Depressive symptoms and cognitive decline in mid and late life: is there a temporal relationship and is it mediated by lifestyle?

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University College London

THESIS DECLARATION FORM

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: 

Name: Roopal Desai

Date: 04th July 2018

OVERVIEW

This thesis focuses on some of the modifiable risk factors of cognitive decline and dementia.

Part 1 is a systematic literature review and meta-analyses on living alone and risk of incident dementia pooling results from 9 longitudinal cohort studies. The overall model was too heterogeneous for meaningful interpretation. Sub-group analysis found that in Europe there was evidence of an elevated risk of living alone and dementia. The Asian sub-group of studies were too heterogeneous to interpret. In Europe living alone may be a proxy measure of general social relationships. Establishing who lives alone may be useful in clinical settings as a quick way to assess elevated risk of dementia from social isolation.

Part 2 is an empirical study examining the temporal relationship between depressive symptoms and cognitive decline and if the relationship is mediated by lifestyle. Cross-lag analysis was used to assess if depressive symptoms were a psychological reaction to, a risk factor for, or prodrome of, cognitive decline. Depressive symptoms may be either a risk factor or prodrome for decline in the cognitive domains of memory, verbal reasoning, spatial working memory and digit span. In addition, decline in executive function and attention may impact on daily life thereby causing distress. There was no evidence that the relationship was mediated by lifestyle. Clinical implications and implications for further research are discussed.

Part 3 is a critical appraisal of the empirical study and literature review. Reflections include working on an external project using secondary data and the time consuming nature of conducting literature reviews.

IMPACT STATMENT

Age is the biggest risk factor for developing dementia. Three percent of those between the ages of 65 and 74 years develop dementia and after the age of 75 years the risk doubles every five years. Fifty percent of those aged over 85 years develop dementia (Burns & Iliffe, 2009). Therefore, as lifespans increase across the world the number of people living with dementia is also increasing. In 2015 the number of people living with dementia globally was estimated at 47 million. This figure is estimated to almost triple by 2050 (Prince et al., 2015). As yet the search for effective treatment or preventative drugs has been unfruitful (Schwarz, Froelich, & Burns, 2012). Therefore, identifying and understanding modifiable lifestyle factors is an important avenue in developing preventative strategies. A recent review found that 35% of the variance of dementia risk could be explained by nine modifiable factors (Livingston et al., 2017). This thesis examined two of these: social factors (living alone) and risk of incident dementia; and depression (depressive symptoms) and relationship to cognitive decline.

The finding from the systematic literature review and meta-analyses was that living alone conferred an elevated risk of incident dementia. This is the first review to report this finding and is important in the cultural context of the UK today with a growing population of over 50's living alone. The finding from the empirical study was that depressive symptoms might be either a risk factor or prodrome for decline in four domains of cognition. For two of these of these four (executive function and attention) the study found support that decline predicts depressive symptoms as well. This was the first study to report a reciprocal relationship of this kind and is an important contribution to the on-going debate.

The aim is to disseminate both of these findings to the research community by publishing in peer-reviewed journals. Adding to the body of knowledge on social

factors and dementia in this way may play a part in influencing the direction of future research and/or feed into forums that inform guidance. For example, the charity Age UK (https://www.ageuk.org.uk/information-advice/health-wellbeing/relationships-family/) currently provides advice on how to adjust to living alone in later life. If future guidance were to take into account that living alone is potentially a risk factor for dementia then more weight may be given on what steps a person could take to mitigate the risk. Similarly, a publication resulting from the empirical study may inform future research specifically in terms of the type of analyses used as currently very few studies in this field of study examine reciprocal relationships. Both these findings will be fed back to the study team. Recommendations will be made that future waves of data collection gather information on living arrangements and that they consider adding a booster sample of participants with clinical levels of depression.

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PART 1: LITERATURE REVIEW

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

1. Abstract

Aims: Poor social relationships are a known risk factor for the development of dementia. However, the relationship between living alone and dementia is less clear. This review aimed to systematically review the literature on living alone and risk of dementia and pool the results in a meta-analysis.

Methods: Embase, Medline and PsycInfo were searched from inception to November 2017 for longitudinal cohort studies of people with dementia living alone. Relative risks (RR) were extracted and effect sizes pooled to establish the association between living alone and risk of dementia.

Results: Nine studies were identified for inclusion. The pooled effect size of the nine studies was too heterogeneous for meaningful interpretation. However, sub-group analysis found that in Europe there was an elevated risk of living alone and incident dementia (RR: 1.23, 95% CI: 1.10-1.39). The Asian sub-group of studies were found to be too heterogeneous for meaningful interpretation.

Conclusions: Living alone in Europe confers an elevated risk of incident dementia. Living alone may be a proxy measure of general social relationships. Establishing who lives alone may be useful in clinical practice as a quick measure of how vulnerable a person is to developing dementia through lack of social interactions.

2. Introduction

Dementia

Dementia is a catchall term used to describe a range of brain diseases that are characterised by an irreversible gradual decrease in cognitive abilities. The most common form of dementia is Alzheimer's disease contributing between 50%- 70% of all dementia cases (Burns & Iliffe, 2009), with the other common forms being; vascular dementia, Lewy body dementia and frontotemporal dementia. Rarer forms of dementia include those related to substance abuse, infection or brain injury (Stevens et al., 2002). Each form of dementia has a typical pattern of disease progression. For example, with Alzheimer's disease one of the earliest symptoms may be difficulties with spatial awareness and result in a person getting lost in familiar surroundings and then progressing to memory and loss of other skills. In the case of frontotemporal dementia an early symptom may be an individual experiencing difficulties with language. Regardless of the pattern of symptoms, most dementias are irreversible and result in a progressive decline in cognitive skills such as memory, language and executive function. Ultimately as the dementia progresses, an individual becomes less and less able to carry out the activities of daily living and living independently.

Dementia: an increasing global health problem

People over the age of 65 years are most at risk of developing dementia, with 3% of the population aged between 65 and 74 years developing dementia. The risk doubles every five years thereafter (WHO, 2016) and 50% of the population aged 85 years and over develop dementia (Burns & Iliffe, 2009). In 2015 the number of people living with dementia globally was estimated at 47 million. As lifespans increase across the globe the number of people living with dementia is also increasing. By 2050 it is estimated that the number of people living with

dementia will be in the region of 131 million (Prince et al., 2015). Linked to the projected increase in dementia cases by 2050, there is an associated increase in the cost of care, management and treatment. Some estimates have suggested that these associated costs could potentially triple by 2050 (Brenowitz, Kukull, Beresford, Monsell, & Williams, 2014).

Dementia prevention

Even though there have been numerous research studies into disease modifying pharmacological interventions, currently the search for such treatments has been unsuccessful (Livingston et al., 2017). However, there is considerable evidence that lifestyle factors play an important role in the onset of the disease (Livingston et al., 2017). Thus, understanding which types of lifestyle factors are associated with dementia could potentially help prevent or delay the onset of the disease.

