

A systematic review and meta-analysis of 90 cohort studies of social isolation, loneliness and mortality

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Supplementary Methods

1. Manual retrieval

After automatic retrieval, manual retrieval is carried out by the "snowball" method. Detailed descriptions are as follows: we looked in the database for studies related to the literature that had been retrieved (e.g. having the same keywords). We also traced potential missing studies through reviewing the reference list of literature that had been found.

2. Measurement methods used to assess social isolation or loneliness

Most studies adopted the Social Network Index (SNI), a measure of SI created by Berkman and Syme¹, to evaluate an individual's marital or partnership relationships, support from friends or family, and religious or other group participation. Interviews are conducted to assess these factors, and responses are combined into a SNI metric on a scale of 0 to 4 (0 being the highest level of isolation)^{2,3}. Other studies used a revised version of the SNI (with questions modified according to the cohort characteristics) as a measure of SI^{4,5}. Additionally, some studies used surveys to assess SI; for example, Sakurai et al.⁶ assessed SI via a widely used questionnaire^{7,8}. In the survey, respondents were asked about the frequency of both face-to-face and non-face-to-face interactions (e.g., telephone, e-mail, letters) with family members who did not live with them, relatives, friends, and neighbors. SI was defined as having contact with anyone less than once a week^{7,8}.

Most studies measured loneliness by asking participants whether they feel lonely⁹⁻¹¹ or how often they felt lonely¹²⁻¹⁴. This one item measure is strongly correlative with multi-item loneliness scales and has been used in a number of previous studies^{15,16}. In addition, there are two of the most widely used scales or their adaptations to assess loneliness--University of California, Los Angeles (UCLA) Loneliness Scale^{17,18} and De Jong Gierveld Loneliness Scale¹⁹. A detailed clarification of the measurements and the methods used in each study was shown in Table S4.

3. Risk of bias assessment

Because all eligible studies had a cohort study design, the Newcastle–Ottawa quality assessment scale for cohort studies was used to evaluate methodological quality²⁰. Using this scale, each study was judged on eight items, categorized into three groups: selection of the study groups; comparability of the groups; and how SI or loneliness was ascertained. A star was awarded for every quality item, with a maximum of nine stars for the highest quality studies. A study could be awarded a maximum of four stars for the selection category, a maximum of two stars for the comparability category, and a maximum of three stars for the outcome/exposure category. Table S10 presents results of the risk of bias assessment.

4. GRADE assessment

The certainty of the evidence was assessed by using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool²¹. This tool rates the evidence as high, moderate, low, or very low quality. Several prespecified criteria have been considered for downgrading or upgrading the evidence. The criteria used to downgrade the evidence include risk of bias (assessed by the Newcastle-Ottawa Scale), inconsistency ($I^2 > 50\%$ and cannot be explained by subgroup analyses), indirect (indirectness of participant and outcome that limit the generality of the results), imprecision (the sample size of each outcome cannot reach the optimal information size) and publication bias (visually asymmetric forest plots and P for Egger's or Begg's test $P < 0.05$). The criteria used to upgrade the certainty of the evidence include a large magnitude of association, a dose-response gradient, and attenuation by plausible confounding.

5. All deviations from the preregistered protocol

Social isolation and loneliness are distinct but related structures that reflect both objective and subjective aspects of social relationships. A growing number of studies have investigated the effects of both structures on morbidity and mortality. Therefore, we added a systematic review of the relationship between loneliness and mortality to the previous registry, which focused only on social isolation, and further discuss

separately the effects of loneliness and social isolation on mortality risk, as well as the potential combined effects of these two structures on mortality.

Reference:

- 1 Berkman, L. F. & Syme, S. L. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *American journal of epidemiology* **109**, 186-204, doi:10.1093/oxfordjournals.aje.a112674 (1979).
- 2 Koh-Bell, A., Chan, J., Mann, A. K. & Kapp, D. S. Social isolation, inflammation, and cancer mortality from the National Health and Nutrition Examination Survey - a study of 3,360 women. *BMC public health* **21**, 1289, doi:10.1186/s12889-021-11352-0 (2021).
- 3 Laugesen, K. *et al.* Social isolation and all-cause mortality: a population-based cohort study in Denmark. *Scientific reports* **8**, 4731, doi:10.1038/s41598-018-22963-w (2018).
- 4 Naito, R. *et al.* Impact of social isolation on mortality and morbidity in 20 high-income, middle-income and low-income countries in five continents. *BMJ global health* **6**, doi:10.1136/bmjgh-2020-004124 (2021).
- 5 Kroenke, C. H. *et al.* Postdiagnosis social networks and breast cancer mortality in the After Breast Cancer Pooling Project. *Cancer* **123**, 1228-1237, doi:10.1002/cncr.30440 (2017).
- 6 Sakurai, R. *et al.* Co-existence of social isolation and homebound status increase the risk of all-cause mortality. *International psychogeriatrics* **31**, 703-711, doi:10.1017/s1041610218001047 (2019).
- 7 Kobayashi, E. *et al.* [Social support availability and psychological well-being among the socially isolated elderly. Differences by living arrangement and gender]. [*Nihon koshu eisei zasshi*] *Japanese journal of public health* **58**, 446-456 (2011).
- 8 Saito, M., Kondo, K., Ojima, T. & Hirai, H. [Criteria for social isolation based on associations with health indicators among older people. A 10-year follow-up of the Aichi Gerontological Evaluation Study]. [*Nihon koshu eisei zasshi*] *Japanese journal of public health* **62**, 95-105, doi:10.11236/jph.62.3_95 (2015).
- 9 Gao, Q. *et al.* Loneliness Among Older Adults in Latin America, China, and India: Prevalence, Correlates and Association With Mortality. *International journal of public health* **66**, 604449, doi:10.3389/ijph.2021.604449 (2021).
- 10 Novak, M. *et al.* Cardiovascular and all-cause mortality attributable to loneliness in older Swedish men and women. *BMC geriatrics* **20**, 201, doi:10.1186/s12877-020-01603-x (2020).
- 11 Henriksen, J., Larsen, E. R., Mattisson, C. & Andersson, N. W. Loneliness, health and mortality. *Epidemiology and psychiatric sciences* **28**, 234-239, doi:10.1017/s2045796017000580 (2019).
- 12 Yu, B., Steptoe, A. & Chen, Y. Social isolation, loneliness, and all-cause mortality: A cohort study of 35,254 Chinese older adults. *Journal of the American Geriatrics Society* **70**, 1717-1725, doi:10.1111/jgs.17708 (2022).
- 13 Tabue Teguio, M. *et al.* Feelings of Loneliness and Living Alone as Predictors of Mortality in the Elderly: The PAQUID Study. *Psychosomatic medicine* **78**, 904-909, doi:10.1097/psy.0000000000000386 (2016).
- 14 Stessman, J., Rottenberg, Y., Shimshilashvili, I., Ein-Mor, E. & Jacobs, J. M. Loneliness,

- health, and longevity. *The journals of gerontology. Series A, Biological sciences and medical sciences* **69**, 744-750, doi:10.1093/gerona/glt147 (2014).
- 15 Luo, Y. & Waite, L. J. Loneliness and mortality among older adults in China. *The journals of gerontology. Series B, Psychological sciences and social sciences* **69**, 633-645, doi:10.1093/geronb/gbu007 (2014).
- 16 Holwerda, T. J. *et al.* Feelings of loneliness, but not social isolation, predict dementia onset: results from the Amsterdam Study of the Elderly (AMSTEL). *Journal of neurology, neurosurgery, and psychiatry* **85**, 135-142, doi:10.1136/jnnp-2012-302755 (2014).
- 17 Hughes, M. E., Waite, L. J., Hawkey, L. C. & Cacioppo, J. T. A Short Scale for Measuring Loneliness in Large Surveys: Results From Two Population-Based Studies. *Res Aging* **26**, 655-672, doi:10.1177/0164027504268574 (2004).
- 18 Russell, D., Cutrona, C. E., Rose, J. & Yurko, K. Social and emotional loneliness: an examination of Weiss's typology of loneliness. *Journal of personality and social psychology* **46**, 1313-1321, doi:10.1037//0022-3514.46.6.1313 (1984).
- 19 de Jong-Gierveld, J. Developing and testing a model of loneliness. *Journal of personality and social psychology* **53**, 119-128, doi:10.1037//0022-3514.53.1.119 (1987).
- 20 Stang, A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European journal of epidemiology* **25**, 603-605, doi:10.1007/s10654-010-9491-z (2010).
- 21 Guyatt, G. H. *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj* **336**, 924-926, doi:10.1136/bmj.39489.470347.AD (2008).

Supplementary Table 1
MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	Introduction, paragraphs 1-2
2	Hypothesis statement	Introduction, paragraphs 3
3	Description of study outcome(s)	Introduction, paragraphs 3
4	Type of exposure or intervention used	Introduction, paragraphs 2
5	Type of study designs used	Introduction, paragraphs 3
6	Study population	Introduction, paragraphs 3
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Methods, paragraph 2
8	Search strategy, including time period included in the synthesis and key words	Methods, paragraph 2, Table S3
9	Effort to include all available studies, including contact with authors	Methods, paragraph 3
10	Databases and registries searched	Methods, paragraph 2
11	Search software used, name and version, including special features used (eg, explosion)	Methods, paragraph 2
12	Use of hand searching (eg, reference lists of obtained articles)	Supplementary methods
13	List of citations located and those excluded, including justification	Results, paragraph 1, Figure 1
14	Method of addressing articles published in languages other than English	Not included
15	Method of handling abstracts and unpublished studies	Methods, paragraph 3
16	Description of any contact with authors	Not described
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Methods, paragraph 5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Methods, paragraph 3, 5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	Methods, paragraph 5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Methods, paragraph 5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Methods, paragraph 6, 7
22	Assessment of heterogeneity	Methods, paragraph 6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Methods, paragraph 6

Item No	Recommendation	Reported on Page No
24	Provision of appropriate tables and graphics	Throughout
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures 2-4, Figures S2, S7, S8, Table S11
26	Table giving descriptive information for each study included	Tables S5-S9
27	Results of sensitivity testing (eg, subgroup analysis)	Results, paragraphs 7-9, Figure S4, Tables S12-13, S15-16
28	Indication of statistical uncertainty of findings	Results, paragraphs 5-12
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Discussion, paragraph 9
30	Justification for exclusion (eg, exclusion of non-English language citations)	Not mentioned
31	Assessment of quality of included studies	Discussion, paragraph 9
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	Discussion, paragraph 2-7
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Discussion, paragraph 1
34	Guidelines for future research	Discussion, paragraph 10
35	Disclosure of funding source	Mention in the abstract

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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PRISMA 2020 Checklist

Supplementary Table 2 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
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P3-4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P13
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.	P13
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P13, Table S3
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.	P14
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.	P14
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.	P14
	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.	P14
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.	P15, Table S10
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.	P14
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)).	P14
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P14
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P14
	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.	P14
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P14
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P14
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P14
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P14
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.	P4, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P4, Figure 1



PRISMA 2020 Checklist

Supplementary Table 2 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.	P4-5, Tables S5-S9
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	P5, Tables S10
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.	Figures 2-4, S2, S7, S8, Table S11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P5-7, Figures S1, S3, S5, S6
	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.	P5-7, Figures 2-4, S2, S7, S8, Table S11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P5-7, Tables S12-13, S15-16
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	P5 and Figure S4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	P5-7, Figures S1, S3, S5, S6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	P5-7
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P8-11
	23b	Discuss any limitations of the evidence included in the review.	P12
	23c	Discuss any limitations of the review processes used.	P12
	23d	Discuss implications of the results for practice, policy, and future research.	P12-13
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.	P14
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P14
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplementary methods
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P2
Competing interests	26	Declare any competing interests of review authors.	P16
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 S5-S9

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 2 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 3

A systematic review and meta-analysis of 90 cohort studies of social isolation, loneliness and mortality

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]) OR (Lonely[MeSH Terms]) OR (Loneliness[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]) OR (Lonely[Text Word]) OR (Loneliness[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)
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)) OR TS=(lonely)) OR TS=(loneliness)
#2	((TS=(mortality*)) OR TS=(death*)) OR TS=(fatal*)
#3	(#1) AND #2
Search strategy for Embase	
#1	'social segregation'/exp OR 'social network index'/exp OR 'social isolation'/exp OR lonely OR 'loneliness'/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 OR 'lonely':ab,ti OR '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

Supplementary Table 4
Measurement methods used to assess social isolation or loneliness

Evaluation of SI¹	Description
Social Isolation Index ¹⁻³	(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 ⁴	(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 ⁵⁻¹¹	(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 ¹²⁻³³	(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 ³⁴	(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 ³⁵	(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 ³⁶⁻³⁸	(1) marital status/cohabitation (2) contacts with close friends/family (3) affiliation with voluntary associations
Combining Information on Partner Status,	(1) no partner

Social Support, and Network Size ³⁹	(2) no social support (3) having a small network size
Questionnaire ⁴⁰	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 ⁴¹	(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 ⁴²	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 ⁴³	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. Social loneliness as social integration
Two Items ⁴⁴	(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 ⁴⁵	meet their children, grandchildren, siblings, relatives or friends less often than once a week (six questions)
Four Measures of Social Ties ⁴⁶	(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 Items ⁴⁷⁻⁴⁹	(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 ⁵⁰	not seeing friends or family members at least once a month
Two Questions ⁵¹	(1) on the frequency of contacts with relatives, friends, and colleagues and the frequency of participation in social or religious activities (2) on the total number of relatives or friends seen once a month or more.
The ABCPP Social Network Index ⁵²	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 ⁵³	(1) You feel that the disease makes it difficult to visit family and friends (2) You feel that the disease makes its 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 Information System(PROMIS) Social Isolation Short Form ⁵⁴	(1) I feel left out (2) I feel that people barely know me (3) I feel isolated from others (4) I feel that people are around me but not with me
lubben social network scale (LSNS-6) ⁵⁵⁻⁵⁷	It comprises six items on social connections (three questions on family ties and three questions on friendship ties). One sample question includes, “How many relatives do you see or hear from at least once a month?”
Evaluation of loneliness²	Description
Feeling of loneliness (1-item)* ^{1,3,8,11,34,45,48,49,58-75}	Such as: (1) How often do you feel onely? (2) Feeling of loneliness in the last 7 days (3) Are you ever bothered by feelings of loneliness? (4) Do you feel lonely? (5) Do you suffer from loneliness? (6) Are you lonely during the day?
An adapted German version of De Jong Gierveld Loneliness Scale (6-items) ^{41,76}	(1) I experience a general sense of emptiness (2) There are plenty of people I can rely on when I have problems (3) There are many people I can trust completely (4) There are enough people I feel close to (5) I miss having people around (6) I often feel rejected
Revised University of California, Los Angeles (3-items) ^{4,23,35,55,77-82}	(1) left out (2) lack of companionship (3) isolated from others
The De Jong Gierveld Loneliness Scale (11-items) ^{10,39,83-88}	(1) There is always someone I can talk to about my day-to-day problems (2) I miss having a really close friend (3) I experience a general sense of emptiness (4) There are plenty of people I can rely on when I have problems (5) I miss the pleasure of the company of others (6) I find my circle of friends and acquaintances too limited (7) There are many people I can trust completely (8) There are enough people I feel close to (9) I miss having people around (10) I often feel rejected

	(11) I can call on my friends whenever I need them
The revised University of California, Los Angeles (UCLA) Loneliness Scale(8 items) ^{13,42,89,90}	(1) I do not feel alone (2) I lack companionship (3) There are people I feel close to (4) I feel isolated (5) There are people I can turn to (6) I feel left out (7) I feel part of a group of friends (8) There are people I can talk to
The revised Social Provisions Scale (SPS) ⁴³	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. Emotional loneliness is operationalized as attachment

¹Social 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 alone⁹¹. But at present, there is no unified international standard to evaluate it.

²Loneliness is a subjective, common and painful feeling that arises from an inadequate assessment of one's social connections⁹². There are two of the most widely used scales for assessing loneliness -- UCLA Loneliness Scale and De Jong Gierveld Loneliness Scale.

*Many studies ask respondents a question about how often they feel lonely. Although there have been some concerns that self-report of an undesirable emotional state with a single item may lead to underestimates of the true prevalence of loneliness, this single-question measure has been widely used and has been reported to have good face and predictive validity.

