**Supplemental Digital Content:**

**Loneliness, social isolation, and living alone associations with mortality risk in individuals living with cardiovascular disease: A systematic review, meta-analysis, and meta-regression**

**Full Medline (Ovid) Search Strategy**

1. cardiovascular disease.mp. or exp Cardiovascular Diseases/
2. ("cardiovascular disease\*" or "heart attack" or "CVD" or "Cardiac" or "angina" or "atheroscelorsis" or "heart\*" or "heart disease\*" or "heart diseases" or "heart failure" or "congestive heart failure" or "coronar\*" or "coronary heart disease" or "coronary artery disease" or stroke or "CVA" or "cerebrovascular accident" or "myocard\* infarct\*" or "myocardial ischaemia" or "acute coronary syndrome").ti. or ("cardiovascular disease\*" or "heart attack" or "CVD" or "Cardiac" or "angina" or "atheroscelorsis" or "heart\*" or "heart disease\*" or "heart diseases" or "heart failure" or "congestive heart failure" or "coronar\*" or "coronary heart disease" or "coronary artery disease" or stroke or "CVA" or "cerebrovascular accident" or "myocard\* infarct\*" or "myocardial ischaemia" or "acute coronary syndrome").ab.
3. 1 or 2
4. exp \*Social Isolation/
5. exp \*Loneliness/
6. 4 or 5
7. ("loneliness" or "lonel\*" or "social\* isolat\*" or "living alone" or "live alone" or "social\* alienat\*" or "social\* network\*" or "solitud\*" or "social relationships" or "social participation" or "social integration").ti. or ("loneliness" or "lonel\*" or "social\* isolat\*" or "living alone" or "live alone" or "social\* alienat\*" or "social\* network\*" or "solitud\*" or "social relationships" or "social participation" or "social integration").ab.
8. 6 or 7
9. exp \*mortality/ or "cause of death"/ or child mortality/ or fatal outcome/ or fetal mortality/ or hospital mortality/ or infant mortality/ or maternal mortality/ or mortality, premature/ or survival rate/
10. (“mortality" or "mortality rate" or "death rate" or "longevity" or "proportional hazard models" or "all cause mortality" or "dead" or "death" or "dying" or "surviv\*" or "cause of death" or "decease\*").ti. or ("mortality" or "mortality rate" or "death rate" or "longevity" or "proportional hazard models" or "all cause mortality" or "dead" or "death" or "dying" or "surviv\*" or "cause of death" or "decease\*").ab.
11. 9 or 10
12. 3 and 8 and 11
13. limit 12 to english language
14. limit 13 to humans

**PRISMA 2020 Checklist**



| **Section and Topic** | **Item #** | **Checklist item** | **Location where item is reported** |
| --- | --- | --- | --- |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review. | 1 |
| **ABSTRACT** | | |  |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | 2 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 4 - 6 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 6 |
| **METHODS** | | |  |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 6-7 |
| 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. | 8 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Medline (OVID) supplementary Material |
| 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. | 8 - 9 |
| 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. | 8 - 9 |
| 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. | 7 |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | 6-7 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 9 |
| 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. | 9 |
| 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)). | 9-10 |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | 9 - 10 |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 10, supplementary material |
| 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. | 9 - 11, 14 - 18 |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | 18 - 20 |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | 20 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 19 - 22 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | 8 - 9, supplementary material  (risk of bias, heterogeneity) |
| **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. | 13 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | 11 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | 11 - 12 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Supplementary material |
| 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. | Supplementary material |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | 14 -18 |
| 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. | 15 - 17 |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | 18 - 20 |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | 20 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | 21 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | 16-22  (risk of bias, heterogeneity, publication bias) |
| **DISCUSSION** | | |  |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | 23 - 25 |
| 23b | Discuss any limitations of the evidence included in the review. | 26 - 28 |
| 23c | Discuss any limitations of the review processes used. | 27-28 |
| 23d | Discuss implications of the results for practice, policy, and future research. | 28 – 29 |
| **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. | 6 |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | 6 |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. |  |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | 1 |
| Competing interests | 26 | Declare any competing interests of review authors. | 1 |
| 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. |  |

*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/>

**Table S1. Overview of studies included in review: studies grouped according to predictor variable i.e. living alone, social isolation, loneliness**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **First author,**  **year published** | **Methods**  1) Participants including total number at point of analysis (n); % male (m); % female (f); Mean (SD)/ ± / Median (IQR), Age, years  2) Median (IQR), Mean or not specified length of follow-up  3) Race/ethnicity | **CVD Diagnosis** | **Outcomes**  1) All-cause mortality  2) Cause-specific mortality | **Method used to assess predictor variable** | **Covariates adjusted for in the analysis** | **Results** |
| **Studies with a measure of loneliness (n = 4)** | | | | | | |
