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Diet quality and colorectal tumor risk in persons with Lynch syndrome

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ABSTRACT

Background: Persons with Lynch syndrome (LS) have an increased risk of developing colorectal tumors (CRTs). Adherence to diet quality indices associated with colorectal cancer (CRC) risk in the general population has not been studied before in LS.

Methods: Dietary habits of 490 participants with LS from a prospective cohort study was collected using a food frequency questionnaire. The Dutch Healthy Diet index 2015 (DHD15-index) and Dietary Approaches to Stop Hypertension (DASH) were used to score food-based diet quality. Diet quality scores were divided into tertiles where a higher tertile reflects a higher diet quality. Multivariable Cox proportional hazard regression models were used to estimate the association between the DHD15-index, DASH score and CRT risk.

Results: During a median follow-up time of 53.4 months, 210 participants (42.9%) developed CRTs. The DHD-index and DASH score were not associated with CRT risk; hazard ratios for highest vs. lowest tertile were 1.00 (95% Confidence Interval (CI): 0.67-1.48) and 1.11 (95% CI: 0.74-1.69), respectively. No linear trends across the DHD-index and DASH score tertiles were observed (P-trend = 0.97 and 0.83 respectively).

Conclusion: In contrast to observations in the general population, no evidence for an association between the food-based DHD15-index or DASH score and CRT risk was observed in persons with LS. Further studies are needed investigating the association between diet quality and mechanisms leading to the development of LS-associated tumors.

1. Introduction

It is estimated that Lynch syndrome (LS) was responsible for more than 50,000 of the 1.8 million colorectal cancer (CRC) cases in 2018 globally [1,2]. This dominantly inherited syndrome is caused by pathogenic variants in genes responsible for DNA mismatch repair (MMR), i.e. *MLH1, MSH2, MSH6* or *PMS2* [3,4], or in the *EPCAM* gene, leading to silencing of the *MSH2* gene [5]. Depending on the mutated gene this results in a lifetime risk of 15-79% of developing CRC [6–11]. Moreover, 70% of the persons with LS develop colorectal adenomas, the precursor lesion to most CRCs [12], before the age of 60 years [13].

CRC risk for persons with LS differs by geographic region and within LS-affected families [14,15]. These differences suggest that CRC development might be modified by factors such as lifestyle and diet. Our group previously showed an inverse association between the consumption of fruit and fiber and the risk of developing colorectal tumors (CRTs), i.e. both colorectal adenoma and CRC, in persons with LS [16]. Moreover, Dashti et al. [17] found a positive association between the consumption of alcohol and CRC risk in persons with LS.

It is difficult to interpret the results of studies investigating the role of

Abbreviations: CRC, Colorectal cancer; CRT, Colorectal tumor; DASH, Dietary Approaches to Stop Hypertension; DHD15-index, Dutch Healthy Diet index 2015; DQI, diet quality indexes; LS, Lynch syndrome; MMR, mismatch repair.

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a single dietary component, since dietary components are highly correlated and might interact [18]. Therefore, in our cohort study of persons with LS, we have previously investigated the association between a combination of dietary components and CRT risk, by using a data-driven approach [19] and by using a hypothesis-driven nutrient--based index [20]. By using a data-driven approach, we observed that a dietary pattern high in snack foods was statistically significantly associated with an increased CRT risk [19]. Moreover, we observed that the nutrient-based index, used to score the inflammatory potential of the diet, was not statistically significantly associated with CRT risk [20]. However, both approaches have their limitations. A data-driven approach will probably yield a different dietary pattern for a different population [21], which makes it difficult to compare findings with other populations. Furthermore, a nutrient-based index does not take into account that foods can have complex effects on health due to the food structure, preparation methods and synergistic or interaction effects of nutrients [18]. A priori defined diet quality indexes (DQIs), using a food-based approach to score diet quality, can be used to overcome the limitations of both a data-driven approach and a nutrient-based index.

