The Lancet Global Health

Performance of Initial Screening Tests for Colorectal Cancer and Subsequent Adherence to Colonoscopy: An Ecological Study

--Manuscript Draft--

Manuscript Number:	LANGLH-D-20-00215
Article Type:	Article (Original Research)
Keywords:	ecological study; colorectal cancer; screening; adherence to colonoscopy
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Abstract:	Summary Background Adherence to colonoscopy in colorectal cancer (CRC) screening is at a low level and varies greatly across populations. No study has examined the influencing factors of colonoscopy adherence at a population level, and this remains to be an unaddressed knowledge gap. We therefore aimed to analyze the correlation between performance of initial CRC screening tests and subsequent adherence to colonoscopy base on an ecological evaluation. Methods The sensitivity, specificity, and positive predictive value (PPV) of initial CRC screening tests and subsequent adherence to colonoscopy in different populations were extracted from relevant studies published in English up to December 31, 2018. The age-standardized incidences (ASR) of CRC across populations in the year of screening were obtained from the Cancer Statistics data. Locally weighted regression smoothing was used to examine the relationship between adherence to colonoscopy and ASR of CRC. Cut-off points of adherence on ASR were identified by Joinpoint Regression and used in Regression Discontinuity as potential thresholds. Spearman's correlation analysis was used to calculate correlation coefficients.

Findings

We identified 192 eligible articles. The median and interquartile range of adherence to colonoscopy was 82·5% (71·8%-90·5%). The adherence was significantly correlated with ASR of CRC in the study populations (r=0·187, p<0·001) and marginally with the PPV of initial screening tests (r=0·105, p=0·077). The change points of the adherence to colonoscopy were identified at the ASR of 32·5 and 142·5/100,000, and the ratio of adherence to colonoscopy at 143/100,000 was 0·900. In countries / areas with a moderate ASR, adherence to colonoscopy was negatively correlated with the sensitivity (r=-0·367, p=0·023) and positively with the PPV (r=0·143, p=0·040), whereas in populations with a high ASR, flexible sigmoidoscopy was more widely used as an initial screening test and achieved a high subsequent adherence to colonoscopy.

Interpretation

Adherence to colonoscopy is correlated with the performance of initial screening tests, particularly among populations with moderate CRC incidence. Initial screening tests with high PPV or specificity may help to increase population adherence to colonoscopy, but different strategies should be used in countries / areas with a high or moderate incidence of CRC.

Performance of Initial Screening Tests for Colorectal Cancer and Subsequent Adherence to Colonoscopy: An Ecological Study

Running title: Initial screening tests for CRC and adherence to colonoscopy

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Summary:

Background Adherence to colonoscopy in colorectal cancer (CRC) screening is at a low level and varies greatly across populations. No study has examined the influencing factors of colonoscopy adherence at a population level, and this remains to be an unaddressed knowledge gap. We therefore aimed to analyze the correlation between performance of initial CRC screening tests and subsequent adherence to colonoscopy base on an ecological evaluation.

Methods The sensitivity, specificity, and positive predictive value (PPV) of initial CRC screening tests and subsequent adherence to colonoscopy in different populations were extracted from relevant studies published in English up to December 31, 2018. The age-standardized incidences (ASR) of CRC across populations in the year of screening were obtained from the Cancer Statistics data. Locally weighted regression smoothing was used to examine the relationship between adherence to colonoscopy and ASR of CRC. Cut-off points of adherence on ASR were identified by Joinpoint Regression and used in Regression Discontinuity as potential thresholds. Spearman's correlation analysis was used to calculate correlation coefficients.

Findings We identified 192 eligible articles. The median and interquartile range of adherence to colonoscopy was 82·5% (71·8%-90·5%). The adherence was significantly correlated with ASR of CRC in the study populations (r=0·187, $p<0·001$) and marginally with the PPV of initial screening tests (r=0·105, p=0·077). The change points of the adherence to colonoscopy were identified at the ASR of 32·5 and 142·5/100,000, and the ratio of adherence to colonoscopy at 143/100,000 was 0·900. In countries / areas with a

moderate ASR, adherence to colonoscopy was negatively correlated with the sensitivity (r=-0·367, p=0·023) and positively with the PPV (r=0·143, p=0·040), whereas in populations with a high ASR, flexible sigmoidoscopy was more widely used as an initial screening test and achieved a high subsequent adherence to colonoscopy.

Interpretation Adherence to colonoscopy is correlated with the performance of initial screening tests, particularly among populations with moderate CRC incidence. Initial screening tests with high PPV or specificity may help to increase population adherence to colonoscopy, but different strategies should be used in countries / areas with a high or moderate incidence of CRC.

Funding This study was supported by the Local High Level University Construction Project of Shanghai and the Health Commission of the Pudong New Area of Shanghai (PW2019A-5).

Key words ecological study; colorectal cancer; screening; adherence to colonoscopy

Introduction

Colorectal cancer (CRC) ranks third in incidence and second in mortality worldwide.[1] Its early detection could be achieved through mass screening,[2,3] and the common initial screening tests include guaiac fecal occult blood test (gFOBT), fecal immunochemical test (FIT), flexible sigmoidoscopy (FS), and / or questionnaire-based risk assessment (RA). CRC screening has been proved effective in reducing both incidence and mortality of the cancer.[4,5] The effectiveness of screening, however, has been greatly hampered due to low adherence to subsequent colonoscopy in subjects with abnormal screening test results. According to the European Union guideline, adherence to colonoscopy should be more than 90% in population-based programs in order to achieve their screening benefits.[6] In reality, however, the adherence varied widely across populations and was as low as less than 50% in some regions.[7-9]

Colonoscopy follow-up for abnormal CRC screening test results is a complex process involving patients, physicians, and environmental factors.[10] To date, most studies on influencing factors for adherence to colonoscopy have focused on the characteristics and behaviors of patients and physicians, which were tailored to a specific population with limited generalizability and public health significance.[7] Environmental factors, particularly those at the population level, would be more important for policy making in CRC screening. In our previous report, we found that adherence to colonoscopy was most strongly correlated with the specificity and PPV of the initial screening tests in Chinese adults.[11] However, our prior study was not specially designed to evaluate the association between initial screening tests and adherence to colonoscopy.

