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SPECIAL REPORT

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Post-diagnosis adiposity and colorectal cancer prognosis: A Global Cancer Update Programme (CUP Global) systematic literature review and meta-analysis

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Abstract

The adiposity influence on colorectal cancer prognosis remains poorly characterised. We performed a systematic review and meta-analysis on post-diagnosis adiposity measures (body mass index [BMI], waist circumference, waist-to-hip ratio, weight) or their changes and colorectal cancer outcomes. PubMed and Embase were searched through 28 February 2022. Random-effects meta-analyses were conducted when at least three studies had sufficient information. The quality of evidence was interpreted and graded by the Global Cancer Update Programme (CUP Global) independent Expert Committee on Cancer Survivorship and Expert Panel. We reviewed 124 observational studies (85 publications). Meta-analyses were possible for BMI and all-cause mortality, colorectal cancer-specific mortality, and cancer recurrence/disease-free survival. Non-linear meta-analysis indicated a reverse J-shaped association between BMI and colorectal cancer outcomes (nadir at BMI 28 kg/m^2). The highest risk, relative to the nadir, was observed at both ends of the BMI distribution (18 and 38 kg/m^2), namely 60% and 23% higher risk for all-cause mortality; 95% and 26% for colorectal cancer-specific mortality; and 37% and 24% for cancer recurrence/disease-free survival, respectively. The higher risk with low BMI was

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attenuated in secondary analyses of RCTs (compared to cohort studies), among studies with longer follow-up, and in women suggesting potential methodological limitations and/or altered physiological state. Descriptively synthesised studies on other adiposity-outcome associations of interest were limited in number and methodological quality. All the associations were graded as limited (likelihood of causality: no conclusion) due to potential methodological limitations (reverse causation, confounding, selection bias). Additional well-designed observational studies and interventional trials are needed to provide further clarification.

KEYWORDS
adiposity, colorectal cancer, evidence grading, systematic review

What's new?

The influence of adiposity on colorectal cancer prognosis remains poorly characterised. Here, as part of CUP Global, the evidence on post-diagnosis adiposity and colorectal cancer outcomes was systematically synthesised using standardised criteria, and a non-linear dose–response meta-analysis was conducted for the first time. Reverse J-shaped associations were observed between post-diagnosis BMI and all-cause mortality, colorectal cancer-specific mortality, and recurrence. Synthesised studies on other adiposity–outcome associations were limited in number and methodological quality. All evidence was graded as 'limited—no conclusion' for the likelihood of causality due to potential methodological limitations, calling for additional well-designed observational studies and intervention trials.

1 | INTRODUCTION

In 2020, colorectal cancer was the third most diagnosed cancer with 1.9 million new cases, and the second most frequent cause of cancer mortality with 930,000 deaths globally.[1] Colorectal cancer incidence has declined or stabilised among adults aged 50 years and above in high-income countries, while it is increasing among younger adults and in low and middle-income countries.[2,3] Colorectal cancer survival rates are gradually improving over time,[4] likely due to improved early detection methods and advances in cancer treatments.[5] The increasing number of colorectal cancer survivors (more than 5.25 million people are living with this disease worldwide[3]), however, highlights the need to better quantify the relationship between post-diagnosis modifiable lifestyle factors (such as diet, physical activity, and adiposity) and survival outcomes to guide the development of evidence-based recommendations for this specific population.[6]

The prevalence of overweight and obesity rapidly increased worldwide[7] from 1975 to 2016. The Third Expert report from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR)[8] concluded that there was strong evidence (likelihood of causality: convincing) that greater adiposity (i.e., expressed by increased body mass index [BMI], waist circumference or waist-to-hip ratio) increases the risk of colorectal cancer. However, the potential impact of excess adiposity after diagnosis on colorectal cancer prognosis is not well understood. Previously published meta-analyses have analysed the association between post-diagnosis BMI and colorectal cancer outcomes (i.e., all-cause mortality, colorectal cancer-specific mortality, and recurrence).[9–13] The most comprehensive and recent one,[13] which included 56 publications assessing BMI at any post-diagnosis period, showed that colorectal cancer survivors who were underweight (<18.5 kg/m^2) had a higher risk of all-cause mortality, colorectal cancer-specific mortality, and recurrence than those with normal weight (18.5–25 kg/m^2). No differences were observed between those with overweight (25–30 kg/m^2) and normal weight. Colorectal cancer survivors with obesity (>30 kg/m^2) had worse disease-free survival, while those with morbid obesity (>35 kg/m^2) had a higher risk for all-cause mortality, colorectal cancer-specific mortality, and recurrence. However, this meta-analysis combined unadjusted and adjusted risk estimates, which can result in confounded associations between adiposity and colorectal cancer outcomes. In addition, questions remain about the shape of the dose–response relationship, as all previous meta-analyses were conducted on categorical data, assuming constant risks within the different BMI categories analysed. Thus, conducting a non-linear dose–response meta-analysis was highly desirable and useful for characterising thresholds, as previously examined in breast cancer survivors.[14]

Therefore, as part of the work for the Global Cancer Update Programme (CUP Global),[15] we conducted a systematic literature review and meta-analysis to summarise the epidemiological evidence on the role of post-diagnosis adiposity in colorectal cancer outcomes.

The current article presents the evidence on adiposity and colorectal cancer outcomes, whereas evidence on diet, physical activity and the overall summary are presented in the accompanied papers.[16–18]

2 | METHODS

This systematic review is part of the ongoing CUP Global, formerly known as the WCRF/AICR Continuous Update Project.[15] The detailed pre-published protocol can be found elsewhere.[19] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist is in Supplementary Table 1.

2.1 | Search strategy, selection criteria and data extraction

A comprehensive search was conducted in PubMed and Embase databases through 28 February 2022. The reference lists of relevant articles, reviews and meta-analyses were manually checked for potential additional publications.

Inclusion criteria were randomised controlled trials (RCTs), longitudinal observational studies, or pooled analyses of these designs, with at least 100 participants diagnosed with first primary colorectal cancer or its subtypes (for brevity the term 'colorectal' is used for any colorectal cancer regardless of the cancer site, colon or rectum) during adulthood; that investigated associations between post-diagnosis BMI, waist circumference, waist-to-hip ratio, weight, or changes in these exposures with all-cause mortality, colorectal cancer and subsite-specific mortality, colorectal cancer recurrence/disease-free survival (as defined in studies) (Supplementary Table 2), any second primary cancer, or cardiovascular disease mortality.

The article with the largest number of outcome events with sufficient information for analysis was selected when multiple articles from the same or similar populations reported the same exposure-outcome associations. Relevant data, including study and participants' characteristics and results of analyses, were extracted into the CUP Global database. A second reviewer independently checked the study selection and data extraction. Any disagreements were resolved by consensus with a third reviewer.

2.2 | Risk of bias assessment

A modified version of the Risk of Bias for Nutrition Observational Studies (RoB-NObs) tool[20] was utilised to assess the risk of bias of the studies included in the dose–response meta-analyses. The tool was originally developed by the U.S Department of Agriculture (USDA) Nutrition Evidence Systematic Review after modifications to the Cochrane's collaboration Risk of bias In Non-randomised Studies of Interventions (ROBINS-I).[21] The Imperial College London (ICL) review team further refined and tested the tool to ensure its suitability for investigating exposure-outcome associations in cancer survivorship studies. This involved adapting the tool's prompting questions and providing additional guidance to encompass adiposity, physical activity, and dietary/nutritional exposures. The tool consists of seven domains, including confounding, participant selection, exposure classification, departures from intended exposures, missing data, outcome measurement, and selective reporting (the working document version dated 11/07/2023 can be found in Supplementary Table 3).

The studies not included in the dose–response meta-analyses, were assessed descriptively considering the most likely influential sources of bias (selection bias, information bias of exposure and outcome assessment, and residual confounding by cancer stage and treatment).

2.3 | Evidence synthesis

Publications were meta-analysed or descriptively synthesised when at least three studies were identified for a given exposure, except for exposures related to the WCRF/AICR Cancer Prevention Recommendations that were descriptively synthesised even when there were fewer than three included studies to identify any potential discrepancies compared to what has been currently recommended to cancer prevention.

2.4 | Statistical methods for meta-analysis

Linear and non-linear dose–response and categorial meta-analyses were conducted using the inverse variance weighted random-effects model[22] to calculate summary relative risk (RR) estimates and 95% confidence intervals (CIs). A descriptive synthesis, which consisted of systematically gathering, tabulating, and descriptively summarising the findings of the individual studies, was performed when results could not be summarised in dose–response or categorical meta-analyses.

