OR Acetysal*[Other Term] OR Acylpyrin*[Other Term] OR Aloxiprimum*[Other Term] OR Colfarit*[Other Term] OR Dispril*[Other Term] OR Easprin*[Other Term] OR Ecotrin*[Other Term] OR Endosprin*[Other Term] OR Magnecyl*[Other Term] OR Micristin*[Other Term] OR Polopirin*[Other Term] OR Polopiryna*[Other Term] OR Solprin*[Other Term] OR Solupsan*[Other Term] OR Zorprin*[Other Term] OR R16C05Y76E[Other Term] OR 50-78-2[Other Term] OR 200-064-1)[Other Term])) OR ((Aspirin*[EC/RN Number] OR "2-(Acetyloxy)benzoic Acid*"[EC/RN Number] OR "Acetylsalicylic Acid*"[EC/RN Number] OR Acetysal*[EC/RN Number] OR Acylpyrin*[EC/RN Number] OR Aloxiprimum*[EC/RN Number] OR Colfarit*[EC/RN Number] OR Dispril*[EC/RN Number] OR Easprin*[EC/RN Number] OR Ecotrin*[EC/RN Number] OR Endosprin*[EC/RN Number] OR Magnecyl*[EC/RN Number] OR Micristin*[EC/RN Number] OR Polopirin*[EC/RN Number] OR Polopiryna*[EC/RN Number] OR Solprin*[EC/RN Number] OR Solupsan*[EC/RN Number] OR Zorprin*[EC/RN Number] OR R16CO5Y76E[EC/RN Number] OR 50-78-2[EC/RN Number] OR 200-064-1)[EC/RN Number])))) AND ((("Neoplasms/prevention and control"[Mesh])) OR (((("Neoplasms"[Mesh]) OR ((((adenocarcinoma*[Title/Abstract] OR adenosarcoma*[Title/Abstract] OR angiosarcoma*[Title/Abstract] OR astrocytoma*[Title/Abstract] OR blastoma*[Title/Abstract] OR cancer*[Title/Abstract] OR carcino*[Title/Abstract] OR Cholangiocarcinoma*[Title/Abstract] OR Craniopharyngioma*[Title/Abstract] OR chondrosarcoma*[Title/Abstract] OR Ependymoma*[Title/Abstract] OR Fibrosarcoma*[Title/Abstract] OR Glioblastoma*[Title/Abstract] OR glioma*[Title/Abstract] OR Hemangioendothelioma*[Title/Abstract] OR Hepatoblastoma*[Title/Abstract] OR Hodgkin*[Title/Abstract] OR Leiomyosarcoma*[Title/Abstract] OR leuk*emia[Title/Abstract] OR Liposarcoma*[Title/Abstract] OR "Lynch Syndrome*"[Title/Abstract] OR lymphoma*[Title/Abstract] OR malignan*[Title/Abstract] OR Medulloblastoma*[Title/Abstract] OR melanoma*[Title/Abstract] OR Meningioma*[Title/Abstract] OR Mesenchymous*[Title/Abstract] OR Mesothelioma*[Title/Abstract] OR metast*[Title/Abstract]

OR microcytic*[Title/Abstract] OR "Mycosis Fungoides"[Title/Abstract] OR Myelodysplastic*[Title/Abstract] OR myeloma*[Title/Abstract] OR neoplas*[Title/Abstract] OR nephroblastoma*[Title/Abstract] OR Neuroblastoma*[Title/Abstract] OR Non-Hodgkin*[Title/Abstract] OR Oligodendroglioma*[Title/Abstract] OR oncolog*[Title/Abstract] OR Osteosarcoma*[Title/Abstract] OR Pancreatoblastoma*[Title/Abstract] OR Paget*[Title/Abstract] OR Pheochromocytoma*[Title/Abstract] OR Pineoblastoma*[Title/Abstract] OR retinoblastoma*[Title/Abstract] OR Rhabdomyosarcoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR teratoma*[Title/Abstract] OR tumo*r*[Title/Abstract] OR Thymoma*)[Title/Abstract])) OR ((adenocarcinoma*[Other Term] OR adenosarcoma*[Other Term] OR angiosarcoma*[Other Term] OR astrocytoma*[Other Term] OR blastoma*[Other Term] OR cancer*[Other Term] OR carcino*[Other Term] OR Cholangiocarcinoma*[Other Term] OR Craniopharyngioma*[Other Term] OR chondrosarcoma*[Other Term] OR Ependymoma*[Other Term] OR Fibrosarcoma*[Other Term] OR Glioblastoma*[Other Term] OR glioma*[Other Term] OR Hemangioendothelioma*[Other Term] OR Hepatoblastoma*[Other Term] OR Hodgkin*[Other Term] OR Leiomyosarcoma*[Other Term] OR leuk*emia[Other Term] OR Liposarcoma*[Other Term] OR "Lynch Syndrome*"[Other Term] OR lymphoma*[Other Term] OR malignan*[Other Term] OR Medulloblastoma*[Other Term] OR melanoma*[Other Term] OR Meningioma*[Other Term] OR Mesenchymous*[Other Term] OR Mesothelioma*[Other Term] OR metast*[Other Term] OR microcytic*[Other Term] OR "Mycosis Fungoides"[Other Term] OR Myelodysplastic*[Other Term] OR myeloma*[Other Term] OR neoplas*[Other Term] OR nephroblastoma*[Other Term] OR Neuroblastoma*[Other Term] OR Non-Hodgkin*[Other Term] OR Oligodendroglioma*[Other Term] OR oncolog*[Other Term] OR Osteosarcoma*[Other Term] OR Pancreatoblastoma*[Other Term] OR Paget*[Other Term] OR Pheochromocytoma*[Other Term] OR Pineoblastoma*[Other Term] OR retinoblastoma*[Other Term] OR Rhabdomyosarcoma*[Other Term] OR sarcoma*[Other Term] OR teratoma*[Other Term] OR tumo*r*[Other Term] OR Thymoma*)[Other Term])))) AND ((((("Primary Prevention"[Mesh]) OR "Secondary Prevention"[Mesh]) OR ((((prevent*[Title/Abstract] OR Prophyla*)[Title/Abstract])) OR ((prevent*[Other Term] OR Prophyla*)[Other Term]))) OR "Chemoprevention"[Mesh]) OR ((((chemoprevent*[Title/Abstract] OR Chemoprophyl*)[Title/Abstract])) OR ((chemoprevent*[Other Term] OR Chemoprophyl*)[Other Term])))))

Web of Science Core Collection

Date searched: 20/2/20

7 3,382 #6 AND #5

6 70,891 TOPIC: ((Aspirin* or "2-(Acetyloxy)benzoic Acid*" or "Acetylsalicylic Acid*" or Acetysal* or Acylpyrin* or Aloxiprimum* or Colfarit* or Dispril* or Easprin* or Ecotrin* or Endosprin* or Magnecyl* or Micristin* or Polopirin* or Polopiryna* or Solprin* or Solupsan* or Zorprin* or R16C05Y76E or 50-78-2 or 200-064-1))

- # 5 238,573 #4 AND #1
- # 4 1,785,437 #3 OR #2
- # 3 33,704 TOPIC: ((((chemoprevent* or Chemoprophyl*))))
- # 2 1,765,228 TOPIC: ((((prevent* or Prophyla*))))

1 4,038,504 TOPIC: ((((adenocarcinoma* or adenosarcoma* or angiosarcoma* or astrocytoma* or blastoma* or cancer* or carcino* or Cholangiocarcinoma* or Craniopharyngioma* or chondrosarcoma* or Ependymoma* or Fibrosarcoma* or Glioblastoma* or glioma* or Hemangioendothelioma* or Hepatoblastoma* or Hodgkin* or Leiomyosarcoma* or leuk?emia or Liposarcoma* or "Lynch Syndrome?" or lymphoma* or malignan* or Medulloblastoma* or melanoma* or Meningioma* or Mesenchymous* or Mesothelioma* or metast* or microcytic* or "Mycosis Fungoides" or Myelodysplastic* or myeloma* or neoplas* or osteosarcoma* or Neuroblastoma* or Paget* or Pheochromocytoma* or Pineoblastoma* or retinoblastoma* or Rhabdomyosarcoma* or sarcoma* or teratoma* or tumo?r* or Thymoma*))))

