

Appendix 1: Literature search strategy for all the databases

1. Search strategy for Pubmed

#1 (((Social isolation[MeSH Terms]) OR (Social Network Index[MeSH Terms])) OR (social loneliness[MeSH Terms])) OR (social segregation[MeSH Terms])

#2 ((((((Social isolation[Text Word]) OR (Social Network Index[Text Word])) OR (social loneliness[Text Word])) OR (social segregation[Text Word])) OR (Feeling isolated[Text Word])) OR (social disaffiliation[Text Word])

#3 (#1) OR (#2)

#4 ((Mortality[MeSH Terms]) OR (Death[MeSH Terms])) OR (Fatal Outcome[MeSH Terms])

#5 ((Mortality[Text Word]) OR (fatal[Text Word])) OR (death[Text Word])

#6 (#4) OR (#5)

#7 (#3) AND (#6)

#8 animals[MeSH Terms]

#9 humans[MeSH Terms]

#10 #8 NOT #9

#11 #7 NOT #10

2. Search strategy for Embase

- #1 'social segregation'/exp OR 'social network index'/exp OR 'social isolation'/exp
- #2 'social segregation':ab,ti OR 'social network index':ab,ti OR 'social isolation':ab,ti
OR 'social disaffiliation':ab,ti OR 'social loneliness':ab,ti
- #3 #1 OR #2
- #4 'mortality'/exp OR 'death'/exp
- #5 mortality:ab,ti OR death:ab,ti OR fatal:ab,ti
- #6 #4 OR #5
- #7 #3 AND #6
- #8 'animal'/exp
- #9 'humans'/exp
- #10 #8 NOT #9
- #11 #7 NOT #10

3. Search strategy for Web of science

#1 (((TS=("Social isolation ")) OR TS=("social segregation ")) OR TS=("social disaffiliation")) OR TS=("social loneliness")) OR TS=("Social Network Index")

#2 ((TS=(mortality*)) OR TS=(death*)) OR TS=(fatal*)

#3 (#1)AND #2



PRISMA 2020 Checklist

Supplementary Table 1 PRISMA Checklist of the systematic review and meta-analysis

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P5, Figure 1, Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P5-6, Figure 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P6-7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P6-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P6, Table S3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P6-7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Figure 2-5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P6-7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P6-7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P6-7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P7-8, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P7-8, Figure 1



PRISMA 2020 Checklist

Supplementary Table 1 PRISMA Checklist of the systematic review and meta-analysis

Section and Topic	Item #	Checklist item	Location where item is reported
Study characteristics	17	Cite each included study and present its characteristics.	P8, Tables 1-3 & S4-5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	P8, Figure S3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2-5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P8, Figure S1 and S5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P8-11, Figure 2-5 and S3 and Table S6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P8-11, Table S8-11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	P8 and Figure S2
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	P8-10, Figure S1 and S4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	P8-11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P11-14
	23b	Discuss any limitations of the evidence included in the review.	P14-15
	23c	Discuss any limitations of the review processes used.	P14-15
	23d	Discuss implications of the results for practice, policy, and future research.	P15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P15
Competing interests	26	Declare any competing interests of review authors.	P15
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Tables 1-3 & S4-5

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
 For more information, visit: <http://www.prisma-statement.org/>



PRISMA 2020 for Abstracts Checklist

Supplementary Table 1 PRISMA Abstracts Checklist of the systematic review and meta-analysis

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

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

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

Supplementary Table 2 Measurement Methods Used to Assess Social Isolation*

Example of measurement methods	Description
Social Isolation Index	(1) unmarried/not cohabiting, (2) lack of contact with children, other family members and friends, (3) do not belong to social clubs or organizations such as residents' groups, religious groups or committees
Eight Community-Related Activities	(1) family or friendship activities outside the household (2) church or religious activities (3) sports or physical activities with others (4) other recreational activities involving others (5) educational and cultural activities involving others (6) service club or fraternal organization activities (7) neighbourhood, community or professional association activities (8) volunteer or charity work
Social Isolation Scale	(1) the frequency of social contact: used items asking the frequency of face-to-face and non-face-to-face contact with children, relatives or friends. (2) a multidimensional risk score: unmarried, less regular contact with children living separately and relatives, less regular contact with friends and no social participation
Social Network Index	(1) partnership (2) contact with family members or friends (3) engagement in religious activities (4) membership in organisations or clubs
The Levels of Participation in Seven Different Social Activities	(1) senior citizen association meetings (2) volunteering activities (3) religious service attendance (4) social club participation (5) hobby activities with others (6) activities in a local organization (7) participation in senior job placements
A Six-Item Scale	(1) unmarried (2) lived alone (3) less than monthly contact with children (4) less than monthly contact with other family members (5) less than monthly contact with friends (6) did not participate monthly in any groups, clubs, or other social organizations
Social Integration Index	(1) marital status/cohabitation (2) contacts with close friends/family (3) affiliation with voluntary associations
Combining Information on Partner Status, Social Support, and Network Size.	(1) no partner (2) no social support

Questionnaire	(3) having a small network size Participants were asked about the frequency of both face-to-face and non-face-to-face (e.g. telephone, e-mail, letters) interactions with family members who did not live with them, relatives, friends, and neighbors.
Social Isolation Score	(1) the social network size (2) the household size (3) the frequency of social or group activities (attending educational, cultural, political, and sport events or meeting friends).
Loneliness Scale	There are six statements on social loneliness, e.g. “there is always someone I can talk to about my day-to-day problems”
Social Provisions Scale	The scale contains 24 items, four for each of the six social provisions elaborated by Weiss (Attachment, Social Integration, and so on). For each provision, two items are phrased negatively and two positively
Two Items	(1) “How often do you see your family members or relatives who are living apart?” (2) “How often do you make contact with your family members or relatives who are living apart by letter, telephone, or email?”
Six Questions	meet their children, grandchildren, siblings, relatives or friends less often than once a week (six questions)
Four Measures of Social Ties	(1) presence of a spouse (2) reported contact with two or more close friends and/or relatives (3) regular church attendance (i.e., at least once per month) (4) membership in other types of groups
Five Questions	(1) What is your current marital status? (2) How often do you visit friends and relatives? (3) On the average, how many different homes of friends or relatives do you visit per month? (4) How many people usually come to see you or call you per day? (5) How often do you go to meetings of clubs, associations, or societies?
One Question	not seeing friends or family members at least once a month
The ABCPP Social Network Index	adapted from the Social Networks Index, including five components: (1) a spouse/intimate partner (2) number of relatives (3) friendship ties (4) religious/social ties (5) community ties.
Four Items	(1) You feel that the disease makes it difficult to visit family and friends (2) You feel that the disease makes it difficult to receive visits from family and friends (3) You feel that the disease makes it difficult to participate in social events You feel that the disease makes it difficult to go on holiday

	with family
	(4) and friends
Patient-Reported Outcomes Measurement	(1) I feel left out
Information System (PROMIS) Social	(2) I feel that people barely know me
Isolation Short Form	(3) I feel isolated from others
	(4) I feel that people are around me but not with me

*Social isolation typically refers to the objective lack of (or limited) social contact with others and is marked by a person having few social network ties, having infrequent social contact, or, potentially, living alone¹. But at present, there is no unified international standard to evaluate it.