Potential non-linear relationships were investigated by performing a one-stage non-linear dose–response meta-analysis[23] using restricted cubic splines with three knots placed at fixed percentiles (10th, 50th, and 90th) of the exposure distribution when at least five or more studies with data for at least three exposure categories were available (Text S1). Studies providing only a dichotomous or linear effect estimate were not included in the non-linear meta-analysis. All categories of BMI (including underweight) were included. Standard imputations were used to estimate missing information required for the analysis.[24,25] The nadir of the dose–response curve for each exposure-outcome association was selected as the referent point. RRs and 95% CIs were calculated relative to this point.

Linear dose–response meta-analysis was conducted when there were at least three studies with sufficient data to do the analysis (Text S1). The dose–response estimate given in the original publications was used directly when available, otherwise, we computed the estimates per exposure increment unit using the generalised weighted least-squares regression model.[26,27] For studies reporting results using BMI categories other than normal weight (BMI 18.5–24.9 kg/m^2 or as defined by studies) as a reference, the RRs and 95% CIs were re-calculated using the Hamling method.[28] The underweight category (BMI <18.5 kg/m^2 or as defined by studies) was excluded where possible from the linear dose–response meta-analysis on BMI to avoid possible influences on the risk estimation. If the study reported results separately by cancer site or other subgroups, we generated an overall estimate for subgroups combined using a fixed-effect model before pooling with other studies.

Categorical meta-analysis was performed to assess colorectal cancer prognosis in patients with underweight (BMI <18.5 kg/m^2 or

as defined by studies), overweight (BMI 25–29.9 kg/m^2 or as defined by studies), and obesity (≥30 kg/m^2 or as defined by studies) compared to those with normal weight (BMI 18.5–24.9 kg/m^2 or as defined by studies). Studies were included regardless of the BMI classification used (World Health Organisation [WHO] International,[29] or other study-defined categories). A few studies reported risk estimates for multiple sub-categories of normal weight,[30] overweight[30–33] or obesity,[30,34–37] and the Hamling method[28] was used to obtain an overall RR and 95% CIs for the comparisons of overweight and obese versus normal weight categories. RRs were re-calculated when the reference category was not the normal weight. Studies reporting two open-ended BMI categories only (e.g., >25 vs. <25 kg/m^2; >30 vs. <30 kg/m^2) or including underweight and normal weight or overweight and obesity in the same category were excluded from the analyses. A sensitivity analysis restricted to studies using the WHO classification system[29] was performed.

Heterogeneity between studies was assessed using the estimate of between study variances (tau^2) and reflected by the range of the estimates (RRs) provided in the forest plots. Additionally, we provided the I^2 metric,[38] which measures the proportion of total variability in effect estimates that is due to between-study heterogeneity rather than sampling error. Unlike I^2, the tau^2 does not depend on the precision of a study (does not systematically increase with the number or size of the studies in a meta-analysis).[39] The 95% prediction interval (PI) was also used to estimate the range of results likely to contain the value of a new study.[40] Sources of heterogeneity were explored with non-linear dose–response subgroup meta-analyses. These analyses were based on a priori defined disease (cancer subsite, stage), study characteristics (sex, geographical location, study type, exposure time relative to primary cancer diagnosis, and length of follow-up) and by risk of bias assessment domains. One of our aims was to perform a subgroup analysis according to the time of BMI (adiposity index) assessment with respect to the cancer diagnosis and/or treatment. However, most studies assessed the exposure at diagnosis or shortly after, and very few at later periods of the cancer course,[10,30,41,42] so it was not possible to perform predefined subgroup meta-analysis by exposure time relative to cancer diagnosis.

To explore the potential impact of bias due to reverse causation, a sensitivity analysis excluding, where possible, metastatic survivors was conducted.[43] When more than 10 studies were available in the linear dose–response meta-analysis, small study effects, such as publication bias, was examined using Egger's test[44] and via visual inspection of the funnel plots for asymmetry.

Statistical analyses were conducted using Stata 16 (StataCorp, College Station, TX, USA).

2.5 | Evidence grading criteria

The CUP Global independent Expert Committee on Cancer Survivorship and Expert Panel, convened by WCRF International, interpreted the findings independently of the ICL team. The Expert Committee made the preliminary conclusions, and the Expert Panel made the final conclusions. The quality of the evidence was graded into strong (subgrades evaluating likelihood of causality: convincing, probable, or substantial effect on risk unlikely), or limited (subgrades evaluating likelihood of causality: suggestive or no conclusion) level, using pre-defined evidence grading criteria (Supplementary Table 4). The grades of the quality of the evidence reflect the independent Expert Committee's and Expert Panel's confidence that the association estimates are correct.

Additional details on the methods can be found in Supplementary Material (Text S1).

3 | RESULTS

3.1 | Study selection process

Figure 1 shows the flow-chart of the study selection process. There were 278 potentially eligible publications on post-diagnosis adiposity and colorectal cancer outcomes. We excluded 193 publications[45–237] due to specific reasons related to the synthesis (Supplementary Table 5). Finally, 85 publications[10,30–37,41,42,238–311] of 124 studies were included in the present review. A total of 96 studies (53 publications) were on BMI and all-cause mortality,[10,30–36,41,42,238–244,246,252,253,255,257,259,261,263,265–270,274,276–280,282–285,287,290,292,295,296,299,300,302,303,307,308,310] 20 studies (19 publications) on BMI and colorectal cancer-specific mortality,[30,36,37,41,238,240–242,245,253,260,265,271,281,289,294,295,304,306] and 72 studies (30 publications) on BMI and colorectal cancer recurrence/disease-free survival.[31–36,42,239,240,247,251,253,256,257,259,269,278,280,285,286,288,292,293,295,298–300,305,307,310] There were very few studies for BMI and second primary cancer[37] (two studies), non-colorectal cancer related mortality[37,289] (three studies) and cardiovascular disease mortality[41] (one study). There were 13 studies (12 publications) on weight change and all-cause mortality,[41,242,248–250,254,272,273,275,280,297,301] four studies (four publications) on weight change and colorectal-cancer-specific mortality,[41,242,248,250] 10 studies (nine publications) on weight change and cancer recurrence/disease-free survival,[249,254,258,273,275,280,291,297,309] and one study on weight change and cardiovascular mortality.[41] A total of six studies (six publications) were on BMI change and all-cause mortality,[248,262,264,275,278,287] one study on BMI change and colorectal cancer-specific mortality[248] and three studies on BMI change and cancer recurrence/disease-free survival.[254,275,278] There was only one study on waist circumference and recurrence/disease-free survival.[311] No studies were found on post-diagnosis waist-to-hip ratio.

Meta-analyses were possible for post-diagnosis BMI and all-cause mortality, colorectal cancer-specific mortality, and recurrence/disease-free survival. Results were descriptively synthesised for post-diagnosis BMI and cardiovascular disease mortality, second primary cancer and non-colorectal cancer-related mortality, and for body weight and BMI change and colorectal cancer prognosis outcomes.

A detailed list of included and excluded studies in each specific meta-analysis or descriptive synthesis (with reasons for exclusion) is provided and referenced in Supplementary Table 5. The corresponding study and participants' characteristics are summarised in Supplementary Tables 6–13.