| Christensen et al. (2020) | 1) Participants from the Den Heart study in Denmark; n = 13 463; m (70%) f (30%); M = 66.1 years (SD unclear) (women); M = 64.9 years (SD unclear) (male)  2) 1 year  3) Race/ethnicity not defined. Participants drawn from Danish heart centres. | IHD; arrhythmia;  HF; heart valve disease | 1) All-cause mortality  2) – | Single self-report question about feeling lonely from the Danish National Health Survey: “*Does it ever happen that you are alone even though you would prefer to be with other people?”* | **Model 1:** Unadjusted  **Model 2:** Adjusted for living alone, age, education level, cardiac diagnosis, comorbidity, BMI, smoking behaviour, alcohol intake and medication compliance | Analysis stratified by gender:  **Women who reported feeling lonely**  **Model 1:** HR 1.9 95% CI (1.29-2.78)  **Model 2**: HR 2.92, 95% C.I (1.55– 5.49)  **Men who reported feeling lonely**  **Model 1:** HR 1.89, 95% CI (1.46-2.44)  **Model 2:** HR 2.14, 95% C.I (1.43-3.22).  Loneliness predicted all-cause mortality among both women and men (unadjusted and adjusted). |
| Herlitz et al. (1998) | 1) Patients who underwent CABG surgery in Sweden, n = 1290, m(82%), f(22%), Median =64 (32-81) years.  2) 5 years  3) Race/ethnicity not defined. Participants drawn from Scandinavian Heart Center in G6teborg. | Patients with CAD who underwent CABG surgery | 1) All-cause mortality  2) – | Single question which participants could endorse “*I feel lonely”* . Categorised into those who feel lonely or not. | **Model 1:** Univariate  **Model 2:** Adjusted for LVEF, current smoker, age, CHF, diabetes, renal dysfunction, previous cerebrovascular disease and intermittent claudication. | **Model 1:** RR, 1.66, 95% CI (1.13-2.43).  **Model 2:** RR, 1.78, 95% CI (1.17-2.71)  The question *“I feel lonely”* associated with mortality. |
| Manneman et al. (2018) | 1) Participants from 11 counties in Minnesota, United States (US). Study used the REP records linkage system, n =1681, m (53.42%), f(46.38%), M = 73.29 (12.51) years.  2) 8 ± 4 months.  3) Race/ethnicity not defined. Participants from the US and authors reported study was conducted in a population of mostly white race in limitations section. | HF | 1) All-cause mortality  2) – | Measure adapted from UCLA Loneliness Scale: 4 items – scored on 5-point scale (score ranges from 4-20). Higher scores = greater *perceived* social isolation Splines were used : low (scores, 4-8), moderate (9-12), high (scores, 13-20) perceived social isolation | Model 1: Unadjusted  Final model: Fully adjusted (age, sex, Charlson comorbidity index, marital status, education) | **Low perceived social isolation**  **Model 1:** HR, 1.00  **Final Model:** HR, 1.00  **High perceived social isolation:**  **Model 1:** HR, 3.23, 95% CI (1.60-6.51)  **Final Model:** HR 3.74, 95% CI (1.82-7.70)  After adjustments for covariates, patients high perceived social isolation > 3.5 times increased risk of all-cause mortality compared to those reporting low perceived social isolation. |
| Yu et al. (2020) | 1) Participants recruited from the NHIS in Taiwan, n = 1267, m (51.85), f(41.6%), Age group 65-74 years (32%), 75+ years (66.2%).  2) 10 years  3) Race/ethnicity not defined. Participants were persons living in Taiwan. | CVD | 1) All-cause mortality  2) - | Loneliness: measured with the single item *‘in the last week have you experienced loneliness?”.* Scored on a scale of 0-3. | **Model 2:** adjusted for demographic variables, health-related behaviours and health status (age, sex, education attainment, working status, monthly income, smoking status, alcohol consumption, physical activity expenditure, BMI, difficulties with daily living, Charlson comorbidity index, depressive symptoms).  Final Model: Both loneliness and social isolation added into the fully adjusted model. | **Model 2:** HR 0.95, 95% CI (0.82-1.09)  **Final Model:** HR, 0.92 95% CI (0.80-1.06)  Loneliness was not associated with an increased risk of mortality after accounting for covariates. |
| **Studies with a measure of social isolation (n = 11)** | | | | | | |
| Birket-Smith et al. (2009) | 1) Cardiology outpatients with and without mental disorders at a university hospital in Denmark, n =85, m (57%), f(43%), M = 72.4  2) 6 years  3) ) Race/ethnicity not defined. Participants were patients attending a Danish university hospital. | Cardiac disease: primary diagnoses were chronic IHD, CHF, atrial arrythmias and hypersensitive heart disease | 1) All-cause mortality  2) – | This was a single item defined as number of social contacts. Authors noted “number of social contacts (less than one to more than five per day) were noted”. | Adjusted for age, sex, education, mental disorder, current and history of mental disorder, cardiac diagnosis and noncardiac comorbidity. | HR 0.669, 95% CI (0.460 – 0.973).  Number of social contacts was a significant predictor of mortality. |
| Brummet et al. (2001) | 1) Patients in this study were participants in the MOSS study in the United States, n = 430, Isolated group m (70.6%), f(29.4%), M = 61.7 (11.3) years  Non isolated group m (66.8%), f (33.2%), M = 63.9 (11.4) years.  2) Mean follow-up = 47.3 months.  3) Isolated group, white ethnicity = 85.4%; Non-isolated group white ethnicity = 75.1%.. | CAD | 1) All-cause mortality  2) CV-specific mortality | Mannheim Social Support Interview (6 items) – yielded a measure of network size; Participants who reported three or fewer network members served as the reference- yielded 5 additional measures- psychological everyday support, psychological crisis support, instrumental everyday support, relationship satisfaction. In addition: asked about confidants and living alone, perception of social support and participation in religious activities. | Adjusted for number of disease vessels, LVEF, CHF, age, co-morbidity. | **All-cause mortality**  Most isolated group:  RR 2.11 (X2 (1) =10.9) , 95% CI (1.39-3.19)  **CV-specific mortality**  Most isolated group:  RR 2.43 (X2 (1) =11.8) , 95% CI (1.52-3.89)  Those with three or fewer people in their social support network were at increased risk for both all-cause and cardiac specific mortality. |
