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The associations of soya intakes with non-communicable diseases: a scoping review of meta-analyses

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Abstract

This scoping review aimed to identify published meta-analyses of the associations of dietary soya intakes with cardiovascular, cancer and diabetes II diseases and the best relative risk estimates. A published novel assessment process combining the well-validated Cochrane Review measures, the AMSTAR 2 checklist and a published algorithm specifically designed for conducting a scoping review of similar meta-analyses was employed. This scoping review identified and evaluated twenty-eight meta-analysis reports, published between 2000 and 2021, on the associations of soya intakes with cardiovascular, cancer and diabetes II diseases. It identified eighteen significantly negatively associated risk–disease pairs for total soya intakes, four significantly negatively associated risk–disease pairs for unfermented soya intakes and four significantly negatively associated risk–disease pairs for fermented soya intakes when compared high against low intakes. The largest significant risk decrease found was gastric cancer mortalities with relative risk (RR) 0·49 (95 % CI: 0·35, 0·68); followed by colorectal cancer mortalities RR 0·59 (95 % CI: 0·41, 0·84); ovarian cancer RR 0·52 (95 % CI: 0·42, 0·66) and endocrine-related gynaecological cancer RR 0·61 (95 % CI: 0·53, 0·72). The fermented soya intake and gastric cancer risk–disease pair were identified to be significantly positively associated, RR 1·22 (95 % CI: 1·02, 1·44) when compared high against low intakes. Four significantly negatively associated risk–disease dose–responses were also identified. Being the products with lower greenhouse gas emission intensities, soya products could be the better dietary alternatives to animal products for reducing cardiovascular, cancer and diabetes II diseases and helping combat climate change.

Key words: **Soya intake: Relative risk: Scoping review: CVD: Cancer: Diabetes**

Soya has a high content of complete protein. Its Protein Digestibility-Corrected Amino Acid Score is 0·9–1[(1)]. It is widely consumed in many Asian countries, especially soya milk, tofu, miso and natto and has increasingly become popular in western countries. In 2018, the average per capita per year soyabean food consumption was 2·06 kg in Asia (7·94 kg in Japan and 3·61 kg in China), compared with 0·21 kg in the USA (0·11 kg in the USA and 1·2 kg in Canada) and 0·28 kg in Europe (0·21 kg in the UK, 0·97 kg in Germany)[(2)]. Soya has been approved as a rich nutrient food containing complex carbohydrates (mainly stachyose and oligosaccharides) that stimulate bifidobacterial[(3)]. It is a good source of dietary fibre, which helps lower glycaemic indexes[(4)], and vitamins and minerals such as vitamin K_1, folate, Fe, Ca, Mg and potassium[(5)]. It stands out from the rest of the legumes for high isoflavone content, a promising agent for cancer chemoprevention and treatment[(6)]. The USA 2020 Dietary Guidelines include soya in the vegetables, dairy, protein foods and oil elements[(7)]. It recommends consuming 5 ounces (142 g) of soya protein products per week.

A systematic review of greenhouse gas emissions for fresh food showed that the average global warming potential of soyabean production (0·58 kg CO2-eq/kg) was much lower than beef (28·73 kg CO2-eq/kg), lamb (27·91 kg CO2-eq/kg), pork (5·85 kg CO2-eq/kg) and chicken (4·12 kg CO2-eq/kg) meat. Meat consumption is positively associated with a list of CVD, cancers and diabetes II[(8)], which are leading causes of death worldwide. Soya products have been increasingly recognised as an alternative to meat intakes to reduce non-communicable diseases and combat climate changes[(5,9,10)]. This scoping review aimed to identify the best-published meta-analysis estimates of observational associations of dietary soya food intakes with CVD, cancers and diabetes II. However, the associations of soya intakes with non-communicable diseases in specific regions or specific groups such as low- and middle-income countries are beyond this study scope.

Abbreviation: BIEs, best-identified meta-analysis estimate.

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Methods

This study adopted well-validated systematic review assessment tools, Cochrane Review measures[11], the AMSTAR 2 checklist[12] and a published algorithm specifically designed for conducting a scoping review of similar meta-analyses[8,13].

Inclusion criteria for studies

In this scoping review, unfermented soya refers to soya food products such as soyabean, soya milk and tofu. Fermented soya refers to soya food products such as miso, natto and tempeh. Total soya refers to a combination of both unfermented and fermented soya. Meta-analyses meeting all the following conditions were included in the scoping review:

1. Estimated the direct associations of dietary total soya intakes and the subgroups: unfermented and fermented food intakes, with non-communicable diseases.
2. Quantified the pooled relative risks (RR), odd ratio (OR) or hazard ratios (HR) directly associated with dietary soya intakes as in a dietary food group, or as protein or isoflavones estimates from dietary soya food intakes.
3. Provided at least the number of individual studies or effects included in the analyses.

Articles that presented conflicts of interest related to the production and commercialisation of soya and its derived products and intervention studies were excluded. Meta-analyses investigating the following were also excluded:

1. The associations of diseases with a specific soya product under the fermented or unfermented subgroup such as tofu only or miso only.
2. The associations of diseases with biomarkers such as urinary or plasma protein or isoflavones instead of estimates from dietary soya food intakes.
3. The associations of disease biomarkers with isoflavones supplements.
4. The associations of disease biomarkers with soya food intakes.

Outcome measures

Two major categories of outcome measures were considered. The first category included RR, OR or HR of CVD, cancer and diabetes II incidences and/or mortalities over some time for high *v.* low food intakes with the 95 % CI provided. The second category included RR, OR or HR per unit of intakes such as per gram(s) or milligram(s), with the 95 % CI provided.

Literature search

Systematic searches were conducted according to Cochrane guidelines[11] in PubMed via Medline, Science Direct, Google Scholar and Cochrane Library databases without limit. A combination of search terms: 'meta-analysis'; 'review'; 'disease'; 'health'; 'soy'; 'isoflavones' and 'humans' were used. Literature searching was last updated in May 2021. Potential abstracts were retrieved and screened. Identified potential full-text articles were then retrieved for further analysis. Full-text articles identified from reference lists of screened reports were also searched, retrieved and screened. All studies meeting the selection criteria were included in the scoping review. Two authors (C. S.C.Y. and W.C.) conducted the literature search and selection independently. Studies were selected based on mutual agreement.