Two of these DQIs, namely the Dutch Healthy Diet index 2015 (DHD15-index) and the Dietary Approaches to Stop Hypertension (DASH) score, are characterized by several components convincingly associated with CRC risk in the general population [22]. These components include wholegrains, dairy, alcohol and red and processed meat. In addition, both the DHD15-index and DASH score were inversely associated with CRC risk in the general population [23,24]. Moreover, both indexes score the intake of fruit and high-fiber containing products and of 'Snack' foods, which, as mentioned before, were associated with CRT risk in persons with LS. Therefore, we aimed to investigate both the DHD15-index and the DASH score in relation to subsequent CRT risk for persons with LS.

2. Materials and methods

2.1. Study population

Participants with LS were selected from the Genetic, Environmental and Other factors that influence tumor risk in persons with Lynch syndrome (GEOLynch) study (ClinicalTrials.gov identifier NCT03303833) [19,25], a prospective cohort study. Between 2006 and 2008, and between 2012 and 2017, potential participants for the GEOLynch study were identified from families registered at the Netherlands Foundation for the Detection of Hereditary Tumors, Radboud University Nijmegen Medical Center and University Medical Center Groningen or they volunteered to participate, e.g. upon response to a request for participants. All included participants had been tested for a pathogenic mutation in one of the DNA MMR or *EPCAM* genes in one of the clinical genetics centers in the Netherlands. Techniques used have been described previously [26]. Eligible participants were Dutch-speaking, mentally competent to participate, men and women between 18 and 80 years of age. Participants were ineligible if they were terminally ill or if they had a type of hereditary colon cancer other than LS. In both recruitment rounds together 1323 participants were contacted. Fifty-eight percent agreed to participate (n = 765). Of these patients 275 were excluded for various reasons (Fig. 1), leaving 490 participants for the analyses. Approval for the GEOLynch study was obtained from the Medical Ethical Review Committee Region Arnhem-Nijmegen. All participants provided written informed consent.

2.2. Exposure assessment

Habitual dietary intake was assessed at recruitment with a self-administered food frequency questionnaire (FFQ), which recalled habitual food intake of 183 food items over the past month. The FFQ was developed and validated by Wageningen University & Research [27,28]. Participants were asked for frequency of food item consumption on a scale ranging from 'not this month' to '6 - 7 times per week'. To obtain grams per day for each food item, frequencies per day were multiplied with standard portion sizes. The Dutch Food Composition Database 2011 [29] was subsequently used to calculate energy and nutrient intakes. Diet quality was scored by using the DHD15-index and the DASH score. For both indices, a higher score equals a higher quality of the diet.

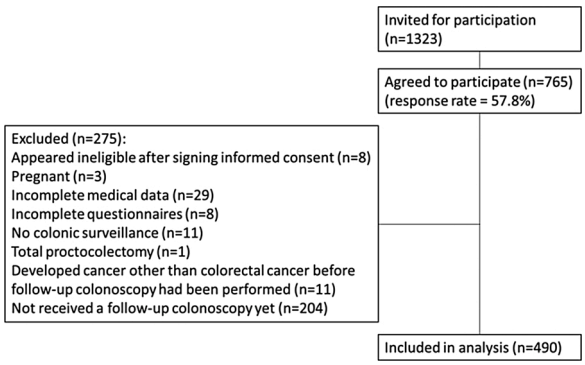

Fig. 1. Flowchart of included participants.

2.2.1. DHD15-index

The DHD15-index as formulated in the article of Looman et al. [30] was used to score a participant's adherence to fifteen food-based Dutch dietary guidelines 2015 [31] (Supplementary Table S1). No distinction could be made between salted and unsalted nut intake with the used FFQ, thus nut intake included both. Filtered coffee, salt and sweetened beverage intake were not included as separate items in the FFQ and therefore not considered in the DHD15-index calculations. Participants received a score for the remaining twelve DHD15-index components, ranging from 0 (no adherence) to 10 (perfect adherence), with intermediate values scored proportionally. This lead to a DHD15-index score between 0 (no adherence) and 120 (perfect adherence).