| Jenkinson et al. (1993) | 1) Participants recruited from ASSET trial in England, n = 1376, m (78%), f(22%), Age range = <60-75+ years.  2) Median follow-up = 3 years  3) Race/ethnicity not defined. Participants were recruited from ASSET trial, conducted on a multicentre basis across centres in Europe (UK, Norway, Sweden and Denmark) | AMI | 1) All-cause mortality  2) – | Used Ruberman et al., (1984) approach: Unvalidated 3-item questionnaire (2 categories). Data categorised into socially isolated or not socially isolated. | **Model 1:** Adjusted for age-group, previous documented infarction, hospital complications, history of diabetes, history of hypertension.  Model 2: Model 1 and car ownership | **Model 1:** HR 1.49 95% CI (1.01-2.18)  **Model 2:** HR 1.33, 95% CI (0.89-1.98).  Social isolation no longer predictive of premature mortality when car ownership added to model. |
| Kreibig et al. (2014) | Patients from the Heart and Soul study in the United States with stable CHD  n= 1019, Socially Isolated  m(82%), f(18%)  Non-Socially Isolated  m(82%), f(18%)  Socially Isolated  M = 63.4 ±10.7  Non-Socially Isolated  M = 68 ±10.7  2) M= 6.7 years  3) Isolated group, white ethnicity = 63%; Non-isolated group white ethnicity = 59%.. | CAD | 1) All-cause mortality  2) – | Berkman Social Network Index (standardised) group membership: low, medium, high levels of Social Integration.  SI was dichotomous for the HR. it was socially isolated versus non-isolated as a predictor. | **Model 1:** Adjusted for age alone  **Final model:** demographic and disease-relevant predictors of mortality (male sex, ethnicity, BMI, urine norepinephrine, CRP, and HbA1c Income, LVEF, inducible ischemia, MI, stroke, COPD, omega-3 fatty acids, smoking and medication adherence for potential confounders and mediators: urine norepinephrine, CRP, HbA1c, omega-3 fatty acids, smoking and medication adherence retained. | **Model 1:** HR 1.61, 95% CI (1.26-2.05).  **Final Model:** HR 1.33, 95% CI 0.92-1.91  After adjustment for demographic and disease-relevant confounders, socially isolated patients had a 50% greater risk of death than non-isolated patients. |
| Lett et al. (2007) | 1) ENRICHD trial, patients with recent AMI screened for depression or low perceived social support in the United States, n= 1,296, Low SNQ: m(58%) f(42%), M = 61 (13) years; High SNQ: m(58%) f(42%), M = 60 (12) years;  2) Mean follow up 2.1 years  3) Caucasian (66%), African American (19%), Hispanic (10%), Asian (3%), American Indian (2%). | AMI | 1) Primary outcome: All-cause mortality or nonfatal MI (combined). Secondary outcome: all-cause mortality  2) Secondary outcome cardiovascular- specfic mortality | Social Networks Questionnaire (SNQ): categorised into low and high social networks. | Age, sex, ethnicity, smoking, BMI, education, income, antidepressant use, risk score (weighted composite of prior AMI, history of CHF, history of stroke and/or transient ischemic attack, history of pulmonary disease, diabetes, Killip class, creatine, ejection fraction, CABG, use of non-ACE vasodilators) | SNQ scores were not related to mortality.  The ENRICHD trial was not powered to test secondary endpoints: all-cause and cardiovascular mortality. |
| Menedez-Villalva et al. (2015) | 1) Patients diagnoses with AHT at the Marinamansa-A Cuna Health Centre in Ourense Spain, n =236, m (32.6%), f(67.4%), M =63.51 years (62.05-64.96)  2) 9-years  3) Race/ethnicity not defined. Participants were patients attending a Health Centre in Spain. | AHT | 1) All-cause mortality  2) – | Social network (number of social contacts measured using the Blake McKay method: 0-1, low social network; and >2, high social network).  Low vs. high social network | **Model 1**: Crude HR for low social network  **Final Model:** Adjusted for blood pressure, heart rate, BMI, CVD risk, alcohol consumption, smoking, hypercholesterolemia, diabetes adherence to treatment. | **Model 1:** HR 1.7, 95% CI (0.9-3.3).  **Final Model:** HR 2.6, 95% CI (1.3-5.5).  Low social network related to higher global mortality. |
| Rodriguez-Artalejo et al. (2006) | Patients admitted for HF-related emergencies at 4 Spanish hospitals, n -371, m (41.8%), f(52.2%), M = 77.2(6.7) years.  2) Mean follow-up = 6.5 months.  3) Race/ethnicity not defined. Participants were recruited from 4 Spanish hospitals. | HF | 1) All-cause mortality  2) – | Social network measured using (continuous) 4-item questionnaire: marital status; living arrangements; saw/telephone contact with family; were at home alone for less than 2 hours per day. Social Network low when 2 or fewer present.  Data stratified on basis of 3 social-network categories (high, moderate, low). | **Model 1:** Unadjusted  **Final Model:** Principal sociodemographic and biomedical variables [sex, age, educational level, functional grade, LVEF, arterial hypertension at discharge, serum creatine, admission, comorbidity, atrial fibrillation, previous hospitalisation, treatment (angiotensin-converting enzyme inhibitors, Beta blockers, digoxin), etiology of heart failure, disability for basic activities of daily living, disability for instrumental activities of daily living, limitation in walking several hundreds of meters), lifestyle related variables (tobacco use, alcohol consumption, excessive alcohol consumption in physician’s opinion) , depressive symptoms , emotional support, functional support, treatment compliance in the physician’s opinion. | **High Social Network:**  **Model 1**: HR 1.00  **Final Model:** HR 1.00  **Low Social Network:**  **Model 1:** HR 1.03 95% CI (0.55-1.92)  **Final Model:** HR 0.67, 95% CI (0.31-1.45) |
| Ruberman et al. (1984) | 1) American male survivors of acute MI from Beta blocker heart attack trial (n = 2319), m (100%), Age range = 60-69 years.  2) 3 years  3) Race/ethnicity not defined. Participants recruited from the CHAT trial in the US. | MI | 1) All-cause mortality  2) – | Unvalidated 3-item questionnaire (2 categories). Data categorised into socially isolated or not socially isolated. | **Model 1:** Univariate: none **Final Model:** age, BHAT risk class, heart rate, taking digitalis, CHF, myocardial summary, ventricular arrhythmia, treatment group, angina (based on MD opinion), cigarettes. | **Model 1:** Log rank *X*21 = 26.9. Greater all-cause mortality risk in univariate model.  **Final Model**: only tested combined effects of social isolation and stress in multivariate model. |
| Rutledge et al. (2016) | 1) Participants included American females from the WISE study, recruited from 4 sites in the United States, n = 517, f(100%), M =58.3 (11.4) years.  2) Median follow-up 9.3 years  3) Non-Hispanic white (81.1%), African American (17.4%), Other (1.4%). | CAD | 1) All-cause mortality  2) – | Cohen’s Social Network Index (SNI).  Continuous measure. | Age, education history, ethnicity, BDI scores, waist-circumference, CAD severity scores (based on percent stenosis), and history of diabetes, smoking, dyslipidaemia, and hypertension | HR 0.85, 95% CI (0.67-1.1)  SNI scores were not associated with increased risk of mortality. |