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Supplementary Table 5

Characteristics of included studies for the association between social isolation and mortality

First author	Year	Country	Sample size	Age* (years)	Follow-up†	Exposure assessment	Events for analysis	Effect Size HR/RR (95% CI)	Adjustment ¶
Bin Yu	2022	China	Male 15486 Female 19768	86.63 (11.39)	4.8 y	five items	All-cause mortality	HR 1.22 (1.18 to 1.25) Male HR 1.19 (1.14 to 1.23) Female HR 1.27 (1.22 to 1.33)	1, 2, 4, 6, 17, 18, 23, 24, 30, 33, 40, 44
Karla Moreno-Ta mayo	2022	Mexico	6393	64.5 (9.3)	12 y	five items	All-cause mortality	HR 1.24 (1.10 to 1.38)	1, 2, 4, 15, 18, 23, 25, 30, 32, 44, 76, 77, 78, 79, 80, 81, 82
Timothy L Barnes	2022	USA	Male 3533 Female 4449	>65	3 y	social network index	All-cause mortality	HR 2.47 (1.91 to 3.18)	1, 2, 4, 27, 30, 83, 84
Juhua Luo	2022	USA	Male 7050 Female 7950	46.3 (19.5)	19.6 y	social network index	All-cause mortality; CVD mortality; Cancer mortality	All-cause mortality HR 1.33 (1.15 to 1.54) CVD mortality HR 1.28 (1.01 to 1.62) Cancer mortality HR 1.02 (0.73 to 1.41)	1, 2, 3, 4, 6, 19

Jelena Kornej	2022	USA	Male 1461 Female 1993	67.4 (9.8)	11.8 y	social network index	All-cause mortality	HR 1.62 (1.14 to 2.29)	1, 2, 10, 18, 37, 41, 45, 85, 86
Yuka Kotozaki	2022	Japan	Male 8059 Female 14874	58.8 (11.8)	5.04 y	lubben social network scale (LSNS-6)	All-cause mortality	Male HR 1.38 (1.04 to 1.83) Female HR 1.49 (1.02 to 2.19)	1, 4, 5, 15, 18, 19, 23, 24, 30, 34, 87, 88, 89, 90, 91, 92
Hyunsuk Jeong	2022	Korea	Male 320 Female 713	>60	2 y	lubben social network scale (LSNS-6)	All-cause mortality	Male HR 4.5 (1.9 to 9.9) Female HR 1.2 (0.5 to 2.8)	1, 4, 15, 37, 38, 93
Masashige Saito	2021	Japan	15313	≥65	10 y	social isolation scale	All-cause mortality	HR 1.30 (1.12 to 1.50)	1, 2, 5, 27, 30, 31, 32
Masashige Saito	2021	UK	5124	≥50	10 y	social isolation scale	All-cause mortality	HR 2.05 (1.52 to 2.73)	1, 2, 5, 6, 27, 30, 31, 32, 33, 34
Carin Lennartsson	2021	Sweden	Male 475 Female 686	≥69	5 y	social isolation index	All-cause mortality	HR 2.544 (1.585 to 4.084) Male HR 2.773 (1.502 to 5.119) Female HR 2.727 (1.229 to 6.053)	1, 2, 4, 33, 39, 40, 41
Ryo Naito	2021	20 countries in five	118764	35–70	9 y	social network index	All-cause mortality; CVD mortality	All-cause mortality HR 1.26 (1.17 to 1.36)	1, 2, 4, 10, 11, 15, 18, 23, 24, 30, 35, 36, 37, 38

continents							CVD mortality		
								HR 1.30 (1.13 to 1.50)	
Mark Ward	2021	Ireland	6915	≥50	7 y	social network index	All-cause mortality;	All-cause mortality	2, 4, 15, 18, 24, 30, 41,
							Circulatory system diseases mortality;	HR 1.43 (1.09 to 1.87)	44, 64, 65, 66
							Cancer mortality	Male HR 1.18 (0.79 to 1.75)	
								Female HR 1.66 (1.08 to 2.54)	
								Circulatory system diseases mortality	
								HR 1.19 (0.75 to 1.88)	
								Cancer mortality	
								HR 1.18 (0.82 to 1.69)	
Yoosik Youm	2021	Korean	Male 289	≥60	5.61 y	the levels of participation in seven different social activities	All-cause mortality	HR 1.53 (0.82 to 2.84)	2, 4, 15, 17, 18, 24, 25, 27, 29, 50
			Female 390						
Christopher L Crowe	2021	US	11302	50 - 95	8 y	a six-item scale	All-cause mortality	HR 1.38 (1.21 to 1.58)	1, 2, 6, 42, 43
Laura C Pinheiro	2021	US	29766	≥45	10.6 y	one question	Cancer mortality	HR 1.20 (0.99 to 1.44)	1, 2

Alexander Koh-Bell	2021	US	Female 3360	≥40	6y	social network index	Cancer mortality	Female HR 0.76 (0.28 to 2.06)	4, 6, 18, 19, 24, 27, 33, 38, 69, 71, 95, 96, 97
Janine Gronewold	2020	Germany	Male 1934	45–75	13.4 y	social integration index	All-cause mortality	HR 1.47 (1.09 to 1.97) Male HR 2.45 (1.54 to 3.87) Female HR 1.11 (0.77 to 1.62)	1, 2
Emiel O Hoogendijk	2020	Netherlands	1333	≥65	22 y	combining information on partner status, social support, and network size	All-cause mortality	HR 1.06 (0.92 to 1.21)	1, 2, 4, 15, 18, 44
Heather Gilmour	2020	Canada	Male 5,408	≥65	8-9 y	eight community-related activities	All-cause mortality	Male HR 1.3 (1.1 to 1.5) Female HR 1.4 (1.2 to 1.6)	1, 4, 5, 18, 30, 68, 69
Siiri-Liisi Kraav	2020	Finland	Male 2588	42–61	23.2 y	social isolation scale	All-cause mortality; CVD mortality; Cancer mortality	All-cause mortality HR 1.086 (1.024 to 1.153) CVD mortality HR 1.063 (0.974 to 1.159)	1, 15, 18, 19, 24, 36, 41, 45, 54, 69, 70, 71, 72

Kassandra I. Alcaraz	2019	US	Male 245554	≥30	15 y	social network index	All-cause mortality;	Cancer mortality	1, 2, 4, 6, 10, 18, 19
								HR 1.073 (0.955 to 1.206)	
								All-cause mortality	
								HR 1.43 (1.36 to 1.50)	
			Female 334628				CVD mortality;	Black Male HR 2.34 (1.58 to 3.46)	
								White Male HR 1.60 (1.41 to 1.82)	
								Black Female HR 2.13 (1.44 to 3.15)	
								White Female HR 1.84 (1.68 to 2.01)	
							Cancer mortality	CVD mortality	
								Black Male HR 1.51 (1.16 to 1.97)	
								White Male HR 1.29 (1.21 to 1.38)	
								Black Female HR 1.49 (1.14 to 1.96)	
								White Female HR 1.47 (1.37 to 1.57)	
								Cancer mortality	
								Black Male HR 1.07 (0.77 to 1.49)	
								White Male HR 1.25 (1.17 to 1.34)	

Black Female HR 0.94 (0.68 to 1.30)

White Female HR 1.26 (1.17 to 1.36)

Ryota Sakurai	2019	Japan	Male 417 Female 606	≥65	6 y	questionnaire	All-cause mortality	HR 1.34 (0.64 to 2.81)	1, 2, 4, 15, 27, 28, 29, 30
Samuel G Smith	2018	UK	Male 3007 Female 3763	≥50	7.7 y	social isolation index	All-cause mortality	HR 1.29 (1.10 to 1.51)	1, 2, 3, 4, 6, 7, 9, 10, 11, 12, 14, 15, 18, 20, 21, 22, 23, 24, 25, 26
Johannes Beller	2018	Germany	4838	≥40	20.83 y	social isolation score	All-cause mortality	HR 1.21 (1.00 to 1.46)	1, 2, 4, 5, 17, 44
Kristina Laugesen	2018	Denmark	Male 10119 Female 11485	25-79	7 y	social network index	All-cause mortality	Male RR 1.7 (1.1 to 2.6) Female RR 1.6 (0.83 to 2.9)	1, 4, 18, 19, 23, 24, 27, 28, 33, 74, 75
Marko Elovainio	2017	UK	Male 254919 Female 211982	40 - 69	6.5 y	social isolation scale	All-cause mortality; Circulatory system diseases mortality Cancer mortality	All-cause mortality HR 1.26 (1.20 to 1.33) Circulatory system diseases mortality HR 1.24 (1.17 to 1.31)	1, 2, 3, 4, 6, 15, 18, 19, 24, 25, 27, 32, 33, 44, 45, 46

								Cancer mortality	HR 1.32 (1.22 to 1.43)	
Andrea Fleisch Marcus	2017	US	Male 6989 Female 8146	≥18	23 y	social network index	Cancer mortality	HR 1.15 (0.92 to 1.43)		1, 2, 4, 6, 98
								Male HR 1.13 (0.85 to 1.50)		
								Female HR 1.23 (0.87 to 1.73)		
Chan, Angelique	2015	Singapore	4522	≥60	1,459 d	social network scale	All-cause mortality	HR 1.28 (0.90 to 1.82)		1, 2, 4, 5, 6, 15, 18, 25, 32, 67
Yang Claire Yang	2013	US	Male 3082 Female 3647	≥40	18 y	social network index	All-cause mortality; Circulatory system diseases mortality Cancer mortality	All-cause mortality Male HR 1.53 (1.26 to 1.87) Female HR 1.45 (1.20 to 1.75) Circulatory system diseases mortality Male HR 1.56 (1.16 to 2.10) Female HR 1.47 (1.11 to 1.95) Cancer mortality Male HR 1.30 (0.87 to 1.95) Female HR 0.86 (0.55 to 1.34)		1, 4, 6, 18, 19, 24, 27, 33, 44, 62
Jorunn Drageset	2013	Norway	Male 63 Female	≥65	5 y	social provisions scale	All-cause mortality	HR 1.02 (0.96 to 1.08)		1, 2, 4, 5, 15, 49, 50, 51, 52, 53

			164						
Matthew Pantell	2013	US	Male 7875	25-89,	14.1 y	social network index	All-cause mortality	Male HR 1.62 (1.29 to 2.02)	1, 4, 6, 27, 68, 73
			Female 8974	> 89				Female HR 1.75 (1.38 to 2.23)	
Masashige Saito	2012	Japan	Male 6508	≥65	4 y	two items	All-cause mortality	HR 1.19 (1.02 to 1.39)	1, 4, 5, 30, 38
			Female 6802					Male HR 1.02 (0.85 to 1.24)	
								Female HR 1.72 (1.31 to 2.25)	
R.S. Tilvis	2012	Finland	Male 1187	> 75	7 y	six questions	All-cause mortality	Male HR 1.03 (0.87 to 1.23)	1
			Female 2671					Female HR 1.00 (0.87 to 1.15)	
Silvia Stringhini	2012	UK	Male 6339	35–55	24.4 y	two questions	All-cause mortality;	All-cause mortality	1, 4, 20, 27, 33
			Female 2994				CVD mortality	Male HR 1.18 (0.99 to 1.40)	
								Female HR 1.18 (0.90 to 1.53)	
								CVD mortality	
								Male HR 1.66 (1.22 to 2.26)	
								Female HR 1.4 (0.77 to 1.54)	
Kathi L.	2011	US	327	≥40	15 y	social integration	Coronary heart	RR 2.66 (1.03 to 6.85)	1, 2, 71, 94

Heffner						index	disease mortality		
Lisa F Berkman	2004	French	Male 12347	Male 40-50	8 y	social integration index	All-cause mortality; CVD mortality; Cancer mortality	All-cause mortality Male RR 2.70 (1.17 to 6.23) Female RR 3.64 (0.72 to 18.58) CVD mortality Male RR 1.29 (0.16 to 10.41) Cancer mortality Male RR 3.60 (0.99 to 13.01)	1, 15, 18, 19, 20, 24, 30, 33
Brenda K Keller	2003	US	Male 370 Female 900	49-97	10 y	social network index	All-cause mortality	HR 1.25 (0.97 to 1.61)	1, 4, 27, 32, 47, 48
Patricia M. Eng	2002	US	Male 28369	42-77	10 y	social network index	All-cause mortality; CVD mortality Cancer mortality	All-cause mortality Male RR 1.20 (0.97 to 1.48) CVD mortality Male RR 1.37 (0.91 to 2.08) Cancer mortality Male RR 0.86 (0.59 to 1.25)	1, 8, 10, 13, 16, 18, 19, 20, 24, 37, 41, 54, 69

Tom K. Greenfield	2002	US	Male 2031 Female 3062	≥18	11 y	social isolation scale	All-cause mortality	Male RR 0.99 (0.71 to 1.39) Female RR 0.83 (0.56 to 1.22)	1, 5, 6, 17, 18, 24, 27
Heiner Maier	1999	Germany	Male 257 Female 256	70-103	6 y	loneliness scale	All-cause mortality	RR 1.11(0.99-1.25)	unadjusted
T E Seeman	1993	US	Male 1431 Female 2330	≥65	5 y	four measures of social ties	All-cause mortality	Male HR 0.99 (0.66 to 1.51) Female HR 1.28 (0.79 to 2.03)	1, 18, 19, 25, 38, 41, 44, 69
T E Seeman	1993	US	Male 1150 Female 1936	≥65	5 y	four measures of social ties	All-cause mortality	Male HR 1.42 (0.87 to 2.32) Female HR 1.89 (1.18 to 3.04)	1, 18, 19, 25, 38, 41, 44, 69
T E Seeman	1993	US	Male 1150 Female 1618	≥65	5 y	four measures of social ties	All-cause mortality	Male HR 2.40 (1.35 to 3.07) Female HR 1.78 (1.05 to 3.03)	1, 18, 19, 25, 38, 41, 44, 69
GEORGE A. KAPLAN	1988	Finland	13301	39-59	5 y	five items	CVD mortality	Male RR 1.8 (0.87 to 3.72)	1, 4, 18, 19, 30, 33, 45, 54, 95

GEORGE A. KAPLAN	1988	Finland	13301	39-59	5 y	five items	Ischemic heart disease mortality	Male RR 1.72 (0.77 to 3.84)	1, 4, 18, 19, 30, 33, 45, 54, 95
GEORGE A. KAPLAN	1988	Finland	13301	39-59	5 y	five items	All-cause mortality	Male RR 2.00 (1.18 to 3.39)	1, 4, 18, 19, 30, 41, 45, 54
V J Schoenbach	1986	US	2059	54.1	12 y	social network index	All-cause mortality	White HR 1.5 (1.0 to 2.2) Black HR 1.4 (0.8 to 2.3) White Male HR 1.5 (0.8 to 2.6) White Female HR 1.3 (0.7 to 2.3) Black Male HR 1.3 (0.6 to 2.7) Black Female HR 1.1 (0.5 to 2.6)	1, 10, 18, 41, 42, 45, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63

HR=hazard ratio; RR=relative risk; 95%CI=95%Confidence interval; M= Male; F=Female; CVD= Cardiovascular disease mortality

*Presented as mean or range.

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

‡Adjustments: age (1), sex (2), wealth (3), education (4), marital status (5), ethnicity (6), long-standing illness (7), time period (8), cancer (9), diabetes (10), coronary heart disease (CHD) (11), chronic lung disease (12), intakes of total fat, saturated fat, folate, and fiber (13), stroke (14), diagnosed depression (15), multivitamin and vitamin E supplement use (16), loneliness (17), smoking status (18), body mass index (19), occupational class (20), functional impairment (21), asthma (22), exercise (23), drinking (24), cognitive function (25), health literacy (26), income level (27), comorbidities (28), subjective health (29), residential areas (30), presence of medical treatment (31), basic activities of daily living (ADL) (32), self-rated health (33), household size

(34), country income (LIC, MIC or HIC) (35), diet score (36), hypertension (37), disabilities (38), mobility limitations (39), psychological distress (40), problems related to cardiovascular diseases (41), age-squared (42), age-sex interactions (43), chronic disease (44), diastolic and systolic blood pressure (45), handgrip strength (46), cumulative illness rating scale (CIRS) (47), informal service use (48), length of stay (49), comorbidity (50), attachment (51), reassurance of worth (52), nurturance (53), serum cholesterol (54), serum cholesterol squared (55), Electrocardiographic abnormality (56), electrocardiographic abnormality (57), quetelet index (58), quetelet index squared (59), social class (60), social class squared (61), off-job physical activity (62), off-job physical activity squared (63), walk minutes (64), obese (65), polypharmacy (66), housing type (67), health status (68), physical activity (69), hours slept at night (70), High-sensitivity C-reactive protein (hs-CRP) (71), low-density lipoprotein cholesterol (72), clinical risk factor (73), past or present use of antidepressants (74), past or present use of strong analgesics (75), age $\times$ time (76), sex $\times$ time (77), health insurance (78), health insurance $\times$ time (79), difficulties in ADL $\times$ time (80), difficulties in IADL (81), difficulties in IADL $\times$ time (82), Hierarchical Condition Category (HCC) score (83), Charlson Comorbidity Index (CCI) (84), height (85), weight (86), working status (87), medical history (88), Athens insomnia scale (89), social capital (90), house damage due to the Great East Japan Earthquake (91), death of family members due to the Great East Japan Earthquake (92), cohabitation status (93), Framingham risk category (94), past history of cardiovascular disease (95), non-steroidal anti-inflammatory drug use (96), fibrinogen (97), poverty income ratio (98)

The percentage of agreement between the two investigators was 96.7%.

Both Smith SG et al.¹ and Saito et al.² presented the results from the English Longitudinal Study of Ageing (ELSA). The results of Smith SG et al.¹ were included in the present meta-analysis because that study included more complete data. However, the study by Saito et al.² reported results of the Japan Gerontological Evaluation Study (JAGES); for this reason, we also included this study in the analysis.

- 1 Smith, S. G., Jackson, S. E., Kobayashi, L. C. & Steptoe, A. Social isolation, health literacy, and mortality risk: Findings from the English Longitudinal Study of Ageing. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association* **37**, 160-169, doi:10.1037/hea0000541 (2018).
- 2 Saito, M. *et al.* Cross-national comparison of social isolation and mortality among older adults: A 10-year follow-up study in Japan and England. *Geriatrics & gerontology international* **21**, 209-214, doi:10.1111/ggi.14118 (2021).

