

Appendix 4: GRADE CLASSIFICATION of quality of evidence for coffee consumption and health outcomes [posted as supplied by author]

Key

Mortality	Cardiovascular	Cancer	Metabolic	Liver & GI	Renal	Pregnancy	Musculoskeletal	Neurological	Gynaecological
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GRADE Classification of quality of evidence

Mortality Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
All-cause Mortality	NLDR	Grosso ²⁸	2016	24	0	24	0	Serious Risk	Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(j)	Would reduce effect	No	Yes	⊕○○○ VERY LOW
Cancer Mortality	NLDR	Grosso ²⁸	2016	15	0	15	0	Serious Risk	Very Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected(j)	Would reduce effect	No	Yes	⊕○○○ VERY LOW
CHD Mortality	NLDR	Grosso ²⁸	2016	12	0	12	0	Serious Risk	Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(j)	Would reduce effect	No	Yes	⊕○○○ VERY LOW
CVD Mortality	NLDR	Grosso ²⁸	2016	23	0	23	0	Serious Risk	Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(j)	Would reduce effect	No	Yes	⊕○○○ VERY LOW
Cirrhosis Mortality	1 extra cup/day	Kennedy ⁹	2016	4	0	4	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(g)	Would reduce effect	No	Yes	⊕⊕○○ LOW
Stroke Mortality	NLDR	Grosso ²⁸	2016	9	0	9	0	Serious Risk	Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(j)	Would reduce effect	No	Yes	⊕○○○ VERY LOW
Post MI-mortality	HIGH versus LOW	Brown ³⁰	2016	2	0	2	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	(h)	Would reduced effect	No	No	⊕○○○ VERY LOW

Cardiovascular Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Atrial Fibrillation	1 extra cup/day	Larsson ³²	2015	6	0	6	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Cardiovascular Disease	HIGH versus LOW	Ding ¹⁹	2014	35	0	35	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Coronary Heart Disease	HIGH versus LOW	Ding ¹⁹	2014	23	0	23	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW

Cardiovascular Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Diastolic Blood Pressure	Coffee versus Control	Steffen ³⁵	2012	12	12	0	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	(h)	Would not reduce effect	No	No	⊕⊕○○ LOW
HDL-Cholesterol	Coffee versus Control	Cai ³⁶	2012	9	9	0	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕⊕○○ LOW
Heart Failure	HIGH versus LOW	Mostofsky ²⁴	2012	5	0	5	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Hypertension	HIGH versus LOW	Zhang ³⁴	2011	6	0	6	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
LDL-Cholesterol	Coffee versus Control	Cai ³⁶	2012	7	7	0	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected	Would not reduce effect	No	No	⊕⊕○○ LOW
Stroke	HIGH versus LOW	Ding ¹⁹	2014	15	0	15	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Systolic Blood Pressure	Coffee versus Control	Steffen ³⁵	2012	12	12	0	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	(h)	Would not reduce effect	No	No	⊕⊕○○ LOW
Total Cholesterol	Coffee versus Control	Cai ³⁶	2012	12	12	0	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Strongly Suspected	Would not reduce effect	No	No	⊕⊕○○ LOW
Triglyceride	Coffee versus Control	Cai ³⁶	2012	6	6	0	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected	Would not reduce effect	No	No	⊕⊕○○ LOW
Venous Thromboembolism	HIGH versus LOW	Lippi ³³	2015	2	0	2	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	(h)	Would not reduce effect	No	No	⊕○○○ VERY LOW

Cancer Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
All Cancer	1 extra cup/day	Yu ³⁸	2011	40	0	40	0	Serious Risk	Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(g)	Would reduce effect	No	Yes	⊕○○○ VERY LOW
Bladder Cancer	1 extra cup/day	Wu ¹³⁵	2015	6	0	6	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected(g)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Breast Cancer	1 extra cup/day	Li ⁵⁶	2013	15	0	15	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(g)	Would not reduce effect	No	Yes	⊕⊕○○ LOW
Colon Cancer	1 extra cup/day	Gan ²⁰	2017	15	0	15	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected	Would reduce effect	No	Yes	⊕○○○ VERY LOW