These potentially modifiable factors include well known physical health risk factors such as: type 2 diabetes which studies have found confers a 1.57 (95% CI: 1.41-1.75) relative risk of developing dementia (Vagelatos & Eslick, 2013); hypertension, which confers a 1.61 (95% CI: 1.16-2.24) relative risk of developing dementia (Norton, Matthews, Barnes, Ya, & Brayne, 2014); and smoking, which confers a 1.37 (95% CI: 1.23-1.52) relative risk of developing dementia (Beydoun et al., 2014). In addition to these established physical health risk factors, over the last few years there has been greater research focus into studying social relationship factors, such as frequency of social contact and social participation and their association to dementia risk. A recent systematic review and meta-analysis of social relationship risk factors reported the relative risk of developing incident dementia as 1.57 (95% CI: 1.32-1.85) associated with less frequent social contact and 1.41 (95% CI: 1.13-1.75) associated with low social participation (Kuiper et al., 2015). These

results led the authors to argue that as some social relationship lifestyle factors have comparable relative risks to the more established physical health risk factors they are therefore equally as important when considering the development of interventions or creating strategies for the prevention of dementia (Kuiper et al., 2015). Adding further weight to the importance of social factors, a recent Lancet Commission report identified social factors as one of nine modifiable risk factors that explained 35% of the variance in the total risk of developing dementia (Livingston et al., 2017).

Social factors and dementia

Social factors that impact on a person's health can be divided into structural and functional social support. Structural social support is defined as the extent of a person's social network and may include, for example, the number of friends, frequency of contact with family and marital status (Barrera, 1986). Structural social support measures focus on the quantity rather than the quality of support. On the other hand, functional social support is a subjective conceptualisation and places more emphasis on the individual's experience of the social contact and may include items like satisfaction with friendships or perceived loneliness (Barrera, 1986). Both structural and functional aspects of social support have been studied and their relationship to both cognitive decline and dementia.

A recent meta-analyses on various different aspects of social relationships and their impact on dementia (Kuiper et al., 2015) reported mixed results. The review focused its investigation on longitudinal cohort studies of community dwelling samples. The Kuiper et al. (2015) review included 19 studies and found that risk of developing dementia increased with two structural social support factors (low social participation and less frequent contact with friends and family), and one functional

aspect (greater perceived loneliness). The review also reported that satisfaction with social network, a functional aspect of social support, was not related to dementia.

A limitation that is common to studies investigating social support is of recall bias. That is, even ostensibly 'objective' structural measures are collected using self-report techniques and therefore influenced by recall or social desirability bias. Notwithstanding the methodological limitations with some of the measures, there is good evidence that some of the aspects of social support may afford protection against the onset of dementia.

Social factors and dementia: possible mechanisms

The exact nature of the mechanism of the relationship between social factors and dementia are currently unknown. However, several plausible explanations have been put forward including: the cognitive activity hypothesis, the vascular hypothesis and the stress-buffering hypothesis (see Valenzuela, Brayne, Sachdev, Wilcock, & Matthews, 2011 for a review of the literature).

The cognitive activity hypothesis proposes that social activities engage and stimulate the brain's neural connections. When the brain is engaged in cognitively stimulating activities, such as when participating in social pursuits, connections between synapses can be forged or strengthened. If, on the other hand, the environment does not provide this type of stimulation, connections between neurons can weaken or be lost. 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 such as a heart attack or stroke as well as an increased risk of mortality (Friedler, Crapser, & McCullough, 2015). There is also evidence that these vascular biomarkers, over prolonged periods of time, impact on cognition. Elevated levels of both 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. In addition, as well as protecting against the impact of negative life events, being socially integrated may also serve the function of encouraging people to engage in pro-health behaviours such as not smoking and remaining physically active (Lubben & Gironda, 2004).

Living alone

People who live alone are potentially vulnerable to all three of the mechanisms described above. However, the literature on living alone and cognitive decline or dementia is mixed. Some studies have reported a link between living alone and increased risk of cognitive decline. For example, one longitudinal study investigating the risk of men living alone found that there was a two fold increase in risk of cognitive decline compared to those who were married or living with others (van Gelder et al., 2006). Another cross-sectional study found living alone had a detrimental effect only on the cognitive domain of processing speed (Gow, Corley, Starr, & Deary, 2013). On the other hand, some studies have found there to be no

benefits for cognition of living with others. In a seven-year longitudinal cohort study there was reported to be no increased risk of developing mild cognitive impairment (MCI) in those living alone compared with living with others (Brenowitz et al., 2014). Likewise a study investigating the link between living alone and risk of dementia found the relationship between the two was non significant (Holwerda et al., 2014). Thus the existing literature between living alone and dementia provides a mixed picture.

However, there are several benefits of reviewing the literature and evaluating whether there is a link between the two and if so how large that association may be. Firstly, living alone is an objective variable that is less likely to be influenced by recall bias. Secondly, there is an upward trend of people living on their own in the Western countries. In the USA it has been reported there has been a 40% increase in people living alone 1980 and 2009 (Green, 2009). In the UK there has been a similar trend. Data from the UK census has revealed that just under a third of households were single occupancy in 2011 (ONS, 2011). Since the previous census in 2001 the number of people living alone has increased by 600 000. When the figures are stratified by age, the greatest increase in people living alone was amongst those aged 45 and over (ONS). Based on these figures it is likely that the number of people in middle and old age living alone will continue to rise.

Aim

To date there have been no reviews on living alone and risk of dementia. The aim of this review was to investigate the relationship between living alone and risk of dementia by conducting a systematic review of the literature and pooling the effect sizes in a meta-analysis.

3. Method

Systematic search and study selection

A systematic literature search was conducted using search strings from a 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 the 5th November 2017. The search terms used are presented in Table 1.

Table 1 *Literature search terms*

MeSH terms	Title and Abstract
Dementia, mild cognitive impairment, cognition disorders	Cognitive function*,cognitive impairment, cognitive decline, cognitive deficit*, cognition loss*, cognitive loss*, cognitive abilit*, dement*, alzheimer*, cognition, cognitive status, cognitive change, cognition change, cognitive performance, cognitive dysfunction*
Loneliness, social isolation, social support, social participation, interpersonal relations	Loneliness, social support, social isolation, social participation, social engagement, social disengagement, social integration, personal network*, social network*, social activit*, social tie*, social relation*, social interaction, social withdrawal, social capital, social contact, social embeddedness, family relation*, kinship relation*, friendship*, social influence, social vulnerability

*Truncated to allow multiple word endings

After duplicates were removed from the search, the remaining studies were screened on title and abstract. Full texts of the remaining studies were examined to assess their eligibility for the current review and meta-analysis.

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.

Only articles published in peer-reviewed journals in English with human participants were considered. Review articles were excluded. However, the reference lists of three review articles (Boss, Kang, & Branson, 2015; Kuiper et al., 2015, 2016) were hand-searched for further relevant studies. Likewise the reference lists of all papers included in the final selection were hand searched for relevant studies.