Web of Science Core Collection: Citation Indexes

- Science Citation Index Expanded (SCI-EXPANDED) -- 1900-present
- Social Sciences Citation Index (SSCI) -- 1900-present
- Arts & Humanities Citation Index (A&HCI) --1975-present
- Conference Proceedings Citation Index- Science (CPCI-S) --1990-present
- Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) --1990present
- Emerging Sources Citation Index (ESCI) -- 2015-present

Appendix A.2: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	le 1 Identify the report as a systematic review, meta-analysis, or both. 35		35
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	36
INTRODUCTION	<u> </u>		
Rationale	3	Describe the rationale for the review in the context of what is already known.	37-38
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	37-38
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	38
Eligibility criteria	ligibility criteria6Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.		38-39
Information sources	formation sources 7 Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.		38
Search	arch 8 Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.		Appendix A.1
Study selection	tion 9 State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). 38-39		38-39
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	39

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	39	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	39-40	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	39	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	40 - narrative synthesis	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A – as I synthesised adherence/ uptake data from the included studies, which is not a main outcome of these studies, publication bias and selective reporting is unlikely to have affected the results of the review	
Additional analyses	alyses 16 Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.		40	
RESULTS	-			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.		
Study characteristics	18	18For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.43, 4		
Risk of bias within studies	19	 Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). 43, 46-4 54 		
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	42-43, 44-49, 50-53	

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A – conducted a narrative synthesis
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A – see item 15 response
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	42, 44-45, 50-51
DISCUSSION	-		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	55-57
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	57
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	55-57
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	58

Appendix A.3: Characteristics of articles reporting all participant uptake rates to a clinical trial involving the use of aspirin for cancer
prevention (<i>n</i> = 4)

Country	Design and quality	Population	Dose/timing	n*	Age, years	All participant trial uptake ^{**}
UK	RCT MMAT Score: 4	Higher risk patients with colorectal adenomas	300mg/daily and/ or eicosapentaenoic acid	709	Mean: 65	18.1%
UK and Canada	RCT MMAT Score: 2	Patients with Barrett's oesophagus	300mg/daily (UK) or 325mg/daily (Canada) plus esomeprazole	2,557	Mean: 58-59	44.7%
UK	RCT MMAT Score: 3	Higher risk patients with colorectal adenomas	300mg/daily or 300mg plus folate/daily	939	Mean (range): 57.8 (27.6–74.6)	13.3%
US	RCT MMAT Score:	Women healthcare providers aged ≥45	100mg/alternate day plus vitamin E	39,876	45-54 (60.2%); 55-64 (29.5%); >65 (10.3%)	3.7%***
	UK UK and Canada UK	qualityUKRCTMMAT Score: 4UK and CanadaRCTMMAT Score: 2UKRCTUKRCTUKRCTUSRCT	qualityImage: definition of the second	qualityImage: constraint of the second	qualityImage: constraint of the second	qualityImage: Constraint of the second

Key: RCT = Randomised controlled Trial; MMAT = Mixed Methods Appraisal Tool; n^* = number of participants enrolled at the beginning of the study; All participant trial uptake** = proportion of individuals who enrolled on the trial, with denominator number of people offered the trial. 3.7%*** = proportion of people who took part in the trial run-in placebo, with denominator the number of people who were sent a questionnaire informing them about the trial. 14.4%**** = proportion of people who took part in the trial run-in placebo, with denominator the number of people who returned the questionnaire.

Author	Offered the trial	Took part in the	All participant	Assessed for	Ineligible	Eligible	Consented	Eligible
		trial	uptake	eligibility			to trial	uptake
Hull et al. 2018	3,911	709	18.1%	3,911	2,179	1,732	709	40.9%
Jankoswki et al.	5,726	2,557	44.7%	5,726	2,437	3,289	2,557	77.7%
2018								
Logan et al.	7,081	939	13.3%	17,200	15,767	1,433	939	65.5%
2008								
Rexrode et al.	1,757,247	65,169	3.7%	194,659	129,490	65,169	39,876	61.2%
2000								
(Calculation 1)								
Rexrode et al.	453,787	65,169	14.4%	-	-	-	-	-
2000								
(Calculation 2)								

Aspirin trial uptake calculations for all participant uptake, and eligible participant uptake

Appendix B: Study Two supplementary materials

Appendix B.1: Interview schedule for people with Lynch syndrome

Thank you for agreeing to take part. Just before we start the interview, I'd like to quickly go over some key points about your rights as a participant in this study. It is completely fine if at any point you would like to stop the interview, or if you do not want to answer a question, please just let me know. You can also withdraw from the study at any point and you do not have to provide a reason for why. Just to remind you the interview will be recorded, but anything you say to me today will be kept confidential, and if you are quoted in any of our reports your name will not be used and instead you will be given a pseudonym, which is a fake name. I will also anonymise anything identifiable, like places, you mention as well. After the interview, if you have any further questions about anything we discussed today, please feel free to contact me. I can also provide a debrief sheet at the end with website links with further information on this topic in case you are interested in reading more. Are you happy to continue?

Lynch syndrome qualitative interview questions

As you read on the information sheet, the study is aiming to understand what people with Lynch syndrome think about using aspirin for cancer prevention, including the reasons why people may or may not be willing to use it. First, before we start the interview questions, I would just like to briefly read a section of the guidelines for bowel cancer which have been adopted by NHS England. The guidance says:

"Consider daily aspirin, to be taken for more than 2 years, to prevent colorectal cancer in people with Lynch syndrome."

Another section of the guideline states some of the side-effects of taking aspirin daily:

"Long-term use of aspirin may slightly increase the risk of bleeding."

I will now move onto the interview questions, which will explore your thoughts on using aspirin regularly for cancer prevention. Just a reminder before we start, no prior knowledge on the use of aspirin for cancer prevention is needed or expected of you, we are just interested in hearing your initial thoughts.

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Domains	Interview questions
Knowledge	Had you heard of the use of aspirin for cancer prevention before this interview?
Enviromental context	If yes, where and how did you hear about this?
and resources	If no, how would you find such information? Prompts: from what sources? Internet?
Intentions	A healthcare professional?
Social influences	Who would you like to tell you about this information? Prompt: Any particular
	healthcare professionals, e.g. your GP?
	[If they are aware of aspirin for cancer prevention, then ask:]
	Do you already take aspirin regularly for cancer prevention?
	[If no] Is there any particular reason why you don't take it?
	[If yes] What factors influenced your decision to use aspirin?
	Have you ever been encouraged or discouraged by someone to take aspirin regularly
	for cancer prevention? Prompt: Why was this?
Optimism	In your opinion, do you think using aspirin would be a good way to reduce your risk
Beliefs about	of developing bowel cancer in the future? Prompt: Why do you think this?
consequences	Do you have any concerns about taking aspirin regularly? Prompts: How do you feel
Emotions	about the side-effects?
Enviromental context	What kind of information do you think you would need to help you make a decision
and resources	on whether to take aspirin regularly for cancer prevention?
	Where would you go to get this information? Prompts: What would your first step
	be to obtain this information? Internet? Healthcare professionals?
Beliefs about	I mentioned before one of potential side-effects of regular aspirin use can be
consequences	internal bleeding. There are several risk factors that make a person more likely to
	experience internal bleeding from regular aspirin use. These include:
	- Active or previous peptic ulceration
	- Bleeding disorders
	- Over the age of 65

	- Uncontrolled hypertension
	- Previous history of stroke
	- Abnormal liver or renal function
	- Experience indigestion on aspirin
	If you had any of these risk factors, your doctor may offer you an additional
	medication to reduce your risk of internal bleeding.
	What are your thoughts on taking regular aspirin alongside another medication to
	reduce your risk of bowel cancer?
Skills	If you were interested in taking aspirin for cancer prevention, do you know how you
Beliefs about	would obtain a prescription for daily aspirin? Please describe how you would go
capabilities	about this. Prompts: What would your first step be?
Emotion	How comfortable would you feel about going through this route to get a
Linotion	prescription for aspirin?
Reinforcement	[If they mention they already have prescription/ tried to get prescription for aspirin]
Enviromental context	Have you previously encountered any problems trying to get a prescription for daily
and resources	aspirin? If yes, please describe these problems.
	Is there anything about this experience that makes you more or less likely to take
	aspirin regularly in the future?
Goals	How much of a priority is taking aspirin for cancer prevention to you? Prompts: how
Memory, attention and	high or low a priority is it
decision processes	Are there any other higher priorities? Prompt: Prevention priorities? What are they?

Lynch syndrome brief quantitative questions

Thank you so much for your answers so far. Just before we end the interview, there are several brief demographic questions that I would just like to go through with you. If you do not want to answer one these questions, please let me know and we can skip it.

