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Age-standardized incidence rate and epidemiology of colorectal cancer in Africa: a systematic review and meta-analysis

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Objectives: Colorectal cancer is the second leading cause of cancer deaths globally with low– and middle–income countries (LMIC) disproportionately affected. Estimates of colorectal cancer rates in LMIC are scarce. The purpose of this meta-analysis is to estimate the sex-specific incidence of colorectal cancer, the trend over time and explores regional variations of cancer rates on the African continent.

Design: Systematic review and meta-analysis

Methods: PubMed (MEDLINE), OVID (Medline), and Scopus and Cochrane Library databases were systematically searched from inception to 12/12/2020. Data for case rates and other relevant clinical information, as well as population denominators, were extracted. Random effect model was used to pool the estimates. Subgroup analyses were employed to explore sources of heterogeneity.

Outcome measures: Overall and sex-specific annual age-standardized incidence rates of colorectal cancer per 100,000 population.

Results: The overall age-standardized incidence rates of colorectal cancer in Africa per 100,000 population was 5.25 (95% CI: 4.08 to 6.75). The rates were slightly higher in males (4.76) than females (4.18), but not significantly different. The between-study heterogeneity of the estimates was moderate (I^2=58%). Subgroup analysis indicated greater point estimates in North Africa (8.66) than Sub-Saharan Africa (SSA) (5.91); higher estimates in Eastern (8.29) and Northern (8.66) Africa compared to Western (3.55) and Southern (3.57) Africa, though not statistically

significant. The trend in ASIR has remained constant at nearly 5 per 100,000 population for the last 6 decades.

Conclusion: Colorectal cancer estimates in Africa are heterogeneous and could be underestimated. Population-based colorectal cancer data are scarce in Africa. High-quality data collection systems such as population-based cancer registries may facilitate country-specific rates and provide accurate information which would be lucrative to the consideration of resources needed for screening, early detection, treatment, and improving overall patient outcomes.

Strengths and limitations of this study

- All United Nations regions (North Africa and sub-Saharan Africa) were represented.
- UN subregions (Eastern, Western, Southern, and Northern) of Africa were represented.
- Country-level data came from only 18% of the continent.
- Middle Africa had no data on colorectal cancer prevalence.

Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer deaths globally.[1] In 2018, there were an estimated 1.8 million new cases of colorectal cancer diagnoses and 862,000 deaths from CRC.[1] The majority of deaths from cancer occurred in low- and middle-income countries (LMIC), with most patients presenting with late-stage disease and commonly unable to obtain medical treatment services.

Even though the incidence of CRC has always been considered to be lower in LMIC, compared to high-income countries (HIC), the rates of colorectal cancer have been increasing in LMIC over time.[2] The rising incidence of cancer in LMIC has been attributed in part to the adoption of high-risk lifestyles such as smoking, excessive alcohol use, physical inactivity, as well as an aging population.[3]

Africa is the second largest and second most populated continent with an estimated population of 1.3 billion people in 2018, accounting for 16% of the world's human population.[4] Despite this vast population, CRC in Africa are not currently well characterized, in part due to deficiencies in the data on the incidence, prevalence, and mortality of all cancers in Africa. A vast majority of available data comes from existing, limited cancer registries which cover less than half of the population.[5] Nevertheless, based on current and available data, colorectal cancer is considered the fifth most common cancer in Africa[6]. The rate of CRC is estimated to be higher in Northern Africa than Sub-Saharan Africa (SSA) due to the absence of screening systems and population-based cancer registries in SSA.[5 6]

This systematic review and meta-analysis aims to comprehensively characterize and estimate the incidence of CRC based on available data. These estimates will raise awareness regarding the

current incidence of colorectal cancer in Africa and will guide future public health allocation of resources to prevent, control and treat colorectal cancer.

METHODS

Search Strategy and Selection Criteria

This study adheres to the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[7 8] We searched PubMed (MEDLINE), OVID (Medline), Scopus and Cochrane Library databases from inception to 12/12/2020. We searched the grey or difficult to locate literature, including Google Scholar and preprint servers. We performed hand-searching of the reference lists of included studies, relevant reviews, or other relevant documents. No limitations were identified relating to study design, language, or date of publication. The search terms of interest were identified by using Medical Search Headings (MeSH). They included “colorectal cancer” OR “colon cancer” OR “rectal cancer” OR” colorectal carcinoma” AND “epidemiology” OR “incidence” OR “prevalence” AND “ Africa”. Duplicate studies were initially extracted via Endnote software. Three reviewers (NA, MT, and PS) independently screened titles and abstracts of the studies for inclusion eligibility. The comprehensive list of studies found from the initial search was transferred into Endnote, which further removed duplicate studies. The inclusion criteria for this meta-analysis and systematic review were defined as studies that 1) reported the incidence or prevalence estimates of colorectal cancer in Africa 2) conducted in human subjects 3) population-based (all cases in a defined geographical area, or hospital or community-based surveillance). Excluded studies were not conducted in humans or did not directly report the rates of colorectal cancer, meta-analyses, literature reviews, or commentaries.

Patient and public involvement

This meta-analysis is based on study-level data and no individual-level data were involved in the study or in defining the research question.

Data Extraction and Quality Assessment

After the reviewers initially screened titles and abstracts of potential articles, full-text articles were independently screened by three reviewers (NA, MT, and PS) for eligibility. In the event of a discrepancy regarding an article's inclusion, a consensus was reached by discussion. Articles that met inclusion criteria had appropriate data extracted using a standard data collection form. We extracted the following information: the year of publication, country, region, cohort and cohort year, study design, sample size, gender percent, sample size of patients with CRC. If duplicate articles identified, we included only mutually exclusive data.

Assessment of Methodological Quality of the Papers

The methodological quality of studies was conducted using the Newcastle-Ottawa Quality Assessment Scale, a validated tool for assessing quantitative cross-sectional, case-control and cohort studies.[9] Scores of 8 to the maximum score of 9 was defined as high quality, scores of 5 to 7 as intermediate quality, and scores of 1 to 4 as low quality.

Standardization

Age standardization of incidence rates was carried out by the direct method, using age specific rates for 5-year age groups and the world standard population and were reported by each paper.[10]

Statistical Analysis

The primary outcome of interest was the overall and sex-specific annual age−standardized incidence rate of colorectal cancer . The metaprop function from the R package *meta* was used to calculate the pooled effect estimates using random-effects models.[11] We applied the DerSimonian and Laird (DL) random-effects method to estimate the pooled between-study variance (heterogeneity).[12] Individual and pooled estimates were graphically displayed using forest plots. A random-effects model assumes the observed estimates of colorectal cancer can vary across studies because of real differences in the effect in each study as well as sampling variability (chance). Between-study heterogeneity was assessed using I^2 statistics, expressed as % (low (25%), moderate (50%), and high (75%) and Cochrane's Q statistic (significance level < 0.05).[13] To investigate the sources of heterogeneity, we conducted subgroup analyses using year of study (Before and after the year 2000), United nations regions (Sub-Saharan African vs. North Africa), United Nations subregions (Western, Eastern, Southern, Northern, and Eastern Africa). Results were reported as the annual age−standardized incidence rate per 100,000 person−time. Potential ascertainment bias (as might be caused by publication bias) was assessed with funnel plots by plotting the study effect size against standard errors of the effect size and Egger/Begg test.[14] All statistical analyses were performed with R software, version 4.0.3 (R Core Team, Vienna, Austria).

Results

Study Selection

Our initial searches yielded 1203 studies, of which 53 underwent full-text screening (Figure 1). Of these, 22 were Conference proceedings, 15 came from overlapping populations and 2 were systematic reviews. A total of 14 studies matched all the eligibility criteria. Of the included studies, 2 were from South Africa,[15 16] 2 from Zimbabwe,[17 18] and 1 from Ghana[19], Eritrea,[20] The Gambia,[21] Guinea,[22] Ivory Coast,[23] Mali[24], Malawi[25] and Tunisia,[26] Uganda,[27] and Sudan[28] each. The paper by Wabinga and colleagues (2000) from Uganda described cancer incidence at 4-time points, 1960-1966; 1967-1971; 1991-1994 and 1995-1997.[27] These time points were analyzed independently to allow for trend analysis. Subjects were 53% male, and the mean age was 58 years. The percentage of colon and rectal cancer were 65% and 35%, respectively. The percentage with locally advanced and metastatic disease (stage III and IV) was 57.9%. Adenocarcinoma represented the majority of diagnosed colorectal cancers with a small proportion representing squamous cell carcinoma. Grade 1, 2, and 3 were 32.4, 60.7, and 8.36%, respectively.

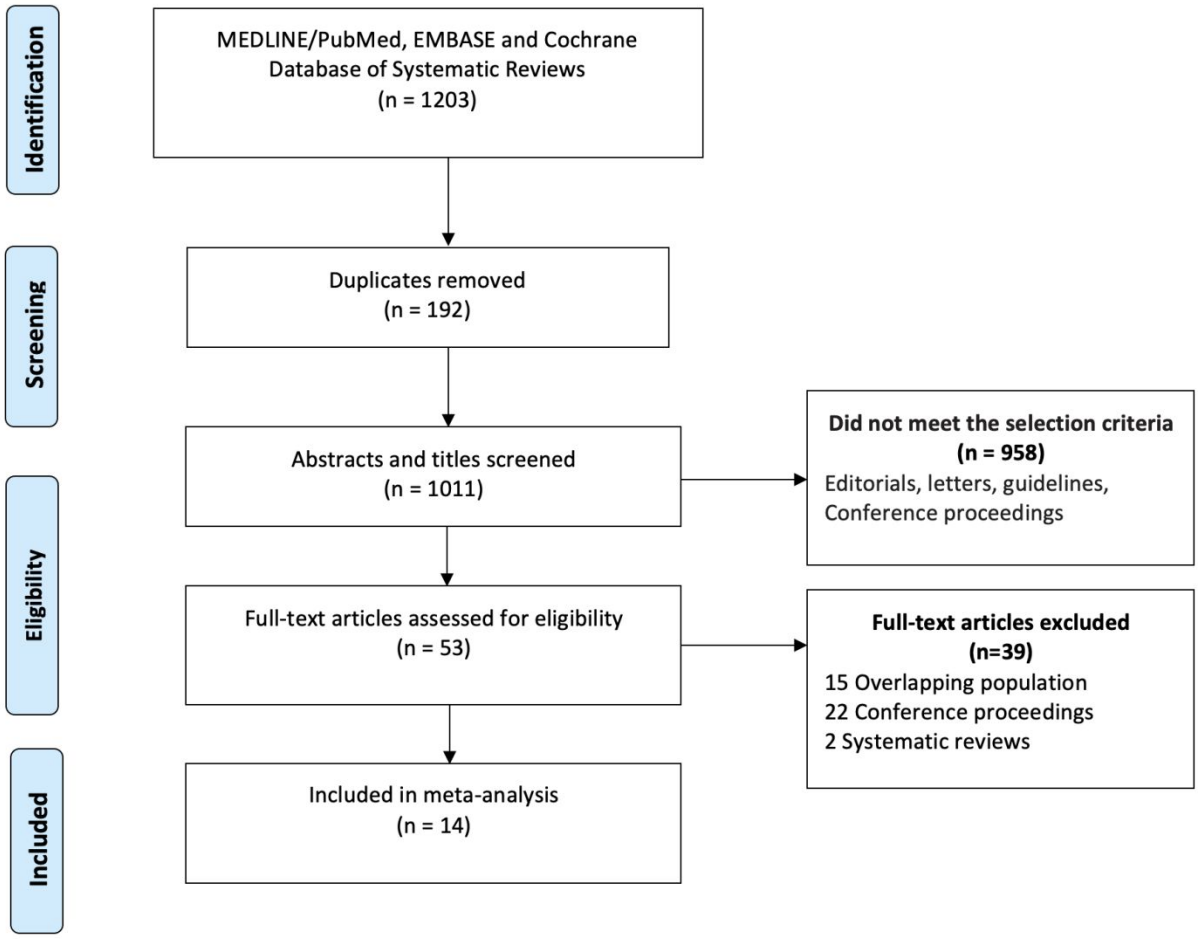

Figure 1: Figure 1: PRISMA flowchart of a systematic review of colorectal cancer incidence in Africa

Annual age−standardized incidence rate of colorectal cancer per 100,000 person-year

As displayed in **Figure 2**, the overall annual age−standardized incidence rate of colorectal cancer per 100,000 person-year was 6.30 (95% CI: 4.59 to 8.65). The rates were slightly higher in males than the female population but not significantly different (4.76 versus 4.18). The heterogeneity was moderate (I^2=58%).

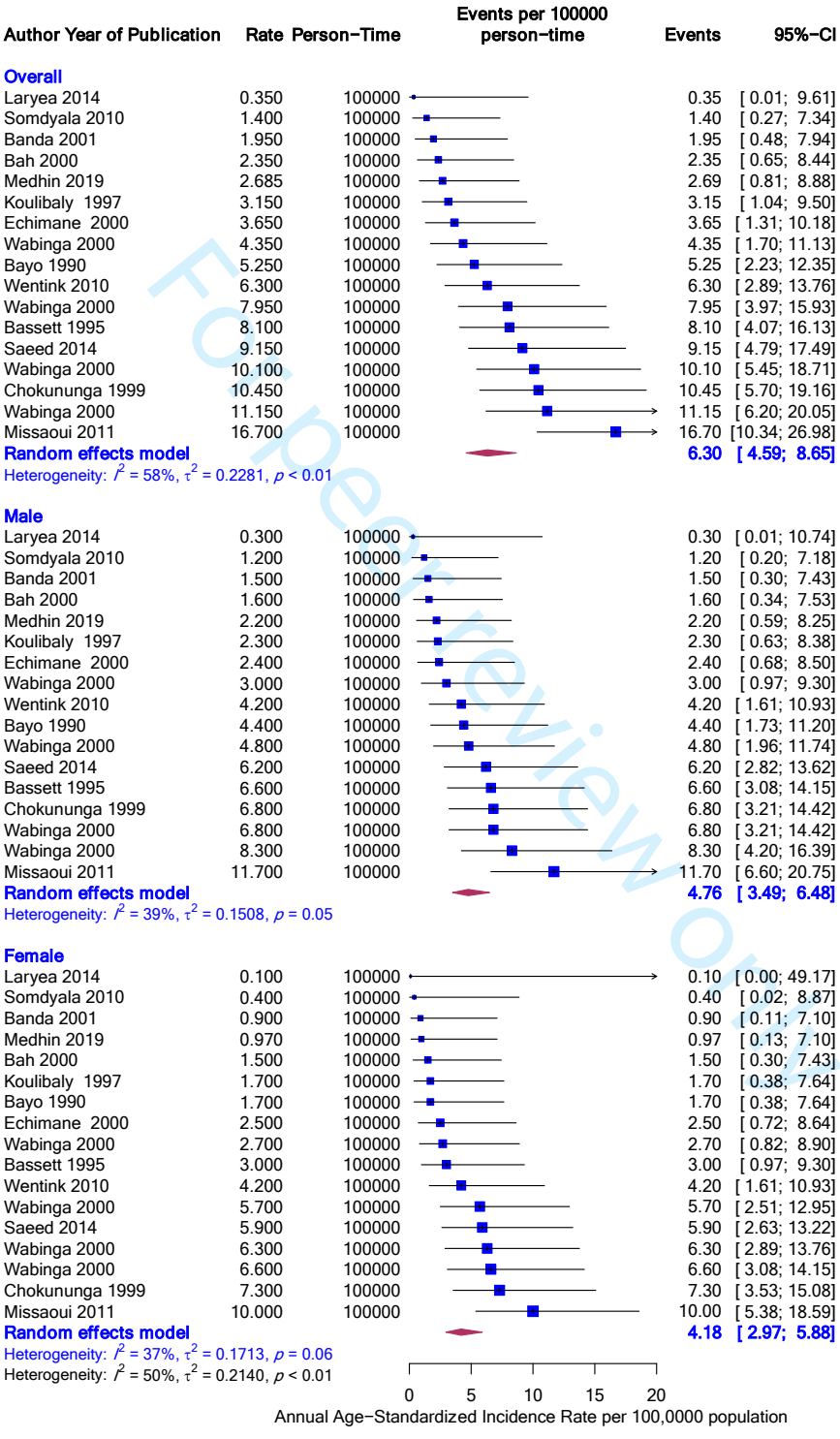

Figure 2: Overall and sex-specific annualized ASIR of colorectal cancer in Africa.

