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REVIEW

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Overcoming underestimation of the association of excess weight with pancreatic cancer due to prediagnostic weight loss: Umbrella review of systematic reviews, meta-analyses, and pooled-analyses

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Summary

Elevated body mass index (BMI) is linked to increased pancreatic cancer (PC) risk. Cancer-associated weight loss can occur years before the malignancy is diagnosed. This might have led to underestimation of the BMI-PC association. However, it is unknown if and to what extent this issue has been considered in previous epidemiological studies. We searched two databases through February 19, 2024 for systematic reviews, meta-analyses, and pooled analyses examining the BMI-PC association. We extracted information on study design with a special focus on the article's examination of prediagnostic weight loss as a potential source of bias, as well as how included cohort studies addressed this concern. Thirteen review articles, meta-analyses, and pooled analyses were identified. Only five (four pooled analyses, one systematic review) considered prediagnostic weight loss in their analyses. Twenty-four of 32 identified cohort studies reported having excluded initial years of follow-up. However, only 13 studies reported results after such exclusions, and effect estimates generally increased with longer periods of exclusion. We conclude that the association of overweight and obesity with PC risk is likely larger than suggested by published epidemiological evidence. Future studies should pay careful attention to avoid or minimize potential bias resulting from prediagnostic weight loss.

KEYWORDS

obesity, overweight, pancreatic cancer, weight loss

1 | INTRODUCTION

Pancreatic cancer (PC) is highly fatal, and its incidence has been rising in many parts of the world including the United States.[1,2] The five-year survival for patients with PC in the United is about 12%,[3] and PC is projected to become the second leading cause of cancer mortality by 2026, overtaking colorectal cancer.[4] According to the World Cancer Research Fund (WCRF), there is strong evidence that overweight and obesity,

Abbreviations: AICR, American Institute for Cancer Research; BMI, body-mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; OR, odds ratio; PC, pancreatic cancer; RR, relative risk; WCRF, World Cancer Research Fund; WHO, World Health Organization.

commonly defined as having a body mass index (BMI) of ≥25 to 30 kg/m^2 and ≥30 kg/m^2,[5] respectively, increase the risk for PC.[6] The World Health Organization (WHO) reported that in 2022, there were around 880 million adults and 159 million children and adolescents living with obesity worldwide.[7] Previous systematic reviews investigating the association of BMI and PC risk have all reported an 8–12% increase in PC risk for each five-unit increase in BMI.[8–11]

Unintentional prediagnostic weight loss is a known issue among patients with PC, with studies suggesting that it occurs in as many as 50%–75% of patients with PC.[12,13] While weight loss is often defined as a decrease in body weight by >5% over six months,[14] there is evidence that the cancer-associated weight change can begin many months or even years before diagnosis.[15–21] Therefore, to fully disclose the true association between excess weight and PC, it is of paramount importance to avoid bias due to prediagnostic cancer-associated weight loss. In case–control studies, in which BMI is ascertained at a single point in time (usually close to the time of diagnosis), it is important to consider weight before cancer-related weight loss could have occurred. Bias due to prediagnostic weight loss may also be of concern in cohort studies in which the body weight is ascertained at baseline, as cancers diagnosed during the initial years of follow-up may have already been present in preclinical state at enrollment.

We aimed to evaluate if and how previous epidemiological studies, systematic reviews, meta-analyses, and pooled analyses considered the issue of potential cancer-associated prediagnostic weight loss in their analyses. In order to examine this issue, we conducted an umbrella review of systematic reviews, meta-analyses, and pooled analyses that investigated the association between BMI and PC. Furthermore, we examined how individual cohort studies included in the identified systematic reviews handled the issue.

2 | METHODS

Our study protocol was registered with PROSPERO prior to initiation of the protocol (registration number: CRD42022333665). We adhered to the standardized methodology guidelines as described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary File 1).[22]

2.1 | Search strategy and selection criteria

Using a predefined search algorithm, we systematically searched PubMed and Web of Science from start of the study through February 19, 2024 for systematic reviews, meta-analyses, and pooled analyses that investigated the association between overweight and obesity with the risk of PC. A detailed search strategy description is available in Supplementary File 2. We also performed a manual search of the references of the included articles to retrieve any missed articles.

Studies were included if they were a systematic review or a meta-analysis or pooled analyses study, had as the primary exposure of interest obesity or overweight (defined by BMI) or excess weight per unit increase in BMI, and had development of PC as the primary outcome. Studies were excluded if they exclusively used measures of adiposity other than BMI (e.g. waist-to-hip ratio, waist circumference weight gain, etc.).

2.2 | Data extraction and evaluation of study quality

Two reviewers (MM and DP) independently performed data extraction of following information from each study: name of the first author, article title, year of publication, number of studies included, exposure definition, summary effect size estimates (using the most adjusted estimate) together with the corresponding confidence intervals (CIs), model type, and measures of heterogeneity. A combined effect estimate for men and women was extracted if available. If not, both effect size estimates were reported. Any disagreements were settled through discussion between the two reviewers or by conferring with a third reviewer (HB). To evaluate the methodological quality of included systematic reviews we used AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews)[23]. Following suggestions in the AMSTAR-2 guidelines, we did not provide an overall score for individual studies.