2.2.2. DASH score

The DASH score of Fung et al. [32] was based on the DASH diet, in which eight food and nutrient components are emphasized or minimized to lower blood pressure [33] (Supplementary Table S2). Participants were divided into quintiles for each dietary component. A higher quintile meant a higher intake of the component. Participants in the lowest quintile of fruit, vegetable, nuts and legumes, low-dairy fat products or whole grains intake received one point, while participants in the highest quintile received five points. Participants in the lowest quintile of red and processed meat intake received five points, while those in the highest quintile received one point. Sweetened beverages and salt intake were not considered in the DASH score calculations, since they were not included as separate items in the used FFQ. The points received for the six remaining components were summed to get a final score, ranging from 6 (worst) to 30 (best).

2.3. CRT assessment

After recruitment, medical records and/or pathology reports were analyzed regularly to collect medical information on colorectal adenoma diagnoses and the number and dates of colonoscopies during follow-up. Information on all diagnosed colorectal adenomas and performed colonoscopies before recruitment were also obtained from these records and reports. According to the Dutch guidelines, colonoscopies should be performed once every two years in patients with LS who are older than 25 years [34]. Medical records and/or pathology reports were used to collect medical data on colorectal resection (none, partial colectomy or subtotal colectomy). Linkage to the national Pathology Archive (PALGA) database provided information on colorectal and non-colorectal carcinomas developed before and after recruitment in the

GEOLynch study.

2.4. Covariate assessment

All participants were asked at recruitment to fill in a self-administered general questionnaire including questions about sex, date of birth, nonsteroidal anti-inflammatory drugs (NSAID) use (non-regular: $<$ 1 time/mo or regular: $\geq$ 1 time/mo), height and weight, education level (low: finished primary school, lower vocational or lower general secondary education; intermediate: finished intermediate vocational or general secondary education; high: finished higher vocational or university education), and smoking habits (never, former or current). Body mass index (BMI) was calculated by dividing the weight by the square of height. Physical activity was measured with the modified Baecke questionnaire [35,36]. A higher score reflected a higher physical activity level.

2.5. Data analysis

Cut-off values for each DQI were determined by dividing the study population into tertiles. Descriptive statistics were used to define the characteristics (median [quartile 1 (Q1), quartile 3 (Q3)], mean $\pm$ SD or N (%)) of the population, overall and by each DQI-tertile. Characteristics of excluded participants (n = 275) were compared with those of the included participants.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to estimate CRT risk for each DQI with Cox proportional hazard regression models. The lowest tertile was used as the reference category. Person-time started at the date of colonoscopy closest to questionnaire completion (median time between questionnaire completion and start was -0.05 (interquartile range -4.80 – 4.80) months. The end date of participants who developed a CRT was set halfway between the date of CRT diagnosis and the date of the previous clean colonoscopy. Participants without a CRT diagnosis were censored at the date of their last known colonoscopy. Participants who withdrew from the study, died, were diagnosed with another type of cancer, underwent a colon resection, got a gastrointestinal disease or participated in a trial were censored at the date of their last colonoscopy before this event occurred, if no CRT was diagnosed before this date. Since some participants were members of the same family, robust sandwich variance estimates were used to adjust for dependency within families. To test for linear trends, the median value of each DQI-tertile was entered as a continuous variable in the model. The goodness-of-fit test using Schoenfeld residuals showed that all models met the proportional hazard assumption.

HRs were stratified by sex and CRT history to explore whether these covariates were causing effect measure modification. CRT history was evaluated as an effect measure modifier to investigate whether the association between diet quality and CRT risk differed for participants with one or more CRTs before the start of the study and those without, i.e. prevalent and incident cohort, respectively. Interaction terms between sex or CRT history and the DQIs tertiles were added to the regression models. The Wald-chi square test was subsequently used to determine P-values for interaction.

A causal diagram, i.e. a directed acyclic graph (DAG), was constructed to determine which covariates were causing confounding (dagitty.net/me0gSn3) [37]. This led to the inclusion of the following covariates into the model: sex, age (years), CRT history (yes/no), cancer history (yes/no), physical activity level (continuous), extent of colon resection (categories), smoking habits (categories), energy intake (kcal, continuous) and alcohol intake (grams/day, continuous). An adjustment for alcohol intake was only applied to the DASH model since the DHD15-index regarded alcohol intake as part of the index.

