Title: Living alone and risk of dementia: A systematic review and meta-analysis

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Abstract

Aims: To systematically review longitudinal studies on living alone and incident dementia, to pool the results in a meta-analysis and calculate the population risk.

Methods: Embase, Medline and PsycInfo were searched from inception to August 2019 for longitudinal cohort studies of people living alone and risk of dementia. Relative risks (RR) were extracted and effect sizes pooled, with a sensitivity analysis for risk of bias (QUIPS quality rating tool). Population Attributable Fraction (PAF) was calculated, with prevalence of living alone calculated from UK Census data.

Results: Twelve studies were identified for inclusion, nine of which had low risk of bias. The pooled effect size indicated an elevated risk of incident dementia when living alone (all studies RR=1.30; 95% CI: 1.15-1.46; low risk of bias studies (RR=1.31; 95% CI: 1.13-1.51). The PAF for living alone was 8.9%.

Conclusions: Social isolation is a more important risk factor for dementia than previously identified, with living alone associated with greater population risk than physical inactivity, hypertension, diabetes and obesity.

1. Introduction

The number of people living with dementia globally is increasing. In 2015 an estimated 47 million people were affected and this is forecast to rise to 131 million by 2050 (Prince et al., 2015). To date there are no effective disease modifying pharmacological interventions, so research has focused on understanding the impact of modifiable lifestyle factors (Livingston et al., 2017). These modifiable lifestyle factors or putative risk factors for dementia are understood to be present throughout the life course (Livingston et al., 2017). Risk factors can be predictive or explanatory (Schooling and Jones, 2018), and the nature of risk is yet to be established in the case of lifestyle factors and dementia. However, modification of lifestyle factors can slow the rate of cognitive decline even after disease onset (Deschaintre et al., 2009).

One way of understanding the importance of a modifiable lifestyle factor is by calculating the Population Attributable Fraction (PAF) as used in the Lancet Commission for dementia (Livingston et al., 2017). The PAF takes into account both the relative risk (RR) and prevalence of the risk factor in the population and is defined as the proportion of incident cases that are attributable to the risk factor. Assuming a causal relationship, if the risk factor in question were to be eliminated, the PAF indicates the proportion of incident cases that would be reduced as a result (Mansournia and Altman, 2018).

Using pooled effect sizes for RRs, Livingston and colleagues (Livingston et al., 2017) reported PAFs for well-established dementia risk factors which included smoking (13.9%), depression (10.1%), physical inactivity (6.5%), hypertension (5.1%), diabetes (3.2%) and obesity (2.0%). In addition to these factors, Livingston et al., (2017), the UK National Institute for Clinical Excellence (NICE, 2015) and the US National Institute for Health

(Daviglus et al., 2010) have identified social isolation as a potential modifiable risk factor for dementia.

Livingston and colleagues identified a systematic review and meta-analysis of social relationship risk factors which reported the relative risk of developing incident dementia as 1.57 (95% CI: 1.32-1.85) associated with low social contact and 1.41 (95% CI: 1.13-1.75) associated with low social participation (Kuiper et al., 2015). Using the RR for low social contact in combination with an estimate for prevalence from a study on loneliness in the elderly by the Economic and Social Research Council (ESRC, 2003), Livingston et al., (2017) reported the PAF for low social contact as 5.9%, similar to hypertension and physical inactivity. However, the authors noted that this figure was likely to be a conservative estimate in the absence of more accurate prevalence data (Livingston et al., 2017). Additionally, the use of social contact as a measure of social isolation is limited by the lack of consensus on the definition. Each of the eight studies included in Kuiper and colleagues' meta-analysis used different definitions of social contact. Four studies captured a frequency component in their definition such as 'visiting children or other relatives (never vs. at least weekly)' (Crooks et al., 2008) and four studies used an absolute definition e.g. 'visiting friends (No vs. Yes)' (He et al., 2000). In addition to the heterogeneity conferred by the frequency aspect of these categories, not all social contact is equitable. Social contact involving friends, but not increased contact with family, is found to be associated with a reduced risk of dementia (Sommerlad et al., 2019). Adding further to the overall heterogeneity in the reported PAF, the prevalence data relied on data from the ESRC study (2003), which defined low social contact as that of 'less than monthly'. Thus, the use of low social contact and its associated PAF as reported by the Lancet Commission (2017) is likely

to be a crude measure of the impact of social isolation on incident dementia in the population.

