Living alone and all-cause mortality in community-dwelling adults: A systematic review and meta-analysis

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Summary

Background The non-causal and causal associations, possible age and sex differences between living alone and all-cause mortality among adults were unclear. We aimed to assess the association and causal relation between living alone and all-cause mortality among community-dwelling adults, addressing the certainty of evidence, possible age and sex differences.

Methods We searched Medline, Embase, and APA PsycINFO for cohort studies examining the association between living alone and all-cause mortality on November 19, 2021. We used the GRADE approach to assess certainty of evidence, and the Instrument for the Credibility of Effect Modification Analyses (ICEMAN) to evaluate credibility of subgroup inferences and conducted a meta-analysis of measures of association between living alone and mortality. The study was registered with PROSPERO, CRD42021290895.

Findings 18 cohort studies with 62,174 adults proved eligible. Living alone was associated with mortality (relative risk (RR) = 1.15, 95% confidence interval (CI) 1.08−1.23). Both age and sex modified the association (high and moderate credibility, separately). Living alone increased the risk of dying only in younger but not older individuals (ratio of RRs = 1.59, interaction $P = 0.003$; younger RR 1.41, 95% CI 1.17−1.71, high certainty for prognosis, low for causation; older RR = 1.05, 95% CI 0.91−1.22, moderate certainty for prognosis, very low for causation). Living alone increased risk to a greater extent in males than females (ratio of RRs = 1.39, 95% CI 1.14−1.70; interaction $P = 0.001$, males RR = 1.41, 95% CI 1.17−1.71, high certainty for prognosis, low for causation; females RR = 1.15, 95% CI 0.99−1.33; moderate for prognosis factor, very low for causation).

Interpretation Living alone is associated with increased mortality in individuals under 65 years (high certainty) but not with those over 75 years; the association may be causal (low certainty). Associations, and possibly effects, may be stronger in men than women.

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Keywords: Living alone; All-cause mortality; Systematic review; Meta-analysis

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Research in context

Evidence before this study

We did systematic searches in Medline, Embase, and APA PsycINFO for cohort studies examining the association between "living alone" and "all-cause mortality" on Nov 19, 2021. Studies were eligible for inclusion if they enrolled community-dwelling individuals 18 years or older without a specific disease at baseline with a follow-up of at least one year, documented living arrangements at baseline and reported adjusted the associations between living alone and all-cause mortality. After removal of duplicate citations, title and abstract screening and full-text review, 18 cohort studies with 62,174 adults were included.

Added value of this study

To our knowledge, this is the first meta-analysis addressing living alone on all-cause mortality among general community-dwelling adults. We found that living alone is associated with increased mortality in individuals under 65 (high certainty) but not in older individuals, in males (high certainty) but less so in females, and it is possible the association may be causal (low certainty) both in younger adults and males. Age-stratified meta-analyses of between-trial comparisons revealed that younger adults living alone increased the risk of mortality by 41%, while older adults did not. In the within-trial comparisons of sex, living alone increased the risk of dying to a greater extent in the males than in females. Sex-stratified meta-analyses of between-trial comparisons suggested that males living alone increased the risk of mortality by 41%, females living alone increased the risk of mortality by 15%.

Implications of all the available evidence

This systematic review and meta-analysis provide compelling evidence of a true association between living alone and mortality in younger but not older adults, an association that appears stronger in men than women. Although the certainty evidence for the causal relations between living alone and all-cause mortality is low in younger adults and men, the high certainty evidence for prognosis suggests that mandating more scrutiny of the physical and emotional problems and illnesses in those who lived alone, could have a major effect on health. Further work is required to verify whether it is beneficial for health to encourage younger people living alone, especially men, to modify their living arrangements.

Introduction

Scientific interest in the possible association of living alone with health has, over the last few decades, been increasing. Many adults live alone — for instance 33.9% in European countries.[1] The number of adults living alone is increasing: by 12% from 1950 to 2019 in the U.S.,[2] 21% from 1950 to 2016 in Canada,[3] and 16% from 1997 to 2017 in the UK.[4] This worldwide increase in those living alone is likely to continue.[5]

Existing research has found associations between living alone and a range of adverse outcomes, including cardiovascular diseases,[6] diabetes[7] and dementia.[8] A previous systematic review found living alone increased the risk of all-cause mortality, but did not address the certainty of evidence, nor address possible age and sex differences.[9] Moreover, additional large cohort studies have been published since then.[10,11]

Associations between living alone may be non-causal (people who live alone may have poorer physical or mental health status than those living with others independent of their living arrangements) or causal (living alone may lead to deterioration in physical or mental health and ultimately to death). A non-causal association of increased risk of death in people living alone would be important in terms of extra alertness to modifiable risk factors for mortality. A causal relation between living alone and mortality would suggest exploration of the possibility of an alternative living arrangement in those living alone. The certainty of evidence regarding both issues would help determine their priority.

Because of the importance of the issue, the limitations of the previous review, and the availability of new evidence, we conducted a systematic review and meta-analysis to evaluate the association between living alone and the risk of all-cause mortality.

Methods

The protocol for this systematic review and meta-analysis, registered with PROSPERO (CRD42021290895), adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.

Eligibility criteria

We included cohort studies that enrolled community-dwelling individuals 18 years or older with a follow-up of at least 1 year and examined the association between living alone defined as not living with someone else (rather than as single). Eligible studies documented living arrangements at baseline and reported adjusted associations between living alone and all-cause mortality. Because patients with a specific disease (e.g., coronary heart disease, stroke, cancer, depression, Alzheimer's disease) may have a higher risk of all-cause mortality, and because their illnesses may influence their decisions on whether to live alone (and thus lead to a different association with all-cause mortality), we excluded the cohort studies focused only on the populations with these diseases at baseline. We excluded case-control studies, review articles, editorials, comments, or dissertations. We applied no restriction on the language of publication.