| Spaderna et al. (2017) | 1) Participants from the Waiting for a New Heart Study in 17 hospitals (16 in Germany, 1 in Austria), n=148, m(81.8%), f(18.2%), M 52.2 (11.7) years.  2) Median follow-up of 70 months.  3) Race/ethnicity not defined. Participants recruited from German and Austrian hospitals. | Adults post heart transplantation surgery | 1) All-cause mortality  2) – | Number of social contacts assessed asking for “the number of relatives and close friends you have contact with during 1 month. Score was reversed by multiplication with -1, so that a higher score reflected more social isolation. | **Model 1:** Univariate  **Final model:** Reduced model only significant terms plus main effects and the interaction between SI and depression (donor age, ischemic dx, depressive symptoms, depression x SI) | **Model 1:** HR 1.048, 95% CI (0.996-1.103)  **Final Model:** HR 1.056, 95% CI (1-1.115).  Social isolation did not independently increase the risk of mortality |
| Yu et al. (2020) | 1) Participants recruited from the NHIS in Taiwan, n = 1267, m (51.85), f(41.6%), Age group 65-74 years (32%), 75+ years (66.2%).  2) 10 years  3) Race/ethnicity not defined. Participants were persons living in Taiwan. | CVD | 1) All-cause mortality  2) – | Index comprised of  different aspects of social network:  marital status; living alone; less than monthly contact with their children and friends; did not participate in any volunteer or social groups in last 3 months. | **Model 1:** adjusted for demographic variables, health-related behaviours and health status (age, sex, education attainment, working status, monthly income, smoking status, alcohol consumption,  physical activity expenditure, BMI, difficulties with daily living, Charlson comorbidity index, depressive symptoms).  **Final Model:** Both SI and loneliness added into the fully adjusted model. | **Model 1:** HR 1.16, 95% CI (1.06-1.26)  **Final Model:** HR, 1.16, 95% CI (1.07-1.27).  Social isolation was associated with an increased risk of mortality after accounting for covariates |
| **Studies with a measure of living alone (n = 22)** | | | | | | |
| Appeleros et al. (2003) | 1) All cases of first-ever stroke registered in Orebro Sweden. Participants with first ever stroke  (n = 377); m (45%);  f (55%); M = 77  2) 1 year  3) Race/ethnicity not defined. Participants were persons living in Sweden. | Stroke | 1) All-cause mortality  2) - | Living arrangements | Unadjusted (univariate model) | Univariate model OR 1.15 (CI 1.1-1.2).  Living alone significant predictor in univariate analysis but not in multivariate analysis. |
| Boru et al. (2007) | 1) Patients with no prior history of stroke hospitalised to Neurology Clinics in Dr. Lutfi Kirdar Katal Training and Research Hospital Neurology Clinics in Turkey (n = 100); m:(60%); f: (40%); M = 66.46 ± 9.95 years  2) Up to 6 months.  3) Race/ethnicity not defined. Participants were patients hospitalised in Dr. Lutfi Kirdar Kartal Training g and Research Hospital Neurology Clinics in Turkey. | Stroke | 1) All-cause mortality  2) - | Questionnaire: living conditions; household status | **Model 1:** Univariate  **Model 2:** Multivariate Model adjusted for age; gender; stroke type; hypertension; smoking; pre-stroke dementia; peripheral atherosclerosis; family history; TIA | **Model 1:** OR 3.756 95% CI (1.633-8.639);  **Model 2:** OR 2.666 95% CI (1.090-6.535). Living alone found to be significant when “forward conditional method applied”. |
| Bucholz et al. (2011) | 1) Patients hospitalised with AMI from PRIEMIER registry in the United States; n = 2,264; Living alone m (57.5%); f (42.5%)  Not living alone  m (70.8%); f (29.2%); Living alone M (62. 7 ± 13.5) years  Not living alone  M (59.3 ± 12.3) years  2) 4 years  3) Living alone: white (68.3%), Black (27.4%), Hispanic (2.6%), Asian (0.4%), Other (1.3%). (57.5%); f (42.5%)  Not living alone  white (75.9%), Black (19.3%), Hispanic (2.4%), Asian (0.3%), Other (2.1%). | AMI | 1) All-cause mortality  2) - | Self-report patient interview; dichotomous variable living alone (yes or no) | **Model 1:** Unadjusted  **Model 2:** adjusted for: age; gender; race; BMI; marital status; employment status; living location; pet ownership; medical care payer; source of care; financial barriers to health care use; hypertension; depression; previous AMI, CHF; LVSF; creatine; angiotensin-converting enzyme inhibitor and β blockers at discharge; ESSI score; baseline health status scores. | **Model 1:** HR 1.56 95% CI (1.24- 1.96)  **Model 2:** HR 1.35 95% CI (0.94-1.93).  Patients who lived alone had higher crude 4-year mortality. After multivariate adjustment patients who lived alone had comparable risk of mortality as patients who lived with others. |
| Case et al. (1992) | 1) Participants from placebo group of the Multicenter Diltiazem Post-Infarction Trial in the United States; n= 1195 Living alone: m (71%); f (29%)  Not living alone: m (81%); f (19%) Living alone : M (61 ± 10) years  Not living alone: M (58 ± 10) years  2) Mean follow-up= 25 months  3) Living alone: white (89%),  Not living alone  white (90%) | AMI | 1) -  2) CV-specific mortality | Self-report: Number of persons living with the patient at time of enrolment to Trial | Adjusted for: NYHA class; LVEF; VCPs; Pulmonary congestion; Prior infarction; Age; race; β- Blockers; Education; disrupted marriage. | HR (adjusted for covariates) 1.58 95% CI (0.91 -2.74).  Living alone is an independent risk factor for prognosis after MI including Cardiac-specific mortality . |
| Christensen et al. (2020) | 1) Participants from the Den Heart study in Denmark; n = 13 463; m (70%) f (30%); M = 66.1 years (SD unclear) (women); M = 64.9 years (SD unclear) (male)  2) 1 year  3) Race/ethnicity not defined. Participants drawn from Danish heart centres. | IHD, arrhythmia, HF, heart valve disease | 1) All-cause mortality  2) - | Objective information on cohabitation was obtained from national registers. Living alone defined as a man or woman not in identifiable cohabitation. Cohabitation defined by the following: married couple, other couple and household consisting of several people from more than one family (e.g. nursing home) | **Model 1:** Unadjusted  **Model 2:** adjusted for loneliness, age, education level, cardiac diagnosis, comorbidity, BMI, smoking behaviour, alcohol intake and medication compliance | Analysis stratified by gender:  **Women living alone** HR (unadjusted) 0.86 95% CI (0.51-1.43)  Women living alone HR (adjusted for  covariates) 0.64, 95% C.I (0.33 – 1.24)  **Men living alone** HR (unadjusted) 1.83, 95% CI (1.35-2.49)  Men living alone HR (adjusted for covariates) 2.14, 95% C.I (1.43-3.22).  Men living alone had an unadjusted increased risk of all-cause mortality. |