Data extraction from each meta-analysis

Descriptive data: author, year of publication, intake soya group (total, unfermented and fermented), the number of component estimates or studies included in each meta-analysis, publication year range of the included component studies and the association status or direction were extracted for each risk–disease pair. For each identified statistically significant risk–disease meta-analysis estimate, the pooled relative risk, OR or HR at 95 % confidence level, heterogeneity (I^2), $P_{Heterogeneity}$ values and significance of publication bias were extracted. For a risk–disease pair, if the pooled case–control studies, cohort studies and case–control and cohort studies combined estimates were provided, the combined estimates were extracted. For each best-identified meta-analysis estimate (BIE), the frequency of geographic regions involved in the estimation, the significant:non-significant ratio of the included component estimates and the total percentage of significant estimates were calculated. Confounding adjustments of each component study for each BIE were also examined. Systematic reviews have shown alcohol, meat, fruit and vegetable intakes were significantly associated with CVD, cancers and diabetes II[8,13–18]. Therefore, the number of component studies adjusted for alcohol, meat, fruit and vegetable intakes in each BIE was also recorded. Full-text component studies were retrieved for any missing variables. Two authors (C.S.C.Y. and Y.C.Y.) conducted the data extraction independently.

Methodologic quality of the included studies

The AMSTAR 2 checklist, a sixteen-item assessment tool with a maximum score of 16, was used to evaluate whether the scientific qualities of the included studies in a meta-analysis study were assessed, whether the methods used to combine the findings of the component studies were appropriate, and whether the conclusions were appropriately formulated[12].

Identification of statistically significant risk–outcome pairs and the best estimates

At the 95 % confidence level, when the *P*-value of an estimate was < 0·05, the association was regarded as statistically significant. Otherwise, the association was regarded as non-significant. For a risk–disease pair, when only one meta-analysis was found, the estimate from the meta-analysis was taken as the BIE. When multiple meta-analyses were identified, the following rules were applied:

1) When all the estimates were significant, the outcome of the meta-analysis that included the most up-to-date component studies was taken as the BIE.
2) When both significant and non-significant occurred:
   i. The outcome of the meta-analysis that included at least 80 % of the most up-to-date component studies captured

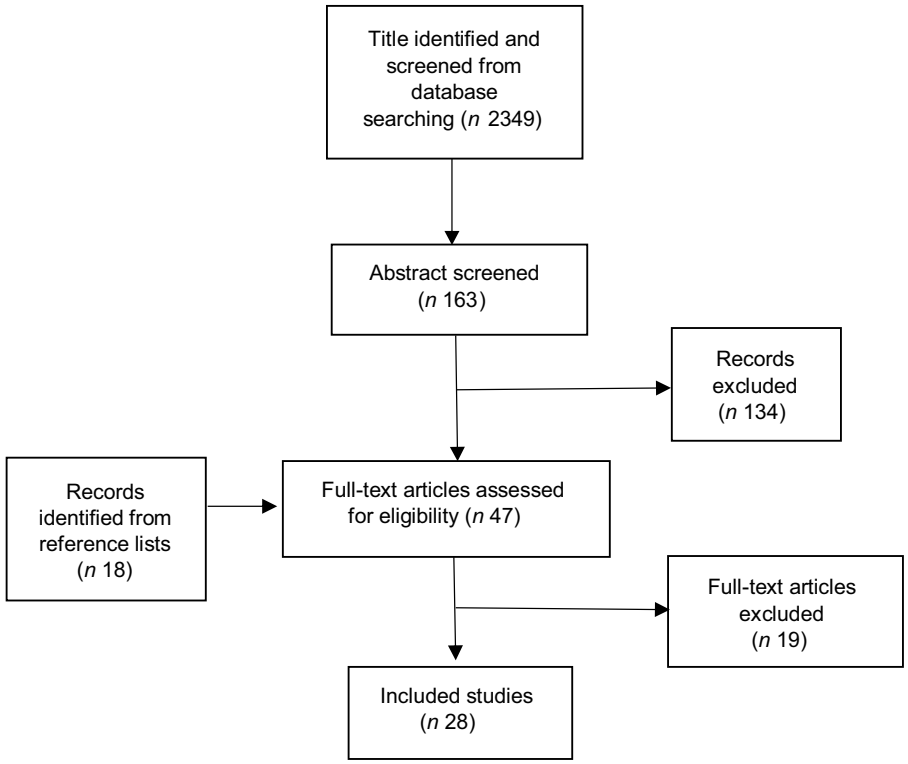

Fig. 1. Literature searching flow chart.

in all the competing meta-analyses was taken as the best estimate, otherwise,

ii. The association was taken as inconclusive.

3) For 1) and 2)i, priorities were given to the meta-analysis outcome that provided the specific heterogeneity (I^2) and $P_{heterogeneity}$ values and the lower I^2 and/or higher $P_{heterogeneity}$ values.

Summaries of main results

Structured narrative presentation of the results.

Results

Included reports

Initially, 2349 titles and 163 abstracts were identified and screened from database searching, of which 134 abstracts were excluded as irrelevant, due to not meeting the inclusion criteria or were duplicates, and twenty-nine full-text articles were retrieved (Fig. 1). Another eighteen full-text articles were identified from the reference lists of the retrieved articles. A total of forty-seven full-text articles were retrieved and evaluated. Eighteen of them did not fully meet the selection criteria, and another had a critical methodological issue. As a result, nineteen full-text reports were excluded (Appendix A1). The remaining twenty-eight articles[19–46], published between 2000 and 2021, were included in the final review (Appendix A2). Six of them were evaluated as high in quality[21,24,25,28,29,42,45], having AMSTAR scores ≥ 13. Ten of them were evaluated as moderate in quality[19,22,23,26,27,40,41,43,44,46]. The rest were evaluated as low in quality, having AMSTAR scores < 10. Most component studies were conducted in Asia, especially in China and Japan, followed by the USA.