Search strategy

In collaboration with a research librarian, we developed a literature search strategy and searched Medline, Embase and APA PsycInfo on November 19, 2021. The search strategy included the keywords "living alone", "live alone", "lives alone", "lived alone", "unaccompanied", "mortality", "death", "case fatality rate", "survival", "prognosis", "regression analysis", "cohort" and "randomised controlled trial" (Appendix, Text S1). We scanned the reference lists of included studies and relevant systematic reviews to identify potentially eligible studies.

Study selection

Reviewers, working in pairs, independently performed the study selection, including screening titles and abstracts, and evaluating full-text eligibility of potentially eligible studies. Reviewers resolved disagreements by discussion or, if necessary, by consultation with a third reviewer.

Data extraction

For each eligible study, two reviewers independently extracted the following items with resolution of disagreements by discussion or adjudication by a third reviewer: study characteristics (author, year of publication, country); participants characteristics (sample size, age, proportion of males); follow-up time and effect measures of associations between living alone and all-cause mortality.

Risk of bias assessment

Two reviewers independently evaluated the risk of bias of included studies according to the Quality In Prognosis Studies (QUIPS).[12] The scale contains six domains, including study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and reporting. The instrument has three options for every domain, including low risk of bias, moderate risk of bias, and high risk of bias. We considered studies with more than five domains at low risk of bias at low risk of bias; those with more than two domains at high risk of bias at high-risk risk of bias; the remainder at moderate risk of bias.

Statistical analysis

We analysed data using STATA, version 15, choosing DerSimonian and Laird random-effects models to pool data. We expressed results as relative risks (RRs) with 95% confidence intervals (CIs). If studies reported estimates at different time points, we used the estimate reported at the longest follow-up. For analysis, we chose each study's most fully adjusted results. If a study provided hazard ratio (HR) instead of RR, we used the formula ($RR = (1 - e^{HR * \ln(1 - r)})/r$; r, the death rate for the reference) to covert HR to RR.[13] If a study provided odds ratio (OR) instead of RR, if the risk of mortality was less than 10%, we interpreted the OR as RR[14]; otherwise, we used generic inverse variance to calculate pooled RR. We assessed heterogeneity according to visual inspection of forest plots and considered I^2 in the context of the degree of similarity of the point estimates.[15,16]

Subgroup analysis

We conducted subgroup analyses for age (using thresholds of 65 or 75 as specified by authors), sex (males verse females), risk of bias (low verse moderate or high risk of bias), and the follow-up time of included studies. Because within-study comparisons provide much more compelling evidence of subgroup effects than between-study comparisons, if there were at least two within-trial subgroup analyses reported (e.g., the study reported results separately for the relative risk of mortality among males and females who lived alone), we based our inferences regarding the credibility of a subgroup effect on the within-trial comparisons.

This proved be the case for both age and sex. Our subgroup analysis for the effect modification by age required classification of studies/groups into younger vs older age group. To conduct the subgroup analysis, for each study we chose the thresholds specified by the authors (either 65 or 75) to define older or younger.

To determine the likelihood that chance could explain differences in results in the older and younger, and in males and females, we calculated the ratio of RRs for each individual study and then used a random-effects model to pool the ratio of RRs. If we observed a possible subgroup effect (the *P*-value of interaction test <= 0.1), to judge the credibility of any apparent subgroup effect, we applied the Credibility of Effect Modification Analyses (ICEMAN) instrument.[17] If we concluded moderate to high credibility, we estimated the association for each subgroup (e.g., males and females) using all comparisons of living alone and not living alone restricted to those subgroups. That is, we used the subgroups (e.g., males) from the within-study comparisons and pooled these with any studies that exclusively enrolled that subgroup (e.g., studies only including males) using the same approach we had taken for the overall analysis.

For risk of bias (low verse moderate or high risk of bias), to assess subgroup effects, we conducted a between-trial analysis. For the impact of follow-up time on the association between living alone and mortality, we performed a random effects meta-regression. For this analysis, the relative risk of living alone for mortality was our dependent variable and the length of follow-up was our independent variable.

Publication bias

When there were more than ten eligible studies, we used funnel plots and Egger's test to examine the

publication bias. If publication bias was found (asymmetric funnel plots and/or *p*-value of Egger's test < 0.05), we would use the trim-and-fill method to evaluate whether publication bias affect our results.[18]

Certainty of evidence

We used GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to assess certainty of evidence according to the study limitations, consistency, directness, precision, and publication bias for the effect of living alone. According to the GRADE framework, observational studies began as high certainty of evidence for assessments of prognosis and low certainty of evidence for causation. We chose a minimally contextualised approach to rating certainty with the null effect as a threshold.[15,19,20] When there was a high or moderate credibility of potential effect modification, we assessed the certainty of evidence for each subgroup separately. Considering that the I^2 statistic can be misleading in the context of prognostic studies, especially when the sample size of included studies was very large,[15] in assessing inconsistency we focused on variability of point estimates, and the possible impact of outlier results. In particular, we considered the weight of outlier studies in contributing to the pooled estimate. If very low (e.g. < 10%) we were disinclined to rate down for inconsistency. We determined the absolute risk difference by applying the relative effect to the control event rate. We developed summary of finding tables using optimal formats in MAGIC.app,[21] presenting both relative and absolute effects and including plain language summaries with wording following GRADE guidance.[22]

Ethics approval and consent to participate

Not applicable.

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study selection and characteristics

Flow diagram presents the details of study selection process (Figure 1). Removal of duplicate citations left 1763 records. After title and abstract screening, we assessed 562 full text articles, of which 18 studies proved eligible.