Event values represent the age-standardized incidence rates of colorectal cancer per 100,000 population. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate of the ASIR, overall and by sex (width denotes 95% CI). Although not statistically significant, the pooled ASIR of colorectal cancer in Africa was higher in males (I^2=39) than the female population (I^2=37). P for interaction comparing the different subgroups =0.37.

Subgroup analysis was performed by the United Nations regions (North Africa vs. Sub-Saharan Africa) and by United Nations subregions. Although the point estimate was higher in North Africa (8.66) compared to SSA (5.91), the difference was not significant (**Figure 3**).

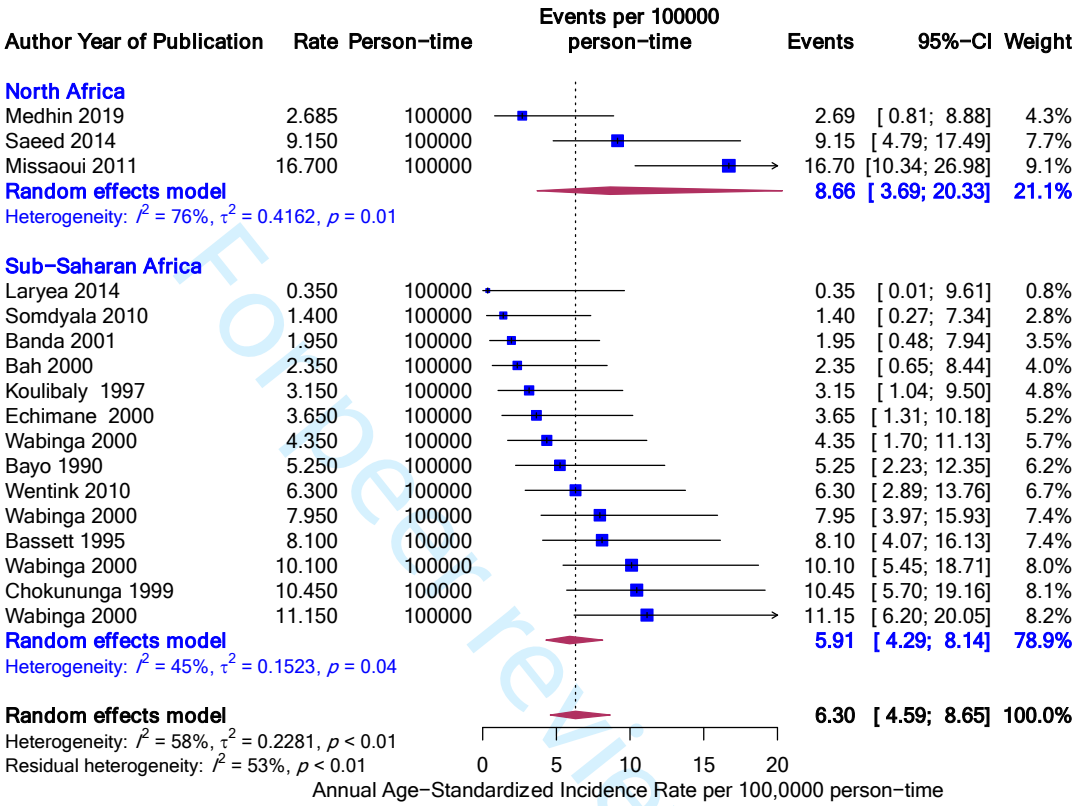

Figure 3: Overall ASIR (per 100,000 population) of colorectal cancer in Africa stratified by United Nations region (North Africa and sub-Saharan Africa).

Event values represent the age-standardized incidence rates of colorectal cancer per 100,000 population. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate of the ASIR, overall and by **United Nations regions** (width denotes 95% CI). Although not statistically significant, the pooled ASIR of colorectal cancer in Africa was higher in North Africa (I^2=76) than SSA (I^2=45). P for interaction comparing the different subgroups =0.21.

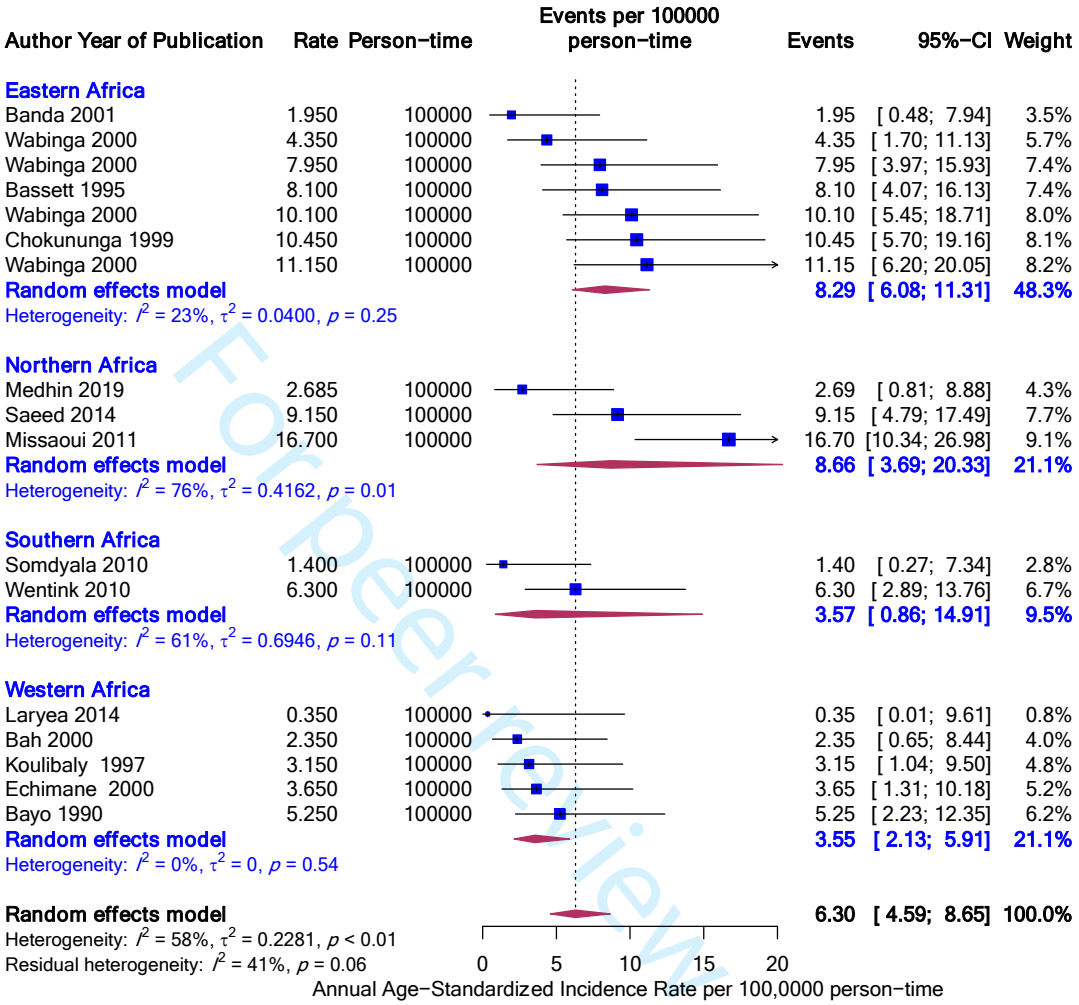

Figure 4: ASIR (per 100,000 population) of colorectal cancer in Africa stratified by United Nations subregions (Northern, Western, Eastern, and Southern Africa).

Event values represent the age-standardized incidence rates of colorectal cancer per 100,000 population. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate of the ASIR, overall and by **United Nations subregion** (width denotes 95% CI).

Furthermore, the rates were greater in Eastern (8.29) and Northern (8.66) Africa compared to Western (3.55) and Southern (3.57) Africa, but not significantly different (**Figure 4**). To assess if the rates from recent studies (2000 and later) are higher than older studies (Before 2000), we carried out a stratified analysis. There was no difference in the rates of CRC 5.55 (95% CI: 2.57 to 11.96) and 6.50 (95% CI: 4.72 to 8.94), respectively (**Figure 5**). The trend in ASIR has remained nearly constant at 4.5 per 100,000 population for the last 6 decades (**Figure 6**)

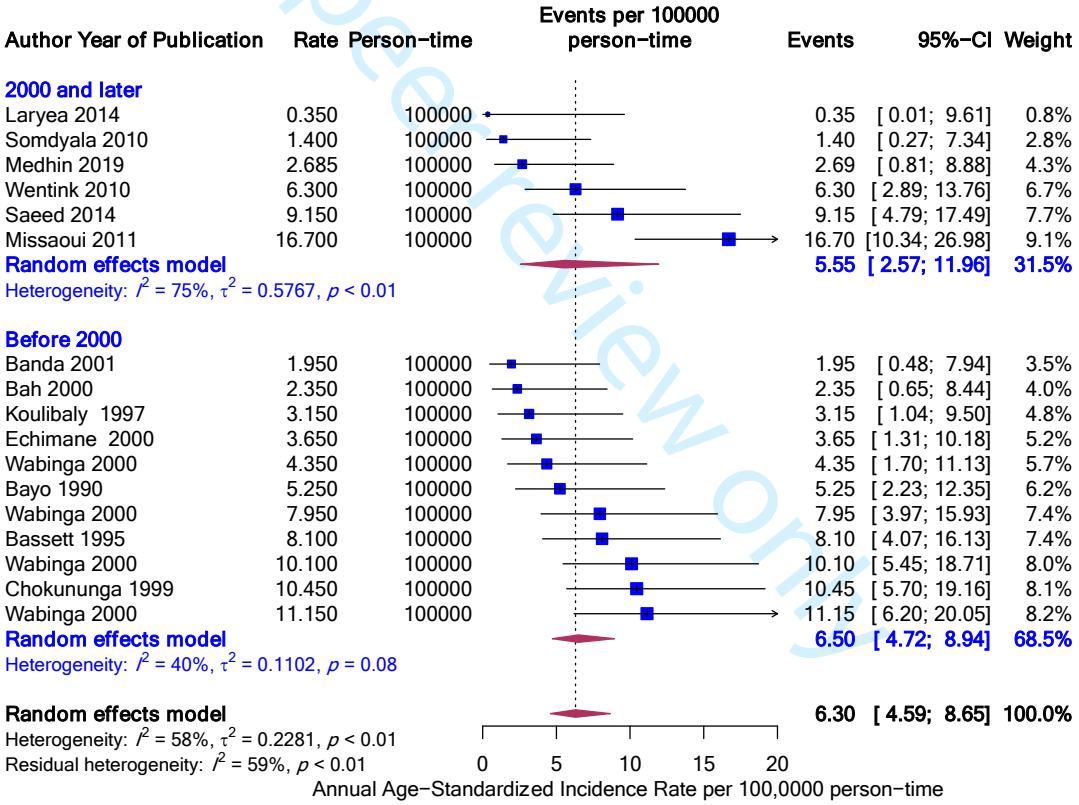

Figure 5: ASIR (per 100,000 population) of colorectal cancer in Africa stratified by year of study (Before 2000 and 2000 and after).

Event values represent the age-standardized incidence rates of colorectal cancer per 100,000 population. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate of the ASIR, overall and by year categorized as before and after 2000 (width denotes 95% CI). No difference in the rates between the year categories.

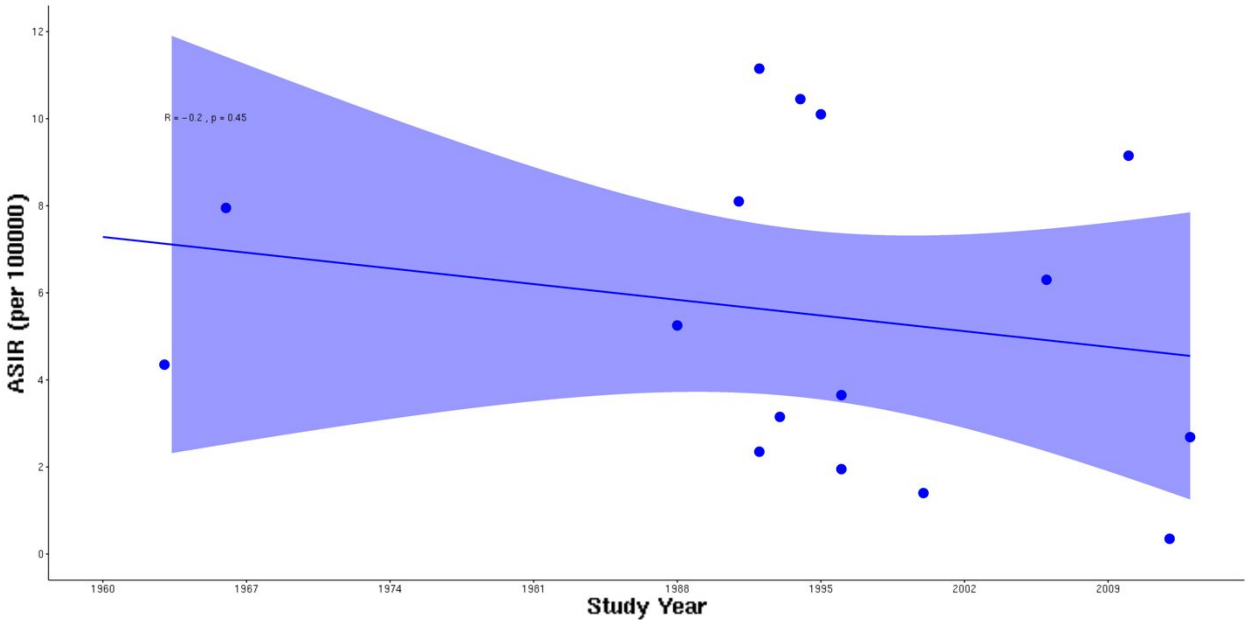

Figure 6: Temporal trends in the incidence rates (per 100,000 population) of colorectal cancer in Africa. Rates are constant over time.