| Hagstrom et al. (2018) | 1) Patients from the STABILITY clinical trial. Cohort from 39 participating countries across South America, Australia, Europe, North America, Asia,  n = 14, 849, m (81.6%); M = 65.0 (59, 71) years.  2) Median = 3.7 years  3) Race/ethnicity not defined. Participants drawn from 39 participating countries, across South America, Australia, Europe, North America, Asia. | CHD | 1) All – cause mortality  2) CV-specific mortality | Patients completed a baseline questionnaire. Living alone : dichotomous variable: yes or no. | **Model 1**( adjusted for age, sex, treatment randomisation)  **Model 2:** adjusted for Model 1 and CV risk factors, previous MI, CABG surgery, PCI, multivessel disease, renal dysfunction, poly vascular disease, systolic and diastolic blood pressures, low density and high density lipoprotein cholesterol, diabetes, smoking status, BMI, family history of CHD, years of education). | **All-cause mortality:** **Model 1:**  HR 1.488, 95% CI (1.270- 1.744)  **Model 2:** (adjusted for covariates) HR 1.476 (1.258 - 1.733)  **CV-specific mortality:**  **Model 1:** HR 1.663 95% CI (1.368- 2.021)  **Model 2:**  (adjusted for covariates) HR 1.682 (1.383 – 2.047)  Living alone associated with higher risk of all-cause mortality and CV-specific death. |
| Gandhi et al. (2019) | 1) Patients from the CLARIFY study included outpatients with stable CAD in 45 countries across South America, Australia, Europe, North America and Asia,; n= 32 367;  Living alone: m (61.8%)  M = 67.2 (10.7) years  Not living alone: m (79.6%); M = 63.8 (10.4) years  2) 5 years  3) Living alone: white (72.5%), South Asian (3.6%), Chinese (4.6%), Japanese/Korean (3.9%), Hispanic (3.0%), Black/African (1.2%), Unknown (11.3%). Not living alone: white (63.8%), South Asian (8%), Chinese (9%), Japanese/Korean (3.1%), Hispanic (5.1%), Black/African (1%), Unknown (10.2%). | CAD | 1) All-cause mortality  2) CV specific mortality | Electronic case report forms at baseline and yearly visits up to 5 years. Living arrangement status: dichotomous variable: ‘living alone” or ‘not living alone’. | **Model 1** (unadjusted); **Model 2** (adjusted for age, sex);  **Model 3** (adjusted for Model 2, geographical region, smoking status, diabetes, peripheral arterial disease, MI, percutaneous coronary intervention, CABG surgery, asthma/chronic obstructive pulmonary disease, CHF, systolic blood pressure, diastolic blood pressure, LVEF and number of vessels with coronary artery stenosis. | **All-cause mortality:**  **Model 1** (unadjusted)  HR 1.31 95% CI (1.17-1.47), **Model 2**: HR 1.13 95% CI (1.01 -1.26); **Model 3**: HR 1.08 95% CI (0.95-1.23)  **CV- specific mortality:**  **Model 1** (unadjusted)  HR 1.37 95% CI (1.20-1.58), **Model 2**: HR 1.18 95% CI (1.02 -1.35); **Model 3:** HR 1.12 95% CI (0.95-1.32).  In unadjusted models, patients living alone had a higher risk of all-cause mortality and CV death. After adjustments for age and sex, living alone remained significant but effect was not seen following multivariate adjustment. |
| Kitamura et al. (2013 | 1) Patients from the OACIS prospective multicentre study that enrols consecutive patients with AMI from the Osaka region of Japan, n = 5845, Living alone: m (66.7%), M = 69.0 median (IQR) 60.0 0 77.0.  Not living alone: m (77.5%), M = 66.0 median (IQR) 58.0 – 74.0.  2) Median = 735 days after discharge  3) Race/ethnicity not defined, patients from the OACIS study in Japan. | AMI | 1) All-cause mortality  2) - | Patients asked at admission whether they lived with family members, others or alone.  Living alone vs. not living alone. | **Model 1** (crude ratio);  **Model 2:** adjusted for age, gender, employment status,  BMI, STEMI, coronary risk factors, Killip class, re-perfusion therapy. | **Model 1** HR 1.18 95% CI (0.90 – 1.53); **Model 2** HR 0.98 (0.71 – 1.33). |
| Lamminatausta et al. (2014) | 1) Participants from FINAMI MI register, a population based register in Finland aimed to evaluate ass suspected MI events, n = 15,330.  age and gender breakdown unclear.  2) 1 year  3) Race/ethnicity not defined, participants from FINAMI MI register, in Finland. | MI | 1) Case fatality: All-cause mortality  2) – | Self-report: record linkage to the MI register.  3 categories for living arrangements: living with  > 2 people; 2 people; living alone. | Unclear | HRs, ORs, RRs not reported.  Results stratified by age groups: 35-64 years, 65-74 years, 75-99 years.  Single living was associated with higher case fatality of incident ACS. |
| Lu et al. (2016) | 1) Adult African-American patients from the United States with a diagnosis of heart failure, n = 611, m (53%); f(47%), M = 66 ± 15 years  2) 1 year  3) African American (100%). | HF | 1) Mortality from any cause  2) – | Self-reported by patients. Living alone, living with family member or spouse, or living in a nursing home. | Adjusted for age, gender, BMI, peak troponin 1, LVEF, β-type natriuretic peptide, hypertension, diabetes, hyperlipidaemia, CAD. | OR 0.69 95% CI (0.43 – 1.10).  Mortality significantly higher in nursing home patients compared to those living alone or with others. |
| Mard et al. (2010) | 1) All surviving employed MI patients admitted consecutively to the Department of Cardiology in two hospitals in Denmark, n = 242, m (87.6%), median age 56 years (IQR 49-60; range 33-77), f (12.4%) median age 56 years (IQR 49-59; range 36-68).  2) Median follow-up was 16.06 years (IQR 9.84 – 16.80)  3) Race/ethnicity not defined, participants recruited from two hospitals in Denmark. | MI | 1) All-cause mortality  2) – | Self-report during interviews completed.  Patients living alone compared to those living with a partner. | **Model 1**: Unadjusted  **Final model:** Age, diabetes, atrial fibrillation, ejection fraction > 45% (reference category, <35%., 35-45% | **Model 1:** Crude mortality ratio 1.82, 95% CI (1.10-2.98).  **Model 2:** HR 2.55, 95% CI (1.52-4.30). |