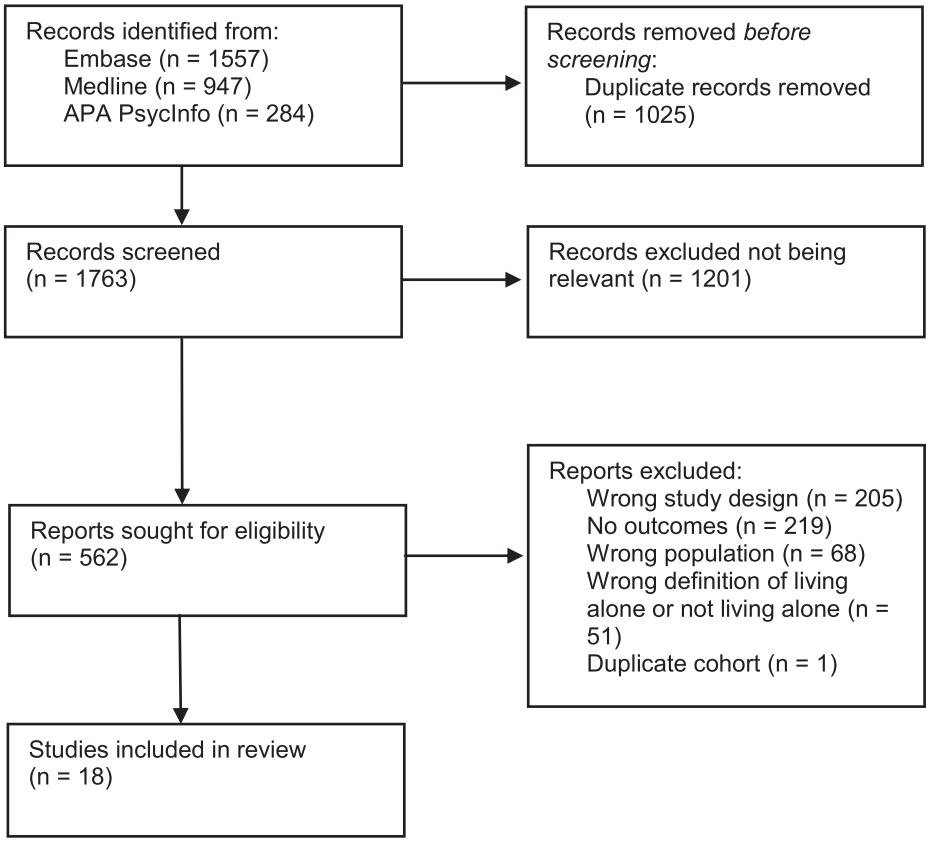

Figure 1. PRISMA flow diagram of studies included in the review.

Table 1 presents the characteristics of the 18 included studies, all of which were cohort studies, with sample sizes ranging from 366[23] to 15,788,[24] enrolling a total of 62,174 community-dwelling adults. Three studies included only adults younger than 75 years old[24–26]; one study only included only adults older than 75 years old[21]; and the remainder included both.[10,11,27–38] Three studies reported the association between living alone and mortality separately for adults younger than 75 years and older than 75 years.[28,31,33] One study reported the association between living alone and mortality separately for the adults younger and older than 65 years.[11] Two studies included only men[30,32] and one only women[27]; among the mixed-sex cohorts, eight reported the association between living alone and mortality separately for males and females.[24,25,30,31,33–35] Most studies reported their outcomes with HR[11,24,25,27-30,32,33,36,37]; four with RR[23,30,31,34] and four with OR.[10,26,35,38] Follow-up time ranged from 1.5[23] to 32.2[30] years.

Risk of bias of individual studies

Table 1 summarises the risk of bias assessments of individual studies. Ten studies had low risk of bias,[10,24,25,28,30,32–36] and eight studies had moderate risk of bias.[11,23,25,27,30,31,37,38] Most bias were due to inadequately representing the population of interest of the study sample, incomplete outcome data (two studies with loss to follow-up >= 10%),[31,34] and lack of optimal control for important confounding factors.

Living alone on all-cause mortality

The pooled RRs of death in eighteen studies showed, as compared to adults not living alone, living alone was associated with an increase in mortality (RR = 1.15, 95% CI 1.08–1.23) (Appendix, Figure S1).

Subgroup analysis

Age. In the within-trial comparisons, living alone increased the risk of dying to a greater extent in younger adults than in the older adults (ratio of RRs = 1.59, 95%