A total of forty-one risk–disease pairs were investigated (Table 1 and Fig. 2). Fifty-four meta-analyses estimated the associations of total soya intakes with twenty-six disease outcomes. Sixteen meta-analyses estimated the associations of unfermented soya intakes with nine disease outcomes, and eleven meta-analyses estimated the associations of fermented soya intakes with six disease outcomes. Most of the meta-analyses estimated the risks of high *v.* low intakes, only a few evaluated dose–response: 47 *v.* 7 for total soya intakes, 16 *v.* 1 for unfermented soya intakes and 11 *v.* 0 for fermented soya intakes, respectively. It could be because the exposure soya product types and level measures varied among the included component studies in each meta-analysis, and the exact quantities of 'high' and 'low' intakes in component studies were different. Therefore, standardisation of exposure measures remained a challenge. Among the seventy-four high *v.* low intake estimates, 57 % were significantly negatively associated, the association of fermented soya and gastric cancer estimate was positive and the rest were non-significant. Among the eight identified dose–response meta-analysis estimates, 50 % were significantly negatively associated, and the rest were non-significant.

The best-identified meta-analysis estimates for high v. low total soya intake

A total of twenty articles[21,22,24–29,31–33,36,38–43,45,46] estimated the associations of total soya intake with CVD, cancers and

Table 1. Selection of best identified meta-analysis studies of the associations of total soya intakes with non-communicable diseases: high *v.* low intakes

Incidence	n	Year	RR (95 % CI)	Sources	Q score Max.=16	Conclusion	Selected best study
Total soya high *v.* low intake							
All-cause mortality	6	2002–2014	NSig	Namazi et al.[29]	14·5	NSig	
	8	2002–2016	NSig	Nachvak et al.[28]	14·5		
CVD mortality	6	2007–2016	NSig	Namazi et al.[29]	14·5	NSig	
	12	1998–2018	NSig	Nachvak et al.[28]	14·5		
Stroke mortality	6	2006–2018	NSig	Nachvak et al.[28]	14·5	NSig	
CHD mortality	6	2006–2017	Negative	Nachvak et al.[28]	14·5	Negative	[28]
Cancer mortality	8	2002–2014	NSig	Nachvak et al.[28]	14·5	Negative	Nachvak et al.[28] included 10 studies, missing one study from Namazi et al.[29] which included only 4 studies
	14	2002–2016	Negative	Nachvak et al.[28]	14·5		
Gastric cancer mortality	6	2004–2007	Negative	Nachvak et al.[28]	14·5	Negative	Nachvak et al.[28]
Colorectal cancer mortality	4	1998–2004	Negative	Nachvak et al.[28]	14·5	Negative	Nachvak et al.[28]
Lung cancer mortality	4	1998–3013	Negative	Nachvak et al.[28]	14·5	Negative	Nachvak et al.[28]
Hepatic cancer mortality	4	1998–2004	NSig	Nachvak et al.[28]	14·5	Negative	Nachvak et al.[28]
CVD	32	2001–2015	Negative	Yan et al.[40]	12·5	Negative	Yan et al.[40]
Stroke	14	2002–2015	Negative	Yan et al.[40]	12·5	Negative	Yan et al.[40] included all studies in[25]
	5	2006–2009	Negative	[25]	13		
	4	2005–2014	NSig	[25]	13		
CHD	16	2001–2014	Negative	Yan et al.[40]	12·5	Negative	Yan et al.[40] included all studies in Lou et al.[25]
	5	2001–2013	Negative	Lou et al.[25]	13		
	11	2001–2014	NSig	Lou et al.[25]	13		
Diabetes II	19	2007–2014	Negative	Li et al.[24]	13·5	Negative	Li et al.[24]
Lung cancer	16	1990–2010	Negative	Yang et al.[45]	13·5	Negative	Yang et al.[45] for higher AMSTAR score
Gastrointestinal cancer	34	1988–2013	Negative	Tse and Eslick[33]	9·5	Negative	Tse and Eslick[33]
	14	2005–2015	Negative	Lu et al.[26]	12·5		
Gastric cancer	8	2005–2015	Negative	Lu et al.[26]	12·5	Negative	Lu et al.[26]
	12	1991–2006	Negative	Tong et al.[32]	8·5		
	4	NR	Negative	Woo et al.[36]	6·5		
Colorectal cancer	7	2007–2009	NSig	Lu et al.[26]	12·5	Negative	Yu et al.[41] included more up-to-date studies, all studies in Yan et al.[39], missing one study in (Lu et al. [26]
	20	1993–2009	NSig	Yan et al.[39]	9		
	24*	1993–2015	Negative	Yu et al.[41]	11		
	3†	2003–2005	NSig	Woo et al.[36]	6·5		
Colon cancer	7	1993–2009	NSig	Yan et al.[39]	9	NSig	
	6*	1993–2007	NSig	Yu et al.[41]	11		
Rectal cancer	5	1993–2009	NSig	Yan et al.[39]	9	NSig	
	4*	1993–1997	NSig	Yu et al.[41]	11		
Endocrine-related gynaecological cancer	7	1997–2008	Negative	Myung et al.[27]	11·5	Negative	Myung et al.[27]
Endometrial cancer	3	1997–2003	Negative	Myung et al.[27]	11·5	Negative	Zhang et al.[42]
	10	1996–2014	Negative	Zhang et al.[42]	13·5		
Ovarian cancer	4	2004–2008	Negative	Myung et al.[27]	11·5	Negative	Myung et al.[27]
Breast cancer	9	1990–2005	Negative	Qin et al.[31]	7·5	Negative	Zhong and Zhang [43]
	3†	NR	Negative	Woo et al.[36]	6·5		
	13	1992–2012	Negative	Chen et al.[21]	15		
	11	1992–2012	Negative	Chen et al.[21]	15		
	28	1991–2010	Negative	Zhong and Zhang [43]	10		
	8	2005–2013	Negative	Nachvak et al.[28]	14·5		
Prostate cancer	5	2000–2007	Negative	Hwang et al.[22]	11·5	Negative	Yan and Spitznagel[46]
	14	1988–2008	Negative	Yan and Spitznagel[46]	11·5		
	8	1998–2004	Negative	Yan and Spitznagel [38]	6		