A sensitivity analysis was performed to investigate if the exclusion of persons who developed a carcinoma (n = 15) changed associations between the DHD15-index, DASH score and CRT risk.

It was decided to present P-values as continuous estimates of the compatibility of the results with the null hypotheses, instead of defining an α cutoff for statistical significance [38]. All data was analyzed with SAS software, version 9.4 (SAS Institute, Cary, NC).

3. Results

During a median follow-up time of 53.4 months (interquartile range 26.6 – 83.8), 210 participants (42.9%) developed a CRT, of whom 15 developed CRC (Table 1). The scores of the DHD15-index ranged from 29.3 to 111.5 and the DASH scores ranged from 7 to 29. Median time between two colonoscopies was 2.0 (interquartile range 1.5 – 2.2) years.

The study population had a mean age of 49.4 years $\pm$ 11.5 and consisted for 56.9% of women (Table 1). The percentage of women, highly educated persons, persons with a CRC history and persons with a cancer history other than CRC, was higher in the highest compared with the lowest tertile of the DHD-index and DASH score. Furthermore, the percentage of current smokers and persons with a colorectal adenoma history, was lower in the highest vs. the lowest tertile of the DHD-index and DASH score (Table 1).

Finally, a higher percentage of males, persons without a CRT history and persons divided in tertile 3 of the DHD15-index were seen in the excluded compared to the included participants (58% vs. 43%, 59% vs. 47% and 41% vs. 34%, respectively). Other characteristics did not differ between included and excluded participants.

3.1. DQIs and colorectal tumor risk

The HR's, 95% CI and P-values for interaction showed that both sex and CRT history were not effect measure modifiers in the analyses on the DHD-index and DASH score (Supplementary Table S3 and S4). Hence, it was decided to show the results of the total population. The DHD-index and DASH score were not statistically significantly associated with CRT risk with adjusted HRs for the highest versus the lowest tertile of 1.00 (95% CI: 0.67 – 1.48) and 1.11 (95% CI: 0.74 – 1.69), respectively. No linear trends were observed between the DHD-index, DASH score and CRT risk (P-values for trend 0.97 and 0.83, respectively) (Table 2).

Lastly, sensitivity analysis showed that removing data from persons who developed a carcinoma from the analyses did not change associations (data not shown).

4. Discussion

In this prospective cohort study, no statistically significant associations between the DHD-15 index or the DASH score and CRT risk were observed in persons with LS.

To our knowledge, this is the first study to investigate the association between food-based diet quality indices and CRT risk in persons with LS. A previous study in the general population showed that every additional DHD15-index component adhered to was associated with a decreased CRC risk (HR: 0.90, 95% CI: 0.85 – 0.96) [23]. In addition, a previous meta-analysis combining five studies, showed that patients in the highest category of the DASH score had a decreased CRC risk compared to patients in the lowest category (HR: 0.80, 95% CI: 0.74 – 0.85) [24]. The 95% CIs of the studies in the general population overlap with, but are much smaller than the 95% CI of our study, which may be due to differences in sample sizes. Another difference between the population studied, i.e. persons with LS vs. the general population may be the mechanisms leading to CRT development. This is supported by studies showing that LS-associated adenomas are mainly microsatellite instability (MSI)-high [39–42], while sporadic adenomas are mainly MSI-low [43]. Previous studies showed that factors such as BMI and smoking were associated with an increased risk of developing MSI-high CRT [44]. However, studies investigating the association between dietary factors and the risk of developing MSI-high CRTs provide inconsistent results [45–47]. This suggests that at least some dietary factors associated with

Table 1
Baseline characteristics of the total cohort and by lowest and highest tertile of diet quality indexes (DQI).[a]