In this study, we systematically searched relevant studies from existing literature and calculated age standardized incidence rates (ASR) of CRC in populations when screened. We hypothesized that performance of the initial screening tests was significantly correlated with adherence to colonoscopy based on an ecological approach.

Research in context

Evidence before this study

Adherence to colonoscopy in colorectal cancer (CRC) screening was at a low level and varied greatly across populations, greatly hampering the effectiveness of the screening. So far, most studies addressing influencing factors of adherence to colonoscopy have focused on the characteristics and behaviors of patients and physicians, which were tailored to a specific population with limited generalizability and public health significance. In our previous report, we found that adherence to colonoscopy was strongly correlated with the specificity and PPV of the assumed initial screening tests in Chinese adults, suggesting an important role of selected initial screening tests in adherence to colonoscopy.

Added value of this study

This study, for the first time, demonstrated that adherence to colonoscopy was correlated with the performance of initial CRC screening tests across populations base on an ecological evaluation. The correlations, in terms of both direction and magnitude, depended on age-standardized incidence of CRC in the populations when screened. Regardless of CRC incidence, high positive predictive value (PPV) and specificity of the initial screening test were found to be significantly related with subsequent adherence to colonoscopy. Quantitative or one-sample fecal immunochemical test was linked with a higher adherence to colonoscopy in countries or areas with moderate risk of CRC, whereas flexible sigmoidoscopy performed well in high risk populations.

Implications of all the available evidence

These findings imply that the performance of the initial screening test may play a crucial role in the success of CRC screening programmes. Different strategies should be used to select initial screening tests in countries / areas with a high or moderate incidence of CRC in current situation.

Methods

Sources of data

We searched the PubMed, Ovid-Embase, Web of Science Core Collection, and the Cochrane Library for studies published in English from their inception up to December 31, 2018 (Supplementary Table 1, appendix pp2-3). We also manually searched the references listed in the identified articles. All original articles published in English that presented CRC screening in average-risk populations were included. The included studies should involve program(s) that apply initial CRC screening tests, followed by subsequent colonoscopy or other diagnostic tests with figures on their adherence level. Pilot studies were also included if adherence to colonoscopy was not reported from the main studies. When results were based on the same population, the article reporting the latest data or including the performance of initial screening tests was included. Two investigators (Y. Y. and W. W.) independently screened the literature and reviewed full texts. Any disagreements were resolved by discussion with a third investigator (J. H).

Procedures

Three two-member groups (S. T. and J. F; T. Y. and D. M.; W. W and S. C) extracted the following items from each study independently: 1) first author and year of publication; 2) country / region where the study was conducted and the study period; 3)

basic characteristics of study subjects; 4) types of study design; 5) initial screening tests and follow-up diagnostic procedures; 6) numbers of subjects screened; subjects with abnormal initial screening results; subjects with abnormal initial tests taking a complete colonoscopy and subjects diagnosed as having CRC; 7) adherence to colonoscopy; 8) the sensitivity, specificity, and PPV of initial screening tests. For studies with no follow-up information on non-adherent participants, PPV was calculated as the number of patients diagnosed with CRC relative to the number of subjects tested positive by the initial tests and subsequently received a diagnostic procedure. Data extracted were examined and summarized by Y. Y and W. W.

The incidence of CRC in different populations during the screening periods was derived from the Global Health Data Exchange (GHDx) database[12] and the *Cancer Incidence in Five Continents* (CI5).[13-15] ASR was further calculated using the world standard population presented by Segi[16] and modified by Doll et al.[17]

Statistical analysis

All data analyses were performed using R 3·6·0 and Joinpoint Regression Program 4·7·0·0. The natural log-transformed adherence to colonoscopy was used in analyses. Locally weighted regression smoothing (LOESS), a nonparametric fitting method, was used to examine the relationship between adherence to colonoscopy and ASR of CRC. The smoothing parameter and degree of the polynomial were chosen based on the residual plot, scatterplot and analysis of variance.[18] To determine the number and location of significant change points of adherence in ASR of CRC, we calculated the average adherence to colonoscopy (both means and medians) in each 5/100,000 interval

of ASR in sequential order. We then performed Joinpoint Regression based on the scatter plot of means or medians of adherence to colonoscopy along with the incidence of CRC.[19] The Joinpoint regression model, if heteroscedastic, was fitted using weighted least squares with reciprocal of variances as weights. The identified cut-off points were then used in a Regression Discontinuity (RD) design as the potential thresholds. RD design is usually used in situations when a threshold is applied to a continuous variable (i.e. running variable) to decide whether candidates have received a treatment or not.[20,21] In RD design, each observation is assigned a weight based on the distance between the running variable and the cutoff point. Only those within a small bandwidth were included in RD design. In order to estimate the changes in adherence to colonoscopy analyzed by screening strategies, we fitted a local linear regression with adherence to colonoscopy as the outcome variable and ASR of CRC as the running variable. Spearman correlation coefficients(r) were employed to evaluate the correlations between adherence to colonoscopy and 1) the ASR of CRC, 2) the sensitivity, specificity and PPV of the initial CRC screening tests across populations. A significance level (or alpha level) of 0·10 was used in the current study.

Sensitivity analysis was further conducted by excluding pilot studies, second or subsequent screening rounds, and records of adherence to multiple diagnostic procedures.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had access to all

the data in the study and had final responsibility for the decision to submit for publication.

Results

Studies selected

The flow chart of literature selection is shown in Figure 1. A total of 9,772 citations published in English were identified. After excluding duplicates (n=3,810) and other ineligible reports (n=5,115), 902 articles were selected for full-text review (including 55 citations identified through manual searching). Of these, 710 citations were further excluded based on the eligibility criteria, and 192 articles were finally included in the analysis.