| Nakatsuma et al. (2014) | 1) The Coronary Revascularization Demonstrating Outcome Study in Kyoto, Japan (CREDO-Kyoto) AMI registry enrolled consecutive patients with AMI undergoing PCI, n = 4109, living alone m (63%), f (37%), M= 68.5 ± 13.0 year; not living alone m (75%), f (25%). M = 67.6 ± 12.10 years  2) Median follow-up = 1844 days, [IQR]: 1508-2163) days.  3) Race/ethnicity not defined, participants from the CREDO-Kyoto AMI registry in Japan. | AMI | 1) All-cause mortality  2) CV-specific death | Living arrangements collected from hospital charts. Living alone vs . not living alone. | **Model 1:** Unadjusted  **Model 2:** Adjusted for 40 clinically relevant factors: Age, sex, BMI, hypertension, smoking status, on insulin therapy, heart failure, multivessel coronary disease, mitral regurgitation grade 3/4, prior myocardial infarction, prior percutaneous coronary intervention, prior stroke, peripheral vascular disease, eGFR (ml/min/1.73 m2) <30, without haemodialysis, haemodialysis, atrial fibrillation, anaemia, thrombocytopenia, chronic obstructive pulmonary disease, | **All-cause mortality**  **Model 1:** HR 0.97, 95% CI (0.79 – 1.19)  **Model 2:** HR 0.82, 95% CI (0.65 – 1.02).  **CV- specific mortality**  **Model 1:** HR 0.94,, 95% CI (0.70– 1.23)  **Model 2:** HR 0.78, 95% CI (0.57– 1.04).  After adjusting for potential confounders, risk of living alone did not significantly increase risk of all-cause or cardiac-specific mortality. |
| Nielsen et al. (2007) | 1) Cohort study of residents in Denmark, in which ACS incidence was determined, n =450, m(72.4%), f(27.6%), Median age = 60.0years.  2) 1 year  3) Race/ethnicity not defined, participants included residents of Denmark. | ACS | 1) All-cause mortality  2) – | Living arrangements obtained from Danish national registers.  Living alone = single variable. | Adjusted for age and sex | OR 2.4, 95% CI (1.1-5.2).  Living alone positively associated with 365-day mortality. |
| Norekval et al. (2010) | 1) All women with MI treated at one university hospital in Norway, n= 145, f(100%), M = 72(5) years.  2) 10 years  3) Race/ethnicity not defied, participants gathered from one university hospital in Norway. | MI | 1) All-cause mortality  2) – | Living arrangements – self-reported.  Categorised as living alone vs. cohabitating | **Model 1:** Unadjusted  **Model 2:** Adjusted for Age and time since MI. | **Model 1**: HR 2.87 95% CI (Unclear)  **Model 2**: HR 6.24, 95% CI (2.68 – 14.51)  Women living alone had a significantly increased all-cause mortality in unadjusted and adjusted analyses. |
| O’Shea et al. (2002) | 1) Data obtained prospectively from patients enrolled in the GUTSO-III study, n = 13,095 patients from 9 countries including North America, Eastern and Western Europe and Australasia, m (72%), f(28%), M age range = 53-72 years.  2) 1 year  3) Unadjusted 20-day mortality rate by race subgroup: Living alone Caucasian (10%), other (6.9%), Not living alone Caucasian (6.7%), Other (3.6%). | AMI | 1) All-cause mortality  2) – | Living arrangements gathered from self-report interview. Data categorised into living alone vs. not living alone group. | Adjusted for age, lower systolic blood pressure, higher Killip class, elevated heart rate, and anterior AMI. | OR 0.93, 95% CI (0.78-1.11)  Multivariate analysis indicated living alone was not a significant risk factor for mortality. |
| Redfors et al. (2016) | 1) Participants from the SAHLSIS study in Sweden, n = 600, m (64%), f (36%), M = 57 years.  2) Median follow-up 8.8 years (IQR 7.7-10.0).  3) Race/ethnicity not defined, participants from the SAHLSIS study in Sweden. | Stroke | 1) All-cause mortality  2- | Information obtained from structured questionnaires, an interview and examinations at inclusion.  Living situation was categorized as living with a partner or an adult family member (sibling or child over 20 years of age or parent) vs. living alone at the time of index stroke for cases and at baseline for controls. | Models stratified by gender:  **Model 1:** Univariate analysis  **Model 2:** Age, sex, diabetes, smoking, occupation, leisure physical activity, self-perceived psychological stress, alcohol consumption, history of CHD, stroke severity and stroke subtype. | **Model 1 (females):** HR 1.38, 95% CI (0.68-2.77); (**males)** HR 3.33, 95% CI (2.14-5.18).  **Model 2 (females):** HR 1.28, 95% CI (0.62-2.64); **(males)** HR 3.47, 95% CI (2.13-5.65).  Among male participants living alone is an independent predictor of all-cause mortality |
| Reeves et al. (2014) | 1) Participants included consecutive patients enrolled with acute stroke to 11 Ontario hospitals (Registry of the Canadian Stroke Network), n= 10048, m (54%); f(46%), M = 72.24 ± 13.16 years.  2) 1 year  3) Race/ethnicity not defined, participants from 11 hospitals in Canada. | Stroke | 1) All-cause mortality  2) – | Data on living arrangements extracted from registry. Data grouped into living alone vs. living with others. | **Model 1:** Unadjusted  **Model 2:** Adjusted for age, sex, stroke type, stroke severity, past medical history, emergency medical service use. | **Model 1:** OR 0.94, 95% CI (0.84-1.05).  **Model 2:** OR 0.97, 95% CI (0.83-1.14)  Living alone did not significantly predict 1 year mortality. |
| Schockmel et al. (2014) | 1) ) Participants included in ODIN (set up to assess the effectiveness of the I-CARE project), in France, n=575, m (58.6%), f (41.4%, M = 71.1 ± 13.5 years.  2) Median follow-up = 19 months, varying from 0.2 – 48.7 months.  3) Race/ethnicity not defined, participants from ODIN project in France. | HF | 1) All-cause mortality  2) CV-specific mortality | Standardised from used to collect characteristics.  Data grouped into living alone or not living alone. | **All-cause mortality:**  **Model 1:** unadjusted  **Model 2:** adjusted for age, sex, diabetes, hypertrophic cardiomyopathy, severe heart failure, atrial fibrillation.  **CV-specific mortality:**  **Model 1:** unadjusted  **Model 2:** adjusted for age, sex, diabetes, low BMI, severe HF and previous heart failure hospitalisations within the year. | **All-cause mortality:**  **Model 1:** Crude HR 1.58, 95% CI (1.12-2.22)  **Model 2**: HR 1.77, 95% CI (1.11-2.81)  **CV-specific mortality:**  **Model 1:** Crude HR 1.80, 95% CI (1.15-2.81)  **Model 2:** HR 2.26, 95% CI (1.24-4.10)  After adjustment for covariates, living alone was associated with an increased risk of both all-cause and CV-specific mortality. |