Study Quality, Publication Bias, and Sensitivity Analyses

The median study quality score for studies reporting on the incidence was 5 out of 8 (range=4–9). The funnel plot (**Figure 7A**) the value of the Egger test (p<0.0001) and Begg test (p<0.0001) indicated the presence of publication bias. We used the trim and fill method to adjust for the publication bias. If the asymmetry is due to publication bias, the adjusted estimates fall in the range of 5.76 to 12.22. Finally, Influence sensitivity analyses were by excluding and replaced one study at a time (leave-one-out method) from the meta-analysis and calculate the pooled ASIR for the remaining studies. No significant change from any of the pooled estimates observed when other studies were removed in turn. The pooled ASIR ranged from 5.93 to 6.67 (**Figure 7B**)

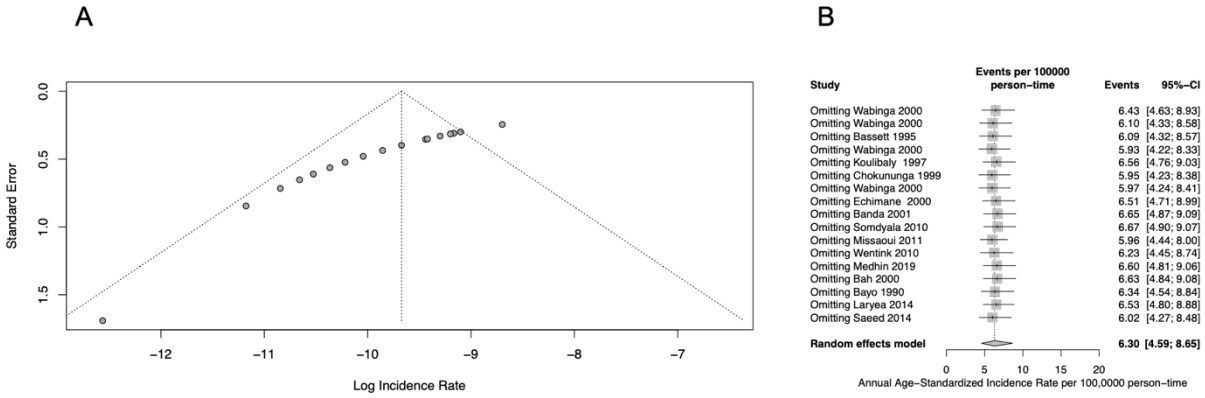

Figure 7: Publication bias and sensitivity analyses. Funnel plot were not interpretable (**Figure 7A**). Influence analysis shows no significant change from any of the pooled estimates observed when other studies were removed in turn. The pooled ASIR ranged from 5.93 to 6.67 (**Figure 7B**)

Discussion

This paper provides a comprehensive meta-analysis of the patterns and trends in the CRC incidence in Africa. The estimated annual age−standardized incidence rate (ASIR) of colorectal cancer per 100,000 persons was 6.30. This rate is higher than that reported in 2012 in a systematic review of only sub-Saharan Africa (SSA) countries by Graham et al. which reported a crude incidence rate of 4.04 per 100,000.[5] When compared to SSA, North Africa had the highest ASIR of 8.66, while SSA had an ASIR of 5.91. Rapid westernization of Northern Africa, including diet and lifestyle changes and readily available cancer registries compared to SSA, could explain these potential differences in colorectal cancer rates[8]. Middle Africa was not represented in this meta-analysis.

CRC is known to be the most common malignancy of the GI tract[29], and while previously thought to be a rare malignancy in Africa, recent data is proving otherwise.[30 31] CRC has been shown to be on the rise in many individual countries in Africa and now represents nearly half of all malignant tumors in some countries. In addition to being more common than previously recognized, CRC in Africa tends to present more commonly in young adults[31]. This trend in young adults is similar to current trends in the United States, Asia and Europe, where patients usually present with advanced stage, left-sided tumors, and poor histology.[32]

In the United States, colorectal cancer is the third most common cancer in both men and women but the 2nd leading cause of cancer death.[33] Rates of colorectal cancer in the United States have been declining since the mid-1980s in patients older than 50 years old, mainly due to increased cancer screening and changes in lifestyle[15]. This is in sharp contrast to young adults < 50 years old

where there is an expected exponential increase over the next decade.[34] According to a study by Siegel et al. (2020), the ASIR of colorectal cancer in the United States from 2012-2016 was 38.7 per 100,000 persons[21]. Furthermore, in the United States, the ASIR in Blacks from 2012-2016 was 45.7 compared to 38.6 in Non-Hispanic Whites. In the United Kingdom, the ASIR for 2017 was 68.0 per 100,000 persons[22]. The incidence of colorectal cancer in people of African descent in the United States is 20% higher compared to Caucasians [23]. Furthermore, in the United States, people of African descent present at a younger age and with more advanced disease at diagnosis and have the highest mortality rate among different ethnic groups[24]. Factors responsible for these differences are multifactorial, including known health disparities, socioeconomic status, genetic factors, and dietary influences[25].

Even though our study provides much lower age-standardized incidence rates, it is assumed that these do not accurately reflect the actual incidence of colorectal cancer in Africa. We suspect this number to be much higher. According to the study by Laiyemo et al. (2016), there is no population-based colorectal cancer screening or guidelines in any African country to date.[35 36]

To better understand the true incidence rates of colorectal cancer in Africa, standardized screening guidelines must be established. Given the lack of screening, patients commonly present with advanced disease. More countries are implementing and establishing population based cancer registries (PBCR)[36] described in this study by Omonisi and his colleagues. These registries should inform us of more specific country incidence rates and allow for further population-based studies that could unravel the mysteries behind the increased risk of colorectal cancer in people of African descent.

The present analysis has major strengths. First, all United Nations regions (North Africa, SSA) and subregions (Eastern, Western, Southern, and Northern Africa) of Africa were represented (except Middle Africa). Thus, our findings can be generalizable at the regional level of Africa. Secondly, we included recent estimates of colorectal cancer in Africa. The present estimates are the most updated figures if the rates of colorecta cancer in Africa and thus can be used to inform the prevention and control strategies. Nevertheless, the present study has some limitations. First, country-level data came from only 18% of the continent, meaning most countries were not represented due to the lack of published literature on CRC incidence in these countries. Therefore, the estimates may not be generalizable at the country-level. To mitigate this limitation, we conducted subgroup analysis by African regions (North Africa, SSA) and subregions (Eastern, Western, Southern, and Northern Africa) to explore possible regional and subregional specific rates. Second, the estimates could suffer from potential selection bias due to a lack of random population-based studies such as those conducted by the demographic and health surveys program and country-based cancer registries. Nevertheless, the present systematic review and meta-analysis

provides the updated estimates of colorectal cancer in Africa using the best available information, and we have applied rigorous sensitivity analysis to minimize bias.

Conclusion

Colorectal cancer estimates in Africa are heterogeneous and could be underestimated. Population-based colorectal cancer data are scarce in Africa. High-quality data collection systems such as population-based cancer registries may facilitate country-specific rates and provide accurate information which would be lucrative to the consideration of resources needed for screening, early detection, treatment and improving overall patient outcomes.

Contributorship NDA, CE, CS and PS envisioned the study. NDA, MT and PS extracted data. PS: carried out the statistical analysis and created figures. NDA and PS drafted the manuscript and made subsequent revisions. CE, JO, CS and supervised the study. All authors read and revised the manuscript and All authors read and approved the final version of this manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Not applicable

Ethical considerations

This is a systematic review using publicly available data. Therefore, no IRB was required.

Provenance and peer review Not commissioned, externally peer reviewed.

Data availability statement All data needed to reproduce the results are included in the manuscript.

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
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.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
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.	6
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.	6
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.	6
	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.	6
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.	6
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.	7
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)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	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).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
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.	8-16
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8
Study characteristics	17	Cite each included study and present its characteristics.	8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8-16
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.	8-16
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-16
	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.	8-16
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-16
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8-16
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	8-16
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	8-16
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	18-21
	23b	Discuss any limitations of the evidence included in the review.	18-21
	23c	Discuss any limitations of the review processes used.	18-21
	23d	Discuss implications of the results for practice, policy, and future research.	20
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.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	22
Competing interests	26	Declare any competing interests of review authors.	22
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.	22

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Age-standardized incidence rate and epidemiology of colorectal cancer in Africa: a systematic review and meta-analysis

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Running head: Colorectal cancer in Africa: a meta-analysis

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Figures: 7

Objectives: Colorectal cancer is the second leading cause of cancer deaths globally, with low– and middle–income countries (LMIC) disproportionately affected. Estimates of colorectal cancer rates in LMIC are scarce. The objective of this meta-analysis is to estimate (1) sex-specific incidence of colorectal cancer, (2) temporal trend and (3) determine regional variations of cancer rates on the African continent.

Design: Systematic review and meta-analysis

Methods: PubMed (MEDLINE), OVID (MEDLINE), Scopus and Cochrane Library databases were systematically searched from inception to 12/12/2020 for articles reporting the incidence rates of colorectal cancers in Africa. Random effects model was used to pool the estimates. Subgroup analyses were employed to explore sources of heterogeneity. The methodological quality of studies was conducted using the Newcastle-Ottawa Scale.

Outcome measures: Overall and sex-specific annual age-standardized incidence rates of colorectal cancer per 100,000 population.

Results: The overall age-standardized incidence rates of colorectal cancer in Africa per 100,000 population was 5.25 (95% CI: 4.08 to 6.75). The rates were slightly higher in males (4.76) than in females (4.18), but not significantly different. The between-study heterogeneity of the estimates was moderate (I^2=58%). Subgroup analysis indicated greater point estimates in North Africa (8.66) compared to Sub-Saharan Africa (SSA) (5.91); and higher estimates in Eastern (8.29) and Northern (8.66) Africa compared to Western (3.55) and Southern (3.57) Africa, but

not statistically significant. The overall trend in ASIR has remained constant at nearly 5 per 100,000 population for the last 6 decades.

Conclusion: Colorectal cancer estimates in Africa are heterogeneous and could be underestimated. Population-based colorectal cancer data are scarce in Africa. High-quality data collection systems such as population-based cancer registries may facilitate accurate estimation of country-specific rates and provide critical information which would be lucrative to the consideration of resources needed for screening, early detection, treatment, and improving overall patient outcomes.

Funding: None.

Strengths and limitations of this study

- All United Nations (UN) regions (North Africa and sub-Saharan Africa) were represented.
- UN subregions (Eastern, Western, Southern, and Northern) of Africa were represented.
- Country-level data came from only 18% of the continent.
- Middle Africa had no data on colorectal cancer prevalence.

Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer deaths globally.[1] In 2018, there were an estimated 1.8 million new cases of colorectal cancer diagnoses and 862,000 deaths from CRC.[1] The majority of deaths from cancer occurred in low- and middle-income countries (LMIC), with most patients presenting with late-stage disease and commonly unable to obtain medical treatment services.

Even though the incidence of CRC has always been considered to be lower in LMIC, compared to high-income countries (HIC), the rates of colorectal cancer have been increasing in LMIC over time.[2] The rising incidence of cancer in LMIC has been attributed in part to the adoption of high-risk lifestyles such as smoking, excessive alcohol use, physical inactivity, as well as an aging population.[3]

Africa is the second largest and second most populated continent with an estimated population of 1.3 billion people in 2018, accounting for 16% of the world's human population.[4] Despite this vast population, CRC in Africa is not currently well characterized, in part due to deficiencies in the data on the incidence, prevalence, and mortality of all cancers in Africa. A vast majority of available data come from existing, limited cancer registries which cover less than half of the population.[5] Nevertheless, based on current and available data, colorectal cancer is considered the fifth most common cancer in Africa[6]. The rate of CRC is estimated to be higher in Northern Africa than Sub-Saharan Africa (SSA) due to the absence of screening systems and population-based cancer registries in SSA.[5 6]

This systematic review and meta-analysis aims to comprehensively characterize and estimate the incidence of CRC based on available data. These estimates will raise awareness regarding the

current incidence of CRC in Africa and will guide future public health allocation of resources to prevent, control and treat CRC.

METHODS

Search Strategy and Selection Criteria

This study adheres to the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in Supplementary Table1.[7 8] We searched PubMed (MEDLINE), OVID (MEDLINE), Scopus and Cochrane Library databases from inception to 12/12/2020 for articles reporting the incidence rates of colorectal cancers in Africa. We searched the grey or difficult to locate literature, including Google Scholar and preprint servers. We performed hand-searching of the reference lists of included studies, relevant reviews, or other relevant documents. The search terms of interest were identified by using Medical Search Headings (MeSH). They included “colorectal cancer” OR “colon cancer” OR “rectal cancer” OR” colorectal carcinoma” AND “epidemiology” OR “incidence” OR “prevalence” AND “ Africa”. Duplicate studies were initially extracted via Endnote software. Three reviewers (NA, MT, and PS) independently screened titles and abstracts of the studies for inclusion eligibility. The comprehensive list of studies found from the initial search was transferred into Endnote, which further removed duplicate studies. The inclusion criteria for this meta-analysis and systematic review were defined as studies that 1) reported the incidence or prevalence estimates of colorectal cancer in Africa 2) were conducted in human subjects 3) were population-based (all cases in a defined geographical area, or hospital or community-based surveillance). Excluded studies were not conducted in humans or did not directly report the rates of colorectal cancer, meta-analyses, literature reviews, or commentaries.

Patient and public involvement

No patient and public involvement in this systematic review and meta-analysis.

Data Extraction and Quality Assessment

After the reviewers initially screened titles and abstracts of potential articles, full-text articles were independently screened by three reviewers (NA, MT, and PS) for eligibility. In the event of a discrepancy regarding an article's inclusion, a consensus was reached by discussion. Articles that met inclusion criteria had appropriate data extracted using a standard data collection form. We extracted the following information: the year of publication, country, region, cohort and cohort year, study design, sample size, gender percent, sample size of patients with CRC. If duplicate articles identified, we included only mutually exclusive data.

Assessment of Methodological Quality of the Papers

The methodological quality of studies was conducted using the Newcastle-Ottawa Scale, a validated tool for assessing quantitative cross-sectional, case-control and cohort studies.[9] Scores of 8 to the maximum score of 9 were defined as high quality, scores of 5 to 7 as intermediate quality, and scores of 1 to 4 as low quality.

Standardization

Age standardization of incidence rates was carried out by the direct method, using age specific rates for 5-year age groups and the world standard population and was reported by each paper.[10]

Statistical Analysis

The primary outcome of interest was the overall and sex-specific annual age−standardized incidence rate of colorectal cancer . The *metaprop* function from the R package *meta* was used to calculate the pooled effect estimates using random-effects models.[11] We applied the DerSimonian and Laird (DL) random-effects method to estimate the pooled between-study variance (heterogeneity).[12] Individual and pooled estimates were graphically displayed using forest plots. A random-effects model assumes the observed estimates of colorectal cancer can vary across studies because of real differences in the effect in each study as well as sampling variability (chance). Between-study heterogeneity was assessed using I^2 statistics, expressed as % (low (25%), moderate (50%), and high (75%) and Cochrane's Q statistic (significance level < 0.05).[13] To investigate the sources of heterogeneity, we conducted subgroup analyses using year of study (Before and after the year 2000), United nations regions (Sub-Saharan African vs. North Africa) and United Nations subregions (Western, Eastern, Southern, Northern, and Eastern Africa). Results were reported as the annual age−standardized incidence rate per 100,000 person−time. Potential ascertainment bias (as might be caused by publication bias) was assessed with funnel plots by plotting the study effect size against standard errors of the effect size and Egger/Begg test.[14] All statistical analyses were performed with R software, version 4.0.3 (R Core Team, Vienna, Austria).