Potential bias arising from weight loss prior to diagnosis was ascertained by two dichotomous items: "timing of BMI ascertainment" and "consideration of sojourn time". "Timing of BMI ascertainment" was used as a criterion for case–control studies and was rated as "considered" in the review/meta-analysis if the exact timing of BMI ascertainment was reported for each of the primary studies and timing was considered in the analysis and estimation of the summary effects (through stratification, subgroup analysis, or exclusion of studies with BMI ascertainment too close to diagnosis, defined as within one year of diagnosis). The criterion "Consideration of sojourn time" was used for cohort studies and was rated as "considered" if summary analyses for cohorts in which at least the first year of follow-up was excluded were presented. For reviews that attempted to address the potential bias due to prediagnostic weight loss, we further investigated the strategies they employed to achieve that.

To further investigate how primary studies handled potential bias due to prediagnostic weight loss, information was extracted from the individual studies included in the 2012 WCRF/AICR systematic review, which included cohort studies only.[10] This review was chosen as other, more recent, identified studies were either analyses of pooled cohorts or systematic reviews of studies looking exclusively at BMI in early adulthood. Since that review ran the systematic search in 2011, we additionally searched PubMed for cohort studies published in the period 2011–2024. For data extraction, we used the table used in the aforementioned review and updated it for the newly identified studies. In studies that extended the exclusion of the initial years of follow-up in sensitivity analyses, we compared hazard ratios (HRs) and their CIs between the primary analysis and sensitivity analysis. R version 4.2.2.[24] was used for all analyses and visualization.

3 | RESULTS

3.1 | Characteristics of the included studies

The systematic search identified 4,046 records. After review, 13 publications were found to have met all inclusion criteria (Figure 1). An overview of the characteristics of included systematic reviews, meta-analyses and pooled analyses is provided in Table 1.[8–11,25–33] Of these, nine included only cohort studies (prospective or retrospective), while the remaining four included cohort and case–control studies. Summary relative risk estimates were most often reported for overweight and obesity compared with normal weight using the WHO BMI definition (underweight: <18.5; normal weight: 18.5 to <25; overweight: 25 to <30; and obesity: ≥30) or for a 5-unit increase in BMI. For men, summary relative risk estimates for overweight, obesity (compared with normal weight), and a 5-unit increase in BMI ranged from 1.13 to 1.28, from 1.28 to 2.29, and from 1.07 to 1.10, respectively. For women, the corresponding estimates ranged from 1.12 to 1.24, from 1.28 to 1.60, and from 1.08 to 1.12.

Analyses of the methodological quality of nine systematic reviews (four publications were not systematic reviews) (Supplementary File 3) revealed that there were methodological concerns regarding multiple items for all reviews, mostly in items 9, 12, and 13 which address if the authors used adequate techniques to assess the risk of bias in the individual studies and if they considered and discussed its impact on the meta-analyses results. Of the 13 identified studies, five[10,27–29,32] fulfilled our predefined criteria for assessing if the study attempted to address the cancer-associated prediagnostic weight loss bias, while the rest did not thoroughly consider or discuss this potential bias. Of the five studies, four studies were pooled analyses of cohort studies, and one was a systematic review.

3.2 | Reviews that considered prediagnostic weight loss

Koyanagi et al.[32] performed a pooled analysis of nine population-based cohort studies investigating the association between BMI and PC risk in the Japanese populations. HRs slightly increased when excluding cases that were diagnosed during the first three years of follow-up (Table 2). However, the case number was quite low for both men and women (15 and 93 cases for the above 27 kg/m^2 BMI category, respectively), with the number likely being even significantly smaller when early cases were excluded, and all of the confidence intervals of the risk estimates were wide and included the null value.

Aune et al.[10] conducted a systematic search for cohort studies looking at the BMI-PC association. This review is the only one that systematically extracted the information on how primary studies