- 1) What is your age?
- 2) Please describe your gender? Male; Female; Non-binary; Another identity; Prefer not to say.

- How would you describe your ethnicity? Examples include White British, Indian, Mixed White and Black Caribbean
- 4) What country in the UK do you live?
- 5) Year of Lynch syndrome diagnosis?
- 6) Have you previously been diagnosed with cancer?

Debrief

Thank you for all your help with answering my questions. We really appreciate your time and hope that it will be useful in the future when we are trying to support people when making a decision about whether to use aspirin for cancer prevention. Before we end, do you have any questions you would like to ask me?

If you would like more information on the topic of the use of aspirin for cancer prevention, I can email you an information sheet with website links with this further information. If you would like to ask me further questions on the study, please do not hesitate to contact me.

Appendix B.2: Interview schedule for healthcare providers

Thank you for agreeing to take part. Just before we start the interview, I'd like to quickly go over some key points about your rights as a participant in this study. It is completely fine if at any point you would like to stop the interview, or if you do not want to answer a question, please just let me know. You can also withdraw from the study at any point and you do not have to provide a reason for why. Just to remind you the interview will be recorded, but anything you say to me today will be kept confidential, and if you are quoted in any of our reports your name will not be used and instead you will be given a pseudonym, which is a fake name. I will also anonymise anything identifiable, like places, you mention as well. After the interview, if you have any further questions about anything we discussed today, please feel free to contact me. I can also provide a debrief sheet at the end with website links with further information on this topic in case you are interested in reading more. Are you happy to continue?

Healthcare provider interview questions

As you read on the information sheet, the study is aiming to understand what healthcare providers think about the use of aspirin for cancer prevention, including the reasons why people may or may not be willing to recommend it. In the interview, we will go through a number of different scenarios and explore your potential responses to them. Each scenario describes a situation which you may encounter with patients with Lynch syndrome enquiring about the use of aspirin for cancer prevention. I would just like to emphasise before we start that no prior knowledge on the topic of aspirin for cancer prevention is needed or expected. We are just interested in exploring your initial reactions to these scenarios.

General Practitioner (GP) interviews

First, I would just like to ask what your initial thoughts are on the use of regular aspirin for cancer prevention?

Next, I would like to read the National Institute of Clinical Excellence (NICE) 2020 clinical guidelines for colorectal cancer [NG151] which states:

"Consider daily aspirin, to be taken for more than 2 years, to prevent colorectal cancer in people with Lynch syndrome."

There is also a brief section on dosage in the NICE guidelines, which states:

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"The optimal dose of aspirin that balances the benefits of aspirin in preventing colorectal cancer and the potential increased bleeding risk (especially with higher doses) remains unclear. Because of this the committee was not able to recommend a dose... Commonly used doses in current practice are 150mg or 300mg."

I will now ask some interview questions to explore your views and attitudes towards this NICE guideline on daily aspirin for people with Lynch syndrome.

Domains	Interview questions
Knowledge	Had you heard about the use of aspirin for cancer prevention, not just in a Lynch syndrome population, before this interview?
	If yes, where and how did you hear about this?
	Had you heard of the new NICE guideline on daily aspirin for people with Lynch Syndrome before this interview?
	If yes, where and how did you hear about this NICE guideline?
	What does the NICE guideline to 'consider daily aspirin to prevent colorectal cancer in people with Lynch syndrome' mean to you? Prompts: What do you think it is
	asking healthcare professionals to do?
Social/ Professional role and identity	What role do you see primary care playing in the implementation of this guidance on the use of aspirin for people with Lynch syndrome?
Skills	What support do you think you need to implement this guidance in practice?
Reinforcement	Do you have any previous experience of prescribing aspirin for cancer prevention? Is there anything about this experience which makes you more or less likely to prescribe aspirin for cancer prevention in the future?
Optimism Enviromental context and resources	In your opinion, do you think regularly using aspirin is an effective way to reduce a patient with Lynch syndrome's risk of developing colorectal cancer? What further information would you need?

Beliefs about	Do you have any concerns about people taking aspirin regularly? Prompts: How do
consequences	you feel about the side-effects?

Imagine a situation where a patient with Lynch syndrome comes into their 10-minute appointment with you to ask about the use of aspirin for cancer prevention.

Skills	Could you describe to me the first steps you might take in supporting this patient?
Intentions	Prompt: Why would you take these steps?
Beliefs about capabilties	How confident would you feel discussing the use of aspirin for cancer prevention with this patient? Prompt: why is this? What do you think could help you overcome
Enviromental context	these problems?
and resources	Do you feel you have enough resources to support people with Lynch syndrome who are considering the use of aspirin for cancer prevention? Prompt: time, materials, training, support? What other resources do you think are needed?
Goals	Taking into consideration all the other things you could discuss in a typical
Memory, attention and decision processes	consultation with a patient with Lynch syndrome, how important do you think discussing the use of aspirin for cancer prevention is? Prompt: Why do you feel this is more/ less important?
Social influences	How do the people you work with influence your decisions around whether to prescribe aspirin for cancer prevention? Prompt: colleagues in your practice team? Colleagues in secondary care? Clinical commissioning groups? Medicine management groups?

Now I will describe a different scenario where you have received a letter from a clinical geneticist requesting for a patient of yours with Lynch syndrome to be prescribed daily aspirin for cancer prevention. The patient then comes into their GP appointment with you to obtain this prescription.

Skills	Taking the letter into consideration, could you describe to me the first steps you
	might take in supporting this patient? Prompt: Why would you take these steps?

Intentions	How comfortable would you feel prescribing daily aspirin to this patient? Prompt:
Beliefs about capabilties	why is this?
Emotions	
Emotions	How comfortable would you feel prescribing regular aspirin to a patient who does not have Lynch syndrome but is interested in using aspirin for cancer prevention? Prompt: why is this?

Community pharmacist, clinical geneticist, genetic counsellor interviews

First, I would just like to ask what your initial thoughts are on the use of aspirin for cancer prevention?

Next, I would like to read the National Institute of Clinical Excellence (NICE) 2020 clinical guidelines for colorectal cancer [NG151] which states:

"Consider daily aspirin, to be taken for more than 2 years, to prevent colorectal cancer in people with Lynch syndrome."

There is also a brief section on dosage in the NICE guidelines, which states:

"The optimal dose of aspirin that balances the benefits of aspirin in preventing colorectal cancer and the potential increased bleeding risk (especially with higher doses) remains unclear. Because of this the committee was not able to recommend a dose... Commonly used doses in current practice are 150mg or 300mg."

I will now ask some interview questions to explore your views and attitudes towards this NICE guideline on daily aspirin for people with Lynch syndrome.

Domains	Interview questions
Knowledge	Had you heard about the use of aspirin for cancer prevention, not just in a Lynch syndrome population, before this interview? If yes, where and how did you hear about this?

	Had you heard of the new NICE guideline on daily aspirin for people with Lynch
	Syndrome before this interview?
	If yes, where and how did you hear about this NICE guideline?
	What does the NICE guideline to 'consider daily aspirin to prevent colorectal cancer
	in people with Lynch syndrome' mean to you? Prompts: What do you think it is
	asking healthcare professionals to do?
Social/ Professional role	What role do you see [community pharmacists/ clinical geneticists/ genetic
and identity	counsellors] playing in the implementation of this guidance on considering the use
	of daily aspirin for people with Lynch syndrome?
Skills	What support do you think you need to implement this guidance in practice?
Optimism	In your opinion, do you think regularly using aspirin is an effective way to reduce a
Enviromental context and resources	patient with Lynch syndrome's risk of developing colorectal cancer? What further information would you need?
Beliefs about consequences	Do you have any concerns about people taking aspirin regularly? Prompts: How do you feel about the side-effects?

Imagine a situation where a patient with Lynch syndrome comes into an [appointment with you/ into the pharmacy you work at] to ask you about the use of aspirin for cancer prevention.

Skills	Could you describe to me the first steps you might take in supporting this patient?
Intentions	Prompt: Why would you take these steps?
Beliefs about capabilties Enviromental context	How confident would you feel discussing the use of aspirin for cancer prevention with this patient? Prompt: why is this? What do you think could help you overcome these problems?
and resources	Do you feel you have enough resources to support people with Lynch syndrome who are considering the use of aspirin for cancer prevention? Prompt: time, materials, training, support? What other resources do you think are needed?