Results

Study Selection

Our initial searches yielded 1203 studies, of which 53 underwent full-text screening (**Figure 1**). Of these, 22 were Conference proceedings, 15 came from overlapping populations and 2 were systematic reviews. A total of 14 studies matched all the eligibility criteria. Of the included studies, 2 were from South Africa,[15 16] 2 from Zimbabwe,[17 18] and 1 from Ghana[19], Eritrea,[20] The Gambia,[21] Guinea,[22] Ivory Coast,[23] Mali[24], Malawi[25] and Tunisia,[26] Uganda,[27] and Sudan[28] each. The paper by Wabinga and colleagues (2000) from Uganda described cancer incidence at 4-time points, 1960-1966; 1967-1971; 1991-1994 and 1995-1997.[27] These time points were analyzed independently to allow for trend analysis. Subjects were 53% male, and the mean age was 58 years. The percentages of colon and rectal cancer were 65% and 35%, respectively. The percentage with locally advanced and metastatic disease (stage III and IV) was 57.9%. Adenocarcinoma represented the majority of diagnosed colorectal cancers with a small proportion representing squamous cell carcinoma. Grades 1, 2, and 3 were 32.4, 60.7, and 8.36%, respectively.

Annual age−standardized incidence rate of colorectal cancer per 100,000 person-year

As displayed in **Figure 2**, the overall annual age−standardized incidence rate of colorectal cancer per 100,000 person-year was 6.30 (95% CI: 4.59 to 8.65). The rates were slightly higher in males

than in females but not significantly different (4.76 versus 4.18). The heterogeneity was moderate (I^2=58%).

Subgroup analysis was performed by the United Nations regions (North Africa vs. Sub-Saharan Africa) and by United Nations subregions. Although the point estimate was higher in North Africa (8.66) compared to SSA (5.91), the difference was not significant (**Figure 3**).

Furthermore, the rates were greater in Eastern (8.29) and Northern (8.66) Africa compared to Western (3.55) and Southern (3.57) Africa, but not significantly different (**Figure 4**). To assess if the rates from recent studies (2000 and later) are higher than older studies (Before 2000), we carried out a stratified analysis. There was no difference in the rates of CRC 5.55 (95% CI: 2.57 to 11.96) and 6.50 (95% CI: 4.72 to 8.94), respectively (**Figure 5**). The trend in ASIR has remained nearly constant at 4.5 per 100,000 population for the last 6 decades (**Figure 6**)

Study Quality, Publication Bias, and Sensitivity Analyses

The median study quality score for studies reporting on the incidence was 5 out of 8 (range=4–9). The funnel plot (Supplemental **Figure 1A**) the value of the Egger test (p<0.0001) and Begg test (p<0.0001) indicated the presence of publication bias. We used the trim and fill method to adjust for the publication bias. If the asymmetry is due to publication bias, the adjusted estimates fall in the range of 5.76 to 12.22. Finally, Influence sensitivity analyses were by excluding and replacing one study at a time (leave-one-out method) from the meta-analysis and calculating the pooled ASIR for the remaining studies. No significant change from any of the pooled estimates was observed when other studies were removed in turn. The pooled ASIR ranged from 5.93 to 6.67 (Supplemental **Figure 1B**)

Discussion

This paper provides a comprehensive meta-analysis of the patterns and trends in the CRC incidence in Africa. The estimated annual age−standardized incidence rate (ASIR) of colorectal cancer per 100,000 persons was 6.30. This rate is higher than reported in a 2012 systematic review of only sub-Saharan Africa (SSA) countries by Graham et al. which reported a crude incidence rate of 4.04 per 100,000.[5] When compared to SSA, North Africa had the highest ASIR of 8.66, while SSA had an ASIR of 5.91. Middle Africa was not represented in this meta-analysis.

CRC is known to be the most common malignancy of the GI tract[29], and while previously thought to be a rare malignancy in Africa, recent data is proving otherwise.[30 31]. In addition to being more common than previously recognized, CRC in Africa tends to present more commonly in young adults[31]. This trend in young adults is similar to current trends in the United States, Asia and Europe, where patients usually present with advanced stage, left-sided tumors, and poor histology.[32]

In the United States, colorectal cancer is the third most common cancer in both men and women but the 2nd leading cause of cancer death.[33] Rates of colorectal cancer in the United States have been declining since the mid-1980s in patients older than 50 years old, mainly due to increased cancer screening and changes in lifestyle[15]. This is in sharp contrast to young adults < 50 years old where there is an expected exponential increase between 2020 through 2030.[34] According to a study by Siegel et al. (2020), the ASIR of colorectal cancer in the United States from 2012-2016

was 38.7 per 100,000 persons[21]. Furthermore, in the United States, the ASIR in Blacks from 2012-2016 was 45.7 compared to 38.6 in Non-Hispanic Whites. In the United Kingdom, the ASIR for 2017 was 68.0 per 100,000 persons[22]. The incidence of colorectal cancer in people of African descent in the United States is 20% higher than the incidence in Caucasians [23]. In the United States, people of African descent present at a younger age and with more advanced disease at diagnosis and have the highest mortality rate among different ethnic groups[35]. Factors responsible for these differences are multifactorial, including known health disparities, socioeconomic status, genetic factors, and dietary influences[36 37].

Even though our study provides much lower age-standardized incidence rates, it is assumed that these do not accurately reflect the actual incidence of colorectal cancer in Africa. We suspect this number to be much higher. According to the study by Laiyemo et al. (2016), there is no population-based colorectal cancer screening or guidelines in any African country to date.[38 39] To better understand the true incidence rates of colorectal cancer in Africa, standardized screening guidelines must be established. Given the lack of screening, patients commonly present with advanced disease. More countries are implementing and establishing population based cancer registries (PBCR)[39] described in this study by Omonisi and his colleagues. These registries should inform us of more specific country incidence rates and allow for further population-based studies that could unravel the mysteries behind the increased risk of colorectal cancer in people of African descent.

The present analysis has major strengths. First, all United Nations regions (North Africa, SSA) and subregions (Eastern, Western, Southern, and Northern Africa) of Africa were represented

(except Middle Africa). Thus, our findings can be generalizable at the regional level of Africa. Secondly, we included recent estimates of colorectal cancer in Africa. The present estimates are the most updated figures of the rates of colorecta cancer in Africa and thus can be used to inform the prevention and control strategies. Nevertheless, the present study has some limitations. First, country-level data came from only 18% of the continent, meaning most countries were not represented due to the lack of published literature on CRC incidence in these countries. Therefore, the estimates may not be generalizable at the country-level. To mitigate this limitation, we conducted subgroup analysis by African regions (North Africa, SSA) and subregions (Eastern, Western, Southern, and Northern Africa) to explore possible regional and subregional specific rates. Second, the estimates could suffer from potential selection bias due to a lack of random population-based studies such as those conducted by the demographic and health surveys program and country-based cancer registries. However, the present systematic review and meta-analysis provides the updated estimates of colorectal cancer in Africa using the best available information, and we have applied rigorous sensitivity analysis to minimize bias.

Conclusion

Colorectal cancer estimates in Africa are heterogeneous and could be underestimated. Population-based colorectal cancer data are scarce in Africa. High-quality data collection systems such as population-based cancer registries may facilitate country-specific rates and provide accurate information which would be lucrative to the consideration of resources needed for screening, early detection, treatment and improving overall patient outcomes.

Contributorship NDA, CE and PS conceived and designed the study. NDA, MT and PS extracted data. PS performed statistical analysis and created figures. NDA and PS drafted the manuscript and made subsequent revisions. CE and JO supervised the study. EJO, CP and CS critically revised the manuscript for intellectual content. All authors read and approved the final version of this manuscript.

Funding None

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Not applicable

Ethical considerations

This is a systematic review using publicly available data. We analyzed aggregated data and no personal identification information was accessed or reported. Therefore, no IRB was required.

Provenance and peer review Not commissioned, externally peer reviewed.

Data availability statement All data needed to reproduce the results are included in the manuscript.

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Figure legend

Figure 1: PRISMA flowchart of a systematic review of colorectal cancer incidence in Africa

Figure 2: Overall and sex-specific annualized ASIR of colorectal cancer in Africa. Event values represent the age-standardized incidence rates of colorectal cancer per 100,000 population. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate of the ASIR, overall and by sex (width denotes 95% CI). Although not statistically significant, the pooled ASIR of colorectal cancer in Africa was higher in males (I^2=39) than in females *(I^2*=37). P for interaction comparing the different subgroups =0.37.

Figure 3: Overall ASIR (per 100,000 population) of colorectal cancer in Africa stratified by United Nations region (North Africa and sub-Saharan Africa). Event values represent the age-standardized incidence rates of colorectal cancer per 100,000 population. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate of the ASIR, overall and by United Nations regions (width denotes 95% CI). Although not statistically significant, the pooled ASIR of colorectal cancer in Africa was higher in North Africa (I^2=76) than SSA *(I^2*=45). P for interaction comparing the different subgroups =0.21.

Figure 4: ASIR (per 100,000 population) of colorectal cancer in Africa stratified by United Nations subregions (Northern, Western, Eastern, and Southern Africa). Event values represent the age-standardized incidence rates of colorectal cancer per 100,000 population. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate of the ASIR, overall and by United Nations subregion (width denotes 95% CI).

Figure 5: ASIR (per 100,000 population) of colorectal cancer in Africa stratified by year of study (Before 2000 and 2000 and after). Event values represent the age-standardized incidence rates of colorectal cancer per 100,000 population. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate of the ASIR, overall and by year categorized as before and after 2000 (width denotes 95% CI). There is no difference in the rates between the year categories.

Figure 6: Temporal trends in the incidence rates (per 100,000 population) of colorectal cancer in Africa. Rates were constant over time.

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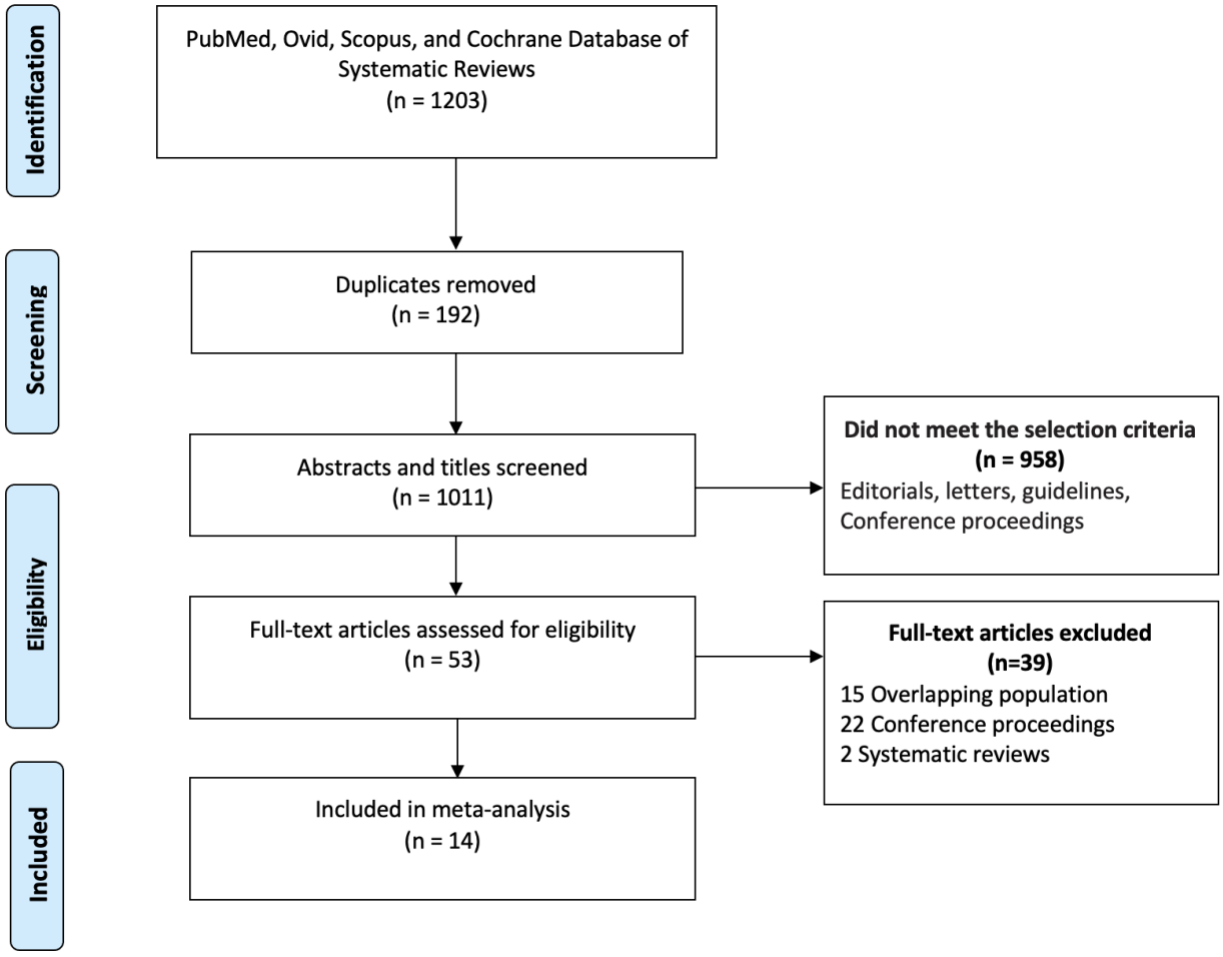