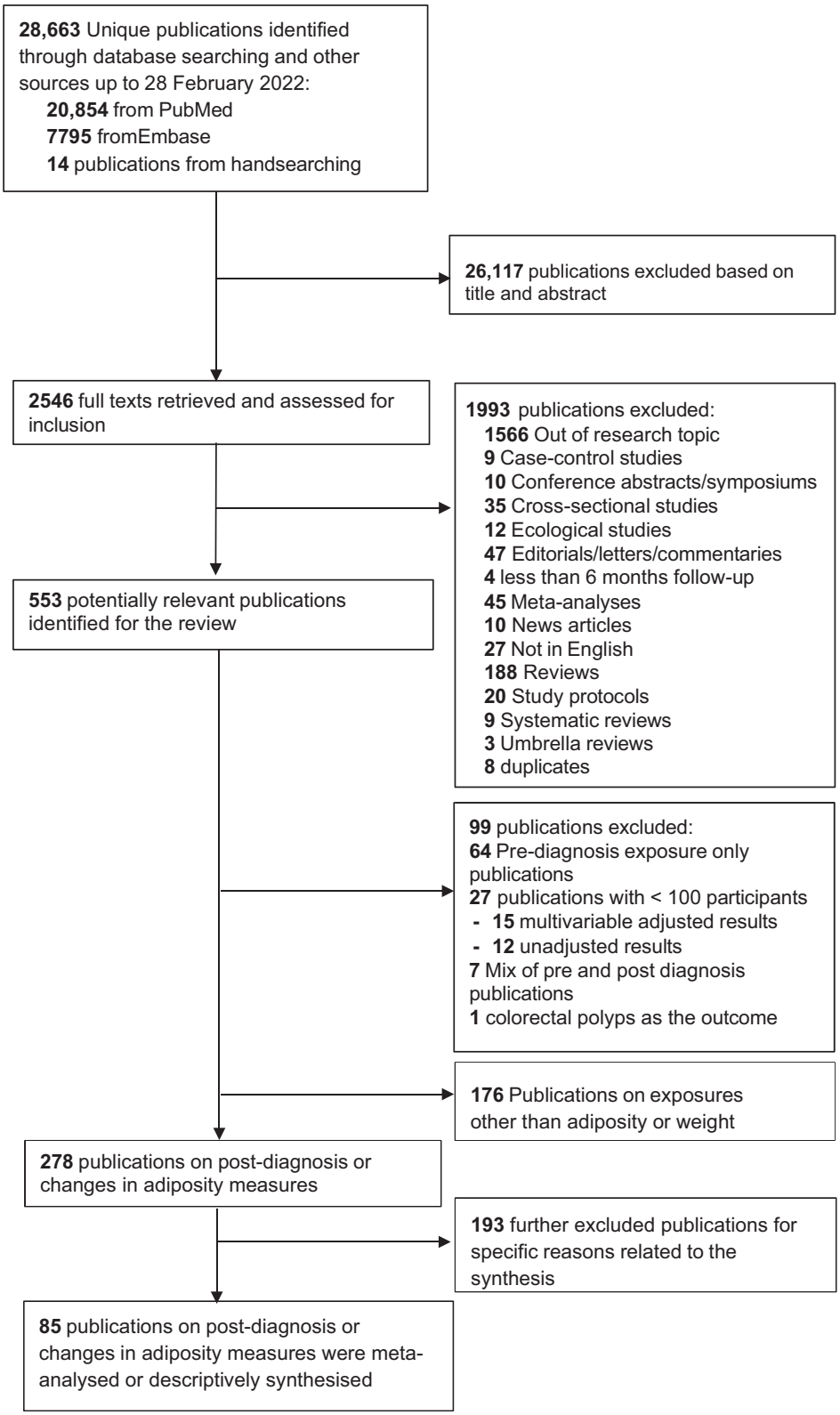


FIGURE 1 Flowchart of study selection process.

3.2 | Study characteristics

The 85 included publications were from 124 studies and comprised more than 294,000 colorectal cancer survivors, of whom more than 43,900 died of any causes, approximately 16,000 died of colorectal cancer and approximately 24,600 experienced an additional colorectal cancer event. All included studies were observational, and no relevant RCTs were identified. Geographically, 24 publications were from Europe,[10,33,35,42,243,253,266,268,272,276–279,282,284,291,293,296–298,303,308,310,311] 20 from North America,[30–32,34,37,41,238,240,244,249,250,254,265,274,283,285,287,288,301,309]

19 from East or Southeast Asia,[36,239,241,246,247,251,252,256,258,262,264,269,280,290,294,295,302,305,307] four from Australia/New Zealand,[242,255,299,300] and 18 from mixed geographic locations[248,257,259,273,275] or elsewhere.[245,260,261,263,267,270,271,281,286,289,292,304,306] Most publications ($n = 54$) involved cancer survivors of any stage,[10,30,33,35,36,41,42,238,239,241–245,247,248,250,252,253,256,260,261,263,266–268,270,271,274,277,279,281–284,286,288–290,292–294,296,298,300,302–308,310,311] 28 of which also included metastatic cancer survivors (median = 19.6%, range = 6%–58.9%; seven publications did not report % metastatic); 8 included stage II–III,[31,32,37,240,258,259,275,280] 9 included stage III or locally advanced[246,249,251,254,264,265,269,295,299] and 14 stage IV cancer survivors only.[34,255,257,262,272,273,276,278,285,287,291,297,301,309]

3.3 | Post-diagnosis body mass index and colorectal cancer outcomes

Supplementary Table 14 shows a summary of the results of the meta-analyses. Overall, linear, non-linear dose–response and categorical meta-analyses were conducted, but evidence of non-linearity was detected, therefore we focussed on the non-linear analyses as the primary analyses. For the few studies[245,257,269,271,277,282,289,303,304,306] that were not possible to include in any meta-analyses, we provided an overview of the findings (Supplementary Material—Text S2).

There was evidence of non-linearity between post-diagnosis BMI and all-cause mortality ($P_{non\text{-}linearity}$ <.001, 46 studies, 37,310 deaths, 25 publications; BMI assessed from at-diagnosis to on average 4 years after diagnosis) (Figure 2A), colorectal cancer-specific mortality ($P_{non\text{-}linearity}$ <.001, 13 studies, 15,366 deaths, 12 publications; BMI assessed from at-diagnosis to on average 18 months after diagnosis) (Figure 2B), and recurrence/disease-free survival ($P_{non\text{-}linearity} = .01$, 39 studies, 23,376 events, 18 publications; BMI assessed from at-diagnosis to on average 6 months after diagnosis or the end of the treatment) (Figure 2C). The shape of the association appeared reverse J-shaped with a common nadir at BMI of 28 kg/m^2. A high risk of colorectal cancer outcomes, relative to the nadir, was observed at the lowest and upper range of the BMI distribution. For BMI 18–24 kg/m^2, an 8%–60% higher risk of all-cause mortality, a 15%–95% higher risk of colorectal cancer-specific mortality, and a 5%–37% higher risk of recurrence/disease-free survival was observed. For BMI 32–38 kg/m^2, a 7%–23% higher risk of all-cause mortality, a 6%–26% higher risk of colorectal cancer-specific mortality, and a 7%–24% higher risk of recurrence/disease-free survival was observed.

Supplementary Figures 1–9 show the results of the categorical meta-analyses. Compared to colorectal cancer survivors of normal weight, underweight survivors had an increased risk of all-cause mortality (RR: 1.63; 95% CI: 1.43–1.84; $I^2 = 84\%$, tau$^2 = 0.07$, RR range = 0.58–10.20), colorectal cancer-specific mortality (RR: 1.60; 95% CI: 1.26–2.02; $I^2 = 71\%$, tau$^2 = 0.07$, RR range = 0.64–3.76) and recurrence/disease-free survival (RR: 1.41; 95% CI: 1.16–1.73; $I^2 = 90\%$, tau$^2 = 0.11$, RR range = 0.49–5.88). Colorectal cancer survivors who were overweight, had a lower risk of all-cause mortality (RR: 0.90; 95% CI: 0.85–0.95; $I^2 = 72\%$, tau^2 =0.01, RR range = 0.56–1.63), colorectal cancer-specific mortality (RR: 0.79; 95% CI: 0.68–0.90; $I^2 = 75\%$, tau$^2 = 0.03$, RR range = 0.35–1.12) and recurrence/disease-free survival (RR: 0.92; 95% CI: 0.85–1.00; $I^2 = 70\%$, tau$^2 = 0.01$, RR range = 0.42–1.58) compared to normal weight survivors. There was little evidence of an inverse association between obesity and all-cause (RR: 0.93; 95% CI: 0.86–1.00; $I^2 = 71\%$, tau$^2 = 0.02$, RR range = 0.69–1.80), and colorectal cancer-specific mortality (RR: 0.90; 95% CI: 0.79–1.03; $I^2 = 57\%$, tau$^2 = 0.02$, RR range = 0.62–1.15) as the CIs crossed the null value, and no association was observed with recurrence/disease-free survival (RR: 0.99; 95% CI: 0.92–1.07; $I^2 = 49\%$, tau$^2 = 0.008$, RR range = 0.58–2.29).

There was no evidence of publication bias with Egger's test (p-value = .93 for all-cause mortality, 0.67 for colorectal cancer-specific mortality and 0.72 for recurrence/disease-free survival) (Supplementary Figures 10–12).