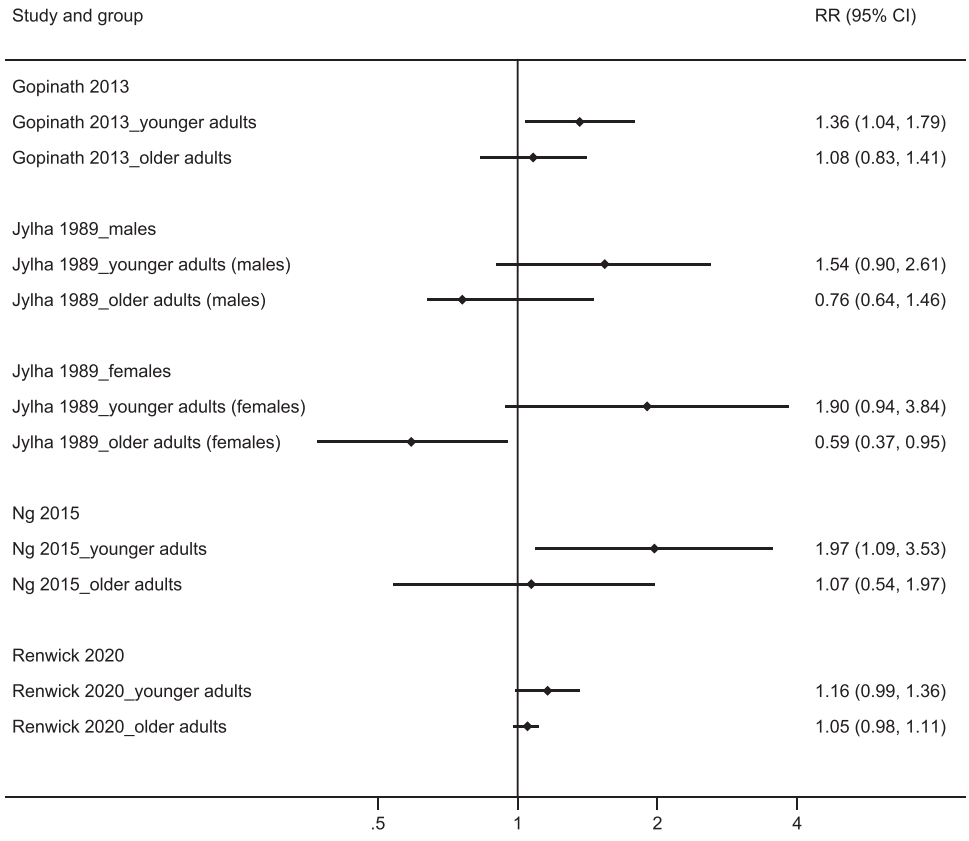

Figure 2. Within-trail comparisons of age (younger adults and older adults).
Notes: interaction $P = 0.003$; RR = relative risk; CI = confidence interval.

Authors	Trail's name	Location	Sample size	Age mean(SD), range (years)	Men (%)	Follow-up time (years)	Loss to follow-up (%)	Adjustment for covariates	QUIPS
Abell 2021	English Longitudinal Study (ELSA)	England	4888	68.6±8.7 56+	44.52	10 8.5 (mean)	0	Age, sex, education, wealth (wave 4), percentage of excess risk explained,current smoking, physical activity, alcohol consumption.	low
Avlund 1998	NR	Denmark	727	70 70	49.86	11	0	Activities outside the home, social support to other tasks, take care of others, help others with repairs, education, functional ability	low
Denollet 2009	Eindhoven Perimenopausal Osteoporosis Study	Netherlands	5073	50.4±2.1 46−54	0	10	0	Age, symptoms of anxiety, symptoms of depression,education, oral contraceptive medication, hormone replacement therapy, smoking, drinking, physical activity, BMI, hypertention, diabetes	moderate
Gopinath 2013	Blue Mountains Eye Study (BMES)	Australia	3486	66.17 49+	40.18	10	0.63	Age, sex, educational status (tertiary qualified or not), current smoking, body mass index, walking disability, prior diagnosis of heart disease, angina, heart attack, diabetes mellitus, cancer, poor self-rated health, and SF-36 mental and physical component summary scores.	low
Iwasa 2006	Longitudinal Interdisciplinary Study on Aging	Japan	2447	62.6 ± 6.8 52−77	42.3	7	1.61	Age, the number of years of education, history of hospitalization during a year, presence of chronic conditions (hypertension, stroke, heart disease, diabetes, cancer and kidney disease)	Low
Jensen 2019	Copenhagen Male Study	Denmark	3346	62.9±5.2 53−75	100	32.2 18 ± 8.4 (mean ± SD)	2.9	Age, previous cardiovascular disease (stroke or myocardial infarction), presence of diabetes, body mass index, systolic blood pressure, smoking, alcohol, self-reported physical activity, se-triglycerides, se-total cholesterol, resting heart rate, workers compensation, satisfaction with current housing situation, mood, self-reported health, and socioeconomic position	low
Jylha 1989	NR	Finland	1060	NR 60−89	49.91	6.5	0	Age, perceived health, functional ability, and disabling disease	moderate
Jylhä 1999	NR	Finland	366	NR 90−101	19.2	1.5	0	Age	moderate
Kandler 2007	MONICA/KORA cohort	Germany	7017	NR 45−74	51.25	18.2 11.4 (mean)	NR	Age, (sex), survey, number of friends, prevalent MI and diabetes, hypertension, self rated health, obesity, participation in screening, dentist visits, physical activity, alcohol consumption, smoking	moderate

Table 1 *(Continued)*

Authors	Trail's name	Location	Sample size	Age mean(SD), range (years)	Men (%)	Follow-up time (years)	Loss to follow-up (%)	Adjustment for covariates	QUIPS
Khalatbari-Soltani 2020	Concord Health and Ageing in Men Project	Australia	1522	77.5 ± 5.5 70+	100	11 9 ± 3.6 (mean ± SD)	10.73	Age, age squared, and country of birth, healthrelated behaviours (alcohol consumption, smoking, and physical activity), and body mass index, self-rated health	low
Mollica 2001	NR	Croatia	529	50 18 +	41.57	3	0.94	Age, sex, education, trauma events, bserved handicap, symptoms of depression, has cardiovascular condition	low
Ng 2015	Singapore Longitudinal Ageing Studies	Singapore	2553	67.47 ± 7.42 55+	36.62	8	2.27	Age, sex, housing type, history of hypertension, diabetes, chronic lung disease, stroke, heart disease, kidney failure, IADL—BADL disability, marital status	low
Pimouguet 2015	Swedish National study on Aging and Care-Kungsholmen	Sweden	2404	77.8 ± 9.0 66+	33.94	6	0	Age, sex, education, recent financial difficulty, BMI, smoking habits, alcohol consumption, diabetes, hypertension, stroke, heart failure, coronary heart disease, depression, dementia, cancer, ADL and IADL disability, MMSE, feeling of loneliness and institutionalization	low
Renwick 2020	Canadian Community Health Survey	Canada	15,788	67.8 55+	41.78	11.3	0	Age,sex, income, smoking status, frailty	moderate
Scafato 2008	Italian Longitudinal Study on Aging (ILSA)	Italy	3884	72.58 65—84	51.28	10 5.8 (mean)	14.09	Age, systolic blood pressure, diastolic blood pressure, blood glucose, total serum cholesterol, high-density lipoprotein, body mass index, education, procreation, smoking habit, alcohol use, ADLs, IADLs, depression and cognitive impairment	low
Tabue Teguo 2016	"Personnes Agées Quid" (PAQUID) cohort study	France	3620	75.27 ± 6.43 65+	41.08	22	4.16	Age, sex, educational level, and depression	low
Takeuchi 2018	NR	Japan	539	77.03 ± 4.29 70-85	44.34	3	4.10	Age, (sex), daily support from family around a participant and having a history of hypertension, cancer, cerebral apoplexy or pneumonia	moderate
Trevisan 2016	Progetto Veneto Anziani Longitudinal Study	Italy	2925	74.4 ± 7.3 65+	43.31	4.4 (mean)	3.37	Age, sex	moderate