Included studies were published from 1984 to 2018. The involved screening programs were conducted during the period from 1976 to 2018, with the number of participants ranging from 92 to 6,337,086. The subjects recruited in most screening programs were at the age of 50 to 75 years. Of 192 articles included, 141 used an observational approach and 51 were of experimental design. Among these studies, 14 were based on pilot data and 28 included data from multiple screening rounds. Most studies were conducted in Europe (110), followed by Asia (41), North America (34), South America (4), Oceania (2) and in multiple countries (1).

A total of 316 records for adherence to colonoscopy, 55 for sensitivity and specificity of initial screening tests and 284 for PPV were extracted from 192 articles. Initial screening tests included FIT (158), gFOBT (92), FS (16), RA (5) and combined tests, mainly parallel or serial tests of FIT and gFOBT (11, 43, respectively) and parallel tests of gFOBT, FIT or both with FS or RA (5, 6, respectively). In addition, 289 records for

adherence to colonoscopy alone were extracted, while others with figures on adherence to diagnostic procedures, including double-contrast barium enema and sigmoidoscopy, were also included (Supplementary Table 2, appendix pp 4-17).

ASR of CRC in screened populations

ASR of CRC in each screened population during the period of screening was presented by records as a Supplementary Table (Supplementary Table 3, appendix pp18-24). ASR of CRC ranged from 17·6 to 352·0/100,000 across the screened populations.

Adherence to colonoscopy across countries

As shown in Table 1, the overall median and interquartile range (IQR) of the adherence levels to colonoscopy in all studies was 82·5% (Range: 71·8%-90·5%). Adherence to colonoscopy in Europe was much higher than that in Asia and North America, and slightly higher in populations using FS than those using occult blood test. The average adherence to colonoscopy was also observed to be higher in populations using quantitative FIT than those using qualitative test. Furthermore, a higher adherence to colonoscopy was generally linked with a higher PPV in subpopulations classified by region, study type, type of FIT and number of samples for FIT, but not by initial screening tests.

Overall, we found a significant correlation between adherence to colonoscopy and PPV of initial screening tests (r=0·105, p=0·077) at the population level, but did not observe a significant correlation in subpopulations using specific initial screening tests (Table 2). A significant correlation was also observed for adherence to colonoscopy and the ASR of CRC at population level (r=0·187, $p<0·001$). Additionally, the correlation was

positive in records using FIT only or those using FS as an initial screening test, but not in records using gFOBT or parallel tests of FIT with other tests (Table 2).

To delineate the relationship between adherence to colonoscopy and the incidence of CRC, we presented the scatter diagram and LOESS curve of adherence to colonoscopy (natural log transformation) by countries or areas according to the respective incidence of CRC. Adherence to colonoscopy was above 70% in most European countries, but very few reached 90%. On the other hand, the adherence varied substantially in countries in Asia and North America, whilst the adherence levels in China, the United States and Korea was less than 50%. Noted that adherence to colonoscopy increased with the incidence of CRC. The adherence reached a peak at an approximate incidence level of 80/100,000, then remained stable until reaching an incidence of 170/100,000, and then decreased thereafter (Figure 2).

A similar pattern of correlation was observed across populations using either FIT or gFOBT as an initial screening test, but with shifted adherence peaks on the incidence of CRC (Figure 3). Interestingly, when FS was used as an initial screening test, adherence to colonoscopy was observed to be higher in populations with a high incidence of CRC.

Change points for adherence to colonoscopy along with CRC incidence

We further identified change points in adherence to colonoscopy along with CRC incidence using Joinpoint regression. When using the medians of adherence to colonoscopy as dependent variable, logarithmic adherence to colonoscopy increased sharply with incidence among populations with ASR of CRC less than 32·5/100,000 (slope=0·052, p=0·111); increased slowly in incidence levels between 32·5 and

142·5/100,000 (slope=0·002, *p*=0·149), and decreased thereafter (slope=-0·003, p=0·005) (Figure 4a). Considering the limited number of studies between the two cut-off points, we performed a sharp RD with a single cutoff point for accurate estimation. As shown in Figure 4c, the ratio of adherence to colonoscopy was 0·900 (95% robust CI: 0·699-0·997) at the CRC incidence of 143/100,000 (Supplementary Table 4 and 5, appendix pp 25-26).

When using the means of adherence to colonoscopy as a dependent variable in Joinpoint regression, a change point was identified at the incidence of 85·2/100,000 (Figure 4b). However, significant discontinuity was not observed via further RD analysis (Figure 4d).

Correlation between performance of initial screening tests and adherence to colonoscopy

Further analysis was conducted to correlate the performance of initial screening tests and adherence to colonoscopy within each interval of CRC incidence classified by change points. No significant correlation was observed for adherence to colonoscopy with the specificity of initial screening tests regardless of CRC incidence. However, adherence to colonoscopy was significantly correlated with the sensitivity (*r*=-0·367, *p*=0·023) and PPV (*r*=0·143, *p*=0·040) of initial screening tests in populations with incidence of 32·5 to 142·5/100,000. In populations with CRC incidence more than 142·5/100,000, an insignificant negative correlation was observed between adherence to colonoscopy and PPV (Table 3).

Sensitivity analysis

Overall, the sensitivity analysis showed that the sensitivity of initial screening tests was higher but their specificity was lower, and adherence to colonoscopy became slightly lower than those in the main analysis. The distribution patterns of adherence to colonoscopy across screened populations were similar to those in the main analysis. Despite the changed cut-off points of CRC incidence for adherence to colonoscopy, adherence to colonoscopy was still positively correlated with PPV of initial screening tests and CRC incidence among populations with low CRC incidence. However, in countries with higher incidence, adherence to colonoscopy was significantly negatively correlated with CRC incidence (Supplementary Table 6-8 and supplementary Figure 1-3, appendix pp 27-33).