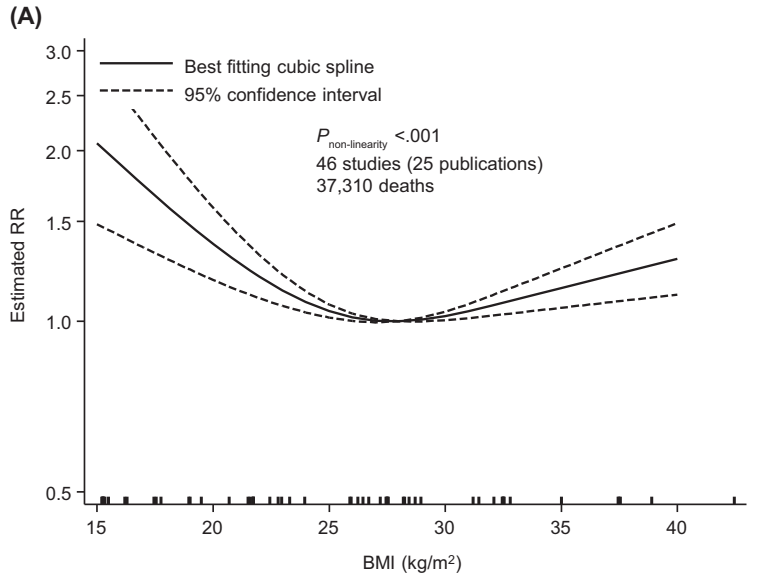
For second primary cancer, non-colorectal cancer mortality and cardiovascular disease death, studies were limited in number, thus could not be summarised in any meta-analysis. An overview of the findings is provided in Supplementary Material—Text S2.

3.4 | Subgroup non-linear meta-analysis

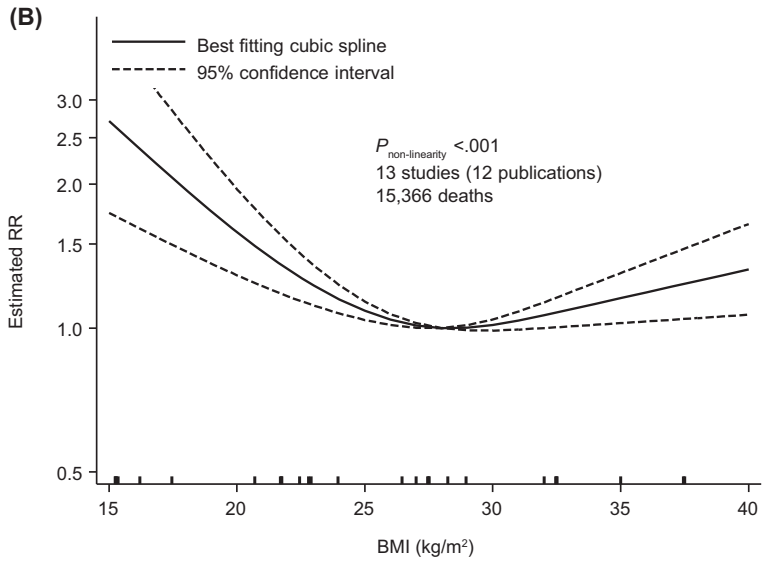
The results from the subgroup non-linear dose–response meta-analyses resembled those of the main analysis, with few exceptions (Supplementary Figures 13–46).

For all-cause mortality, there were differences when the analysis was stratified by cancer stage, sex, and study design. In the non-linear dose–response meta-analysis by cancer stage, the reverse J-shaped curve remained among any stage (excluding metastatic) colorectal cancer survivors ($P_{non\text{-}linearity}$ <.001; 41 studies, 20 publications). However, a non-linear inverse association was observed in metastatic colorectal cancer survivors. A gradual reduction in risk was observed from the lowest levels of BMI up to 28 kg/m^2, that reached a plateau above this point ($P_{non\text{-}linearity} = .004$; 6 studies, 6 publications) (Supplementary Figure 14). In the non-linear dose–response meta-analysis by sex, the shape of the curve appeared reversed J-shaped in men ($P_{non\text{-}linearity}$ <.001; 5 studies, 5 publications) and U-shaped in women ($P_{non\text{-}linearity}$ <.001; 6 studies, 6 publications), reflecting a stronger positive association with low BMI among studies that included only men compared to women, with very little overlap in CIs between the two strata (Supplementary Figure 15). In the non-linear dose–response meta-analysis by study design (retrospective cohort, prospective cohort, or secondary analysis of clinical trials [i.e., observational follow-up analyses of patients enrolled in clinical treatment RCTs not aiming to evaluate body composition or weight management interventions]), the shape of the curve across strata was similar to the main analysis, but the increased risk of all-cause mortality in the low BMI range was attenuated for the secondary analysis of clinical trials (Supplementary Figure 17).

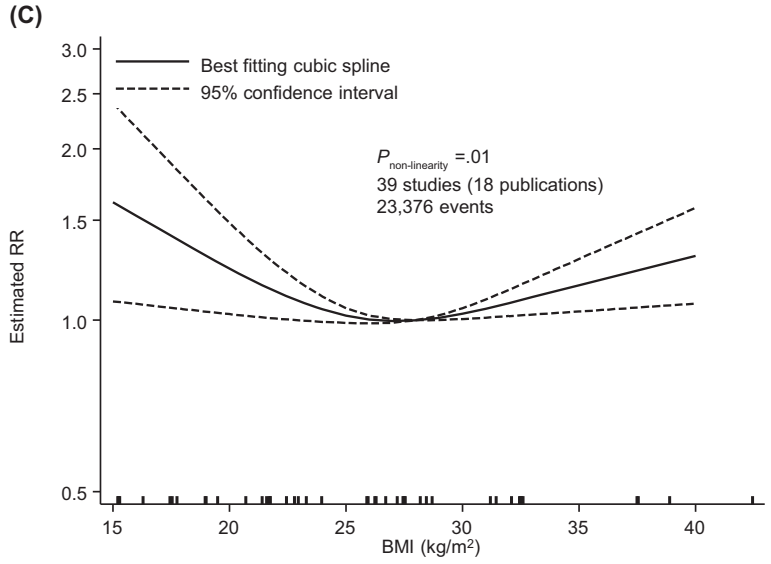
For colorectal cancer recurrence/disease-free survival, there were differences by the average length of follow-up, with little overlap of



BMI (kg/m²)	RR (95% CI)
18	1.60 (1.29, 1.99)
20	1.37 (1.18, 1.59)
22	1.20 (1.10, 1.31)
24	1.08 (1.04, 1.13)
26	1.02 (1.00, 1.03)
28	1 (Ref.)
30	1.02 (1.00, 1.04)
32	1.07 (1.02, 1.11)
34	1.12 (1.05, 1.19)
36	1.17 (1.07, 1.29)
38	1.23 (1.09, 1.38)



BMI (kg/m²)	RR (95% CI)
18	1.95 (1.45, 2.62)
20	1.59 (1.29, 1.95)
22	1.33 (1.16, 1.51)
24	1.15 (1.07, 1.23)
26	1.04 (1.01, 1.07)
28	1 (Ref.)
30	1.01 (0.99, 1.04)
32	1.06 (1.00, 1.13)
34	1.12 (1.02, 1.24)
36	1.19 (1.03, 1.37)
38	1.26 (1.05, 1.50)



BMI (kg/m²)	RR (95% CI)
18	1.37 (1.05, 1.79)
20	1.23 (1.02, 1.48)
22	1.12 (1.01 1.25)
24	1.05 (0.99, 1.10)
26	1.00 (0.99, 1.02)
28	1 (Ref.)
30	1.03 (1.01, 1.05)
32	1.07 (1.02, 1.13)
34	1.12 (1.03, 1.23)
36	1.18 (1.04, 1.33)
38	1.24 (1.06, 1.45)

FIGURE 2 Legend on next page.

CIs between the two strata (i.e., ≤ 5 years and >5 to ≤10 years) at low BMI levels. In studies with more than 5–10 years of follow-up, the shape of the curve was flat (nadir observed at BMI of 25 kg/m^2), with little evidence of a higher risk of recurrence/disease-free survival below and above the nadir ($P_{non\text{-}linearity}$ <.001; 28 studies, 8 publications). However, among studies with an average length of follow-up of 5 or less years, the shape of the curve appeared J-shaped with the nadir at BMI of 25 kg/m^2. The risk increased gradually from a BMI lower than 25 kg/m^2, while above this point a sharply higher risk was observed but with very wide CIs ($P_{non\text{-}linearity}$ = .06; 10 studies, 9 publications) (Supplementary Figure 40).