***Table 1*: Summary of included studies on associations between living alone and all-cause mortality among community-dwelling adults.**

Notes: NR, not reported; SD, standard; QUIPS, Quality In Prognosis Studies; BMI, body mass index; SF-36, the MOS item short from health survey; ADL, activities of daily living; IADL, instrumental activities of daily living; BADL, basic activities of daily living; MMSE, Mini-Mental State Examination.

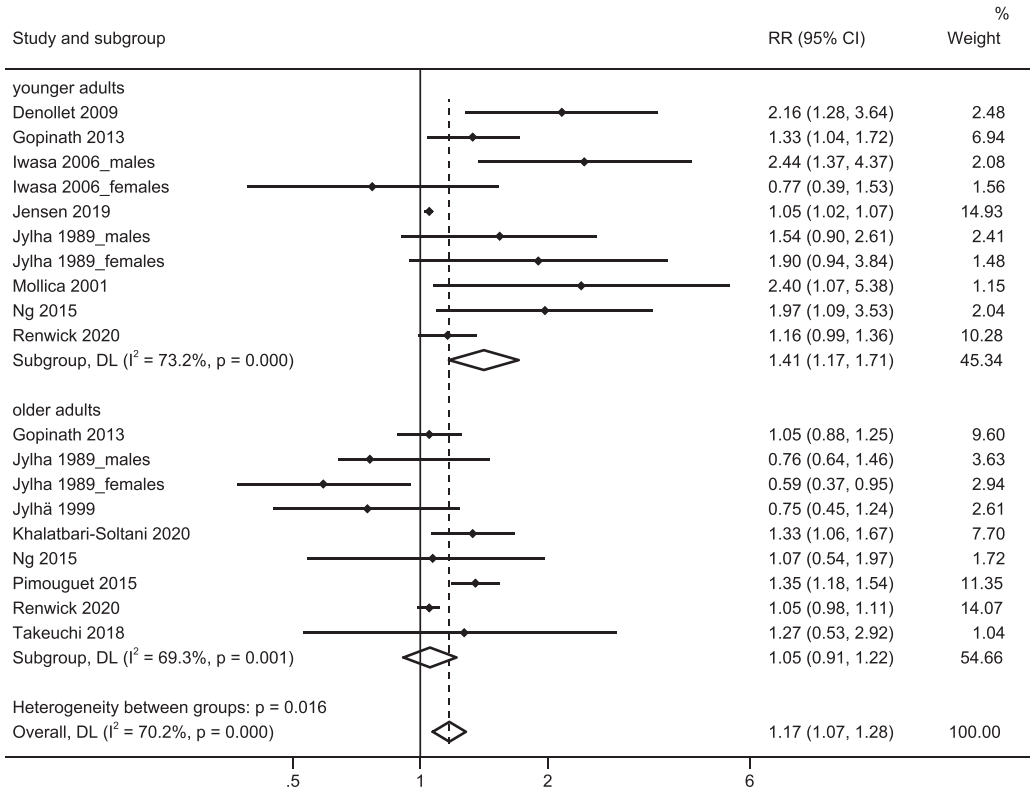

Figure 3. Forest plot for relative risk of adults living alone on all-cause mortality according to age (younger adults and older adults).

Notes: RR = relative risk; CI = confidence interval.

CI 1.17–2.15, test of interaction P = 0.003) (Figure 2). Applying ICEMAN criteria, the within-trial comparison, the similarity of results from trial to trial, the implausibility of chance as explanation, the consistent use of similar thresholds in the trials, and the use of an appropriate random effect model in the analysis all support the credibility of the subgroup effect. The lack of an a priori specified direction of the effect decreases the credibility. Overall, we judged the credibility as high bordering on moderate (Appendix, Text S2).

Including all groups of younger adults (from the within-trial comparisons[11,28,31,33] and studies that enrolled only younger individuals[26,27,30] the association between living alone and mortality demonstrated a RR of 1.41, 95% CI 1.17–1.71, 21 more per 1000. Including all groups of older adults (from the within-trial comparisons[11,28,31,33] and studies that enrolled only older individuals[23,32,34,37]), the association between living alone and mortality demonstrated a RR of 1.05, 95% CI 0.91–1.22, 10 more per 1000 (Figure 3).

Sex. In the within-trial comparisons, living alone had stronger association with mortality in males than in the females (ratio of RRs = 1.39, 95% CI 1.14–1.70, test of interaction P = 0.001) (Figure 4). Applying ICEMAN criteria, only the lack of a priori specified direction of the effect decreases the credibility. Overall, we judged the credibility as moderate bordering on high (Appendix, Text S2).