Supplementary Table 6
Characteristics of included studies for the association between loneliness and mortality

First author	Year	Country	Sample size	Age* (years)	Follow-up†	Exposure assessment	Events for analysis	Effect Size HR/RR (95% CI)	Adjustment¶
Bin Yu	2022	China	Male 19768 Female 15486	86.63 (11.39)	4.8 y	How often do you feel lonely? (1-item)	All-cause mortality	HR 1.01 (0.98 to 1.04) Male HR 1.01 (0.97 to 1.05) Female HR 1.01 (0.96 to 1.06)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15
Karla Moreno-Tamayo	2022	Mexico	6393	64.5 (9.3)	12 y	Feeling of loneliness in the last 7 days (1-item)	All-cause mortality	HR 1.17 (1.05 to 1.29)	1, 2, 3, 4, 6, 8, 10, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25
Johannes Beller	2022	Germany	4442	61.80 (11.88)	12.2 y	An adapted German version of De Jong Gierveld Loneliness Scale (6-items)	All-cause mortality	HR 3.34 (1.67 to 6.71)	1, 2, 3, 6, 28, 29, 30, 31
Timothy L Barnes	2022	USA	Male 3533 Female 4449	>65	3 y	Revised University of California, Los Angeles (3-items)	All-cause mortality	HR 1.57 (1.28 to 2.93)	1, 2, 3, 4, 32, 33, 34
Carin Lennartsson	2021	Sweden	Male 475 Female 686	≥65	5 y	Are you ever bothered by feelings of loneliness? (1-item)	All-cause mortality	HR 1.201 (0.740 to 1.949) Male HR 1.142 (0.503 to 2.592) Female HR 1.110 (0.598 to 2.060)	1, 2, 3, 9, 14, 15, 26, 27
Yoosik Youm	2021	Korea	Male 289 Female 390	73.9 (7.5)	5.61 y	The Center for Epidemiologic Studies Depression Scale (CES-D) (1-item)	All-cause mortality	HR 1.01 (0.43 to 2.36)	2, 3, 6, 7, 11, 24, 34, 35, 36, 37, 38, 39
Mark Ward	2021	Ireland	6915	≥50	7 y	A modified version of the University of	All-cause mortality; cancer mortality;	All-cause mortality HR 1.26 (0.94 to 1.68)	2, 3, 4, 6, 7, 14, 20, 25, 40, 41, 42

						California Los Angeles Loneliness scale	Circulatory system mortality	Cancer mortality HR 1.02 (0.68 to 1.53) Circulatory system mortality HR 1.28 (0.77 to 2.12)	
Natasja Schutter	2021	Netherland s	Male 281 Female 162	60-93	6 y	The De Jong Gierveld Loneliness Scale (11-items)	All-cause mortality	All HR 1.06 (0.99 to 1.14)	None
Qian Gao	2021	Cuba Dominican Republic Peru Venezuela Mexico Puerto Rico China India	Cuba 2590 Dominican Republic 1696 Peru 1707 Venezuela Mexico 1679 Mexico 1833 Puerto Rico 1492 China 1931 India 745	≥65	4 y	The Geriatric Mental State (GMS)-Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) packag : “Do you feel lonely?” (1-item)	All-cause mortality	Cuba HR 1.19 (0.97 to 1.46) Dominican Republic HR 1.13 (0.92 to 1.39) Peru HR 0.74 (0.49 to 1.11) Venezuela HR 1.37 (0.96 to 1.94) Mexico HR 1.11 (0.82 to 1.49) Puerto Rico HR 1.10 (0.83 to 1.46) China HR 1.58 (1.03 to 2.41) India HR 1.03 (0.65 to 1.62)	1, 2, 3, 20, 52, 53, 54, 55, 56
Christoph er L. Crowe	2021	USA	11302	50-95	8 y	A 3-item version of the Revised UCLA (R-UCLA) Loneliness Scale	All-cause mortality	All HR 1.48 (1.28 to 1.72)	1, 2, 5, 57, 58
Siiri-Liisi Kraav	2020	Finland	Male 2588	42-61	23.2 y	The Loneliness Scale consists of 11 items	All-cause mortality; Cancer mortality; CVD mortality	All-cause mortality HR 1.106 (1.034 to 1.183) Cancer mortality HR 1.089 (0.958 to 1.237)	1, 6, 7, 14, 20, 43, 44, 45, 46, 47, 48, 49, 50, 51

								CVD mortality	
								HR 1.120 (1.013 to 1.238)	
Masuma Novak	2020	Sweden	Male 240 Female 272	70	12 y	Do you feel lonely?" (1-item)	All-cause mortality CVD mortality	All-cause mortality Male HR 1.32 (0.77 to 2.28) Female HR 1.64 (0.98 to 2.76) CVD mortality Male HR 1.52 (0.78 to 2.96) Female HR 2.25 (1.14 to 4.45)	None
Elvira Lara	2020	Spain	4467	47.7 (17.7)	6 y	The three-item UCLA Loneliness Scale	All-cause mortality	HR 1.02 (0.94 to 1.12)	1, 2, 3, 6, 20, 46, 51, 56, 60, 61
Emiel O Hoogendijk	2020	Netherlands	Male 692 Female 735	75.7 (6.6)	22 y	The De Jong Gierveld Loneliness Scale	All-cause mortality	HR 1.06 (0.92 to 1.22)	1, 2, 3, 6, 20, 25, 59
Heather Gilmour	2020	Canada	13037	≥65	8-9 y	The three-Item Loneliness Scale was based on the Revised UCLA Loneliness Scale	All-cause mortality	Male HR 0.9 (0.8 to 1.2) Female HR 1.1 (0.9 to 1.3)	1, 3, 4, 6, 38, 46, 56, 59
Josep L Conde-Salazar	2020	Europe	48691	≥50	2 y	A short scale of Loneliness (3 items)	All-cause mortality	HR 1.19 (1.04 to 1.37)	1, 2, 6, 8, 9, 10, 20, 24, 39, 59, 62, 63
Páraic S O'Suilleabháin	2019	Germany	Male 223 Female 190	84.53 (8.61)	19 y	The revised University of California, Los Angeles (UCLA) Loneliness Scale (8 items)	All-cause mortality	HR 1.176 (1.074 to 1.289)	None
J.	2019	Sweden	Male 642	62	14 y	Do you feel lonely?"	All-cause mortality	HR 0.90 (0.70 to 1.15)	1, 6, 12, 13, 14, 59,

Henriksen			Female 721			(1-item)		Male HR 0.50 (0.32 to 0.80) Female HR 1.27 (0.92 to 1.74)	64, 65
Hanyuyin g Wang	2018	UK	Male 207 Female 458	81-103	10 y	“Do you feel lonely?” (1-item)	All-cause mortality	HR 1.0 (0.8 to 1.4)	1, 2, 3, 4, 20, 25, 38, 59
Silvia Stringhini	2018	UK	Male 4291 Female 3555	66.4 (9.6)	8.4 y	An abridged version of the 20-item Revised UCLA loneliness scale	All-cause mortality; CVD mortality	All-cause mortality HR 1.23 (1.10 to 1.38) CVD mortality HR 1.44 (1.19 to 1.74)	1, 2, 6, 7, 12, 46, 48, 50, 51, 53, 66, 67, 68
Johannes Beller	2018	Germany	4838	60.09 (12.19)	20.83 y	The six-item de Jong-Gierveld Loneliness Scale	All-cause mortality	HR 0.98 (0.86 to 1.10)	1, 2, 3, 15, 25, 59
Beatriz Olaya	2017	Spain	Male 931 Female 1182	71.75	3 y	The three-item UCLA Loneliness Scale	All-cause mortality	HR 1.003 (0.614 to 1.637)	1, 2, 3, 6, 7, 20, 59, 68, 69
Marko Elovainio	2017	UK	Male 211 982 Female 254919	56.5 (8.1)	6.5 y	“Do you often feel lonely?” “How often are you able to confide in someone close to you?”	All-cause mortality; Circulatory system diseases mortality; Cancer mortality	All-cause mortality HR 0.99 (0.93 to 1.06) Circulatory systemdiseases mortality HR 0.95 (0.88 to 1.02) Cancer mortality HR 1.09 (0.99 to 1.20)	1, 2, 5, 6, 7, 9, 20, 24, 25, 46, 49, 51, 70
Jussi Tanskanen	2016	Finland	8650	44.97 (16.35)	17 y	“Do you ever feel lonely?” (1-item)	All-cause mortality	HR 1.064 (1.012 to 1.119)	1, 2, 3, 7, 8, 9, 34, 51, 71
Maturin Tabue Teguo	2016	France	Male 1524 Female 2096	76.5 (7.1)	22 y	Item 14 (I felt lonely) of the French version of the Centre for Epidemiological Studies Depression Scale	All-cause mortality	HR 1.11 (1.00 to 1.23)	1, 2, 3, 13, 14, 72, 73
Jolien E	2016	Netherland	Male 719	64-85	25 y	The Loneliness Scale of De	All-cause mortality	All-cause mortality	1, 3, 6, 7, 14, 25, 46,

Julsing		s				Jong Gierveld(11-items)	CVD mortality	HR 1.40 (0.85 to 2.31) CVD mortality HR 1.18 (0.58 to 2.39)	49, 50, 51, 74, 75
Tjalling J Holwerda	2016	Netherland s	Male 1397 Female 1481	70.35	19 y	The Loneliness Scale of de Jong Gierveld(11-items)	All-cause mortality	Male HR 1.13 (0.97 to 1.32) Female HR 0.99 (0.85 to 1.16)	1, 2, 3, 14, 20, 24, 25, 53, 59
Lea Ellwardt	2015	Netherland s	Male 1498 Female 1413	54-85	20 y	11-item De Jong Gierveld Loneliness Scale	All-cause mortality	HR 1.023 (0.989 to 1.059)	1, 2, 20, 24, 38, 46, 76
Chan, Angelique	2015	Singapore	4522	≥60	6-1459 d	The University of California, Los Angeles' (UCLA) three-item loneliness scale	All-cause mortality	HR 1.34 (0.99 to 1.82)	1, 2, 3, 4, 5, 6, 10, 20, 22, 24, 39, 53, 59, 77
Jochanan Stessman	2014	Israel	Male 837 Female 729	70-90	20 y	How often do you feel lonely? (1-item)	All-cause mortality	HR 70–78: 1.06 (0.54 to 2.1) 78–85: 1.10 (0.69 to 1.77) 85–90: 0.84 (0.56 to 1.27)	2, 3, 12, 13, 14, 25, 46, 59
Andrew Steptoe	2013	UK	Male 2953 Female 3547	≥52	7.25 y	The Revised UCLA loneliness scale(3 items)	All-cause mortality	HR 0.92 (0.78 to 1.09)	1, 2, 3, 5, 13, 20, 26, 59, 78
Jorunn Drageset	2013	Norway	Male 63 Female 164	≥65	5 y	The revised Social Provisions Scale (SPS)	All-cause mortality	HR 0.96 (0.90 to 1.06)	1, 2, 3, 39, 59, 80, 81, 82, 83
R.S. Tilvis	2012	Finland	Male 1187 Female 2671	>75	7 y	“Do you suffer from loneliness?”	All-cause mortality	Male HR 1.39 (1.15 to 1.68) Female HR 1.16 (1.01 to 1.33)	1, 15, 56, 85
Carla M	2012	USA	Male 651	70.9	6 y	The Revised UCLA	All-cause mortality	HR 1.45 (1.11 to 1.88)	1, 2, 3, 4, 5, 6, 7, 10,

Perissinotto			Female 953			Loneliness Scale (R-UCLA) (3 items)			20, 39, 46, 51, 63, 86, 87, 88
Ye Luo	2012	USA	Male 848 Female 1253	≥50	6 y	The Revised UCLA Loneliness Scale(3 items)	All-cause mortality	HR 1.07 (0.99 to 1.17)	1, 2, 3, 5, 6, 8, 9, 20, 34, 52, 59, 84, 89, 90, 91
T. J. Holwerda	2012	Netherlands	Male 1509 Female 2495	65-84	117.8 m	“do you feel lonely ?” (1-item)	All-cause mortality	Male HR 1.30 (1.04 to 1.62) Female HR 1.01 (0.87 to 1.17)	1, 3, 13, 14, 15, 20, 24, 73, 84, 92, 93, 94, 95
Reijo S. Tilvis	2012	Finland	Male 812 Female 1678	≥75	57 m	“Do you suffer from loneliness?” (1-item)	All-cause mortality	HR 1.18 (0.99 to 1.42)	1, 2, 20, 103, 104, 105, 106
Reijo S. Tilvis	2011	Finland	Male 1131 Female 2556	81	57 m	“Do you suffer from loneliness?” (1-item)	All-cause mortality	HR 1.17 (1.02 to 1.33)	1, 2, 9
Sharon Shiovitz-Ezra	2010	USA	Male 3152 Female 4486	59.23 (0.04)	4 y	The item asks respondents whether they felt lonely much of the time over the past week.	All-cause mortality	HR 1.83 (1.71 to 1.87)	1, 2, 3, 20, 84, 96
Max L. Stek	2005	Germany	Male 171 Female 305	85	5 y	The De Jong Gierveld Loneliness Scale (11-items)	All-cause mortality	RR 1.3 (0.8 to 1.9)	1, 2, 3, 6, 7, 20, 25, 59, 102
K.H. Pitkala	2004	Finland	Male 137 Female 354	75, 80, 85	10 y	“Do you suffer from loneliness?” (1-item)	All-cause mortality	HR 1.16 (0.99 to 1.39)	1, 2, 101
Heiner Maier	1999	Germany	Male 257 Female 256	70-103	62 m	The UCLA Loneliness Scale	All-cause mortality	RR 1.28 (1.14 to 1.44)	None
Brenda W. J. H.	1997	Netherlands	Male 1377 Female	55-85	29 m	A scale developed by De Jong Gierveld Loneliness	All-cause mortality	HR 1.06 (1.00 to 1.12)	1, 2, 3, 6, 7, 9, 97, 98, 99, 100

Penninx			1452			Scale			
Elaine D. Eaker	1992	USA	Female 749	45-64	20 y	“Are you lonely during the day?”(1-item)	CVD mortality	RR 4 (1.8 to 9.2)	1, 6, 13, 49, 50, 51
Olsen, R. B.	1991	Denmark	Male 715 Female 1037	70-100	15 y	“Do you feel lonely?” (1-item)	CVD mortality	Male HR 1.70 (1.03 to 2.81) Female HR 1.09 (0.79 to 1.49)	1, 9, 26, 46, 65
A. GRAND	1990	France	Male 290 Female 355	≥60	4 y	“Do you often feel lonely?” (1-item)	All-cause mortality	HR 1.42 (0.81 to 2.50)	1
Jylhä, M	1989	Finland	Male 472 Female 464	60-89	6.5 y	“Do you feel lonely?” (1-item)	All-cause mortality	Male HR 1.02 (0.75 to 1.40) Female HR 1.17 (0.79 to 1.74)	1, 9, 60, 84

HR=hazard ratio; RR=relative risk; 95%CI=95%Confidence interval; M= Male; F=Female; CVD= Cardiovascular disease mortality

*Presented as mean or range.

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

‡Adjustments: age (1), sex (2), education (3), living areas (4), ethnicity (5), smoking (6), drinking (7), exercise (8), self-rated health (9), activities of daily living (ADL) (10), psychological well-being (11), hypertension (12), diabetes (13), cardiovascular disease (14), social isolation (15), age × time (16), sex × time (17), health insurance (18), health insurance × time (19), depressive symptoms (20), difficulties in ADL × time (21), difficulties in IADL (22), difficulties in IADL × time (23), cognitive function (24), chronic condition (25), mobility (26), psychological distress (27), positive affect (28), multimorbidity (29), health checkup (30), loneliness * positive affect (31), Hierarchical Condition Category (HCC) score (32), Charlson Comorbidity Index (CCI) (33), household income (34), social disengagement (35), segregation (36), living with spouse (37), physical health (38), comorbidity (39), walk minutes (40), obese (41), polypharmacy (42), year of examination (43), adulthood socioeconomic status (44), Baltic Sea Diet Score (45), physical activity (46), hours slept at night (47), hs-CRP (48), blood pressure (49), cholesterol (50), body mass index (BMI) (51), household assets (52), social network (53), dependence (54), dementia (55), living alone (56), age-squared (57), age-sex interactions (58), marital status (59), disability (60), social participation (61), frailty (62), income (63), childlessness (64), psychiatric disease (65), triglycerides level (66), fibrinogen level (67), positive and negative support (68), memory function (69), handgrip strength (70), employment or student status (71), angina pectoris (72), respiratory problems (73), dispositional optimism (74), family history of stroke of myocardial infarction (75), anxiety (76), housing type (77), wealth (78), long-standing illness (79), length of stay (80), social integration (81), reassurance of worth (82), nurturance (83), functioning (84), social inactivity (85), net worth (86), working status (87), hearing and vision problems (88), relatives living nearby (89), friends living nearby (90), sleep quality poor (91), cancer (92), arthritis (93), epilepsy (94), parkinson's disease (95), medical status (96), specific diseases (97), physical limitations (98), social support (99), personal coping resources (100), comprehensive health measure (101), institutionalized (102), satisfied with life (103), feeling needed (104), plans for future (105), zest for life (106)

Supplementary Table 7
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	Male 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	Female 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	Female 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	Female 896	30-55	9.5 y	social network 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	Female 896	30-55	9.5 y	social network 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 Female 1947 NHS cohort Female 2221	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

			SBCSS cohort Female 2,127						
Candyce H Kroenke	2017	US	LACE cohort: Female 1,947 NHS cohort Female 2,221 SBCSS cohort Female 2,127	56.1	LACE cohort 1.8y NHS cohort 0.9y SBCSS cohort 6 mo	the ABCPP social network index	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 H Kroenke	2017	US	WHEL cohort F 2,972	56.1	WHEL cohort 1.8y	the ABCPP social network index	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 H Kroenke	2017	US	WHEL cohort F 2,972	56.1	WHEL cohort 1.8y	the ABCPP social network index	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 H Kroenke	2013	US	Female 2264	58	10.8 y	social network index	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 H Kroenke	2013	US	Female 2264	58	10.8 y	social network index	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 M Beasley	2010	US	Female 4589	59	5.6 y	social network index	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 M	2010	US	Female 4589	59	5.6 y	social network	breast cancer	Female	1, 2, 3, 4, 5, 6, 12, 13, 14,

Beasley						index	mortality after breast cancer diagnosis	HR 1.18 (0.62 to 2.22)	15, 18, 19, 20, 21, 22
Candyce H Kroenke	2006	US	Female 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	Female 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 8
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	Male 645 Female 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	479054	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	479054	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	Female 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 Kreibig	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	Male 85 Female 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	2004	US	Female	F 59	2.3 y	social network index	all-cause mortality among	RR	1, 6, 12, 34

Rutledge			503				women	2.4 (1.04 to 5.4)	
							with suspected myocardial ischemia		
C M	1993	UK	Male	unclear	3 y	social isolation scale	all-cause mortality after	HR	1, 2, 35, 37, 39, 40, 41
Jenkinson			1,073				acute myocardial infarction	1.33 (0.89 to 1.98)	
			Female						
			303						

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 9
Characteristics of included studies for the association between loneliness 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¶
Mitti Blakoe	2022	Denmark	7169	65.4 (10.6)	1 y	(1) Does it ever happen that you are alone even though you would prefer to be with other people? (2) Do you have somebody to talk to if you experience problems or need support?	all-cause mortality in patients with coronary heart disease	(1) HR 2.24 (1.24 to 4.03) (2) HR 2.65 (1.32 to 5.32)	1, 2, 3, 4, 5, 6, 7
Bin Yu	2020	China	Male 645 Female 622	≥65	10 y	The Chinese version of Center for Epidemiologic Studies Depression Scale (CES-D)	all-cause mortality in patients with cardiovascular disease	HR 0.95 (0.82 to 1.09)	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
Anne Vinggaard Christensen	2020	Denmark	Male 9368 Female 4078	M 64.9 F 66.1	1 y	“Does it ever happen that you are alone even though you would prefer to be with other people?”	all-cause mortality among cardiac patients	Male HR 2.14 (1.43 to 3.22) Female HR 2.92 (1.55 to 5.49)	1, 2, 3, 4, 5, 6, 14, 15
Christian Hakulinen	2018	UK	479054	40-69	7.1 y	“Do you often feel lonely? and How often are you able to confide in someone close to you?”	(1) all-cause mortality after acute myocardial infarction (2) all-cause mortality after stroke	(1) HR 0.97 (0.75 to 1.23) (2) HR 1.00 (0.78 to 1.29)	1, 2, 4, 5, 7, 8, 10, 11, 13, 16, 17, 18, 19, 20

