Lifestyle predictors of colorectal cancer in European populations: a systematic review

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ABSTRACT

Background Colorectal cancer (CRC) is the second most prevalent cancer in Europe, with one-fifth of cases attributable to unhealthy lifestyles. Risk prediction models for quantifying CRC risk and identifying high-risk groups have been developed or validated across European populations, some considering lifestyle as a predictor.

Purpose To identify lifestyle predictors considered in existing risk prediction models applicable for European populations and characterise their corresponding parameter values for an improved understanding of their relative contribution to prediction across different models.

Methods A systematic review was conducted in PubMed and Web of Science from January 2000 to August 2021. Risk prediction models were included if (1) developed and/or validated in an adult asymptomatic European population, (2) based on non-invasively measured predictors and (3) reported mean estimates and uncertainty for predictors included. To facilitate comparison, model-specific lifestyle predictors were visualised using forest plots.

Results A total of 21 risk prediction models for CRC (reported in 16 studies) were eligible, of which 11 were validated in a European adult population but developed elsewhere, mostly USA. All models but two reported at least one lifestyle factor as predictor. Of the lifestyle factors, the most common predictors were body mass index (BMI) and smoking (each present in 13 models), followed by alcohol (11), and physical activity (7), while diet-related factors were less considered with the most commonly present meat (9), vegetables (5) or dairy (2). The independent predictive contribution was generally greater when they were collected with greater detail, although a noticeable variation in effect size estimates for BMI, smoking and alcohol.

Conclusions Early identification of high-risk groups based on lifestyle data offers the potential to encourage participation in lifestyle change and screening programmes, hence reduce CRC burden. We propose the commonly shared lifestyle predictors to be further used in public health prediction modelling for improved uptake of the model.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Colorectal cancer is the second most prevalent cancer in Europe with one-fifth of cases attributable to unhealthy lifestyles, hence employing lifestyle data in a risk prediction model would facilitate identification of high-risk groups or individuals that would benefit the most from participation in lifestyle change and screening programmes.

⇒ Most of the available models for colorectal cancer risk prediction have been developed in the USA, carrying intrinsic risk factors, and those available for European populations have not been comprehensively compared and evaluated.

WHAT THIS STUDY ADDS

⇒ The study provides a comprehensive summary of population-based risk prediction models of primary colorectal cancer, that are applicable for European adult populations and incorporate easily available predictors, such as lifestyle data.

⇒ Beyond older age, and male sex, commonly shared easily available predictors for colorectal cancer risk prediction were family history of (colorectal) cancer, the use of non-steroidal anti-inflammatory drugs, overweight or obesity, and lifestyle variables such as alcohol consumption, smoking and physical inactivity, while diet-related factors were less considered.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings from this study will be relevant for future public health prediction modelling and propose the use of lifestyle data for enhanced credibility and uptake of the prediction model across different settings and populations.

BACKGROUND

Colorectal cancer (CRC) was estimated to be the second most frequently diagnosed cancer after breast cancer, and the second leading cause of cancer-related death (after lung cancer) in Europe, with nearly 520 000 new cases and 245 000 deaths in 2020, corresponding to one-eight of the total cancer burden.[1] Population-based screening has contributed substantially to reductions in this burden,[2] with 20 Member States of the European Union offering screening programmes.[3] In addition to the implementation of CRC screening strategies targeting the average-risk population aged 50–75 years, the gradual development of CRC (between 10–15 years) provides an opportunity for primary prevention by reducing modifiable CRC risk factors,

such as excess body weight, smoking, alcohol consumption, physical inactivity and unhealthy diets. Lack of adherence to healthy lifestyle recommendations, potentially also partly due to barriers to prevention policy implementation, has been associated to be responsible to almost one-fifth of CRC in Europe.[4] Early identification of high-risk groups or individuals would offer the potential for them to participate in tailored lifestyle programmes as well as existing screening programmes.