			Diet quality index			
		Total study population	DHD15-index		DASH score	
			Tertile 1 (range 29.3 – 62.0)	Tertile 3 (range 74.6 – 111.5)	Tertile 1 (range 7 – 15)	Tertile 3 (range 20 – 29)
Participants	N (%)	490	162 (33.1)	162 (33.1)	149 (30.4)	184 (37.6)
CRT diagnosis	N (%)	210 (42.9)	78 (48.2)	61 (37.7)	67 (45.0)	80 (43.5)
CRC diagnosis	N (%)	15 (3.1)	5 (3.1)	4 (2.5)	4 (2.7)	7 (3.8)
Follow-up, months	Median (Q1 – Q3)	53.4 (26.6 – 83.8)	53.3 (25.6 – 83.4)	51.6 (26.2 – 83.9)	50.0 (27.5 – 81.7)	56.9 (27.1 – 95.0)
Age, y	Mean ± SD	49.4 ± 11.5	48.5 ± 11.4	51.0 ± 11.2	48.6 ± 11.5	51.1 ± 11.2
Sex (Women)	N (%)	279 (56.9)	80 (49.4)	98 (60.5)	80 (53.7)	109 (59.2)
Education level[b]						
Low	N (%)	151 (30.8)	66 (40.7)	33 (20.4)	69 (46.3)	38 (20.7)
Intermediate	N (%)	160 (32.7)	51 (31.5)	43 (26.5)	46 (30.9)	58 (31.5)
High	N (%)	175 (35.7)	43 (26.5)	85 (52.5)	32 (21.5)	86 (46.7)
Physical activity level[c]	Median (Q1 – Q3)	8.3 (7.6 – 9.0)	8.0 (7.3 – 8.7)	8.5 (7.7 – 9.1)	8.1 (7.3 – 8.7)	8.5 (7.8 – 9.2)
BMI, kg/m^2	Median (Q1 – Q3)	24.5 (22.6 – 26.9)	24.7 (23.0 – 27.5)	24.1 (22.1 – 26.0)	25.0 (22.8 – 27.5)	24.2 (22.3 – 26.2)
Smoking habits[d]						
Current	N (%)	85 (17.4)	49 (30.3)	16 (9.9)	43 (28.9)	16 (8.7)
Former	N (%)	212 (43.4)	57 (35.2)	71 (43.8)	53 (35.6)	87 (47.5)
Never	N (%)	191 (39.1)	56 (34.6)	75 (46.3)	53 (35.6)	80 (43.7)
Energy intake, kcal/day	Median (Q1 – Q3)	2124.8 (1725.0 – 2616.1)	2207.8 (1738.2 – 2665.1)	2054.1 (1784.1 – 2554.1)	2029.3 (1630.8 – 2491.6)	2159.8 (1815.9 – 2654.4)
NSAID use, (regular)[e]	N (%)	93 (19.0)	30 (18.5)	31 (19.1)	31 (20.8)	33 (17.9)
Alcohol intake (g/day)	Median (Q1 – Q3)	7.1 (1.4 – 16.6)	8.5 (1.7 – 20.5)	5.3 (1.4 – 11.7)	7.3 (1.2 – 16.3)	6.1 (1.1 – 14.9)
Colorectal adenoma history	N (%)	125 (25.5)	49 (30.3)	30 (18.5)	51 (34.2)	40 (21.7)
CRC history	N (%)	129 (26.3)	41 (25.3)	57 (35.2)	32 (21.5)	61 (33.2)
History of cancer other than colorectal cancer	N (%)	102 (20.8)	25 (15.4)	48 (29.6)	22 (14.8)	49 (26.6)
Mutated MMR gene						
MLH1	N (%)	181 (36.9)	59 (36.4)	52 (32.1)	53 (35.6)	63 (35.2)
MSH2	N (%)	197 (40.2)	68 (42.0)	68 (42.0)	63 (42.3)	75 (40.8)
MSH6	N (%)	99 (20.2)	34 (21.0)	34 (21.0)	30 (20.1)	41 (22.3)
PSM2	N (%)	13 (2.7)	1 (0.6)	8 (4.9)	3 (2.0)	5 (2.7)
No. of colonoscopies during follow-up	Median (Q1 – Q3)	2 (1 – 3)	2 (1 – 3)	2 (1 – 3)	2 (1 – 3)	2 (1 – 3)
Median time between two colonoscopies during follow-up, years	Median (Q1 – Q3)	2.0 (1.5 – 2.2)	2.0 (1.6 – 2.3)	2.0 (1.3 – 2.2)	2.0 (1.7 – 2.3)	1.9 (1.3 – 2.1)
Colorectal resection						
Partial colon resection	N (%)	76 (15.5)	25 (15.4)	29 (17.9)	18 (12.1)	31 (16.9)
Subtotal colectomy	N (%)	45 (9.2)	10 (6.2)	22 (13.6)	12 (8.1)	24 (13.0)

