Supplementary Table 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Section and Topic	Item #	Checklist item	Location
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P11
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	S.Table 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P11
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P11
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P11
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P11
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P11
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	-

	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	-
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	-
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	S. Table 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 2-4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P7
	23b	Discuss any limitations of the evidence included in the review.	P9/10

	23c	Discuss any limitations of the review processes used.	P9/10
	23d	Discuss implications of the results for practice, policy, and future research.	P9/10
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P10
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P10
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Available at PROSPERO
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P12
Competing interests	26	Declare any competing interests of review authors.	P12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	P12

Supplementary Table 2. Search strategy and results

PubMed	#1 (colorect*[Title/Abstract] OR colon[Title/Abstract] OR colonic[Title/Abstract] OR rectal*[Title/Abstract] OR rectum*[Title/Abstract] OR “large bowel”[Title/Abstract]) AND (cancer*[Title/Abstract] OR malignan*[Title/Abstract] OR carcinom*[Title/Abstract] OR tumo*[Title/Abstract] OR CRC[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR adenom*[Title/Abstract] OR lesion*[Title/Abstract] OR neoplas*[Title/Abstract]) *343,477 results*
	#2 (metabolomics[MeSH Terms] OR metabolome[MeSH Terms] OR metabolite*[Title/abstract] OR metabolo*[Title/abstract] OR metabonom*[Title/abstract] OR metabolite network*[Title/abstract] OR metabolite profile*[Title/abstract] OR lipidom*[Title/abstract]) *395,855 results*
	#3 (screen*[Title/Abstract] OR cohort[Title/Abstract] OR prospective[Title/Abstract] OR prediagnostic[Title/Abstract] OR pre-diagnostic[Title/Abstract] OR asymptomatic[Title/Abstract] OR detection[Title/Abstract] OR diagnosis[Title/Abstract] OR diagnostic[Title/Abstract]) *5,442,088 results*
	#4 editorial[Publication Type] OR letter[Publication Type] OR Comment*[Publication Type] OR news[Publication Type] *2,440,529 results*
	#5 (animal*[Title] OR “animal experiment”[Title] OR “animal model”[Title] OR “animal tissue”[Title] OR “non human”[Title] OR nonhuman[Title] OR rat[Title] OR rats[Title] OR mice[Title] OR mouse[Title] OR swine[Title] OR porcine[Title] OR murine[Title] OR sheep[Title] OR lambs[Title] OR pig[Title] OR pigs[Title] OR piglet*[Title] OR rabbit*[Title] OR monkey[Title] OR bovine[Title]) *2,140,655 results*
	#1 AND #2 AND #3 NOT #4 NOT #5 ***976 results***
Web of Science	#1 ((TS=(((colorect* OR colon OR colonic OR rectal* OR rectum* OR “large bowel”) AND (cancer* OR malignan* OR carcinom* OR tumo* OR CRC OR adenocarcinoma* OR adenom* OR lesion* OR neoplas*)))) AND LA=(English)) AND DT=(Article OR Abstract of Published Item OR Early Access OR Reprint) *289,459 results*
	#2 ((TS=((metabolomics OR metabolome OR metabolite* OR metabolo* OR metabonom* OR metabolite network* OR metabolite profile* OR lipidom*))) AND LA=(English)) AND DT=(Article OR Abstract of Published Item OR Early Access OR Reprint) *391,826 results*
	#3 ((TS=((screen* OR cohort OR prospective OR prediagnostic OR pre-diagnostic OR asymptomatic OR detection OR diagnosis OR diagnostic))) AND LA=(English)) AND DT=(Article OR Abstract of Published Item OR Early Access OR Reprint) *4,804,881 results*
	#4 TI=(animal* OR “animal experiment” OR “animal model” OR “animal tissue” OR “non human” OR nonhuman OR rat OR rats OR mice OR mouse OR swine OR porcine OR murine OR sheep OR lambs OR pig OR pigs OR piglet* OR rabbit* OR monkey OR bovine) *2,786,310 results*
	#1 AND #2 AND #3 NOT #4 ***1,224 results***