3.5 | Sensitivity analyses

In the non-linear analysis, the reverse J-shaped curve remained in the sensitivity analysis excluding (when possible) cancer survivors with metastatic stages (Supplementary Figures 47–49). Restricting the non-linear analysis to studies without including deaths in the recurrence definition, showed a suggestive J-shaped association between post-diagnosis BMI and cancer recurrence (nadir at a BMI around 25 kg/m^2). Compared to the nadir, a higher risk was observed from BMI below 25 kg/m^2, and a higher risk of cancer recurrence was also observed above this point, but CIs were wide ($P_{non\text{-}linearity}$ = .06; 34 studies, 13 publications) (Supplementary Figure 50). In categorical meta-analyses restricted to the studies that used the WHO classification system, results were similar (Supplementary Figures 51–59).

3.6 | Post-diagnosis body weight and BMI change and colorectal cancer outcomes

Post-diagnosis body weight and BMI change were evaluated for the timeframes (1) from before to 3 months or more after diagnosis (pre- to post-diagnosis; three and two publications, respectively); (2) from diagnosis or after diagnosis to any period post-diagnosis (post-diagnosis; two and one publications, respectively); and (3) specifically during/after cancer treatment (six and five publications, respectively). Meta-analyses were not possible because absolute or relative weight change categories across the studies were not homogeneous to pool them. These exposures were descriptively synthesised separately (Supplementary Tables 7–12).

Overall, pre- to post-diagnosis (Figure 3A) and post-diagnosis body weight loss (unknown causes) (Figure 3B) was associated with a higher risk of all-cause and colorectal cancer-specific mortality. There was a suggestion that weight loss during/after cancer treatment (Figure 3C) was associated with a higher risk of all-cause mortality (only one out of nine comparisons showing a RR <1) and recurrence/disease-free survival (only one out of eight comparisons showing a RR <1). In general, there was no association between weight gain and colorectal cancer outcomes (Figure 3). Some studies (n = 4; three publications) were not directly comparable with the others and were excluded from the forest plot. The results of those studies are reported in Supplementary Material—Text S3.

The few studies investigating BMI change suggested a positive association between pre- to post-diagnosis and post-diagnosis BMI loss, but not gain, and all-cause and colorectal cancer-specific mortality (Supplementary Tables 10 and 11). There was a suggestion that BMI change (loss and gain) during/after cancer treatment was associated with a higher risk of all-cause mortality and disease-free survival/disease progression but, in general, wide CIs were observed across the different associations investigated (Supplementary Table 12).

3.7 | Post-diagnosis waist circumference and colorectal cancer outcomes

Only one retrospective study was identified, showing a lower risk of disease-free survival (hazard ratio, HR = 0.39; 95% CI = 0.21–0.75) in Dukes A-D colon cancer survivors with high waist circumference (≥94 cm in men and ≥80 cm in women) compared to those with a low waist circumference (<94 cm in men and <80 cm in women).[311]

3.8 | Risk of bias assessment

About 52%, 43%, and 60% of the studies on all-cause mortality, colorectal cancer-specific mortality and recurrence/disease-free survival, respectively, were rated as having a moderate risk of bias due to confounding (which is the best judgement they can reach in this domain), and 40%, 43% and 36%, respectively, as having critical risk of bias due to the lack of adjustment for the critically important confounding factors (i.e., age, stage and cancer treatment). Most studies (~80%) had serious risk of bias in participant selection related to the need for survival and a health status well enough to participate in a study. None of the included studies employed adjustment techniques to counteract the potential for selection bias. The percentage of studies with low/moderate risk of bias in classification of exposures was 54% in all-cause mortality, 72% in colorectal cancer-specific mortality, and 64% in recurrence/disease-free

FIGURE 2 Non-linear dose–response meta-analysis of post-diagnosis BMI and (A) all-cause mortality, (B) colorectal cancer-specific mortality, and (C) recurrence/disease-free survival in colorectal cancer survivors regardless of the stage. The solid line represents the estimated summary dose–response relationship and the short-dashed line the 95% confidence intervals. The tick marks inside the x-axis indicate the BMI values for which relative risk estimate(s) were available. Non-linear curve was estimated using restricted cubic spline regressions with three knots placed at fixed percentiles (10%, 50%, and 90%) of the body mass index distribution, which were pooled by fitting one-stage random-effects mixed models. The nadir of the dose–response curve (body mass index = 28 kg/m^2) was chosen as reference. The table shows selected body mass index values and their corresponding relative risk (95% confidence intervals) estimated in the non-linear dose–response meta-analysis.

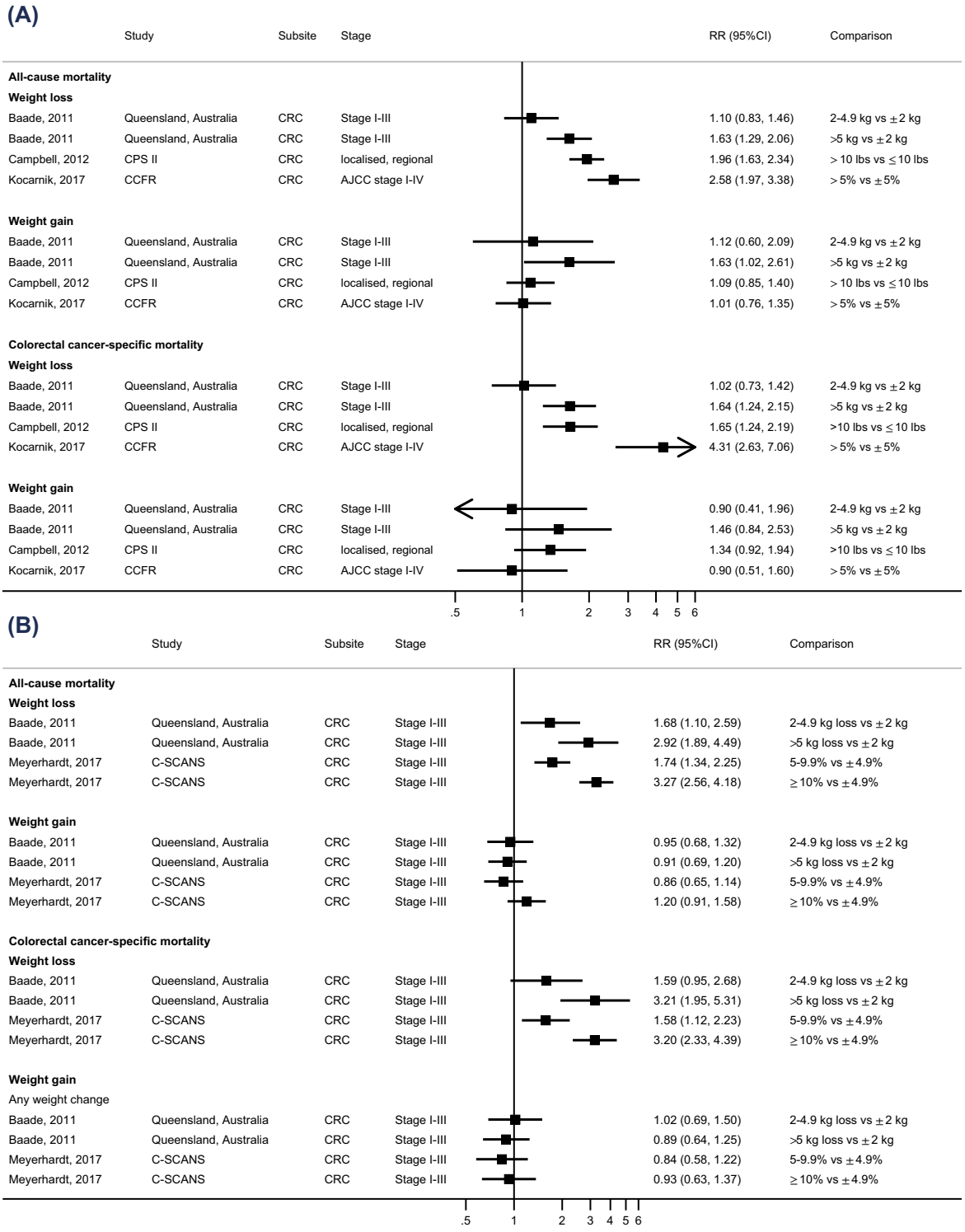


FIGURE 3 Forest plot showing the relative risk with 95% confidence interval for colorectal cancer outcomes by categorical comparison of (A) pre- to post-diagnosis weight change, (B) post-diagnosis (any period) weight change, and (C) during/right after treatment weight change. Individual studies reporting results for any weight change (%, kg, or lbs) categories are presented in the upper (weight loss) and lower (weight gain) panels of the graph by colorectal cancer outcomes. The same study may be represented more than once if different weight change categories were investigated. The squares represent the relative risk estimate (RR) for the different weight change categories and the horizontal line across each square represents the 95% confidence interval (CI) of the RR estimate. This figure does not represent a quantitative summation of results. Best, 2021[301] reported results at 3, 6 and 12 months. The forest plot only show results for at 12 months. Lee, 2020[275] reported results for absolute and relative weight change. Only results for relative change were plotted. AJCC, American Joint Committee on Cancer; CALGB, BC, British Columbia; Cancer and Leukemia Group B; CCFR, Colon Cancer Family Registry; COL, colon; CPS-II, Cancer Prevention Study II Nutrition Cohort; CRC, colorectal cancer; C-SCANS, Colorectal Cancer-Sarcopenia And Near-term Survival study; MGH, Massachusetts General Hospital; UICC, Union for International Cancer Control.