Table 1. (*Continued*)

Incidence	n	Year	RR (95 % CI)	Sources	Q score Max.=16	Conclusion	Selected best study
Unfermented soya high *v.*. low intake							
CVD mortality	5	NR	NSig	Namazi et al.[29]	14·5	NSig	
Cancer mortality	4	NR	NSig	Namazi et al.[29]	14·5	NSig	
Diabetes II	11	2008–2016	NSig	[20]	9	NSig	
	6†	NR	NSig	Li et al. [24]	13·5		
Lung cancer	4†	1999–2009	Negative	Yang et al.[45]	13·5	Negative	Yang et al.[45]
	6†	NR	NSig	Li et al. [24]	13·5		
Gastrointestinal	NR	NR	NSig	Tse and Eslick[33]	9·5	NSig	
Gastric cancer	23	1992–2009	Negative	Kim et al.[23]	10·5	Negative	Kim et al.[23], Weng and Yuan[35] rejected for small sample size, Wu et al.[37] rejected for low AMSTAR score and outdated
	4†	NR	Negative	Weng and Yuan[35]	9·5		
	11	NR	Negative	Wu et al.[37]	3		
Colorectal cancer	3†	NR	Negative	Zhu et al.[44]	11	Inconclusive	
	3†	NR	NSig	Woo et al.[36]	6·5		
Endometrial cancer	6	1996–2014	Negative	Zhang et al.[42]	13·5	Negative	Zhang et al.[42]
Prostate cancer	11	1989–2008	Negative	Applegate et al.[19]	12	Negative	Applegate et al.[19]
	8	1989–2004	Negative	[22]	11·5		
	8	1998–2008	Negative	[46]	11·5		
Fermented soya high *v.*. low intake							
CVD mortality	5	NR	Negative	Namazi et al.[29]	14·5	Negative	Namazi et al.[29]
Cancer mortality	3	NR	NSig	Namazi et al.[29]	14·5	NSig	
Diabetes II	5†	NR	NSig	[24]	13·5	NSig	
Lung cancer	5†	1997–2009	NSig	[45]	13·5	NSig	
Gastrointestinal	NR	NR	NSig	[33]	9·5	NSig	
Gastric cancer	29	1988–2009	Positive	Kim et al.[23]	10·5	Positive	Kim et al.[23]
	4†	2002–2015	NSig	[35]	9·5		
	17	1970–1998	Negative	Wu et al.[37]	3		
Prostate cancer	8	1989–2008	NSig	Applegate et al.[19]	12	NSig	
	5	NR	NSig	Hwang et al.[22]	11·5		
	6	1988–2007	NSig	Yan and Spitznagel[46]	11·5		
Total soya intake dose–response							
All-cause mortality	6	2002–2017	NSig	Nachvak et al.[28]	14·5	NSig	
CVD mortality	4	2007–2017	NSig	Nachvak et al.[28]	14·5	NSig	
Cancer mortality	8	2010–2014	Negative	Nachvak et al.[28]	14·5	Negative	Nachvak et al.[28]
Breast cancer mortality	7	2010–2013	Negative	Nachvak et al.[28]	14·5	Negative	Nachvak et al.[28]
Diabetes II	9	2021	NSig	Pearce et al.[30]	9	NSig	
Gastric cancer	7†	NR	NSig	Weng and Yuan[35]	9·5	NSig	
Breast cancer	9	1999–2019	Negative	Wei et al.[34]	13·5	Negative	Wei et al.[34]
Unfermented intake dose–response							
Gastric cancer	4	NR	Negative	Weng and Yuan [35]	9·5		Weng and Yuan [35]

RR, relative risk.
n: number of component estimate.
* Estimates based on information presented in the report.
† Number of included studies might include higher number of component estimate in the analysis. Year: publication years of component studies. NR, Not reported/unclear; NSig, non-significant; Q score, AMSTAR score.