Cancer Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Colorectal Cancer	1 extra cup/day	Gan ²⁰	2017	17	0	17	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would reduce effect	No	No	⊕○○○ VERY LOW
Endometrial Cancer	1 extra cup/day	Wang ³⁹	2016	11	0	11	0	Serious Risk	Very Serious Inconsistency(h)	No Serious Indirectness	No Serious Risk	(h)	Would reduce effect	No	Yes	⊕○○○ VERY LOW
Gastric Cancer	1 extra cup/day	Zeng ⁵¹	2015	9	0	9	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Glioma	1 extra cup/day	Malerba ⁶¹	2012	3	0	3	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Laryngeal Cancer	HIGH versus LOW	Ouyang ⁵⁹	2014	8	0	1	7	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Leukaemia	HIGH versus LOW	Yu ³⁸	2011	2	0	2	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(g)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Liver Cancer	1 extra cup/day	Bravi ⁴³	2016	12	0	12	0	Serious Risk	No Serious Inconsistency(g)	No Serious Indirectness	No Serious Risk	Undetected	Would reduce effect	Large(k)	Yes	⊕⊕○○ LOW
Lymphoma	HIGH versus LOW	Wang ³⁹	2016	3	0	3	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected(j)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Lung Cancer	1 extra cup/day	Galarraga ⁴⁷	2016	21	0	8	13	Very Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Detected	Would not reduce effect	No	Yes	⊕○○○ VERY LOW
Melanoma	1 extra cup/day	Wang ⁴⁵	2015	7	0	6	1	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(g)	Would reduce effect	No	Yes	⊕○○○ VERY LOW
Non-melanoma skin cancer	HIGH versus LOW	Cain ⁴²	2017	4	0	4	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	(h)	Would reduce effect	No	No	⊕○○○ VERY LOW
Oesophageal Cancer	1 extra cup/day	Zheng ⁵⁸	2013	NP	0	NP	NP	Serious Risk	No serious Inconsistency(g)	No Serious Indirectness	Serious Risk	Undetected(g)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Oral Cancer	HIGH versus LOW	Wang ³⁹	2016	6	0	6	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(i)	Would reduce effect	No	No	⊕○○○ VERY LOW
Ovarian Cancer	1 extra cup/day	Braem ⁵³	2012	6	0	6	0	Serious Risk	Serious Inconsistency(g)	No Serious Indirectness	Serious Risk	Undetected(g)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Pancreatic Cancer	1 extra cup/day	Ran ¹³⁶	2016	9	0	9	0	Serious Risk	No Serious Inconsistency(g)	No Serious Indirectness	Serious Risk	Undetected(g)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Prostate Cancer	1 extra cup/day	Wang ³⁹	2016	10	0	10	0	Serious Risk	No Serious Inconsistency(g)	No Serious Indirectness	No Serious Risk	Undetected(g)	Would reduce effect	No	Yes	⊕⊕○○ LOW

Cancer Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Rectal Cancer	1 extra cup/day	Gan ²⁰	2017	14	0	14	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Renal Cancer	1 extra cup/day	Huang ¹³⁷	2014	4	0	4	0	Serious Risk	No Serious Inconsistency(g)	No Serious Indirectness	Serious Risk	(h)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Thyroid Cancer	HIGH versus LOW	Han ⁵⁴	2017	2	0	2	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	(h)	Would reduce effect	No	No	⊕○○○ VERY LOW
Urinary Tract Cancer	ANY versus NONE	Zeegers ⁴⁹	2001	14	0	0	14	Very Serious Risk	^Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW

Pregnancy Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
1 st Trimester Preterm Birth	HIGH versus LOW	Maslova ⁸⁵	2010	NP	0	NP	NP	Serious Risk	Very Serious Inconsistency(h)	No Serious Indirectness	No Serious Risk	Undetected(g)	Would not reduce effect	No	No	⊕○○○ VERY LOW
2 nd Trimester Preterm Birth	HIGH versus LOW	Maslova ⁸⁵	2010	NP	0	NP	NP	Serious Risk	Very Serious Inconsistency(h)	No Serious Indirectness	No Serious Risk	Undetected(g)	Would not reduce effect	No	No	⊕○○○ VERY LOW
3 rd Trimester Preterm Birth	HIGH versus LOW	Maslova ⁸⁵	2010	NP	0	NP	NP	Serious Risk	Very Serious Inconsistency(h)	No Serious Indirectness	Serious Risk	Undetected(g)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Acute Leukaemia of Childhood	HIGH versus LOW	Thomopoulos ⁸⁹	2015	6	0	0	6	Very Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	(h)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Birth weight	Coffee versus Control	Jahanfar ⁸⁸	2015	1	1	0	0	Serious Risk	N/A	No Serious Indirectness	Serious Risk	N/A	Would not reduce effect	No	No	⊕⊕○○ LOW
Cardiovascular Malformations	HIGH versus LOW	Browne ⁸⁷	2006	4	0	1	3	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	(h)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Low Birth Weight	1 extra cup/day	Chen ¹³⁴	2014	2	0	1	1	Serious Risk	Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(g)	Would not reduce effect	No	Yes	⊕○○○ VERY LOW
Neural Tube Defects	ANY versus NONE	Li ⁸⁶	2015	7	0	1	6	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Oral Cleft Malformations	HIGH versus LOW	Browne ⁸⁷	2006	3	0	1	2	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	(h)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Pregnancy Loss	1 extra cup/day	Li ²³	2015	6	0	4	2	Serious Risk	*Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(g)	Would not reduce effect	No	Yes	⊕○○○ VERY LOW