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), educational level (2), comorbidity (3), smoking (4), alcohol intake (5), medicine compliance (6), body mass index(7), sex (8), working status (9), income (10), physical activity (11), activities of daily living (ADL) (12), depressive symptoms (13), living alone (14), cardiac diagnosis (15), ethnicity (16), diastolic and systolic blood pressure (17), grip strength (18), Townsend Deprivation Index(19), history of chronic illness (20)

Supplementary Table 10
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	
2022	Social isolation, loneliness, and all-cause mortality: A cohort study of 35,254 Chinese older adults	★	★	☆	★	☆ ★	★	★	★	7
2022	The Relationship Between Social Isolation and Mortality Among Adults Aged 50 and Older in a 12-year Follow-Up Analysis in Mexico	★	★	☆	★	☆ ★	★	★	★	7
2022	Prognostic value of a brief loneliness questionnaire for patients with coronary heart disease: Proposal for a prediction model	☆	★	★	★	☆ ★	★	★	☆	6
2022	Loneliness and mortality: The moderating effect of positive affect	★	★	★	★	☆ ★	★	★	★	8

2022	Loneliness, Social Isolation, and All-Cause Mortality in a Large Sample of Older Adults	☆	★	★	★	☆☆	★	★	☆	6
2022	Mediation analysis of social isolation and mortality by health behaviors	★	★	★	★	☆☆	★	★	★	8
2022	The association between social network index, atrial fibrillation, and mortality in the Framingham Heart Study	☆	★	★	★	☆☆	★	★	★	7
2022	Association between Social Isolation and Total Mortality after the Great East Japan Earthquake in Iwate Prefecture: Findings from the TMM CommCohort Study	☆	★	★	★	☆☆	☆	★	★	6
2022	Independent predictors of depressive symptoms and social isolation on 2-year all-cause mortality among the Korean elderly in a population-based cohort study: gender differences	☆	★	★	★	☆☆	☆	★	★	6

2021	The association between loneliness, social isolation and all-cause mortality in a nationally representative sample of older women and men	★	★	★	★	☆ ★	★	★	★	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	Mortality risk associated with combinations of loneliness and social isolation. Findings from The Irish Longitudinal Study on Ageing (TILDA)	★	★	★	★	☆ ★	★	★	☆	7
2021	Associations of Loneliness and Social Isolation with Healthspan and Lifespan in the US Health and Retirement Study	★	★	★	★	☆ ★	★	★	★	8
2021	Loneliness, social network size, and mortality in older adults and the role of cortisol	★	☆	★	★	☆ ★	★	☆	★	6
2021	Loneliness Among Older Adults in Latin America, China, and India: Prevalence, Correlates and Association With Mortality	★	☆	★	★	☆ ★	☆	★	★	6

2021	Cross-national comparison of social isolation and mortality among older adults: A 10-year follow-up study in Japan and England	★	★	★	★	☆ ★	★	★	★	8
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	Social Determinants of Health and Cancer Mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort Study	★	★	★	★	☆ ★	★	★	★	8
2021	Loneliness and social isolation increase cancer incidence in a cohort of Finnish middle-aged men	☆	★	★	★	☆ ★	☆	★	★	6
2020	Social Isolation, Loneliness, and All-Cause Mortality in Patients With Cardiovascular Disease: A 10-Year Follow-up Study	☆	★	★	★	★ ★	★	★	★	8

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	Social isolation and mortality among Canadian seniors	★	★	★	★	☆ ★	★	★	★	8
2020	Cardiovascular and all-cause mortality attributable to loneliness in older Swedish men and women	☆	★	★	★	☆ ★	★	★	★	7
2020	Exploring the effect of loneliness on all-cause mortality: Are there differences between older adults and younger and middle-aged adults?	★	★	★	★	☆ ★	★	★	★	8
2020	CAUSES, mortality rates and risk factors of death in community-dwelling Europeans aged 50 years and over: Results from the Survey of Health, Ageing and Retirement in Europe 2013–2015	★	★	★	★	☆ ★	★	☆	★	7

2020	Significantly increased risk of all-cause mortality among cardiac patients feeling lonely	☆	★	☆	★	☆ ★	★	★	★	6
2020	Association of social relationships with incident cardiovascular events and all-cause mortality	★	★	★	★	☆ ★	★	★	★	7
2020	Prediagnosis social support, social integration, living status, and colorectal cancer mortality in postmenopausal women from the women's health initiative	☆	★	★	★	☆ ★	★	★	★	7
2019	Loneliness, Living Alone, and All-Cause Mortality: The Role of Emotional and Social Loneliness in the Elderly During 19 Years of Follow-Up	☆	★	★	★	★ ★	★	★	★	8
2019	Loneliness, health and mortality	★	★	☆	★	☆ ★	★	★	☆	6
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	☆	★	★	★	☆ ★	★	★	★	7

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	Mortality risk of loneliness in the oldest old over a 10-year follow-up	★	★	☆	★	☆ ★	★	★	★	7
2018	Socio-economic trajectories and cardiovascular disease mortality in older people: the English Longitudinal Study of Ageing	★	★	★	★	☆ ★	★	★	★	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	★	★	★	★	☆ ★	★	★	★	8
2018	Perceived Social Isolation and Outcomes in Patients With Heart Failure	☆	★	★	★	☆ ★	★	☆	★	6
2018	Social integration and survival after diagnosis of colorectal cancer	☆	★	★	★	☆ ★	★	★	★	7

2017	Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study	★	★	★	★	☆ ★	★	★	★	8
2017	All-cause mortality and multimorbidity in older adults: The role of social support and loneliness	★	★	★	★	☆ ★	★	☆	★	7
2017	Relationships between social isolation, neighborhood poverty, and cancer mortality in a population-based study of US adults	★	★	★	★	☆ ★	★	★	★	8
2017	Postdiagnosis social networks and breast cancer mortality in the After Breast Cancer Pooling Project	☆	★	★	★	☆ ★	★	★	★	7
2016	A Prospective Study of Social Isolation, Loneliness, and Mortality in Finland	★	★	☆	★	☆ ★	★	★	★	7
2016	Feelings of Loneliness and Living Alone as Predictors of Mortality in the Elderly: The PAQUID Study	★	★	★	★	☆ ★	★	★	☆	7
2016	Loneliness and all-cause, cardiovascular and non-cardiovascular mortality in older men: The Zutphen Elderly Study	★	★	★	★	☆ ★	★	★	★	8

2016	Impact of loneliness and depression on mortality: results from the Longitudinal Ageing Study Amsterdam	★	★	★	★	☆ ★	★	★	★	8
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	★	★	★	★	☆ ★	★	★	★	8
2015	Personal Networks and Mortality Risk in Older Adults: A Twenty-Year Longitudinal Study	★	★	★	★	☆ ★	★	★	★	8
2014	Loneliness, Health, and Longevity	★	★	☆	★	☆ ★	★	★	★	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	☆	★	★	★	☆ ★	★	★	★	7
2013	Social isolation, loneliness, and all-cause mortality in older men and women	★	★	★	★	☆ ★	★	★	★	8
2013	Social isolation: a predictor of mortality comparable to traditional clinical risk factors	★	★	★	★	☆ ★	★	★	★	8
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	★	★	☆	★	☆ ★	★	★	★	7
2012	Loneliness in Older Persons: A predictor of functional decline and death	★	★	☆	★	☆ ★	★	★	★	7

2012	Loneliness, Health, and Mortality in Old Age: A National Longitudinal Study	★	★	★	★	☆☆	★	★	★	8
2012	Increased risk of mortality associated with social isolation in older men: only when feeling lonely? Results from the Amsterdam Study of the Elderly (AMSTEL)	★	★	☆☆	★	☆☆	★	★	★	7
2012	Positive life orientation predicts good survival prognosis in old age	★	★	☆☆	★	☆☆	★	★	★	7
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	Suffering from Loneliness Indicates Significant Mortality Risk of Older People	★	★	☆☆	★	☆☆	★	★	★	7
2011	Social isolation, C-reactive protein, and coronary heart disease mortality among community-dwelling adults	☆☆	★	★	★	☆☆	★	★	★	7

2010	Situational versus chronic loneliness as risk factors for all-cause mortality	★	★	☆	★	☆☆	★	★	★	7
2010	Social networks and survival after breast cancer diagnosis	☆	★	★	★	☆☆	★	★	★	7
2006	Social networks, social support, and survival after breast cancer diagnosis	☆	★	★	★	☆☆	★	★	★	7
2005	Is depression in old age fatal only when people feel lonely?	☆	★	★	★	☆☆	★	★	★	7
2004	Positive life orientation as a predictor of 10-year outcome in an aged population	☆	★	☆	★	☆☆	★	★	★	6
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
1997	Effects of Social Support and Personal Coping Resources on Mortality in Older Age: The Longitudinal Aging Study Amsterdam	☆	★	★	★	☆☆	★	☆	★	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
1992	Myocardial Infarction and Coronary Death among Women: Psychosocial Predictors from a 20-Year Follow-up of Women in the Framingham Study	☆	★	☆	★	☆ ★	★	★	★	6
1991	Social networks and longevity. A 14 year follow-up study among elderly in Denmark	★	★	☆	★	☆ ★	★	★	★	7
1990	Disability, psychosocial factors and mortality among the elderly in a rural French population	☆	★	☆	★	☆ ★	★	★	★	6
1989	Social ties and survival among the elderly in Tampere, Finland	★	★	☆	★	☆ ★	★	★	★	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 11
The pooled effect estimates of social isolation or loneliness and all causes, cardiovascular or circulatory system diseases, and cancer mortality

Social isolation and mortality	No. of Papers (Participants)	ES(95% CI)	P_{ES}	$I^2(\%)$	Egger's (P -value)	Begg's (P -value)	Adjust ES ¹ (95% CI)	GRADE Certainty of Evidence
All-cause mortality	38 (1,485,469)	1.32 (1.26, 1.39)	<0.001	77.8	0.006	0.019	1.23 (1.17, 1.30)	⊕○○○ Very low Downgraded due to inconsistency and publication bias
All-cause mortality in men	21 (383,687)	1.39 (1.27, 1.51)	<0.001	78.6	0.003	0.053	1.27 (1.16, 1.39)	⊕○○○ Very low Downgraded due to inconsistency and publication bias
All-cause mortality in women	18 (439,348)	1.44 (1.28, 1.61)	<0.001	79.4	0.306	0.612	NA	⊕○○○ Very low Downgraded due to inconsistency
Cardiovascular or circulatory system diseases mortality	12 (1,265,108)	1.34 (1.25, 1.44)	<0.001	63.3	0.160	0.363	NA	⊕○○○ Very low Downgraded due to inconsistency
Cancer mortality	11 (1,171,644)	1.22 (1.18, 1.27)	<0.001	42.8	0.042	0.488	1.24 (1.19, 1.28)	⊕○○○ Very low Downgraded due to publication bias
All-cause mortality in breast and colorectal cancer patients	6 (21,264)	1.47 (1.33, 1.63)	<0.001	20.2	0.473	0.548	NA	⊕⊕○○ Low
Cancer-specific mortality in breast and colorectal cancer patients	7 (21,913)	1.26 (1.04, 1.52)	0.016	63.1	0.268	0.108	NA	⊕○○○ Very low Downgraded due to inconsistency
All-cause mortality in breast cancer patients	4 (18,955)	1.51 (1.34, 1.70)	<0.001	34.6	0.540	1.000	NA	⊕⊕○○ Low

Cancer-specific mortality in breast cancer patients	4 (18,955)	1.33 (1.02, 1.75)	0.038	59.5	0.836	0.806	NA	⊕○○○ Very low Downgraded due to inconsistency
Cancer-specific mortality in colorectal cancer patients	3 (2,976)	1.07 (0.96, 1.20)	0.205	21.9	0.265	0.296	NA	⊕⊕○○ Low
All-cause mortality in patients with cardiovascular disease	8 (487,722)	1.28 (1.10, 1.48)	0.001	64.9	0.113	0.076	NA	⊕○○○ Very low Downgraded due to inconsistency
Loneliness and mortality								
All-cause mortality	45 (1,209,407)	1.14 (1.08, 1.20)	<0.001	91.1	0.465	0.021	NA	⊕○○○ Very low Downgraded due to inconsistency
All-cause mortality in men	11 (42,034)	1.09 (0.99, 1.20)	0.080	69.8	0.506	0.755	NA	⊕○○○ Very low Downgraded due to inconsistency
All-cause mortality in women	9 (37,313)	1.03 (0.99, 1.08)	0.105	15.4	0.031	0.348	1.01 (0.98, 1.05)	⊕○○○ Very low Downgraded due to publication bias
Cardiovascular or circulatory system diseases mortality	8 (487,982)	1.30 (1.09, 1.54)	<0.001	77.3	0.012	0.371	1.14 (0.97, 1.35)	⊕○○○ Very low Downgraded due to inconsistency and publication bias
Cancer mortality	3 (476,404)	1.09 (1.01, 1.17)	0.030	0.0	0.147	0.296	NA	⊕⊕○○ Low
All-cause mortality in patients with cardiovascular disease	4 (50,936)	1.49 (1.09, 2.03)	<0.001	83.7	0.003	0.072	1.26 (0.94, 1.68)	⊕○○○ Very low Downgraded due to inconsistency and publication bias
Social isolation and loneliness coexist								
All-cause mortality	5 (54,561)	1.18 (1.05, 1.32)	<0.001	79.2	0.849	0.806	NA	⊕○○○ Very low Downgraded due to inconsistency

ES: effect size

¹: Adjusted effect size through trim and fill method

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

The statistical tests used were two-sided

Supplementary Table 12
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					0.869 ⁴
Men	25	1.39 (1.27, 1.51)	78.6	<0.001	
Women	22	1.44 (1.28, 1.61)	79.4	<0.001	
Country					0.039*
US	21	1.45 (1.33, 1.58)	60.8	<0.001	
Others	34	1.24 (1.18, 1.31)	72.3	<0.001	
Follow-up duration					0.079
0-5 years	15	1.50 (1.31, 1.72)	86.4	<0.001	
5-10 years	22	1.28 (1.21, 1.36)	52.8	0.002	
10-15 years	10	1.38 (1.24, 1.54)	59.0	0.009	
15-20 years	3	1.41 (1.28, 1.56)	0.0	0.508	
20-25 years	5	1.10 (1.05, 1.16)	0.0	0.675	
Social isolation assessment tools					0.170
Social Network Index	31	1.38 (1.29, 1.47)	76.3	<0.001	
Others	24	1.25 (1.16, 1.34)	74.0	<0.001	
Adjustment for depression					0.239
Yes	17	1.23 (1.14, 1.33)	75.1	<0.001	
No	38	1.36 (1.28, 1.44)	75.2	<0.001	
Adjustment for education					0.424
Yes	33	1.34 (1.27, 1.42)	80.0	<0.001	
No	22	1.29 (1.18, 1.42)	71.0	<0.001	
Adjustment for smoking					0.950
Yes	34	1.31 (1.24, 1.38)	68.8	<0.001	
No	21	1.36 (1.23, 1.51)	84.4	<0.001	
Adjustment for drinking					0.445
Yes	18	1.37 (1.27, 1.47)	59.7	0.001	
No	37	1.26 (1.19, 1.33)	81.7	<0.001	
Adjustment for body mass index					0.211
Yes	35	1.40 (1.28, 1.53)	77.3	<0.001	
No	20	1.29 (1.22, 1.37)	76.1	<0.001	
Adjustment for ethnicity					0.657
Yes	14	1.37 (1.27, 1.46)	79.9	<0.001	
No	41	1.32 (1.23, 1.41)	73.5	<0.001	
Adjustment for chronic disease					0.934
Yes	14	1.32 (1.26, 1.39)	57.2	0.004	

No	41	1.34 (1.26, 1.44)	81.2	<0.001
Overall	55	1.32 (1.26, 1.39)	77.8	<0.001

N denotes the number of studies. ES: effect size

Inconsistency - percentage of variation across studies due to heterogeneity

P^I 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
The statistical tests used were two-sided

Supplementary Table 13
Subgroup analyses on the association between loneliness and risk of all-cause mortality

Subgroup	N	ES (95% CI)	<i>I</i> ² (%)	<i>P</i> ¹	<i>P</i> ²
Gender³					0.918 ⁴
Men	11	1.09 (0.99, 1.20)	69.8	<0.001	
Women	9	1.05 (0.99, 1.12)	15.4	0.306	
Country					0.056
China	2	1.20 (0.78, 1.84)	76.4	0.040	
USA	5	1.45 (1.09, 1.94)	96.8	<0.001	
UK	4	1.04 (0.91, 1.19)	76.2	<0.001	
Germany	5	1.22 (1.03, 1.44)	79.1	0.001	
Netherlands	9	1.05 (1.02, 1.08)	6.6	0.380	
Finland	9	1.12 (1.07, 1.18)	21.2	0.254	
Sweden	4	1.16 (0.87, 1.54)	43.1	0.153	
Others	22	1.08 (1.03, 1.14)	26.6	0.123	
Follow-up duration					0.137
0-5 years	21	1.19 (1.04, 1.36)	96.2	<0.001	
5-10 years	21	1.13 (1.06, 1.19)	68.8	<0.001	
10-15 years	5	1.32 (0.99, 1.76)	73.1	0.005	
15-20 years	8	1.06 (1.02, 1.11)	36.3	0.139	
20-25 years	5	1.08 (1.03, 1.14)	5.4	0.376	
Loneliness assessment tools					0.368
Feeling of loneliness (1-item)	32	1.15 (1.04, 1.28)	94.0	<0.001	
Others	28	1.10 (1.06, 1.15)	71.2	<0.001	
Adjustment for depression					0.941
Yes	29	1.14 (1.03, 1.26)	94.6	<0.001	
No	31	1.12 (1.07, 1.18)	69.3	<0.001	
Adjustment for education					0.408
Yes	40	1.13 (1.04, 1.22)	93.4	<0.001	
No	20	1.15 (1.09, 1.22)	72.9	<0.001	
Adjustment for smoking					0.439
Yes	21	1.09 (1.04, 1.14)	63.1	<0.001	
No	39	1.15 (1.06, 1.25)	93.0	<0.001	
Adjustment for drinking					0.699
Yes	12	1.08 (1.03, 1.13)	61.9	0.002	
No	48	1.15 (1.07, 1.23)	91.7	<0.001	

Adjustment for body mass index					0.770
Yes	7	1.09 (1.02, 1.17)	69.3	0.003	
No	53	1.14 (1.07, 1.22)	91.8	<0.001	
Adjustment for ethnicity					0.835
Yes	7	1.11 (1.01, 1.22)	84.2	<0.001	
No	53	1.14 (1.07, 1.22)	90.9	<0.001	
Adjustment for chronic disease					0.179
Yes	13	1.05 (1.00, 1.11)	19.5	0.247	
No	47	1.16 (1.09, 1.23)	92.8	<0.001	
Overall	61	1.14 (1.08, 1.20)	91.1	<0.001	

N denotes the number of studies. ES: effect size

Inconsistency - percentage of variation across studies due to heterogeneity

P^I 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
The statistical tests used were two-sided

Supplementary Table 14
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*=0.001, the test for trend was performed with a polynomial contrast procedure.