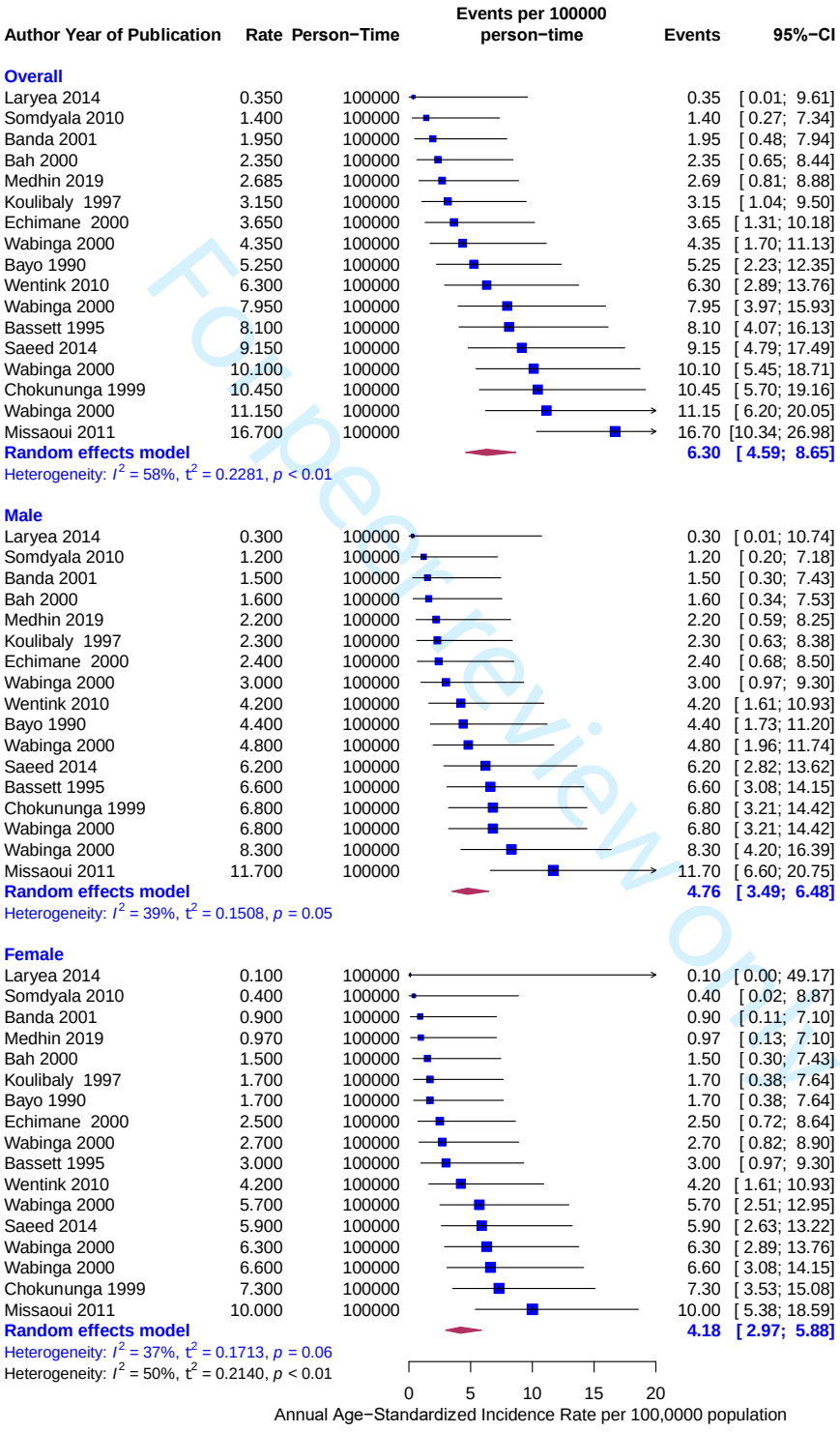

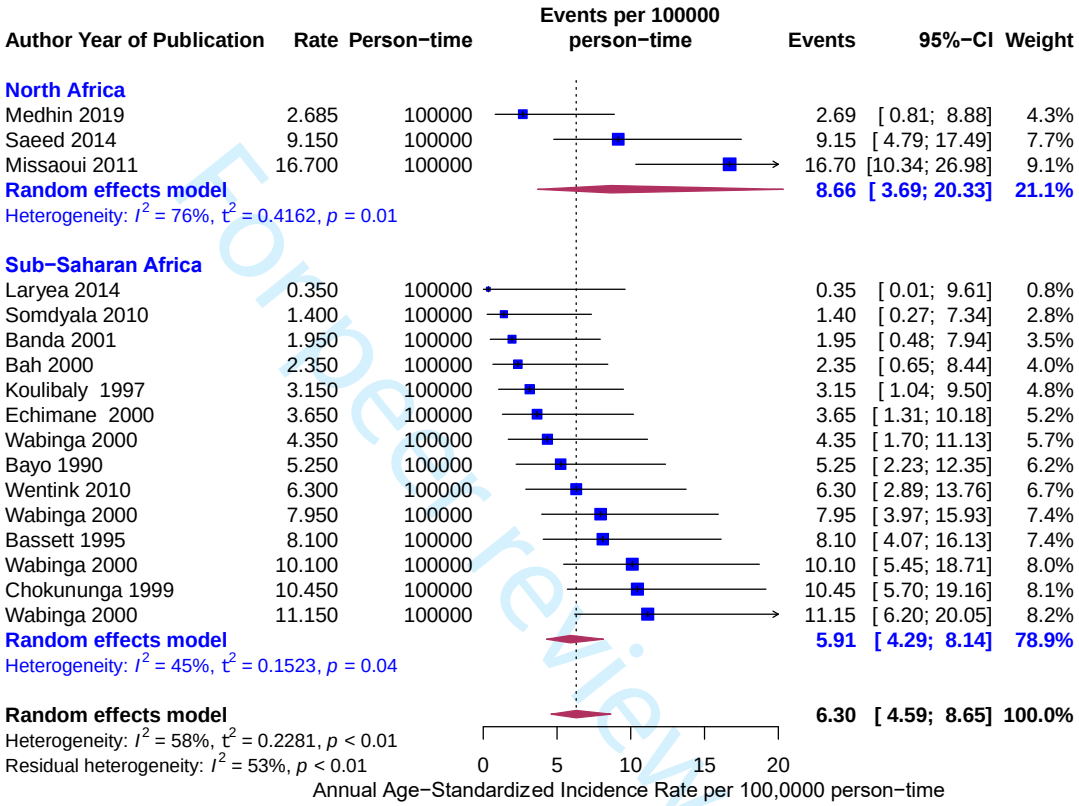

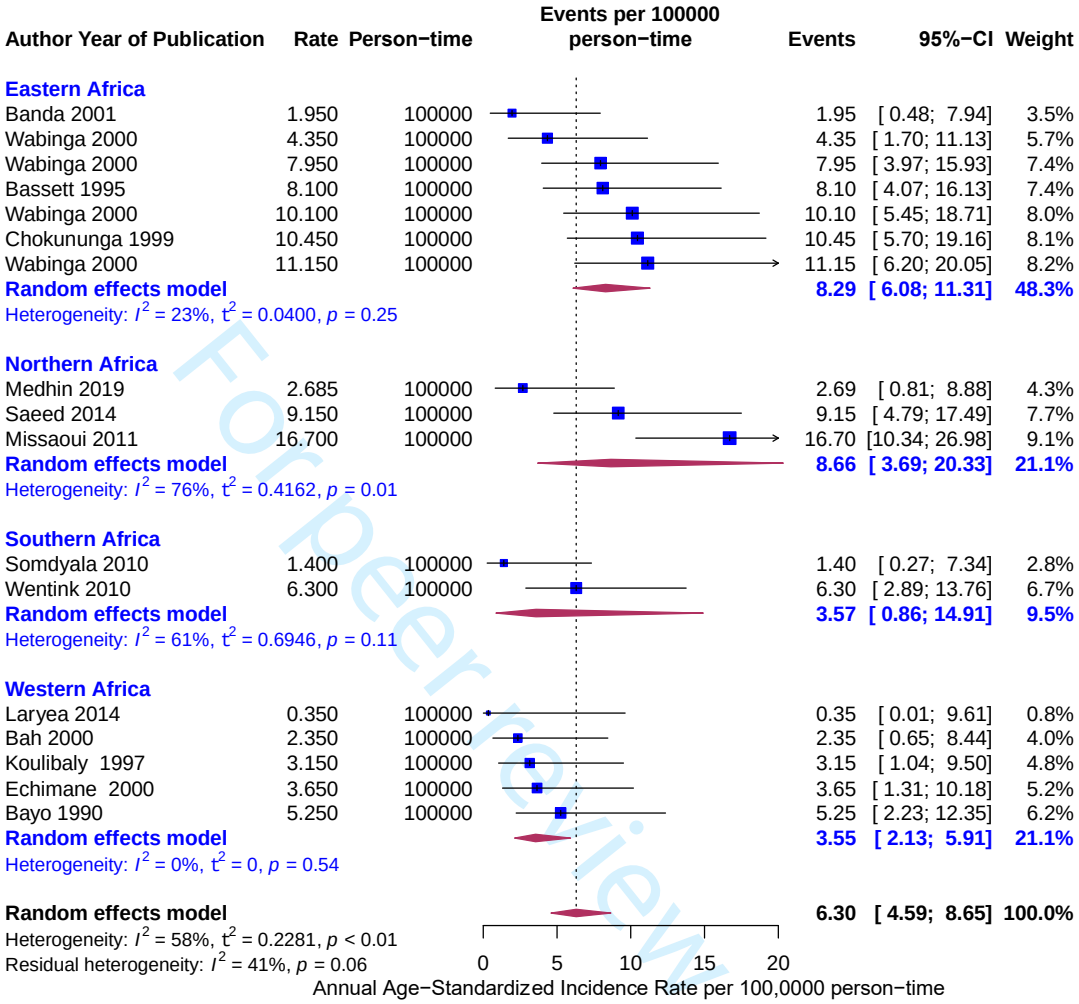

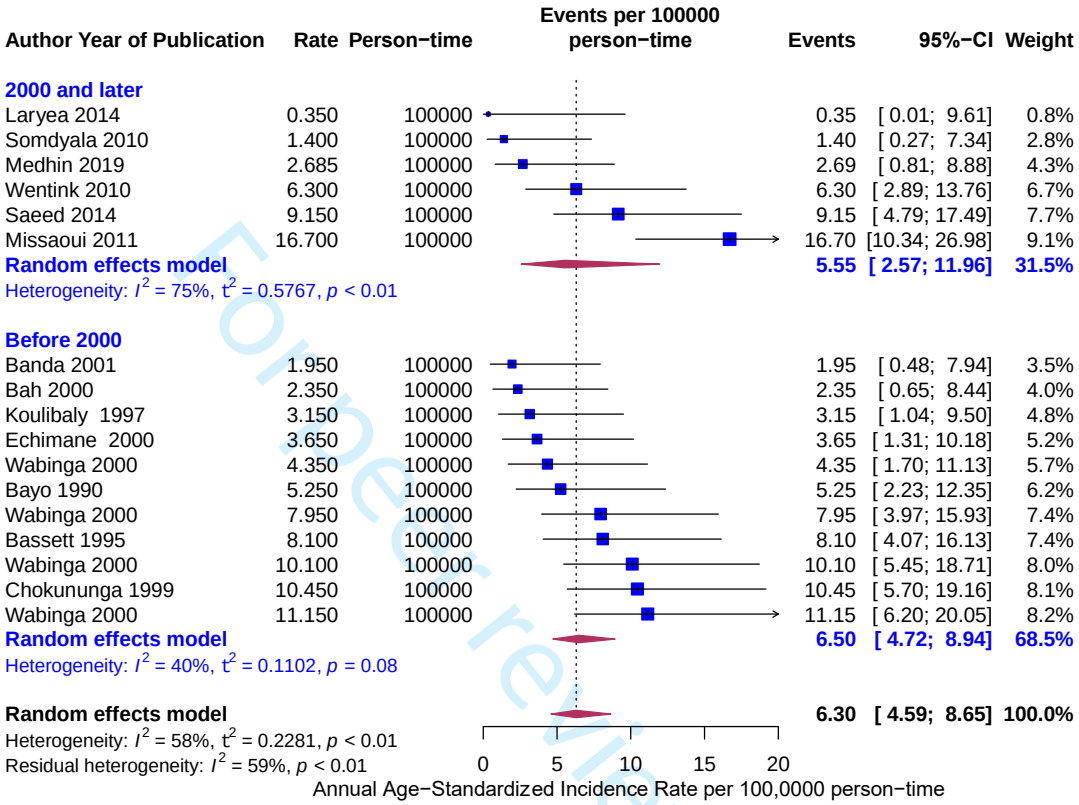

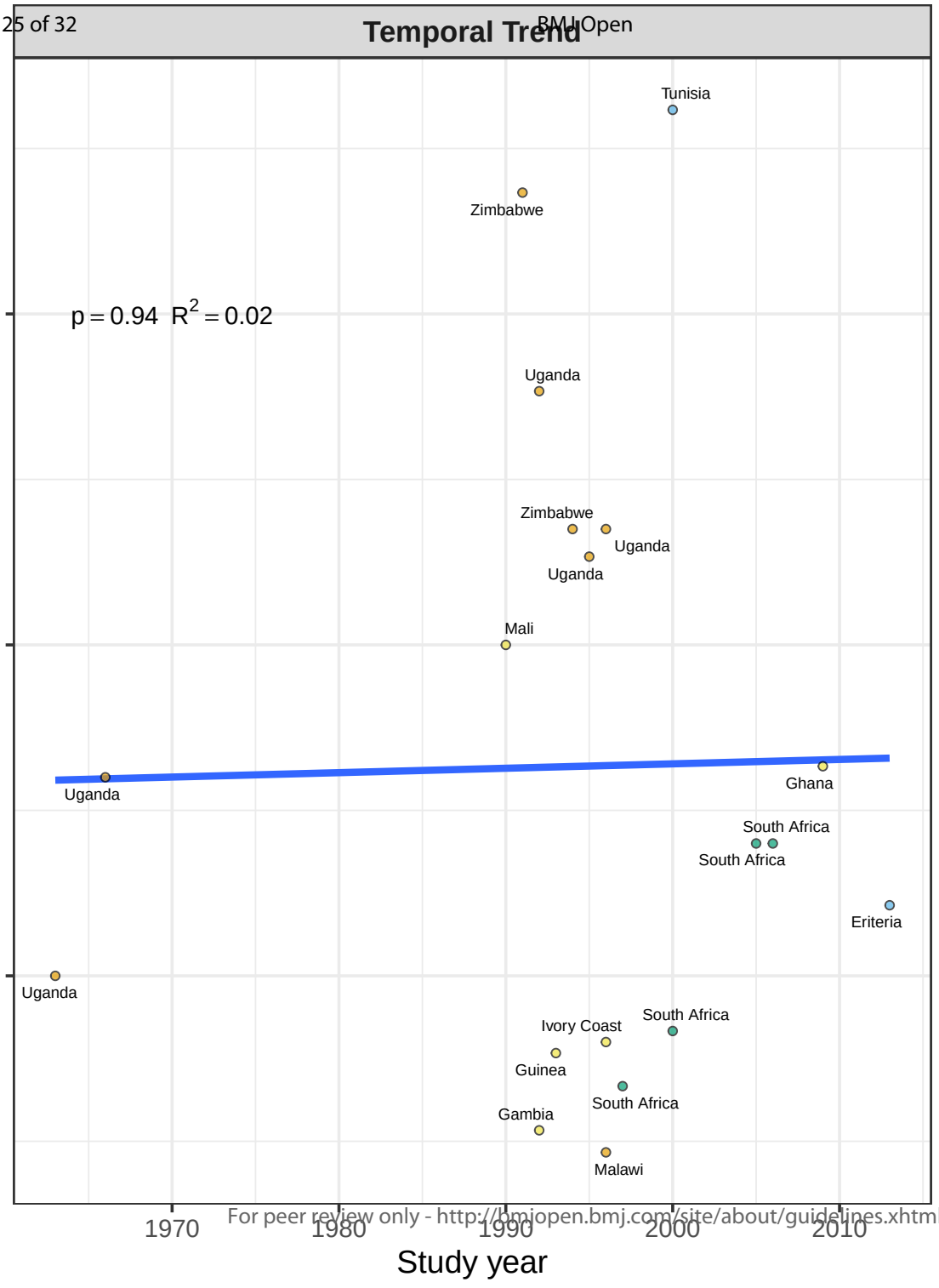

SUPPLEMENTARY MATERIAL FOR THE MANUSCRIPT

Age-standardized incidence rate and epidemiology of colorectal cancer in Africa: a systematic review and meta-analysis

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Running head: Colorectal cancer in Africa: a meta-analysis