Discussion

To our knowledge, this comprehensive ecological study is the first effort to investigate the profile of adherence to colonoscopy across geographic regions by the ASR of CRC. We found that adherence to colonoscopy was positively correlated with the PPV of initial screening tests at the population level. However, the correlation differed by incidence of CRC in screened populations, particularly in populations with moderate CRC incidence. Adherence to colonoscopy was positively correlated with PPV but negatively with the sensitivity of initial screening tests, suggesting the importance to improve the specificity of initial screening tests in countries with a moderate but increasing incidence of CRC like China.

Benefits of CRC screening in early detection of CRC could be achieved only if abnormal results were adequately followed up. A microsimulation model estimated that

individuals who never received colonoscopy were four times as likely as to die of CRC when compared with subjects who received colonoscopy subsequent due to abnormal initial screening tests.[22] However, along the continuum of CRC screening, timely colonoscopy follow-up was not of a substantial concern among the participants[10]. Unlike initial screening tests which are usually well organized and advocated, colonoscopy examinations are conducted in hospitals through clinic visits by those with abnormal results. Whether these subjects would seek further colonoscopy examination is greatly dependent on their trust on the accuracy of the test results.

The major finding in current study is the significant positive correlation between adherence to colonoscopy with the PPV of initial screening tests in populations with a moderate incidence of CRC. Our finding is consistent with our previous report, in which we assumed several screening modalities among Chinese adults who received RA and two-sample FIT as initial screening tests.[11] This indicated that a tradeoff decision between costs and effectiveness should be made in selection of initial screening tests to ensure adherence to colonoscopy among positive subjects in China and other low and middle income countries or areas with moderate CRC incidence.

The PPV of a screening test is not only affected by the specificity and sensitivity of the test, but also by the prevalence of CRC in the screened population. Unlike results from our previous report,[11] we did not find a significant positive correlation between adherence to colonoscopy and the specificity of initial screening tests in this ecological study. However, the significant negative correlation with sensitivity of initial tests across populations with moderate CRC incidence strongly supports the importance to improve

PPV by increasing specificity.

In reality, however, CRC cancer screening is usually carried out as a public health service program. In order to avoid missing CRC, policy-makers tend to select initial screening tests with high sensitivity. Under the circumstance, a large number of false positive results may discourage positive subjects to take relatively invasive and "useless" colonoscopy examination, and thus impair the effectiveness of CRC screening. A cost-effectiveness analysis is warranted to examine the impact of initial screening tests on adherence to colonoscopy in CRC screening program based on the real-world data.

In populations with a high incidence of CRC, selection of initial screening tests is also the key to ensure adherence to colonoscopy although an insignificant negative correlation was observed between the PPV and adherence to colonoscopy across the populations. It is of note that in these populations, use of FS resulted in an average adherence to colonoscopy of more than 90%. Considering the higher sensitivity and specificity of FS than other screening tests,[23] our results suggest that accuracy of initial screening tests as well as the test results, is the main driver for colonoscopy uptake in these countries/areas. Due to the high cost and invasive nature of the examination, however, the cost-effectiveness of screening programs should be optimized by predefining screened population when using it as an initial screening test.

In this study, we found that one-sample FIT and quantitative FIT were linked with higher adherence to colonoscopy, which may be partly explained by their higher specificity or PPV.[24,25] Compared with one-sample FIT, multiple rounds of two-sample FIT screening failed to improve diagnostic yield at the cost of higher colonoscopy supply.[26,27]

Owing to its limited additional benefit, two-sample FIT should not be routinely recommended as an initial screening test instead of one-sample FIT.

Quantitative FIT, on the other hand, is more accurate than qualitative FIT partly due to the methods of faecal sampling. In quantitative FIT, stool sample is taken by scratching the whole surface of feces and measured with an accurate concentration of hemoglobin through automated machines, whereas in qualitative FIT stool sample is just sampled by inserting a stick in several sites of faces and the result is obtained by observing the colored bands.[25] The observed higher specificity of quantitative FIT and higher adherence to colonoscopy provide supporting evidence for its use as an initial screening test. Moreover, test specificity can be modified by adjusting the cut-off points for positive results, making it possible to optimize the initial screening test.

There are several strengths in this first ecological study that linked the performance of initial screening test and colonoscopy adherence. First, the ecological study design enables us to evaluate the potential influence of initial screening tests on adherence to colonoscopy, which could not be examined at the individual level. Second, the thorough literature search of this study guaranteed the wide coverage of publications, enabling us to overview panorama of adherence to colonoscopy in CRC screening programs around the world. Third, the combined use of LOESS, joinpoint regression and RD design helps us to profile variations in adherence to colonoscopy along with incidence of CRC at population level. Particularly, we applied Joinpoint regression to identify change points and used the points as potential thresholds in RD design. Although the cut-off points identified by the two methods did not match perfectly due to their different algorithms, a

significant jump in RD was observed very close to the change points identified by joinpoint regression. Moreover, we conducted correlation analyses in subgroups classified by initial screening tests or by intervals of CRC incidence, allowing us to reveal the different correlations across sub-populations. Finally, the incidence of CRC in each screened population at specific year of screening was adjusted to the world population, minimizing the confounding effect of age and screening time in CRC incidence.

Our study has also several limitations. First, due to the nature of ecological study design, our results were observed at population level and might not be directly applied at the individual level. Interpretation of the findings should take into account the presence of potential confounders. Second, the small number of records or studies in some subgroups lowered the statistical power in estimation of the correlation coefficients between adherence to colonoscopy and performance of some initial screening tests like quantitative FIT and FS. Finally, the included articles varied in sample size, quality, and implementation procedures, which have not been considered in correlation and regression analyses.

Conclusions

This ecological study reported CRC incidence-dependent correlations between adherence to colonoscopy and performance of initial screening tests at the population level. Our results suggest that high PPV or specificity of initial screening tests is central to optimize subsequent colonoscopy follow-up, but different strategies should be used in countries / areas with a high or moderate incidence of CRC. FS should be used in high risk populations, while quantitative or one-sample FIT should be employed in countries or

areas with moderate risk of CRC in current situation.