Social influences	How do the people you work with influence your decisions around whether to recommend aspirin for cancer prevention? Prompts: colleagues in your practice
	team? Colleagues in secondary care? Clinical commissioning groups? Medicine management groups?
Goals Memory, attention and decision processes	Taking into consideration all the other things you could discuss with a patient with Lynch syndrome, how important do you think discussing the use of aspirin for cancer prevention is? Prompt: Why do you feel this is more/ less important?
Emotions	How comfortable would you feel recommending regular aspirin use to a patient who does not have Lynch syndrome but is interested in using aspirin for cancer prevention? Prompt: why is this?

Healthcare provider brief quantitative questions

Thank you so much for your answers so far. Just before we end the interview, there are several brief demographic questions that I would just like to go through with you. If you do not want to answer one these questions, please let me know and we can skip it.

- 1) What is your age?
- 2) How would you describe your gender? Male; Female; Non-binary; Another Identity; Prefer not to say
- How would you describe your ethnicity? (Examples include White British, Indian, Mixed White and Black Caribbean, etc.)
- 4) What country in the UK do you live?
- 5) What is your profession?
- 6) How many years have you worked in your profession?
- 7) Do you know if you have you previously encountered any patients with Lynch syndrome in your work? If so, approximately how often, e.g. Daily, weekly, monthly, once or twice a year?

Debrief

Thank you for all your help with answering my questions. We really appreciate your time and hope that it will be useful in the future when we are trying to support people when making a decision

about whether to use aspirin for cancer prevention. Before we end, do you have any questions you would like to ask me?

If you would like more information on the topic of the use of aspirin for cancer prevention, I can email you an information sheet with website links with this further information. If you would like to ask me further questions on the study, please do not hesitate

Appendix C: Study Three supplementary materials

Appendix C.1: Short survey questions on aspirin use

- 1. Do you ever take aspirin?
 - a. Yes
 - b. No
- 2. Do you take aspirin regularly (i.e. most days or every day)?
 - a. Yes
 - b. No
 - c. N/A do not take aspirin
- 3. What is the main reason you take aspirin?
 - a. Pain relief
 - b. Prevention of cardiovascular disease (i.e. heart and circulatory disease)
 - c. Prevention of cancer
 - d. Other reason, please specify _____
 - e. N/A do not take aspirin
- 4. Prior to completing this survey, were you aware that aspirin could reduce the risk of developing certain types of cancers?
 - a. Yes
 - b. No
- 5. Has your doctor or any other healthcare professional talked to you about how aspirin may lower your risk of developing bowel cancer or any other cancers?
 - a. Yes
 - b. No
- 6. Have you previously been diagnosed with cancer?
 - a. Yes, please specify which cancer(s): _____

- b. No
- 7. How would you describe your gender?
 - a. Male
 - b. Female
 - c. Non-binary
 - d. Different identity
 - e. Prefer not to say
- 8. What is your age?
- 9. How would you describe your ethnicity?
 - a. White English/ Welsh/ Scottish/ Northern Irish/ British
 - b. White Irish
 - c. White Gypsy or Irish Traveller
 - d. Any other White background
 - e. Mixed White and Black Caribbean
 - f. Mixed White and Black African
 - g. Mixed White and Asian
 - h. Any other mixed/ multiple ethnic background
 - i. Asian or Asian British Indian
 - j. Asian or Asian British Pakistani
 - k. Asian or Asian British Bangladeshi
 - I. Asian or Asian British Chinese
 - m. Any other Asian background
 - n. Black or Black British African
 - o. Black or Black British Caribbean
 - p. Any other Black/ African/ Caribbean background
 - q. Arab or Arab British
 - r. Any other ethnic group

10. What is the highest level of educational or professional qualification you have obtained?

- a. GCSE/ O-level/ CSE
- b. Vocational qualifications (e.g. NVQ1+2)
- c. A-Level or equivalent (e.g. NVQ3)
- d. Bachelor's degree or equivalent (e.g. NVQ4)
- e. Masters/ PhD or equivalent
- f. Other qualifications
- g. No formal qualifications

Thank you for taking part in the survey study. If you are interested in taking part further, we are looking for people to take part in a follow-up interview study to explore their thoughts on the use of aspirin for bowel cancer prevention. The interviews will take between 30 to 60 minutes to complete and will be take place either over the telephone, video call or face-to-face, depending upon your preference. You will receive £25 for taking part in the follow-up interview study. You do not need to use aspirin or know anything about this topic to take part.

If you are interested in taking part in the interview study, we will ask you to provide your contact details.

- 11. Are you interested in taking part in the follow-up interview study?
 - a. Yes, please provide your contact details (e.g. email, phone number) and we will contact you further about the study: ______
 - b. No

Appendix C.2: Interview schedule for general public

Thank you for agreeing to take part. Just before we start the interview, I'd like to quickly go over some key points about your rights as a participant in this study. It is completely fine if at any point you would like to stop the interview, or if you do not want to answer a question, please just let me know. You can also withdraw from the study at any point and you do not have to provide a reason for why. Just to remind you the interview will be recorded, but anything you say to me today will be kept confidential, and if you are quoted in any of our reports your name will not be used and instead you will be given a pseudonym, which is a fake name. I will also anonymise anything identifiable, like places, you mention as well. After the interview, if you have any further questions about anything we discussed today, please feel free to contact me. I can also provide a debrief sheet at the end with website links with further information on this topic in case you are interested in reading more. Are you happy to continue?

General public interview questions

As you read on the information sheet, the study is aiming to understand what people think about using aspirin for cancer prevention, including the reasons why people may or may not be willing to use it. Aspirin has previously been found to effectively reduce people's risk of bowel cancer in a healthy population sample. At the moment, aspirin is only officially recommended by the NHS for cancer prevention in people who have a genetic condition that makes them higher risk of developing bowel cancer. There is potential in the future though for this medication to be offered more widely to the general public for the purpose of bowel cancer prevention.

While there is the potential benefit of having a reduced likelihood of developing bowel cancer in the future, there are also side-effects to regular aspirin use. The main side-effect is an increased likelihood of experiencing internal bleeding.

I will now move onto the interview questions, which will explore your thoughts on using aspirin regularly for cancer prevention. Just a reminder before we start, you do not need to know anything about the use of aspirin for cancer prevention to answer these questions. We are just interested in hearing your initial thoughts.

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Domains	Interview questions
Knowledge	Had you heard of the use of aspirin for cancer prevention before this interview?
Enviromental context	If yes, where and how did you hear about this?
and resources	If no, how would you find such information? Prompts: from what sources? Internet?
Intentions	A healthcare professional?
Social influences	Have you ever been encouraged or discouraged by someone to take aspirin regularly
	for cancer prevention? Prompt: Why was this?
Optimism	In your opinion, do you think using aspirin would be a good way to reduce your risk
Beliefs about	of developing bowel cancer in the future? Prompt: Why do you think this?
consequences	Do you have any concerns about taking aspirin regularly? Prompt: How do you feel
Emotions	about the side-effects?
Enviromental context	What kind of information do you think you would need to help you make a decision
and resources	on whether to take aspirin regularly for cancer prevention?
Skills	Where would you go to get this information? Prompts: What would your first step
	be to obtain this information? Internet? Healthcare professionals?
Beliefs about capabilities	[If they do take aspirin for cancer prevention] Have you previously encountered any
cupuonnes	problems with trying to get further information on the use of aspirin for cancer
Reinforcement	prevention? If yes, please describe these problems.
	[If yes to above question] Is there anything about this experience that makes you
	more or less likely to try and take aspirin regularly in the future?
Beliefs about	I mentioned before one of potential side-effects of regular aspirin use can be
consequences	internal bleeding. There are several risk factors that make a person more likely to
	experience internal bleeding from regular aspirin use. These include:
	- Active or previous stomach ulcers
	- Bleeding disorders
	- Being over the age of 65

	 Uncontrolled hypertension Previous history of stroke Abnormal liver or renal function Experience indigestion on aspirin
	If you had any of these risk factors, your doctor may offer you an additional medication to reduce your risk of internal bleeding.
	What are your thoughts on taking regular aspirin alongside another medication to reduce your risk of bowel cancer?
Goals Memory, attention and	How much of a priority is taking aspirin for cancer prevention to you? Prompts: how high or low a priority is it?
decision processes	Are there any other higher priorities? Prompt: Prevention priorities? What are they?

General public brief quantitative questions

Thank you so much for your answers so far. Just before we end the interview, there are several brief demographic questions that I would just like to go through with you. If you do not want to answer one of these questions, please just let me know and we can skip it.