Including all groups of males (from the within-trial comparisons[24,25,30,31,33-35,37] and studies that enrolled only[30,32]) the association between living alone and mortality demonstrated a RR of 1.41, 95% CI 1.17–1.71, 88 more per 1000. Including all groups of females (from the within-trial comparisons[24,25,30,33-35,37] and studies that enrolled only females individuals[27]), the association between living alone and mortality demonstrated a RR of 1.15, 95% CI 0.99–1.33, 18 more per 1000 (Figure 5).

Risk of bias and follow-up time

Our comparison of high and low risk of bias studies provided no support for a subgroup effect according to risk of bias (P = 0.6) (Appendix, Figure S2). The meta-regression provided no support for a subgroup effect according to duration of follow-up time (P = 0.1) (Appendix, Figure S3).

Publication bias

The asymmetrical funnel plot (Appendix, Figure S4) and Egger's test (P = 0.02), indicate potential

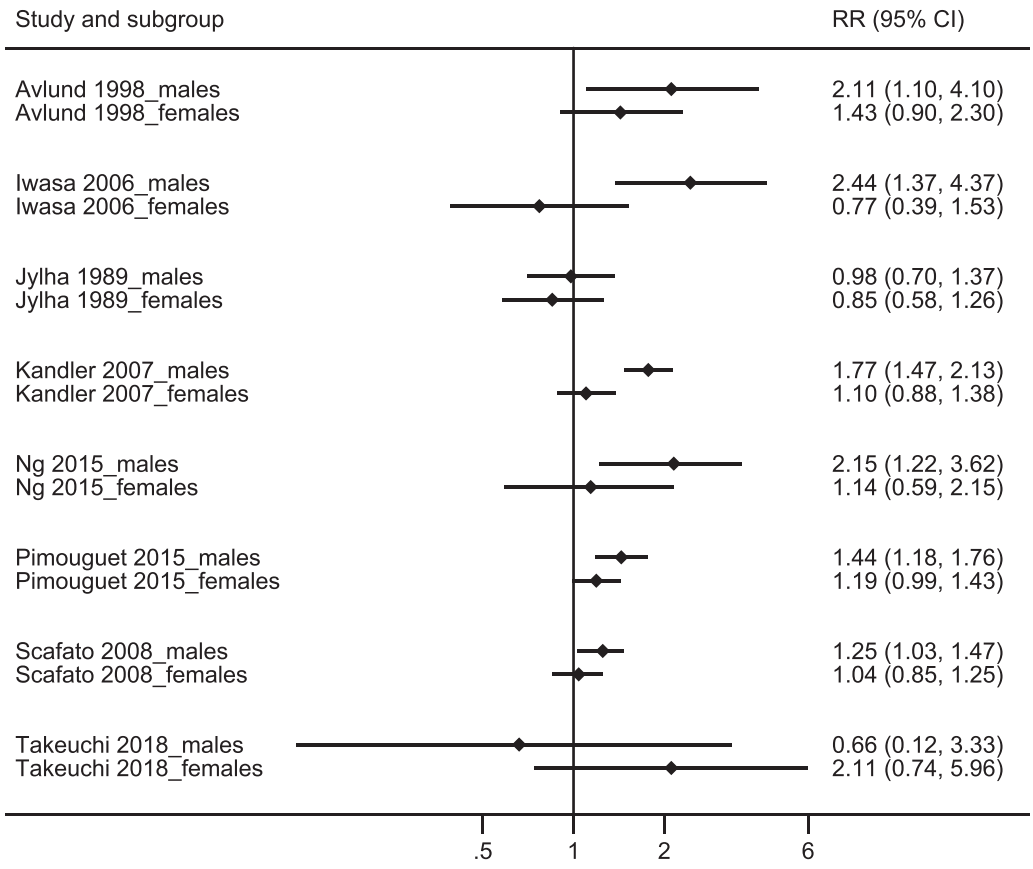

Figure 4. Within-trial comparisons of sex.
Notes: interaction $P = 0.001$; RR = relative risk; CI = confidence interval.

publication bias among the included studies. Based on the trim-and-fill method, six studies were imputed (Appendix, Figure S5), and correction for potential publication bias did not alter the association between living alone and all-cause mortality (RR = 1.08, 95% CI 1.01 −1.16).

Evidence certainty

We identified eighteen studies, including ten at low and eight at moderate risk of bias. Although there was potential publication bias, the correction for this bias using the trim-and-fill method did not alter the association between living alone and mortality. We did not rate down for publication bias in this review. Due to the credible subgroup effects of age and sex, we evaluated our certainty in the results of each subgroup separately (Table 2).

For the subgroup analysis of age, in younger adults we rated the certainty of evidence as high for living alone as a prognostic risk factor for mortality and low as a causal factor for mortality. In the older adults we rated the certainty of evidence as moderate for living alone as a prognostic factor and very low as a causal factor.

For the subgroup analysis of sex, in males we rated the certainty of evidence as high for living alone as a prognostic factor for mortality and low as a causal factor for mortality. In females, we rated the certainty of evidence was moderate for living alone as a prognostic factor and very low for living alone as a causal factor. Although the I^2 statistic was 86%, only one study (10% of the weight in the analysis) has the CI that does not overlap with the 95% CI of our pooled estimate.[29] Due to the very large sample size of included studies, as is the case in most prognostic factor review, the I^2 statistic can be misleading the judgments of inconsistency.[15] We therefore didn't rate down for the inconsistency in the analysis of males.