Contributors

Y.H.Y. designed the search strategy, performed literature search, extracted and examined data, analyzed and interpreted the data and drafted the manuscript. J.J.H. devised the search strategy, performed the literature search, provided statistical suggestions and revised the manuscript. W. M.W. devised the search strategy, performed the literature search, extracted and examined data. S. S.T. performed the literature search and extracted the data. J.X.F., T.Y., D.D.M., S. K.C extracted data. F.F.M., M.W., D.T.H., J.F.S., N.H.L. and M.C.W. interpreted the data and revised the manuscript. W.H.X. conceived and designed the study, revised the manuscript and supervised the quality of the study throughout the conduct of the project. All authors have approved the final draft submitted.

Declaration of interest

We declare that we have no competing interests.

Data sharing statement

All data generated or analyzed during this study are included in this Article and its supplementary information files.

Supplementary Material

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Figure Legends

Figure 1 Flow chart of literature search and study selection

CRC, colorectal cancer.

Figure 2 Adherence to colonoscopy by the age-standardized incidence of CRC across countries / areas

The loess curve was fitted with span=0·7 and degree=2.

Red point: Europe; Green point: Asia; Blue point: North America; Yellow point: South America; Grey point: Oceania.

CRC, colorectal cancer; UK, United Kingdom; USA, United States of America.

Figure 3 Adherence to colonoscopy along with the age-standardized incidence of CRC by initial screening tests

The loess curves were fitted with span=0·5, degree=2 (FIT), span=0·6, degree=1 (gFOBT) and span=0·6, degree=2 (FS).

CRC, colorectal cancer; FIT, fecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac fecal occult blood test.

Figure 4 Joinpoint and discontinuity regressions of average adherence to colonoscopy along with age-standard incidence of CRC (A. using medians of colonoscopy adherence in each 5/100,000 interval of incidence; B. using means of colonoscopy adherence in each 5/100,000 interval of incidence； C. using medians of colonoscopy adherence in each 5/100,000 interval of incidence; D. using means of colonoscopy adherence in each 5/100,000 interval of incidence)

Note: Quantile-spaced bins in the RD plot were constructed by mimicking variance method. RD model was fitted using local linear regression with a triangular kernel and mean-squared error (MSE)-optimal bandwidth.

* p value <0·10; ** p value <0·05; *** p value <0·01.

CRC, colorectal cancer; RD, regression discontinuity.

Table 1. Summarized age-standardized incidence of CRC, performance of initial screening tests and adherence to colonoscopy

Median (IQR)	Incidence of CRC (1/100,000)	Sensitivity (%)	Specificity (%)	PPV (%)	Adherence to colonoscopy (%)
Overall	118·1 (92·6~145·3)	66·7 (47·2~83·3)	96·2 (94·1~97·8)	5·9 (3·6~8·2)	82·5 (71·8~90·5)
By continent					
Europe	125·1 (109·1~149·2)	63·1 (46·5~82·5)	97·2 (94·4~98·3)	6·4 (4·6~8·4)	87·7 (80·2~92·0)
Asia	79·8 (42·3~105·9)	75·4 (49·2~88·3)	95·4 (89·0~96·4)	4·5 (1·8~7·9)	72·0 (53·4~81·3)
North America	122·0 (109·0~150·1)	74·4 (68·0~78·4)	96·0 (95·0~96·6)	3·1 (1·6~6·8)	65·8 (53·5~80·6)
By study type					
Experimental	114·8 (93·3~151·5)	55·6 (43·6~66·7)	96·4 (92·3~98·9)	6·0 (3·0~9·8)	85·5 (74·0~91·1)
Observational	118·4 (91·8~142·5)	73·6 (50·0~84·3)	96·0 (94·2~97·6)	5·9 (4·0~7·7)	81·5 (70·9~89·6)
By initial screening tests					
FIT	120·8 (98·3~136·9)	83·3 (75·0~86·3)	94·9 (93·6~95·9)	5·2 (3·1~7·4)	80·9 (70·6~89·0)
gFOBT	111·5 (92·1~149·8)	47·9 (41·9~62·3)	98·2 (97·6~98·5)	7·5 (5·8~11·2)	87·5 (77·5~90·8)
FS	152·2 (114·5~171·3)	..	..	3·7 (1·5~6·6)	90·4 (75·3~95·7)
By type of FIT					
Quantitative	122·0 (106·6~139·8)	82·5 (74·1~85·6)	94·9 (94·1~96·1)	5·3 (3·9~7·1)	81·3 (73·3~90·2)
Qualitative	86·5 (54·7~106·9)	..	..	4·8 (1·4~8·0)	78·0 (69·6~82·0)
By no. of samples for FIT					

1-sample FIT	118·1 (91·9~137·6)	83·5 (73·7~86·5)	94·8 (94·0~95·8)	5·7 (3·9~8·0)	81·9 (69·1~89·2)
2-sample FIT or more	118·2 (107·9~147·8)	86·0 (81·5~89·6)	94·4 (92·8~94·6)	5·0 (3·9~6·2)	81·5 (79·6~91·2)

Incidence of CRC adjusted to the world population.

CRC, colorectal cancer; FIT, fecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac fecal occult blood test; IQR, interquartile range; PPV, positive predictive value.

Table 2 Spearman's correlation coefficients (r) between adherence to colonoscopy and age-standardized incidence of CRC and PPV of initial screening tests

	Incidence of CRC		PPV	
	No· of records	r	No· of records	r
All records	316	0·187***	284	0·105*
By initial screening tests				
FIT	155	0·436***	142	0·012
gFOBT	92	-0·168	84	0·140
FS	16	0·091	14	0·117
Parallel tests of FIT and/or gFOBT	13	-0·436	12	-0·049
Parallel tests of FIT/gFOBT & RA	6	-0·943***	6	0·600

Incidence of CRC adjusted to the world population.

*p value <0·10; **p value<0·05; ***p value <0·01.

CRC, colorectal cancer; FIT, fecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac fecal occult blood test; PPV, positive predictive value; RA, questionnaire-based risk assessment.