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 6 domains of study quality. These are comprised of; study participation, study attrition, determinant measurement, confounding measurement and account, and analysis. A review of the QUIPS tool found that the tool had good inter-rater agreement (*k* statistic =0.75) and 74% of the reviewers reported that it was easy to reach consensus (Hayden, van der Windt, Cartwright, Côté, & Bombardier, 2013). The tool assesses each domain: quality item met - indicating low risk of bias; quality item not met -indicating high risk of bias; or insufficient information reported to assess risk of bias. The authors of the tool, in line with guidance from the Cochrane Handbook, recommend that an overall quality score is not calculated (Hayden et al., 2013). Instead individual studies are 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 by the review that few quality items would be defined as 4-6 quality items met, medium defined as 7-8 quality items met and the maximum quality items met was 9. In addition, the authors further suggest when determining which studies to be given an overall rating as 'low risk of bias' the most important quality items should be met and these 'required' quality items are

determined in advance by the reviewers. For the purpose of this review the following quality items were determined as 'required' items to be met in order for a study to be given an overall rating of 'low risk of bias': (1) Study participation rate (adequate participation rate was deemed as >70%); (2) Study attrition rate (at least 70% of data on dementia at follow-up was collected); (3) Outcome measurement (dementia was diagnosed based on assessment by a multidisciplinary team using a set criteria e.g. DSM-V); (4) Confounder of age was measured; (5) Confounder of depression was measured; (6) Confounder of alcohol use was measured; (7) Confounder of age was accounted for in the analyses; (8) Confounder of depression was accounted for in the analyses; (9) Confounder of alcohol use was accounted for in the analyses. Thus, nine items were determined as 'required' (see Table 3. for complete list of quality items).

Data extraction

Where possible the estimate of the effect size of living alone versus not living alone and the association to 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. In studies that did not report the estimate of interest but did report the frequencies of incident dementia for people living alone or with others, the frequency data were used to calculate the risk ratio (RR). The relative risk was calculated as the probability of incident dementia when exposed to living alone divided by the probability of incident dementia when not exposed. Where possible, adjusted estimates that controlled for age, depression and alcohol use were extracted. 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 & Green, 2011).

Meta-analysis

A meta-analysis was conducted to calculate a pooled effect size for the risk of incident dementia associated with living alone. To account for the presence of heterogeneity, between the studies a random-effects model was used (Higgins & Green, 2011). Heterogeneity was estimated using the *Q*-test and the I^2 statistic. Where the test suggested that there was significant heterogeneity between the studies the pooled effect size was not reported (Higgins & Green, 2011) and subsequent sub-group analysis was conducted to establish if this could account for the heterogeneity.

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 R programming language and the statistical programming environment provided by RStudio (2016) software version 1.1.419. The meta-analyses were conducted using the metafor package for R (Viechtbauer, 2010).

4. Results

A total number of 30952 articles were identified from the initial data base search. After removal of duplicates the articles were screened on title and abstract leaving a total of 136 articles which were subjected to a full text screen. This resulted in 9 studies being identified as meeting the inclusion criteria for the present review (Akbaraly et al., 2009; Arai, Katsumata, Konno, & Tamashiro, 2004; Chen et

al., 2011; Fratiglioni et al., 2000; He, Zhang, & Zhang, 2000; Holwerda et al., 2014; Li et al., 2013; Paillard-Borg, Fratiglioni & Winbald, 2009; Rawtaer et al., 2017; Sörman, Rönnlund, Sundström, Adolfsson, & Nilsson, 2015). The flow diagram of study selection is presented in Figure 1.

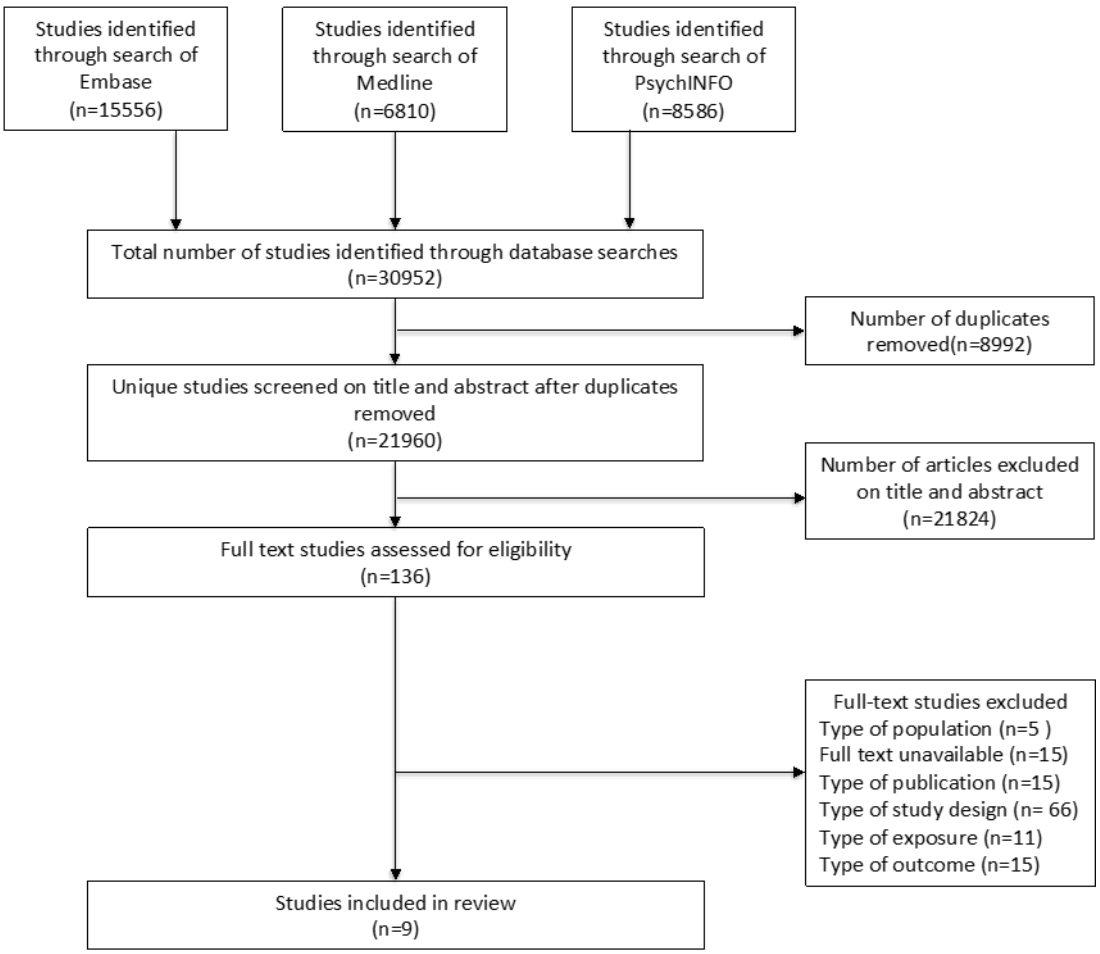

Figure 1 *Flow diagram of study selection*

The characteristics of the included studies are presented in Table 2. The year of baseline data collected ranged from 1987 to 2005. Sample sizes in the studies ranged from 776 to 5698 with follow-up periods ranging from 3 to 16 years. The study population cohorts were located either in Europe (five studies) or Asia (four studies). 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%).