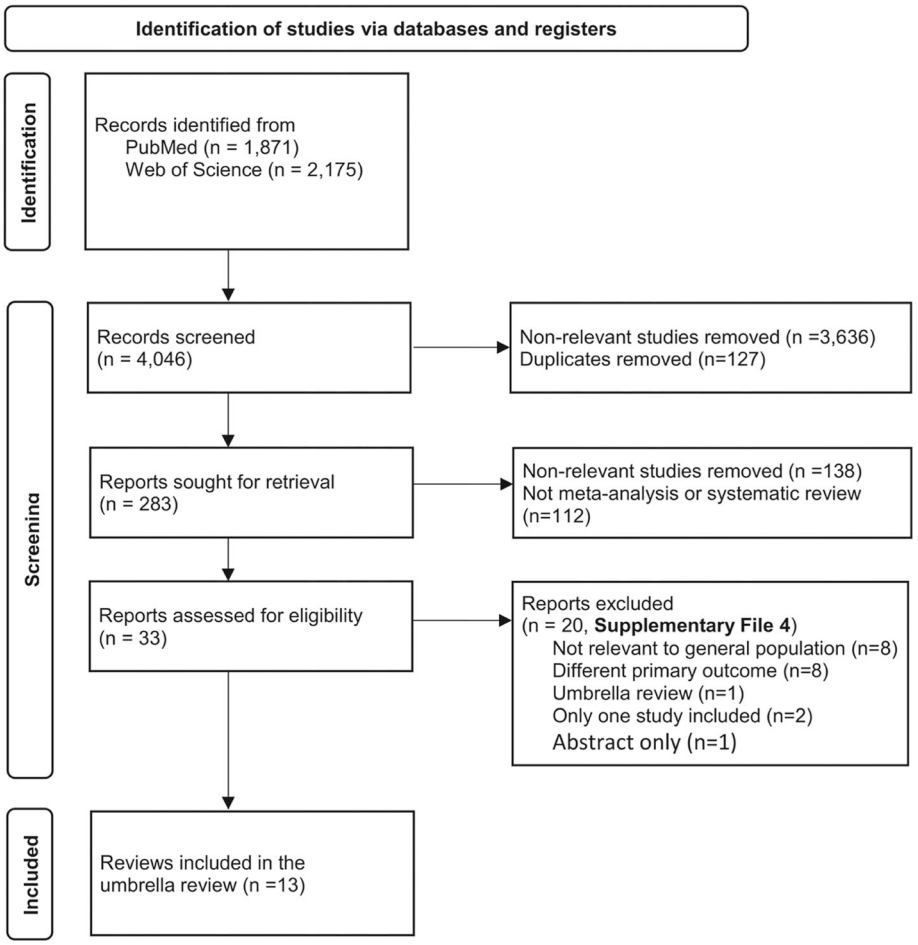

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

TABLE 1 Overview of characteristics of the included studies.

First author, year	Study type	Included study designs	No. of studies	Sample size[a]	Exposure definition[b]	Preclinical sojourn time considered	Summary RR[c] (95% CI)	I^2 (%) or Q-test (*p*-value)
Berrington de Gonzales et al. 2003[25]	SRMA	Mixed	8 CCS 6 nCCS	1,445/5,702 4,946/5,562	5 kg/m^2 increase	No	1.10 (1.05–1.06)	NR
Larsson et al. 2007[8]	SRMA	Cohort	21	8,062/3,495,981	5 kg/m^2 increase	No	1.12 (1.06–1.17)	26.1
Renehan et al. 2008[9]	SRMA	Cohort	12	4,443/3,338001	5 kg/m^2 increase	No	M: 1.07 (0.93–1.23) F: 1.12 (1.02–1.22)	M: 70.0 F: 43.0
Guh et al. 2009[26]	SRMA	Cohort	6	M: NR/366,626 F: NR/609,960	Overweight (WHO definition) Obesity (WHO definition)	No	M: 1.28 (0.94–1.75) F: 1.24 (0.98–1.56) M: 2.29 (1.65–3.19) F: 1.60 (1.17–2.20)	M: $p = 0.09$ F: $p = 0.23$
Arslan et al. 2010[27]	Pooled analysis	Mixed	1 CCS 11 nCCS	2,095/2,141	Overweight (WHO definition) Obesity type I (WHO definition) Obesity type II (WHO definition)	**Yes**	1.22 (1.04–1.42) 1.22 (0.98–1.51) 1.32 (0.94–1.87)	$p = 0.36$
Jiao et al. 2010[28]	Pooled analysis	Cohort	7	2,454/943,759	Overweight (WHO definition) Obesity type I (WHO definition) 5 kg/m^2 increase	**Yes**	1.13 (1.03–1.23) 1.19 (1.05–1.35) 1.08 (1.03–1.14)	0.0
Genkinger et al. 2011[29]	Pooled analysis	Cohort	14	2,135/846,340	≥30 kg/m^2 vs 21 to 22.9 kg/m^2 ≥25 to <30 kg/m^2 vs 21 to 22.9 kg/m^2	**Yes** (results NR)	1.18 (1.03–1.36) 1.47 (1.23–1.75)	9.0
Aune et al. 2012[10]	SRMA	Cohort	23	9,504/5,037,555	5 kg/m^2 increase	**Yes**	1.10 (1.07–1.14)	19.0
Dobbins et al. 2013[30]	SRMA	Cohort	9 (M) 10 (F)	NR	Obesity (WHO definition)	No	M: 1.36 (1.07–1.73) F: 1.34 (1.22–1.46)	M: $p = 0.01$ F: p = 0.83
Xue et al. 2016[31]	SRMA	Cohort	14	10,076/4,369,382	Overweight (WHO definition) Obesity (WHO definition)	No	M: 1.09 (1.02–1.16) F: 1.15 (1.03–1.29) M: 1.45 (1.21–1.75) F: 1.28 (1.07–1.54)	NR
Wang et al. 2016[11]	SRMA	Mixed	4 CCS 30 CS	72,430/5,997,716	5 kg/m^2 increase	No	M: 1.10 (1.01–1.19) F: 1.08 (1.02–1.13)	M: 69.9 F: 47.1
Koyanagi et al. 2018[32]	Pooled analysis	Cohort	9	1,593/345,799	M: ≥30 kg/m^2 vs 23 to 25 kg/m^2 F: ≥27 kg/m^2 vs 23 to 25 kg/m^2	**Yes**	M: 1.71 (1.03–2.86) F: 1.04 (0.80–1.35)	M: 0.0 F: 0.0
Hidayat et al. 2018[33]	SRMA	Mixed*	13 CCS 20 CS	1,498/3,770 5,722/2,646,314	5 kg/m^2 increase	No	1.17 (1.11–1.24)	52.9

Abbreviations: BMI, body mass index; CCS, case–control study; CI, confidence interval; CS, cohort study; F, female; M, male; nCCS, nested case–control study; n/a, not applicable; NR, not reported; Ref, reference; RR, relative risk; s.d., standard deviation; SRMA, Systematic review and meta-analysis; WHO, World Health Organization.