The statistical tests used were two-sided

Supplementary Table 15
Subgroup analyses on the association between social isolation and risk of cardiovascular or circulatory system diseases mortality

Subgroup	N	ES (95% CI)	I^2 (%)	P^1	P^2
Gender					0.186
All	5	1.25 (1.19,1.32)	0.0	0.576	
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					0.085
US	9	1.40 (1.31, 1.50)	28.3	0.193	
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					0.535
>10 years	11	1.38 (1.24, 1.53)	76.1	<0.001	
≤10 years	7	1.25 (1.19, 1.32)	0.0	0.903	
Adjustment for education					0.024*
Yes	14	1.36 (1.28, 1.44)	40.2	0.060	
No	4	1.24 (0.92, 1.67)	38.8	0.179	
Adjustment for smoking					0.403
Yes	14	1.32 (1.23, 1.43)	68.6	<0.001	
No	4	1.45 (1.21, 1.73)	11.9	0.333	
Adjustment for drinking					0.056
Yes	8	1.25 (1.13, 1.37)	54.1	0.033	
No	10	1.41 (1.31, 1.51)	27.8	0.188	
Overall	18	1.34 (1.25, 1.44)	63.3	<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

The statistical tests used were two-sided

Supplementary Table 16
Subgroup analyses on the association between social isolation and risk of cancer mortality

Subgroup	N	ES (95% CI)	I^2 (%)	P^1	P^2
Gender					0.564
All	5	1.23 (1.12,1.35)	21.7	0.276	
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					0.651
US	11	1.19 (1.12, 1.27)	19.3	0.259	
Others	4	1.19 (0.98, 1.45)	75.0	0.007	
Follow-up duration					0.634
>10 years	10	1.18 (1.11, 1.25)	28.2	0.185	
≤10 years	5	1.12 (0.83, 1.51)	59.5	0.043	
Adjustment for education					0.061
Yes	11	1.23 (1.16, 1.30)	20.6	0.247	
No	4	1.10 (0.92, 1.32)	49.2	0.116	
Adjustment for smoking					0.782
Yes	12	1.18 (1.09, 1.27)	52.0	0.018	
No	3	1.15 (1.01, 1.31)	0.0	0.702	
Adjustment for drinking					0.673
Yes	8	1.11 (0.95, 1.31)	62.6	0.009	
No	7	1.23 (1.17, 1.29)	0.0	0.468	
Overall	15	1.22 (1.18, 1.27)	42.8	0.040	

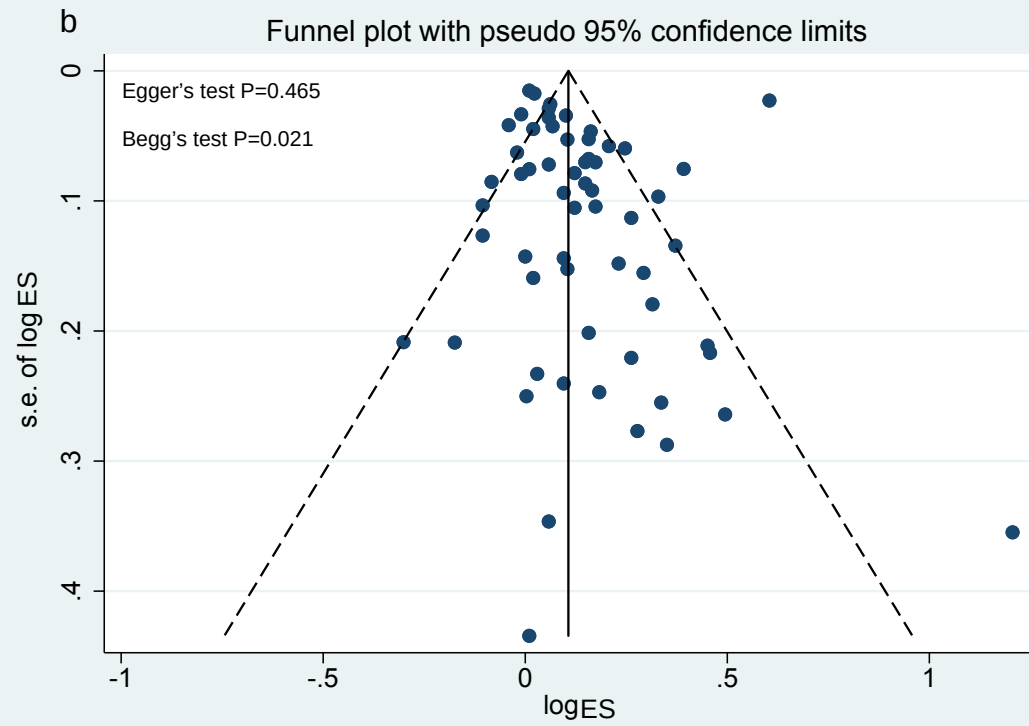
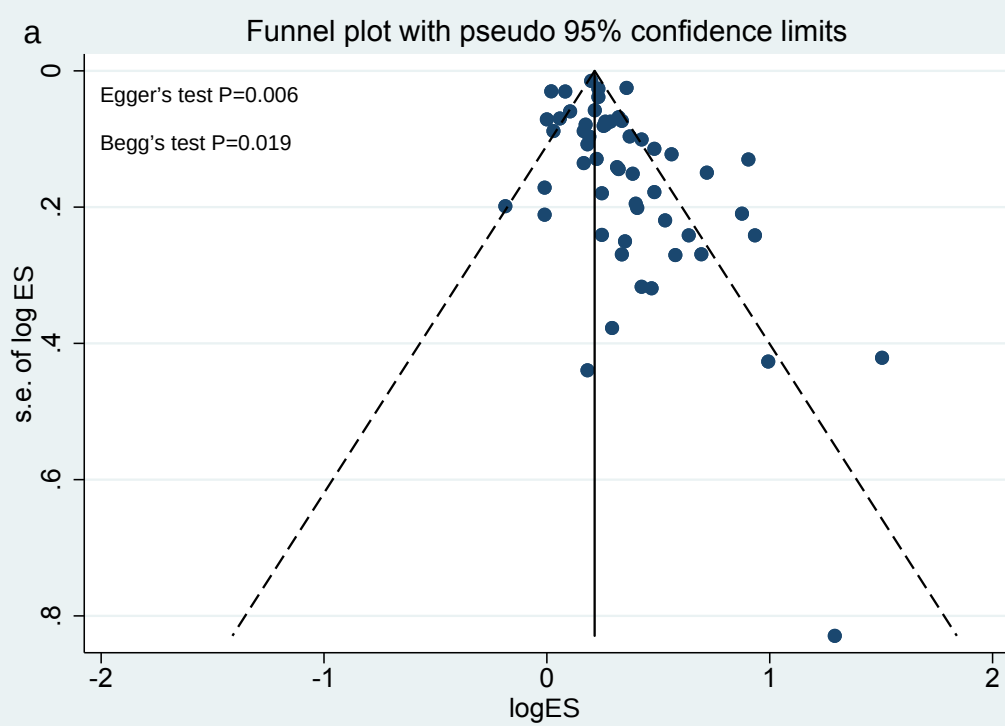
N denotes the number of studies. ES: effect size

Inconsistency - percentage of variation across studies due to heterogeneity

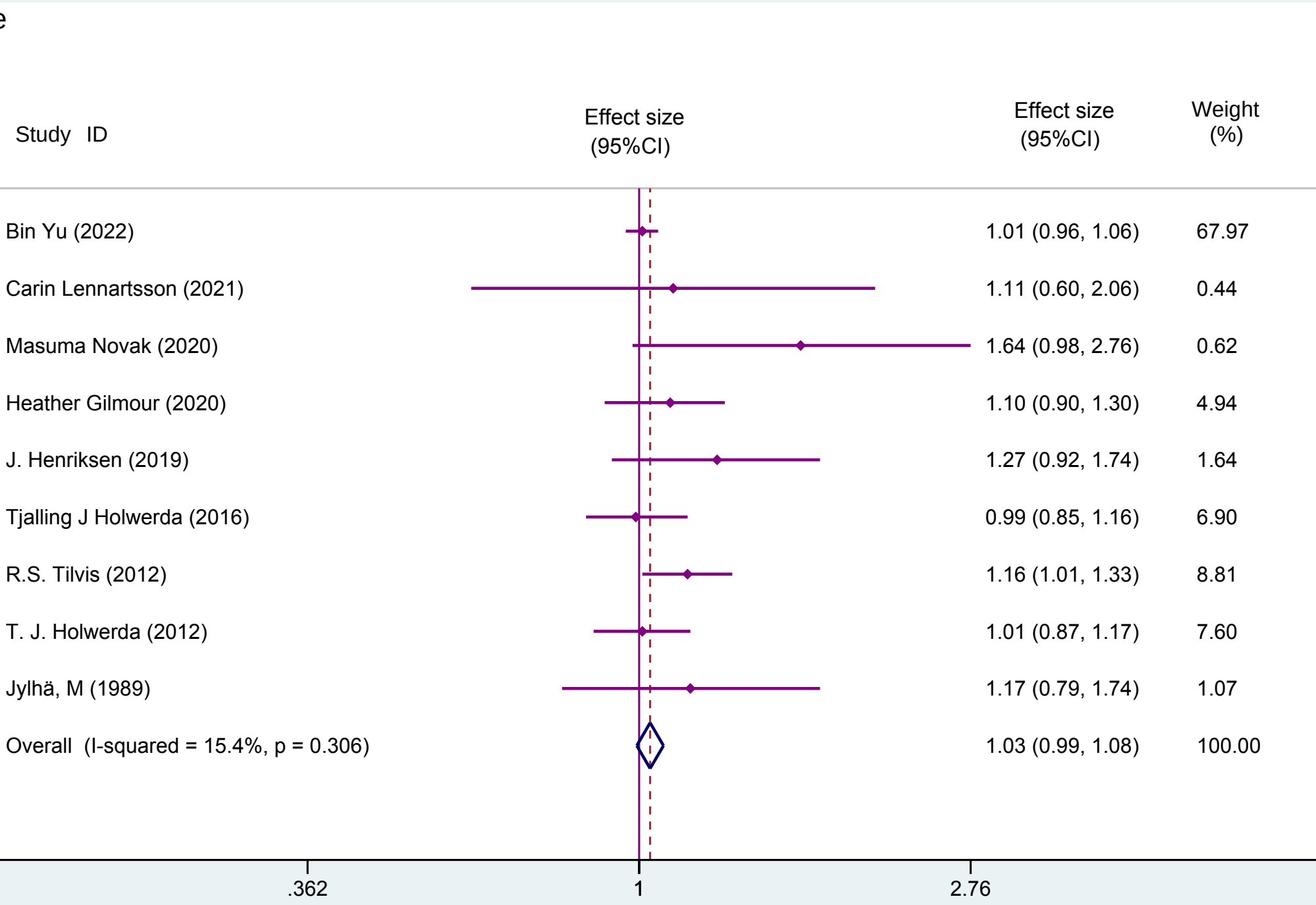
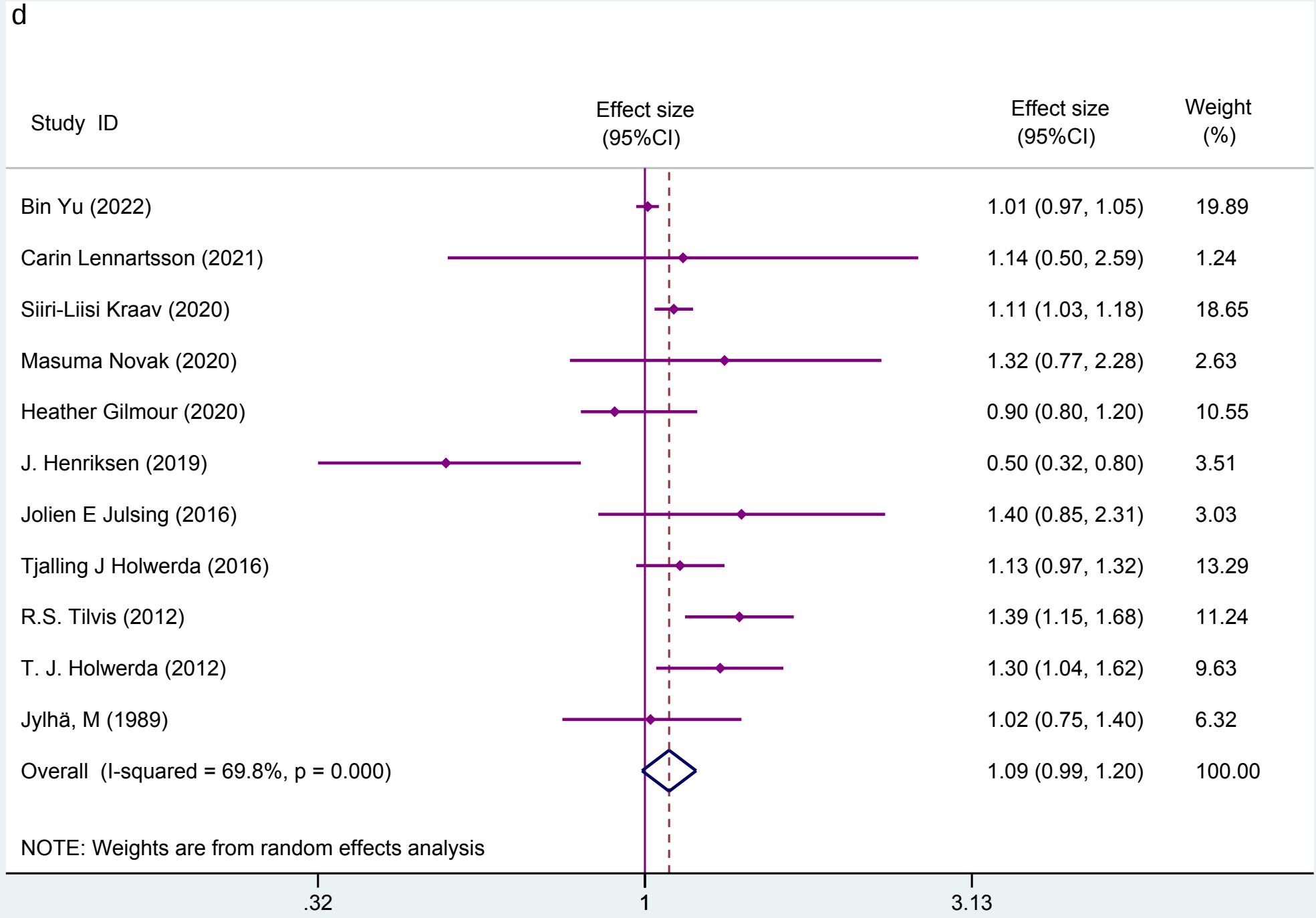
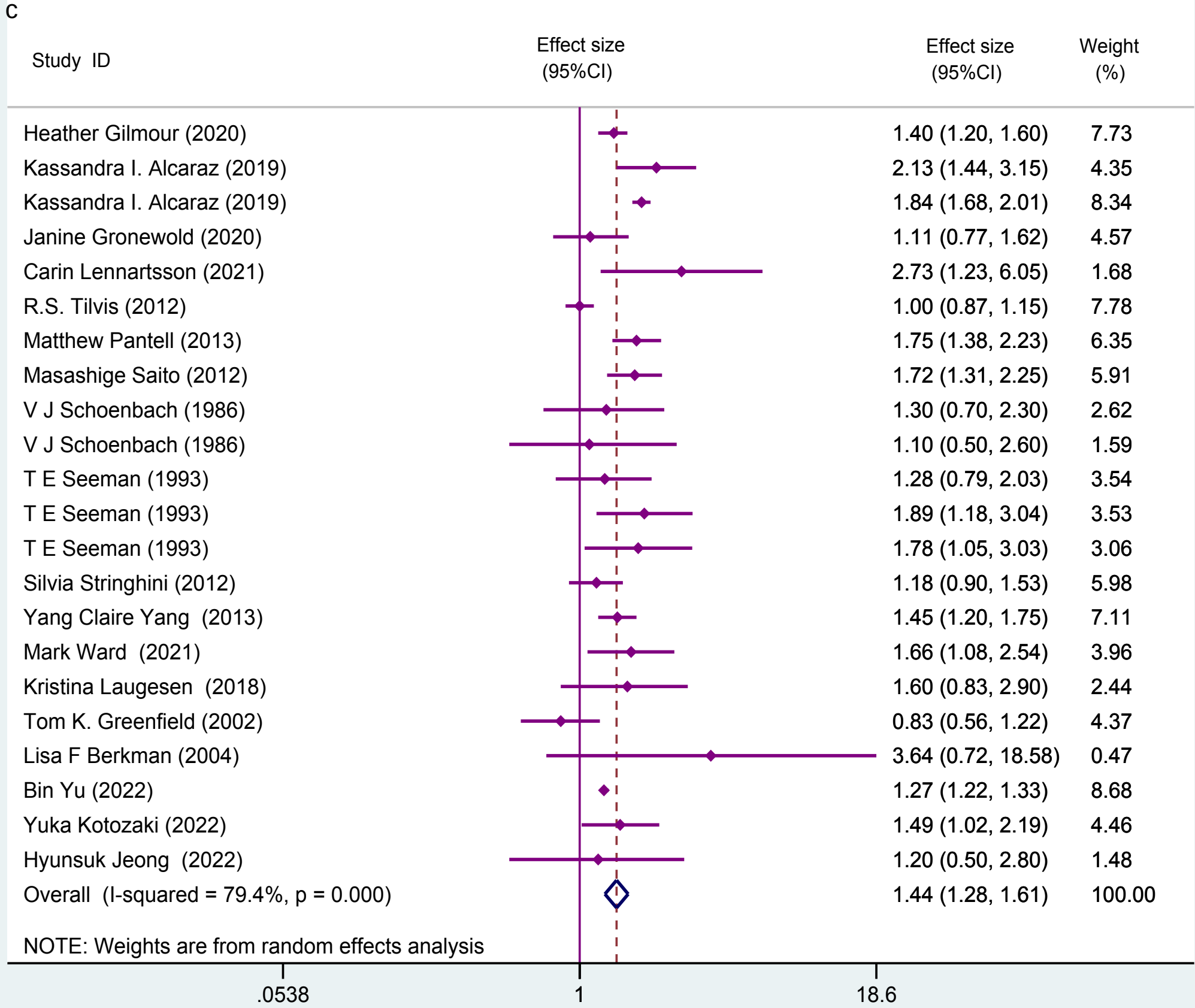
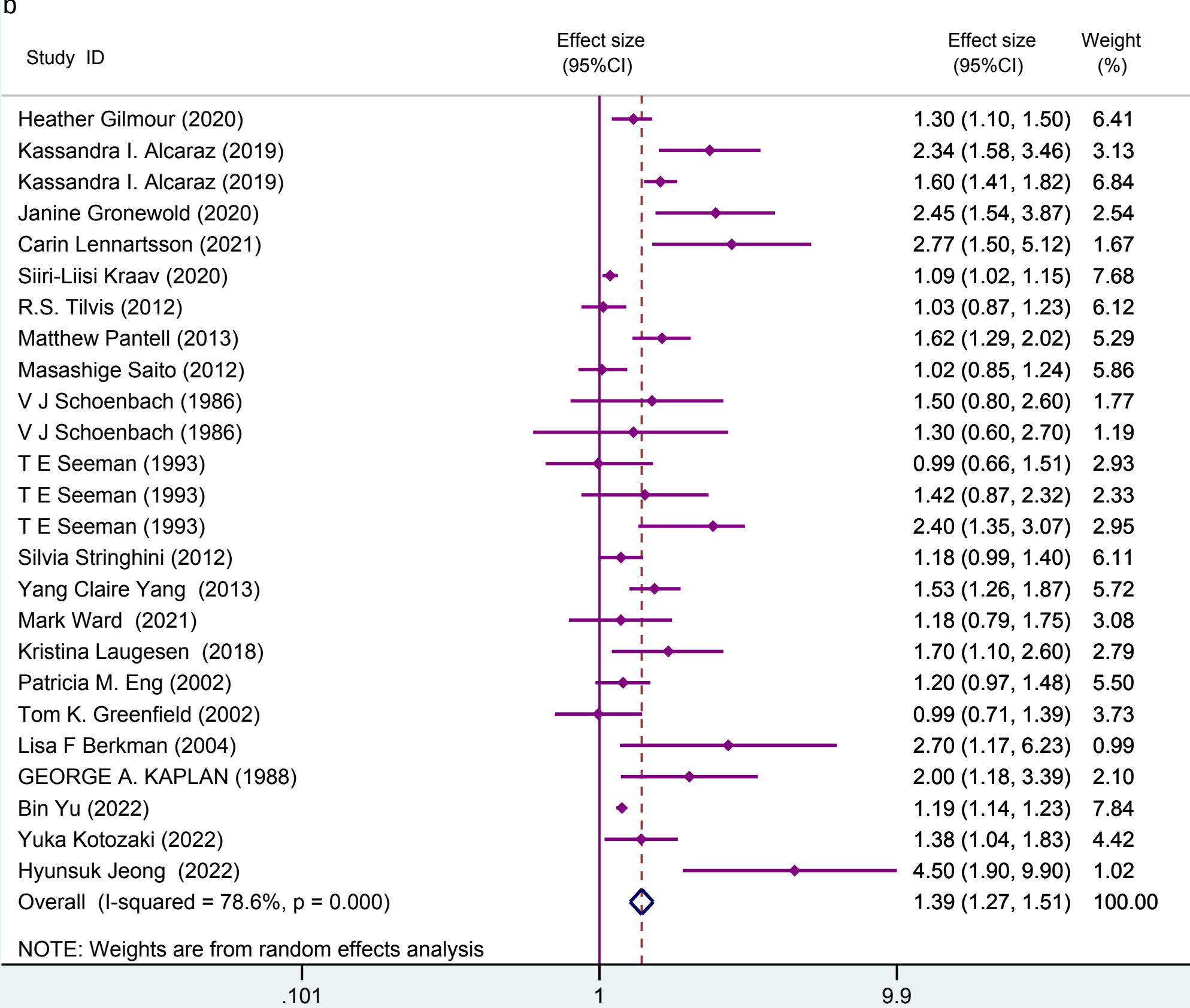
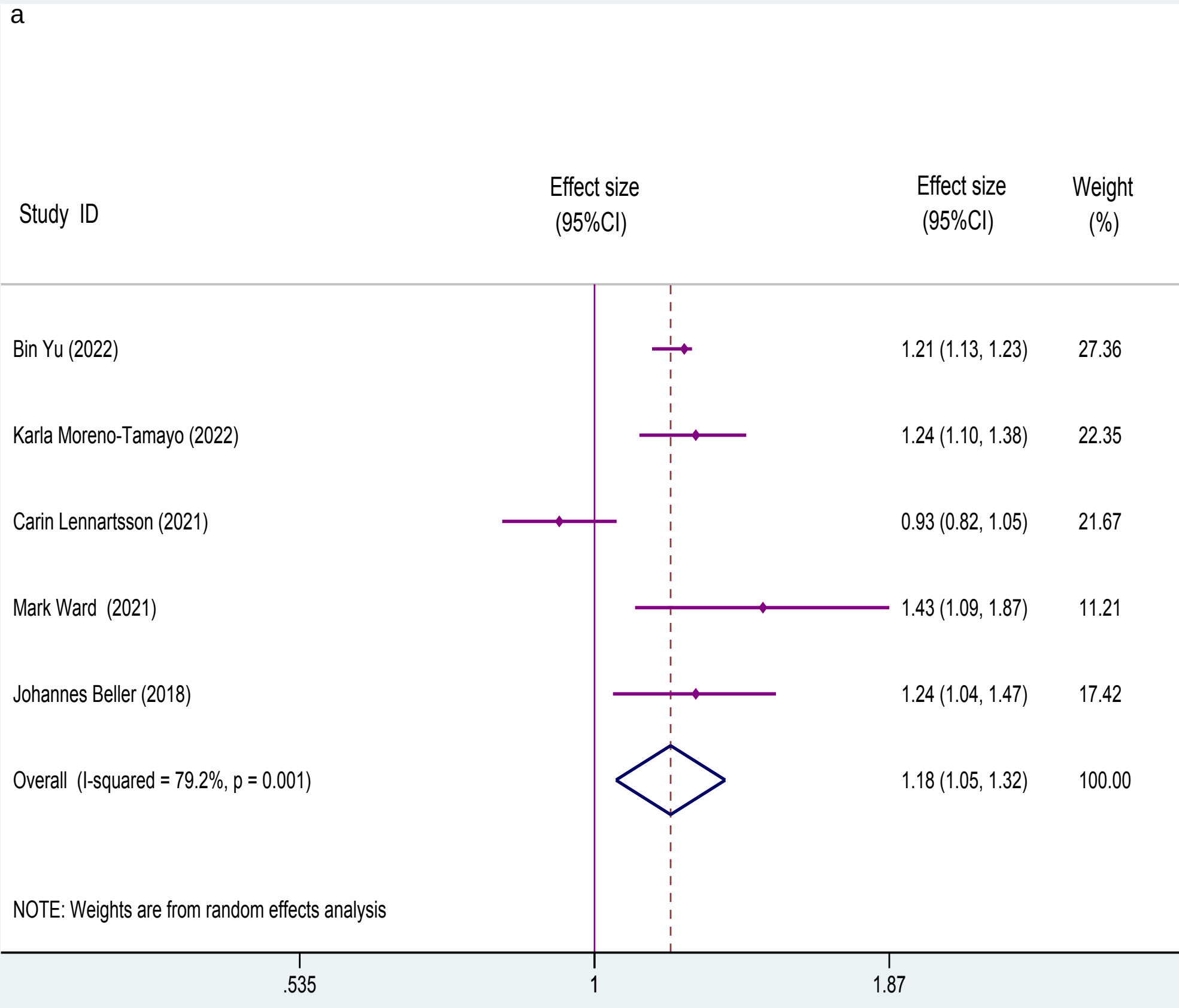
P^1 for heterogeneity within each subgroup