Table 2 *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
Akbaraly et al., (2009)	France	1999-2001	4	5698	Community dwelling individuals aged 65 years or older	69.7 (5.3) 65+	62.6	Living alone: Yes/No	Unadjusted for living alone and incident dementia (association between leisure activities and incident dementia adjusted for, sex, age, education, manual worker, living alone, hypertension, diabetes, hypercholesterolemia, vascular disease, depression, $APOE_E4$ genotype, functional incapacity, cognitive impairment)	Incident dementia
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 souse)	Adjusted for age and sex	Incident dementia
Chen et al., (2011)	China	2001	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	Adjusted for age and sex	Incident dementia

Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses	Population[b]	Age mean (SD), range (years)	Woman (%)	Living alone assessment	Adjustment for covariates	Outcome Assessment
Fratiglioni et al., (2000)	Sweden	1987	3	1204	Community dwelling people aged 75 years and older. Participants with MCI at baseline were excluded	NR 75+	75.6	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	Adjusted for age, sex, education and baseline MMSE Score	Incident dementia
He et al., (2000)	China	1987	10	1203	Participants were invited to take part if they were living in a randomly selected neighbourhood and were aged 55 and over	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
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

Authors	Location	Year of Baseline collection	Follow-up period (years)	N in the analyses	Population[b]	Age mean (SD), range (years)	Woman (%)	Living alone assessment	Adjustment for covariates	Outcome Assessment
Palliard-Borg et al., (2009)	Sweden	1987	9	776	All residents of the Kungsholmen district of Stockholm aged 75+ were invited to participate. Participants living in an institution or with a MMSE <24 were excluded.	NR 75+	74.2	Living arrangement: living with spouse/partner, living alone	Unadjusted for living alone and incident dementia (association between active lifestyle index and dementia risk adjusted for age, sex, education, co-morbidity, cognitive and physical functioning, living arrangements, depressive symptoms, physical activity, mental stimulation and social engagement)	Incident dementia
Rawtaer et al., (2017)	Singapore	2003-2005	8	1601	All residents of a region in Singapore aged 55+	64.9 (6.8) 55+	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
Sörman et al., (2015)	Sweden	1988	16	1715	Participants randomly selected from a population register aged 65+	55+	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

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

Methodological quality assessment

Table 3. displays the results of the methodological quality assessment of the nine studies. One study (Sörman et al., 2015) met 100% of the quality items and was therefore given an overall quality rating as ‘low risk of bias’. Six studies met some of the quality items including four studies (R. Chen et al., 2011; Fratiglioni et al., 2000; He et al., 2000; Rawtaer et al., 2017), which met seven out of nine of the ‘required’ quality items, and two studies (Holwerda et al., 2014; Paillard-Borg et al., 2009), which met six out of nine of the ‘required’ quality items. These six studies were given an overall quality rating as ‘medium’ risk of bias. The remaining two studies met five (Akbaraly et al., 2009) and four (Arai et al., 2004) of the ‘required’ quality items and were therefore given an overall rating of, ‘high risk of bias’.

Table 3 *Methodological quality assessment based on the QUIPS (*indicates pre-determined 'required' item)*

	1. Study participation		**2. Study attrition**		**3. Determinant measurement**		**4. Outcome measurement**		**5. Confounding measurement and account**							**6. Analysis**
Author (year)									Potential confounders measured			Accounted for potential confounders in the study design or analysis				
	1a. Consecutive participants	1.b Participation rate >70%*	2a. 70% data on dementia on follow-up*	2b. No differences between participants and dropouts	3a. Using sufficient methods	3b. 70% complete data for living style	4a. Dementia diagnosis [a] *	4b. Outcome assessors blinded to baseline exposures	5a1. Age*	5a2. Depression*	5a3. Alcohol use*	5b1. Age*	5b2. Depression*	5b3. Alcohol use*	5c. Reverse causality	6. No over fitting[b]
Akbaraly et al., (2009)	+	?	+	?	+	?	+	?	+	+	-	+	+	-	+	+
Arai et al., (2004)	-	?	+	?	+	+	+	?	+	-	-	+	-	-	+	+
Chen et al., (2011)	+	+	+	?	+	+	-	?	+	+	+	+	+	-	+	-
Fratiglioni et al., (2000)	+	+	+	-	+	+	+	?	+	+	-	+	+	-	+	?
He et al., (2000)	+	+	+	?	+	+	+	?	+	+	+	+	-	-	+	+
Holwerda et al., (2014)	+	+	-	?	+	+	-	?	+	+	+	+	+	-	+	+
Paillard-Borg et al., (2009)	+	+	+	?	+	+	+	?	+	+	-	+	-	-	+	+
Rawtaer et al., (2017)	+	?	+	?	+	+	-	?	+	+	+	+	+	+	+	+
Sörman et al., (2015)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

QUIPS: Quality of Prognosis Studies in Systematic Review Judgement:
'+' the quality item was met indicating low risk of bias;
'-' the quality item was not met indicating high risk of bias;
'?' there was insufficient information reported to assess the risk of bias
[a] diagnosis of incident dementia was based on assessment by a multidisciplinary team using set criteria e.g. DSM-IV
[b] minimum of 10 participants in the smallest group per predictor and outcome variable

The quality assessment ratings ranged across the studies with the most common methodological flaws being; measuring and controlling for alcohol use, blinding of assessors to baseline exposures and reporting the differences between participants completing the study and those who dropped out before follow-up data could be collected.

The majority of studies (eight of nine studies) recruited consecutive, or the equivalent of consecutive, participants. Six out of the nine studies had a 70% or greater participation rate whilst the remaining three studies did not report the number of individuals who had been approached but declined to participate in the study. In terms of study attrition, eight out of the nine studies reported they had collected at least 70% of the data on dementia at the end of the follow-up period. Only two papers reported the analysis on the differences between participants who had remained in the study until the follow-up period and those who had dropped out before this. Only one of these two reported there were no significant differences between study completers and dropouts. The determinant measurement of living alone or not was adequately assessed by all the studies. Eight of the nine studies had data on the participants' living arrangement for 70% or more of their sample. In terms of assessing for dementia, six of the nine studies used multidisciplinary clinical teams and established criteria whilst the remaining three studies relied on screening tools that were correlated to clinical diagnosis. One study reported that the dementia assessment team were blinded to the exposure variables the remaining eight studies did not report either way. All studies measured the potential confounder of age, eight of nine studies measured depression and five of nine studies measured alcohol use. Similarly, all studies accounted for age in the analysis, seven of nine studies accounted for depression and two of nine studies accounted for alcohol use.

Living alone and risk of incident dementia

All but one (Holwerda et al., 2014) studies reported an increased risk of incident dementia for those living alone versus living with another (Table 4).

Eight studies reported an increased risk of dementia associated with living alone. One high quality (Sörman et al., 2015) and two medium quality(Chen et al., 2011; Fratiglioni et al., 2000) studies found the increased risk to be significant. Chen et al. (2011) investigated the predictors of incident dementia in an older Chinese population. The Chen et al. (2011) study found that there was increased risk of dementia associated with increasing age, being female, low educational attainment, smoking, suffering from angina, being employed in a manual occupation and living with few family members. This study categorised living arrangement into living alone, living with spouse or parents only, living with children or grandchildren only or living with spouse and/or grandchildren and/or parents. The study found a 'dose-response' effect of living with more family members and the protective effect for the risk of incidence dementia. That is, the greater the number of family members living together the lower the risk of incident dementia. Fratiglioni et al. (2000) investigated the influence of social network as measured by, marital status, living arrangement (living alone versus living with someone), having children, frequency of social contact and satisfaction with social contacts. The study reported that individuals living alone with few friends or relatives had an increased risk of developing dementia. However, having infrequent contact with friends or relatives did not increase the risk of dementia if the quality of the contacts was reported as satisfactory. The third study to find a significant association between living alone and risk of dementia was principally aimed at investigating the relationship between social relationships as measured by; living arrangement, frequency of social contact, satisfaction with social contact, having a close friend, and risk of incident dementia (Sörman et al., 2015). Sörman et al. (2015) combined the measures of

social relationships to generate a social relationship composite score. The main finding of the Sörman et al. (2015) study was that a higher social relationship composite score was associated with a lower risk of incident dementia.