[a]For CCSs and nCCSs — number of cases/number of controls; for CSs — number of cases/participants.

[b]"WHO definition" refers to the comparison of WHO-defined obesity (BMI ≥ 30.0 kg/m^2) with normal weight (BMI ≥ 18.5 kg/m^2 and BMI < 25.0 kg/m^2). "Obesity Type I" corresponds to obesity in the range of 30–35 kg/m^2.

[c]All systematic reviews used random-effect models.

*Included the studies of Koyanagi et al. 2018[32] and part of Genkinger et al. 2011[29].

TABLE 2 Comparison of results from main and sensitivity analysis in the reviews that reported results with and without exclusion of initial years of follow-up.

				Main analysis		Sensitivity analysis	
Study	**Exposure (exposure vs. reference)**	**Sex**	**Region**	**Years excluded**	**HR (95% CI)**	**Years excluded**	**HR (95% CI)**
Arslan et al. 2010[27]	25–29.9 vs. 18.5–24.9 kg/m^2	MF	Global	0	1.15 (1.00–1.33)	2	1.22 (1.04–1.42)
Arslan et al. 2010[27]	30–34.9 vs. 18.5–24.9 kg/m^2	MF	Global	0	1.13 (0.93–1.37)	2	1.22 (0.98–1.51)
Arslan et al. 2010[27]	≥35 vs. 18.5–24.9 kg/m^2	MF	Global	0	1.26 (0.93–1.71)	2	1.32 (0.94–1.87)
Arslan et al. 2010[27]	25–29.9 vs. 18.5–24.9 kg/m^2	M	Global	0	1.06 (0.86–1.30)	2	1.08 (0.87–1.35)
Arslan et al. 2010[27]	30–34.9 vs. 18.5–24.9 kg/m^2	M	Global	0	1.13 (0.85–1.51)	2	1.21 (0.87–1.68)
Arslan et al. 2010[27]	≥35 vs. 18.5–24.9 kg/m^2	M	Global	0	1.26 (0.77–2.06)	2	1.07 (0.58–1.97)
Arslan et al. 2010[27]	25–29.9 vs. 18.5–24.9 kg/m^2	F	Global	0	1.27 (1.03–1.55)	2	1.40 (1.12–1.76)
Arslan et al. 2010[27]	30–34.9 vs. 18.5–24.9 kg/m^2	F	Global	0	1.12 (0.87–1.46)	2	1.23 (0.92–1.64)
Arslan et al. 2010[27]	≥35 vs. 18.5–24.9 kg/m^2	F	Global	0	1.29 (0.88–1.89)	2	1.50 (0.98–1.50)
Aune et al. 2012[10]	5 kg/m^2 increase	MF	Global	0	1.10 (1.07–1.14)	1	1.11 (1.05–1.18)
Aune et al. 2012[10]	5 kg/m^2 increase	MF	Global	0	1.10 (1.07–1.14)	2	1.13 (1.05–1.21)
Koyanagi et al. 2018[32]	25–27 vs. 23–25 kg/m^2	M	Japan	0	0.84 (0.61–1.15)	3	0.87 (0.64–1.19)
Koyanagi et al. 2018[32]	≥27 vs. 23–25 kg/m^2	M	Japan	0	1.04 (0.80–1.35)	3	1.11 (0.84–1.47)
Koyanagi et al. 2018[32]	25–27 vs. 23–25 kg/m^2	F	Japan	0	1.01 (0.64–1.59)	3	1.07 (0.69–1.67)
Koyanagi et al. 2018[32]	≥27 vs. 23–25 kg/m^2	F	Japan	0	0.77 (0.44–1.36)	3	0.90 (0.50–1.64)

Abbreviations: CI, confidence interval; F, female; f-up, follow-up; HR, hazard ratio; M, male.

TABLE 3 Comparison of results from main and sensitivity analysis in the individual cohort studies.