1. National Academies of Sciences E, Medicine, Division of B, et al. Social Isolation and Loneliness in Older Adults: Opportunities for the Health Care System. Washington (DC): National Academies Press (US)

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Supplementary Table 3 Quality assessment of included studies based on the Newcastle-Ottawa scale

Year	Study (Title)	Selection				Comparability		Outcome		Scores
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
2021	Cross-national comparison of social isolation and mortality among older adults: A 10-year follow-up study in Japan and England	☆	★	★	★	☆ ★	★	★	★	7
2021	Social isolation, inflammation, and cancer mortality from the National Health and Nutrition Examination Survey - a study of 3,360 women	☆	★	★	★	☆ ★	★	★	★	7
2021	Impact of social isolation on mortality and morbidity in 20 high-income, middle-income and low-income countries in five continents	★	★	★	★	☆ ★	★	★	★	8
2021	The association between loneliness, social isolation and all-cause mortality in a nationally representative sample of older women and men	★	★	★	★	☆ ★	★	★	★	8

2021	Associations of Loneliness and Social Isolation with Healthspan and Lifespan in the US Health and Retirement Study	★	★	★	★	☆ ★	★	★	★	8
2021	Loneliness and social isolation increase cancer incidence in a cohort of Finnish middle-aged men	☆	★	★	★	☆ ★	★	★	★	7
2021	Mortality risk associated with combinations of loneliness and social isolation. Findings from The Irish Longitudinal Study on Ageing (TILDA)	★	★	★	★	☆ ★	★	★	★	8
2021	All-cause mortality and three aspects of social relationships: an eight-year follow-up of older adults from one entire Korean village	☆	★	★	★	☆ ★	★	★	★	7
2021	Social Determinants of Health and Cancer Mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort Study	★	★	★	★	☆ ★	★	★	★	8
2020	Social isolation and mortality among Canadian seniors	★	★	★	★	☆ ★	★	★	★	8
2020	Social Isolation, Loneliness, and All-Cause Mortality in Patients With Cardiovascular Disease: A 10-Year Follow-up Study	☆	★	★	★	★ ★	★	★	★	8

2020	Association of social relationships with incident cardiovascular events and all-cause mortality	★	★	★	★	☆☆	★	★	★	7
2020	The effects of loneliness and social isolation on all-cause, injury, cancer, and CVD mortality in a cohort of middle-aged Finnish men. A prospective study	☆☆	★	★	★	☆☆★	★	★	★	7
2020	Frailty Combined with Loneliness or Social Isolation: An Elevated Risk for Mortality in Later Life	★	★	★	★	☆☆★	★	★	★	8
2020	Prediagnosis social support, social integration, living status, and colorectal cancer mortality in postmenopausal women from the women's health initiative	☆☆	★	★	★	☆☆★	★	★	★	7
2019	Social Isolation and Mortality in US Black and White Men and Women	★	★	★	★	☆☆★	★	★	★	8
2019	Co-existence of social isolation and homebound status increase the risk of all-cause mortality	★	★	★	★	☆☆★	★	★	★	8
2018	Social isolation and all-cause mortality: a population-based cohort study in Denmark	★	★	☆☆	★	★★★	★	★	★	8
2018	Social isolation, health literacy, and mortality risk: Findings from the English Longitudinal Study of Ageing	★	★	★	★	★★★	★	★	★	9

2018	Social isolation and loneliness as risk factors for myocardial infarction, stroke and mortality: UK Biobank cohort study of 479 054 men and women	★	★	★	★	☆ ★	★	★	★	8
2018	Loneliness, social isolation, their synergistic interaction, and mortality	★	★	★	★	☆ ★	★	★	★	8
2018	Perceived Social Isolation and Outcomes in Patients With Heart Failure	☆	★	★	★	☆ ★	★	★	★	7
2018	Social integration and survival after diagnosis of colorectal cancer	☆	★	★	★	☆ ★	★	★	★	7
2017	Relationships between social isolation, neighborhood poverty, and cancer mortality in a population-based study of US adults	★	★	★	★	☆ ★	★	★	★	8
2017	Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study	☆	★	★	★	☆ ★	★	★	★	7
2017	Postdiagnosis social networks and breast cancer mortality in the After Breast Cancer Pooling Project	☆	★	★	★	☆ ★	★	★	★	7

2016	Psychosocial predictors of long-term mortality among women with suspected myocardial ischemia: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation	☆	★	★	★	☆ ★	★	★	★	7
2015	Loneliness and all-cause mortality in community-dwelling elderly Singaporeans	☆	★	★	★	☆ ★	★	★	★	7
2014	Social integration and mortality in patients with coronary heart disease: Findings from the heart and soul study	☆	★	★	★	☆ ★	★	★	★	7
2013	Emotional loneliness is associated with mortality among mentally intact nursing home residents with and without cancer: a five-year follow-up study	★	★	★	★	☆ ★	★	★	★	8
2013	Social isolation: a predictor of mortality comparable to traditional clinical risk factors	★	★	☆	★	☆ ★	★	★	★	7
2013	Social isolation and adult mortality: the role of chronic inflammation and sex differences	★	★	★	★	☆ ★	★	★	★	8
2013	Social networks, social support, and burden in relationships, and mortality after breast cancer diagnosis in the Life After Breast Cancer Epidemiology (LACE) study	☆	★	★	★	☆ ★	★	★	★	7

2012	Social isolation, social activity and loneliness as survival indicators in old age;a nationwide survey with a 7-year follow-up	★	★	☆	★	☆ ☆	★	★	★	6
2012	Gender differences on the impacts of social exclusion on mortality among older Japanese: AGES cohort study	☆	★	★	★	☆ ★	★	★	★	7
2012	Socioeconomic status, structural and functional measures of social support, and mortality: The British Whitehall II Cohort Study, 1985-2009	☆	★	☆	★	☆ ★	★	★	★	6
2011	Social isolation, C-reactive protein, and coronary heart disease mortality among community-dwelling adults	☆	★	★	★	☆ ★	★	★	★	7
2010	Social networks and survival after breast cancer diagnosis	☆	★	★	★	☆ ★	★	★	★	7
2006	Social networks, social support, and survival after breast cancer diagnosis	☆	★	★	★	☆ ★	★	★	★	7
2004	Long-term effect of social relationships on mortality in patients with congestive heart failure	☆	★	★	★	☆ ★	★	★	★	7
2004	Social integration and mortality: a prospective study of French employees of Electricity of France-Gas of France: the GAZEL Cohort	☆	★	★	★	☆ ★	★	★	★	7

2004	Social networks are associated with lower mortality rates among women with suspected coronary disease: the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation study	☆	★	★	★	☆ ★	★	☆	★	6
2003	The significance of social network in a geriatric assessment population	☆	★	★	★	☆ ★	★	★	★	7
2002	Social ties and change in social ties in relation to subsequent total and cause-specific mortality and coronary heart disease incidence in men	☆	★	★	★	☆ ★	★	★	★	7
2002	Effects of depression and social integration on the relationship between alcohol consumption and all-cause mortality	★	★	★	★	☆ ★	★	☆	★	7
1999	Psychological predictors of mortality in old age	★	★	☆	★	☆ ☆	★	★	★	6
1993	Intercommunity variations in the association between social ties and mortality in the elderly. A comparative analysis of three communities	☆	★	★	★	☆ ★	★	★	★	7
1993	The influence of psychosocial factors on survival after myocardial infarction	☆	★	★	★	☆ ★	★	★	★	7
1988	Social connections and mortality from all causes and from cardiovascular disease: prospective evidence from eastern Finland	★	★	★	★	☆ ★	★	★	★	8

1986	Social ties and mortality in Evans County, Georgia	★	★	★	★	☆★	★	★	★	8
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Supplementary Table 4 Characteristics of included studies for the association between social isolation and all-cause, cancer-specific mortality in cancer patients