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

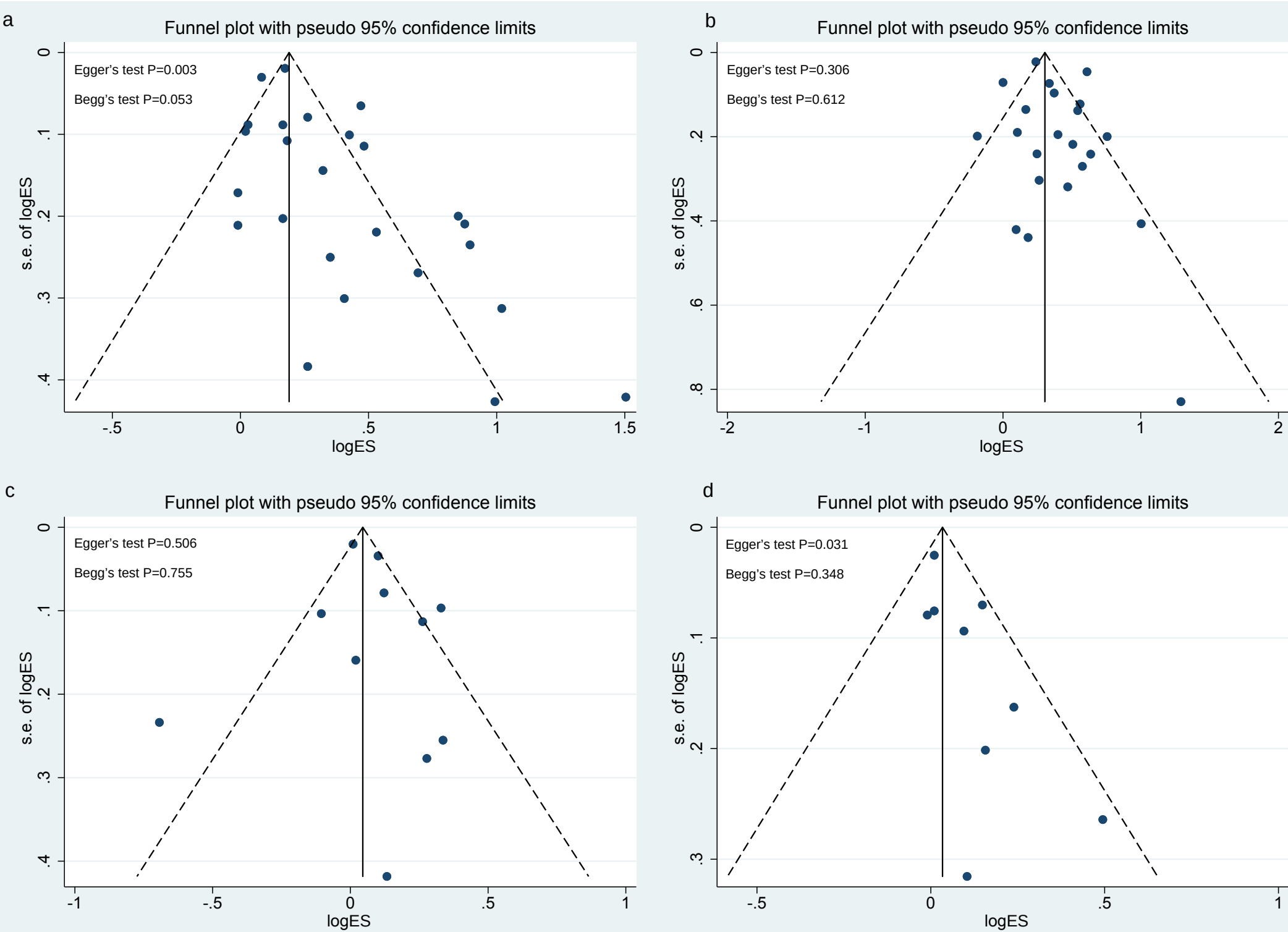
The statistical tests used were two-sided



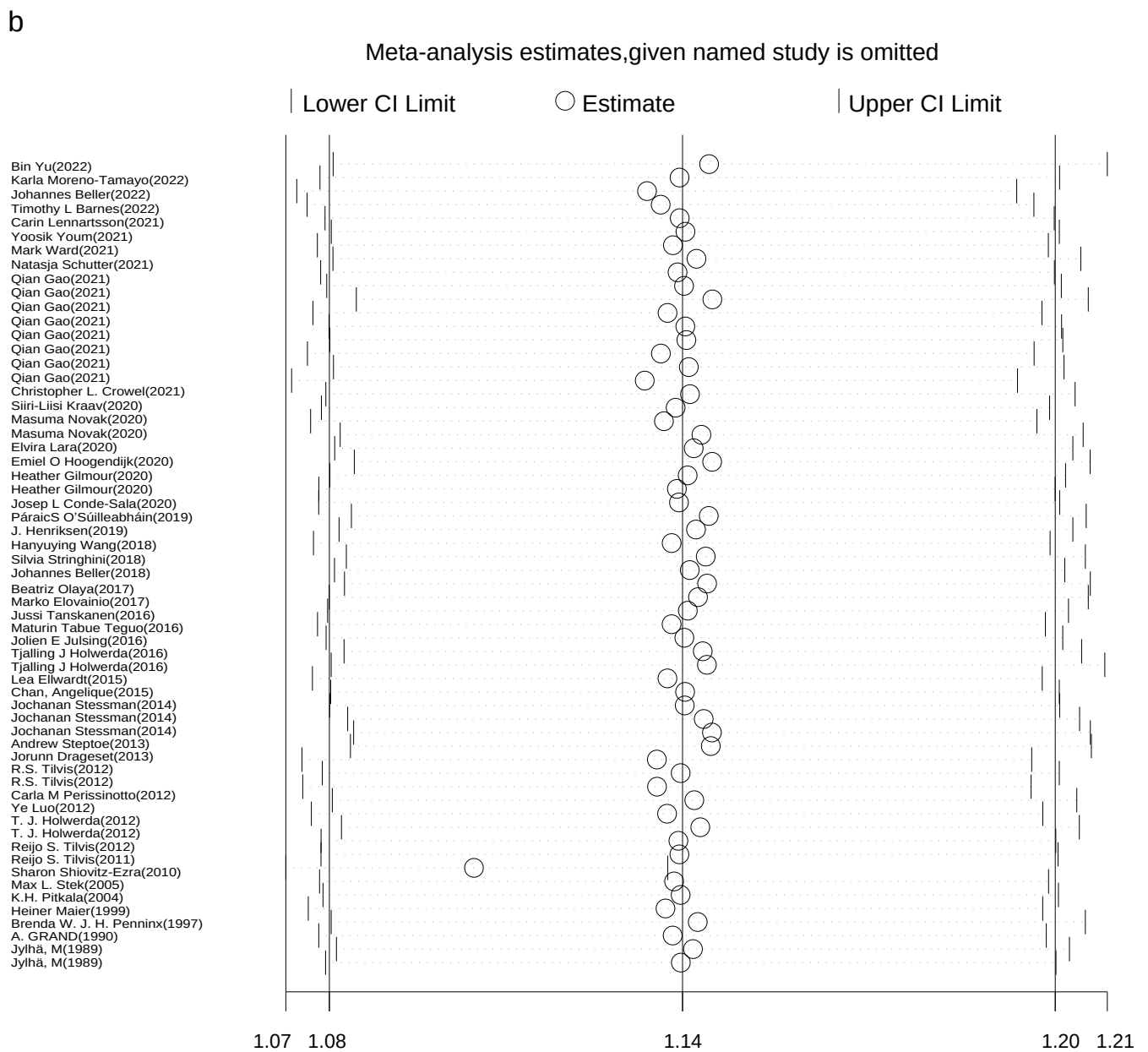
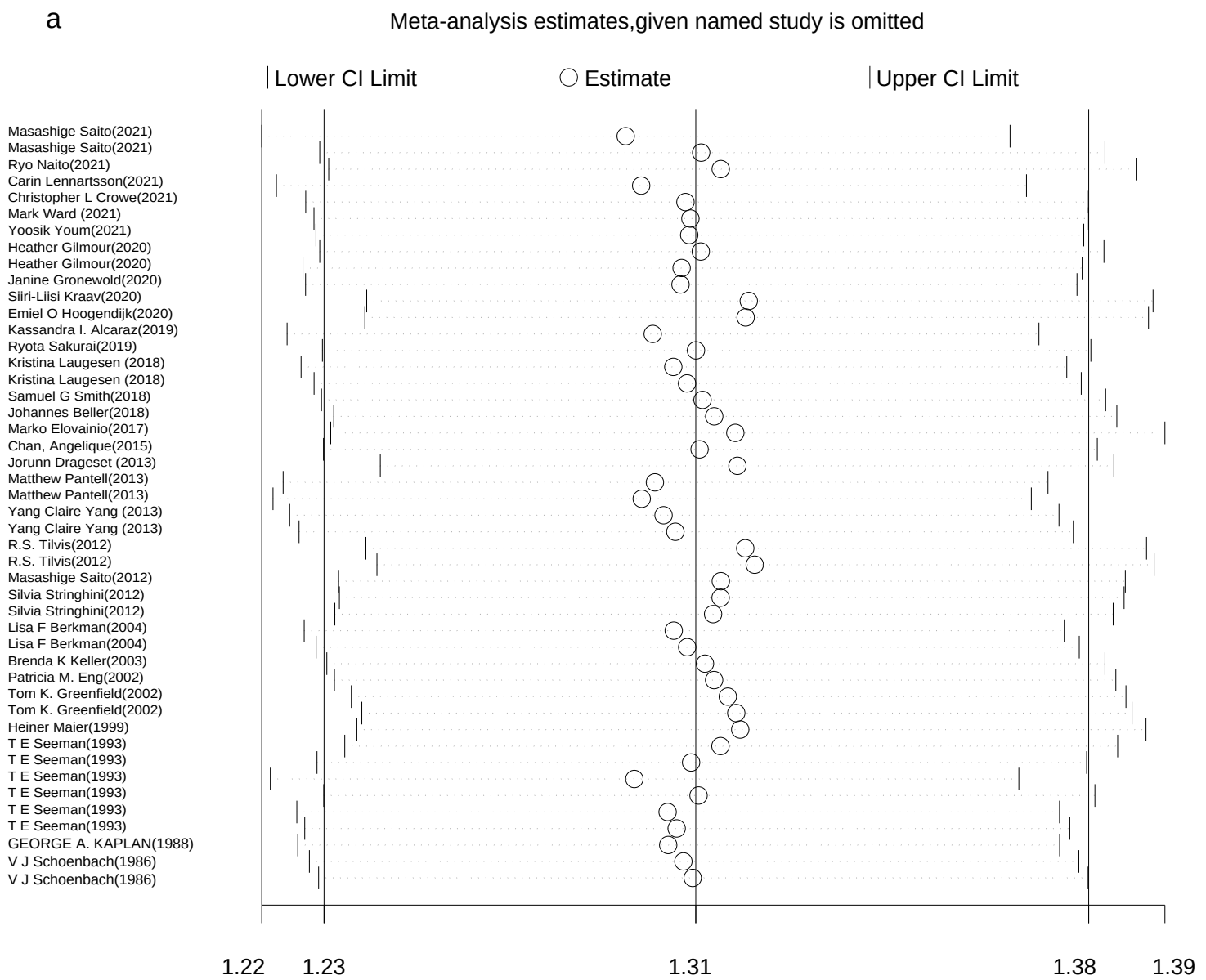
Supplementary Figure 1 Funnel plots for publication bias regarding the association of social isolation, loneliness, and all-cause mortality. a. Funnel plot for the association of social isolation and all-cause mortality; b. funnel plot for the association of loneliness and all-cause mortality. ES= Effect Size. The statistical tests were two-sided.