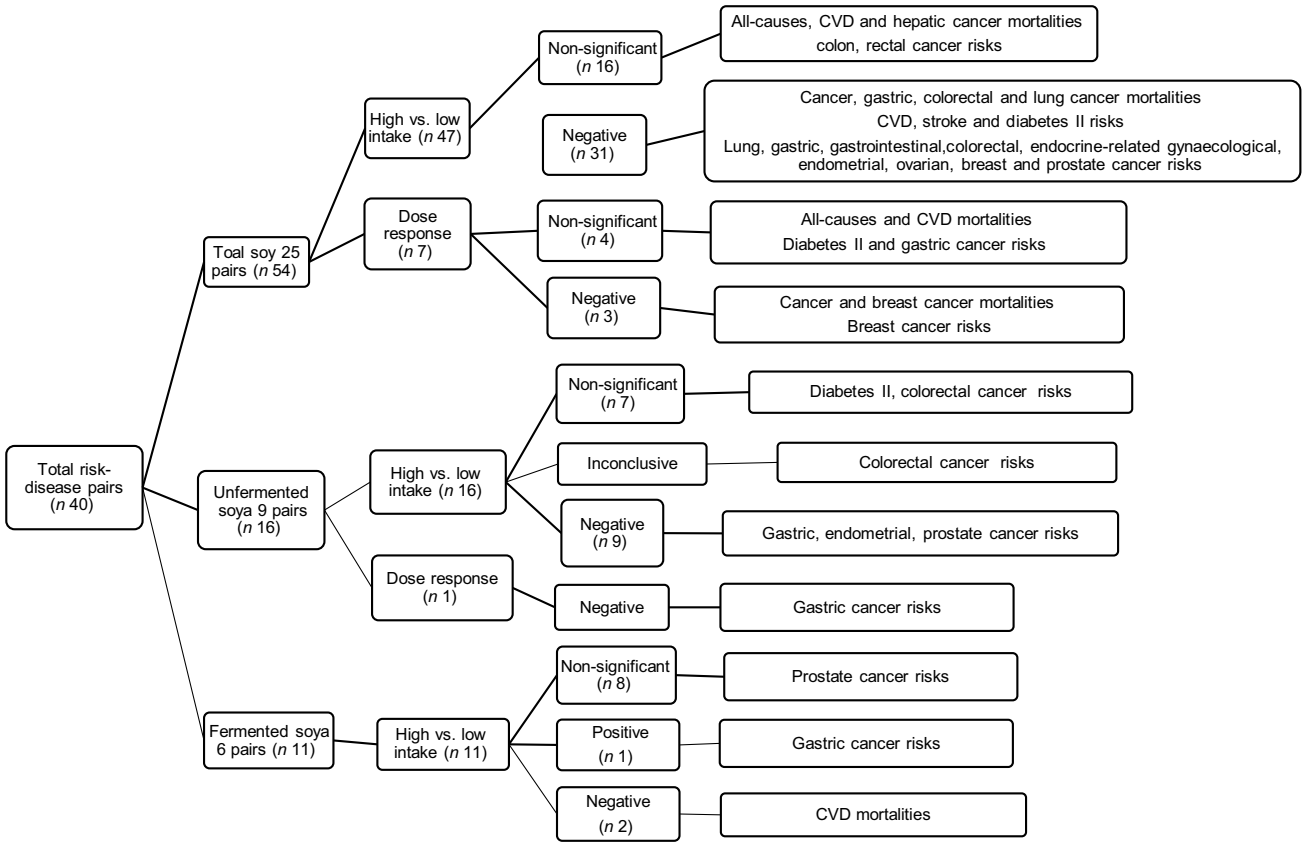

Fig. 2. Number of investigated associations between soya intakes and burden of diseases.

diabetes II. Twenty-four risk–disease pairs were investigated (Table 1). No high *v.* low intake estimate was identified for the total soya intake-breast cancer mortality pair but a dose–response. Multiple meta-analyses were identified for the all-cause, CVD and cancer mortalities; stroke, CHD incidences and gastrointestinal, gastric, colorectal, colon, rectal, endometrial, breast and prostate cancer incidences. Meta-analyses of cancer mortalities; and stroke, CHD and colorectal cancer risks yielded mixed results. The significant negative associations found in Nachvak *et al.*[28], Yan *et al.*[40] and Yu *et al.*[41] were evaluated as the BIE for these risk–disease pairs, as they included all or more than 80 % of the component studies captured in the competing meta-analyses.

Estimates from eleven reports[24,26–28,33,40,42,43,45,46] were identified as the BIE for total soya intakes (Table 2 and Fig. 3). The component studies were adjusted for confounding effects ranging from zero to more than forty confounders. But most of them were not adjusted for alcohol, meat, fruit and vegetable intakes. Nachvak *et al.*[28] were identified as the BIE for CHD and cancer mortalities. The study found high intakes might reduce CHD mortalities by 21 %, cancer mortalities by 10 %, gastric cancer mortalities by 51 %, colorectal cancer mortalities by 41 % and lung cancer mortalities by 21 % when compared against low intakes. The heterogeneities were non-significant except for CHD mortality. However, all component studies were conducted in Asia, except for cancer mortalities, where two out of the nine studies were conducted in America. Furthermore, the number of component studies involved in each meta-analysis was unclear. Therefore, the significant-to-non-significant ratios and the significant percentage weightings of the analyses were also unclear. Yan *et al.*[40] were identified as the BIE for CVD, stroke and CHD risks, and Li *et al.*[24] were identified for diabetes II risks. The studies found high soya intakes might reduce CVD incidences by 16 %, stroke incidences by 18 %, CHD incidences by 17 % and diabetes II incidences by 23 % when compared against low soya intakes. However, the heterogeneities were significant, and most of the components studies were conducted in Asia. The ratios of significance among the case–control component estimates were high but very low among the cohort component estimates. The significant percentage weightings for the CVD, stroke and CHD estimates were also low. Most of the component studies for the BIE for lung, gastrointestinal, gastric, colorectal and postal cancers were conducted in Asia. High soya intakes might reduce lung cancer incidences by 23 %[45], gastrointestinal cancer incidences by 7 %[33], gastric cancer incidences by 15 %[26], colorectal cancer incidences by 21 %[41] and prostate cancer incidences by 26 % when compared against low soya intakes. A higher number of component studies done in regions other than Asia were involved in the BIE for endocrine-related gynaecological, endometrial, ovarian and breast cancers. High soya intakes might reduce endocrine-related gynaecological cancer incidences by 39 %[27], endometrial cancer incidences by 19 %[42], ovarian cancer incidences by 48 %[27] and breast cancer incidences by 14 %[43]. However,

Table 2. The best identified meta-analysis pooled estimates for the associations of soya intakes with non-communicable diseases