First author	Year	Country	Sample size	Age* (years)	Follow-up†	Exposure assessment	Events for analysis	Effect Size HR/RR (95% CI)	Adjustment¶
Siiri-Liisi Kraav	2021	Finland	M 649	42–61	20.44 y	social isolation scale	Cancer mortality among cancer patients	Male HR 1.044 (0.925 to 1.179)	1, 13, 15, 29, 39, 41, 42, 43, 44, 45, 46, 47
Candyce H Kroenke	2020	US	F 1431	50-79	5.8 y	social network index	all-cause mortality after colorectal cancer diagnosis	Female HR 1.27 (0.97 to 1.66)	1, 2, 3, 4, 6, 12, 13, 14, 15, 21, 23, 29, 30, 32, 33, 34, 35, 36, 37, 38, 39, 40
Candyce H Kroenke	2020	US	F 1431	50-79	5.8 y	social network index	colorectal cancer mortality after colorectal cancer diagnosis	Female HR 1.14 (0.81 to 1.61)	1, 2, 3, 4, 6, 12, 13, 14, 15, 21, 23, 29, 30, 32, 33, 34, 35, 36, 37, 38, 39, 40
Elizabeth A Sarma	2018	US	F 896	30-55	9.5 y	social networks index	all-cause mortality after colorectal cancer diagnosis	Female HR 1.54 (1.09 to 2.17)	1, 3, 13, 14, 15, 23, 29, 31, 32, 33, 34
Elizabeth A Sarma	2018	US	F 896	30-55	9.5 y	social networks index	colorectal cancer mortality after colorectal cancer diagnosis	Female HR 1.59 (0.94 to 2.63)	1, 3, 13, 14, 15, 23, 29, 31, 32, 33, 34
Candyce H Kroenke	2017	US	LACE cohort F 1,947 NHS cohort F2,221 SBCSS cohort F 2,127	56.1	LACE cohort 1.8y NHS cohort 0.9y SBCSS cohort 6 mo	the ABCPP social network index	all-cause mortality after breast cancer diagnosis	Female HR 1.69 (1.43 to 1.99)	17, 19, 20, 21, 23, 26, 33, 38, 48

Candyce Kroenke	H	2017	US	LACE cohort: F 1,947 NHS cohort F 2,221 SBCSS cohort F 2,127	56.1	LACE cohort 1.8y NHS cohort 0.9y SBCSS cohort 6 mo	the social index	ABCPP network	breast cancer mortality after breast cancer diagnosis	Female HR 1.64 (1.33 to 2.03)	17, 19, 20, 21, 23, 26, 33, 38, 48
Candyce Kroenke	H	2017	US	WHEL cohort F 2,972	56.1	WHEL cohort 1.8y	the social index	ABCPP network	all-cause mortality after breast cancer diagnosis	Female HR 1.16 (0.90 to 1.51)	17, 19, 20, 21, 23, 26, 33, 38, 48
Candyce Kroenke	H	2017	US	WHEL cohort F 2,972	56.1	WHEL cohort 1.8y	the social index	ABCPP network	breast cancer mortality after breast cancer diagnosis	Female HR 1.00 (0.75 to 1.34)	17, 19, 20, 21, 23, 26, 33, 38, 48
Candyce Kroenke	H	2013	US	F 2264	58	10.8 y	social index	network	all-cause mortality after breast cancer diagnosis	Female HR 1.50 (1.11 to 2.03)	1, 2, 3, 4, 5, 6, 7, 13, 14, 15, 17, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29
Candyce Kroenke	H	2013	US	F 2264	58	10.8 y	social index	network	breast cancer mortality after breast cancer diagnosis	Female HR 1.16 (0.76 to 1.77)	1, 2, 3, 4, 5, 6, 7, 13, 14, 15, 17, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29
Jeannette Beasley	M	2010	US	F 4589	59	5.6 y	social index	network	all-cause mortality after breast cancer diagnosis	Female HR 1.39 (0.96 to 2.04)	1, 2, 3, 4, 5, 6, 12, 13, 14, 15, 18, 19, 20, 21, 22
Jeannette Beasley	M	2010	US	F 4589	59	5.6 y	social index	network	breast cancer mortality after breast cancer diagnosis	Female HR 1.18 (0.62 to 2.22)	1, 2, 3, 4, 5, 6, 12, 13, 14, 15, 18, 19, 20, 21, 22

Candyce H Kroenke	2006	US	F 2835	46-71	10 y	social network index	all-cause mortality after breast cancer diagnosis	Female HR 1.66 (1.04 to 2.65)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17
Candyce H Kroenke	2006	US	F 2835	46-71	10 y	social network index	breast cancer mortality after breast cancer diagnosis	Female HR 2.14 (1.11 to 4.12)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17

HR=hazard ratio; RR=risk ratio; 95%CI=95%Confidence interval; F=Female; M= Male

*Presented as mean or range.

†Number of years that individuals were followed up in the prospective cohort studies.

¶Adjustments: age (1), time between diagnosis and assessment of social networks (2), cancer stage at diagnosis (3), chemotherapy (4), tamoxifen (5), radiation (6), age at menarche (7), oral contraceptive use (8), birth index(9), menopausal status (10), age at menopause (11), use of hormone replacement therapy (12), smoking status (13), body mass index(14), physical activity (15), protein intake (16), estrogen-receptor status (17), state of residence (18), menopausal status (19), parity (20), education (21), weight change from pre-diagnosis to follow-up (22), race (23), any family history of breast cancer (24), tumor size (25), HER-2 neu status (26), nodal status (27), age at first birth (28), alcohol intake (29), surgery (30), year of diagnosis (31), aspirin use (32), cancer grade (33), cancer site (34), study (35), income (36), family history of colorectal cancer (37), comorbidity (38), depressive symptoms (39), colorectal cancer screening (40), diastolic and systolic blood pressure (41), cardiovascular disease (CVD) (42), adulthood socioeconomic status (43), diet score (44), hours slept at night (45), high-sensitivity C-reactive protein (hs-CRP) (46), low-density lipoprotein cholesterol (47), cohort(48).

Supplementary Table 5 Characteristics of included studies for the association between social isolation and all-cause mortality in patients with cardiovascular disease

First author	Year	Country	Sample size	Age* (years)	Follow-up†	Exposure assessment	Events for analysis	Effect Size HR/RR (95% CI)	Adjustment¶
Bin Yu	2020	China	M 645 F 622	≥65	10 y	social isolation index	all-cause mortality in patients with cardiovascular disease	HR 1.16 (1.06 to 1.26)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Christian Hakulinen	2018	UK	479 054	40–69	7.1 y	social isolation scale	all-cause mortality after acute myocardial infarction	HR 1.25 (1.03 to 1.51)	1, 2, 3, 5, 6, 7, 8, 9, 12, 13, 14, 15, 16, 17
Christian Hakulinen	2018	UK	479 054	40–69	7.1 y	social isolation scale	all-cause mortality after stroke	HR 1.32 (1.08 to 1.61)	1, 2, 3, 5, 6, 7, 8, 9, 12, 13, 14, 15, 16, 17
Sheila M Manemann	2018	US	1681	73.29	8±4 m	Patient-Reported Outcomes Measurement Information System (PROMIS) Social Isolation Short Form	all-cause mortality in patients with congestive heart failure	HR 3.74 (1.82 to 7.70)	1, 2, 3, 21, 22
Thomas Rutledge	2016	US	F 517	F 58.3	9.3 y	social network index	all-cause mortality among women with suspected myocardial ischemia	HR 0.85 (0.67 to 1.1)	1, 6, 12, 33, 34, 35, 36, 37, 38
Sylvia D Kreibitz	2014	US	1019	63.4/ 68.0	6.7 y	social network index	all-cause mortality in patients with coronary heart disease	HR 1.36 (0.91 to 2.04)	2, 3, 5, 7, 8, 9, 11, 12, 13, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33
Terje A Murberg	2004	Norway	M 85 F 34	M 65.7 F 66.8	6 y	four items	all-cause mortality in patients with congestive heart failure	HR 1.36 (1.04 to 1.78)	1, 2, 18, 19, 20
Thomas Rutledge	2004	US	F 503	F 59	2.3 y	social network index	all-cause mortality among women with suspected myocardial	RR 2.4 (1.04 to 5.4)	1, 6, 12, 34

C	M	1993	UK	M 1,073 F 303	unclear	3 y	social isolation scale	ischemia all-cause mortality after acute myocardial infarction	HR 1.33 (0.89 to 1.98)	1, 2, 35, 37, 39, 40, 41
Jenkinson										

HR=hazard ratio; RR=risk ratio; 95%CI=95%Confidence interval; M=Male; F=Female.

*Presented as mean or range.

†Number of years that individuals were followed up in the prospective cohort studies.