Table 3 Spearman's correlation coefficient (r) between performance of initial screening tests and adherence to colonoscopy by incidence of CRC

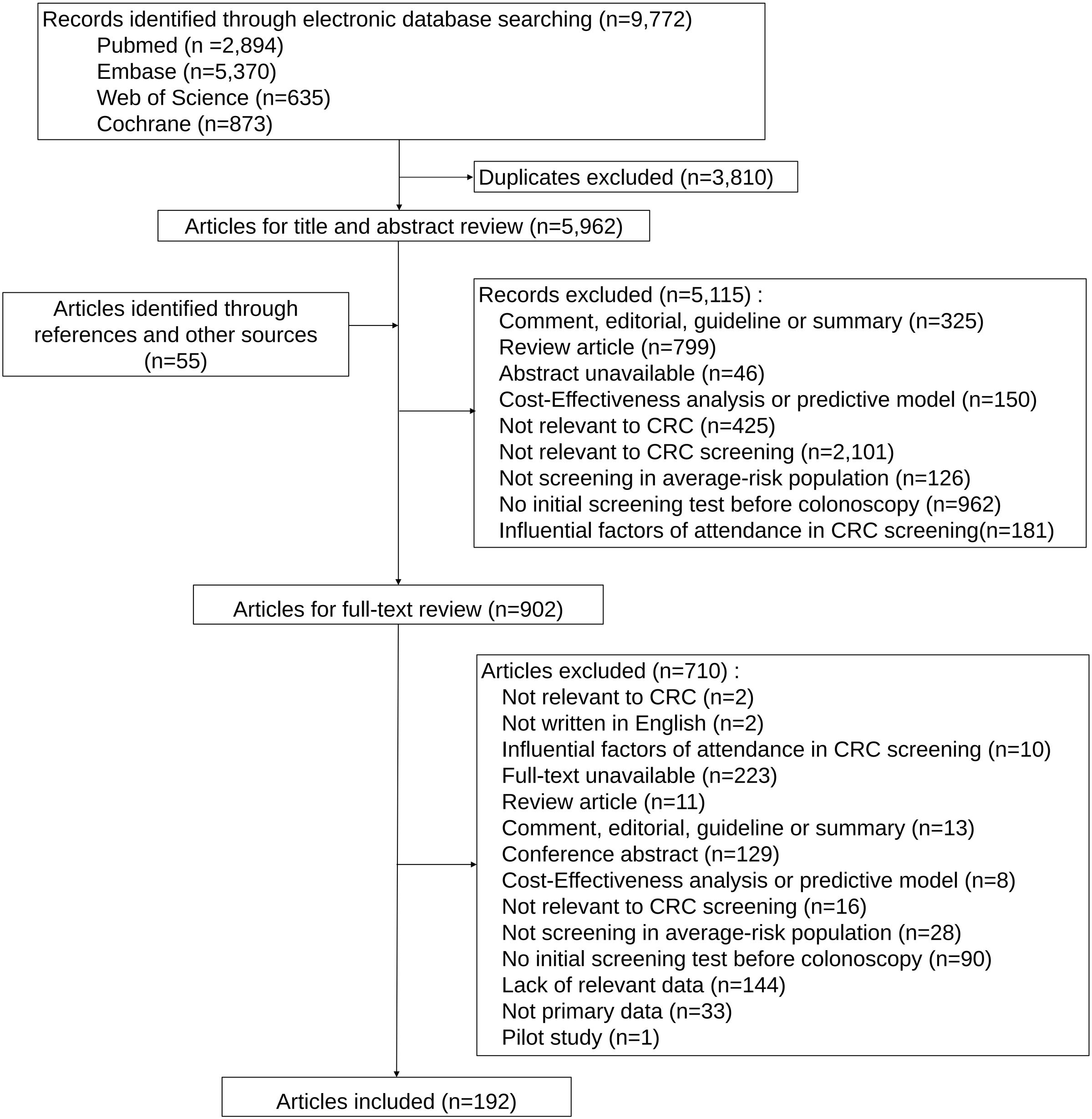
Incidence of CRC	Incidence of CRC		Sensitivity		Specificity		PPV	
(1/100,000)	No. of records	r	No. of records	r	No. of records	r	No. of records	r
Cutoff points determined using medians of adherence to colonoscopy								
[17·6, 32·5)	4	0·200	1	··	1	··	4	0·400
[32·5,142·5)	231	0·150**	38	-0·367**	38	0·247	207	0·143**
[142·5, 352·0]	81	-0·076	16	0·152	16	0·029	73	-0·059
Cut-off points determined using means of adherence to colonoscopy								
[17·6, 82·5)	55	0·273**	9	-0·233	9	0·550	48	0·297**
[82·5, 352·0]	261	0·067	46	-0·144	46	0·136	236	0·022

Incidence of CRC adjusted to the world population.

*p value <0·10; **p value<0·05; ***p value <0·01.

CRC, colorectal cancer; PPV, positive predictive value.