The Holwerda et al. (2014) study investigated the link between social isolation (living alone, being unmarried and/or being without social support), feelings of loneliness and incident dementia. The main finding of this study was that feelings of loneliness but not social isolation predicted dementia onset. The results of the Holwerda et al. (2014) study also suggested that compared to living with others, living alone was slightly protective against the onset of dementia. However, this result did not reach statistical significance.

Four medium quality (Akbaraly et al., 2009; He et al., 2000; Paillard-Borg et al., 2009; Rawtaer et al., 2017) and one low quality (Arai et al., 2004) studies reported a non-significant increased risk of living alone and incident dementia. The main aim of the Akbaraly et al. (2009) study was to investigate the association between leisure activities as measured by four index scores of; frequency of participation in 'stimulating leisure activities' (e.g. doing a crossword puzzle), 'social support activities' (e.g. visits from or visiting friends), 'physical leisure activities' (e.g. going for a walk) and 'passive leisure activities' (e.g. watching television). The study found that engaging in more 'stimulating leisure activities' and 'social support activities' were associated with a reduced risk of dementia whilst engaging in 'physical leisure activities' or 'passive leisure activities' had no significant impact on the risk of dementia. The data for living arrangement in this study were collected as part of the baseline characteristics of the study and not used in the main analysis. Arai et al. (2004) examined the relationship between sociodemographic factors including: age, gender, living arrangement (grouped into three categories; living alone, living with spouse and others, and living with others). The results of the study suggested that living with a spouse provided a significant protective factor

with regard to the risk of developing dementia. However, when living alone was compared to living with others there was no significant association with risk of dementia. He et al. (2000) used a large sample in Shanghai to investigate psychosocial risk factors including; educational attainment, occupation, current employment status, living arrangement (living alone, living without spouse, living without a son or daughter, small family), life style, engagement in social activities, engagement in leisure activities, having no friends, experiencing negative life events, depression, poor well-being, poor psychological well-being, dissatisfaction with life, being lonely, and their association to risk of Alzheimer's disease. The main finding of the this study was that low educational attainment, low occupational status, infrequent social interaction, few leisure activities and poor well-being were all significant predictors of the onset of Alzheimer's disease. Living alone in this study was not a significant predictor of Alzheimer's disease. Paillard-Borg et al. (2009) investigated the relationship between various lifestyle factors and incident dementia. The researchers collected data on a wide range of lifestyle factors and used principle component analysis to identify three factors, physical (e.g. going on walks), mental (e.g. reading) and social (e.g. contact from friends). The main findings of this study were that higher scores on all three lifestyle factors were found to be protective against the risk of incident dementia during the nine-year follow-up period. Information on the nature of the participants' living arrangements was collected as part of the baseline characteristics but living alone was not found to be significantly associated with the risk of developing dementia. Rawtaer et al. (2017) also set out to examine various psychosocial factors and their link to risk of dementia. This study's variables of interest were living alone, loneliness, being married and satisfaction with life. The fully adjusted model found that only being married and being highly satisfied with life were significant protective factors in the risk of developing dementia.

Meta-analysis

The RRs of living alone and risk of incident dementia for all nine studies were combined in a meta-analysis. However, the results of the *Q* test indicated that there was significant heterogeneity in the full model (χ^2 =104.80, d*f* =8, *p* <.0001, I^2=84%) and therefore a pooled effect size was not reported. To try and account for this heterogeneity post-hoc sub-group analyses were conducted, dividing the studies based on the location of the country they were carried out in. The nine studies were split into either studies conducted in Asia or Europe.

Table 4 *Associations between living alone and incident dementia*

Author (year)	Comparison	Statistic reported	Risk of incident dementia	95% Confidence interval	*p* value	Risk of bias
Akbaraly et al., (2009)	Living alone versus living with other/s	RR	1.04	0.76-1.43	.81	medium
Arai et al., (2004)	Living alone versus living with family	RR	1.67	0.74-3.73	>.05	high
Chen et al., (2011)	Living alone versus living with spouse and/or grand/children and/or parents	OR	2.78	2.46-3.10	.012	medium
Fratiglioni et al., (2000)	Living alone versus living with other/s	RR	1.5	1.0-2.1	<.05	medium
He et al., (2000)	Living alone versus living with other/s	RR	1.25	0.44-3.58	>.05	medium
Holwerda et al., (2014)	Living alone versus living with other/s	OR	0.96	0.48-1.93	>.05	medium
Paillard-Borg et al., (2009)	Living alone versus living with spouse/partner	RR	1.29	0.98-1.70	.06	medium
Rawtaer et al., (2017)	Living alone versus living with other/s	HR	1.41	0.86-2.32	.17	medium
Sörman et al., (2015)	Living alone versus living with other/s	HR	1.23	1.02-1.44	<.05	low

RR: Risk ratio; OD: Odds ratio; HR: Hazards ratio

Asian studies sub-group analysis

Four studies were conducted in, and recruited their study cohorts from, populations residing in Asian countries with two in China (R. Chen et al., 2011; He et al., 2000); one in Japan (Arai et al., 2004); and one in Singapore (Rawtaer et al., 2017). Where as Chen et al. (2011) reported a statistically significant risk of developing dementia in those living alone, the other three studies reported slightly

increased risks of developing dementia that were not statistically significant. All four studies were entered into the meta-analysis to calculate a pooled effect size. The pooled effect size indicated that there was a significant risk of developing incident dementia in people living alone versus those living with others (RR=1.90; 95% CI: 1.22-2.96) (Figure 2). However, the results of the *Q*-test suggested that although there was less heterogeneity in the Asian sub-group model than there was in the overall model there was still a significant amount of heterogeneity present (χ^2 = 10.12, d*f* = 3, *p* = .02, I^2 = 65%).

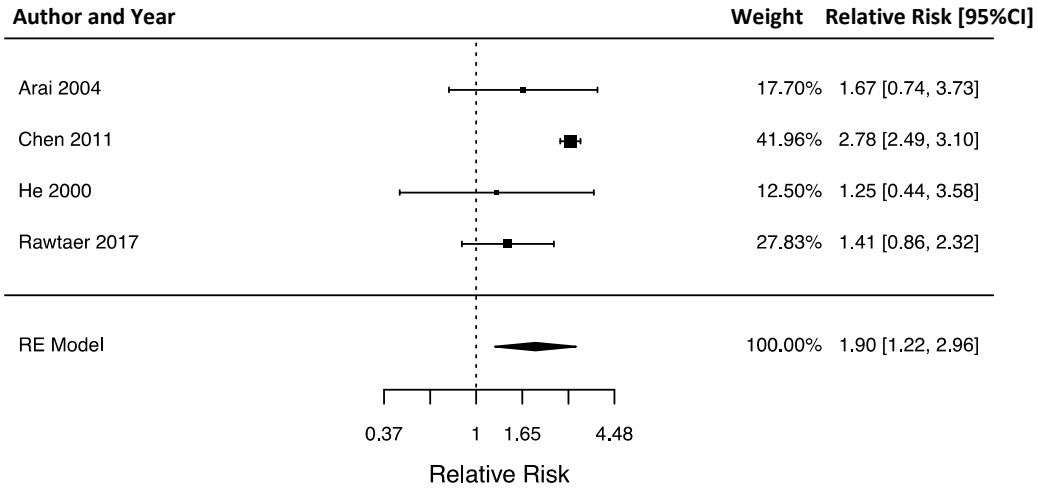

Figure 2 *Asia sub-group forest plot for living alone and risk of incident dementia*

The overall quality rating in the studies included in the Asian sub-group analysis ranged from high (one study) to medium (three studies).