- 7) What is your age?
- 8) Please describe your gender? Male; Female; Non-binary; Another identity; Prefer not to say.
- How would you describe your ethnicity? Examples include White British, Indian, Mixed White and Black Caribbean
- 10) What country in the UK do you live?
- 11) Have you previously been diagnosed with cancer?

Debrief

Thank you for all your help with answering my questions. We really appreciate your time and hope that it will be useful in the future when we are trying to support people when making a decision about whether to use aspirin for cancer prevention. Before we end, do you have any questions you would like to ask me?

If you would like more information on the use of aspirin for cancer prevention, I can email you an information sheet with links to website with further information on this topic. If you would like to ask me further questions on the study, please do not hesitate to contact me.

Appendix D: Study Four supplementary materials

Appendix D.1: CONSORT 2010 Checklist

Section/Topic	ltem No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	111
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	112
Introduction			
Background and	2a	Scientific background and explanation of rationale	113
objectives	2b	Specific objectives or hypotheses	113
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	114
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A – no changes were made
Participants	4a	Eligibility criteria for participants	113-114
	4b	Settings and locations where the data were collected	113-114
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	114 and Appendix D.2

Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	115-116
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A - no changes were made
Sample size	7a	How sample size was determined	115
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A – no interim analyses or stopping guidelines
Randomisation:			
Sequence	8a	Method used to generate the random allocation sequence	114
generation	generation 8b Type of randomisation; details of any restriction (such as blocking and block size)		114
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	114
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	113-114
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A – no blinding was done, see page 114

	11b	If relevant, description of the similarity of interventions	N/A – no blinding was done
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	116
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	116
Results Participant flow (a diagram is strongly	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	116 and Appendix D.4
recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	116 and Appendix D.4
Recruitment	14a	Dates defining the periods of recruitment and follow-up	116
	14b	Why the trial ended or was stopped	116 and Appendix D.4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	117 and Appendix D.5
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	118-123 and Appendices D.6-9
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	119-122 and Appendices D.6-8
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A - Primary and secondary outcomes were not

			binary. Odds Ratios only have been provided for exploratory research findings.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	113, 118, 122- 123, and Appendix D.9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A – online survey
Discussion Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	124
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	124-125
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	124-125
Other information			
Registration	23	Registration number and name of trial registry	114
Protocol	24	Where the full trial protocol can be accessed, if available	114
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	126

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Appendix D.2: Case studies/vignettes describing a hypothetical patient with Lynch syndrome who is interested in using aspirin for colorectal cancer prevention

	NICE guidance provided	NICE guidance not provided
	Peter is a 45-year-old man with Lynch syndrome, a genetic condition which increases the lifetime risk of colorectal cancer, and several other cancers such as stomach, pancreatic, and kidney. Dr Taylor, a clinical geneticist, has recommended daily aspirin for colorectal cancer prevention	Peter is a 45-year-old man with Lynch syndrome, a genetic condition which increases the lifetime risk of colorectal cancer, and several other cancers such as stomach, pancreatic, and kidney. Dr Taylor, a clinical geneticist, has recommended daily aspirin for colorectal cancer prevention to Peter.
	to Peter.	In making this recommendation, Dr Taylor has considered evidence from the CAPP2 trial, which randomly assigned over
	This recommendation was based on the National Institute of Health and Care Excellence (NICE) guidance 'Colorectal cancer (NG151)': 'Consider daily aspirin, to be taken for more than 2 years, to prevent colorectal cancer in people with Lynch syndrome'.	800 people with Lynch syndrome to either 600mg daily aspirin or no treatment. After 10 years, people who took aspirin for 2 years had a significantly reduced risk of developing colorectal cancer compared with the control group (hazard ratio of 0.65, 95% CI: 0.43–0.97, in intention-to-treat analysis). There is currently an ongoing dose non-inferiority trial (CaPP3) that is
	In making this recommendation, Dr Taylor has considered evidence from the CAPP2 trial, which randomly assigned over 800 people with Lynch syndrome to either 600mg daily aspirin	comparing the effectiveness of aspirin at different doses (100mg, 300mg or 600mg) for colorectal cancer prevention.
CAPP2 trial results provided, and risk/ benefit information not provided	or no treatment. After 10 years, people who took aspirin for 2 years had a significantly reduced risk of developing colorectal cancer compared with the control group (hazard ratio of 0.65, 95% CI: 0.43–0.97, in intention-to-treat analysis). There is currently an ongoing dose non-inferiority trial (CaPP3) that is	Dr Taylor has discussed the potential harms and benefits of taking aspirin with Peter, and he has expressed an interest in taking aspirin. Peter has no contraindications and is taking no other medications. Dr Taylor requests that you write the first prescription and continue to act as the main prescriber.

	NICE guidance provided	NICE guidance not provided
	comparing the effectiveness of aspirin at different doses (100mg, 300mg or 600mg) for colorectal cancer prevention.	Commonly used aspirin doses in current practice are 150mg or 300mg. Aspirin is not licensed for the prevention of cancer, and therefore prescriptions are made off-label.
	Dr Taylor has discussed the potential harms and benefits of taking aspirin with Peter, and he has expressed an interest in taking aspirin. Peter has no contraindications and is taking no other medications. Dr Taylor requests that you write the first prescription and continue to act as the main prescriber. Commonly used aspirin doses in current practice are 150mg or 300mg. Aspirin is not licensed for the prevention of cancer, and therefore prescriptions are made off-label.	
	Peter is a 45-year-old man with Lynch syndrome, a genetic condition which increases the lifetime risk of colorectal cancer, and several other cancers such as stomach, pancreatic, and kidney. Dr Taylor, a clinical geneticist, has recommended daily aspirin for colorectal cancer prevention to Peter.	Peter is a 45-year-old man with Lynch syndrome, a genetic condition which increases the lifetime risk of colorectal cancer, and several other cancers such as stomach, pancreatic, and kidney. Dr Taylor, a clinical geneticist, has recommended daily aspirin for colorectal cancer prevention to Peter.
Risk/ benefit information provided, and CAPP2 trial results not provided	This recommendation was based on the National Institute of Health and Care Excellence (NICE) guidance 'Colorectal cancer (NG151)': 'Consider daily aspirin, to be taken for more than 2 years, to prevent colorectal cancer in people with Lynch syndrome'.	On average, for every 100 people with Lynch syndrome who do not take aspirin, 13 people will get colorectal cancer over 10 years. Among those taking aspirin for at least two years, an estimated 7 people with Lynch syndrome will get colorectal cancer over 10 years. Regular aspirin use has known adverse effects. Between 1 and 10 people in every 100 taking aspirin will experience indigestion, bruising more easily and prolonged

	NICE guidance provided	NICE guidance not provided
	On average, for every 100 people with Lynch syndrome who do not take aspirin, 13 people will get colorectal cancer over 10 years. Among those taking aspirin for at least two years, an estimated 7 people with Lynch syndrome will get colorectal cancer over 10 years. Regular aspirin use has known adverse effects. Between 1 and 10 people in every 100 taking aspirin will experience indigestion, bruising more easily and prolonged bleeding. More rarely, aspirin can cause gastrointestinal haemorrhage, affecting between 1 and 10 people in 10,000. Dr Taylor has discussed the potential harms and benefits of taking aspirin. Peter has no contraindications and is taking no other medications. Dr Taylor requests that you write the first prescription and continue to act as the main prescriber. Commonly used aspirin doses in current practice are 150mg or 300mg. Aspirin is not licensed for the prevention of cancer, and therefore prescriptions are made off-label.	bleeding. More rarely, aspirin can cause gastrointestinal haemorrhage, affecting between 1 and 10 people in 10,000. Dr Taylor has discussed the potential harms and benefits of taking aspirin with Peter, and he has expressed an interest in taking aspirin. Peter has no contraindications and is taking no other medications. Dr Taylor requests that you write the first prescription and continue to act as the main prescriber. Commonly used aspirin doses in current practice are 150mg or 300mg. Aspirin is not licensed for the prevention of cancer, and therefore prescriptions are made off-label.
Risk/ benefit information provided, and CAPP2 trial results provided	Peter is a 45-year-old man with Lynch syndrome, a genetic condition which increases the lifetime risk of colorectal cancer, and several other cancers such as stomach, pancreatic, and kidney. Dr Taylor, a clinical geneticist, has	Peter is a 45-year-old man with Lynch syndrome, a genetic condition which increases the lifetime risk of colorectal cancer, and several other cancers such as stomach, pancreatic, and