¶Adjustments: age (1), sex (2), education attainment (3), working status (4), income (5), smoking status (6), alcohol consumption (7), physical activity (8), body mass index (9), activities of daily living (ADL) (10), charlson comorbidity index (11), depressive symptoms (12), ethnicity (13), diastolic and systolic blood pressure (14), grip strength (15), Townsend Deprivation Index (16), history of chronic illness (17), ProANP (plasma N-atrial terminal natriuretic peptide) (18), NYHA (is the most widely used measure of functional status in individuals with chronic heart disease.) (19), neuroticism (20), charlson index (21), marital status (22), cardiac disease severity (23), risk factors (24), medication use (25), stress-related (26), inflammatory (27), glycemic (28), cholesteric biomarkers (29), diet (30), subjective sleep quality (31), medication adherence (32), anxiety (33), CAD severity (34), diabetes history (35), dyslipidemia history (36), hypertension history (37), self-rated health (38), previous documented infarct (39), hospital complications (40), car owner (41).

Supplementary Table 6 Effect estimates of social isolation and all causes, cardiovascular or circulatory system diseases, and cancer mortality

Outcomes	No. of Studies	ES(95%CI)	P_{ES}	$I^2(\%)$	Egger's(P -value)	Begg's(P -value)	Adjust ES ¹ (95%CI)	$P_{adjusted-ES}$
All-cause mortality	31	1.31 (1.23, 1.38)	<0.001	77.6	0.037	0.036	1.22 (1.16, 1.29)	<0.001
All-cause mortality in men	22	1.41 (1.26, 1.58)	<0.001	79.1	0.005	0.159	1.35 (1.20, 1.51)	<0.001
All-cause mortality in women	19	1.46 (1.27, 1.69)	<0.001	77.4	0.751	0.484	NA	NA
Cardiovascular or circulatory system diseases mortality	11	1.35 (1.25, 1.45)	<0.001	65.5	0.160	0.592	NA	NA
Cancer mortality	10	1.23 (1.18, 1.27)	<0.001	44.2	0.067	0.443	NA	NA
All-cause mortality in breast and colorectal cancer patients	6	1.47 (1.33, 1.63)	<0.001	20.2	0.473	0.548	NA	NA
Cancer-specific mortality in breast and colorectal cancer patients	7	1.26 (1.04, 1.52)	0.016	63.1	0.268	0.108	NA	NA
All-cause mortality in breast cancer patients	4	1.51 (1.34, 1.70)	<0.001	34.6	0.540	1.000	NA	NA
Cancer-specific mortality in breast cancer patients	4	1.33 (1.02, 1.75)	0.038	59.5	0.836	0.806	NA	NA
Cancer-specific mortality in colorectal cancer patients	3	1.07 (0.96, 1.20)	0.205	21.9	0.265	0.296	NA	NA
All-cause mortality in patients with cardiovascular disease	8	1.28 (1.10, 1.48)	0.001	64.9	0.113	0.076	NA	NA

ES: effect size

¹: Adjusted effect size through trim and fill method

P_{ES} : P for the significant test of effect size

$P_{adjusted-ES}$: P for the significant test of adjusted-ES

Supplementary Table 7 Effect size estimates of social isolation on all-cause mortality at different Social Network Index levels

First author	Year	Country	SNI level	Effect Size HR (95%CI)
Masashige Saito	2021	Japan	1	1.11 (1.02, 1.21)
Masashige Saito	2021	Japan	2	1.18 (1.06, 1.3)
Masashige Saito	2021	Japan	3	1.3 (1.12, 1.5)
Masashige Saito	2021	UK	1	1.24 (1.11, 1.39)
Masashige Saito	2021	UK	2	1.45 (1.22, 1.72)
Masashige Saito	2021	UK	3	2.05 (1.52, 2.73)
Kristina Laugesen	2018	Denmark	1	1.3 (0.8, 1.9)
Kristina Laugesen	2018	Denmark	2	1.1 (0.74, 1.7)
Kristina Laugesen	2018	Denmark	3	1.7(1.1, 2.6)
Kristina Laugesen	2018	Denmark	1	0.98 (0.59, 1.6)
Kristina Laugesen	2018	Denmark	2	1.2 (0.73, 2.1)
Kristina Laugesen	2018	Denmark	3	1.6 (0.83, 2.9)
Chan, Angelique	2015	Singapore	1	1.36 (0.97, 1.91)
Chan, Angelique	2015	Singapore	2	1.19 (0.84, 1.67)
Chan, Angelique	2015	Singapore	3	1.28 (0.9, 1.82)
Matthew Pantell	2013	US	1	1.14 (0.91, 1.44)
Matthew Pantell	2013	US	2	1.29 (1.03, 1.61)
Matthew Pantell	2013	US	3	1.75 (1.38, 2.23)
Matthew Pantell	2013	US	1	1.04 (0.85, 1.27)
Matthew Pantell	2013	US	2	1.18 (0.97, 1.45)
Matthew Pantell	2013	US	3	1.62 (1.29, 2.02)
Lisa F Berkman	2004	French	1	1.37 (0.92, 2.04)
Lisa F Berkman	2004	French	2	1.95 (1.25, 3.04)
Lisa F Berkman	2004	French	3	2.7 (1.17, 6.23)
Lisa F Berkman	2004	French	1	0.65 (0.14, 3.15)
Lisa F Berkman	2004	French	2	1.35 (0.3, 6.13)
Lisa F Berkman	2004	French	3	3.64 (0.72, 18.58)
Patricia M. Eng	2002	US	1	0.97 (0.83, 1.13)
Patricia M. Eng	2002	US	2	1.18 (1.03, 1.34)
Patricia M. Eng	2002	US	3	1.2 (0.97, 1.48)
<i>P*</i>				<0.001

HR=hazard ratio; 95%CI =95%Confidence interval.

P* is the significance of simple linear regression

Supplementary Table 8 Subgroup analyses on the association between social isolation and risk of all-cause mortality

Subgroup	N	ES (95% CI)	<i>I</i> ² (%)	<i>P</i> ¹	<i>P</i> ²
Gender³					0.521 ⁴
Men	19	1.41 (1.26, 1.58)	79.1	<0.001	
Women	22	1.46 (1.27, 1.69)	77.4	<0.001	
Country					0.070
US	18	1.41 (1.30, 1.52)	46.5	0.016	
Others	28	1.24(1.17, 1.32)	73.6	<0.001	
Follow-up duration					0.191
0-5 years	11	1.47 (1.21, 1.78)	79.5	<0.001	
5-10 years	20	1.27 (1.20, 1.35)	56.1	0.001	
10-15 years	8	1.39 (1.22, 1.60)	56.5	0.024	
15-20 years	2	1.49 (1.30, 1.71)	0.0	0.700	
20-25 years	5	1.10 (1.05, 1.16)	0.0	0.675	
Social isolation assessment tools					0.172
Social Network Index	28	1.34 (1.26, 1.43)	73.1	<0.001	
Others	18	1.24 (1.13, 1.36)	73.7	<0.001	
Adjustment for depression					0.127
Yes	12	1.19 (1.10, 1.29)	77.7	<0.001	
No	34	1.34 (1.26, 1.44)	67.8	<0.001	
Adjustment for education					0.489
Yes	25	1.33 (1.24, 1.42)	79.5	<0.001	
No	21	1.28 (1.16, 1.41)	71.0	<0.001	
Adjustment for smoking					0.514
Yes	29	1.32 (1.24, 1.41)	70.9	<0.001	
No	17	1.29 (1.17, 1.42)	80.5	<0.001	
Adjustment for drinking					0.684
Yes	15	1.27 (1.17, 1.37)	65.4	<0.001	
No	31	1.33 (1.23, 1.44)	81.1	<0.001	

Adjustment for body mass index					0.091
Yes	17	1.41 (1.28, 1.56)	79.6	<0.001	
No	29	1.26 (1.18, 1.35)	73.3	<0.001	
Adjustment for ethnicity					0.125
Yes	12	1.40 (1.29, 1.51)	71.5	<0.001	
No	34	1.25 (1.18, 1.33)	66.7	<0.001	
Adjustment for chronic disease					0.501
Yes	12	1.35 (1.21, 1.50)	60.3	0.004	
No	34	1.29 (1.21, 1.38)	80.7	<0.001	