Arguably a more objective measure of social isolation is that is that of living alone. The metric of living alone lends itself more favourably to a precise binary definition and, in countries where census data are collected, prevalence data are accurate and readily available.

Thus, the aims of this review were to further investigate social isolation as a risk factor for dementia by conducting a systematic review of the literature on living alone and incident dementia, pooling the effect sizes and calculating the associated PAF.

2. Methods

2.1 Systematic search and study selection

A systematic literature search was conducted using search strings from the previously published systematic review on social relationships and the risk of incident dementia (Kuiper et al., 2015). Three databases (Embase, Medline and PsycInfo) were searched from inception to 8th August 2019. Duplicates were removed, a title and abstract screen conducted and then the full texts of the remaining studies were assessed.

Studies were included if they were: longitudinal cohort studies; comprised of community dwelling participants; reported effect sizes or frequency data for the association between living alone at baseline and incident dementia at follow-up; published in peer-reviewed journals in English; used human participants. Review articles were excluded. However, the reference lists of three review articles (Boss et al., 2015; Kuiper et al., 2016,

2015) were hand-searched for further relevant studies as were the reference lists of all papers included in the final selection.

2.2 Methodological quality assessment

The Quality of Prognosis Studies in Systematic Reviews (QUIPS) tool (Hayden, Côté, & Bombardier, 2006) was used to assess the quality of the studies. The QUIPS tool assesses studies based on six domains of study quality, which are further divided into various subdomains. As per the authors' recommendations, the subdomains were selected for relevance, giving 12 subdomains. These subdomains consisted: description of the baseline study sample; participation rate greater than 70%; 70% data on dementia at follow-up; no differences between participants and drop outs; clear prognostic factor measurement; 70% complete data for living arrangement; dementia diagnosis made by a multidisciplinary team using set criteria (e.g. DSM-IV); potential confounders or age and sex measured; confounders accounted for in design or analysis; the selected statistical model is adequate for the design of the study. Studies were given an overall rating for risk of bias from 'low' where all, or the majority of the quality items have been met, to 'high' where few quality items have been met. For the purposes of this review it was pre-determined that studies with high risk of bias (defined as 0-4 subdomain quality items met) would be excluded. Studies defined as medium or low risk of bias (5-9 and >9 subdomain quality items, respectively) would be included.

2.3 Data extraction

Two researchers (RD and AJ) extracted all data presented in Table 1. Disagreements were resolved in discussion meetings. Where possible the estimate of the effect size of living alone versus not living alone and the association with incident dementia was extracted from the studies. In the case where a study reported multiple estimates of living style (e.g. living alone versus living with partner and living alone versus living with partner plus child) the estimate for living alone versus living with the greatest number of others was used. Where studies reported estimates at different time points, the estimate reported at the longest follow-up period was used. Where studies reported unadjusted and adjusted models the most fully adjusted effect size was selected. In studies that did not report the estimate of interest but reported frequencies of incident dementia for people living alone or with others, the frequency data were used to calculate the risk ratio (RR). In the studies that reported odds ratios (OR) or hazard ratios (HR) instead of RR these figures were extracted and interpreted as RR as long as the incidence of dementia in the study participants was less than 10% as per the guidelines provided by the Cochrane handbook (Higgins and Green, 2011).

2.4 Meta-analysis

A meta-analysis was conducted to calculate a pooled effect size for the risk of incident dementia associated with living alone. A random-effects model was used to account for heterogeneity (Higgins and Green, 2011). Publication bias was assessed by plotting the standard error of each estimate against its log risk ratio for each study to produce funnel plots. Egger's test was used to assess for funnel plot asymmetry.