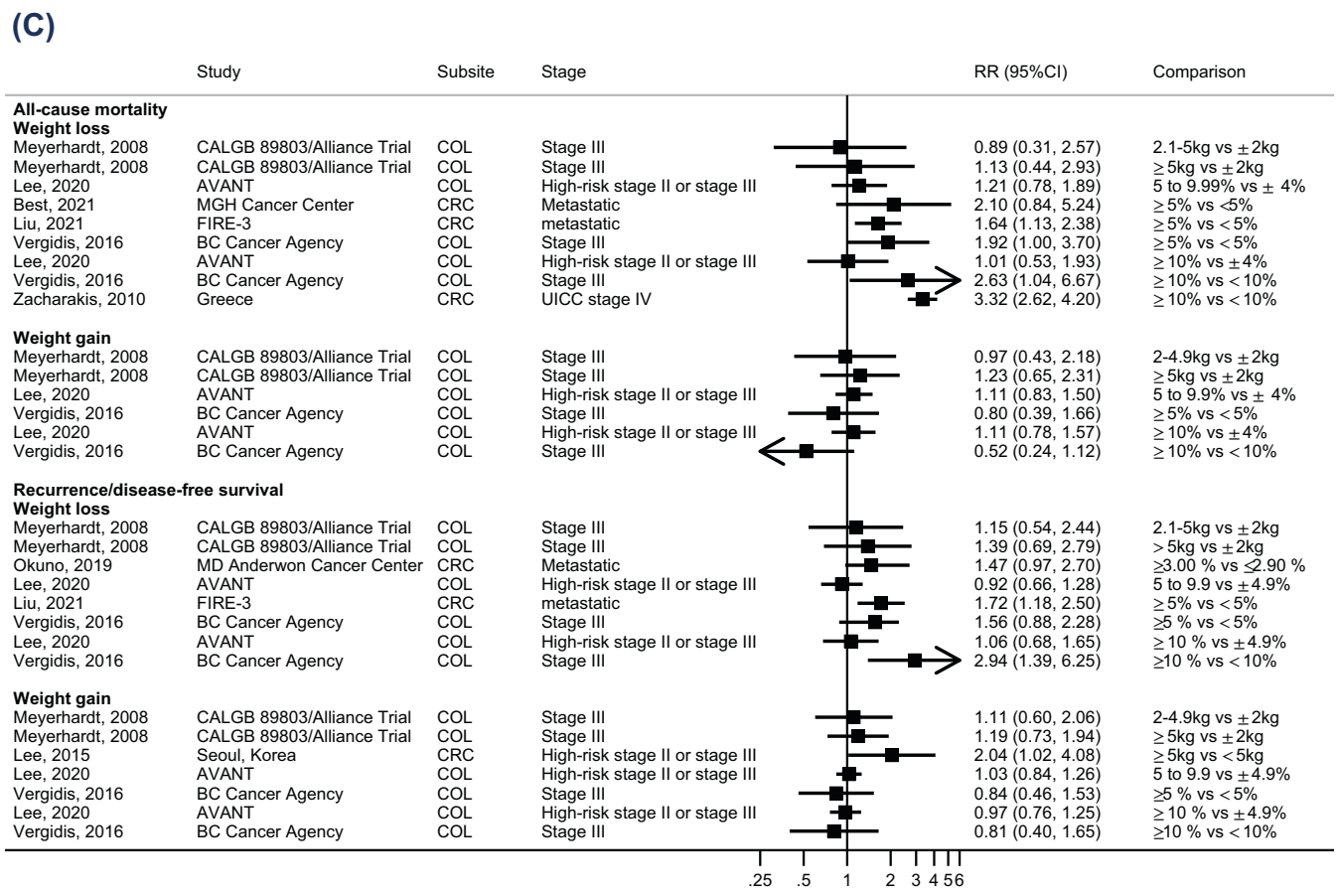


FIGURE 3 (Continued)

survival meta-analyses, with 44%, 29%, and 36%, respectively, rated with serious risk of bias, often due to the inclusion of a mixture of metastatic and non-metastatic colorectal cancer survivors (exposure may be influenced by undetected disease progression or recurrence). All the studies were rated as having a critical risk of bias due to departures from intended exposures, as time-varying exposure analysis was not performed. Approximately half of the studies (40%–56%) did not provide sufficient information to judge the risk of bias due to missing data. Most of the studies had low/moderate risk of bias in the measurement of the outcomes and selection of reported results (Supplementary Figures 60–65).

3.9 | Evidence grading

Table 1 presents the evidence grading. The evidence on post-diagnosis BMI and all-cause mortality, colorectal cancer-specific mortality, and colorectal cancer recurrence/disease-free survival was substantial, showing a reverse J-shaped relationship. However, due to high concerns of reverse causation, selection bias, confounding and errors in measuring and classifying the exposure, pertaining to studies of cancer survival, the evidence was graded as limited (subgrade for likelihood of causality: no conclusion).

The evidence on post-diagnosis BMI and second primary cancer, non-related colorectal cancer mortality and cardiovascular disease death was graded as limited-no conclusion due to the sparsity of studies and the same methodological issues mentioned previously.

The evidence on post-diagnosis waist circumference, body weight and BMI change was scarce and subject to the same aforementioned biases, and no conclusions could be made.

4 | DISCUSSION

This systematic review and meta-analysis showed evidence of non-linearity between post-diagnosis BMI and colorectal cancer outcomes (all-cause mortality, colorectal cancer-specific mortality, and cancer recurrence/disease-free survival). The associations appeared reverse J-shaped with a common nadir at BMI of 28 kg/m^2. A higher risk of poor colorectal cancer outcomes, relative to the nadir, was observed at the extremes of the BMI distributions. In most subgroups, the non-linear association was consistent. However, there was an indication that all-cause mortality differed according to study design. We observed weaker positive associations for low BMI (up to ~28 kg/m^2) in secondary analysis of clinical trials compared with prospective cohorts and retrospective cohorts of cancer survivors. Similar

TABLE 1 Evidence grading and main findings from the meta-analyses and descriptive synthesis on post-diagnosis adiposity measures and colorectal cancer outcomes.

		Exposure	Outcome	Summary of findings	Conclusions
Strong evidence	Convincing	–	–	–	–
	Probable	–	–	–	–
Limited evidence	Suggestive	–	–	–	–
	No conclusion	Post-diagnosis BMI	All-cause mortality	46 studies (25 publications), 37,310 deaths. Reverse J-shaped association with nadir at BMI of 28 kg/m^2 and higher risk at both ends of the BMI distributions (8%–60% for 18–24 kg/m^2 and 7%–23% for 32–38 kg/m^2, compared with 28 kg/m^2)	Substantial amount of observational data, showing evidence of a non-linear relationship, limited in methodological quality (confounding, selection bias, reverse causation, measurement error and classification of exposures).
			Colorectal cancer-specific mortality	13 studies (12 publications), 15,366 deaths. Reverse J-shaped curve with nadir at BMI of 28 kg/m^2 and higher risk at both ends of the BMI distributions (15%–95% for 18–24 kg/m^2 and 6%–26% for 32–38 kg/m^2, compared with 28 kg/m^2)	
			Recurrence/disease-free survival	39 studies (18 publications), 23,376 events. Reverse J-shaped curve with nadir at BMI of 28 kg/m^2 and higher risk at both ends of the BMI distributions (5%–37% for 18–24 kg/m^2 and 7%–24% for 32–38 kg/m^2, compared with 28 kg/m^2)	
			Non-colorectal cancer related mortality	3 studies (2 publications). No meta-analysis.	The evidence is sparse and subject to potential methodological issues.
			Second primary cancer	2 studies (1 publication). No meta-analysis.	
			CVD mortality	1 study (1 publication). No meta-analysis.	
		Pre- to post-diagnosis weight change (gain or loss)	All-cause mortality	3 studies (3 publications). No meta-analysis. Consistent pattern of positive associations with weight loss. RRs ranging from 1.10 to 2.58. In 3/4 categorical comparisons the 95% CIs did not include the null. No association with weight gain.	The evidence is sparse and subject to potential methodological issues.
			Colorectal cancer-specific mortality	3 studies (3 publications). No meta-analysis. Consistent pattern of positive associations with weight loss. RRs ranging from 1.02 to 4.31. In 3/4 categorical comparisons the 95% CIs did not include the null. No association with weight gain.	
			CVD mortality	1 study (1 publication). No meta-analysis.	
			All-cause mortality	2 studies. No meta-analysis.	