N denotes the number of studies. ES: effect size

Inconsistency- percentage of variation across studies due to heterogeneity

P^1 for heterogeneity within each subgroup

P^2 for heterogeneity between subgroups with meta-regression analysis

³Studies on gender are not fully included in the overall study, the data used are different from the overall study, and when a study includes both the results of the whole population and the results of men and women separately, the data are extracted separately

⁴This value is the P value of the difference between groups when performing subgroup analysis

Supplementary Table 9 Subgroup analyses on the association between social isolation and risk of cardiovascular or circulatory system diseases mortality

Subgroup	N	ES (95% CI)	<i>I</i> ² (%)	<i>P</i> ¹	<i>P</i> ²
Gender					0.213
All	4	1.25 (1.19,1.32)	0.0	0.414	
Men	9	1.35 (1.18,1.54)	65.5	0.003	
Women	4	1.47 (1.38,1.56)	0.0	0.994	
Country					0.083
US	8	1.41 (1.31, 1.53)	34.7	0.152	
UK	3	1.35 (1.13, 1.61)	46.2	0.156	
Finland	3	1.26 (0.88, 1.82)	39.6	0.191	
Others	3	1.29 (1.13, 1.48)	0.0	0.937	
Follow-up duration					0.480
>10 years	11	1.39 (1.25, 1.55)	76.1	<0.001	
≤10 years	6	1.25 (1.19, 1.32)	0.0	0.851	
Adjustment for education					0.029
Yes	13	1.37 (1.29, 1.46)	44.5	0.042	
No	4	1.24 (0.92, 1.67)	38.8	0.179	
Adjustment for smoking					0.200
Yes	14	1.32 (1.23, 1.43)	68.6	<0.001	
No	3	1.59 (1.27, 1.99)	0.0	0.442	
Adjustment for drinking					0.052
Yes	8	1.25 (1.13, 1.37)	54.1	0.033	
No	9	1.43 (1.32, 1.54)	33.4	0.151	

N denotes the number of studies. ES: effect size

Inconsistency- percentage of variation across studies due to heterogeneity

*P*¹ for heterogeneity within each subgroup

*P*² for heterogeneity between subgroups with meta-regression analysis

Supplementary Table 10 Subgroup analyses on the association between social isolation and risk of cancer mortality

Subgroup	N	ES (95% CI)	<i>I</i> ² (%)	<i>P</i> ¹	<i>P</i> ²
Gender					0.460
All	4	1.26 (1.16,1.37)	11.9	0.333	
Men	6	1.14 (1.00,1.31)	55.9	0.045	
Women	4	1.05 (0.83,1.35)	53.2	0.093	
Country					0.728
US	10	1.20 (1.12, 1.28)	20.0	0.259	
Others	4	1.19 (0.98, 1.45)	75.0	0.007	
Follow-up duration					0.690
>10 years	9	1.18 (1.11, 1.26)	30.6	0.174	
≤10 years	5	1.12 (0.83, 1.51)	59.5	0.043	
Adjustment for education					0.058
Yes	10	1.24 (1.17, 1.31)	19.2	0.266	
No	4	1.10 (0.92, 1.32)	49.2	0.116	
Adjustment for smoking					0.979
Yes	12	1.18 (1.09, 1.27)	52.0	0.018	
No	2	1.18 (1.02, 1.36)	0.0	0.773	
Adjustment for drinking					0.594
Yes	8	1.11 (0.95, 1.31)	62.6	0.009	
No	6	1.23 (1.18, 1.29)	0.0	0.502	

N denotes the number of studies. ES: effect size

Inconsistency- percentage of variation across studies due to heterogeneity

*P*¹for heterogeneity within each subgroup

*P*² for heterogeneity between subgroups with meta-regression analysis

Supplementary Table 11 Subgroup analyses on the association between social isolation and risk of all-cause mortality in patients with cardiovascular disease