All analyses were performed using RStudio (2016) software version 1.1.419 and the metafor package for R (Viechtbauer, 2010).

2.5 Population attributable fraction

The population attributable fraction (PAF) was calculated in line with the Lancet Commission (Livingston et al., 2017) using the Levin formula which is recommended for use with unadjusted estimates (Benichou, 2001):

$$PAF = \frac{Pe(RRe-1)}{1+Pe(RRe-1)}$$

Where *Pe* is the prevalence of the exposure and *RRe* the relative risk of disease due to that exposure. The PAF was calculated using prevalence figures from the UK 2001 census on the proportion of the population living alone aged 65+.

3. Results

3.1 Study Selection

A total number of 36402 articles were identified from the initial database search. After removal of duplicates, articles were screened on title and abstract leaving a total of 227 articles, which were subjected to full text screen. This resulted in 12 studies (Akbaraly et al., 2009; Arai et al., 2004; Bickel and Cooper, 1994; Chen et al., 2011; Fratiglioni et al., 2000; He et al., 2000; Helmer et al., 1999; Holwerda et al., 2014; Paillard-Borg et al., 2009; Rawtaer et al., 2017; Rodriguez et al., 2018; Sörman et al., 2015) identified as meeting inclusion. The flow diagram of study selection is presented in Figure 1.