(Continues)

TABLE 1 (Continued)

Exposure	Outcome	Summary of findings	Conclusions
Post-diagnosis (any period) weight change (gain or loss)		Consistent pattern of positive associations with weight loss. RRs ranging from 1.74 to 3.27 (none of the 95% CIs included the null). No association with weight gain.	
	Colorectal cancer-specific mortality	2 studies. No meta-analysis. Consistent pattern of positive associations with weight loss. RRs ranging from 1.58 to 3.21. In 3/4 categorical comparisons the 95% CIs did not include the null. No association with weight gain.	
During/after cancer treatment weight change (gain or loss)	All-cause mortality	6 studies (6 publications). No meta-analysis. Consistent pattern of positive associations with weight loss (only one categorical comparison with RR <1). In the 8 categorical comparisons showing positive associations, the RRs ranged from 1.01 to 3.32, in 4 of which the 95% CIs did not include the null. No association with weight gain.	
	Recurrence/disease-free survival	5 studies (5 publications). No meta-analysis. Consistent pattern of positive associations with weight loss (only one categorical comparison with RR <1). In the 7 categorical comparisons showing positive associations, the RRs ranged from 1.06 to 2.94, in 2 of which the 95% CIs did not include the null. No association with weight gain.	
Pre- to post-diagnosis BMI change (gain or loss)	All-cause mortality	2 studies (2 publications). No meta-analysis. In general, positive associations with BMI loss but not gain.	The evidence is sparse and subject to potential methodological issues
	Colorectal cancer-specific mortality	1 study (1 publication). 13% higher risk per each 1 kg/m^2 BMI loss (RR: 1.13; 95% CI: 1.06–1.20)	
Post-diagnosis (any period) BMI change (gain or loss)	All-cause mortality	1 study (1 publication). RR and 95% CI of 1.50 (1.10–2.10) and 1.90 (1.30–2.80) for BMI loss 5%–10% and >10% vs. <5%, respectively.	
During/after cancer treatment weight change (gain or loss)	All-cause mortality	4 studies (4 publications). No meta-analysis. Suggestive pattern of positive associations with BMI loss and gain but, in general, wide CIs across the different associations investigated.	

TABLE 1 (Continued)

	Exposure	Outcome	Summary of findings	Conclusions
		Recurrence/disease-free survival	3 studies (3 publications). No meta-analysis. Suggestive pattern of positive associations with BMI loss and gain but, in general, wide CIs across the different associations investigated.	
	Post-diagnosis waist circumference	Recurrence/disease-free survival	1 study (1 publication). RR and 95% CI of 0.39 (0.21–0.75) for those with high waist circumference compared to those with a low waist circumference.	The evidence is sparse and subject to potential methodological issues

Abbreviations: BMI, body mass index; CIs, confidence intervals; CVD, cardiovascular disease; RR relative risk.

associations were also observed for recurrence/disease-free survival but the CIs were wide. The association between BMI and all-cause mortality appeared U-shaped in women and reverse J-shaped in men, showing a stronger positive association with low BMI in men than in women. Moreover, an inverse non-linear association between BMI and all-cause mortality was observed in metastatic colorectal cancer survivors, with a reduction in risk observed from the lowest BMI levels up to a BMI of 28 kg/m^2, but a flat line above this point. Besides, the higher risk of all-cause mortality and recurrence/disease-free survival with low BMI, relative to the nadir, was attenuated among studies with longer duration of follow-up. This observation was more evident for recurrence/disease-free survival, where there was little overlap of CIs between the strata at low BMI levels, while wide CIs were observed for all-cause mortality.

In the present non-linear meta-analysis on post-diagnosis BMI, colorectal cancer survivors with obesity had a higher risk of mortality and recurrence. The underlying biological mechanisms for these observations are poorly defined and might be related to factors that are also associated with colorectal cancer incidence, including obesity-related insulin resistance[312] and inflammation.[313] High insulin levels and consequent alterations in the insulin-like growth factor axis,[314] leading to activation of several oncogenic pathways that favour tumour growth,[315] have been proposed as one putative explanation. However, while there is substantial evidence to support this hypothesis in colorectal cancer incidence, the evidence on this potential mechanism is limited and inconsistent in relation to survival and recurrence.[316–318] The effects of systemic inflammation on colorectal cancer progression are extensive, including the promotion of proliferation, angiogenesis and metastasis, and the suppression of anti-tumour immunity.[319] In fact, inflammatory parameters such as high neutrophil-lymphocyte ratio[320,321] and platelet-lymphocyte ratio[322] have been associated with poor clinical outcomes in colorectal cancer survivors. In addition, patients with obesity may also be more likely to have poorer outcomes due to possible suboptimal chemotherapy dosing[323] or increased frequency of complications.[64,324]

Non-linear meta-analysis also showed higher mortality and recurrence rates on the left side of the curve (up to BMI 24 kg/m^2), especially at the lower end of the BMI range (18 kg/m^2). This increased risk could be the result of other comorbidities, such as chronic respiratory conditions,[325] or disease severity rather than BMI itself. Colorectal cancer survivors with more aggressive cancer or advanced stage may experience illness-related weight loss that results in low/normal BMI categories at diagnosis.[326] In addition, cancer treatment may contribute to changes in body composition through its adverse effects on lean muscle mass.[327] Therefore, the higher risk of mortality and recurrence observed in underweight or normal-weight colorectal cancer survivors could be due to the cachexia present in these patients. The depletion of skeletal muscle and elevated coagulation state caused by cancer-associated cachexia may contribute to a worse prognosis and death rate.[328,329]

To explore the potential impact of reverse causality, we performed a sensitivity analysis excluding (where possible) studies of metastatic survivors. The results remained similar possibly because

most studies included colorectal cancer survivors of any stage and most, with few exceptions, did not provide results by stage. Nonetheless, a gradual reduction in all-cause mortality risk was observed from the lowest levels of BMI up to 28 kg/m^2, that reached a plateau above this point in the subgroup of only metastatic colorectal cancer survivors. These data suggest that unfavourable disease characteristics, such as tumour biology and poor response to treatment, and cancer-related cachexia resulting in low BMI may have a more negative impact on survival than the potential adverse effects related to high BMI.[330] Moreover, in the recurrence/disease-free survival and all-cause mortality meta-analyses, there was a suggestion of heterogeneity by average length of follow-up. Increasing follow-up duration results in an increase in the number of deaths and a decrease in the proportion of deaths occurring early in follow-up (when sicker cachectic survivors would most likely have died). The higher risk of mortality and recurrence for low BMI, relative to the nadir, was attenuated among studies with more than 5–10 years of follow-up, compared to the studies with 5 or less years. These results suggest that the worse survival and cancer outcomes observed in the low/normal BMI categories is at least partially due to reverse causation.

The association between low BMI and mortality and recurrence might also be confounded by smoking,[331,332] which increases mortality risk and is typically inversely associated with BMI.[333] Moreover, our results showed a stronger association for low BMI in men than in women, which may be due to greater residual confounding by smoking in men. However, we could not explore the potential influence of smoking in our dose–response meta-analyses, since a limited number of included studies adjusted for smoking. The only study that reported results stratified by smoking status[10] demonstrated an inverse association between overweight, compared to normal weight, and all-cause mortality for ever smokers, but not in never smokers.