A number of risk prediction models for primary CRC have been developed and summarised in previous systematic reviews,[5–8] including two identifying all published models incorporating known genetic markers.[9 10] Introducing genetic information into a risk model that also includes family history and/or phenotypic variables has been shown to modestly improve discriminatory performance,[11–13] though their clinical use in routine real-life settings remains uncertain, as it requires considerations on the wider financial, ethical, legal, social and health concerns, including the cost-benefit/health risk-benefit of measuring additional (genetic) risk factors among others.[14] On the other hand, risk prediction models incorporating easily available predictors, such as lifestyle data, are particularly relevant to facilitate risk stratification among the general population. However, most of the available models for CRC risk prediction have been developed in the USA carrying intrinsic risk factors,[15] and those available in Europe have not been comprehensively compared and evaluated.

The aim of this review is to systematically assess population-based risk prediction models of primary CRC, based on demographic and phenotypic factors, developed and/or validated for European adult populations, including an evaluation of the risk of bias in the model development and validation. In addition, this review aims to identify the lifestyle predictors considered in existing risk prediction models applicable for European populations and to characterise and compare their corresponding parameter values for an improved understanding of their relative contribution to prediction across the different models.

MATERIALS AND METHODS

A systematic literature review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines during all stages of the design, implementation and reporting of systematic review.[16]

Search strategy

We performed an electronic literature search in PubMed and Web of Science from January 2000 to August 2021 using key words related to "colorectal cancer", "risk", and "model" and "prediction/assessment/estimation". We then carried out hand searches of the citations of the retrieved systematic reviews. In addition, through hand searches, studies describing the development of models

that were validated in the eligible studies but developed in non-European populations were retrieved and considered for inclusion.

Study selection

To be included in the systematic review, studies had to be published as a primary research paper in a peer-reviewed journal and either describe the development and/or the validation (performance assessment) of a risk prediction model identifying groups or individuals at higher risk of CRC or advanced colorectal neoplasia. Source data had to concern European populations of asymptomatic (for cancer) adults from the general population or information on adults presenting at a preventive CRC screenings. The risk model had to be based on two or more phenotyping predictors that are readily available from individuals or from their medical records without the need for laboratory tests. Other frequent variables from patients' consultation questionnaires, such as colon-related symptoms on rectal bleeding, change in bowel habits, diarrhoea, constipation, abdominal pain, weight loss, loss of appetite, mucous in the stool, extensive laboratory analysis and/or genetic information, such as single nucleotides polymorphisms and omics, were not considered for inclusion. Furthermore, studies were included in the quantitative analyses if estimates and uncertainty of the predictors were reported. Conference proceedings, papers in languages other than English and studies of a specific population subgroup with (multi)morbidity as well as risk models incorporating extensive patient consultation and/or genetic information were excluded.

Title and abstract screening, followed by a full-text review of the studies complying with the inclusion/exclusion criteria, were independently analysed by two investigators. Any discrepancy during the selection of the studies was resolved by consensus, and where necessary, group discussions among all investigators.

Data extraction and synthesis

Data extraction for each paper was performed in duplicate using a standardised electronic excel template based on the framework of critical appraisal and data extraction for systematic reviews of prediction modelling studies checklist[17] to extract information on each risk prediction model. When the same study described multiple risk prediction models or applied multiple data sources for validation, each prediction model or data source was included separately. Any discrepancy after comparing the data extracted in duplicate was resolved by consensus, and where necessary group discussion among all investigators.

Extracted information included publication details (author, year, country, study name if applicable); study setting and population (outcome to be predicted, time-frame of prediction, source of data, sample size including total number for development and/or validation, number with outcome and number excluded); methods of model development (type of the regression model, variable selection method, missing data handling); predicting variables

(including the number of potential predictors considered and selected, and, their associated parameters (ie, exponentiated regression coefficients and a measure of uncertainty, that is, SE or 95% CI)); and, if available, reported performance measures in internal or external validation for calibration (calibration plot, the ratio of expected to observed (E/O) probabilities, Hosmer-Lemeshow test) and discrimination (area under the receiver operating characteristic curve (AUROC)).

Bias assessment was performed in parallel to data extraction, also in duplicate, and for both model development and validation, following the framework of prediction model risk of bias assessment tool (PROBAST),[18] allowing to classify each study as having a high, unclear or low risk of bias for the domain of participants, predictors, outcome and analyses. No studies were excluded based on bias assessment alone.