European studies sub-group analysis

Five studies had been conducted and recruited their participants from populations residing in European countries including three Swedish studies (Fratiglioni et al., 2000; Paillard-Borg et al., 2009; Sörman et al., 2015) plus one French (Akbaraly et al., 2009) and one Dutch study (Holwerda et al., 2014). Of

these, two studies (Fratiglioni et al., 2000; Sörman et al., 2015) reported a statistically significant increased risk associated with living alone and incident dementia whilst the remaining three studies reported estimates that did not meet threshold for statistical significance. All five studies were included in the sub-group meta-analysis to determine a pooled effect size (Figure 3). The pooled estimate indicated that the there was a significant increased risk of incident dementia in those living alone (RR=1.23; 95% CI: 1.10-1.39). In addition, the *Q*-test indicated that the level of heterogeneity in the model was not significant (χ^2 = 3.00, d*f* = 4, *p* =.56, I^2 < .001%).

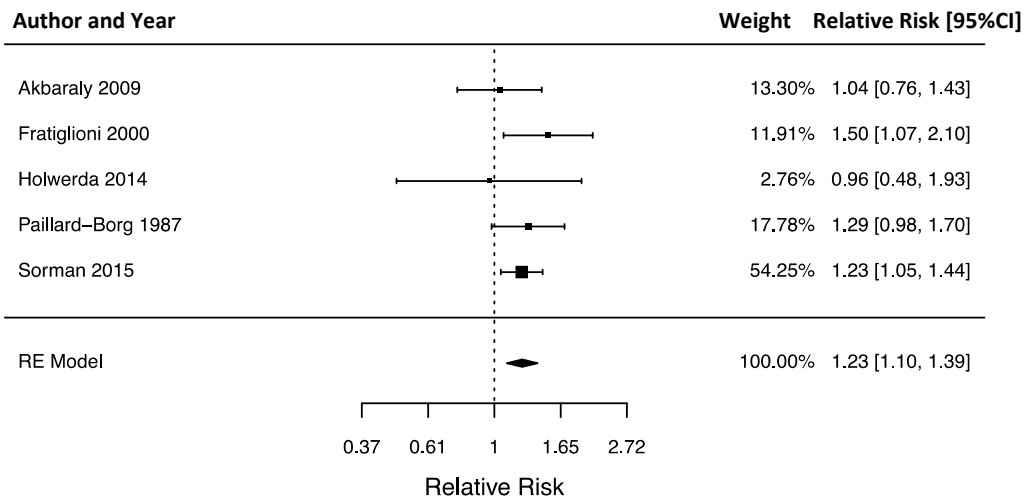

Figure 3 *Europe subgroup forest plot for living alone and incident dementia*

The overall quality rating in the studies included in the European sub-group analysis ranged from low (one study) to medium (four studies).

Publication bias

Funnel plots were used to assess publication bias for the Asian sub-group of studies (Figure 4) and the European sub-group of studies (Figure 5). Egger's test

was used to assess for funnel plot asymmetry in the two subgroups. For the sub-group of Asian studies there was found to be significant asymmetry (z = -2.58, p = .01) indicating that publication bias was likely. For the sub-group of European studies there was low likelihood of publication bias as indicated by a non-significant result for Egger's test (z = -.36, p = .72).

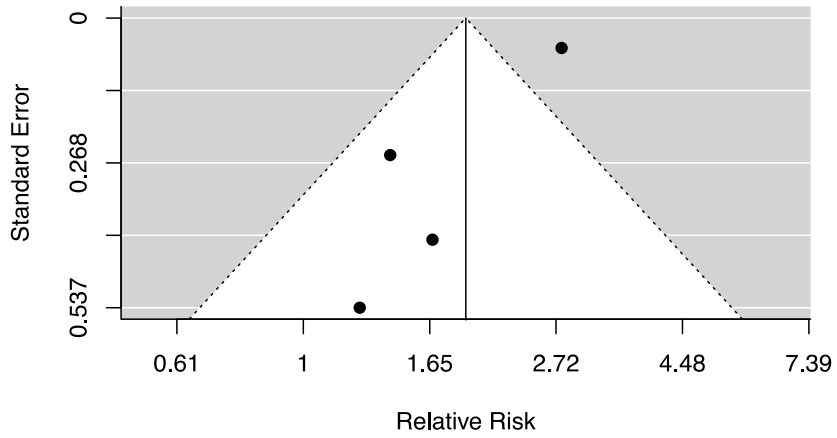

Figure 4 *Funnel plot of Asian studies*

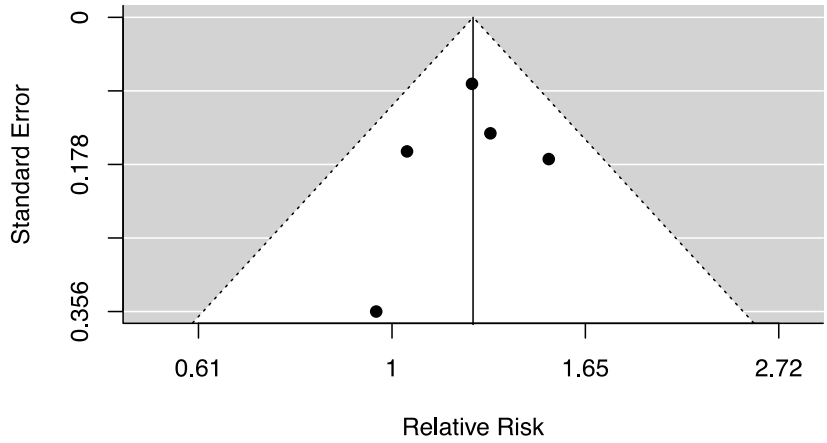

Figure 5 *Funnel plot of European studies*

5. Discussion

Summary of results

This review and meta-analysis aimed to summarise the literature and pool the effect of living alone and associated risk of incident dementia. The review found that when grouped together the studies were too different from each other for the results to be meaningfully interpreted. However, sub-group analysis based on country of study location yielded more meaningful results. The sub-group analysis of Asian studies found that although there was still significant heterogeneity in the model it was greatly reduced. Although not meeting the significance threshold, the trend was that there was an increased risk of incident dementia in those living alone. The European meta-analysis did not have significant heterogeneity in the model and found that people residing alone are at an increased risk of developing dementia.