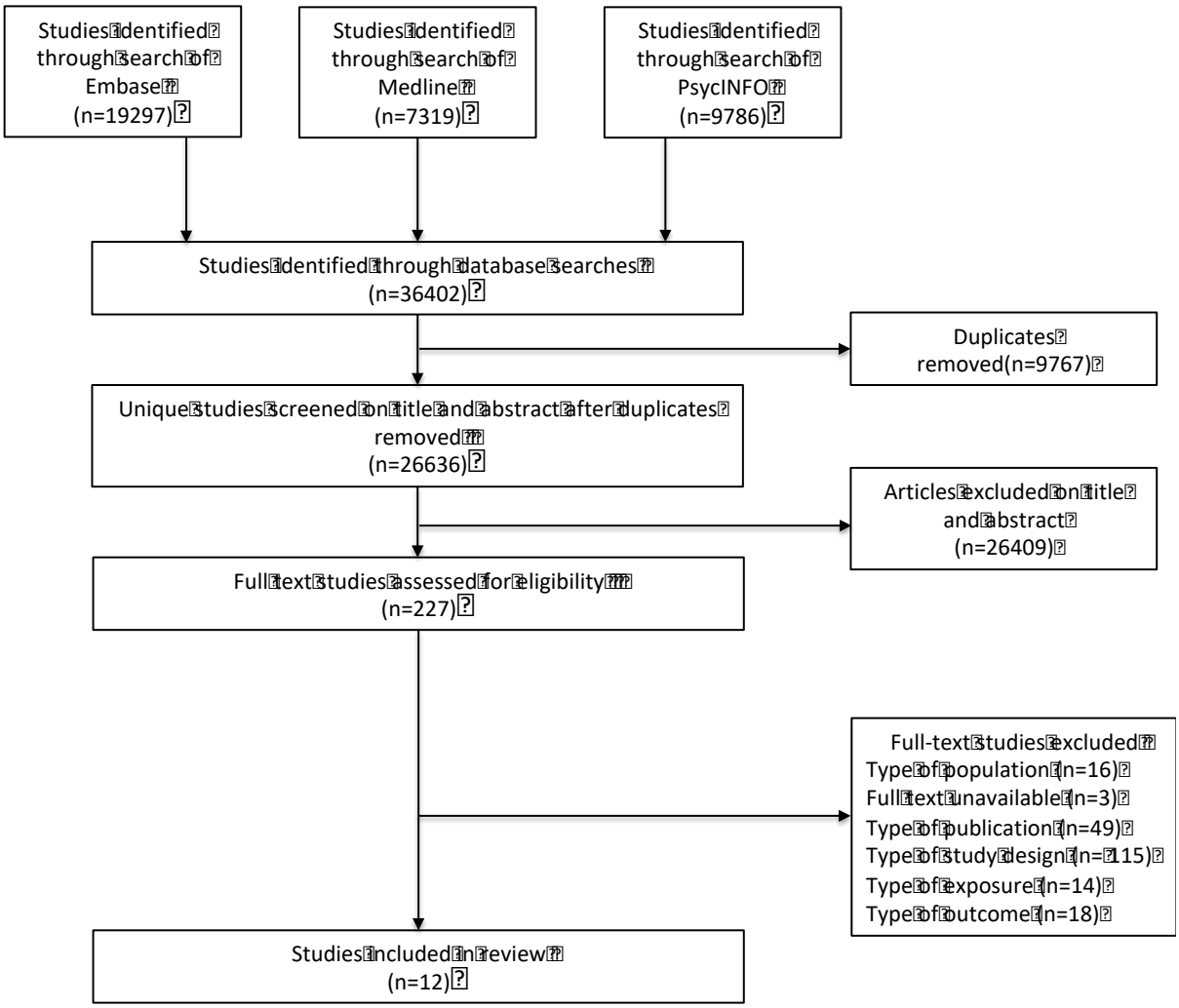

Fig. 1. Flow diagram of study selection

3.2 Characteristics of the studies

The characteristics of the included studies are presented in Table 1. The year of baseline data collected ranged from 1987 to 2005. Sample sizes in the studies ranged from 343 to 5698 with follow-up periods ranging from three to 16 years. Eight studies took place in Europe (France [2], Germany[2], Netherlands, Sweden[3]) and the reminder in Asia

(China[2], Japan, Singapore). The age of the population in all studies was 55+ with all study populations comprising of a greater female proportion (50.8% to 75.6%). Nine of the twelve studies met criteria for low risk of bias and the remaining three (Arai et al., 2004; Holwerda et al., 2014; Paillard-Borg et al., 2009) medium risk.

Table 1 Characteristics of included studies

Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses [a]	Population[b]	Age mean (SD), range (years)	Woman (%)	Living alone assessment	Adjustment for covariates	Outcome Assessment	Statistic reported	Risk of incident dementia (95% CI)	*p* value
Akbaraly et al., (2009)	France	1999-2001	4	5698	Community dwelling individuals aged 65 years or older	73.72	60.9	Living alone: Yes/No	None	Incident dementia	RR	1.04 (0.76-1.43)	.82
Arai et al., (2004)	Japan	1998	5	782	Community dwelling individuals aged 65 years or older	NR 65+	50.8	Household composition: living alone, living with spouse, living with spouse with other family members, living with other family (not including spouse)	Age and sex	Incident dementia	RR	1.67 (0.74-3.73)	>.05
Bickel & Cooper (1994)	Germany	NR	7.8	343	Random sample of people aged 65+	73.8	64.1	Single person household versus not single person household	Age	Incident dementia	RR	1.64 (.8-3.3)	>.05
Chen et al., (2011)	China	2001-2003	7.5	1526	Randomly selected community dwelling people aged 65 years and older	NR 65+	NR	Living with: no one, spouse only or parents only, children and/or grandchildren only, spouse and/or grand/children and/or parents	Age and sex	Incident dementia	OR	2.78 (1.25-6.25)	.0012

Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses [a]	Population[b]	Age mean (SD), range (years)	Woman (%)	Living alone assessment	Adjustment for covariates	Outcome Assessment	Statistic reported	Risk of incident dementia (95% CI)	*p* value
Fratiglioni et al., (2000)	Sweden	1987	3	1203	Community dwelling people aged 75 years and older. Participants with MCI at baseline were excluded	NR 75+	74.6	Marital status and living arrangement: married and living with someone, single and living alone, widowed/divorced and living alone, married and living alone, single and living with someone, widowed/divorced and living with someone	Age, sex, education and baseline MMSE score	Incident dementia	RR	1.5 (1.0-2.1)	<.05
He et al., (2000)	China	1987	10	1203	Participants were invited to take part if they were living in a randomly selected neighbourhood and aged 55+	NR 55+	58.0	Style of dwelling: living alone, living without spouse, living without son or daughter, living with small family	Age, sex	Incident AD	RR	1.25 (0.44-3.58)	>.05
Helmer et al., (1999)	France	1988	5	3675	Sample of community dwelling people aged 65+	NR 65+	58.0	Living alone versus living with others	Marital status, number of people in network, satisfaction with network, number of leisure activities, depression, education, alcohol	Incident dementia	RR	1.22 (0.76-1.96)	.41

Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses [a]	Population[b]	Age mean (SD), range (years)	Woman (%)	Living alone assessment	Adjustment for covariates	Outcome Assessment	Statistic reported	Risk of incident dementia (95% CI)	*p* value
Holwerda et al., (2014_	Netherlands	1990-1991	3	2173	Participants were randomly selected from general practice registers	NR 65-86	63.1	Social isolation: living alone	Feelings of loneliness, not/no longer married, no social support, age, sex, education level, depression, physical health conditions, COPD, Parkinson's disease, traumatic brain injury, cognitive impairment, no dementia MMSE, functional impairment	Incident dementia	HR	0.96 (0.48-1.93)	>.05
Palliard-Borg et al., (2009)	Sweden	1987	9	732	All residents of a district of Stockholm aged 75+ Participants living in an institution or with a MMSE <24 were excluded	81.1 (4.9)	74.2	Living arrangement: living with spouse/partner, living alone	None	Incident dementia	RR	1.29 (0.98-1.70)	.06

Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses [a]	Population[b]	Age mean (SD), range (years)	Woman (%)	Living alone assessment	Adjustment for covariates	Outcome Assessment	Statistic reported	Risk of incident dementia (95% CI)	*p* value
Rawtaer et al., (2017)	Singapore	2003-2005	8	1601	All residents of a region in Singapore aged 55+	64.9 (6.8)	64.5	Living alone: Yes/No	Age, sex, education, ethnicity, smoking, alcohol, dyslipidemia, hypertension, diabetes, obesity, history of stroke/heart disease, APOE-ε4 allele carrier, depression, physical activity, social activity, feelings of loneliness, married, satisfied with life	Incident dementia	HR	1.41 (0.86-2.32)	.17
Rodriguez et al., (2018)	Germany	1997-1998	9	1015	Systematic random sampling of people aged 75+	81.7	74.0	Living alone versus living with others	Age, gender, marital status, education smoking, diabetes, stroke, depression, and ischemic heart disease	Incident dementia	HR	1.75 (1.03-2.97)	.04
Sörman et al., (2015)	Sweden	1988	16	1715	Participants randomly selected from a population register aged 65+	74.2	55.9	Living status: living with spouse/partner and children, living with other, living with siblings, living alone	Age, gender, education, MMSE, alcohol, smoking, cardiovascular risk, obesity, stress and depressive symptoms	Incident dementia	HR	1.20 (.96-1.54)	.10

NR: Not reported; MMSE: Mini Mental State Examination; MCI: Mild cognitive impairment; AD: Alzheimer's disease, RR: Risk ratio; OD: Odds ratio; HR: Hazards ratio; NR: Not reported.
[a]Indicates the baseline measurement included in the analysis of interest, [b] All studies excluded participants with dementia at baseline

3.3 Meta-analysis

All twelve studies were entered into the meta-analysis to calculate a pooled effect size. Only three of the twelve individual studies indicated a significant risk of dementia. However, pooling the effect sizes indicated that there was a significant risk of developing incident dementia associated with living alone versus living with others (RR=1.30; 95% CI: 1.15-1.46). The results of the *Q*-test indicated that the level of heterogeneity in the model was non-significant (χ^2 = 9.23, *df* = 11, *p* = .60, I^2 <.001%).