Incidence	Sources	RR	95 % CI	Heterogeneity, I^2 %, *P*	Publication Bias	*n* Included study regions	*n* Adjustment	Sig: NSig	Sig weighting %
Total soya high *v.* low intake									
CHD mortality	Nachvak et al.[28]	0·79	0·63, 0·99	68·3, 0·004	NR	6AS†	3A,0M,2F,1V†	NR	
Cancer mortality	Nachvak et al.[28]	0·90	0·81, 1·00	41·8, 0·06	NR	2AM,7AS†	4A,2F,1V	NR	
Gastric cancer mortality	Nachvak et al.[28]	0·49	0·35, 0·68	0, 0·64	NR	3AS†	0A,0M,0F,0V	NR	
Colorectal cancer mortality	Nachvak et al.[28]	0·59	0·41, 0·84	0, 0·59	NR	2AS†	1A,0M,1F,0V	NR	
Lung cancer mortality	Nachvak et al.[28]	0·79	0·71, 0·87	0, 0·83	NR	3AS†	1A,0M,2F,1V	NR	
CVD	Yan et al.[40]	0·84	0·75, 0·94	71·4, < 0·001	Sig	3AM,24AS,5 EU	14 DV	CC 7:4; CH 2:19 (25)	
Stroke	Yan et al.[40]	0·82	0·68, 0·99	78·8, < 0·001	Sig	2AM,10AS, 2EU	7DV	CC 3:2; CH 1:8 (24)	
CHD	Yan et al.[40]	0·83	0·72, 0·95	64·6, < 0·001	NSig	1AM,13AS,2EU	7DV	CC 4:2; CH 1:9 (28)	
Diabetes II	Li et al.[24]	0·77	0·66, 0·91	91·6, < 0·001	Egger: Sig Begg: NSig	13AS,2India,4ME	13A,9M,2F,11V, 2DV	8:11,	42
Lung cancer	Yang et al.[45]	0·77	0·65, 0·92	82·3, < 0·001	NSig	2AM,14AS	4A,2M,7F,5V	4:12, Not applied	
Gastrointestinal cancer	[33]	0·93	0·87,0·99	NR, 0·01	NSig	4AM,30AS*,†	8A,1M,3F,2V	NR	
Gastric cancer	Lu et al.[26]	0·85	0·72, 0·99	52, 0·52	NSig	7AS	5A,1M,3F,3V	3:4	21
Colorectal cancer	Yu et al.[41]	0·79	0·69, 0·89	46·2, 0·006	NR	4AM,20AS*	13A,1M,2F,2V,2DV*	5:21*, (NR)	
Endocrine-related gynaecological cancer	Myung et al.[27]	0·61	0·53, 0·72	12·1, NR	NSig	3AM,2AS,2EU	2A,0M,1F,1V	CC 5:0; CH 1:1 (97)	
Endometrial cancer	Zhang et al.[42]	0·81	0·72, 0·91	20, 0·26	NSig	5AM,3AS,1AU,1EU	4A,0M,0F,0V	3:7	45
Ovarian cancer	Myung et al.[27]	0·52	0·42, 0·66	0, NR	NSig	1AM,1AS,2EU	1A,0M,0F,0V	3:1	70
Breast cancer	Zhong and Zhang[43]	0·86	0·78, 0·94	CC 59, < 0·001 CH 45, 0·12	Sig	5AM,16AS,7EU	5A,2M,4F,4V	CC 6:17; CH 2:3 (65)	
Prostate cancer	Yan and Spitznagel[46]	0·74	0·63, 0·89	NR	NSig	4AM, 8AS,1EU,1ME	NR	5:9, (NR)	
Unfermented soya high *v.*. low intake									
Lung cancer	[45]	0·83	0·58, 0·87	0, 0·767	NR	4AS	0A,1M,1F,2V	NR	
Gastric cancer	Kim et al.[23]	0·64	0·54, 0·77	64·27, 0·001	NSig	23AS	0A,1M,0F,0V	CC 6:8; CH 2:9	65
Endometrial cancer	Zhang et al.[42]	0·81	0·67, 0·97	0·0, 0·59	NR	3AM, 2AS, 1EU	1A,0M,0F,0V	2:4*, (NR)	
Prostate cancer	Applegate et al.[19]	0·65	0·52, 0·83	60·3, 0·005	NSig	6AM, 5AS	2A,1M,0F,0V	5:6,	46
Fermented high *v.*. low intake									
CVD mortality	Namazi et al.[29]	0·84	0·73, 0·97	0	NR	NR	0A,1M,3F,3V	NR	
Gastric cancer	Kim et al. [23]	1·22	1·02, 1·44	71·48, 0·001	NSig	29AS	0A,1M,3F,3V	CC: 6:11; CH 2:10	53
Total soya intake dose–response									
Cancer mortalities	Nachvak et al.[28]	0·93 (0·89, 0·98)/10 mg/d soya isoflavones intake		50·8, 0·047	NR	1AM, 7China	1A,0M,1F,1V	3:5	52
Breast cancer mortalities	Nachvak et al.[28]	0·91 (0·84,0·99) /10 mg/d soya isoflavones intake		57·9,0·027	NR	1AM, 6AS	1A,0M,0F,0V	2;5	31
Breast cancer	Wei et al.[34]	0·97 (0·95, 0·99)/10 mg/d soya isoflavone intake		19·8, 0·267	NSig	1AM, 7AS, 1EU	4A,2M,2F,3V	2:7	39

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Table 2. (*Continued*)

Incidence	Sources	RR	95 % CI	Heterogeneity, I^2 %, *P*	Publication Bias	*n* Included study regions	*n* Adjustment	Sig: NSig	Sig weighting %
Unfermented intake dose–response									
Gastric cancer	Weng and Yuan[35]	< 150 g/d Non-significant 150 g/d 0·57	0·41, 0·79	NR	NR	4† NR	NR	NR	

NR, not reported/unclear; AM, America; AS, Asia; AU, Australia; EU, Europe; ME, multi-ethnic; A, alcohol intake; M, meat intake; F, fruit intake; V, vegetable; DV, unspecified dietary variables; CC, case–control study; CH, cohort study; WC, Western country; AC, Asian country; Sig, significant; NSig, non-significant; *n*, number of component estimate.
* Estimates based on information presented in the report.
† Number of included studies, might include higher number of number of component estimate in the analysis.

not all the BIE reported full heterogeneity estimates or reported/applied an appropriate weighting for combining component estimates in the meta-analysis process.