Data analysis

Eligible studies and their prediction models were summarised in evidence tables. Furthermore, we inquired the established lifestyle aetiological risk factors, as taken from the Continuous Update Project (CUP) steered by the World Cancer Research Fund Network,[19] to be employed in the different risk prediction models. After identifying those lifestyle factors with an explanatory and predictive character, their retrieved estimates and uncertainty were standardised to be visually compared in forest plots, stratified according to their choice of comparison; for continuous variables per X-level increment, and for categorical variables, the contrast between the groups, using the extremes if more than two groups available. The type of the estimates varied between the studies included in our systematic review, hence conversion of ORs and HRs into a risk ratio (also known as relative risk, RR) was necessary for comparability. All non-RR point estimates were converted to RR using one of the following equations:

$$RR = \frac{OR}{(1-p_0)+(p_0 \times OR)}$$

or

$$RR = \frac{1-e^{HR \times \ln(1-r)}}{r}$$

where p_0, and r represent the baseline risk and the incidence rate, respectively, of the outcome for the reference group, or when not reported for the referent of a particular risk factor class under study, the incidence proportion or rate for the overall study population was taken. Studies were omitted from the quantitative analyses when they did not report a measure of uncertainty for the predictors included in their final prediction model, or when their risk prediction model was built on estimates of RRs taken from the literature. Statistical analyses were carried out in R V.4.1.2, and a p value of <0.05 was considered statistically significant.

RESULTS

The initial search yielded 2365 articles, and after removing duplicates, 1613 abstracts were screened yielding 23 articles to be retrieved for full-text review (figure 1). After exclusion of 18 articles for varied reasons (as mentioned in figure 1), and an additional inclusion of 12 full-text articles identified through hand searching from citations (ie, five from previously published review, and seven from studies reporting the validation for a European population of a prediction model developed elsewhere), a total of 17 studies were included in the present review.

Model development studies

This review identified eight studies,[20–27] describing the development of risk prediction models developed in a European population (accounting for a total of 10 different models), and eight studies,[28–35] describing risk prediction models developed elsewhere but validated in Europe (accounting for a total of 11 different models) (online supplemental table 1). The majority of the latter were developed in US populations (seven models).[28–30 32 35]

In addition to the country of origin of the model, the risk prediction models identified were differentiated by their choice of predicted outcome: either prevalent advanced neoplasia at screening[20–25] or CRC incidence at 5–20 year from assessment.[26–35] The former has the aim to classify at-risk individuals as eligible for screening (ie, screening eligibility) and the latter to identify population groups at higher risk of CRC who should benefit most from preventive programmes (ie, population-wide primary prevention). In this respect, the data sources and the methods used for model development were different: for prevalence models discerning screening eligibility models, a logistic regression with cross-sectional data from screening records was used, while models predicting incidence used generally a Cox (proportional hazards) regression model with data from prospective cohorts including a record linkage with cancer registries.

When assessing bias according to PROBAST, most models developed were considered to carry an either unclear or high risk of bias for the domain of analyses (A) due mainly to inadequate handling of participants with missing data,[20–23 25 27 29–32] and/or applying univariate analysis for selecting predictors[20 29 31 33] as well as lack of accounting for optimism and overfitting.[20 22 23 25 30 34]

Variables included in the risk prediction models

Predictors were categorised into five types: demographic, medical history (family and personal) and lifestyle (anthropometrics and lifestyle factors) (online supplemental table 2). The number of predicting variables varied widely: from two (as in Taylor *et al* model)[32] to thirteen (as in Colditz *et al* women-only model).[28] From the list of variables selected in the risk prediction models, age was included in all risk prediction models (16 models),[20–25 27 29–35] while other most common identified predictors were body mass index (BMI) (13 models),[20 21 23 26 28–31 33–35] smoking (13 models),[23–27 29–31 34] alcohol consumption