SCOPUS	#1 TITLE-ABS-KEY ((colorect* OR colon OR colonic OR rectal* OR rectum* OR "large bowel") AND (cancer* OR malignan* OR carcinom* OR tumo* OR crc OR adenocarcinoma* OR adenom* OR lesion* OR neoplas*)) AND DOCTYPE (ar) *407,351 results*
	#2 TITLE-ABS-KEY ((metabolomics OR metabolome OR metabolite* OR metabolo* OR metabonom* OR metabolite AND network* OR metabolite AND profile* OR lipidom*)) AND DOCTYPE (ar) *48,332 results*
	#3 TITLE-ABS-KEY ((screen* OR cohort OR prospective OR prediagnostic OR pre-diagnostic OR asymptomatic OR detection OR diagnosis OR diagnostic)) AND DOCTYPE (ar) *8,773,644 results*
	#4 TITLE ((animal* OR "animal experiment" OR "animal model" OR "animal tissue" OR "non human" OR nonhuman OR rat OR rats OR mice OR mouse OR swin OR porcine OR murine OR sheep OR lambs OR pig OR pigs OR piglet* OR rabbit* OR monkey OR bovine)) *2,588,753 results*
	#1 AND #2 AND #3 AND NOT #4 AND (LIMIT-TO (LANGUAGE , "English")) ***284 results***

Supplementary Table 3. Articles excluded from full-text screening

(A) No longitudinal cohort study or screening trial
1. Altobelli E, Angeletti PM, Latella G. Role of Urinary Biomarkers in the Diagnosis of Adenoma and Colorectal Cancer: A Systematic Review and Meta-Analysis. J Cancer. 2016;7(14):1984-2004. doi: 10.7150/jca.16244.
2. Bezabeh T, Ijare OB, Nikulin AE, Somorjai RL, Smith IC. MRS-based Metabolomics in Cancer Research. Magn Reson Insights. 2014;7:1-14. doi: 10.4137/MRI.S13755.
3. Bosch S, Berkhout DJ, Ben Larbi I, de Meij TG, de Boer NK. Fecal volatile organic compounds for early detection of colorectal cancer: where are we now? J Cancer Res Clin Oncol. 2019;145(1):223-34. doi: 10.1007/s00432-018-2821-3.
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5. Di Lena M, Porcelli F, Altomare DF. Volatile organic compounds as new biomarkers for colorectal cancer: a review. Colorectal Dis. 2016;18(7):654-63. doi: 10.1111/codi.13271.
6. Erben V, Bhardwaj M, Schrotz-King P, Brenner H. Metabolomics Biomarkers for Detection of Colorectal Neoplasms: A Systematic Review. Cancers (Basel). 2018;10(8). doi: 10.3390/cancers10080246.
7. Gallardo-Gomez M, De Chiara L, Alvarez-Chaver P, Cubiella J. Colorectal cancer screening and diagnosis: omics-based technologies for development of a non-invasive blood-based method. Expert Rev Anticancer Ther. 2021;21(7):723-38. doi: 10.1080/14737140.2021.1882858.
8. Gan X, Wang T, Chen ZY, Zhang KH. Blood-derived molecular signatures as biomarker panels for the early detection of colorectal cancer. Mol Biol Rep. 2020;47(10):8159-68. doi: 10.1007/s11033-020-05838-0.
9. Gold A, Choueiry F, Jin N, Mo X, Zhu J. The Application of Metabolomics in Recent Colorectal Cancer Studies: A State-of-the-Art Review. Cancers (Basel). 2022;14(3). doi: 10.3390/cancers14030725.
10. Harlid S, Gunter MJ, Van Guelpen B. Risk-Predictive and Diagnostic Biomarkers for Colorectal Cancer; a Systematic Review of Studies Using Pre-Diagnostic Blood Samples Collected in Prospective Cohorts and Screening Settings. Cancers (Basel). 2021;13(17). doi: 10.3390/cancers13174406.
11. Hashim NAA, Ab-Rahim S, Suddin LS, Saman MSA, Mazlan M. Global serum metabolomics profiling of colorectal cancer. Mol Clin Oncol. 2019;11(1):3-14. doi: 10.3892/mco.2019.1853.
12. Mallafre-Muro C, Llambrich M, Cumeras R, Pardo A, Brezmes J, Marco S, et al. Comprehensive Volatilome and Metabolome Signatures of Colorectal Cancer in Urine: A Systematic Review and Meta-Analysis. Cancers (Basel). 2021;13(11). doi: 10.3390/cancers13112534.
13. Nannini G, Meoni G, Amedei A, Tenori L. Metabolomics profile in gastrointestinal cancers: Update and future perspectives. World J Gastroenterol. 2020;26(20):2514-32. doi: 10.3748/wjg.v26.i20.2514.
14. Ni Y, Xie G, Jia W. Metabonomics of human colorectal cancer: new approaches for early diagnosis and biomarker discovery. J Proteome Res. 2014;13(9):3857-70. doi: 10.1021/pr500443c.
15. Piras C, Pibiri M, Leoni VP, Cabras F, Restivo A, Griffin JL, et al. Urinary(1)H-NMR Metabolic Signature in Subjects Undergoing Colonoscopy for Colon Cancer Diagnosis. Applied Sciences-Basel. 2020;10(16). doi: 10.3390/app10165401.
16. Rasmussen L, Wilhelmsen M, Christensen IJ, Andersen J, Jorgensen LN, Rasmussen M, et al. Protocol Outlines for Parts 1 and 2 of the Prospective Endoscopy III Study for the Early Detection of Colorectal Cancer: Validation of a Concept Based on Blood Biomarkers. JMIR Res Protoc. 2016;5(3):e182. doi: 10.2196/resprot.6346