The best-identified meta-analysis estimates for high v. low unfermented and fermented soya intakes. A total of fourteen reports[4,19,20,22–24,29,35–37,42,44,46,47] estimated the associations of unfermented and fermented soya intakes with the risks of cancers and diabetes II (Table 1, Appendix A3). Namazi *et al.*[29] found high fermented soya intakes reduced CVD mortalities by 16 %. Multiple meta-analysis estimates were identified for the risks of diabetes II and lung, gastric, colorectal and prostate cancers. Kim *et al.*[23] included more numbers of up-to-date component estimates compared with Weng and Yuan[35] and Wu *et al.*[37] and Wu *et al.*[37] also had a low AMSTAR score. Therefore, estimates in Kim *et al.*[23] were identified as the BIE for the associations of unfermented and fermented soya intakes with the risk of gastric cancer. The study found high unfermented soya intakes reduced the risk by 36 %, but high fermented soya intakes increased the risk by 22 %, and the heterogeneities of both of BIE were significant (Table 2 and Fig. 3). Zhang *et al.*[42] were identified as the BIE for the associations of unfermented soya intakes with the risk of endometrial cancer. The study found high unfermented soya intakes might reduce the risk by 19 %, and heterogeneity was non-significant. Applegate *et al.*[19] were identified as the BIE for the association of unfermented soya intakes with the risk of prostate cancer. The study found high unfermented soya intakes might reduce the risk by 35 %, and the heterogeneity was significant. Zhu *et al.*[44] and Woo *et al.*[36] investigated the association of unfermented soya with the risk of colorectal cancer, which yielded mixed results. As the number of component estimates involved in the meta-analyses in each of the studies was unclear, the association was deemed inconclusive.

Dose–responses best-identified meta-analysis estimates. Four articles provided meta-analysis dose–response estimates[28,30,34,35] (Table 1). Nachvak *et al.*[28] used soya isoflavones intake estimates as a exposure measure. Wei *et al.*[34] converted soya food intakes into soya isoflavones intakes for all component studies. On the other hand, Pearce *et al.*[30] and Weng and Yuan[35] used g/d of soya intake and soya food intake, respectively, but did not clearly define the difference between soya and soya food in the articles. Nachvak *et al.*[28] found each 10 mg/d increase in soya isoflavones intake might reduce cancer mortalities by 7 % and breast cancer mortalities by 9 %, while Wei *et al.*[34] found it might reduce breast cancer incidences by 3 % (Table 2). Weng and Yuan[35] found taking 150 g/d of soya food might reduce gastric cancer incidences by 43 % while taking 50 g/d and 100 g/d made no significant difference. But the study did not provide the details of the included studies.

Discussion

Summary of main results

This scoping review identified and evaluated twenty-eight meta-analysis reports of the associations between soya intakes and

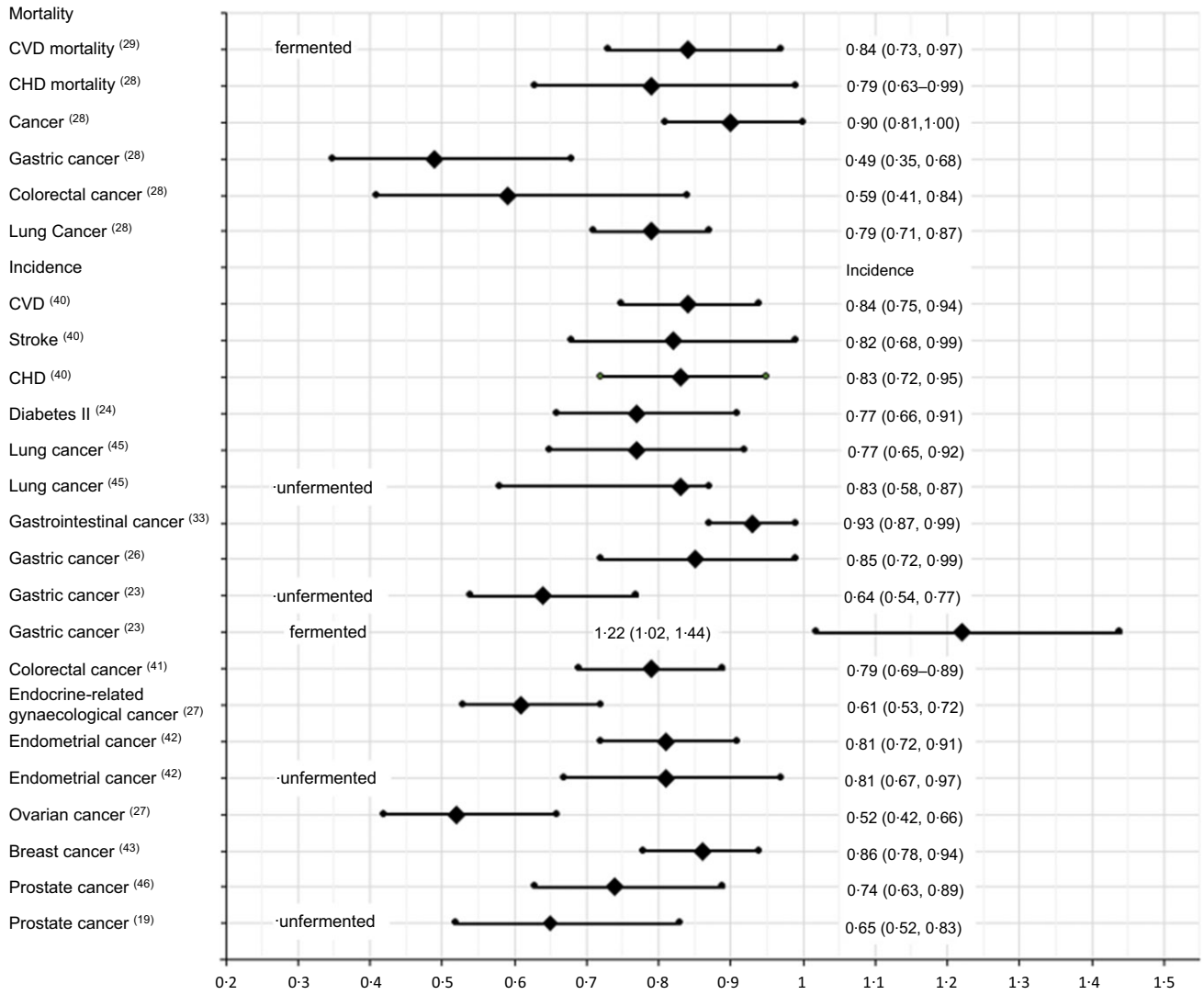

Fig. 3. The best identified meta-analysis estimates of the associations of soya intakes with burden of diseases: high *v.* low intakes.

non-communicable diseases published between 2000 and 2021. It identified eighteen significantly negatively associated risk–disease pairs for total soya intakes, four significantly negatively associated risk–disease pairs for unfermented soya intakes, four significantly negatively associated risk–disease pairs and one significantly positively associated risk–disease pair for fermented soya intakes when compared high *v.* low intakes (Table 2). The largest significant risk decrease found was gastric cancer mortalities, followed by colorectal cancer mortalities, then ovarian and endocrine-related gynaecological cancers incidences (Fig. 3). Significantly negatively associated risk–disease dose–responses were also identified. However, the estimations might be subject to confounding effects from other factors such as alcohol, meat, fruit and vegetable intakes.