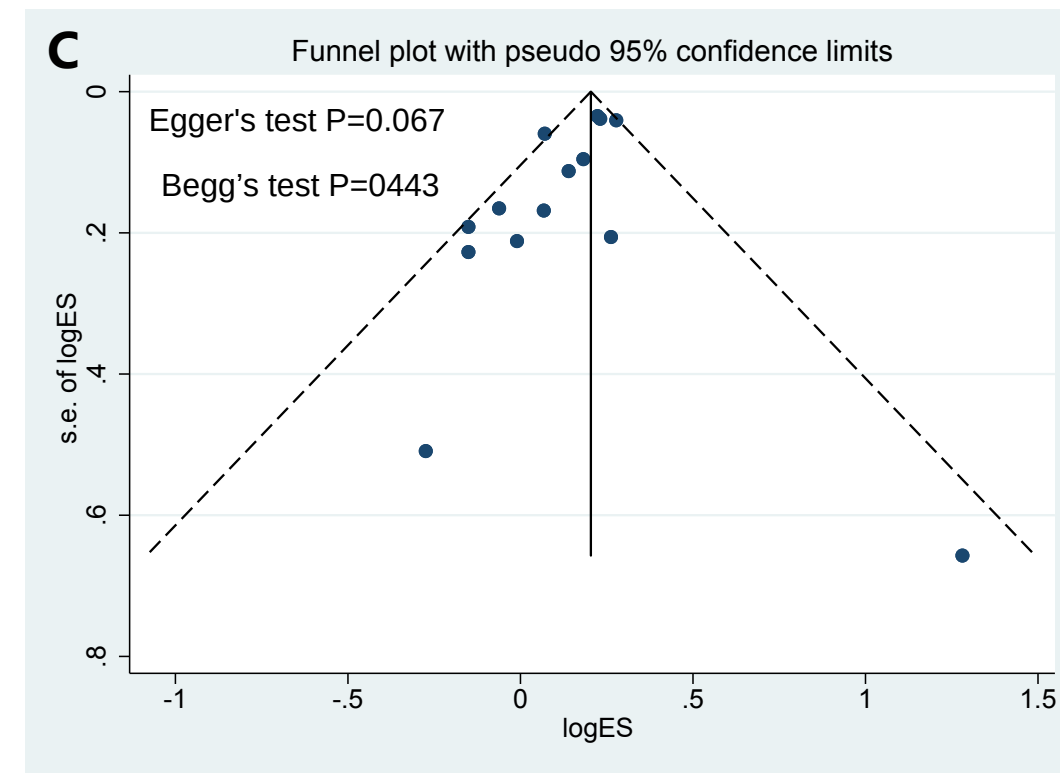
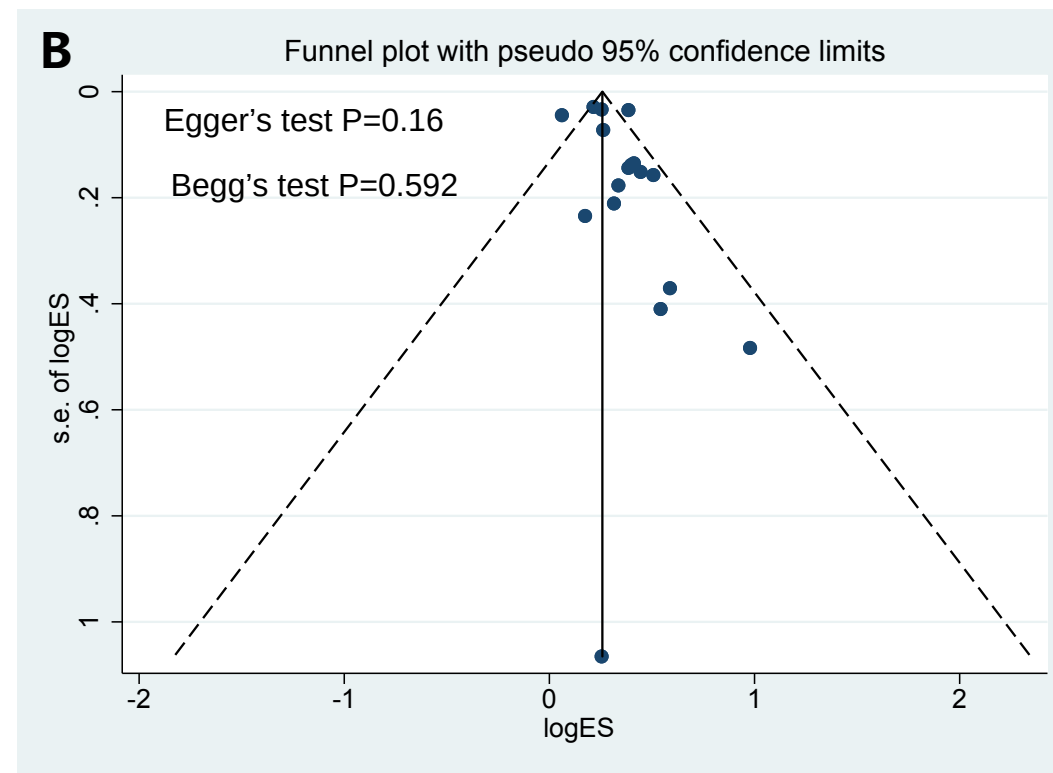
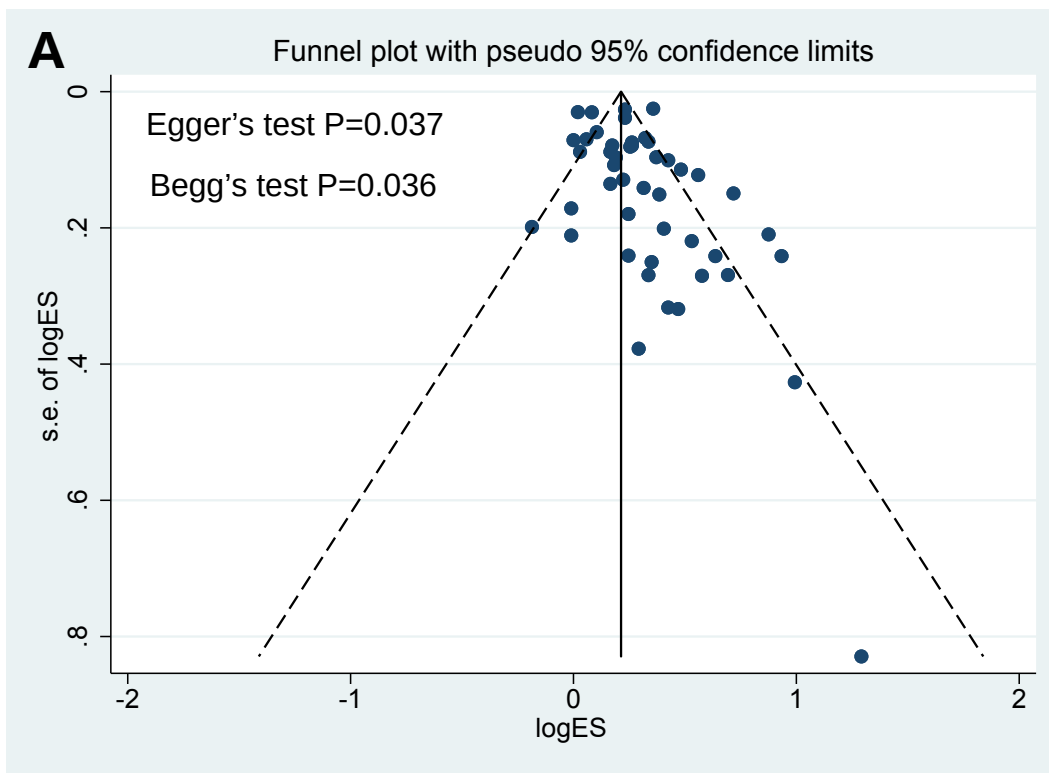
Subgroup	N	ES (95% CI)	$I^2(\%)$	P^1	P^2
Country					0.653
US	4	1.65 (0.89, 3.06)	84.7	<0.001	
UK	3	1.29 (1.13,1.47)	0.0	0.915	
Others	2	1.19 (1.06, 1.34)	18.0	0.269	
Follow-up duration					0.092
>5 years	6	1.19 (1.06, 1.34)	49.9	0.076	
≤5 years	3	2.16 (1.11, 4.21)	69.8	0.037	
Adjustment for education					0.637
Yes	5	1.32 (1.11, 1.56)	65.2	0.022	
No	4	1.25 (0.88, 1.76)	72.1	0.013	
Adjustment for smoking					0.261
Yes	5	1.17 (1.01, 1.37)	64.3	0.024	
No	4	1.55 (1.13, 2.13)	57.9	0.068	
Adjustment for drinking					0.666
Yes	4	1.20 (1.12, 1.29)	0.0	0.570	
No	5	1.51 (1.00, 2.28)	80.8	<0.001	

N denotes the number of studies. ES: effect size

Inconsistency- percentage of variation across studies due to heterogeneity

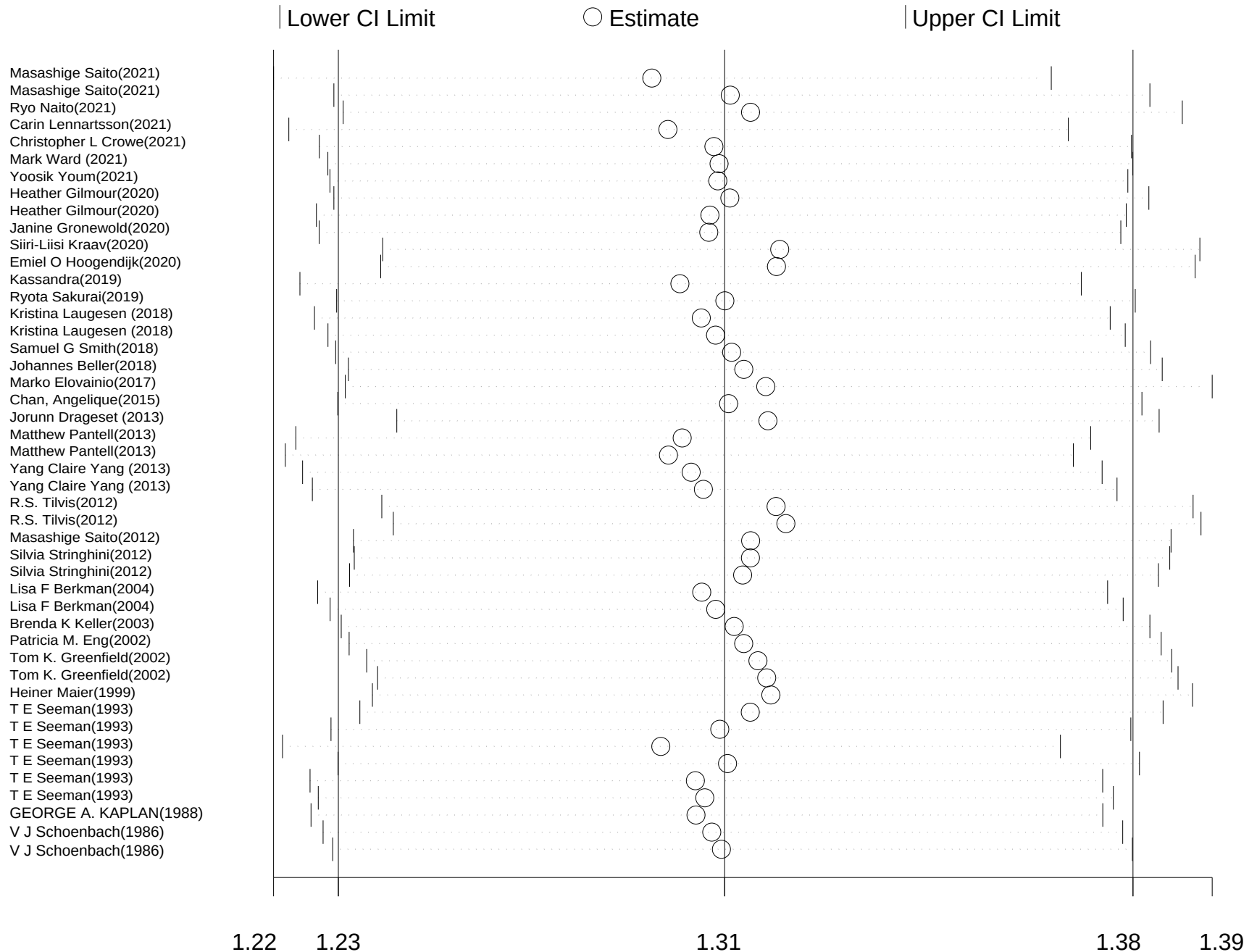
P^1 for heterogeneity within each subgroup