					Main analysis		Sensitivity analysis	
Study	**Exposure (exposure vs reference)**	**Avg. f-up (years)**	**Sex**	**Region**	**Years excluded**	**HR (95% CI)**	**Years excluded**	**HR (95% CI)**
Michaud et al. 2001[49]	≥30 vs. <23 kg/m^2	20	F	USA	0	1.70 (1.09–2.64)	4	1.94 (1.26–2.98)
Michaud et al. 2001[49]	≥30 vs. <23 kg/m^2	12	M	USA	0	1.76 (0.90–3.45)	4	2.03 (0.90–4.57)
Berrington de G et al. 2006[35]	5 kg/m^2 increase	6	MF	Europe	0	1.09 (0.95–1.24)	2	1.14 (0.97–1.33)
Luo et al. 2007[36]	25–40 vs. 21–25 kg/m^2	11	M	Japan	0	0.70 (0.40–1.10)	4	0.70 (0.40–1.20)
Luo et al. 2007[36]	25–40 vs. 21–25 kg/m^2	11	F	Japan	0	1.10 (0.70–1.60)	4	1.20 (0.70–1.90)
Reeves et al. 2007[37]	10 kg/m^2 increase	5.4	F	UK	0	1.24 (1.03–1.48)	2	1.28 (1.03–1.58)
Stevens et al. 2009[62]	≥25 vs. <25 kg/m^2	7.2	F	UK	0	1.14 (1.02–1.28)	2	1.17 (1.04–1.33)
Stevens et al. 2009[62]	≥25 vs. <25 kg/m^2	7.2	F	UK	0	1.14 (1.02–1.28)	4	1.12 (0.96–1.29)
Bhaskaran et al. 2014[45]	5 kg/m^2 increase	7.5	MF	UK	0	1.05 (1.00–1.10)	1	1.04 (0.99–1.09)
Bhaskaran et al. 2014[45]	5 kg/m^2 increase	7.5	MF	UK	0	1.05 (1.00–1.10)	3	1.10 (0.99–1.21)
Recalde et al. 2021[46]	1 kg/m^2 increase	8.3	MF	Spain	1	1.00 (0.99–1.00)	2	1.00 (1.00–1.01)
Recalde et al. 2021[46]	1 kg/m^2 increase	8.3	MF	Spain	1	1.00 (0.99–1.00)	4	1.00 (0.99–1.01)
Arjani et al. 2022[40]	25–29.9 vs. 18.5–24.9 kg/m^2	13.1	MF	USA	0	1.15 (1.06–1.25)	5	1.10 (1.00–1.20)
Arjani et al. 2022[40]	30–34.9 vs. 18.5–24.9 kg/m^2	13.1	MF	USA	0	1.28 (1.15–1.43)	5	1.27 (1.12–1.42)
Arjani et al. 2022[40]	≥35 vs. 18.5–24.9 kg/m^2	13.1	MF	USA	0	1.35 (1.15–1.59)	5	1.45 (1.22–1.73)
Arjani et al. 2022[40]	5 kg/m^2 increase	13.1	MF	USA	0	1.09 (1.04–1.13)	5	1.10 (1.05–1.15)
Arjani et al. 2022[40]	25–29.9 vs. 18.5–24.9 kg/m^2	13.1	M	USA	0	1.19 (1.07–1.32)	5	1.16 (1.04–1.30)
Arjani et al. 2022[40]	30–34.9 vs. 18.5–24.9 kg/m^2	13.1	M	USA	0	1.34 (1.17–1.53)	5	1.37 (1.18–1.60)
Arjani et al. 2022[40]	≥35 vs. 18.5–24.9 kg/m^2	13.1	M	USA	0	1.61 (1.29–2.00)	5	1.81 (1.43–2.29)
Arjani et al. 2022[40]	5 kg/m^2 increase	13.1	M	USA	0	1.13 (1.07–1.19)	5	1.17 (1.10–1.24)
Arjani et al. 2022[40]	25–29.9 vs. 18.5–24.9 kg/m^2	13.1	F	USA	0	1.10 (0.95–1.26)	5	1.01 (0.86–1.17)
Arjani et al. 2022[40]	30–34.9 vs. 18.5–24.9 kg/m^2	13.1	F	USA	0	1.22 (1.02–1.46)	5	1.13 (0.93–1.37)
Arjani et al. 2022[40]	≥35 vs. 18.5–24.9 kg/m^2	13.1	F	USA	0	1.13 (0.89–1.44)	5	1.15 (0.88–1.49)
Arjani et al. 2022[40]	5 kg/m^2 increase	13.1	F	USA	0	1.04 (0.99–1.10)	5	1.03 (0.97–1.10)

Abbreviations: CI, confidence interval; F, female; f-up, follow-up; HR, hazard ratio; M, male.

handled potential cancer-associated prediagnostic weight loss bias. Furthermore, the authors performed a stratified analysis based on the exclusion of the early follow-up period. First, the meta-analysis was restricted to studies that excluded at least the first year of follow-up, followed by a restriction to those that excluded at least the first two years. The summary relative risk (RR) for a 5-unit increment in BMI was 1.10 (95% CI 1.07–1.14) when 23 studies were included. When using the first restriction criterion (six studies),[34–39] the RR was 1.11 (1.05–1.18), and the second restriction (four studies)[35–37,39] yielded a RR of 1.13 (1.05–1.21).

Arslan et al.[27] conducted a pooled analysis of one case–control and 11 cohort studies exploring the association of BMI and PC. In one of the models, cases diagnosed in the first 2 years of follow-up were excluded. For all three high BMI categories (overweight [25 to <30 kg/m^2], obesity class I [30 to <35 kg/m^2], obesity class II [≥35 kg/m^2]), there was a moderate increase in OR estimates after such exclusion: for overweight, from 1.15 (1.00–1.33) to 1.22 (1.04–1.42), for obesity class I, from 1.13 (0.93–1.37) to 1.22 (0.98–1.51), and for obesity class II from 1.26 (0.93–1.71) to 1.32 (0.94–1.87).

Jiao et al.[28] carried out a pooled analysis of seven prospective Japanese cohorts evaluating the association between BMI and PC. The follow-up time was calculated starting from 1 year after the completion of the baseline questionnaire. The summary RR for a 5-unit increase in BMI was 1.06 (0.99–1.13) for men and 1.12 (1.05–1.19) for women. No risk estimates were reported without exclusion of the first year, and no further exclusion of follow-up beyond the first year was done.