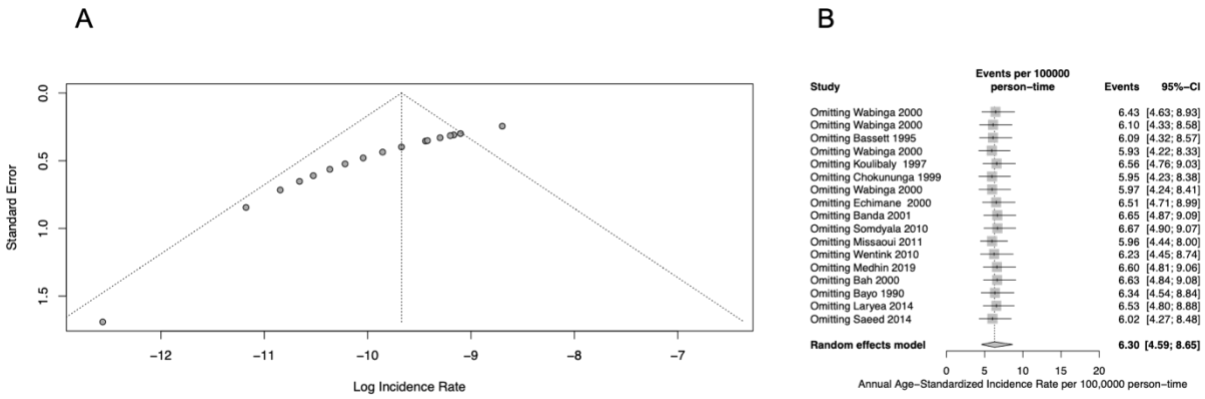
Search terms used in PubMed (MEDLINE)

1. ((colon cancer[MeSH Terms]) OR (Colorectal Cancer) OR (rectal cancer[MeSH Terms])) OR (colorectal carcinoma[MeSH Terms]))

2. (Epidemiology[MeSH Terms])) OR (Incidence[MeSH Terms])) OR (Prevalence[MeSH Terms]))]

3. (Africa OR Africa South of the Sahara OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroun OR Cameroon OR Cape Verde OR Chad OR Central African Republic of Comoros OR Congo OR Cote d'Ivoire OR Democratic Republic of the Congo OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Sao Tome OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR Swaziland OR Togo OR Uganda OR Tanzania OR Zambia OR Zimbabwe OR Africa, Northern, OR Algeria OR Egypt OR Libya OR Morocco OR Tunisia OR western Sahara OR South Africa OR Africa, Western OR Africa, Southern OR Africa, Northern OR Africa, Eastern OR Africa, Central)

4. 1 AND 2 AND 3



Supplemental Figure 1: Publication bias and sensitivity analyses. Funnel plot was not interpretable (A). Influence analysis shows no significant change from any of the pooled estimates observed when other studies were removed in turn. The pooled ASIR ranged from 5.93 to 6.67 (**B**)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
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.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
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.	6
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.	6
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.	6
	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.	6
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.	6
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.	7
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)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics,	7

Section and Topic	Item #	Checklist item	Location where item is reported
		or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	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).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7
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.	8-16
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	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.	8-16
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-16
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8-16
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	8-16
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	8-16

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	18-21
	23b	Discuss any limitations of the evidence included in the review.	18-21
	23c	Discuss any limitations of the review processes used.	18-21
	23d	Discuss implications of the results for practice, policy, and future research.	20
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.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	22
Competing interests	26	Declare any competing interests of review authors.	22
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.	22

Supplemental Table 1: PRISMA checklist

PRISMA 2020 Checklist

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
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From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

PRISMA 2020 Checklist

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BMJ Open

Age-standardized incidence rate and epidemiology of colorectal cancer in Africa: a systematic review and meta-analysis

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Age-standardized incidence rate and epidemiology of colorectal cancer in Africa: a systematic review and meta-analysis

Nina D. Arhin, MD[1*], Paddy Ssentongo, MD, MPH, PhD[2,3*], Morris Taylor[4], Elizabeth J. Olecki, MD[5], Colette Pameijer, MD, FACS[5], Chan Shen, PhD[5], John Oh, MD, FACS[5], Cathy Eng, MD, FACP, FASCO[1]

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Running head: Colorectal cancer in Africa: a meta-analysis

Total number of words: 2256
Figures: 7

Objectives: Colorectal cancer (CRC) is the second leading cause of cancer deaths globally, with low– and middle–income countries (LMIC) disproportionately affected. Estimates of CRC rates in LMIC are scarce. We aimed to estimate (1) sex-specific incidence of CRC, (2) temporal trend and (3) determine regional variations of rates on the African continent.

Design: Systematic review and meta-analysis

Methods: PubMed (MEDLINE), OVID (MEDLINE), Scopus and Cochrane Library databases were systematically searched from inception to 12/12/2020. We included population-based studies that reported the incidence or prevalence estimates of CRC in Africa. Studies not conducted in humans or did not directly report the rates of CRC were excluded. Random effects model was used to pool the estimates. The methodological quality of studies was assessed with the Newcastle-Ottawa Scale.

Outcome measures: Overall and sex-specific annual age-standardized incidence rates (ASIR) of CRC per 100,000 population.

Results: The meta-analysis included 14 studies consisting of 3365 individuals with CRC (mean age, 58 years, 53% male). The overall ASIR of CRC in Africa per 100,000 population was 5.25 (95% CI: 4.08 to 6.75). The rates were slightly higher in males (4.76) than in females (4.18), but not significantly different. Subgroup analysis indicated greater point estimates in North Africa (8.66) compared to Sub-Saharan Africa (SSA) (5.91); and higher estimates in Eastern (8.29) and Northern (8.66) Africa compared to Western (3.55) and Southern (3.57) Africa, but not

statistically significant. The overall trend in ASIR has remained constant at nearly 5 per 100,000 population for the last 6 decades.

Conclusion: CRC estimates in Africa are heterogeneous and could be underestimated. High-quality data collection systems such as population-based cancer registries may facilitate accurate estimation of country-specific rates and provide critical information which would be lucrative to the consideration of resources needed for screening, early detection, treatment, and improving overall patient outcomes.

Funding: None.

Registration: None.

Strengths and limitations of this study

- All United Nations (UN) regions (North Africa and sub-Saharan Africa) were represented.
- UN subregions (Eastern, Western, Southern, and Northern) of Africa were represented.
- Country-level data came from only 18% of the continent.
- Middle Africa had no data on colorectal cancer prevalence.

Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer deaths globally.[1] In 2018, there were an estimated 1.8 million new cases of colorectal cancer diagnoses and 862,000 deaths from CRC.[1] The majority of deaths from cancer occurred in low- and middle-income countries (LMIC), with most patients presenting with late-stage disease and commonly unable to obtain medical treatment services.

Even though the incidence of CRC has always been considered to be lower in LMIC, compared to high-income countries (HIC), the rates of colorectal cancer have been increasing in LMIC over time.[2] The rising incidence of cancer in LMIC has been attributed in part to the adoption of high-risk lifestyles such as smoking, excessive alcohol use, physical inactivity, as well as an aging population.[3]

Africa is the second largest and second most populated continent with an estimated population of 1.3 billion people in 2018, accounting for 16% of the world's human population.[4] Despite this vast population, CRC in Africa is not currently well characterized, in part due to deficiencies in the data on the incidence, prevalence, and mortality of all cancers in Africa. A vast majority of available data come from existing, limited cancer registries which cover less than half of the population.[5] Nevertheless, based on current and available data, colorectal cancer is considered the fifth most common cancer in Africa[6]. The rate of CRC is estimated to be higher in Northern Africa than Sub-Saharan Africa (SSA) due to the absence of screening systems and population-based cancer registries in SSA.[5 6]

This systematic review and meta-analysis aims to comprehensively characterize and estimate the incidence of CRC based on available data. These estimates will raise awareness regarding the

current incidence of CRC in Africa and will guide future public health allocation of resources to prevent, control and treat CRC.

METHODS

Search Strategy and Selection Criteria

This study adheres to the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in Supplementary Table1.[7 8] We searched PubMed (MEDLINE), OVID (MEDLINE), Scopus and Cochrane Library databases from inception to 12/12/2020 for articles reporting the incidence rates of colorectal cancers in Africa. We searched the grey or difficult to locate literature, including Google Scholar and preprint servers. We performed hand-searching of the reference lists of included studies, relevant reviews, or other relevant documents. The search terms of interest were identified by using Medical Search Headings (MeSH). They included “colorectal cancer” OR “colon cancer” OR “rectal cancer” OR” colorectal carcinoma” AND “epidemiology” OR “incidence” OR “prevalence” AND “ Africa”. Duplicate studies were initially extracted via Endnote software. Three reviewers (NA, MT, and PS) independently screened titles and abstracts of the studies for inclusion eligibility. The comprehensive list of studies found from the initial search was transferred into Endnote, which further removed duplicate studies. The inclusion criteria for this meta-analysis and systematic review were defined as studies that 1) reported the incidence or prevalence estimates of colorectal cancer in Africa 2) were conducted in human subjects 3) were population-based (all cases in a defined geographical area, or hospital or community-based surveillance). Excluded studies were not conducted in humans or did not directly report the rates of colorectal cancer, meta-analyses, literature reviews, or commentaries.

Patient and public involvement

No patient and public involvement in this systematic review and meta-analysis.

Data Extraction and Quality Assessment

After the reviewers initially screened titles and abstracts of potential articles, full-text articles were independently screened by three reviewers (NA, MT, and PS) for eligibility. In the event of a discrepancy regarding an article's inclusion, a consensus was reached by discussion. Articles that met inclusion criteria had appropriate data extracted using a standard data collection form. We extracted the following information: the year of publication, country, region, cohort and cohort year, study design, sample size, gender percent, sample size of patients with CRC. If duplicate articles identified, we included only mutually exclusive data.

Assessment of Methodological Quality of the Papers

The methodological quality of studies was assessed with the Newcastle-Ottawa Scale, a validated tool for assessing quantitative cross-sectional, case-control and cohort studies.[9] Scores of 8 to the maximum score of 9 were defined as high quality, scores of 5 to 7 as intermediate quality, and scores of 1 to 4 as low quality.

Standardization

Age standardization of incidence rates was carried out by the direct method, using age specific rates for 5-year age groups and the world standard population and was reported by each paper.[10]

Statistical Analysis

The primary outcome of interest was the overall and sex-specific annual age−standardized incidence rate of colorectal cancer . The *metaprop* function from the R package *meta* was used to calculate the pooled effect estimates using random-effects models.[11] We applied the DerSimonian and Laird (DL) random-effects method to estimate the pooled between-study variance (heterogeneity).[12] Individual and pooled estimates were graphically displayed using forest plots. A random-effects model assumes the observed estimates of colorectal cancer can vary across studies because of real differences in the effect in each study as well as sampling variability (chance). Between-study heterogeneity was assessed using I^2 statistics, expressed as % (low (25%), moderate (50%), and high (75%) and Cochrane's Q statistic (significance level < 0.05).[13] To investigate the sources of heterogeneity, we conducted subgroup analyses using year of study (Before and after the year 2000), United nations regions (Sub-Saharan African vs. North Africa) and United Nations subregions (Western, Eastern, Southern, Northern, and Eastern Africa). Results were reported as the annual age−standardized incidence rate per 100,000 person−time. Potential ascertainment bias (as might be caused by publication bias) was assessed with funnel plots by plotting the study effect size against standard errors of the effect size and Egger/Begg test.[14] All statistical analyses were performed with R software, version 4.0.3 (R Core Team, Vienna, Austria).

Results

Study Selection

Our initial searches yielded 1203 studies, of which 53 underwent full-text screening (**Figure 1**). Of these, 22 were Conference proceedings, 15 came from overlapping populations and 2 were systematic reviews. A total of 14 studies matched all the eligibility criteria. Of the included studies, 2 were from South Africa,[15 16] 2 from Zimbabwe,[17 18] and 1 from Ghana[19], Eritrea,[20] The Gambia,[21] Guinea,[22] Ivory Coast,[23] Mali[24], Malawi[25] and Tunisia,[26] Uganda,[27] and Sudan[28] each. The paper by Wabinga and colleagues (2000) from Uganda described cancer incidence at 4-time points, 1960-1966; 1967-1971; 1991-1994 and 1995-1997.[27] These time points were analyzed independently to allow for trend analysis. A total of 3365 individuals with colorectal cancer (mean age, 58 years, 53% male) were analyzed. The percentages of colon and rectal cancer were 65% and 35%, respectively. The percentage with locally advanced and metastatic disease (stage III and IV) was 57.9%. Adenocarcinoma represented the majority of diagnosed colorectal cancers with a small proportion representing squamous cell carcinoma. Grades 1, 2, and 3 were 32.4, 60.7, and 8.36%, respectively.

Annual age−standardized incidence rate of colorectal cancer per 100,000 person-year

As displayed in **Figure 2**, the overall annual age−standardized incidence rate of colorectal cancer per 100,000 person-year was 6.30 (95% CI: 4.59 to 8.65). The rates were slightly higher in males than in females but not significantly different (4.76 versus 4.18). The heterogeneity was moderate (I^2=58%).

Subgroup analysis was performed by the United Nations regions (North Africa vs. Sub-Saharan Africa) and by United Nations subregions. Although the point estimate was higher in North Africa (8.66) compared to SSA (5.91), the difference was not significant (**Figure 3**).

Furthermore, the rates were greater in Eastern (8.29) and Northern (8.66) Africa compared to Western (3.55) and Southern (3.57) Africa, but not significantly different (**Figure 4**). To assess if the rates from recent studies (2000 and later) are higher than older studies (Before 2000), we carried out a stratified analysis. There was no difference in the rates of CRC 5.55 (95% CI: 2.57 to 11.96) and 6.50 (95% CI: 4.72 to 8.94), respectively (**Figure 5**). The trend in ASIR has remained nearly constant at 4.5 per 100,000 population for the last 6 decades (**Figure 6**)

Study Quality, Publication Bias, and Sensitivity Analyses

The median study quality score for studies reporting on the incidence was 5 out of 8 (range=4–9). The funnel plot (Supplemental **Figure 1A**) the value of the Egger test ($p<0.0001$) and Begg test ($p<0.0001$) indicated the presence of publication bias. We used the trim and fill method to adjust for the publication bias. If the asymmetry is due to publication bias, the adjusted estimates fall in the range of 5.76 to 12.22. Finally, Influence sensitivity analyses were by excluding and replacing one study at a time (leave-one-out method) from the meta-analysis and calculating the pooled ASIR for the remaining studies. No significant change from any of the pooled estimates was observed when other studies were removed in turn. The pooled ASIR ranged from 5.93 to 6.67 (Supplemental **Figure 1B**)

Discussion

This paper provides a comprehensive meta-analysis of the patterns and trends in the CRC incidence in Africa. The estimated annual age−standardized incidence rate (ASIR) of colorectal cancer per 100,000 persons was 6.30. This rate is higher than reported in a 2012 systematic review of only sub-Saharan Africa (SSA) countries by Graham et al. which reported a crude incidence rate of 4.04 per 100,000.[5] When compared to SSA, North Africa had the highest ASIR of 8.66, while SSA had an ASIR of 5.91. Middle Africa was not represented in this meta-analysis.