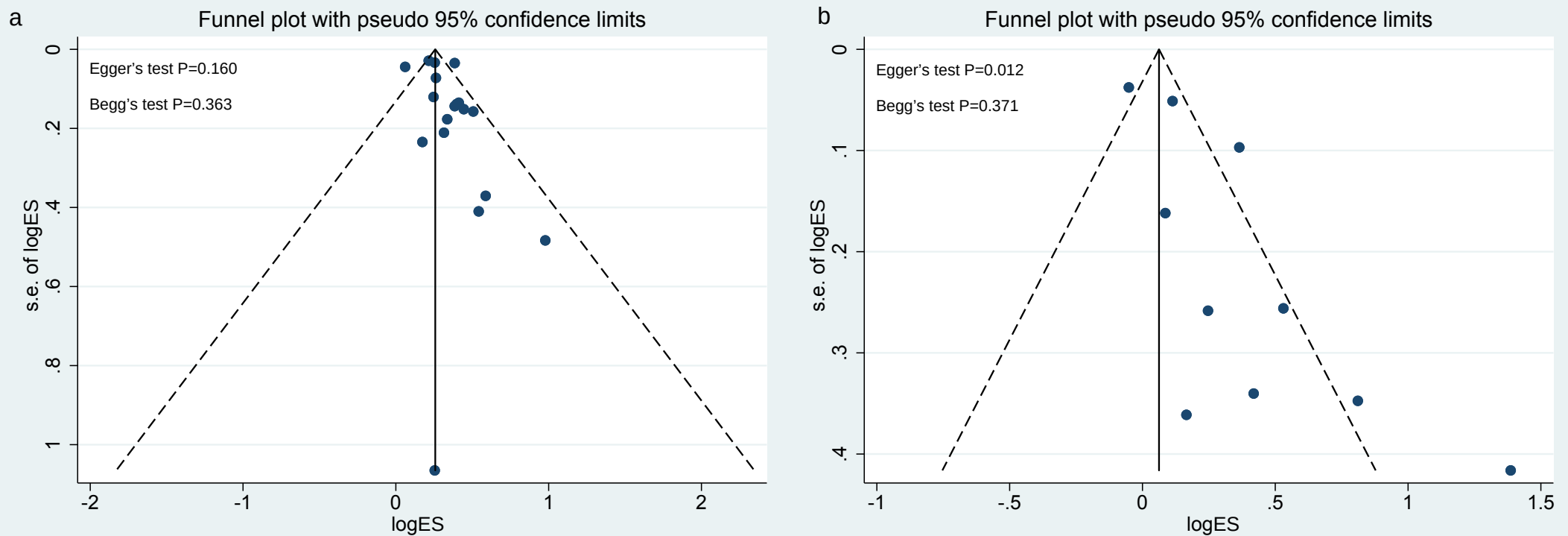
Supplementary Figure 2 Association of social isolation or loneliness and risk of all-cause mortality. a. Combined effect of social isolation and loneliness on the risk of all-cause mortality (n=5 of included studies); b. associations between social isolation and risk of all-cause mortality in men (n=21); c. associations between social isolation and risk of all-cause mortality in women (n=18); d. association of loneliness and risk of all-cause mortality in men (n=11); e. associations between loneliness and risk of all-cause mortality in women (n=9). a, b, c, d: The pooled effect estimates were generated using a random-effects model. e: The pooled effect estimates were generated using a fixed-effects model. The statistical tests were two-sided. Each solid diamond represents the effect size of each study. Horizontal bars parallel to the X-axis represent 95% confidence intervals for each study effect size. The hollow diamond represents the overall estimated effect and its 95% confidence interval. Data are presented as HR, 95%CI.



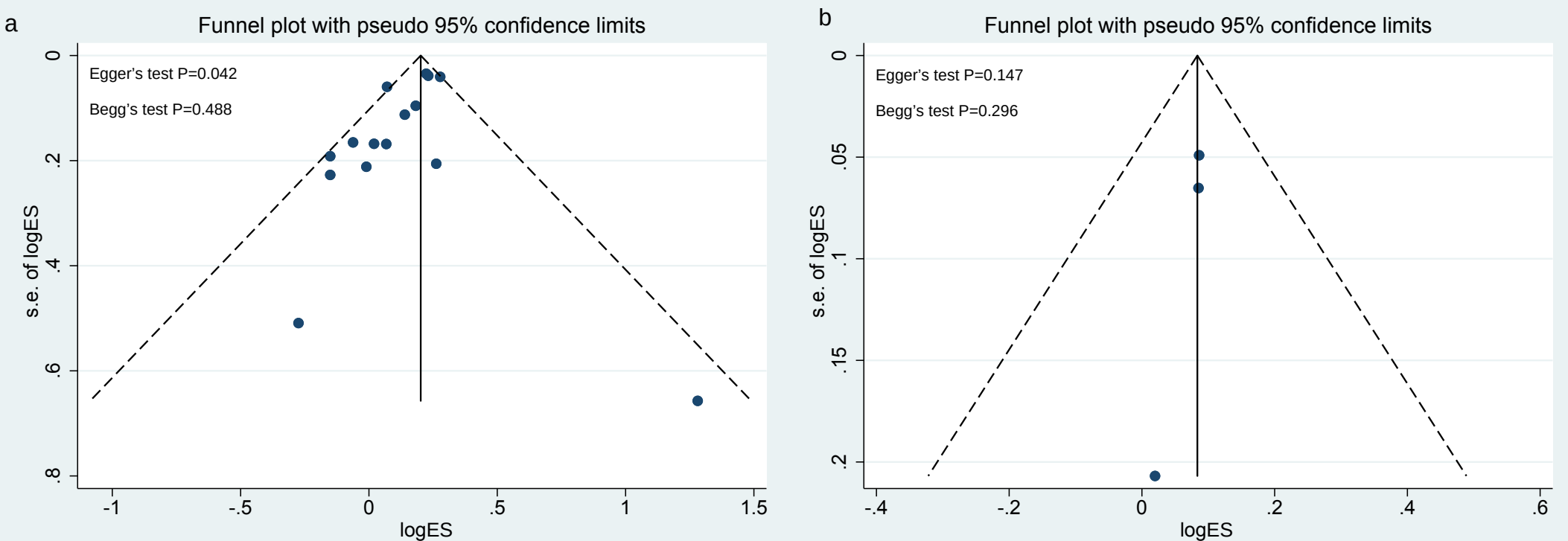
Supplementary Figure 3 Funnel plots for publication bias in different genders. a. Funnel plot for the association of social isolation and all-cause mortality in men; b. funnel plot for the association of social isolation and all-cause mortality in women; c. funnel plot for the association of loneliness and all-cause mortality in men; d. funnel plot for the association of loneliness and all-cause mortality in women. ES= Effect Size. The statistical tests were two-sided.



Supplementary Figure 4 Sensitivity analyses of the association between social isolation or loneliness and risk of all-cause mortality. a. Sensitivity analysis of the association between social isolation and risk of all-cause mortality; b. Sensitivity analysis of the association between loneliness and risk of all-cause mortality.

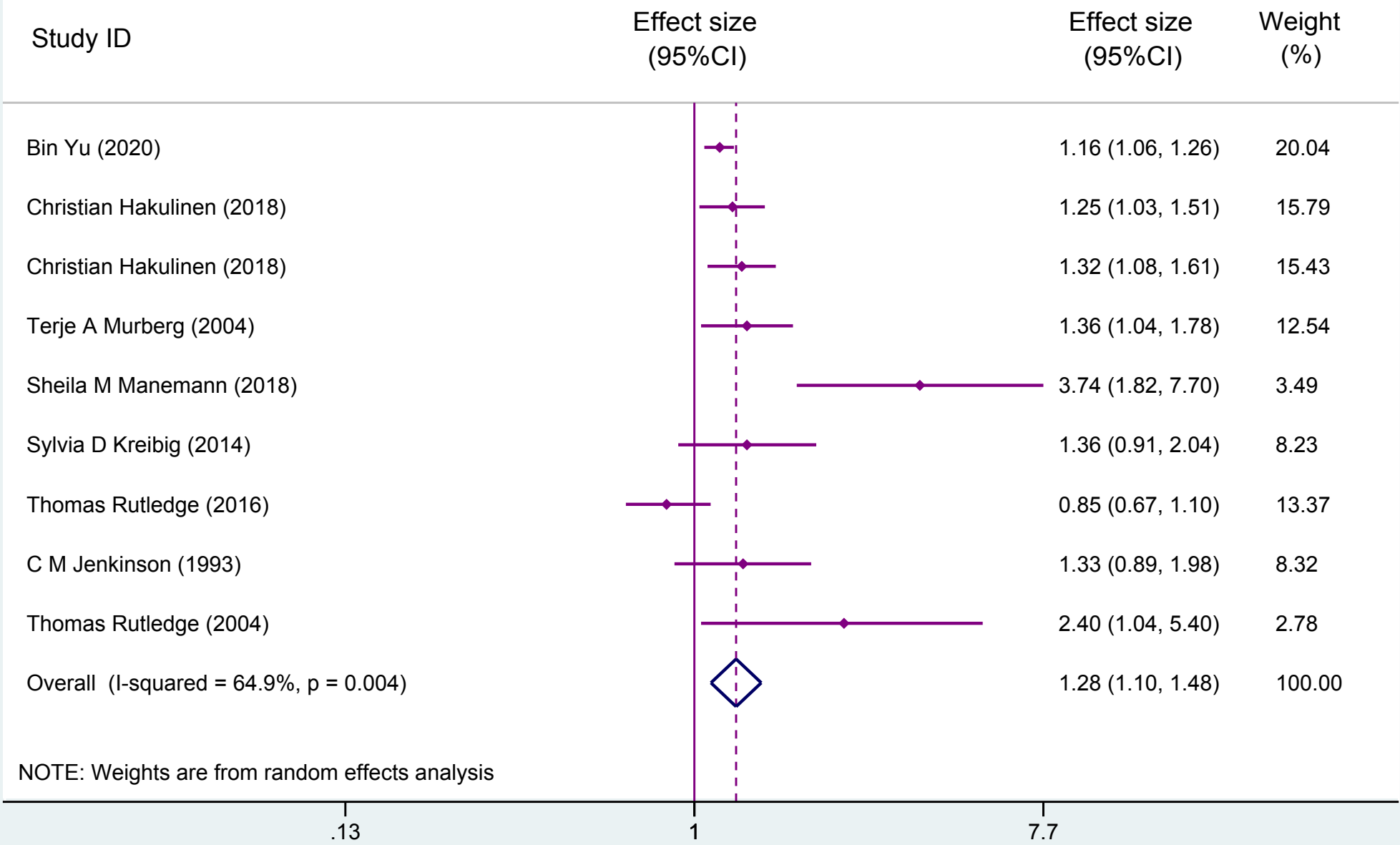


Supplementary Figure 5 Funnel plots for the publication bias between social isolation or loneliness and cardiovascular or circulatory system diseases mortality. a. Funnel plot for the association between social isolation and cardiovascular or circulatory system diseases mortality; **b.** Funnel plot for the association between loneliness and cardiovascular or circulatory system diseases mortality. ES= Effect Size. The statistical tests were two-sided.

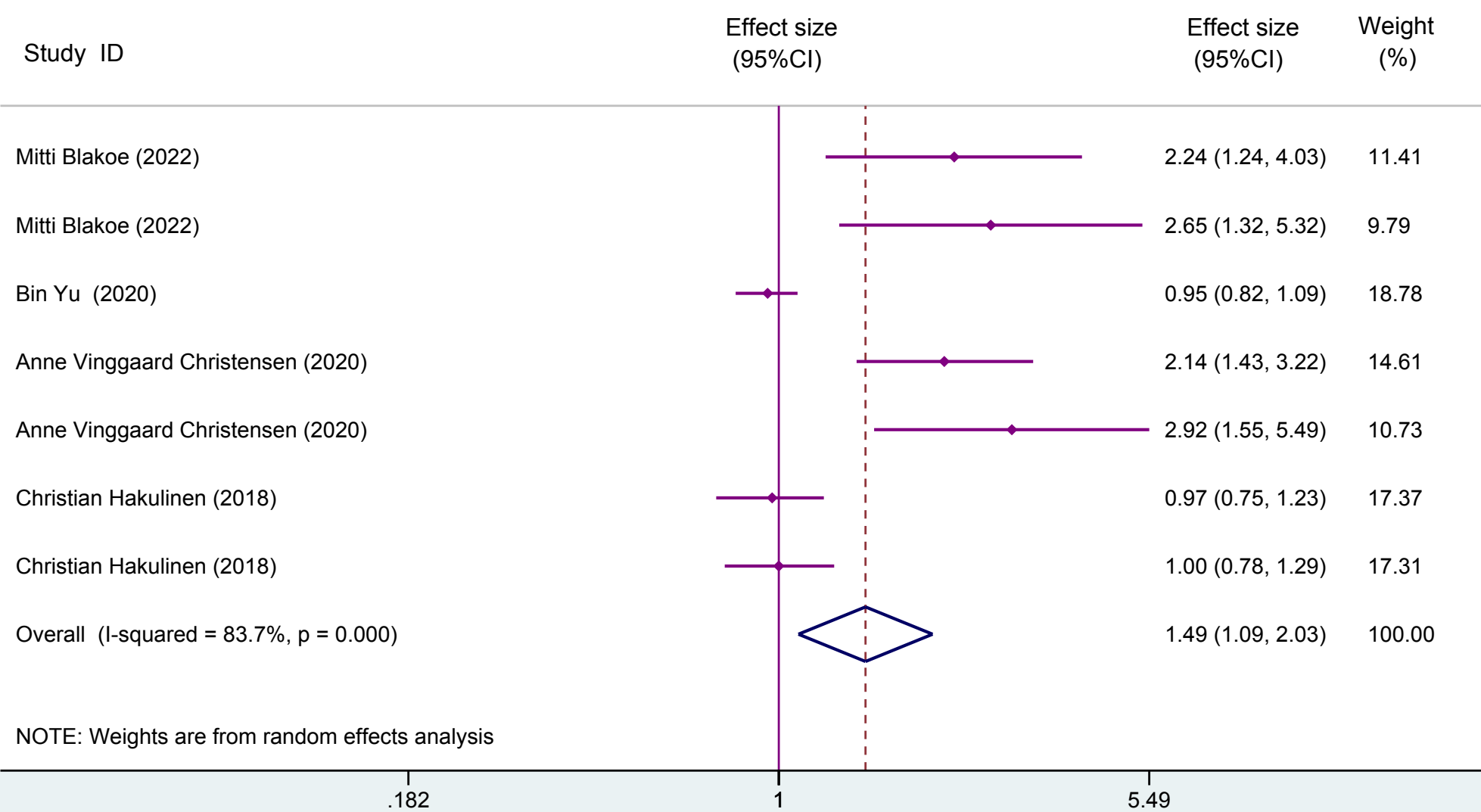


Supplementary Figure 6 Funnel plots for the publication bias between social isolation or loneliness and cancer mortality. a. Funnel plots for publication bias between social isolation and cancer mortality; b. Funnel plots for publication bias between loneliness and cancer mortality. ES= Effect Size. The statistical tests were two-sided.