Genkinger et al.[29] performed a pooled analysis of 14 Japanese cohorts analyzing the BMI-PC association. However, although it was mentioned that the first two and first 5 years of follow-up were excluded in the sensitivity analyses, no pertinent results were reported.

3.3 | A closer look at individual cohort studies

Expanding on the systematic search conducted by Aune et al., we identified seven new publications[40–46] adding to a total of 32 studies investigating the BMI-PC association.[34–63] Characteristics of included studies are provided in Supplementary Table 1. While 24 studies (24/32, 75%)[34–40,43–46,49,52–60,62] reported having carried out some exclusion of the initial years of follow-up, only about half of them (13/32, 39%)[35–40,43–46,49,62] reported the results of their analysis after the exclusion. Of these, six excluded the 1st year,[34,38,43–46] five the first 2 years,[35,37,39,57,62] one the first 3 years,[45] four the first 4 years,[36,46,49,62] and one the first 5 years of follow-up.[40] Comparison of results from main and sensitivity analyses from studies which excluded more initial years of follow-up in their sensitivity analysis than in their main analysis and have reported their estimates are shown in Table 3. Estimates from the sensitivity analyses were mostly

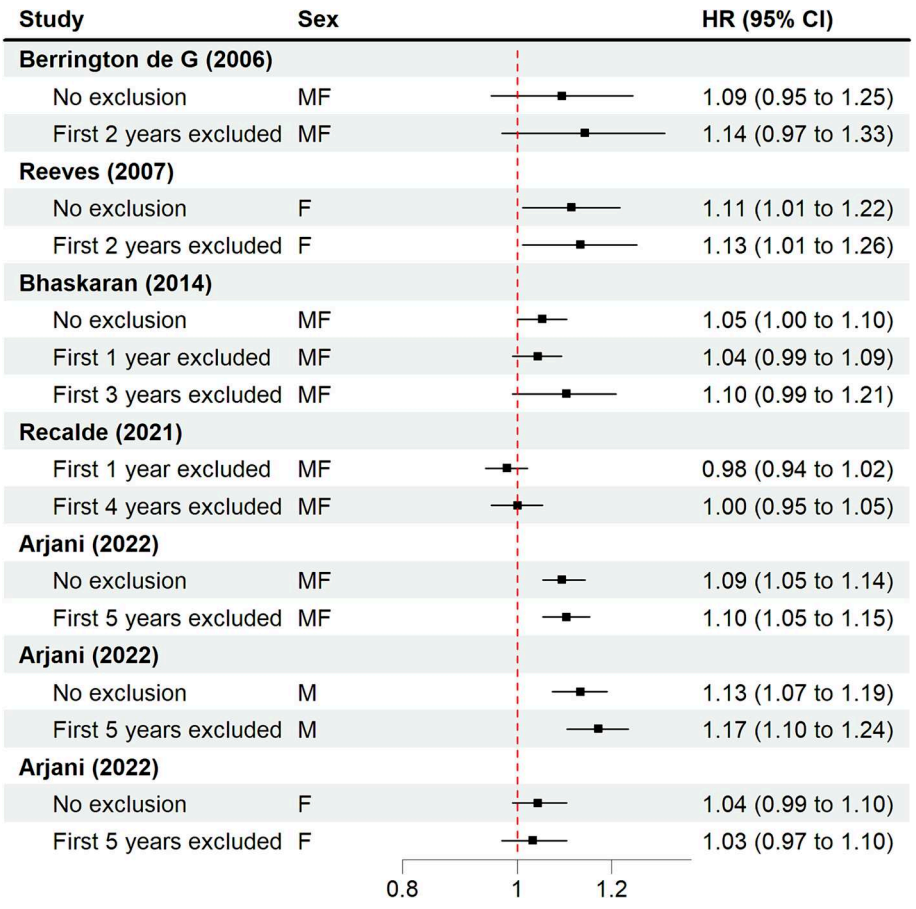

FIGURE 2 Forest plot comparing estimates for a 5-unit increase in BMI without and with exclusion of first years of follow-up. **Abbreviations**: CI, confidence interval; F, female; HR, hazard ratio; M, male.