17. Raza A, Khan AQ, Inchakalody VP, Mestiri S, Yoosuf Z, Bedhiafi T, et al. Dynamic liquid biopsy components as predictive and prognostic biomarkers in colorectal cancer. J Exp Clin Cancer Res. 2022;41(1):99. doi: 10.1186/s13046-022-02318-0.

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22. Wang M, Long Z, Xue W, Peng C, Jiang T, Tian J, et al. Discovery of plasma biomarkers for colorectal cancer diagnosis via untargeted and targeted quantitative metabolomics. Clin Transl Med. 2022;12(4):e805. doi: 10.1002/ctm2.805.

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(B) No measurement of metabolites in pre-diagnostic samples

1. Amir Hashim, N. A., Ab-Rahim, S., Wan Ngah, W. Z., Nathan, S., Ab Mutalib, N. S., Sagap, I., . . . Mazlan, M. (2021). Global metabolomics profiling of colorectal cancer in Malaysian patients. Bioimpacts, 11(1), 33-43. doi:10.34172/bi.2021.05

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(C) No blood, urine, or stool samples

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(D) Lack of sufficient statistical data

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Supplementary Table 4. QUADAS-2 Risk of Bias assessment

	Risk of bias				Applicability concerns		
First author, Year ref.	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Cai, 2006 [14]	☺	?	?	☺	☺	☺	☺
Cross, 2014 [15]	☺	?	?	☺	☺	☺	☺
Kühn, 2016 [17]	☺	☺	?	☺	☺	☺	☺
Myte, 2017 [20]	?	☺	☺	☹	☺	☺	☺
Pickens, 2017 [37]	☺	?	☺	?	☹	☺	☺
Geijsen, 2019 [16]	?	?	?	?	☹	☺	☺
Kühn, 2020 [28]	☺	☺	☺	?	☺	☺	☺
McCullough, 2021 [19]	☺	☺	☺	?	☺	☺	☺
Papadimitriou, 2021 [29]	?	?	☺	☹	☹	☺	☺
Tevini, 2022 [39]	?	?	☺	?	☺	☺	☺
Hang, 2022 [36]	?	?	?	☹	☹	☺	☺
Pham, 2022 [21]	☺	☺	☺	?	☹	☺	☺
Vidman, 2023 [26]	☺	☺	☺	☹	☺	☺	☹
Eisner, 2013 [34]	?	?	☺	☹	☹	☺	☺
Wang, 2014 [35]	☺	☺	☺	☹	☺	☺	☺
Amiot, 2015 [38]	☺	?	?	☺	☺	☺	☺
Farshidfar, 2016 [30]	☺	☺	☺	☺	☹	☺	☺
Deng, 2017a [32]	☺	?	?	☺	☺	☺	☺
Deng, 2017b [33]	☺	?	?	☹	☹	☺	☺