Discussion

This review demonstrated living alone is associated with increased mortality in individuals under 65 (high certainty) but not in older individuals, in males (high certainty) but less so in females, and it is possible the association may be causal (low certainty) both in younger adults and males. Age-stratified meta-analyses of between-trial comparisons revealed living alone was

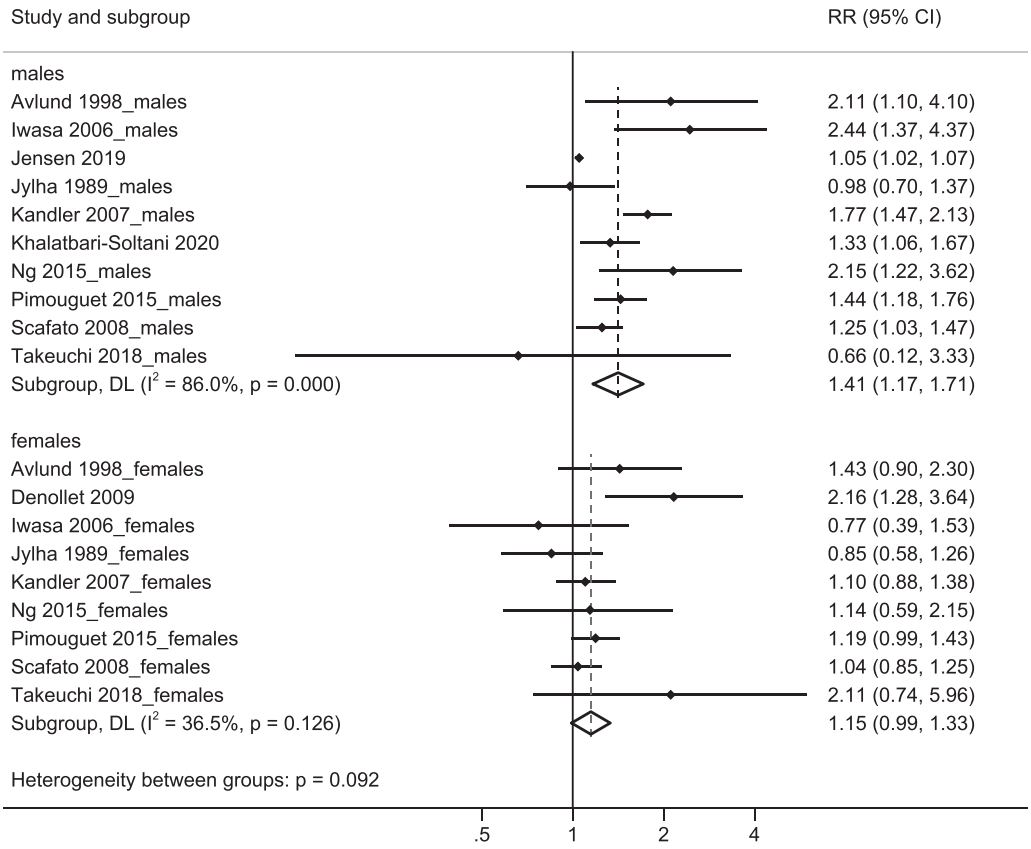

Figure 5. Forest plot for relative risk of males and females lived alone on all-cause mortality.
Notes: RR = relative risk; CI = confidence interval.

associated with an increase in the risk of mortality by 41% in younger adults with no association in older adults. Sex-stratified meta-analyses of between-trial comparisons revealed living alone was associated with an increase in the risk of mortality by 41% in males and by 15% in females.

This is the first meta-analysis addressing living alone on all-cause mortality among community-dwelling adult populations heterogeneous with respect to underlying medical conditions. Strengths of this review include a comprehensive search for eligible studies and duplicate selection, data extraction, risk of bias assessment. We explored possible effect modification by age and sex, focusing on within-study comparisons, and applied criteria from a rigorously developed instrument, ICEMAN,[17] to address the credibility of the apparent subgroup effects. Finally, we used the GRADE approach to assess the certainty of evidence addressing both living alone as a prognostic factor[15,19] and a causal factor for mortality.[20]

Limitations include the unavailability of the evidence to explore other subgroup effects of possible interest and the substantial levels of clinical heterogeneity in some subgroup analyses. For example, different structures of households (people living with others are doing so as a couple, with parents, with children, or with friends), and different cultural backgrounds (Western countries or non-Western countries), could result in differences in the association between living alone and mortality. Studies have addressed a separate question, the association between marital status and mortality, and we did not address this question, which might have provided further insight. Because there was only one study that reported the effects stratified by both age and sex, we could not ascertain the relative contributions of age and sex to the associations. Besides, the clinical heterogeneity (e.g., different structures of households, cultural backgrounds and follow-up time) of eligible trials included in one subgroup analysis may also devote to substantial levels of heterogeneity.

Statistical heterogeneity as reflected in the I^2 was high in all analyses. This was the case despite point estimates indicating, to a great extent, a consistent message. The apparent discrepancy is due to the very large sample size of included studies and the resulting narrow confidence intervals. It is well established that in such situations large statistical heterogeneity can exist