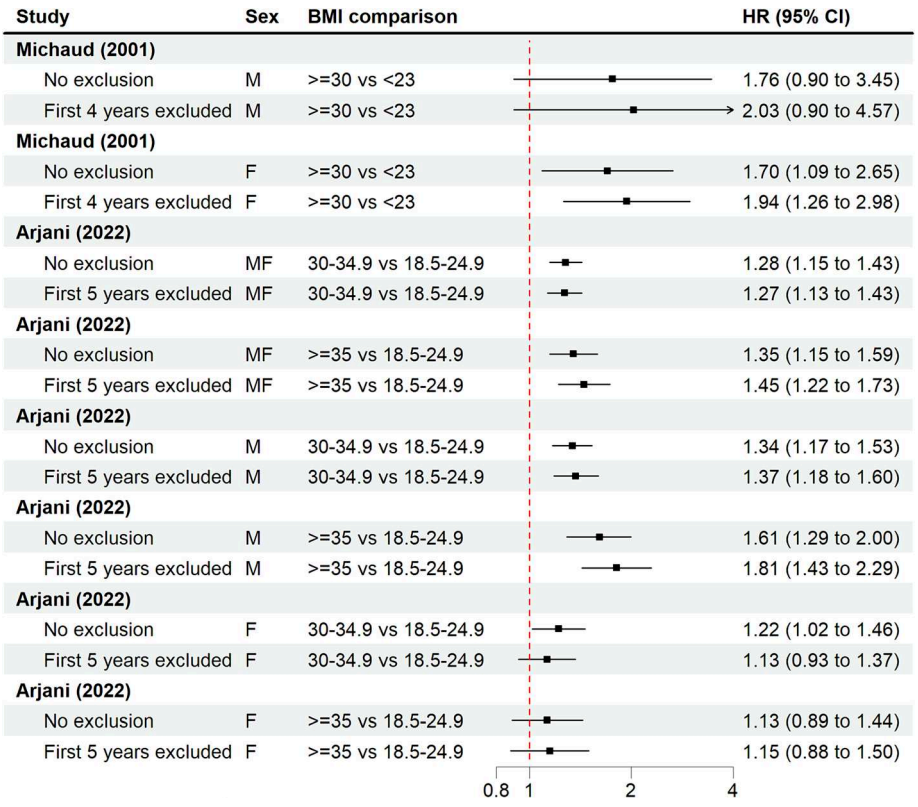

FIGURE 3 Forest plot comparing estimates for above 30 kg/m^2 categories without and with exclusion of first years of follow-up. **Abbreviations**: CI, confidence interval; F, female; HR, hazard ratio; M, male.

larger than the corresponding estimates in the main analyses, with the difference being more noticeable for BMI in the obesity range (obesity class I or II). However, patterns were not consistent across all analyses (Figures 2 and 3). Comparison of results from main and sensitivity analysis in the individual cohort studies.

Next, as done in the review by Aune et al., we performed analyses for a 5-unit increase in BMI after stratification of studies according to the exclusion of the first years of follow-up. We used estimates reported by Aune and colleagues for all the studies they identified. For the newly identified studies, we used the original estimates, or, if not reported for a 5-unit increase in BMI, we used the method of Greenland & Longnecker[64] for calculating them. Results of stratified meta-analyses were similar to those from the 2012 review (Supplementary Figure 1). Restricting the meta-analysis to the results with no exclusion of the early follow-up yielded a summary relative risk (RR) for a 5-unit increment in BMI of 1.08 (95% CI 1.06–1.11; $I^2 = 21\%$, 24 studies). When we restricted the analysis to the results for when at least the first year was excluded the RR was 1.07 (95% CI 1.03–1.11; $I^2 = 75\%$, nine studies).[34,35,37,39,40,43–46] Further restricting the analysis to the studies that excluded at least the first 2 years of follow-up slightly increased the estimate (summary RR = 1.08, 95% CI 1.03–1.14; $I^2 = 58\%$, six studies).[35,37,39,40,45,46]

4 | DISCUSSION/CONCLUSION

To our current understanding, this umbrella review represents the first comprehensive examination of how previous systematic reviews, meta-analyses and pooled analyses, as well as the primary studies included in them, looking into the association of body-mass index and PC, approached prediagnostic weight loss as a potential source of bias. Our results highlight the need for more thorough consideration of this potential source of bias in order to fully describe the impact of overweight and obesity on PC risk.

Although it is well established that excess weight is positively associated with PC risk, many patients with PC experience unintentional weight loss prior to diagnosis.[12,13] Cancer cachexia weight loss is commonly defined as a loss of 5% of body weight within 6 months.[14] However, a number of studies have shown that weight loss in patients with PC can start years before the diagnosis.[15–21] In a 2024 study investigating the association of weight loss in prior 2 years with cancer risk, Wang et al.[65] found that people who experienced 5.1–10.0% weight loss had a 91% (95% CI 43% to 255%), and people who experienced >10% weight loss had a 328% (232% to 463%) increased risk of PC compared with individuals with no weight loss. In another recent study, a large nested case–control study (28,137 PC cases and 261,219 matched controls), Tan et al. showed a U-shaped relationship between BMI and PC, and by exploring the 5-year trend of BMI prior to PC diagnosis showed evidence of biphasic decrease in BMI among cases but not in controls. This decrease in BMI in cases began as early as 33 months before diagnosis, starting with an early gradual decline phase followed by a rapid decline phase from about 9 months prior to diagnosis.[21] Calculating weight change from about 3 years to about 1 year before cancer diagnosis, Yuan et al. showed a 1.26- (95% CI 1.04 to 1.54), 1.29- (1.03 to 1.62), and a 1.69-fold (1.38 to 2.05) increase in HRs for PC, for a 1–4 lb, 5–8 lb,

and a > 8 lb weight loss (compared with no weight loss reference), respectively.[17] The effect seems to be even more pronounced in patients with recent-onset diabetes (HRs: 2.15 (1.29 to 3.57), 3.47 (2.05 to 5.87), and 6.44 (4.31 to 9.62)) for the same exposure groups, compared with non-diabetics with no weight change. This was confirmed by a case–control study comparing body weight at least 3 years before diagnosis to body weight at diagnosis: ORs of 2.16 (1.55 to 3.03), 6.32 (4.36 to 9.16), and 13.42 (9.23 to 19.50) for a 3–9.9%, 10–14.9%, and >15% body weight loss, in comparison with participants without weight change (<3%).[18]

Therefore, it is crucial that studies looking at the excess weight-PC association take utmost effort to avoid potential bias due to pre-diagnostic weight loss. Nonetheless, most of the case–control studies ascertained BMI close to the time of diagnosis, which likely led to an underestimation of the relationship of overweight and obesity with PC. Although most of the reviews, meta-analyses and pooled analyses identified in our umbrella review included cohort studies only, cancer-associated weight loss occurring before enrollment may have again led to an underestimation of the BMI-PC association, unless the initial years of follow-up were excluded from the analysis.