Potential biases in the review process

A recent umbrella review investigated the health outcomes of soya and isoflavone intakes[48]. The study included a mixture of published English reports of randomised trials and observational studies of dietary or supplementary soya or isoflavone among healthy or having pre-existing illness humans. The study found that soya and isoflavone intakes were beneficial for a list of CVD and cancer diseases and gynaecological, metabolic, musculoskeletal, endocrine, neurological and renal outcomes but harmful for gastric cancer. However, among the '114 identified eligible full texts with meta-analyses', which the report claimed, the report only presented information and findings from twenty-eight published meta-analysis reports. The evaluation and selection process of the final twenty-eight reports from the '114 eligible full texts with meta-analyses'. The titles of the twenty-eight selected reports were not presented in the reference list, and information about the rest of the eighty-six full texts could not be found. Therefore, most of the included studies were unknown. As a result, the relative quality of the meta-analysis outcomes compared with those 'involved but unknown' studies remained unknown. Furthermore, mixing randomised trials and observational studies, dietary and supplementary soya and isoflavone and healthy and having pre-existing illness humans in a meta-analysis may create high uncertainty in dietary outcomes

and intervention outcomes, therefore, providing little dietary or clinical utility.

This scoping review used a combination of well-validated and published assessment tools, especially the more advanced AMSTAR 2 checklist and the algorithm tailored to capture the specific characteristics of interest in the targeted meta-analyses and minimise potential biases. The assessment algorithm, format and criteria were clearly defined to ensure consistent and systematic evaluation of each meta-analysis and its component estimates. It applied the Cochrane search strategies in a broad range of databases and search terms without the limit to ensure as many relevant studies were identified as possible and minimised exclusion of relevant studies that met the well-defined selection criteria. Hand searching addressed the insufficiencies in electronic database searches. As a result, a total of twenty-eight reports were identified meeting this scoping review selection criteria of dietary soya food product intakes compared with only six articles found by Li *et al.*[48]. Hence, a list of eligible publications might be missing from Li *et al.*[48]'s umbrella review. Literature search and data extraction were performed by multiple researchers, where inconsistencies were resolved by further investigation and mutual agreement, hence minimising individual personal bias and data extraction errors. Reviewing the direct impacts of dietary soya food product intakes instead of biological components and mortalities and disease incidences instead of biomarker risk factors minimised the uncertainties that other foods' constituents might be the causal factors and provided daily dietary utility for non-specialists. Additional clearly defined procedures to handle inconsistencies and qualities comparison of competing meta-analyses in a specific risk–disease pair also further ensured the quality of the BIE. Therefore, every effort has been made to minimise potential bias and ensure integrity. Providing the source and quality details of each meta-analysis included in the scoping review ensured the best transparency and minimum effort in future review quality verification, modifications and update work.

Limitations of the scoping review

In addition to the heterogeneities, publication bias and potential confounding effects from alcohol, meat, fruit and vegetable intakes, the BIE were also subject to other limitations and uncertainties presented in the component estimations and the meta-analyses themselves. Some component estimates were not adjusted for any confounding effects. Some BIE might not apply any weighting in the pooled evaluations. Therefore, the BIE were subject to different levels and extent of uncertainties and potential residual confounding effects. However, this would not affect the BIE selection outcomes. It is because high-level duplication of component estimates occurred when multiple meta-analyses existed for a specific risk–disease pair. Additionally, to ensure that the best estimates were selected, the selection process used in this scoping review was also designed to manage such characteristics. All estimates were obtained from case–control and cohort studies, hence subject to uncertainties in natural intervention practices and past dietary patterns. This scoping review reported the BIE for total soya, unfermented and fermented soya intakes. The associations of other subcategories such as tofu, soya milk and miso could be different[22,31–33,36,39].

The ratios of fermented and unfermented soya in the total soya category; the ratios of soya product subcategories under each fermented, unfermented and total soya category and the exact amount of 'high' and 'low' intakes were generally unclear and non-uniform across the component studies involved in each meta-analysis. Between-study heterogeneities were common in meta-analyses. Heterogeneities could be driven by differences in study designs, combinations of subtypes and combination ratios within each fermented, unfermented and total soya category resulting in different effect sizes, characteristics of the study populations, duration of follow-up, geographic locations, sample sizes and different combinations of confounder adjustments. Attention should also be paid to the followings:

1. Regional, population and selection biases
2. Where component studies identified in competing meta-analyses were excluded or missing without justification
3. High heterogeneities $I^2 > 60\,\%$ and $P < 0{\cdot}05$
4. The potential biases in meta-analyses of a small number of component studies (such as $n < 5$).

Although the benefits of consuming soya products have been reported in many studies, consuming soya products containing phytoestrogens raises concerns[49]. Studies suggest that they may be associated with endocrine-metabolic dysfunctions in adult life[50], and maternal consumption of soya protein isolate during lactation worsened the atherogenic indices of the offsprings in adulthood[51]. While soya products are often coming from genetically modified soya seeds whose effect on the body is unknown, more studies are needed to investigate the long-term effects of soya consumption.

Conclusions

This scoping review suggested that soya intakes might potentially reduce cardiovascular, cancer and diabetes II diseases. Being the products with lower greenhouse gas emission intensity, soya products could be the better dietary alternatives to animal products for reducing these non-communicable diseases and helping combat climate change.

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Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114522000691

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