Figure



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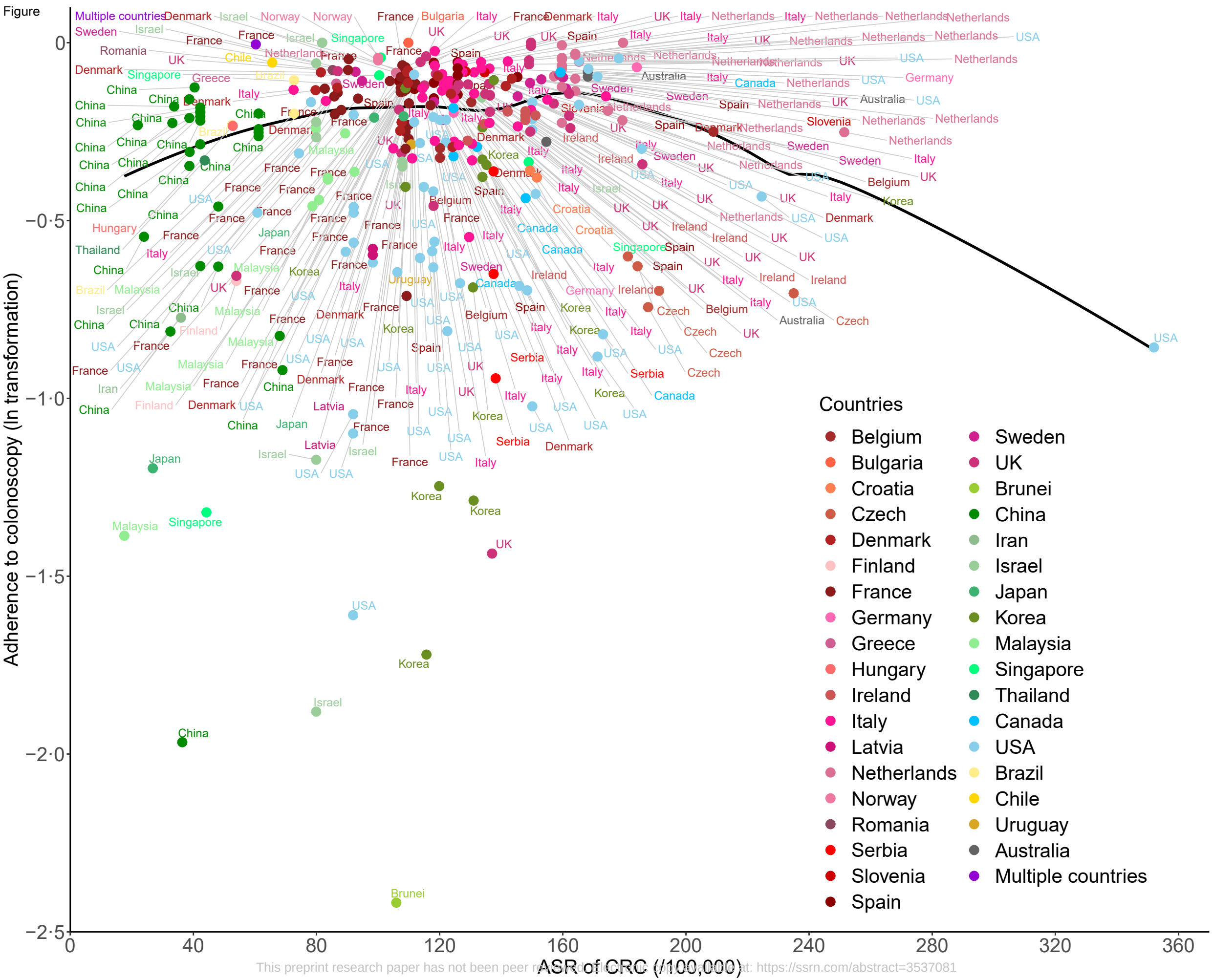