Through the systematic search, we have found nine systematic reviews and meta-analyses. Only one[10] thoroughly considered pre-diagnostic weight loss in the analyses. Expanding on that review's 2011 search we arrived at 32 cohort studies investigating the BMI-PC association. A closer look at these studies revealed that 24 (75%) studies reported having excluded some years of follow-up in their analyses, but only about half of those reported the actual estimates for when the exclusion was performed. The exclusion in these studies was mostly limited to the first two years, and the reporting of the results was very heterogeneous. Nonetheless, a moderate increase in the risk estimates was observed in most studies that reported estimates before and after exclusion of the first years of follow-up. Restricting the dose–response meta-analysis to studies that reported the estimates when at least the first 2 years of follow-up were excluded (only six studies out of 24) did not change the summary relative risk estimate for a 5-unit increase in BMI. However, because of the high heterogeneity in included studies, this comparison needs to be interpreted with caution.

Our study focused on the role of prediagnostic weight loss as a potential source of bias. However, other sources of bias and heterogeneity must also be considered. These include various lengths of follow-up, variation in the method of weight determination (self-reported or measured), differences in populations (e.g. generally weaker BMI-PC associations in Asian populations), and different adjustments for other factors (e.g. diabetes, smoking). While virtually all reviews reported a significant positive BMI-PC association, there are a few primary studies that did not show such an association. For example, Saeed et al.[44] (Norwegian cohort of approximately 1.7 million participants with around 9,000 cases) and Recalde et al.[46] (Catalan cohort of around 3.7 million participants with more than 4,000 cases) showed no increased PC risk for a 5-unit increase in BMI. However, a closer look at the two studies reveals major differences in the study design, study population, and statistical analyses reflecting the general high heterogeneity in the identified 32 cohorts. For example, the study by Saeed et al. had an average follow-up of 32 years since BMI measurement (started in 1963) with adjustment only for age and sex, whereas the study of Recalde et al. had an average follow-up of 8 years after baseline (2006–2017) with comprehensive confounder adjustment. Additionally, the two cohorts recruited participants aged 16–75 and 18–100 years, respectively, which may not be comparable to middle and late adulthood exposures found in most other identified cohorts. In studies with a very long follow-up, BMI ascertained at baseline may only be a poor proxy measure for BMI during most of the follow-up period.

Recently, we conducted a similar umbrella review looking at the reviews investigating the association of BMI and colorectal cancer (CRC).[66] Although mean sojourn time for CRC in the preclinical state has been consistently estimated to be about 3–6 years,[67–69] and weight loss occurring months or years before CRC diagnosis is a common phenomenon, none of the previous 18 reviews thoroughly considered prediagnostic weight loss as a potential source of bias. As with PC, excess weight may have a greater influence on the risk of colorectal cancer (CRC) than what is suggested by existing epidemiological evidence.

The main strength of this umbrella review is that it includes a comprehensive review of existing systematic reviews, meta-analyses and pooled analyses, and primary studies included in them, investigating the relationship between BMI and PC. However, several limitations also need to be noted. First, although we systematically searched two databases and the reference list of obtained articles, we cannot exclude the possibility that we missed some reviews. Nonetheless, even if that should be the case, this would not invalidate our findings as we aimed to explore if and how previous studies generally approached the prediagnostic weight loss issue and how this may have affected previous evidence. Second, our study focused exclusively on BMI at a single point in time as an indicator of excess weight. Further studies should also consider other measures of adiposity such as waist-to-hip ratio, waist circumference, as well as cumulative lifetime exposure to BMI, and assess if and how estimates of associations of these measures with PC risk may be affected by the prediagnostic weight loss bias.

In conclusion, our umbrella review suggests that the association of excess weight with PC may have been underestimated by previous systematic reviews, meta-analyses, and pooled analyses, because they were based on primary studies that paid limited or no attention to prediagnostic weight loss. Future studies investigating the association between excess weight and PC should pay careful attention to weight change before cancer diagnosis, and the exclusion of the first few years of follow-up should become a standard in statistical analyses of cohort studies. Our umbrella review also points to prediagnostic weight loss as a potential marker for early detection of PC. However, most importantly, our results underline the necessity for better prevention of overweight and obesity, which are rapidly becoming more prevalent all over the world, and which may be stronger risk factors for PC and other obesity-related cancers than suggested by existing epidemiological evidence.

AUTHOR CONTRIBUTIONS

Conception and design of the study: HB, MM. Acquisition of data: MM and DP. Data analysis and interpretation: MM and HB. Drafting of the manuscript: MM and HB. All authors provided comments, revised the draft, and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

We declare no competing interests.

DATA AVAILABILITY STATEMENT

All extracted and calculated data are available by emailing to the corresponding author on reasonable request.

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SUPPORTING INFORMATION

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