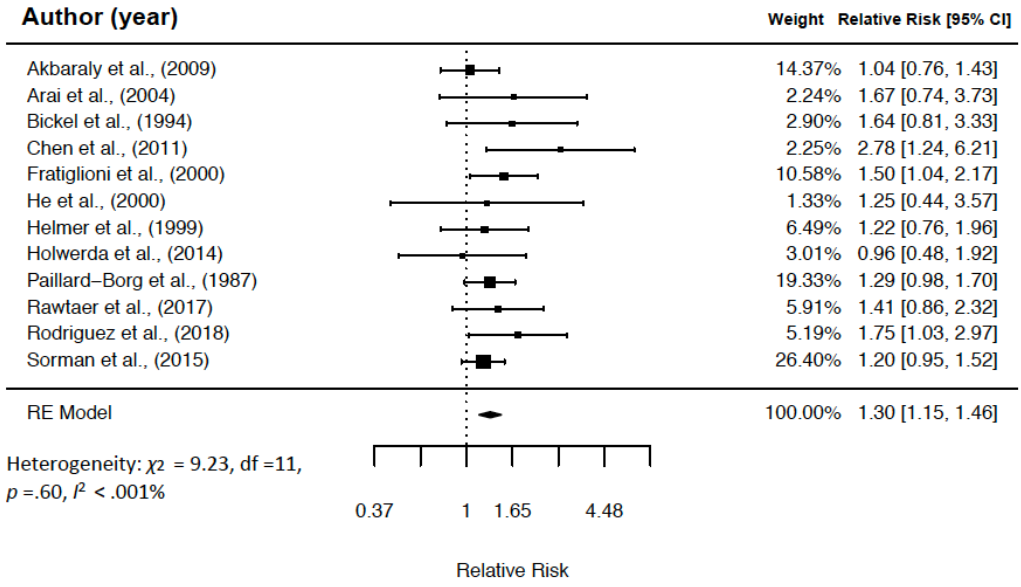

Fig.2. Forest plot for living alone and risk of incident dementia

A sensitivity analysis was conducted excluding the three studies at medium risk of bias. The results were similar (RR=1.31; 95% CI: 1.13-1.51) and indicated the overall meta-analysis result was robust to potential effects of bias.

3.4 Population attributable fraction

The PAF indicated that 8.9% of the cases of incident dementia in those aged 65 and above was attributable to living alone.

3.5 Publication bias

A funnel plot and Egger's test was used to assess for publication bias (Fig. 3.). The relatively symmetrical appearance of the funnel plot and Egger's test (z=1.49, p=.14) indicated that there was low likelihood of publication bias.

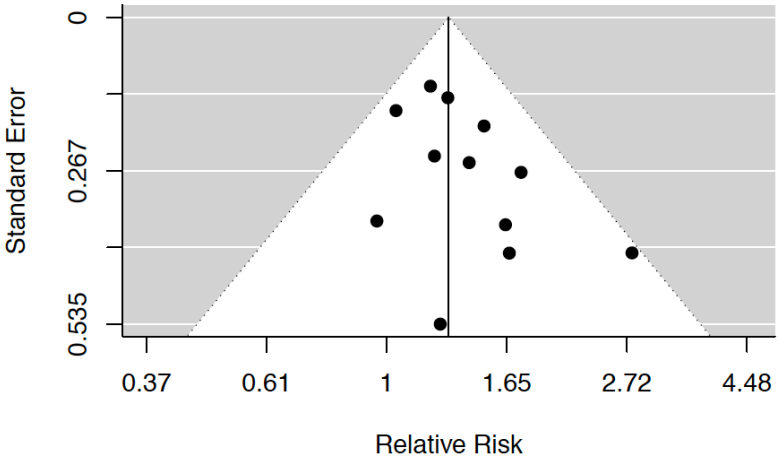

Fig. 3. Funnel plot of studies

4. Discussion

This is the first review to systematically draw together the literature on living alone and risk of incident dementia. The meta-analysis demonstrated an elevated risk of incident dementia in people who live alone. The PAF calculation indicates 8.9% of the cases of incident dementia in those aged 65 and over are attributable to living alone suggesting that social isolation is more important than previously thought in understanding risk of dementia.