BMI: Body mass index, CRC: Colorectal cancer, CRT: Colorectal tumor, DASH: Dietary Approaches to Stop Hypertension, DHD15-index: Dutch Healthy Diet index 2015, MMR: Mismatch repair, NSAID: Nonsteroidal anti-inflammatory drugs, Q1: Quartile 1, Q3: Quartile 3, SD: Standard deviation.

[a] Only the baseline characteristics of the total population and of participants in the lowest (tertile 1) and highest (tertile 3) DQI-specific tertile are shown.

[b] Low education level: finished primary school, lower vocational or lower general secondary education. Intermediate education level: intermediate vocational or general secondary education. High education level: higher vocational or university education. Percentages do not add up to a 100 because of 4 missing data regarding educational level.

[c] 39 people had missing data regarding physical activity level.

[d] Percentages do not add up to a 100 because of 2 missing data regarding smoking status.

[e] Regular NSAID use: once or more per month. Percentages do not add up to a 100 because eleven participants had missing data regarding NSAID use.

Table 2
Hazard ratios (HRs) (95% confidence intervals (CI)) for colorectal tumor (CRT) risk by tertiles of diet quality indexes.

			HR (95% CI)	
DQI	Cases, n	Person-time, years	Crude model	Adjusted model[a]
DHD15-index				
Tertile 1	78	747.3	1.00 (reference)	1.00 (reference)
Tertile 2	71	770.4	0.89 (0.65 – 1.22)	1.13 (0.80 – 1.59)
Tertile 3	61	737.8	0.80 (0.56 – 1.14)	1.00 (0.67 – 1.48)
P-trend[b]			0.22	0.97
DASH score				
Tertile 1	67	671.5	1.00 (reference)	1.00 (reference)
Tertile 2	63	726.4	0.87 (0.60 – 1.25)	1.08 (0.70 – 1.65)
Tertile 3	80	857.5	0.94 (0.66 – 1.32)	1.11 (0.74 – 1.69)
P-trend[b]			0.77	0.83

DASH: Dietary Approaches to Stop Hypertension, DHD15-index: Dutch Healthy Diet index 2015, DQI: Dietary quality index.

[a] Risk estimate adjusted for sex, age, CRT history, cancer history, physical activity level, extent of colon resection, smoking habits and energy intake. Risk estimates for the DASH score were additionally adjusted for alcohol intake.

[b] Two-sided P-values were calculated by entering the median value of each DQI-tertile as a continuous variable to the model.

CRT risk might act along pathways other than those involved in MSI. Hence, diet quality might not be associated with LS-associated tumors. Furthermore, diets might differ between these two populations. It was found that persons with LS in our study have slightly better, but not more homogenous, dietary habits compared to the general Dutch population (mean DHD15-index score: 68.5 vs. 61.7) [30]. Because of the small difference and same spread in diet quality, it is unlikely that different dietary habits explain the difference in observed associations. Moreover, results could differ due to different endpoints used, i.e. CRC in the general population vs. CRTs in this LS population. As studies investigating the association between the DHD15-index, DASH score and CRT risk in the general population are lacking, we cannot compare results of these DQIs in relation to tumors versus carcinomas in the general population directly. In addition, only 15 of our patients developed a carcinoma, making it impossible to investigate the association between diet quality and CRC risk in the current study.