Interpretation of results

The results of the overall model indicated that there was a great deal of heterogeneity between the included studies. One study (Chen et al., 2011) appeared to be an outlier and may have been a significant contributor to the heterogeneity in the overall model. A future study should include a sensitivity analysis to assess this possibility. One factor that explained some of this variance was whether the study was conducted in Asia or Europe. There are likely to be specific cultural differences regarding family structure, views on living arrangement and care of the elderly between participants from the Asian and European studies that may all be relevant to the present study. Collectivist cultures, represented in the Asian studies, place higher value on group cohesion and interdependence than the individualist cultures typically found in Northern Europe (Oyserman, 1993). Thus, in collectivistic countries, care of the elderly is more likely to be seen as the

responsibility of the extended family. On the other hand, individualistic countries may place more value on independence and independent living arrangements of older family members. Some of these cultural differences may have accounted for the reduction in heterogeneity when studies were grouped according to country.

The results from the European studies indicate that in, at least some, European countries people who live alone are more vulnerable to developing dementia than those who live with others. It is important to note that the results of the quality assessment of studies included in the European group ranged from low to medium risk of bias and the test for publication bias indicted there was no significant risk of bias. Taken together this suggests that the overall risk of bias of this meta-analysis is low and the finding reported here is robust.

People who live alone may have less opportunity to engage in social contact and may experience more feelings of isolation and loneliness. This is in line with the results of a previous meta-analysis which found that certain aspects of social relationships namely; low social participation, less contact and greater feelings of loneliness are related to incident dementia (Kuiper et al., 2015). It may be that the single measure of 'living alone' captures, or is a proxy measure of, a few different social relationship factors that impact on cognition.

There are three mechanisms that may be at play explaining the relationship between living alone and risk of dementia. First, people who live alone are living in environments that provide less opportunity for social contact on a daily basis. Thus, the opportunity to use and maintain synaptic connections in the brain are less and may be at risk of being lost as proposed by the cognitive activity hypothesis. Second, although it is not necessarily the case that all people who live alone are socially isolated it is likely that there is correlation between living alone and social isolation. Previous research has shown that social isolation is associated with an elevation of certain biomarkers that have a detrimental impact on the vascular

system and certain brain structures (Friedler et al., 2015). As a result people who live alone may be more at risk of cognitive decline and dementia via this mechanism. Lastly, daily life can be stressful especially for the elderly as they transition through a life stage from working adult to retired adult, or when dealing with the consequences of age-related physical health problems. When there is no other available to share this with, and provide practical support, the stresses of daily life may be experienced as more stressful. Stress in itself is related to increase in cortisol levels and adverse health outcomes. People who live alone may also be vulnerable to the mechanisms of cognitive decline as proposed by the stress-buffer hypothesis.

Although there was greatly reduced heterogeneity when the studies were separated on the basis of study location, there was still significant heterogeneity present in the Asian sub-group meta-analysis model. One potential reason for this is that three (Arai et al., 2004; R. Chen et al., 2011; He et al., 2000) out of the four Asian studies classified living arrangement as a multi-level variable. Rather than the dichotomous distinction (living alone: Yes/No) used by the majority of European studies, living arrangement captured more information by most of the Asian studies. Arai et al.'s (2004) Japanese study divided the living alone 'No' category into: living with family including spouse and living with family not including spouse. Likewise, the Chen et al. (2011) study conducted in China divided the 'No' category into: living with spouse/parents, living with children/grandchildren, or living with spouse and parents/children/grandchildren. This level of distinction in the Asian studies may have introduced heterogeneity in the Asian model. There was also a risk that the results of the Asian studies may have been impacted by bias. There was a risk that there were missing studies as highlighted by the result of significant risk of publication bias and the overall quality assessment of these studies indicated high to medium risk of bias.

Strengths & Limitations

This is the first study to systematically draw together the literature on living alone and risk of incident dementia. The findings of this study are particularly relevant in today's society as the number of people and, in particular, the number of older adults starting to live in single occupancy households increases. The review only included longitudinal cohort studies and as the measure of social relationships used was objective, the findings that living alone is a risk factor for dementia is unlikely to be an artefact of reverse causality.

A limitation of the studies included in the review, and therefore a limitation on the results of this meta-analysis, is that the studies only captured living arrangement at one time point. In the course of a lifetime, and arguably more so in the latter years, living arrangement changes. For example, Gow et al.'s (2016) birth cohort study found that during the study period the proportion of those living alone rose from 13.1% to 54.2%. Out of all the research papers examined in the course of this review only one study (van Gelder et al., 2006) captured living arrangement at two time points over a five-year period and then evaluated the impact of all those different permutations of living arrangement on dementia over a subsequent ten-year follow-up period. The van Gelder et al. (2006) study was not included in this meta-analysis because it did not meet inclusion criteria. However, it reported a difference between men who started to live alone within the two initial points and those who had lived alone from the beginning. The men who had lived alone from the start had a far stronger cognitive decline than those who started to live alone within the initial two points. This suggests that there may be a dose-response effect of time spent living alone and subsequent risk of incident dementia that the current investigations into living alone are not considering.

One limitation of the QUIPS tool was that a study could be rated as having a medium risk of bias on the bases of having controlled for all the confounders in question. Thus, studies with poor follow-up rates or diagnostic criteria could have been potentially rated as medium risk of bias. Although this is a potential limitation in the use of the tool, this did not apply to any of the studies covered in the present review.

Implications for further research

As discussed above, including the variable 'time lived alone' in future studies could provide further insights into the relationship between this social factor and incident dementia. This is important because a life-time spent living alone could be worse for cognition than someone who starts to live alone in the latter years of their life. The dose-response effect of time living-alone should be considered in future studies.

Another dose-response relationship that was not considered in this analysis is that of number of living in the household. One of the Asian studies (R. Chen et al., 2011) reported that the risk of incident dementia decreases as the number of persons living in the household increases. Living in a household with greater numbers of people could provide an environment that has more opportunities to access social stimulation and provide more practical and emotional support. On the other hand living in a large household could create more stress due to overcrowding and sharing limited resources. There may also be cultural variation in this regard with independence and smaller households valued in the individualistic cultures of the Europe and interdependence and larger households valued in the collectivistic cultures of Asia. However, this provides interesting avenues for future research. A related point is the fact that the European sub-group of studies were northern European countries. There is the potential for variation in culture between some of

the northern and southern European countries especially in terms of attitudes towards intergenerational dwelling. In some southern European countries intergenerational households may be more common and therefore these countries may have more in common with Asian countries than the European countries studied in this review. More research would need to be conducted into this, as currently these results are not necessarily generalizable to all of Europe.

One study (Holwerda et al., 2014) included in this review reported that there was no risk of incident dementia conferred by living alone. This study was also one of the only study designs that measured and controlled for feelings of loneliness in its analysis. Loneliness can be thought of as a negative affective state resulting from the perception that an individual's emotional and social needs are not met (Peplau & Perlman, 1982). Feelings of loneliness have been found to increase with age (Hawkley & Cacioppo, 2010) and to be correlated with living alone (Holmén, Ericsson, & Winblad, 2000). Loneliness has also been linked to elevated levels of vascular disease biomarkers (O'Luanaigh et al., 2012) potentially suggesting a link between living alone, loneliness and support for the vascular hypothesis. Thus, an avenue for further research would be to investigate if the relationship between living alone and incident dementia is mediated by feelings of loneliness.