P^2 for heterogeneity between subgroups with meta-regression analysis

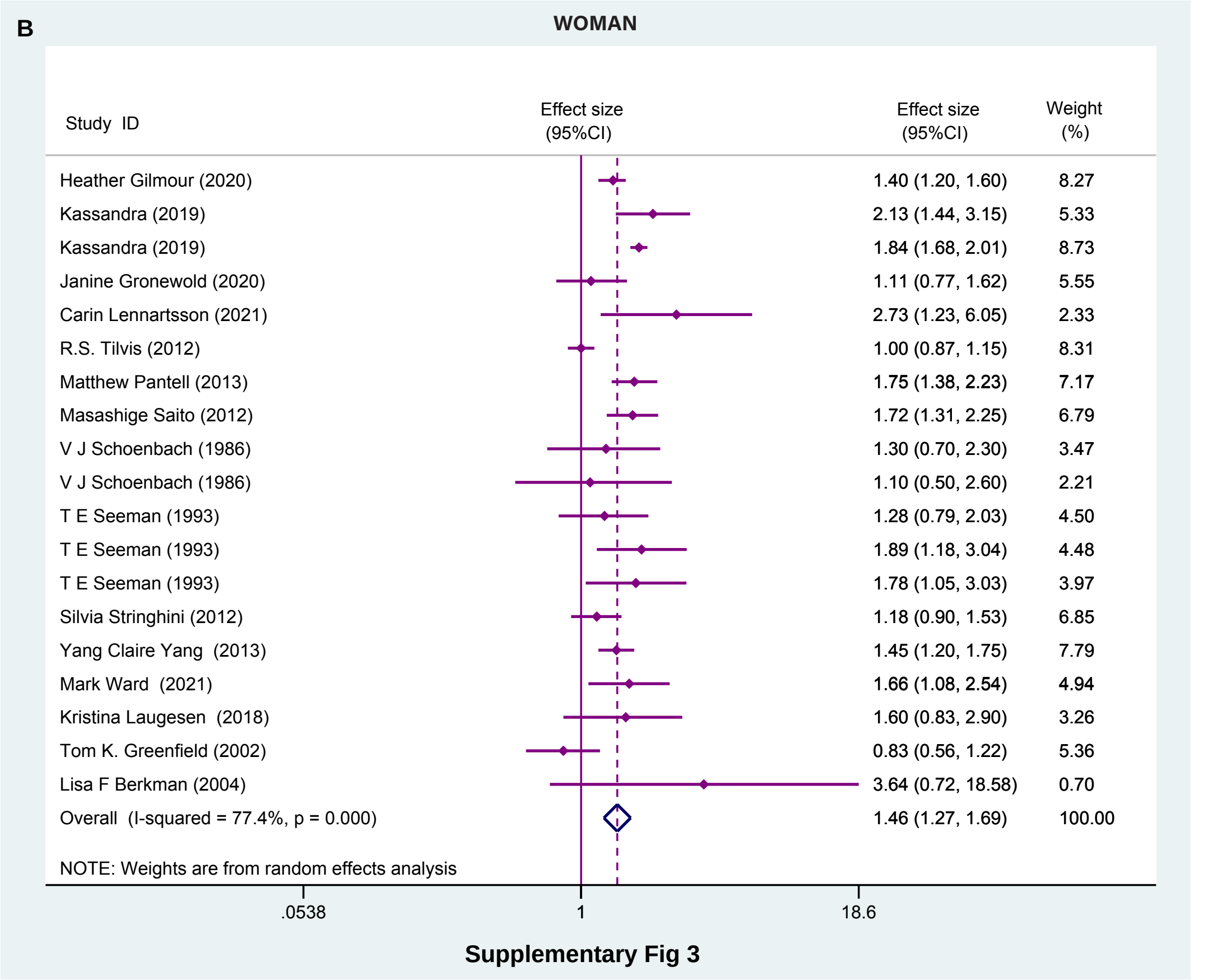
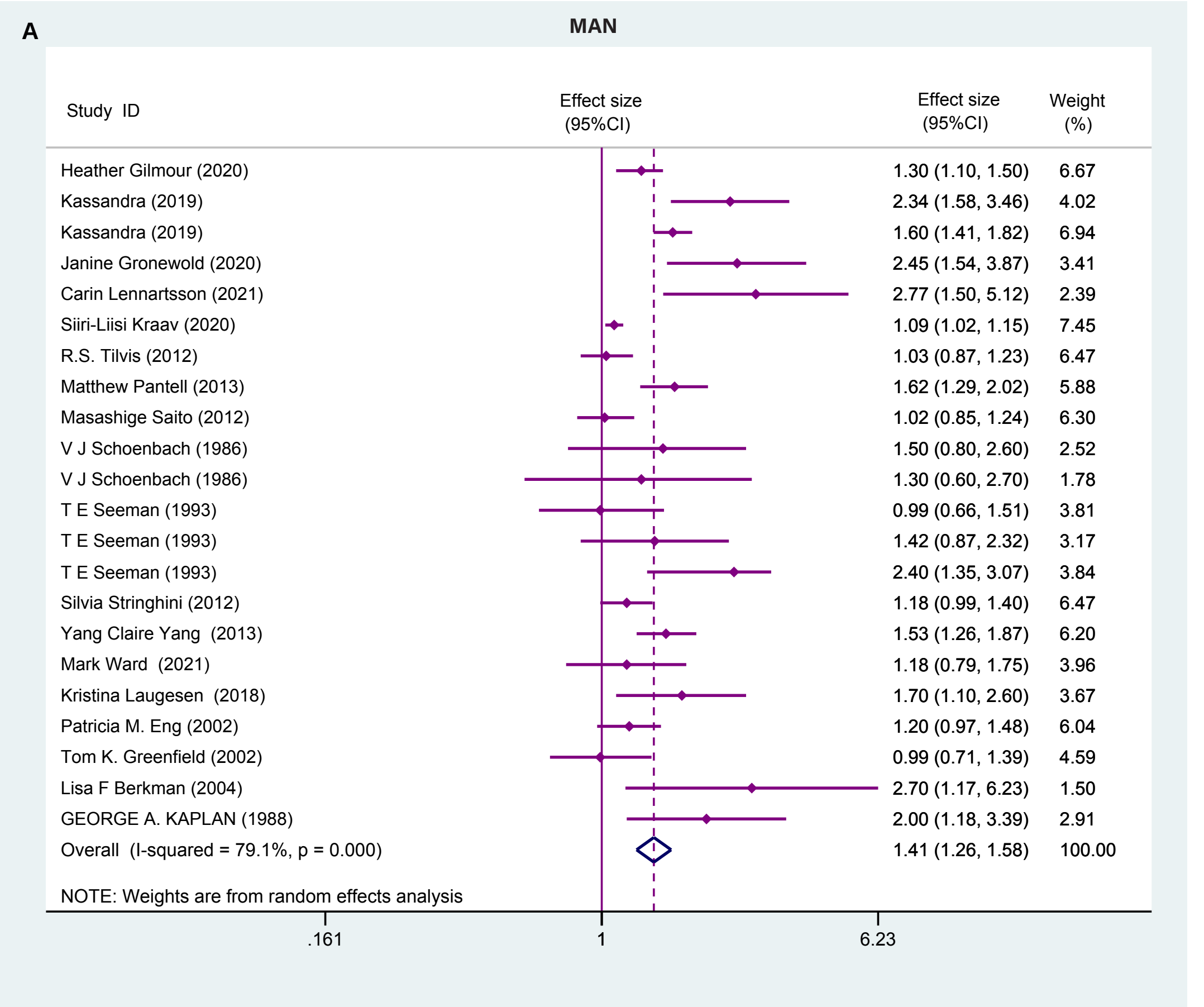