Some of the dietary components scored by these DQIs, such as fruit, vegetables and fiber, are known to influence mechanisms which reduce or increase colorectal adenoma risk in the general population [48–57]. Previous studies have investigated whether (a combination of) these dietary components were also associated with CRT risk in persons with LS [16,19,20,58,59]. A study previously performed by our group, found that a high intake of fruit and fiber decreased CRT risk in persons with LS (odds ratio (OR) for highest vs. lowest tertile: 0.4, 95% CI: 0.4 – 0.9; and OR: 0.5, 95% CI: 0.2 – 1.0, respectively) [16]. In addition, a study performed by our group did not find an association between the intake of meat and CRT risk (OR for high vs. low consumption: 0.6, 95% CI: 0.2 – 1.6) [59]. Moreover, our cohort study observed no association between CRT risk and methionine intake (HR for highest vs. lowest tertile: 1.35, 95% CI: 0.83 – 2.20), dietary vitamin B intake (e.g., HR for highest vs. lowest tertile of vitamin B2: 0.77, 95% CI: 0.39 – 1.51) and the inflammatory potential of the diet (HR for highest vs. lowest tertile: 1.37, 95% CI: 0.80 – 2.34) [20,58]. Lastly, our cohort study previously found that a dietary pattern high in snack food was associated with an increased CRT risk (HR for highest vs. lowest tertile: 2.16, 95% CI: 1.03 – 4.49) [19]. These studies provide inconsistent results on whether a high quality diet is associated with CRT risk in persons with LS and hence whether a high quality diet might induce mechanisms which reduce the risk of developing colorectal adenomas in this population.

Limitations of this study include the exclusion of coffee, salt and sweetened beverage intake from the DQI scores calculations. This could have resulted in poorer estimations of diet quality. However, since studies investigating the association between these dietary factors and CRC risk are lacking or inconclusive [22] it is not known how and if exclusion of those items affected the results. Moreover, the used FFQ was not able to distinguish between salted and unsalted nut intake, which might have resulted in an overestimation of the diet quality, especially for those who eat a high amount of salted nuts, and therefore a bias towards the null. The response rate of our study participants was 57.8%, which is perceived as adequate. Data of a number of participants who agreed to participate were removed for the current study, mainly because these participants did not receive a follow-up colonoscopy yet, as they had been included in the study between 2012 and 2017. It is unclear, on the basis of the differences in characteristics between excluded and included participants, whether excluded participants were more or less likely to develop CRTs. Therefore, exclusion of participants could have biased the results in both directions. Finally, results of studies using diet quality only once, at the start of the study, should be interpreted with caution, as diet might change over time. However, in our study, we observed no marked changes in dietary quality over time, comparing diet quality at the start of the study with diet quality 4 to 6 years after study inclusion (data not shown). Hence, we do not expect that using only a single measurement will have strongly affected our results.

Strengths of this study include the prospective design with inclusion of confirmed MMR-gene mutations carriers, a relatively long follow-up of this high risk population and measurement of a large number of potential confounders. Additionally, a causal diagram was used to select confounding variables ensuring that the analyses were adjusted for all covariates needed to minimize confounding bias [15]. However, residual confounding might still be present. Moreover, the usage of food-based DQIs, which are hypothesis-driven instead of data-driven, makes it possible to extrapolate results to other LS-patients who undergo regular colonoscopy.

To conclude, this prospective cohort study does not provide support for an association between food-based diet quality and CRT risk in persons with LS. Our study thus shows that associations found in the general population between diet quality and CRC risk might not hold in persons with LS. Further research into the mechanisms related to LS-associated CRT risk and whether these can be influenced by diet quality is needed before effective prevention strategies in terms of dietary quality can be developed for this high-risk population.

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CRediT authorship contribution statement

Anouk H. Eijkelboom: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Jesca G.M. Brouwer:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Supervision, Project administration. **Hans F.A. Vasen:** Investigation, Resources, Writing - review & editing, Funding acquisition. **Tanya M. Bisseling:** Investigation, Resources, Writing - review & editing. **Jan J. Koornstra:** Investigation, Resources, Writing - review & editing. **Ellen Kampman:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition. **Fränzel J.B. van Duijnhoven:** Conceptualization, Methodology, Writing - original draft,

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2020.101809.

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