We observed the lowest risk of mortality and recurrence among overweight colorectal cancer survivors (BMI 28 kg/m^2). Some plausible biological mechanisms have been proposed. For example, higher BMI has been associated with better tolerance to some anticancer therapies and with higher energy reserves to support the body during the stress of cancer treatment.[43] However, the observed associations in the overall analyses are likely to be due to methodological issues in observational studies of BMI and cancer survival and are not necessarily causal. These include collider bias (a type of selection bias), confounding and reverse causality,[43,326,334] which could explain not only the increased risk of poor outcomes at low/normal BMI levels but also why being overweight appears to be protective. Moreover, BMI is not a perfect measure of adiposity since it does not differentiate between muscle and fat mass.[335] Despite having the same BMI, individuals can have different adipose tissue distributions and metabolic profiles. In fact, an analysis of the Colorectal Cancer-Sarcopenia And Near-term Survival study (C-SCANS) study showed that a large percentage of survivors with a BMI 18–25 kg/m^2 were at higher risk of mortality due to low muscle mass. However, those with a BMI between 25 and 30 kg/m^2 had the lowest risk of mortality and presented adequate muscle mass and low or modest adiposity mass.[336] To better understand the association of adiposity and prognosis in colorectal cancer survivors, more precise and direct measures of body composition, including fat free mass, are needed.

Despite the substantial body of evidence, considering all the aforementioned potential methodological limitations of the observational studies included in the present work, the CUP Global independent Expert Panel agreed to cautiously grade the evidence as limited (subgrade for likelihood of causality: no conclusion) for post-diagnosis BMI and colorectal cancer outcomes. The CUP Global Expert Panel recognised that the limitations of the evidence represent an opportunity for further research to clarify the nature of the consistent associations between measures of adiposity and cancer related outcomes. Furthermore, the panel recognised a need to better inform cancer patients about the links between adiposity and cancer survivorship, beyond making firm recommendations based on high quality evidence.

Meta-analysis was not possible for body weight and BMI change. The descriptive synthesis showed a suggestion of a positive pattern between weight loss, but not weight gain, and colorectal cancer outcomes. One of the main limitations of the included studies is the lack of information on the intentionality of weight loss, which could be secondary to cancer treatment or progressive disease. In non-cancer studies, unintentional weight loss has been associated with higher mortality, while intentional weight loss has not.[337,338] Interventional clinical trials could offer better insights into the potential consequences of intentional weight loss. Unfortunately, to date no trials on colorectal cancer survivors have directly looked at the impact of weight loss on mortality and recurrence. Additionally, with regards to weight gain, studies did not specify whether it was after unintentional weight loss (recovery), due to side effects of cancer treatment, or other reasons.

Several limitations in relation to the evidence should be considered when interpreting the results of the present systematic review and meta-analysis. All included studies were observational in nature, thus susceptible to different biases, such as survival bias, measurement error, residual confounding, and reverse causation. In general, in the included studies, BMI was only assessed at one point in time; few examined the associations together with pre-diagnosis weight status, and time-varying analysis, which might better reflect the cumulative effect of adiposity on cancer survival, was not performed. Similarly, confounding factors (e.g., treatment dose and duration, disease severity, smoking behaviour) most likely also change over time and this was not considered. We could not perform subgroup analysis by BMI assessment timeframe relative to cancer diagnosis because most studies assessed BMI at diagnosis or shortly after, and very few included assessments later in the cancer course.[10,30,41,42] Colorectal cancer survivors are likely to experience weight fluctuations during and/or after cancer treatment because of the disease and/or its treatment. Hence, BMI could have a different influence on survival and recurrence depending on the timing of the assessment. The limited number of studies included in certain subgroups resulted in very wide confidence intervals, which may have limited the power to detect differences between strata. It was also not possible to evaluate the potential variability in the strength and direction of the associations

by race or ethnicity and molecular cancer subtypes because the included studies did not provide sufficient data. Furthermore, despite the worse long-term outcomes being reported for emergency compared with elective presentations of colorectal cancer,[339] the included studies lacked data on the impact of presentation mode on adiposity measurements and oncological outcomes. In addition, although BMI is widely used as a measure of obesity, it does not distinguish between body fat and lean body mass and does not capture adiposity distribution.[335] Unfortunately, we identified only one study on post-diagnosis waist circumference[311] and none on post-diagnosis waist-to-hip ratio. Moreover, our search strategy was not specific enough for identifying other body composition measures that might be more accurate in assessing adiposity than BMI, weight, waist circumference, waist-to-hip ratio or their changes. Finally, the literature search ended on 28 February 2022. Thereby, any relevant studies published after this date were not included. However, given that RCTs are considered the most influential studies in our evidence grading criteria, we conducted a literature search focusing on RCTs that were published after this date until 31 August 2023, but we did not identify any related to body composition or weight management among colorectal cancer survivors. In addition, because of the already large number of studies included in the meta-analysis, any further observational studies would most likely have little or modest influence on the results of the main analyses. As such, we anticipate that the conclusions on the present evidence would remain unchanged.

Despite limitations, this is the most comprehensive systematic review and dose–response meta-analysis on post-diagnosis adiposity and colorectal cancer outcomes conducted to date. Using standardised criteria and a rigorous approach, the substantial body of evidence (124 studies and over 294,000 colorectal cancer survivors) was systematically synthesised and interpreted and graded by the CUP Global independent Expert Committee on Cancer Survivorship and Expert Panel following pre-defined standardised grading criteria.

5 | CONCLUSION

In conclusion, the present work suggests a reverse J-shaped association between post-diagnosis BMI and all-cause mortality, colorectal cancer-specific mortality, and recurrence, with higher risks for these outcomes at both ends of the BMI distribution (18–24 and 32–38 kg/m^2). However, despite the substantial body of evidence, the associations were graded as 'limited-no conclusion' for the likelihood of causality owing to methodological limitations of individual studies in this field. For changes in post-diagnosis weight and BMI, the evidence was also 'limited-no conclusion' due to the limited number of studies and same methodological issues. Well-designed observational studies with more accurate measures of adiposity, longer follow-up, repeated measures, detailed information on participant's medical and lifestyle factors, and stratified analysis (e.g., by cancer stage, smoking status [including amount and duration], ethnicity and molecular subtypes), as well as high-quality trials are needed to strengthen the evidence that contributes towards the development of specific lifestyle recommendations for colorectal cancer survivors. Nevertheless, even in the absence of such trials, there is a need to better inform cancer patients about the links between obesity and cancer-related, and other, outcomes.

AUTHOR CONTRIBUTIONS

Konstantinos K. Tsilidis and Doris S. M. Chan are co-principal investigators of CUP Global at Imperial College London (ICL). Doris S. M. Chan and Konstantinos K. Tsilidis implemented the study according to the protocol reviewed by the CUP Global Protocol Expert Group (PEG). Katia Balducci and Sonia Kiss did the literature search. Katia Balducci, Sonia Kiss, Margarita Cariolou and Rita Vieira did the study selection. Katia Balducci, Sonia Kiss, Margarita Cariolou, Rita Vieira, Georgios Markozannes and Nerea Becerra-Tomás did the data extraction and checking. Georgios Markozannes, Margarita Cariolou and Nerea Becerra-Tomás did the risk of bias assessment. Nerea Becerra-Tomás did the study selections, data extraction, and checked, analysed, and interpreted the data. Dagfinn Aune was a WCRF International CUP Global ICL team member who revised the manuscript. Darren C. Greenwood was a statistical adviser. Amanda J. Cross was a CUP Global advisor at ICL. Laure Dossus was a CUP Global collaborator on biological processes and provided input into the biological mechanism citations in the manuscript. Ellen Copson was a PEG member, Chair of CUP Global Expert Committee on Cancer Survivorship, and Expert Panel member. Wendy Demark-Wahnefried and Galina Velikova were PEG, OACD, and CUP Global Expert Committee members. Andrew G. Renehan was PEG member and Deputy Chair of CUP Global Expert Committee on Cancer Survivorship. John Krebs, Matty P. Weijenberg, Monica Baskin, Sarah J. Lewis, Jaap Seidell, Rajiv Chowdhury, and Lynette Hill were CUP Global Expert Panel members. Anne M. May, Anne Tjonneland, Karen Steindorf, Martijn Bours, Melissa M. Hudson, Roderick Skinner, and Folakemi T. Odedina were CUP Global Expert Committee members. All members of the CUP Global Expert Committee and Expert Panel provided input into the judgements on the evidence and advised on the interpretation of the review, the public representative (LH) did not contribute to the final decisions made by the Panel. Nerea Becerra-Tomás drafted the original manuscript. All authors reviewed and provided comments on the manuscript. Doris S. M Chan is the guarantor and has full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

Ellen Copson declared research support from Seca. Galina Velikova declared honoraria from Pfizer, Novartis, and Eisai, an institutional grant from Pfizer, and advisory board and consultancy fees from AstraZeneca, Roche, Novartis, Pfizer, Seagene, Eisai, and Sanofi. All other authors have no conflict of interest related to this work.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in our study. Data sources and handling of these data are described in the materials and methods section. Further details are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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