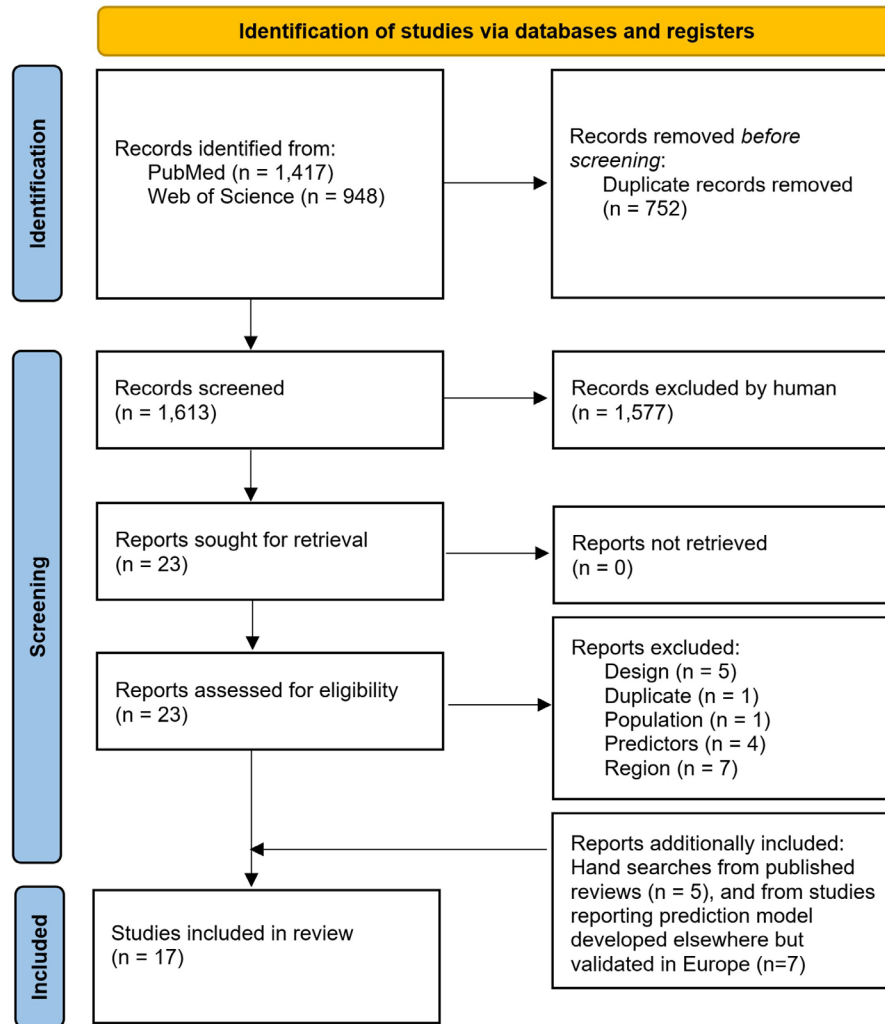**Identification of studies via databases and registers**

Identification

Records identified from:
PubMed (n = 1,417)
Web of Science (n = 948)

→ Records removed *before screening*:
Duplicate records removed (n = 752)

Screening

Records screened (n = 1,613)

→ Records excluded by human (n = 1,577)

Reports sought for retrieval (n = 23)

→ Reports not retrieved (n = 0)

Reports assessed for eligibility (n = 23)

→ Reports excluded:
Design (n = 5)
Duplicate (n = 1)
Population (n = 1)
Predictors (n = 4)
Region (n = 7)

Reports additionally included:
Hand searches from published reviews (n = 5), and from studies reporting prediction model developed elsewhere but validated in Europe (n=7)

Included

Studies included in review (n = 17)

Figure 1 Flowchart of studies included in the review. From: Page MJ *et al.*[52] For more information, visit: http://www.prisma-statement.org/.

(11 models),[25–29 31 33–35] family history of colorectal/colon cancer (11 models),[21 23–25 28 30 32 33 35] followed by physical activity (7 models),[26–31 35] sex (8 models),[20–25 34] and the use of non-steroidal anti-inflammatory drugs (NSAIDs); four models.[25 28 30 35] Diet-related factors were selected as predictor only in a limited number of models, with the most shared being the consumption of meat (included in nine models within two as total meat,[33] four as red meat[25–28] and three as processed meat)[26 27] and vegetables (five models).[27 28 30] No lifestyle factors were included in two models.[22 32]

For a visual comparison of model-specific estimates of lifestyle predictors that are also recognised as aetiological factor, data from 12 studies representing 16 risk prediction models (half of them developed in Europe[20 21 23–27] and half only validated in Europe[29–35] were depicted). The predictors from Usher-Smith *et al*[26] and Colditz *et al* model[28] were excluded because they obtained RR estimates from literature.