Pregnancy Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Preterm birth	Coffee versus Control	Jahanfar ⁸⁸	2015	1	1	0	0	Serious Risk	N/A	No Serious Indirectness	Serious Risk	N/A	Would not reduce effect	No	No	⊕⊕○○ LOW
Small for gestational age	Coffee versus Control	Jahanfar ⁸⁸	2015	1	1	0	0	Serious Risk	N/A	No Serious Indirectness	Serious Risk	N/A	Would not reduce effect	No	No	⊕⊕○○ LOW

Metabolic & Gastrointestinal Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Chronic Liver Disease	1 extra cup/day	Bravi ⁴³	2016	6	0	6	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(g)	Would reduce effect	Yes	Yes	⊕⊕○○ LOW
Cirrhosis	1 extra cup/day	Kennedy ⁹	2016	7	0	7	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(g)	Would reduce effect	No	Yes	⊕⊕○○ LOW
Gallstones	1 extra cup/day	Zhang ²⁵	2015	3	0	3	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected(g)	Would not reduce effect	No	Yes	⊕○○○ VERY LOW
Gastrointestinal Reflux Disease	HIGH versus LOW	Kim ⁶⁶	2013	15	0	0	15	Very Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Gout	HIGH versus LOW	Park ⁶⁹	2016	2	0	2	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	(h)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Liver Fibrosis	ANY versus NONE	Liu ⁶³	2015	8	0	7	1	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	(h)	Would reduce effect	No	No	⊕○○○ VERY LOW
Metabolic Syndrome	HIGH versus LOW	Shang ²⁶	2015	4	0	4	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	Strongly suspected(g)	Would not reduce effect	No	No	⊕○○○ VERY LOW
NAFLD	ANY versus NONE	Wijarnpreecha ⁶²	2017	3	0	1	1	Very Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	(h)	Would reduce effect	No	No	⊕○○○ VERY LOW
Renal Stones	1 extra cup/day	Wang ⁶⁸	2014	5	0	3	2	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected	Would not reduce effect	No	Yes	⊕⊕○○ LOW
Type II diabetes	1 extra cup/day	Jiang ⁶⁷	2014	20	0	20	0	Serious Risk	No Serious Inconsistency(g)	No Serious Indirectness	No Serious Risk	Undetected(g)	Would not reduce effect	No	Yes	⊕⊕○○ LOW

Renal Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
CKD	ANY versus NONE	Wijarnpreecha ⁷¹	2016	4(e)	0	0	0	Very Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	(h)	Would reduce effect	No	No	⊕○○○ VERY LOW
Urinary Incontinence	ANY versus NONE	Sun ⁷⁰	2016	3(e)	0	1	0	Very Serious Risk	Very Serious Inconsistency	No Serious Indirectness	Serious Risk	(h)	Would reduce effect	No	No	⊕○○○ VERY LOW
Musculoskeletal Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Fracture	1 extra cup/day	Liu ⁷³	2012	10	0	10	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Strongly Suspected(g)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Hip Fracture	1 extra cup/day	Li ⁷⁵	2013	4	0	4	0	Serious Risk	Serious Inconsistency(g)	No Serious Indirectness	Serious Risk	Undetected(g)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Rheumatoid Arthritis	HIGH versus LOW	Lee ^{76,77}	2015	3	0	3	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected(g)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Neurological Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Alzheimer's Disease	1 extra cup/day	Liu ⁸²	2016	2	0	2	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	(h)	Would not reduce effect	No	No	⊕○○○ VERY LOW
Cognitive Decline	1 extra cup/day	Liu ⁸²	2016	8	0	8	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Depression	1 extra cup/day	Wang ⁸¹	2016	5(e)	0	2	1	Very Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Strongly Suspected	Would not reduce effect	No	Yes	⊕○○○ VERY LOW
Parkinson's Disease	1 extra cup/day	Hernan ⁷⁸	2002	4	0	4	0	Serious Risk	Very Serious Inconsistency(g)	No Serious Indirectness	No Serious Risk	Undetected(j)	Would not reduce effect	No	Yes	⊕○○○ VERY LOW
Gynaecological Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Endometriosis	ANY versus NONE	Chiaffarino ⁸³	2014	3	0	1	2	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW

(e) Included cross-sectional studies

- (g) Based on heterogeneity/publication bias of overall study
- (h) No heterogeneity/publication bias published
- (i) Based on alternative measure of heterogeneity
- (j) Stated as undetected
- (k) Based on HIGH versus LOW comparisons