The findings are particularly relevant in societies where there are increases in the number of people, especially older people, in single occupancy households. For example, data from the UK census indicates that in 2011 just under a third of households were single occupancy (ONS, 2011) with an increase of 600 000 from 2001. When the figures are stratified by age, the greatest increase in single occupancy was amongst those aged 45 and

over (ONS, 2011) indicating the likelihood of an ongoing rise in the number of people in middle and old age living alone.

4.1 Clinical and research implications

Living alone as a proxy measure for social isolation has potential important implications for clinical practice. Living alone is an easily identified risk factor for dementia allowing clinicians to suggest interventions aimed at mitigating the detrimental effects of social isolation, for example through social prescribing (www.kingsfund.org.uk/publications/social-prescribing). However, care must be taken to avoid the assumption that living alone per se is elevating the dementia risk. Few of the reviewed studies adjusted for loneliness, which may be a greater driver than living alone, given some people seek solitude by choice (Long and Averill, 2003). Two systematic reviews (Kuiper et al., 2015; Lara et al., 2019) have demonstrated that more loneliness is significantly associated with incident dementia.

The exact nature of the relationship between social isolation and incident dementia is currently unknown. Several plausible explanations have been put forward including: the cognitive activity hypothesis, the vascular hypothesis and the stress-buffering hypothesis (Valenzuela, Brayne, Sachdev, Wilcock, & Matthews, 2011). The cognitive activity hypothesis proposes that social activities engage and stimulate the brain, forging and strengthening neural connections which are weakened or lost in the absence of stimulation. Support for this theory comes from animal models, where socially impoverished mice have been found to have smaller brain volumes and increased atrophy in certain brain structures (Dong et al., 2004). The vascular hypothesis proposes that people who are socially isolated are vulnerable to increased levels of hormones associated with stress e.g. cortisol (Cole, 2008)

and increased levels of inflammatory biomarkers e.g. interleukin-6 (Loucks et al., 2006). These vascular biomarkers are known to be detrimental to physical health and have been linked to increased risk of cardiovascular diseases as well as an increased risk of mortality (Friedler et al., 2015). There is evidence that these vascular biomarkers, over prolonged periods, affect cognition. Elevated levels of cortisol and interleukin-6 have been linked to cognitive decline (Lara et al., 2013; Marsland et al., 2006). The stress-buffering hypothesis suggests that having access to social resources may mitigate some of the negative impacts of stressful life events. For example, having a social buffer may prevent a person from falling into severe depression after experiencing a loss. As a result, they may also be less likely to suffer from the adverse consequences of having high levels of stress hormones or inflammatory biomarkers circulating in their system (Lubben and Gironda, 2004). In addition, living alone is associated with greater exposure to vascular risk factors including higher levels of smoking, physical inactivity and poorer diets (Jeong and Cho, 2017), which may also contribute to cognitive decline.

Further research is needed to better understand the relationship between social contact and dementia. For example, observational studies may be carried out to ascertain whether the relationship between living alone and incident dementia can be accounted for by feelings of loneliness, number of years spent living alone or recent bereavement. Natural experiments could also provide useful answers to the questions e.g. does social prescribing mitigate the risks of living alone?

4.2 Strengths and limitations

The methods used for study identification, quality rating and PAF calculation derive from previous high quality reviews (Kuiper et al., 2015; Livingston et al., 2017) with the

added strength of 'living alone' being more clearly definable than 'low social contact', with prevalence data available from National Census figures. However, a limitation in common with the Lancet Commission is the calculation of PAF using UK-only prevalence data when risk estimates are derived from studies across the globe. A limitation of the reviewed studies is the absence of explanation for living alone. Some reasons for living alone may be more harmful than others. For instance, living alone following bereavement may be more detrimental than living alone as a lifestyle choice. As this is a meta-analysis of epidemiological studies, with most studies having follow-up periods of less than ten years, it is not possible to draw any inferences on the causal relationship between living alone and dementia.

4.3 Conclusions

The risk of incident dementia in people who live alone is greater than previously realised, with a higher population risk factor than physical inactivity, hypertension, diabetes and obesity. Further work is needed to understand, potential mechanisms, confounding and mitigating factors.

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