Group	Study results and measurements	Absolute risk difference		Certainty of evidence	Plain language summary
		Not living alone	Living alone		
In younger adults					
Mortality	Relative risk: 1.41 (CI 95% 1.17—1.71) Based on data from 23833 participants in 8 studies	50 per 1000	71 per 1000	Certainty in association High: for prognosis, observational studies begin as high certainty, no further reason to rate down.	Living alone is associated with increased mortality for the younger adults.
		Difference: 21 more per 1000 (CI 95% 9 more - 36 more)		Certainty in causal association Low: for causation, observational studies begin as low certainty because of residual confounding, no further reason to rate down.	Living alone may increase mortality for the younger adults.
In older adults					
Mortality	Relative risk: 1.05 (CI 95% 0.91—1.22) Based on data from 15,787 participants in 8 studies	190 per 1000	200 per 1000	Certainty in association Moderate: for prognosis, observational studies begin as high certainty Further rating down due to serious imprecision	Living alone is probably associated with little or no increase mortality for the older adults
		Difference: 10 more per 1000 (CI 95% 17 fewer - 42 more)		Certainty in causal association Very low: for causation, observational studies begin as low certainty because of residual confounding Further rating down due to serious imprecision	We are uncertain whether living alone increases or decreases mortality for the older adults
In males					
Mortality	Relative risk: 1.41 (CI 95% 1.17—1.71) Based on data from 14,634 participants in 10 studies	214 per 1000	302 per 1000	Certainty in association High: for prognosis, observational studies begin as high certainty, no further reason to rate down.	Living alone is associated with increased mortality for males.
		Difference: 88 more per 1000 (CI 95% 36 more - 152 more)		Certainty in causal association Low: for causation, observational studies begin as low certainty because of residual confounding, no further reason to rate down.	Living alone may increase mortality for males.
In females					
Mortality	Relative risk: 1.15 (CI 95% 0.99—1.33) Based on data from 16,443 participants in 8 studies	123 per 1000	141 per 1000	Certainty in association Moderate: for prognosis, observational studies begin as high certainty Further rating down due to serious imprecision.	Living alone is probably associated with little or no increase mortality for females.
		Difference: 18 more per 1000 (CI 95% 1 fewer - 41 more)		Certainty in causal association Very low: for causation, observational studies begin as low certainty because of residual confounding Further rating down due to serious imprecision	We are uncertain whether living alone increases or decreases mortality for females.

***Table 2*: Summary of findings of living alone as prognostic factor for all-cause mortality vs cause of all-cause mortality.**
Notes: CI = confidence interval.

in the face of point estimates that are essentially consistent.[15]

One previous systematic review and meta-analysis found that living alone increased the relative risk of mortality by 32%.[9] That systematic review differed from ours: whereas we restricted our sample to studies with adjusted analysis that are therefore at lower risk of bias, the previous review included studies irrespective of adjustment for covariates. The prior review also included studies with participants with specific diseases (e.g., depression, cardiovascular diseases). Our review included only studies that enrolled a representative sample of all community-dwelling adults, and excluded studies focusing on participants with specific diseases, thus allowing inferences to the populations heterogeneous with respect to underlying medical conditions.

A further difference is the failure of the prior review to undertake subgroup analysis. In our review, we performed subgroup analysis to explore potential effect modifiers and found, applying rigorously developed criteria,[17] important age and sex differences in the association of living alone and all-cause mortality. The prior review did not provide a structured assessment of certainty of evidence, in contrast to our use of the GRADE approach addressing the issue from both the perspective of prognosis/association and causation.

This systematic review provides information regarding the potential association and possible adverse effect of living alone on mortality among community-dwelling adults. Results showed a substantial association in younger but not older adults, and an apparent stronger association among males but not females. Although the explanation of the association of living alone and the higher risk of death among younger individuals are unclear, the following may be potential explanations. Firstly, the association might not be causal, but rather because younger adults who live alone have greater exposure to vascular factors, such as smoking, drinking, eating salty foods, lower consumption of some core foods groups (vegetables, fruits, and seafood) and physical inactivity.[39,40] Compared to older adults who lived alone, younger adults living alone had higher proportions of smoking[41] and lower vegetables intake.[42] In comparison to those to those living with others, older adults who live alone may be physically healthier.[43,44] It is plausible this may be case in younger but not older adults living alone, which would explain the association being restricted to the younger age group. Moreover, it may be more true in males than females, explaining the stronger association in males.

It it also possible that living alone has a causal relation with mortality. Individuals who live with others may gain more encouragement to maintain a healthy lifestyle, and this may be more important in younger individuals[41,42] and in males.[39,45] Further, individuals who live with others may get faster contact with medical services and first aid help in the event of illness, though it seems implausible that this factor would differ by age or sex. Living alone may result in loneliness and depression, and this may be a greater problem in younger individuals and in males who tend to have fewer social networks than females.[46]

Inflammation could be considered as one of the pathogenesis for living alone and all-cause mortality. Studies have reported associations between living alone and higher levels of C-reactive protein (CRP) and/or interleukin-6 (IL-6).[47–49] These inflammatory markers have been associated with many diseases,[50–53] which may increase the risk of mortality. One recent cohort study found a strong association between years lived alone and elevated IL-6 and CRP for middle-aged males, but not for females,[54] providing another possible explanation for our findings.

Our results provide compelling evidence of a true association between living alone and mortality in younger but not older adults, an association that appears stronger in males than females. The findings, based on high certainty evidence, mandate more careful scrutiny, in younger people living alone, with physical and emotional problems and illnesses that may result in premature death. Action that might be mandated was the relation between living alone and mortality causal — actively encouraging younger people living alone to modify their living arrangements — is less secure. For causation, the low certainty of the evidence leaves the advisability of such initiatives in greater doubt. Future studies assessing the association between living alone and all-cause mortality should ideally consider different structures of households and different cultural backgrounds.

High certainty of evidence suggests that living alone is associated with a increased risk of all-cause mortality among younger adults, and that the association may be stronger in males than females. For the causal inference — living alone actually causes increased deaths — the evidence is only low certainty.

Contributors

Yunli Zhao and Gordon Guyatt conceived and designed the study; Yunli Zhao, Ya Gao, Ream Abdullah and John Basmaji acquired data (including selecting the study, extracting the data and assessing the risk of bias); Yunli Zhao, Farid Foroutan and Qiukui Hao analysed data; Yunli Zhao, Gordon Guyatt, Farid Foroutan, Ya Gao and Qiukui Hao interpreted the data; Yunli Zhao drafted the article; Gordon Guyatt and Farid Foroutan, critically revised the article; all authors reviewed the submitted version of manuscript and approved the final version of the manuscript. Yunli Zhao and Ya Gao accessed and verified the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Not applicable.

Declaration of interests

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101677.

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