From the lifestyle risk factors considered convincing or probable by the CUP programme,[19] the following factors were also included in the risk prediction models: BMI and waist circumference as anthropometric predictors, and as lifestyle factors physical activity, alcohol, meat (red, processed and total) and dairy consumption as well as smoking. Online supplemental table 3 presents the model-specific effect sizes as reported, as well as the RR, as displayed in the forest plots (figure 2).

For anthropometrics, the model-specific estimates for BMI of RR ranged from 0.90 (95% CI 0.58 to 1.36) to 1.50 (1.00; 2.10) for overweight (nine models,[20 23 29 30 33 35] from 0.95 (0.58 to 1.52) to 1.93 (1.27 to 2.82) for obesity (eight models,[20 23 29 30] and varied between 1.00 (0.90 to 1.10) and 1.05 (1.02 to 1.08) per one unit increment in BMI (three models.[21 31 34] For waist circumferences between 1.05 (1.01 to 1.09) and 1.19 (1.13 to 1.23) per 10 cm increment (3 models[27] (figure 2A). These estimates for continuous RR were slightly greater than those calculated by the CUP dose-response meta-analysis (online supplemental table 3A).

For the lifestyle behaviour predictors, their independent predictive contribution was generally greater when they were collected with greater detail, allowing for comparison of extremes instead of a two-level categorical
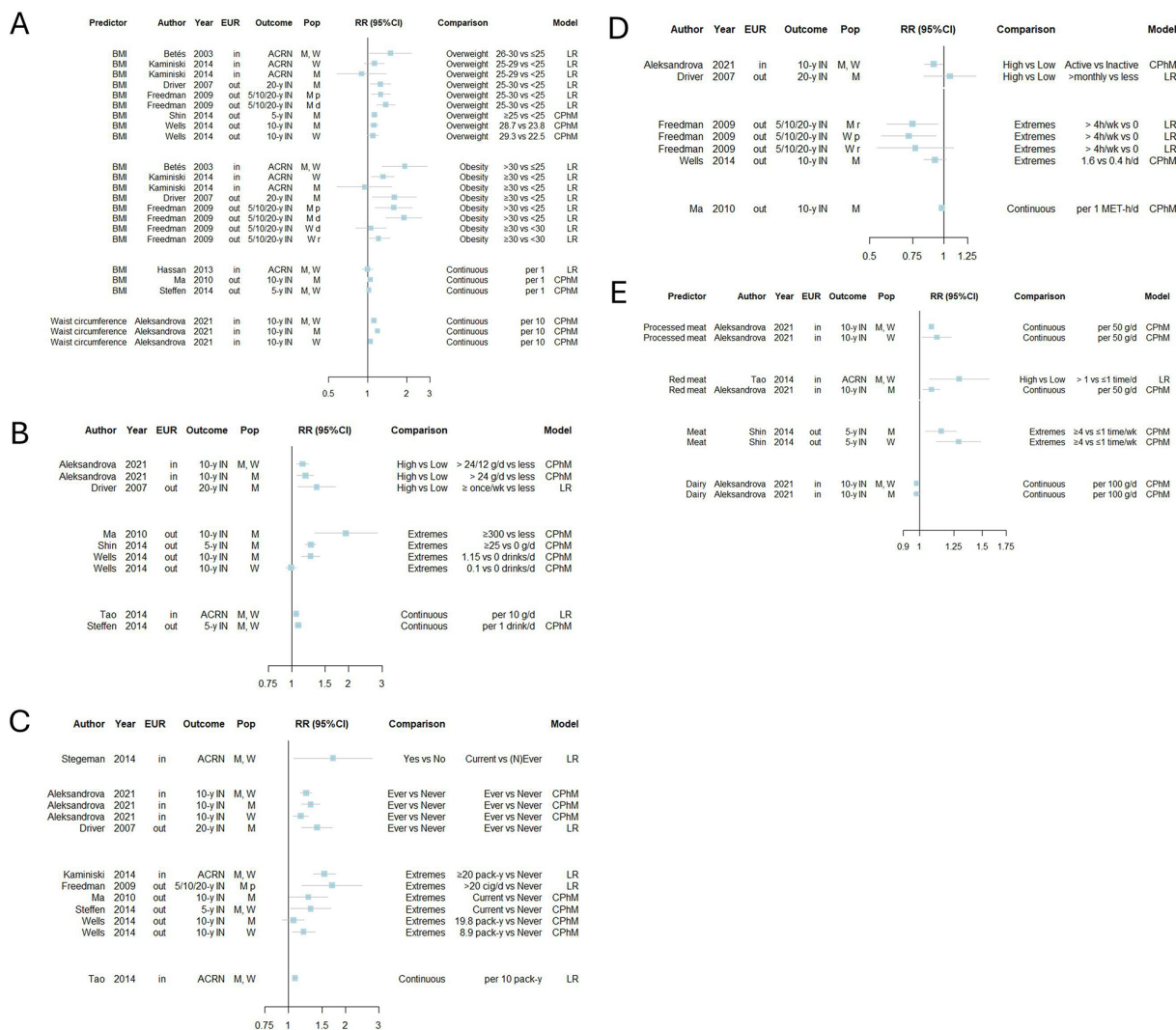
Figure 2 Forest plots of standardised (RR and corresponding 95% CI) estimates of lifestyle predictors, that are also recognised as aetiological factors, across risk prediction models stratified by their choice of comparison group.[1] [1]Excluded from the plots are the model of Usher-Smith *et al*[26]; Colditz *et al*[28] because they obtained their relative risk estimates from literature. (A) Anthropometrics (BMI in kg/m² and waist circumferences in cm). (B) Lifestyle factors: alcohol. (C) Lifestyle factors: smoking. (D) Lifestyle factors: physical activity. (E) Lifestyle factors: Diet. ACRN, advanced colorectal neoplasia; BMI, body mass index; cig, cigarettes; CPhM, Cox Proportional-hazards model; d, distal colon; EUR, European population ('in' developed in a European population, and 'out' developed outside a European population); IN, incidence; LR, logistic regression; M, model developed in men; p, proximal colon; r, rectal colon; RR, relative risk; W, model developed in women.