| Takeuchi et al. (2020) | 1) Data from a single-centre observational study of consecutive patients who underwent PCI for ACS in Japan, n = 2547, m (73.3%), f(26.7%), M= 68 ± 11.8 years  2) Median follow-up = 5.3 years  3) Race/ethnicity not defined, participants from Japan. | ACS | 1) All-cause mortality  2) – | Demographics including living arrangements retrospectively collected from medical records.  Data grouped into living alone vs. living together. | **Crude Model:** Unadjusted  **Final Model:** adjusted for age, sex, hypertension, diabetes, smoking status, dyslipidaemia, family history of CAD, BMI, statin variables, CKD, STEMI, prior MI, and Killip 2-4 | \*Crude Model: HR 1.81, 95% CI (1.13-2.88),  \*Final Model: HR 2.30, 95% CI (1.38-3.84).  \*Results given for younger population < 65 year. The cumulative incidence of all-cause death was not significantly higher in older group (≥65 years). |
| Udell et al. (2012) | 1) Eligible participants enrolled in the REACH Registry from 44 countries, n = 44573.  Living alone: m(44.2%), f(55.8%), Median = 73.1 years IQR (65.2-79.0)  Not Living alone: m(69.6%), f(30.4%), Median = 68.5 years IQR (60.6 – 74.9)  2) 4 years  3) Living alone: Black (5.8%), White (75.15%), East Asian (10.4%), Hispanic (2.8%), South Asian (0.3%), Other Asian (2.1%), Other (3.4%). Not living alone: Black (3.1%), White (60%), East Asian (18.5%), Hispanic (5.5%%), South Asian (1%), Other Asian (6.2%), Other (3.7%) | Atherothrombosis: Participants included those with established atherothrombosis and those with at least 3 CV risk factors. | 1) All-cause mortality  2) CV – specific mortality | Participants were asked at baseline whether they lived alone (yes/no) | **Model 1**: Unadjusted  **Model 2**: adjusted for age, sex, employment , education, race/ethnicity, geographic region, history of smoking, diabetes mellitus, BMI, atrial fibrillation/flutter, heart failure, vascular disease status, prior ischemic event, statins (baseline), aspirin (baseline). | **All-cause mortality:**  **Model 1:** Unadjusted HR 1.27, 95% CI (1.19-1.37)  **Model 2:** Adjusted Outcomes reported by age-group:  45-65 years:  HR 1.24, 95% CI (1.01-1.51)  66-80 years:  HR 1.12, 95% CI (1.01-1.26)  > 80 years:  HR 0.92, 95% CI (0.79-1.06)  **CV-specific mortality:**  **Model 1:** Unadjusted HR 1.25, 95% CI (1.14-1.37)  **Model 2:** Adjusted Outcomes reported by age-group:  45-65 years:  HR 1.29, 95% CI (1.01-1.64)  66-80 years:  HR 1.11, 95% CI (0.96-1.28)  > 80 years:  HR 0.93, 95% CI (0.77-1.12 |
| Vujcic et al. (2015) | 1)Participants admitted to the coronary care unit of Institute of Cardiovascular Disease, Clinical Centre of Serba in Belgrade, n = 135, m (75.6%), f (24.4%), M = 57.82 ± 10.8 years.  2) Median follow up = 77 months (5.9 years)  3) Race/ethnicity not defined, participants from Belgrade. | MI | 1) All-cause mortality  2) - | Patients completed a questionnaire including whether or not they lived alone and if not, they were asked about the number and nature of family members residing with them. Classified into two groups living alone and living with family (nobody reported living with a friend or in a group setting). | **Model 1:** Unadjusted  **Model 2:** Adjusted for age, sex, obesity, individuals smoking currently (yes or no), hyperlipidaemia, hypertension, diabetes, previous CVD, previous disease other than CVD, localisation of myocardial infarction, thrombolytic therapy, marital status, education (<12 years, >12 years) | **Model 1:** HR 5.65, 95% CI (2.59-12.34).  **Model 2:** HR 7.60, 95% CI (1.99-29.08)  Living alone was an independent predictor or mortality after AMI. |
| Zhu et al. (2021) | 1) Participants enrolled in the TOPCAT trial across 6 countries: the Americas (United States, Canada, Argentina, Brazil), Russia and Georgia, n = 3103, Living alone: m(33%), f(67%), M = 72 (64-79) years.  Not Living alone: m(56.8%), f)43.2%), M = 67 (60-74) years.  2) M = 3.3 years  3) Living alone: white (85.2%), Not living alone (92%). | HF | 1) All-cause mortality  2) CV – specific mortality | All participants asked at baseline, “Do you currently live alone?” or “Do you live with a spouse or significant others?”  Data categorised into living alone, not living alone. | **Model 1:** Unadjusted  **Model 2:** Adjusted for age, sex, New York Association functional class, diastolic blood pressure, serum creatine, haemoglobin, previous hospitalization for CHF, diabetes. | **All-cause mortality:**  **Model 1:** Crude HR 1.34, 95% CI (1.10-1.63)  **Model 2:** HR 1.12, 95% CI (0.91-1.38)  **CV-specific mortality:**  **Model 1**: Crude HR 1.28 95% CI (1.00-1.65)  **Model 2**: HR 1.13, 95% CI (0.87-1.48)  In unadjusted models, living alone participants had higher incident rates of all-cause mortality. The crude incident rate of cardiovascular-specific death was comparable for the two living conditions. |

m= male; f = female; Μ =mean; SD = standard deviation; IQR = interquartile range; BMI = body mass index; HR = hazards ratio; CI = confidence interval; IHD =Ischemic heart disease; HF = heart failure; CABG= coronary artery bypass grafting; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; CHF = congestive heart failure; RR = relative risk ; UCLA = University of California Los Angeles; BHAT = Beta blocker heart attack trial; WISE = Women’s Ischemia Syndrome Evaluation; NHIS = national health interview survey; IHD = ischemic heart disease; MOSS = ; ASSET = Anglo-Scandinavian Study of Early; CRP = C-reactive protein; HbA1c = hemoglobin A1c; MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; ENRICHD = enhancing recovery in coronary heart disease; SNQ = Social Network Questionnaire; CV = cardiovascular; AMI = acute myocardial infarction; AHT= arterial hypertension; WISE = ; TIA= transient ischemic attack; OR = odds ration; NYHA = New York Heart Association ;PREMIER= prospective registry evaluating myocardial infarction; LVSF = left ventricular systolic dysfunction; STABILITY = ; CLARIFY = prpspeCtive observational LongitudinAL Registry of patients with stable coronary artery disease; OACIS = Osaka Acute Coronary Insufficiency Study; STEMI = ST-elevation myocardial infarction; FINAMI MI = ;ACS = acute coronary syndrome; GUTSO-III = Global Use of Strategies to Open occluded coronary arteries; SAHLSIS =Sahlgrenska Academy Study of Ischemic Stroke; PCI= percutaneous coronary intervention; TOPCAT = Treatment of Pre- served Cardiac Function Heart Failure with an Aldosterone Antagonist.