CRC is known to be the most common malignancy of the GI tract[29], and while previously thought to be a rare malignancy in Africa, recent data is proving otherwise.[30 31]. In addition to being more common than previously recognized, CRC in Africa tends to present more commonly in young adults[31]. This trend in young adults is similar to current trends in the United States, Asia and Europe, where patients usually present with advanced stage, left-sided tumors, and poor histology.[32]

In the United States, colorectal cancer is the third most common cancer in both men and women but the 2nd leading cause of cancer death.[33] Rates of colorectal cancer in the United States have been declining since the mid-1980s in patients older than 50 years old, mainly due to increased cancer screening and changes in lifestyle[15]. This is in sharp contrast to young adults < 50 years old where there is an expected exponential increase between 2020 through 2030.[34] According to a study by Siegel et al. (2020), the ASIR of colorectal cancer in the United States from 2012-2016

was 38.7 per 100,000 persons[21]. Furthermore, in the United States, the ASIR in Blacks from 2012-2016 was 45.7 compared to 38.6 in Non-Hispanic Whites. In the United Kingdom, the ASIR for 2017 was 68.0 per 100,000 persons[22]. The incidence of colorectal cancer in people of African descent in the United States is 20% higher than the incidence in Caucasians [23]. In the United States, people of African descent present at a younger age and with more advanced disease at diagnosis and have the highest mortality rate among different ethnic groups[35]. Factors responsible for these differences are multifactorial, including known health disparities, socioeconomic status, genetic factors, and dietary influences[36 37].

Even though our study provides much lower age-standardized incidence rates, it is assumed that these do not accurately reflect the actual incidence of colorectal cancer in Africa. We suspect this number to be much higher. According to the study by Laiyemo et al. (2016), there is no population-based colorectal cancer screening or guidelines in any African country to date.[38 39] To better understand the true incidence rates of colorectal cancer in Africa, standardized screening guidelines must be established. Given the lack of screening, patients commonly present with advanced disease. More countries are implementing and establishing population based cancer registries (PBCR)[39] described in this study by Omonisi and his colleagues. These registries should inform us of more specific country incidence rates and allow for further population-based studies that could unravel the mysteries behind the increased risk of colorectal cancer in people of African descent.

The present analysis has major strengths. First, all United Nations regions (North Africa, SSA) and subregions (Eastern, Western, Southern, and Northern Africa) of Africa were represented

(except Middle Africa). Thus, our findings can be generalizable at the regional level of Africa. Secondly, we included recent estimates of colorectal cancer in Africa. The present estimates are the most updated figures of the rates of colorecta cancer in Africa and thus can be used to inform the prevention and control strategies. Nevertheless, the present study has some limitations. First, country-level data came from only 18% of the continent, meaning most countries were not represented due to the lack of published literature on CRC incidence in these countries. Therefore, the estimates may not be generalizable at the country-level. To mitigate this limitation, we conducted subgroup analysis by African regions (North Africa, SSA) and subregions (Eastern, Western, Southern, and Northern Africa) to explore possible regional and subregional specific rates. Second, the estimates could suffer from potential selection bias due to a lack of random population-based studies such as those conducted by the demographic and health surveys program and country-based cancer registries. However, the present systematic review and meta-analysis provides the updated estimates of colorectal cancer in Africa using the best available information, and we have applied rigorous sensitivity analysis to minimize bias.

Conclusion

Colorectal cancer estimates in Africa are heterogeneous and could be underestimated. Population-based colorectal cancer data are scarce in Africa. High-quality data collection systems such as population-based cancer registries may facilitate country-specific rates and provide accurate information which would be lucrative to the consideration of resources needed for screening, early detection, treatment and improving overall patient outcomes.

Contributorship NDA, CE and PS conceived and designed the study. NDA, MT and PS extracted data. PS performed statistical analysis and created figures. NDA and PS drafted the manuscript and made subsequent revisions. CE and JO supervised the study. EJO, CP and CS critically revised the manuscript for intellectual content. All authors read and approved the final version of this manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Not applicable

Ethical considerations

This is a systematic review using publicly available data. We analyzed aggregated data and no personal identification information was accessed or reported. Therefore, no IRB was required.

Provenance and peer review Not commissioned, externally peer reviewed.

Data availability statement All data needed to reproduce the results are included in the manuscript.

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Figure legend

Figure 1: PRISMA flowchart of a systematic review of colorectal cancer incidence in Africa

Figure 2: Overall and sex-specific annualized ASIR of colorectal cancer in Africa. Event values represent the age-standardized incidence rates of colorectal cancer per 100,000 population. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate of the ASIR, overall and by sex (width denotes 95% CI). Although not statistically significant, the pooled ASIR of colorectal cancer in Africa was higher in males (I^2=39) than in females *(I^2*=37). P for interaction comparing the different subgroups =0.37.

Figure 3: Overall ASIR (per 100,000 population) of colorectal cancer in Africa stratified by United Nations region (North Africa and sub-Saharan Africa). Event values represent the age-standardized incidence rates of colorectal cancer per 100,000 population. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate of the ASIR, overall and by United Nations regions (width denotes 95% CI). Although not statistically significant, the pooled ASIR of colorectal cancer in Africa was higher in North Africa (I^2=76) than SSA *(I^2*=45). P for interaction comparing the different subgroups =0.21.

Figure 4: ASIR (per 100,000 population) of colorectal cancer in Africa stratified by United Nations subregions (Northern, Western, Eastern, and Southern Africa). Event values represent the age-standardized incidence rates of colorectal cancer per 100,000 population. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate of the ASIR, overall and by United Nations subregion (width denotes 95% CI).

Figure 5: ASIR (per 100,000 population) of colorectal cancer in Africa stratified by year of study (Before 2000 and 2000 and after). Event values represent the age-standardized incidence rates of colorectal cancer per 100,000 population. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate of the ASIR, overall and by year categorized as before and after 2000 (width denotes 95% CI). There is no difference in the rates between the year categories.

Figure 6: Temporal trends in the incidence rates (per 100,000 population) of colorectal cancer in Africa. Rates were constant over time.

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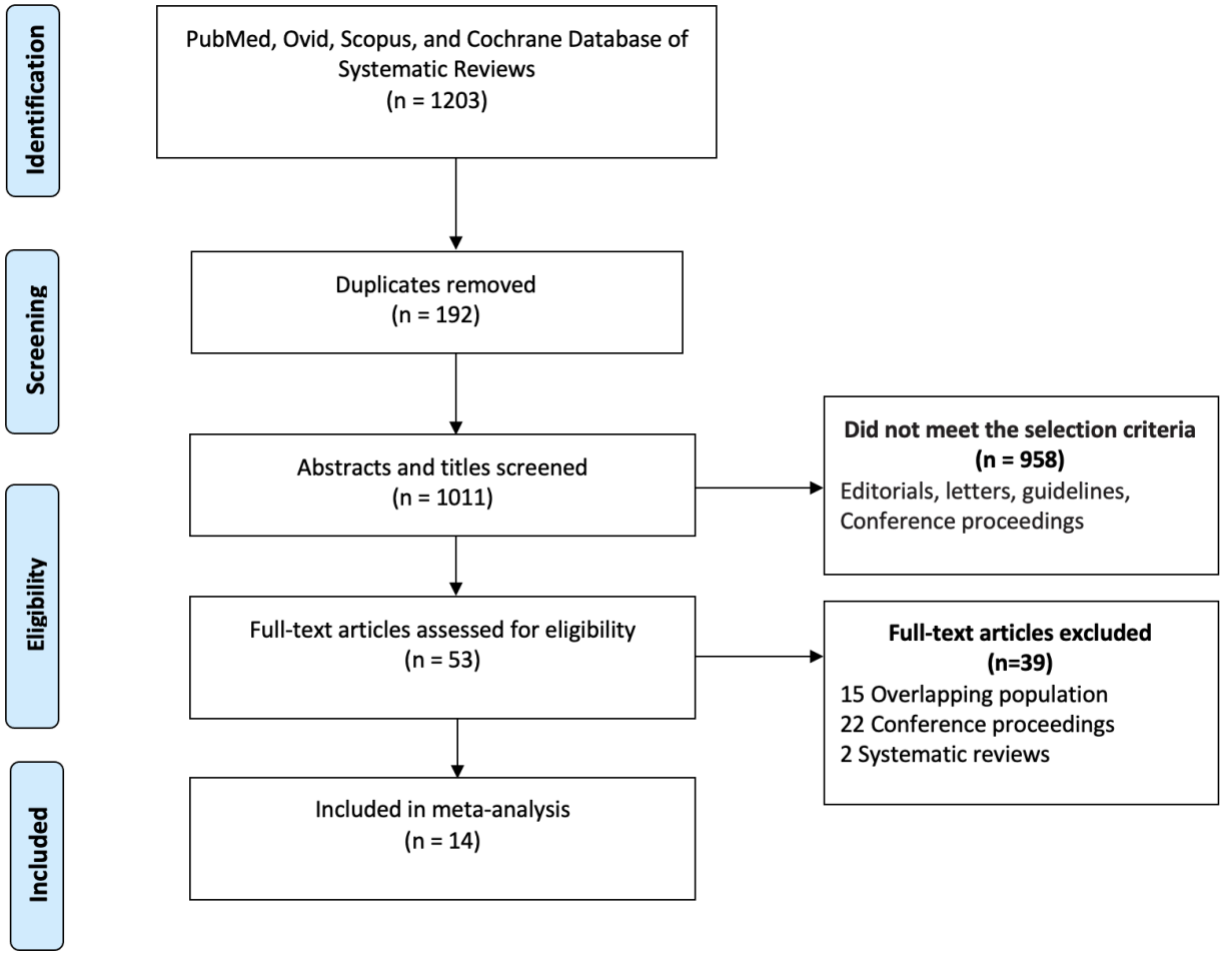