Troisi, 2022 [25]	☹	☹	☺	?	☺	☺	☺
Rothwell, 2022 [22]	☺	☺	☺	?	☹	☺	☺
Telleria, 2022 [24]	?	?	☺	☺	☺	☺	☺
Liu, 2023 [31]	?	?	?	?	☺	☺	☺
Xie, 2023 [27]	☹	?	☺	?	☹	☺	?
Shu, 2018 [23]	☺	☺	☺	☹	☺	☺	☺
Loftfield, 2022 [18]	☺	?	?	☺	☺	☺	☺

☺ Low concern/risk

? Unclear concern/risk

☹ High concern/risk

Supplementary Table 5. Covariates included in the panel of metabolites/in the analysis for the individual metabolites

First author, Year ref.	Age	Sex	Smoking	Alcohol consumption	Weight-related covariates	Diet-related covariates	Educational level	Physical activity	Fasting time before sample collection	Anti-inflammatory medication	Others
Individual Metabolites											
Cai, 2006 [14]	-	*	-	-	-	-	-	-	-	-	
Cross, 2014 [15]	x	-	-	-	x	-	-	-	-	-	
Kühn, 2016 [17]	x	x	x	x	x	x	x	-	-	x	
Myte, 2017 [20]	-	-	x	x	x	-	-	x	-	-	
Pickens, 2017 [37]	x	*	x	-	-	-	-	-	-	-	
Geijsen, 2019 [16]	x	x	x	-	x	-	-	-	-	-	
Kühn, 2020 [28]	-	-	x	-	x	x	x	x	-	-	
McCullough, 2021 [19]	-	-	x	x	x	x	-	x	x	x	
Papadimitriou, 2021 [29]	x	x	x	-	x	x	x	-	-	-	
Tevini, 2022 [39]	-	-	-	-	-	-	-	-	-	-	
Hang, 2022 [36]	x	*	-	-	-	-	-	-	-	-	CRC screening
Pham, 2022 [21]	-	-	-	-	-	-	-	-	-	-	
Vidman, 2023 [26]	-	-	x	x	x	-	x	x	-	-	Diabetes
Metabolite Panel											
Eisner, 2013 [34]	-	x	x	-	-	-	-	-	-	-	Gastro-intestinal bleeding
Wang, 2014 [35]	x	-	-	-	-	-	-	-	-	-	
Amiot, 2015 [38]	-	-	-	-	-	-	-	-	-	-	
Farshidfar, 2016 [30]	x	-	-	-	-	-	-	-	-	-	
Deng, 2017a [32]	x	x	x	-	-	-	-	-	-	-	
Deng, 2017b [33]	x	x	x	-	-	-	-	-	-	-	
Troisi, 2022 [25]	-	-	-	-	-	-	-	-	-	-	
Rothwell, 2022 [22]	-	-	x	x	x	x	x	-	-	-	Height
Telleria, 2022 [24]	-	-	-	-	-	-	-	-	-	-	Hemoglobin
Liu, 2023 [31]	-	-	-	-	-	-	-	-	-	-	
Xie, 2023 [27]	-	-	-	-	-	-	-	-	-	-	
Individual Metabolites & Metabolite Panel											
Shu, 2018 [23]	x	-	x	x	x	x	-	x	x	-	
Loftfield, 2022 [18]	x	-	x	x	x	x	x	x	-	-	

Notes. * only included male/female participants; Abbreviations. CRC, colorectal cancer