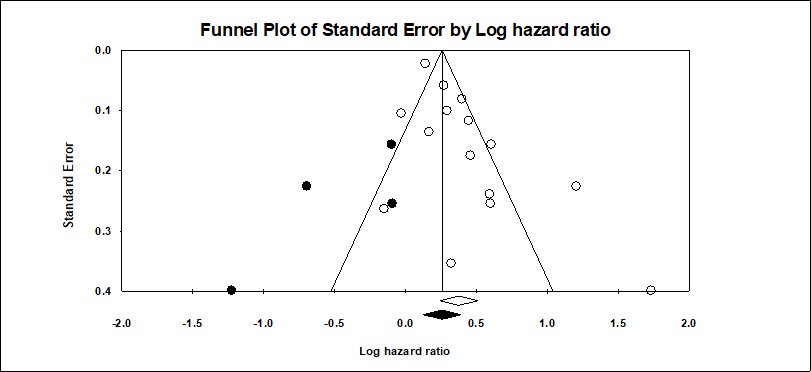
**Table S2. Quality Assessment of Included Studies**

| **Selection** | | | | | **Comparability** | | **Outcome** | | |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Representativeness of exposed cohort | Selection of nonexposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Adjust for the most important risk factors | Adjust for other risk factors | Assessment of outcome | Follow-up length | Loss to follow-up rate | Total quality score |
| Appelros et al. (2003)  (57) | \* | \* | \* | - | - | \_ | \* | \* | \* | 6 |
| Birket-Smith et al. (2009)  (58) | \* | \* | \* | - | \* | \* | \* | \* | \* | 8 |
| Boru et al., (2007) (59) | \* | - | - | - | \* | \* | - | - | - | 3 |
| Brummert et al., (2001) (71) | \* | \* | \* | - | \* | \* | - | \* | \* | 7 |
| Bucholz et al, (2011) (43) | \* | \* | \* | - | \* | \* | \* | \* | - | 7 |
| Case et al., (1992) (40) | \* | \* | - | - | - | - | \* | \* | - | 4 |
| Christensen et al., (2020) (38) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Hagstrom et al., (2018) (39) | \* | - | \* | - | \* | \* | \* | \* | \* | 7 |
| Herlitz et al., (1998) (68) | \* | \* | - | - | \* | \* | - | \* | \* | 6 |
| Gandhi et al., (2019) (42) | \* | \* | \* | - | \* | \* | \* | \* | - | 7 |
| Jenkinson et al., (1993) (60) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Kitamura et al., (2013) (79) | \* | \* | - | - | \* | \* | - | \* | \* | 6 |
| Kreibig et al., (2014) (72) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Lammunitausta et al., (2014) (61) | \* | \* | \* | - | - | - | \* | \* | - | 5 |
| Lett et al., (2007) (73) | - | - | - | - | \* | \* | \* | \* | - | 4 |
| Lu et al., (2016) (74) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Maneman et al., (2018) (75) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Nielsen et al., (2010) (70) | - | \* | - | - | \* | \* | \* | \* | \* | 6 |
| Menendez et al., (2015) (62) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Nakatsuma et al., (2014) (80) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Nielsen et al., (2007) (63) | \* | - | \* | - | \* | - | \* | \* | \* | 6 |
| Norekval et al., (2010) (64) | - | \* | - | - | \* | \* | \* | \* | \* | 6 |
| O’Shea et al., (2002) (82) | \* | \* | - | - | \* | \* | - | \* | \* | 6 |
| Reeves et al., (2013) (76) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Redfors et al. (2016) (65) | \* | \* | \* | - | \* | \* | \* | \* | \* | 8 |
| Rodriguez et al., (2006) (66) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Ruberman et al., (1984) (78) | - | \* | \* | - | - | - | \* | \* | - | 4 |
| Rutledge et al., (2016) (77) | - | \* | \* | - | \* | \* | \* | \* | \* | 7 |
| Schokmel et al., (2017) (41) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Spaderna et al., (2017) (67) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Takeuchi et al., (2015) (81) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Udell et al. (2012) (34) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Vujuic et al., (2015) (69) | \* | \* | - | - | \* | \* | - | \* | \* | 6 |
| Yu et al., (2020) (22) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |
| Zhu et al., (2021) (23) | \* | \* | - | - | \* | \* | \* | \* | \* | 7 |

Each of the included studies was examined for methodological quality using the Newcastle Ottawa scale for cohort studies. This scale consists of nine items regarding selection (4 items), compatibility (2 items) and outcome (3 items). The following characteristics of each study were assessed: representativeness of sample of participants, participants being drawn from same sample, the predictor (loneliness, social isolation or living alone) being measured using a validated scale or recure record (e.g. medical record; the study controlled for important potential confounders including sociodemographic, baseline health and co-morbidities as the assessment of bassline health is important to predict changes (24) (of note, a statement of no history of disease or incident earns a star). Studies were awarded one star for each of the criteria that they met. The following cut-odds were used as previous research had done: high quality (5-9 stars), moderate quality (3-4 stars) and low quality (0-2) stars.

Funnel Plots

**Figure S1.** Funnel plot of Standard Error by unadjusted Log hazard ratio after the trim and fill method applied.



**Figure S2.** Funnel plot of Standard Error by adjusted Log hazard ratio after the trim and fill method applied.