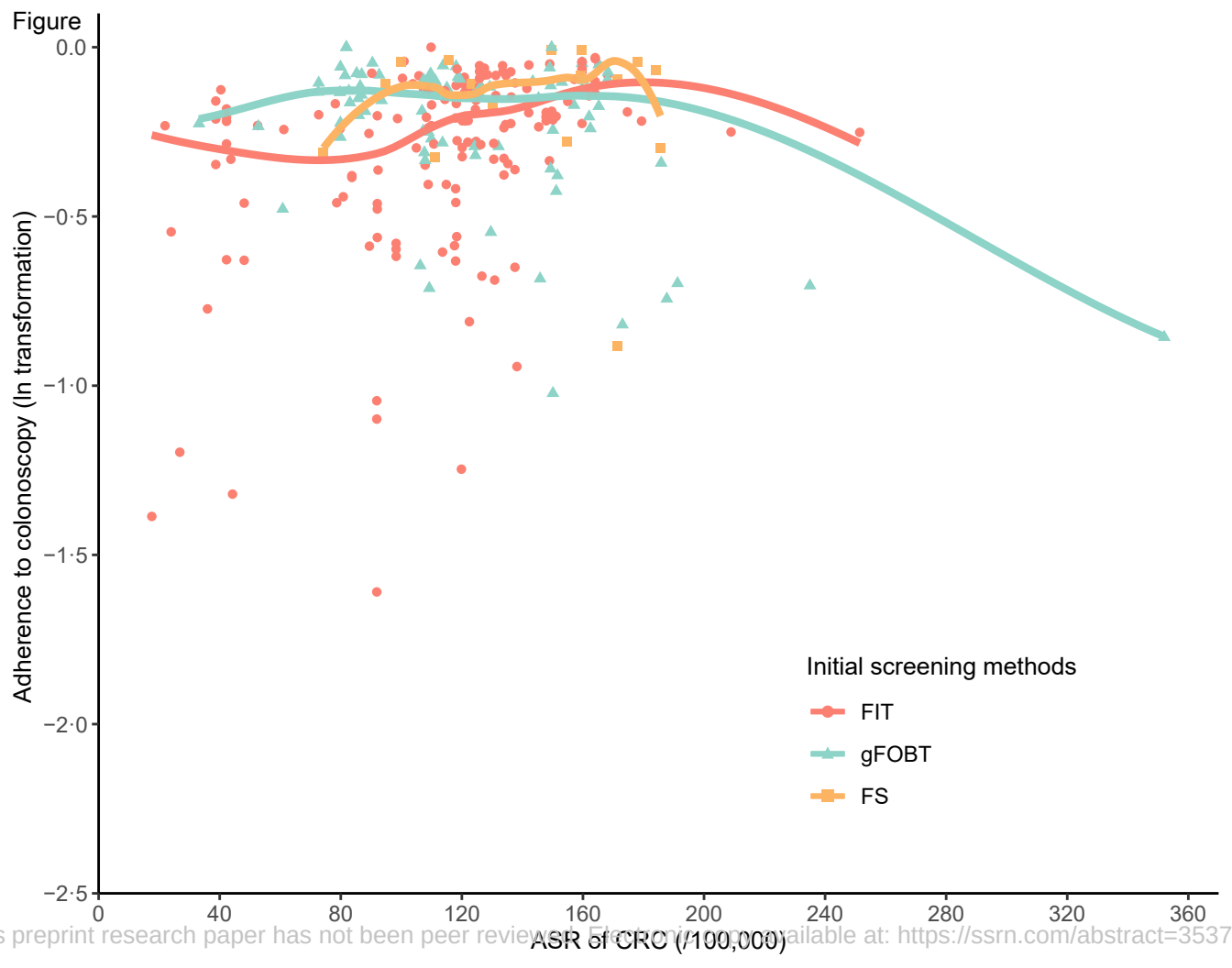

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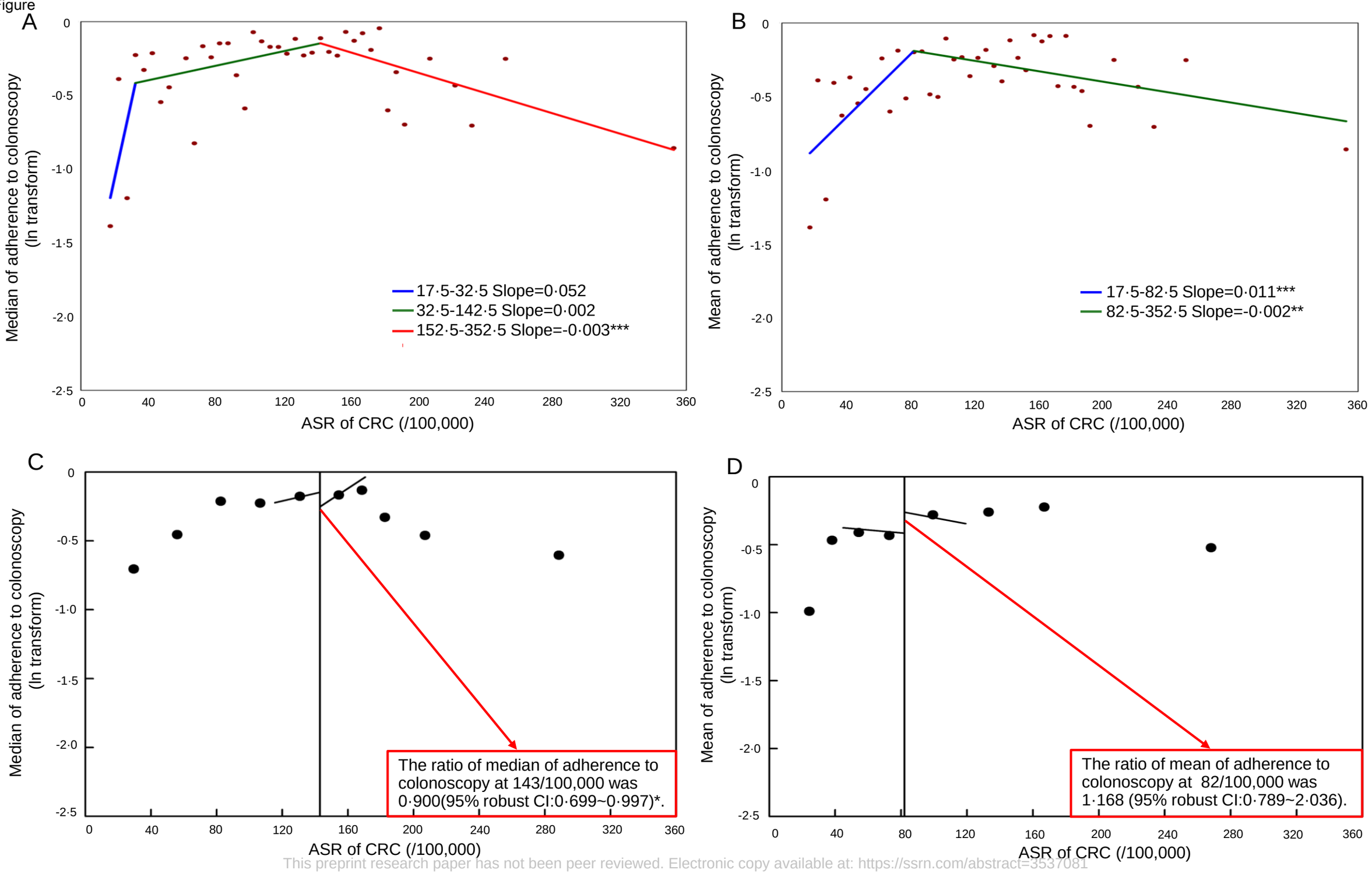

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Manuscript title: Performance of Initial Screening Tests for Colorectal Cancer and Subsequent Adherence to Colonoscopy: An Ecological Study

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Article type: Article

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Y.H.Y. designed the search strategy, performed literature search, extracted and examined data, analyzed and interpreted the data and drafted the manuscript. J.J.H. devised the search strategy, performed the literature search, provided statistical suggestions and revised the manuscript. W.M.W. devised the search strategy, performed the literature search, extracted and examined data. S. S.T. performed the literature search and extracted the data. J.X.F., T.Y., D.D.M., S. K.C extracted data. F.F.M., M.W., D.T.H., J.F.S., N.H.L. and M.C.W. interpreted the data and revised the manuscript. W.H.X. conceived and designed the study, revised the manuscript and supervised the quality of the study throughout the conduct of the project. All authors have approved the final draft submitted.

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Role of the funding source

Please disclose any funding sources and their role, if any, in the writing of the manuscript or the decision to submit it for publication. Examples of involvement include: data collection, analysis, or interpretation; trial design; patient recruitment; or any aspect pertinent to the study. Please also comment whether you have been paid to write this article by a pharmaceutical company or other agency. If you are the corresponding author, please indicate if you had full access to all the data in the study and had final responsibility for the decision to submit for publication. The information provided here must match the role of the funding source statement in the manuscript.

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

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