variable (online supplemental table 3B). Additionally, the predictive contribution of alcohol consumption and smoking showed a noticeable variation, particularly for alcohol ranging from 1.14 (1.06 to 1.22) to 1.35 (1.08 to 1.69) when comparing high versus low (three models,[27 29] and from 0.99 (0.93 to 1.06) to 1.93 (1.21 to 2.83) when comparing extremes (four models)[25 33 35] (figure 2B), and for smoking from 1.16 (1.06 to 1.27) to 1.41 (1.17 to 1.70) when comparing ever versus never (four models)[27 29] and from 1.06 (0.93 to 1.21) to 1.70 (1.12 to 2.33) when comparing extremes (six models)[23 30 31 34 35] (figure 2C). For the lifestyle predicting factors of physical activity and diet, the model-specific effect sizes across risk prediction equations were found to be of similar magnitude, although the limited number of risk model equations (figures 2D and 2E).

Model validation studies

A total of 11 studies were identified describing the validation of a risk prediction model for CRC in a European population, either for models developed in Europe (8 studies[20–27] validating a total of 10 models) or for models developed elsewhere (1 study[36] validating a total of 11 models) (online supplemental table 4). For the models developed in a European population, four of them[20–22 24] were only internally validated, that is, the development was also used for validation, while four[23 27] were validated by splitting the data into training and testing sets, and two externally validated using a different data source.[25 26] Model calibration was reported by a calibration plot displaying the observed against the predicted probabilities (5 studies)[20 24 26 27 36] and/or Hosmer-Lemeshow test (5 studies),[21–25] all suggesting no evidence

for significant over- nor underprediction of risk. All studies, except one,[21] reported the discriminating ability of the risk prediction model, as operationalised using the AUROC, that is, the c-statistic. In general, various levels of estimated discrimination were observed with c-statistics varying between 0.58[30] and 0.76,[24] yet this was irrespectively of the origin of the model and the data sources used for validation.

According to PROBAST, most models validated were considered to carry an either unclear or high risk of bias for the domain of 'analyses' (A) because of inadequate handling of participants with missing data[20–23 25 27 29–32 36] and/or only considering calibration instead of both calibration and discrimination.[21] External validation studies were considered to carry an unclear risk of bias for the domain of 'predictors' (P) and 'outcome' (O) in case of divergent predictor assessment and prediction time interval, respectively, for the external data source as intended with model development.[36]

DISCUSSION

This systematic review and meta-analysis summarised and quantified the evidence published over the last two decades on primary CRC risk prediction models with routinely available or easily ascertained predictors, validated for a European population. In addition to older age, and male sex, other commonly shared risk factors identified in the risk prediction models reviewed were family history of (colorectal) cancer, the use of NSAIDs, overweight or obesity, and lifestyle variables such as alcohol consumption, smoking and physical inactivity. Validation studies suggested overall good calibration, as showed by calibration plot and/or Hosmer-Lemeshow test, and acceptable discrimination, as shown by c-statistics closely to 0.7 for most models.