NICE guidance provided	NICE guidance not provided
recommended daily aspirin for colorectal cancer prevention to Peter.	kidney. Dr Taylor, a clinical geneticist, has recommended daily aspirin for colorectal cancer prevention to Peter.
This recommendation was based on the National Institute of Health and Care Excellence (NICE) guidance 'Colorectal cancer (NG151)': 'Consider daily aspirin, to be taken for more than 2 years, to prevent colorectal cancer in people with Lynch syndrome'.	In making this recommendation, Dr Taylor has considered evidence from the CAPP2 trial, which randomly assigned over 800 people with Lynch syndrome to either 600mg daily aspirin or no treatment. After 10 years, people who took aspirin for 2 years had a significantly reduced risk of developing colorectal
In making this recommendation, Dr Taylor has considered evidence from the CAPP2 trial, which randomly assigned over 800 people with Lynch syndrome to either 600mg daily aspirin or no treatment. After 10 years, people who took aspirin for 2 years had a significantly reduced risk of developing colorectal	cancer compared with the control group (hazard ratio of 0.65, 95% CI: 0.43–0.97, in intention-to-treat analysis). There is currently an ongoing dose non-inferiority trial (CaPP3) that is comparing the effectiveness of aspirin at different doses (100mg, 300mg or 600mg) for colorectal cancer prevention.
cancer compared with the control group (hazard ratio of 0.65, 95% CI: 0.43–0.97, in intention-to-treat analysis). There is currently an ongoing dose non-inferiority trial (CaPP3) that is comparing the effectiveness of aspirin at different doses (100mg, 300mg or 600mg) for colorectal cancer prevention.	On average, for every 100 people with Lynch syndrome who do not take aspirin, 13 people will get colorectal cancer over 10 years. Among those taking aspirin for at least two years, an estimated 7 people with Lynch syndrome will get colorectal cancer over 10 years. Regular aspirin use has known adverse effects. Between 1 and 10 people in every 100 taking aspirin
On average, for every 100 people with Lynch syndrome who do not take aspirin, 13 people will get colorectal cancer over 10 years. Among those taking aspirin for at least two years, an estimated 7 people with Lynch syndrome will get colorectal	will experience indigestion, bruising more easily and prolonged bleeding. More rarely, aspirin can cause gastrointestinal haemorrhage, affecting between 1 and 10 people in 10,000.

cancer over 10 years. Regular aspirin use has known adverse

	NICE guidance provided	NICE guidance not provided
	effects. Between 1 and 10 people in every 100 taking aspirin will experience indigestion, bruising more easily and prolonged bleeding. More rarely, aspirin can cause gastrointestinal haemorrhage, affecting between 1 and 10 people in 10,000. Dr Taylor has discussed the potential harms and benefits of taking aspirin with Peter, and he has expressed an interest in taking aspirin. Peter has no contraindications and is taking no other medications. Dr Taylor requests that you write the first prescription and continue to act as the main prescriber. Commonly used aspirin doses in current practice are 150mg or 300mg. Aspirin is not licensed for the prevention of cancer, and therefore prescriptions are made off-label.	Dr Taylor has discussed the potential harms and benefits of taking aspirin with Peter, and he has expressed an interest in taking aspirin. Peter has no contraindications and is taking no other medications. Dr Taylor requests that you write the first prescription and continue to act as the main prescriber. Commonly used aspirin doses in current practice are 150mg or 300mg. Aspirin is not licensed for the prevention of cancer, and therefore prescriptions are made off-label.
CAPP2 trial results not provided, and risk/ benefit information not provided	Peter is a 45-year-old man with Lynch syndrome, a genetic condition which increases the lifetime risk of colorectal cancer, and several other cancers such as stomach, pancreatic, and kidney. Dr Taylor, a clinical geneticist, has recommended daily aspirin for colorectal cancer prevention to Peter. This recommendation was based on the National Institute of Health and Care Excellence (NICE) guidance 'Colorectal cancer	Peter is a 45-year-old man with Lynch syndrome, a genetic condition which increases the lifetime risk of colorectal cancer, and several other cancers such as stomach, pancreatic, and kidney. Dr Taylor, a clinical geneticist, has recommended daily aspirin for colorectal cancer prevention to Peter. Dr Taylor has discussed the potential harms and benefits of taking aspirin with Peter, and he has expressed an interest in taking aspirin. Peter has no contraindications and is taking no

NICE guidance provided	NICE guidance not provided
 (NG151)': 'Consider daily aspirin, to be taken for more than 2 years, to prevent colorectal cancer in people with Lynch syndrome'. Dr Taylor has discussed the potential harms and benefits of taking aspirin with Peter, and he has expressed an interest in taking aspirin. Peter has no contraindications and is taking no other medications. Dr Taylor requests that you write the first prescription and continue to act as the main prescriber. Commonly used aspirin doses in current practice are 150mg or 300mg. Aspirin is not licensed for the prevention of cancer, and therefore prescriptions are made off-label. 	other medications. Dr Taylor requests that you write the first prescription and continue to act as the main prescriber. Commonly used aspirin doses in current practice are 150mg or 300mg. Aspirin is not licensed for the prevention of cancer, and therefore prescriptions are made off-label.

Appendix D.3: GP survey questions

Before we start, we are interested in some basic information about you and your practice to ensure the study is relevant for you.

Screening questions

- 1) What is your medical specialty?
 - a. GP
 - b. Endocrinology (Terminate)
 - c. Pulmonology (Terminate)
 - d. Oncology (Terminate)
 - e. Other (Terminate)
- 2) Are you currently practising as a GP?
 - a. Yes
 - b. No (Terminate)
- 3) In which country are you currently practising?
 - a. England
 - b. Wales
 - c. Scotland (Terminate)
 - d. Northern Ireland (Terminate)

Demographic questions

- 12) How would you describe your gender?
 - a. Male
 - b. Female
 - c. Non-binary
 - d. Another Identity
 - e. Prefer not to say
- 13) GP status
 - a. GP partner
 - b. Salaried/locum GP
 - c. GP retainers
 - d. GP specialist trainee
 - e. Other
- 14) Number of years you have been qualified as a doctor?

- a. 0-4
- b. 5-9
- c. 10-14
- d. 15-19
- e. 20+
- 15) Specialisms
 - a. Cancer
 - b. Preventive medicine
 - c. Family history
 - d. Genetics
 - e. Other
 - f. N/A no speciality

Use of aspirin for cancer preventive therapy

Background

We are interested in the use of aspirin for preventive therapy (i.e. chemoprevention) in the NHS. Preventive therapy is the use of medication to lower the risk of a person developing cancer. Aspirin is one form of preventive therapy commonly used for colorectal cancer prevention. In the UK, aspirin is recommended to people with Lynch syndrome, which is a genetic condition that makes a person at higher risk of developing colorectal cancer and a spectrum of other cancers (e.g., endometrial, stomach).

Prescribing aspirin

There is no generally accepted care pathway in England and Wales for prescribing aspirin to a person with Lynch syndrome for the prevention of colorectal cancer. Aspirin will usually be discussed with patients in secondary or tertiary care, and interested and eligible patients will typically be referred back to primary care. Aspirin is not licensed for the prevention of cancer, and therefore prescriptions are made off-label.

For the first part of the survey, we will show you a case study describing a hypothetical patient with Lynch syndrome. After you have read the case study, we will ask you some follow-up questions. Please take your time to read the case study carefully before answering the questions.

[Insert vignette here]

Now we will ask you several follow-up questions in regard to the case study.

- 1) Would you be willing to write the prescription for Peter?
 - a. Not at all willing
 - b. Probably not willing
 - c. Probably willing
 - d. Definitely willing
- 2) How comfortable would you feel discussing the possible benefits and harms of aspirin with Peter?
 - a. Very uncomfortable
 - b. Quite uncomfortable
 - c. Quite comfortable
 - d. Very comfortable
- 3) A number of factors have been identified in interviews with GPs that could influence whether they would be willing to prescribe aspirin. How much do you **agree** or **disagree** that the following factors affected your decision of whether or not to write a prescription for Peter?