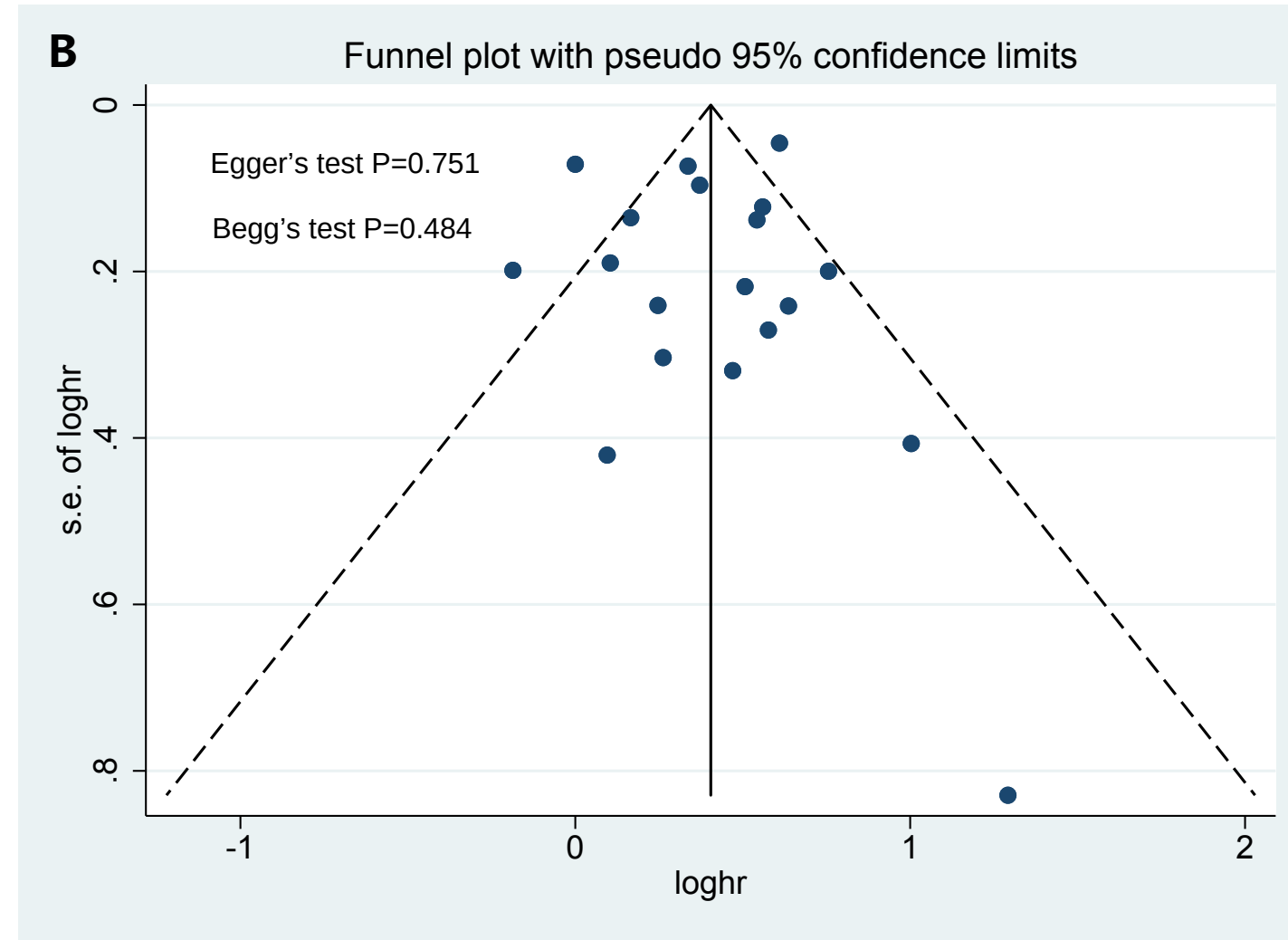
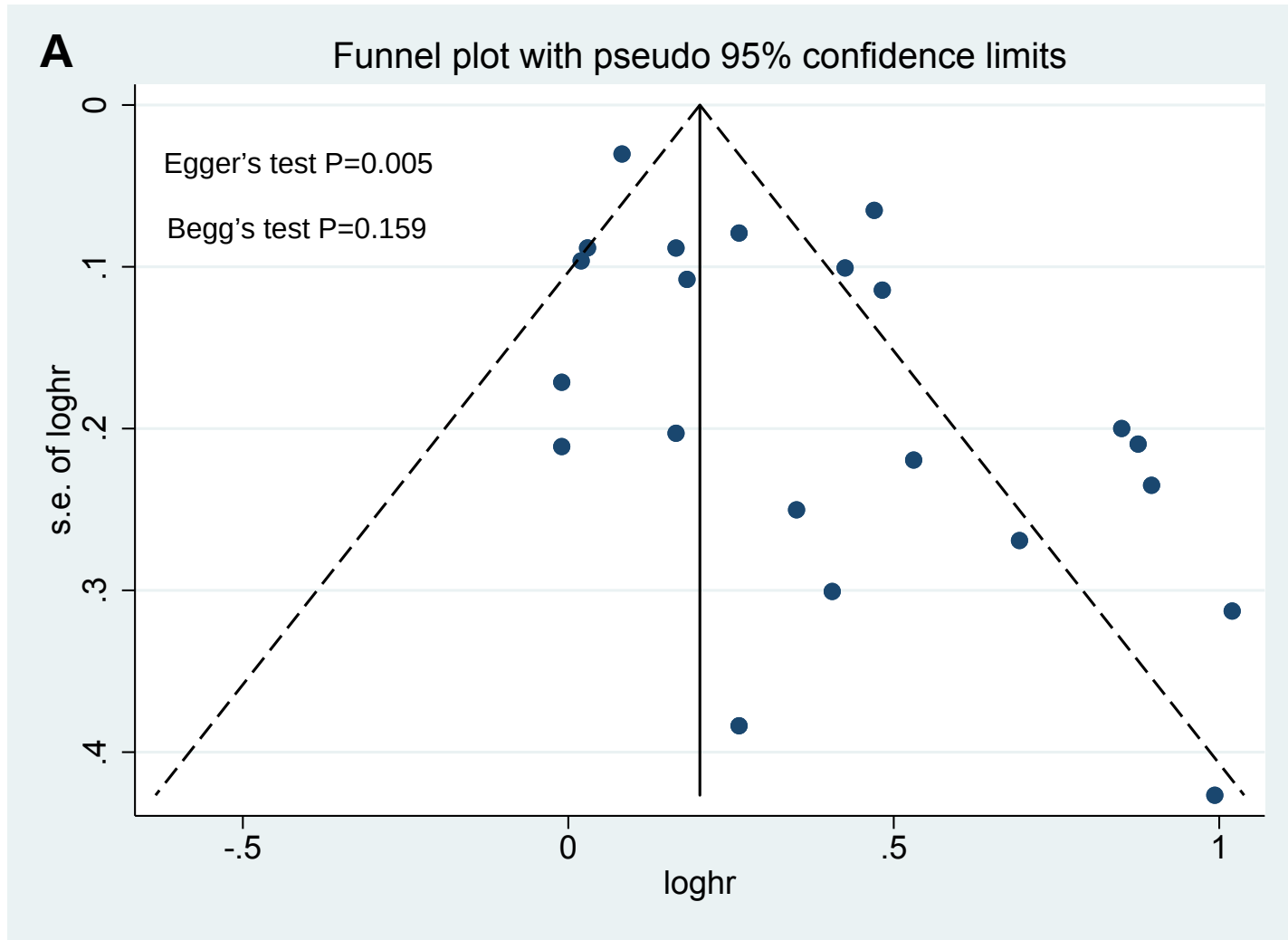
Supplementary Fig 1

Meta-analysis estimates,given named study is omitted



Supplementary Fig 2





Supplementary Fig 4