To the best of our knowledge, this work is the first to visualise the predictive value of commonly present lifestyle predictors, that are also recognised as aetiological, employed in CRC risk prediction models. Supported by these results and proven associations from aetiological studies, targeting lifestyle factors, including diet, in those at highest risk could complement CRC screening prevention programmes as means to reduce cancer risk and improve overall health and survival after cancer diagnosis.[37 38] Particularly, dietary exposures, which may play a prominent role in the CRC prevention,[39] is inherently challenging to assess, and therefore barely considered as a predictor. Though predictors may be any variable associated with outcome, casually or otherwise, considering particularly the previously identified causal factors as predictors would enhance credibility and uptake of the model in different settings and populations.[40 41] Both the models of Usher-Smith et al[26] and of Colditz et al[28] summarised the probable/convincing evidence of associations into a risk score using RR available in published literature. This establishing a claim of prediction from association studies is a recognised conflation in causal

research, and likewise the most frequent conflation type in prediction studies is the aetiological interpretation of prediction results, attributing causal meaning to the individual predictors.[42 43]

Still, various remaining key statistical considerations were often not addressed in the existing CRC risk prediction studies, and hence they were considered to be at unclear or high risk of bias for their analyses. In particular, not only in the selection of predictors (ie, univariate prior to multivariate)[18] but also in the handling of missing data and the corrections for optimism and overfitting. Consistent with the literature, the most commonly adopted approach for handling missing data was the complete-case analysis, that is, (automatically) removing individuals with missing data on predictor or outcome variables from the analysis, in spite of its increased susceptibility to bias in estimated model parameters and model's predictive performance.[44 45] Instead, multivariable imputation models, that is, to generate (multiple) imputation(s) conditionally on observed patient characteristics, has been generally recommended to avoid bias in model development and validation[44 45] as well as during model application in clinical practice,[46 47] but barely implemented (also in this review in only four studies). Furthermore, with the increasing interest in accurate risk prediction, it is key to evaluate its external validity, that is, its predictive performance outside of the development sample. While a vast majority of external validation studies were poorly reported/performed,[48 49] current research recognises a potentially inferior performance of prediction models in external validation studies.[49] This relates back to the need for model development studies to adjust for model overfitting and optimism in model performance by including internal validation techniques of cross-validation or bootstrapping.[49] If optimism is present, adjusting or shrinking the model predictive performance estimates and predictors in the final model may be needed, provided that an adequately large development sample with a reasonable number of events per variables are available.[50] Future (CRC) risk prediction model development studies should, therefore, incorporate improved methodological quality by at least avoiding univariable selection before multivariable modelling, applying multiple imputation for missing data, and adjusting for model overfitting and optimism.

Evidence synthesis of studies assessing a model's performance in new individuals (ie, external validation) plays a key role in interpretating the potential applicability and generalisability of a prediction model across different settings and populations.[51] However, in this study, the retrieved estimates of model discrimination and calibration could not be summarised into a weighted average because external validation studies for CRC risk prediction models were limited for European populations. Nevertheless, model performance was similar for models developed inside or outside of Europe, suggesting a high generalisability of models incorporating demographic and phenotypic (eg, lifestyle) factors. Particularly models with high predictive performance across different

population and subgroups might, therefore, have a good potential for future implementation in screening and clinical settings.

CONCLUSIONS

In conclusion, lifestyle factors, beyond age and sex, were identified as significant modifiable predictors in multiple risk prediction models for CRC. Early identification of high-risk groups or individuals based on lifestyle-based data would, therefore, offer the potential to encourage participation in tailored lifestyle and screening programmes and subsequently reduce the CRC burden. However, external validation of the models identified is recommended to further investigate their predictive performance across different settings and populations, aiding the selection and optimisation of the best models for use in clinical practice.

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