	Strongly disagree	Disagree	Agree	Strongly agree
The benefits of aspirin				
The harms of aspirin				
The dose of aspirin you are being asked to consider prescribing				
Prescribing off-label because aspirin is not licensed for cancer prevention				
The clinical geneticist recommending to you to prescribe aspirin				
The patient's interest in using aspirin				
The patient's awareness of the possible harms and benefits				
Feeling you would want to speak with someone working in genetics (e.g. clinical geneticist, genetic counsellor) before prescribing				

Strongly disagree	Disagree	Agree	Strongly agree

Feeling you would want to speak with a specialist in colorectal cancer (e.g. gastroenterologist, colorectal surgeon, oncologist) before prescribing

Feeling you would want to speak with another GP before prescribing

The patient's age

Your confidence in your knowledge of aspirin in general

Your confidence in your knowledge of aspirin as a form of cancer preventive therapy

The prescribing budget in your general practice

Are there any other factors not listed here that you believe would influence your decision making? (Please specify)

If you do not have any further comments, please type 'n/a'

Thank you for taking the time to read and answer questions on the hypothetical case study. For the second part of the survey, we have supplied some information below for you to read, with some follow-up questions. Please take your time to read this information.

Aspirin: The National Institute of Health and Care Excellence (NICE) guidance

In 2020, NICE released a recommendation (NG151) to consider daily aspirin for a minimum of 2 years to prevent colorectal cancer in people with Lynch syndrome. The NICE committee did not recommend a dose, as the optimal dose of aspirin that balances the benefits of preventing colorectal cancer and the potential increased risk of bleeding (especially with higher doses) remains unclear. NICE stated that 150-300mg is commonly used in clinical practice.

- 1) Has a patient with Lynch syndrome (also termed 'Hereditary Nonpolyposis Colorectal Cancer [HNPCC]) ever consulted you? [If no, skip to question 4]
 - a. Yes
 - b. No

- c. Unsure
- 2) Have you ever discussed the use of aspirin for colorectal cancer prevention with a patient with Lynch syndrome?
 - a. Yes
 - b. No
 - c. Unsure
- 3) Have you ever prescribed aspirin for colorectal cancer prevention for a patient with Lynch syndrome?
 - a. Yes
 - b. No
 - c. Unsure
- 4) Before today, were you aware that aspirin can be used to reduce the risk of colorectal cancer in people with Lynch syndrome? [If no, skip to question 7]
 - a. Yes
 - b. No
- 5) Before today, were you aware of the NICE clinical guideline (NG151) outlining recommendations regarding the use of aspirin for colorectal cancer prevention for people with Lynch syndrome?
 - a. Yes
 - b. No
- 6) How did you first become aware that aspirin can be used to reduce the risk of colorectal cancer in people with Lynch syndrome? Please tick all that apply.

Tick all that apply

Previously raised by a patient

Training days/educational meetings

Charities

Academic journals

GP magazines, for example, Pulse

Informal discussion with colleagues

National media

Tick all that apply

Local guidelines

National guidelines (for example, NICE or national equivalent)

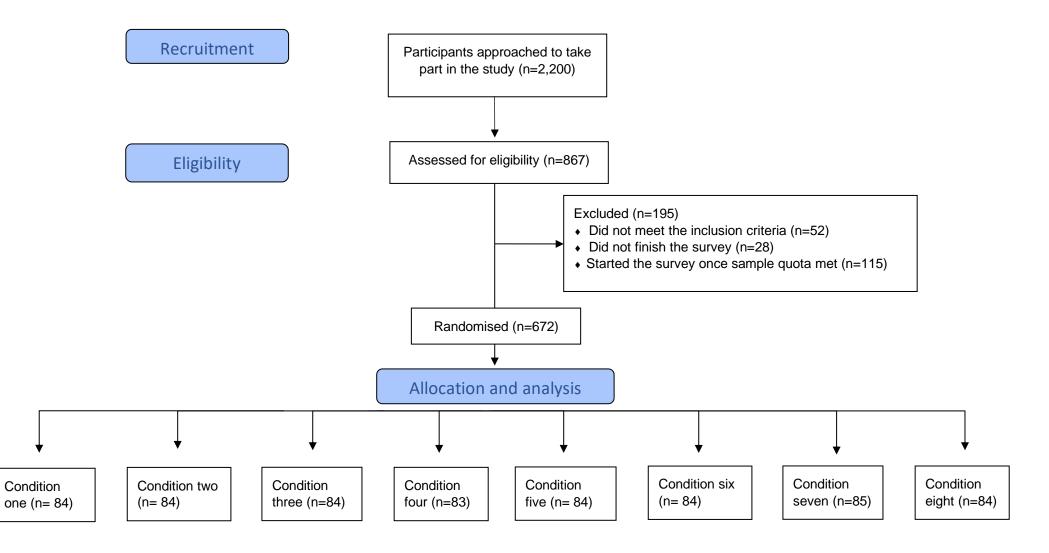
Practice meetings

Other (please specify)

Unsure

7) Do you have any additional comments regarding the prescription of aspirin for people with Lynch syndrome?

Appendix D.4: Adapted CONSORT Flow Diagram showing the numbers of participants who were randomly assigned, received intended the intervention, and were analysed for the outcomes.



r	ographic and professional characteristics of the GP sample across the eight conditions (<i>n</i> = 672)							
	Condition one n (%)	Condition two <i>n</i> (%)	Condition three <i>n</i> (%)	Condition four <i>n</i> (%)	Condition five n (%)	Condition six n (%)	Condition seven <i>n</i> (%)	
	81 (96.4%)	83 (98.8%)	83 (98.8%)	76 (91.6%)	84 (100.0%)	79 (94.0%)	83 (97.6%)	
	3 (3.6%)	1 (1.2%)	1 (1.2%)	7 (8.4%)	0 (0.0%)	5 (6.0%)	2 (2.4%)	
	54 (64.3%)	43 (51.2%)	45 (53.6%)	49 (59.0%)	51 (60.7%)	41 (48.8%)	44 (51.8%)	

Condition

eight *n* (%)

Appendix D.5: Demographic and p , 72)

Country								
England	81 (96.4%)	83 (98.8%)	83 (98.8%)	76 (91.6%)	84 (100.0%)	79 (94.0%)	83 (97.6%)	82 (97.6%)
Wales	3 (3.6%)	1 (1.2%)	1 (1.2%)	7 (8.4%)	0 (0.0%)	5 (6.0%)	2 (2.4%)	2 (2.4%)
Gender								
Female	54 (64.3%)	43 (51.2%)	45 (53.6%)	49 (59.0%)	51 (60.7%)	41 (48.8%)	44 (51.8%)	46 (54.8%)
Male	28 (33.3%)	40 (47.6%)	36 (42.9%)	33 (39.8%)	32 (38.1%)	43 (51.2%)	41 (48.2%)	37 (44.0%)
Non-binary	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Another identity	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prefer not to say	1 (1.2%)	1 (1.2%)	2 (2.4%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
GP status								
Salaried/locum GP	54 (64.3%)	45 (53.6%)	45 (53.6%)	47 (56.6%)	52 (61.9%)	47 (56.0%)	48 (56.5%)	51 (60.7%)
GP partner	24 (28.6%)	34 (40.5%)	33 (39.3%)	28 (33.7%)	26 (31.0%)	33 (39.3%)	28 (32.9%)	27 (32.1%)
GP specialist	5 (6.0%)	4 (4.8%)	5 (6.0%)	8 (9.6%)	5 (6.0%)	3 (3.6%)	8 (9.4%)	6 (7.1%)
trainee								
GP retainers	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)
Years qualified								
0-4 years	3 (3.6%)	0 (0.0%)	3 (3.6%)	7 (8.4%)	3 (3.6%)	2 (2.4%)	3 (3.5%)	3 (3.6%)
5-9 years	28 (33.3%)	13 (15.4%)	18 (21.5%)	19 (22.9%)	21 (25.0%)	11 (13.1%)	19 (22.4%)	22 (26.2%)
10-14 years	21 (25.0%)	24 (28.6%)	22 (26.2%)	22 (26.5%)	18 (21.4%)	28 (33.3%)	20 (23.5%)	19 (22.6%)
15-19 years	8 (9.5%)	23 (27.4%)	18 (21.4%)	15 (18.1%)	19 (22.6%)	21 (25.0%)	19 (22.4%)	20 (23.8%)
20+ years	24 (28.6%)	24 (28.6%)	23 (27.4%)	20 (24.1%)	23 (27.4%)	22 (26.2%)	24 (28.2%)	20 (23.8%)
Specialisms								