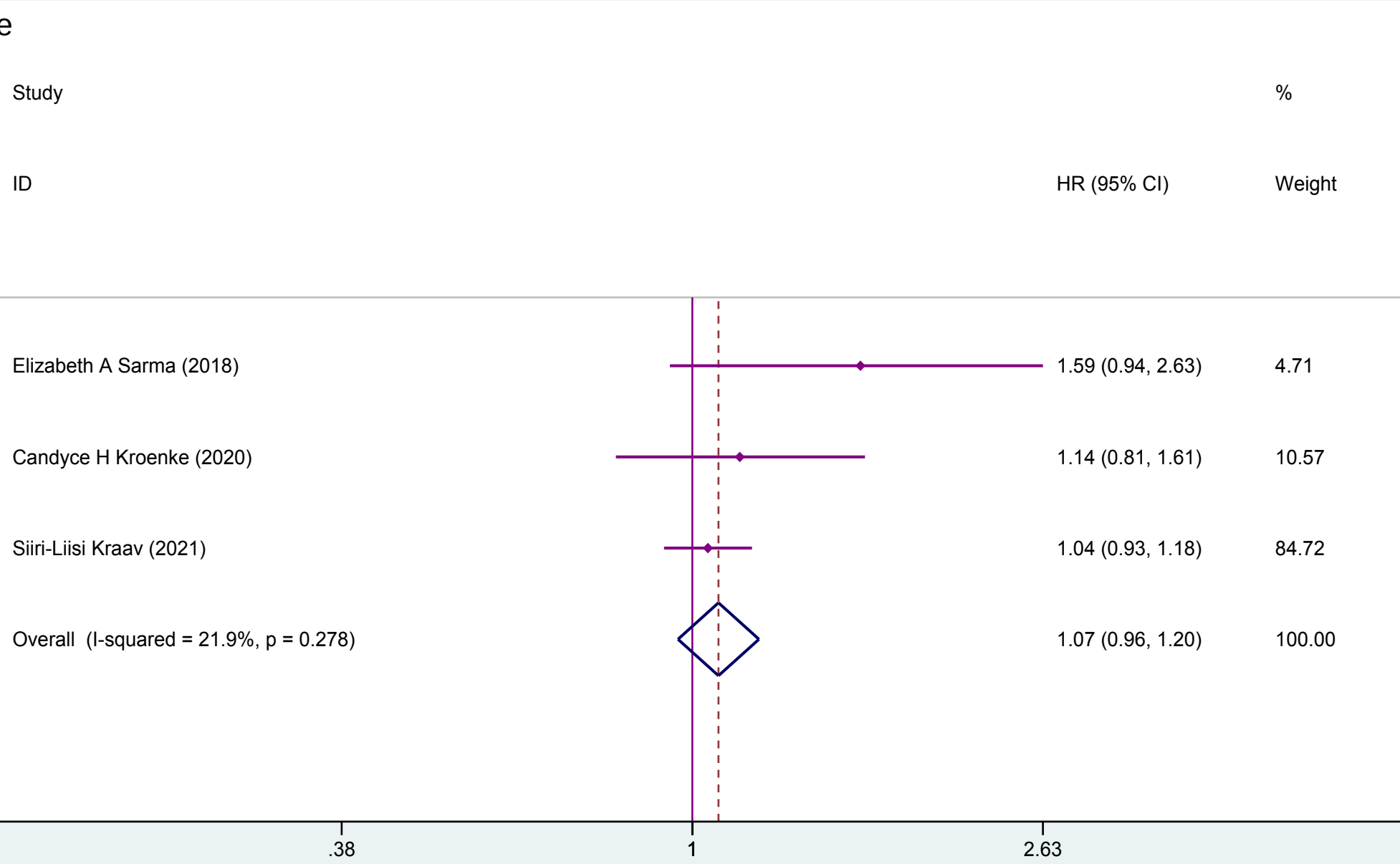
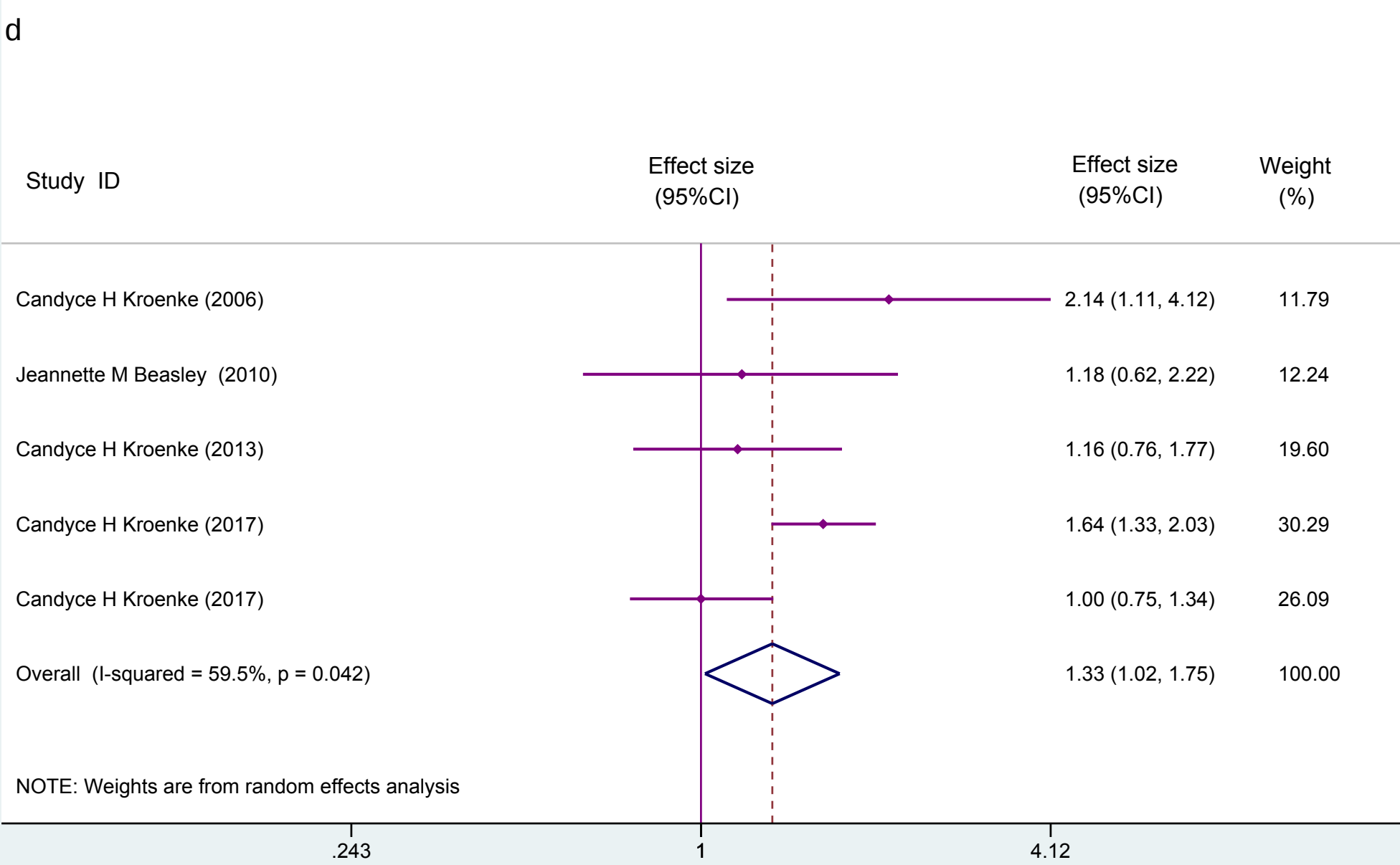
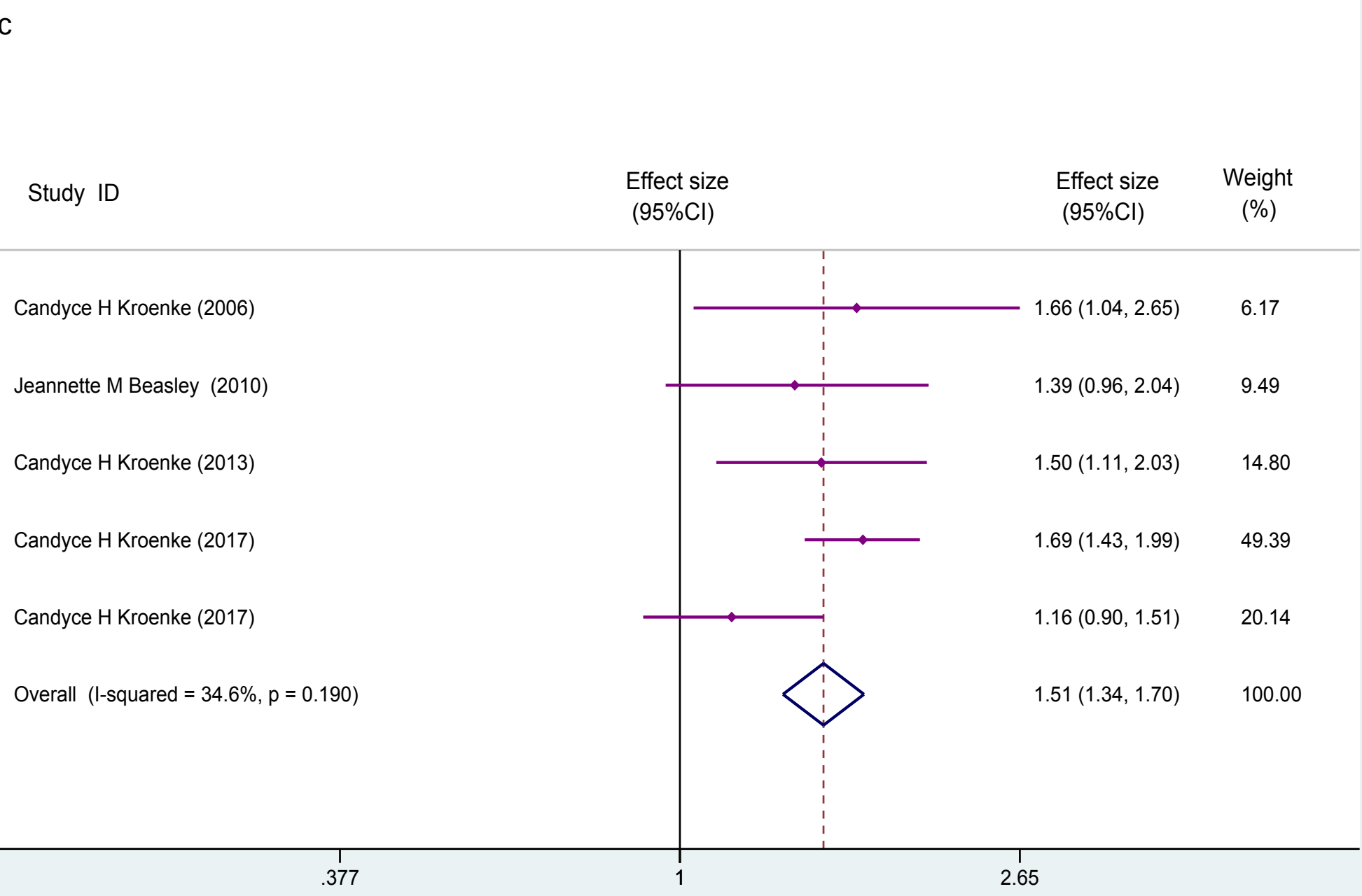
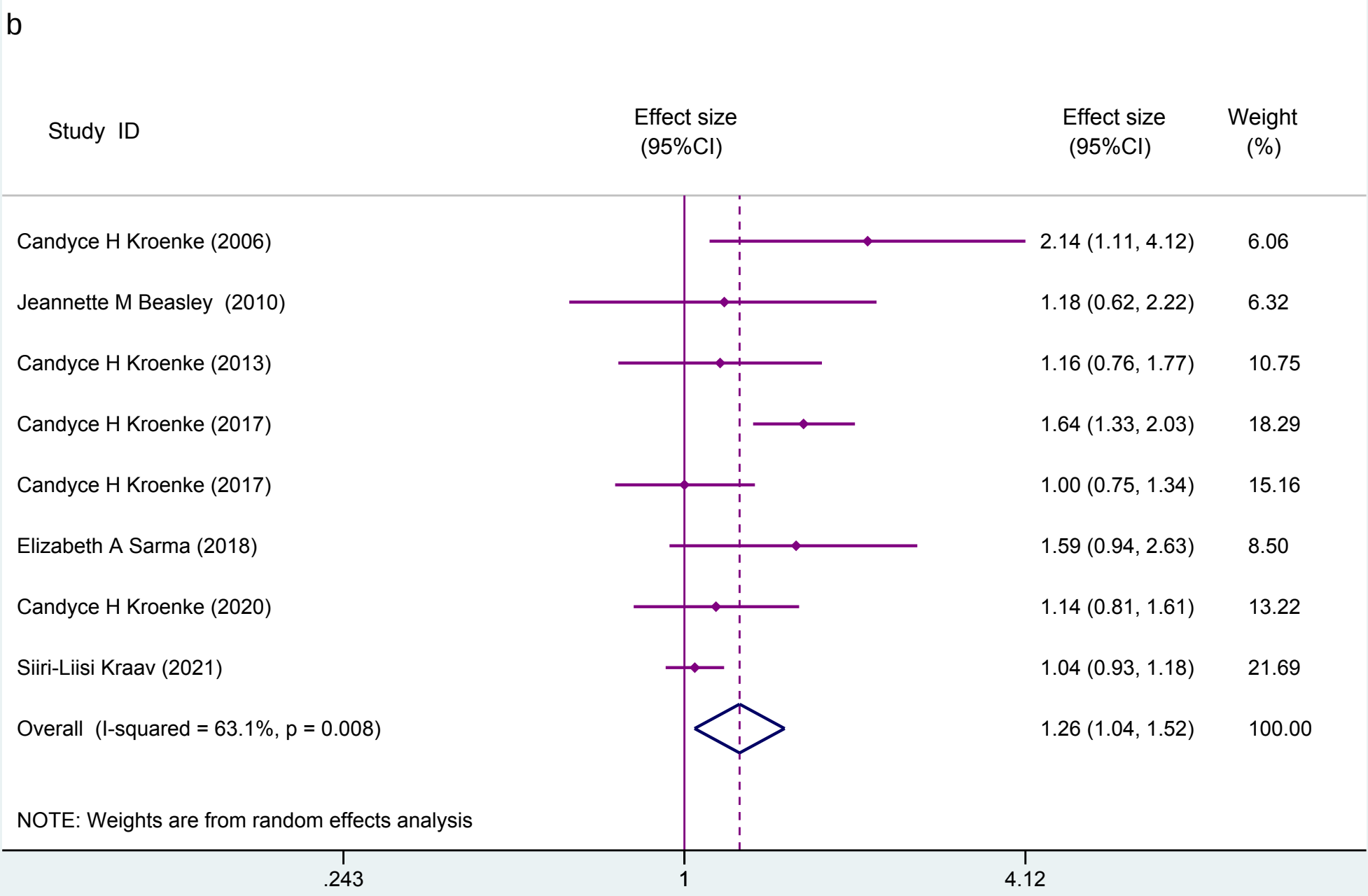
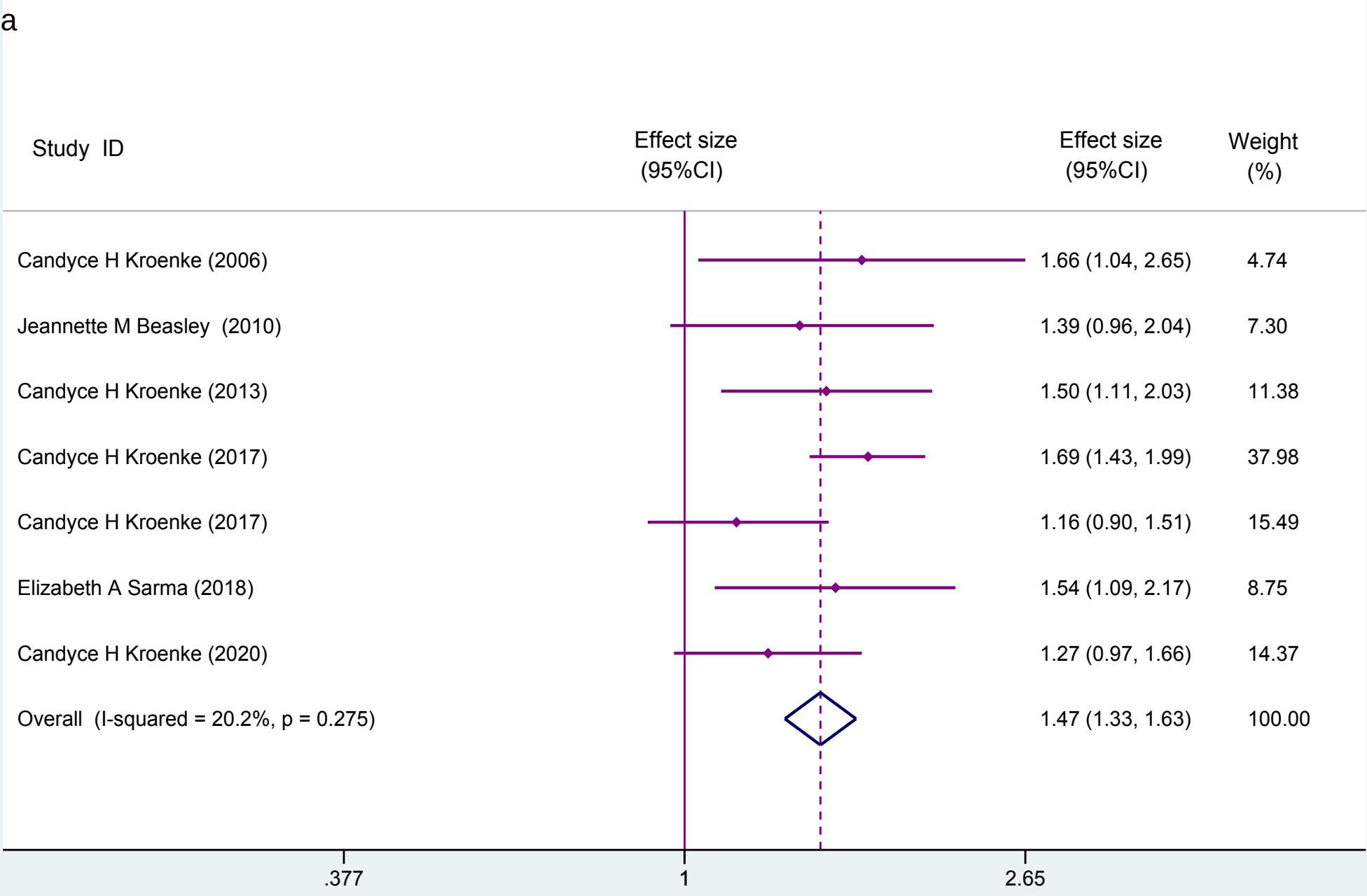
a



b



Supplementary Figure 7 Association between social isolation or loneliness and all-cause mortality in patients with CVD. a. Association of social isolation and all-cause mortality in patients with CVD (n=8 of included studies); b. association of loneliness and all-cause mortality in patients with CVD (n=4). The pooled effect estimates were generated using a random-effects model. The statistical tests were two-sided. Each solid diamond represents the effect size of each study. Horizontal bars parallel to the X-axis represent 95% confidence intervals for each study effect size. The hollow diamond represents the overall estimated effect and its 95% confidence interval. Data are presented as HR, 95%CI.



Supplementary Figure 8 Association between social isolation and all-cause mortality, cancer-specific mortality in patients with cancer. a. Association of social isolation and all-cause mortality in patients with cancer (n=6 of included studies); b. association of social isolation and cancer-specific mortality in patients with cancer (n=7); c. association of social isolation and all-cause mortality in patients with breast cancer (n=4); d. association of social isolation and cancer-specific mortality in patients with breast cancer (n=4); e. association of social isolation and cancer-specific mortality in patients with colorectal cancer (n=3). b,c,d: The pooled effect estimates were generated using a random-effects model. a, e: The pooled effect estimates were generated using a fixed-effects model. The statistical tests were two-sided. Each solid diamond represents the effect size of each study. Horizontal bars parallel to the X-axis represent 95% confidence intervals for each study effect size. The hollow diamond represents the overall estimated effect and its 95% confidence interval. Data are presented as HR, 95%CI.