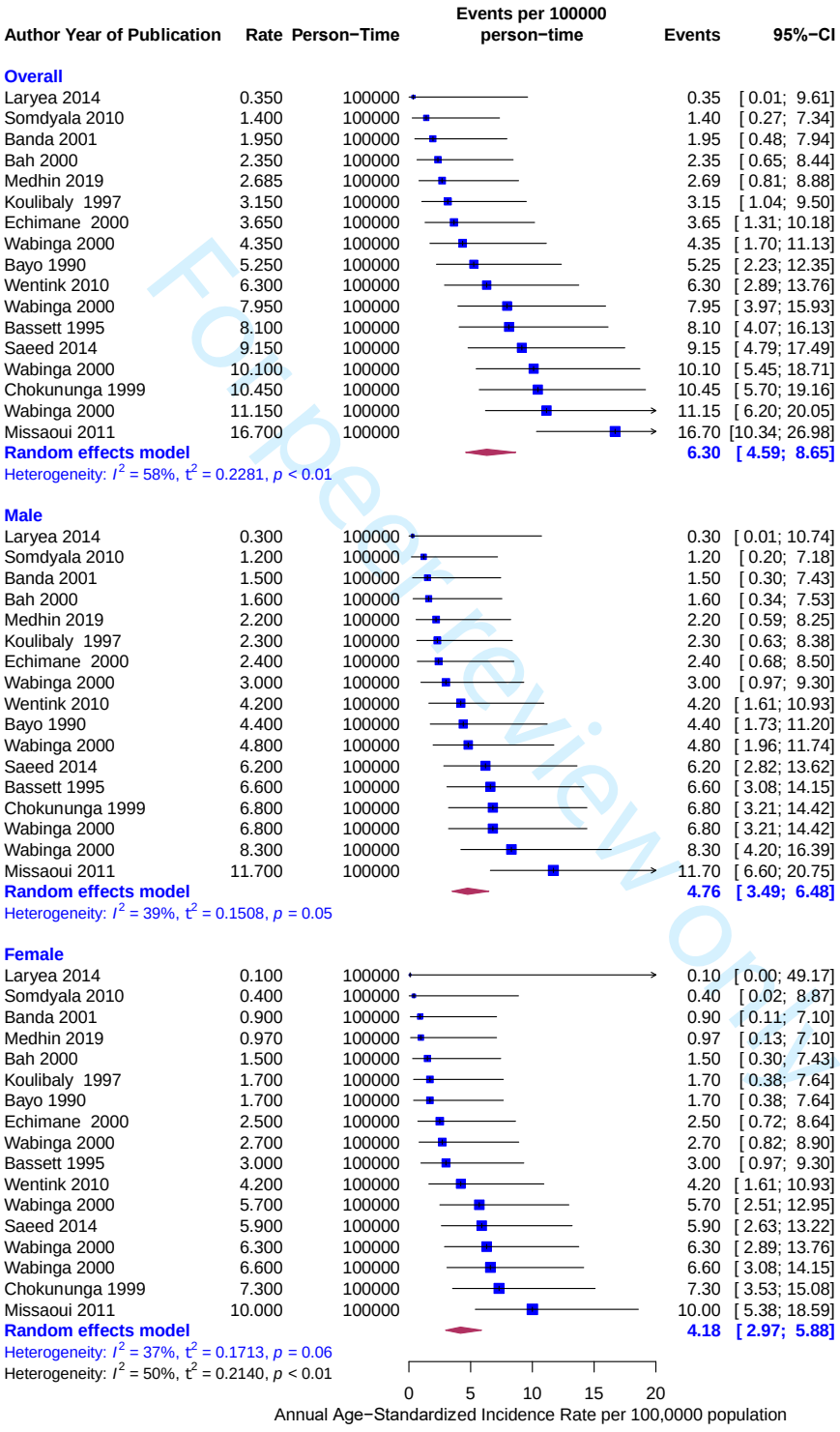

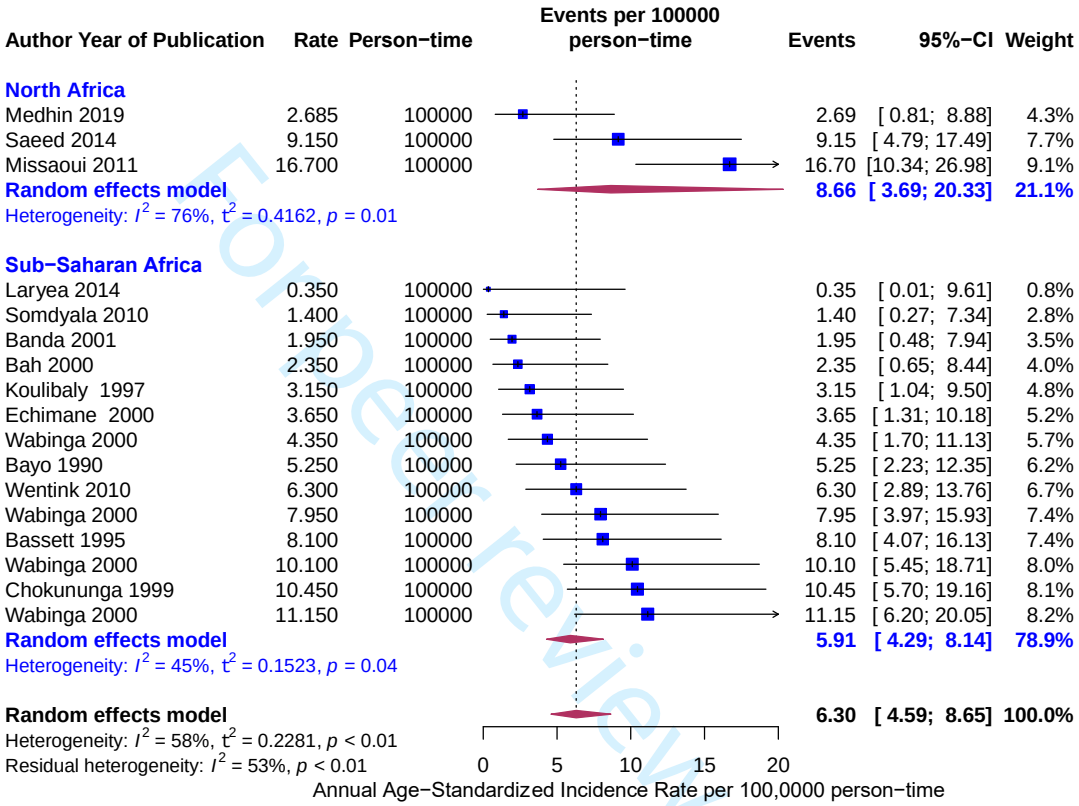

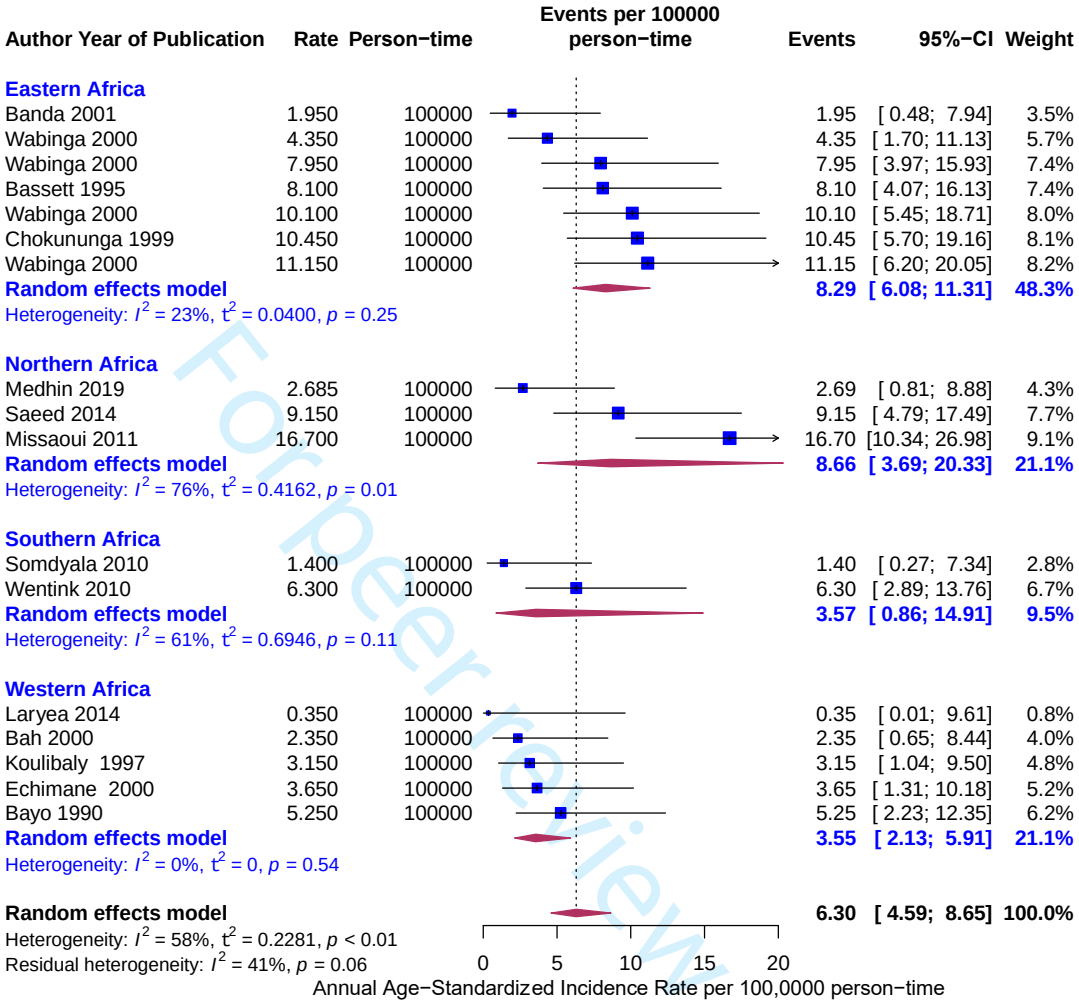

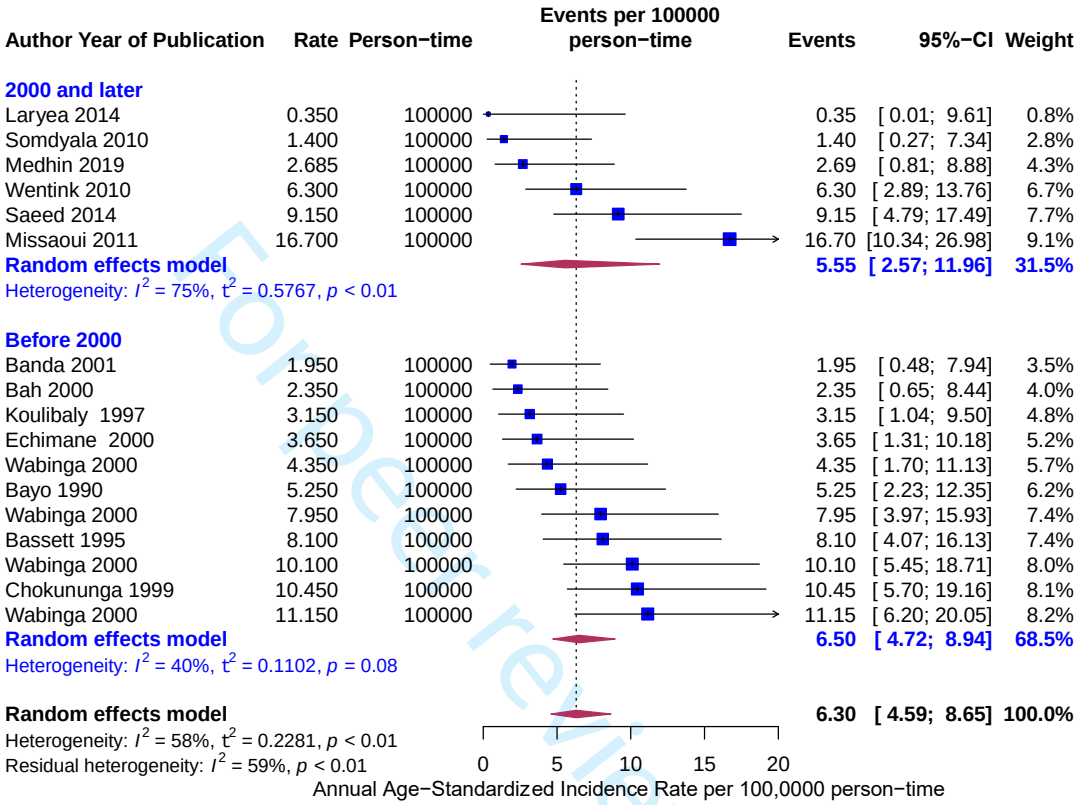

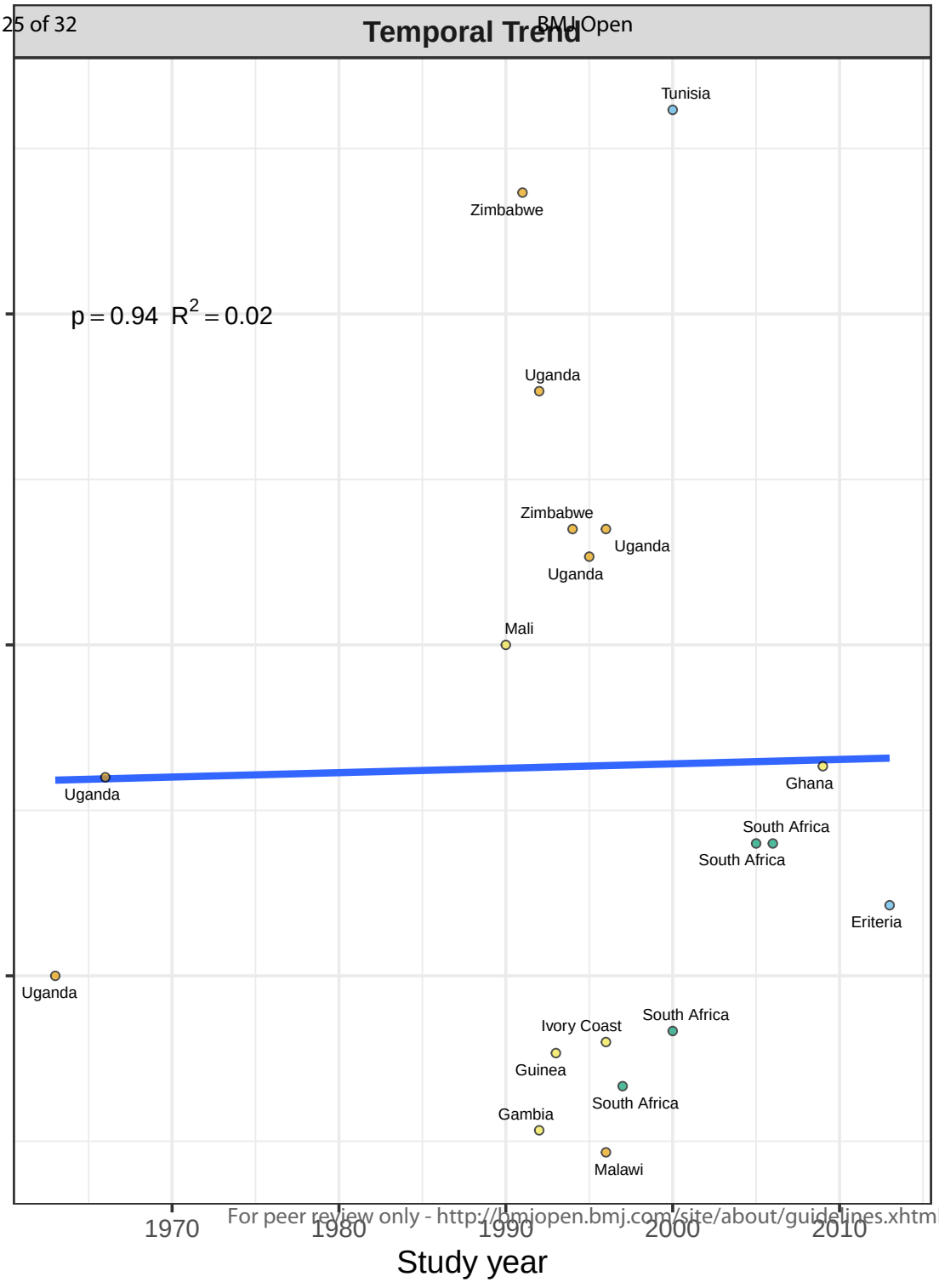

SUPPLEMENTARY MATERIAL FOR THE MANUSCRIPT

Age-standardized incidence rate and epidemiology of colorectal cancer in Africa: a systematic review and meta-analysis

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Running head: Colorectal cancer in Africa: a meta-analysis

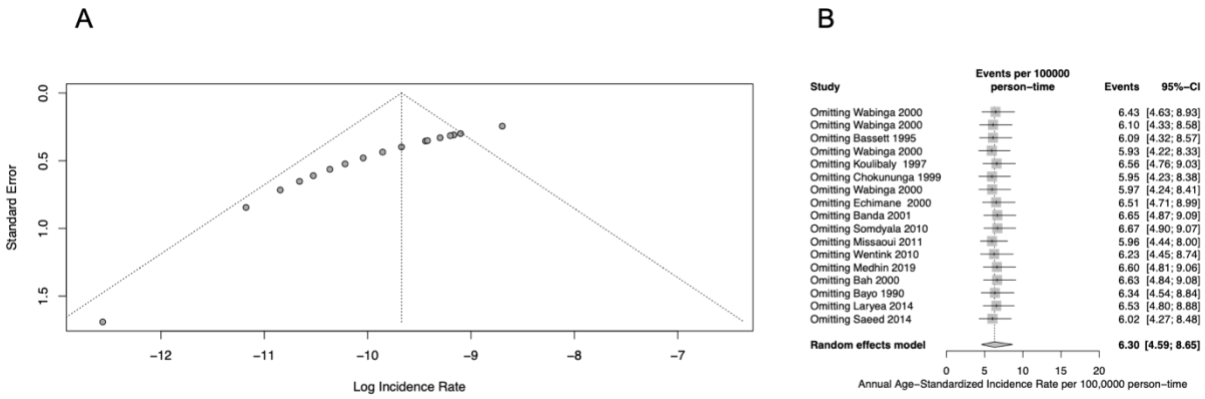
Search terms used in PubMed (MEDLINE)

1. ((colon cancer[MeSH Terms]) OR (Colorectal Cancer) OR (rectal cancer[MeSH Terms])) OR (colorectal carcinoma[MeSH Terms]))

2. (Epidemiology[MeSH Terms])) OR (Incidence[MeSH Terms])) OR (Prevalence[MeSH Terms]))]

3. (Africa OR Africa South of the Sahara OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroun OR Cameroon OR Cape Verde OR Chad OR Central African Republic of Comoros OR Congo OR Cote d'Ivoire OR Democratic Republic of the Congo OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Sao Tome OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR Swaziland OR Togo OR Uganda OR Tanzania OR Zambia OR Zimbabwe OR Africa, Northern, OR Algeria OR Egypt OR Libya OR Morocco OR Tunisia OR western Sahara OR South Africa OR Africa, Western OR Africa, Southern OR Africa, Northern OR Africa, Eastern OR Africa, Central)

4. 1 AND 2 AND 3



Supplemental Figure 1: Publication bias and sensitivity analyses. Funnel plot was not interpretable (A). Influence analysis shows no significant change from any of the pooled estimates observed when other studies were removed in turn. The pooled ASIR ranged from 5.93 to 6.67 (**B**)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
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.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
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.	6
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.	6
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.	6
	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.	6
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.	6
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.	7
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)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics,	7

Section and Topic	Item #	Checklist item	Location where item is reported
		or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	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).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7
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.	8-16
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8
Study characteristics	17	Cite each included study and present its characteristics.	8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8-16
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.	8-16
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-16
	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.	8-16
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-16
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8-16
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	8-16
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	8-16

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	18-21
	23b	Discuss any limitations of the evidence included in the review.	18-21
	23c	Discuss any limitations of the review processes used.	18-21
	23d	Discuss implications of the results for practice, policy, and future research.	20
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.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	22
Competing interests	26	Declare any competing interests of review authors.	22
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.	22

Supplemental Table 1: PRISMA checklist

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
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.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
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.	6
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.	6
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.	6
	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.	6
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.	6
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.	7
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)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	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).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
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.	8-16
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8
Study characteristics	17	Cite each included study and present its characteristics.	8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8-16
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.	8-16
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-16
	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.	8-16
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-16
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8-16
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	8-16
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	8-16
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	18-21
	23b	Discuss any limitations of the evidence included in the review.	18-21
	23c	Discuss any limitations of the review processes used.	18-21
	23d	Discuss implications of the results for practice, policy, and future research.	20
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.	5
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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.	22

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

PRISMA 2020 Checklist

For more information, visit: http://www.prisma-statement.org/