Cancer	5 (6.0%)	4 (4.8%)	5 (6.0%)	4 (4.8%)	5 (6.0%)	6 (7.1%)	6 (7.1%)	2 (2.4%)
Family history	2 (2.4%)	4 (4.8%)	1 (1.2%)	4 (4.8%)	5 (6.0%)	4 (4.8%)	2 (2.4%)	6 (7.1%)
Genetics	1 (1.2%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Preventive	14 (16.7%)	8 (9.5%)	11 (13.1%)	9 (10.8%)	7 (8.3%)	14 (16.7%)	13 (15.3%)	11 (13.1%)
medicine								
Other	18 (21.4%)	20 (23.8%)	20 (23.8%)	19 (22.9%)	18 (21.4%)	13 (15.5%)	13 (15.3%)	11 (13.1%)
N/A - no speciality	44 (52.4%)	48 (57.1%)	46 (54.8%)	47 (56.6%)	48 (57.1%)	47 (56.0%)	51 (60.0%)	53 (63.1%)
Previous								
experience								
Consulted a	Yes: 29	Yes: 36	Yes: 41	Yes: 38	Yes: 47	Yes: 40	Yes: 39	Yes: 41
patient with Lynch	(34.5%)	(42.9%)	(48.8%)	(45.8%)	(56.0%)	(47.6%)	(45.9%)	(48.8%)
syndrome	Unsure: 15	Unsure: 13	Unsure: 10	Unsure: 17	Unsure: 9	Unsure: 16	Unsure: 20	Unsure: 12
	(17.9%)	(15.5%)	(11.9%)	(20.5%)	(10.7%)	(19.0%)	(23.5%)	(14.3%)
Discussed aspirin	Yes: 2 (2.4%)	Yes: 10	Yes: 11	Yes: 4 (4.8%)	Yes: 6 (7.1%)	Yes: 10	Yes: 10	Yes: 8 (9.5%)
with a patient		(11.9%)	(13.1%)			(11.9%)	(11.8%)	
with Lynch	Unsure: 6	Unsure: 3	Unsure: 2	Unsure: 1	Unsure: 4	Unsure: 1	Unsure: 7	Unsure: 4
syndrome	(7.1%)	(3.6%)	(2.4%)	(1.2%)	(4.8%)	(1.2%)	(8.2%)	(4.8%)
Prescribed aspirin	Yes: 4 (4.8%)	Yes: 11	Yes: 12	Yes: 6 (7.2%)	Yes: 10	Yes: 9 (10.7%)	Yes: 10	Yes: 11
for a patient with		(13.1%)	(14.3%)		(11.9%)		(11.8%)	(13.1%)
Lynch syndrome	Unsure: 7	Unsure: 7	Unsure: 4	Unsure: 4	Unsure: 4	Unsure: 4	Unsure: 7	Unsure: 3
	(8.3%)	(8.3%)	(4.8%)	(4.8%)	(4.8%)	(4.8%)	(8.2%)	(3.6%)
Awareness								
Aware of aspirin	34 (40.5%)	40 (47.6%)	41 (48.8%)	39 (47.0%)	40 (47.6%)	33 (39.3%)	42 (49.4%)	31 (36.9%)
in Lynch								
syndrome								
Aware of the NICE	12 (14.3%)	19 (22.6%)	14 (16.7%)	15 (18.1%)	15 (17.9%)	11 (13.1%)	16 (18.8%)	15 (17.9%)
guidance NG151								

Appendix D.6: ANOVAs to investigate the main effects and interactions of the three information components on willingness to prescribe aspirin, and comfort discussing the harms and benefits of aspirin (n = 672)

	-	Willingness to prescribeaspirinF valuep value		cussing aspirin			
	F value			<i>p</i> value			
Three components				,			
NICE guidance	0.012	0.914	0.623	0.430			
CAPP2 results	0.742	0.389	0.088	0.767			
Risks/ benefits	>0.000	0.998	0.009	0.926			
Interactions	Interactions						
NICE guidance and Risks/	1.671	0.197	0.995	0.319			
benefit							
CAPP2 results and Risks/	0.297	0.586	0.092	0.762			
benefit							
NICE guidance and CAPP2	0.044	0.834	1.435	0.231			
results							
NICE guidance and Risks/	0.289	0.591	>0.000	0.999			
benefit and CAPP2 results							

Appendix D.7: Comfort discussing the harms and benefits of aspirin among GPs across the three information components (n = 672)

	NICE guidance	CAPP2 results	Risks/ benefits	
	n (%)	n (%)	n (%)	
Very comfortable	79 (52.7%)	72 (48.0%)	75 (50.0%)	
Quite comfortable	179 (49.6%)	188 (52.1%)	182 (50.4%)	
Quite uncomfortable	62 (47.7%)	62 (47.7%)	63 (48.5%)	
Very uncomfortable	15 (48.4%)	14 (45.2%)	17 (54.8%)	

Appendix D.8: GPs' comfort discussing the harms and benefits of aspirin by participant

Comfortable discussing aspirin n (%) OR (95% CI) p value Country 1.06 (0.36-2.71) England 496 (76.2%) 0.915 Wales 15 (71.4%) Ref Ref Gender Female 276 (74.0%) Ref Ref Male 231 (79.7%) 1.31 (0.88-1.98) 0.184 Another identity* 0 (0.0%) 0.991 -Non-binary^{*} 1 (100.0%) 0.993 _ Prefer not to say 3 (42.9%) 0.21 (0.04-1.07) 0.062 **GP** status Salaried/locum GP 296 (76.1%) 1.31 (0.86-1.99) 0.202 GP partner 175 (75.1%) Ref Ref GP retainers* 3 (100.0%) 0.986 -GP specialist trainee 34 (77.3%) 1.45 (0.62-3.61) 0.404 Other* 0.986 3 (100.0%) -Years qualified 0-4 years 16 (66.7%) Ref Ref 120 (79.5%) 0.220 5-9 years 1.84 (0.67-4.78) 10-14 years 125 (71.8%) 1.26 (0.47-3.19) 0.630 15-19 years 108 (75.5%) 1.47 (0.53-3.82) 0.438 20+ years 142 (78.9%) 1.59 (0.58-4.12) 0.351 Specialism Cancer 32 (86.5%) 2.00 (0.78-6.2) 0.180 Family history 18 (64.3%) 0.53 (0.23-1.27) 0.138 Genetics* 3 (75.0%) _ 0.920 Preventive medicine 67 (77.0%) 0.99 (0.56-1.81) 0.972 Other 103 (78.0%) 1.10 (0.68-1.83) 0.700 N/A – no speciality 288 (75.0%) Ref Ref

characteristics, previous experience, and awareness (n = 672)

Previous experience			
Consulted a patient with Lynch			
syndrome			
Consulted – yes	243 (78.1%)	1.08 (0.70-1.67)	0.727
Consulted – unsure	85 (75.9%)	0.89 (0.51-1.58)	0.682
Consulted – no	183 (73.5%)	Ref	Ref
Discussed aspirin with a patient with			
Lynch syndrome			
Discussed aspirin - yes	52 (85.2%)	1.09 (0.37-3.36)	0.875
Discussed aspirin - unsure	23 (82.1%)	0.73 (0.20-2.88)	0.635
Discussed aspirin – no	436 (74.8%)	Ref	Ref
Prescribed aspirin to a patient with			
Lynch syndrome			
Prescribed aspirin - yes	61 (83.6%)	1.12 (0.43-3.08)	0.823
Prescribed aspirin - unsure	37 (92.5%)	6.30 (1.61-36.67)	0.019
Prescribed aspirin - no	413 (73.9%)	Ref	Ref
Awareness			
Prior awareness of aspirin in Lynch			
syndrome population			
Yes	243 (81.0%)	1.68 (1.06-2.72)	0.031
No	268 (72.0%)	Ref	Ref
Prior awareness of NICE guidance			
NG151			
Yes	94 (80.3%)	0.78 (0.41-1.47)	0.436
No	417 (75.1%)	Ref	Ref

* OR (95% CI) not reported due to insufficient cases.

Appendix D.9: Additional factors listed as influencing decision-making among GPs

unwilling to prescribe (*n* = 36)

	n
Clinical geneticist should initiate the first prescription	16
Patient should acquire aspirin from the pharmacy	10
Prefer a shared care agreement/ protocol	5
Patient's contraindications	3
Patient's comorbidities	3
Local prescribing protocols	2
Further long-term data on risk/benefit of aspirin	2
Time for the discussion with the patient	1
Does not trust the specialist to have fully discussed harms and benefits of aspirin with the patient	1
Prefer to prescribe aspirin at a lower dose (e.g. 75mg)	1