Clinical implications

Unlike some of the other measures of social relationships that have been found to be associated with an increased risk of dementia, living alone involves asking a single question and is easily identifiable. Therefore, identifying the group of people who are at elevated risk of dementia due to social factors would be relatively easy in a clinical setting. The question, 'do you live alone?' could be asked by an individual's healthcare provider as part of a routine appointment in the same way information on smoking or weight is obtained. Once living alone is identified, an

additional assessment on how lonely they felt could be made and if identified as both living alone and lonely they could be given information on the risks and the strategies that may help to potentially mitigate the risks. For example, offering group support or information on social activities.

Conclusion

This meta-analysis found that in northern Europe there was an increased risk of developing incident dementia in people who live alone. Living alone may be a proxy measure for social isolation or loneliness. This finding is in line with previous systematic reviews on the literature of social relationships and incident dementia. People who live alone may be vulnerable to the impact of all three social hypotheses relating to cognitive decline although further research is needed to clarify the exact mechanism. Further research may help to establish if there are dose-response effects of time spent living alone and number in household, as well as examining the relationship between loneliness and living alone. Establishing if someone lives alone is useful in clinical settings in identifying those who are at elevated risk of dementia.

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PART 2: EMPIRCAL PAPER

Depressive symptoms and cognitive decline in mid and late life: is there a temporal relationship and is it mediated by lifestyle?

1. Abstract

Aims: Debate exists over if depressive symptoms are a risk factor for, psychological reaction to, or prodrome of cognitive decline. This study examined the bi-directional temporal relationship between depressive symptoms and cognitive decline in relation to these three hypotheses. A further aim was to examine if the relationship was mediated by lifestyle factors.

Methods: A longitudinal population cohort (N=11855) with 1-year follow-up was used to carry out cross-lag analysis. Measures were collected via an on-line portal. Depressive symptoms were measured by the PHQ-9; Paired Associate Learning (PAL), Verbal Reasoning (VR), Spatial Working Memory (SWM) and Digit Span (DS) measured cognition. Mediation analysis was conducted on a subsample of participants reporting clinical levels of depression and/or anxiety.

Results: Depressive symptoms predicted a decline in PAL (β = -.020, p = .015) and VR (β = -.043, p = .014) but not vice versa. Depressive symptoms predicted (β = -.043, p < .001) and were predicted by (β = -.031, p = < .001) a decline in SWM. Depressive symptoms predicted (β = -.029, p < .001) and were predicted by (β = -.25, p = .002) a decline in DS. There was no evidence in support of the hypothesis that a relationship is mediated by lifestyle.

Conclusions: Depressive symptoms may be either a risk factor or prodrome for decline for in PAL, VR, SWM and DS. As well, a decline in SWM and DS may impact daily life and thereby cause distress. Clinical implications and implications for further research are discussed.

2. Introduction

Cognitive decline

Cognitive decline can be viewed as a normal part of the ageing process as a result of the loss of neurons and associated function with age. However, there is a great deal of variation in this process with some individuals retaining much or all of their cognitive functioning well into old age and others developing dementia.

Dementia has serious consequences for an individual's quality of life, their ability to carry out activities of daily living and live independently (Department of Health, 2009). Dementia is an increasing global health problem with some estimates forecasting that by 2050 the number of people living with dementia globally will be around 131 million (Prince et al., 2015). To date there are no effective pharmacological interventions for the treatment of dementia (Schwarz et al., 2012). Therefore, understanding which modifiable lifestyle factors are at play and how they interact with the progression of cognitive decline is key to furthering our understanding and developing preventative strategies for those who are at risk of developing dementia (Livingston et al., 2017).

Risk factors

Livingston and colleagues identified nine specific risk factors for dementia in their 2017 Lancet commission on dementia prevention and care. These are: fewer years of formal education; midlife (between 45-65 years) hypertension, obesity and hearing loss; and later life (over 65 years) smoking, depression, physical inactivity, social isolation and diabetes. Together these nine risk factors account for 35% of

the variance in dementia incidence. Although depression was identified as one of the later life risk factors for dementia, accounting for 4% of the variance in incident dementia, the nature of the relationship between depression and cognitive decline and/or dementia is the source of debate in the research literature.

Depression and cognitive decline

There is debate in the research literature as to the nature of the relationship between depressive symptoms and cognitive decline. Jorm (2000), in his systematic review, proposed several hypotheses on how the two may be related. Three of these were: depression is a prodromal sign of cognitive decline and /or dementia; depression is a psychological reaction to the subjective experience of a decline in cognitive functioning; and depression is a causal risk factor for cognitive decline and/or dementia. There is on-going debate in the research literature over these three hypotheses.

Depression as a risk factor

Evidence in support of the 'depression as a causal risk factor' hypothesis comes from longitudinal studies investigating chronicity of depression throughout the life course, severity of depression or the interval between depressive episode and time to onset of dementia. One study found over a period of 24 years that each episode of depression increased the risk of all-cause dementia by 14% (Dotson, Beydoun, & Zonderman, 2010). A Danish nationwide case register study examined the most severe forms of affective disorders compared to physical health conditions and their relative risks of incident dementia. Patients who had been hospitalised with major affective disorders had more than a two-fold increased risk of being diagnosed with dementia compared to patients hospitalised with physical health

conditions (Kessing & Nilsson, 2003). This was the case even when compared to vascular health conditions such as diabetes, which is in itself a risk factor for dementia. The length of time between depression and onset can help differentiate between the various hypotheses. Providing further support for the 'risk factor' hypothesis, a systematic review and meta-analysis of 20 studies found that distal rather than proximal depression was associated with increased risk of dementia (Ownby, Crocco, Acevedo, John, & Loewenstein, 2006).

One proposed mechanism explaining why people with depressive symptoms are at elevated risk of cognitive decline is that some of the behaviours associated with depression increase the risk of vascular disease (Carney & Freedland, 2017). Vascular disease is in itself a risk factor for stroke and vascular dementia (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006; Van der Kooy et al., 2007) and therefore behaviours associated with depressive symptoms may increase the risk of cognitive decline via this route. Behaviours such as physical inactivity (Nocon et al., 2008), poor diet leading to obesity (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003) and higher levels of alcohol consumption are associated with an increased risk of vascular disease (Ronksley, Brien, Turner, Mukamal, & Ghali, 2011) and are more likely to occur in conjunction with depressive symptoms. Thus, a proposed mechanism for the 'risk factor' hypothesis is that when people experience depressive symptoms they are more likely to engage in poor health related behaviours, which place them at an increased risk of vascular disease and thereby cognitive decline (Butters et al., 2008).

Depression as a psychological reaction

An alternative explanation for the association between depression and cognitive decline/dementia is that psychological distress is a reaction to the subjective experience of declining cognition. Studies lending support to this theory

have focused on the temporal relationship between depression and cognitive decline. The idea being that if depression arises either after or at the same time as the decline in cognition the most likely explanation is the depressive symptoms are a reaction to, rather than a risk factor of or prodrome for cognitive decline. For example, one study found that cognitive decline preceded depressive symptoms (Vinkers, Gussekloo, Stek, Westendorp, & Van Der Mast, 2004) and another found that depression and cognitive decline were cross-sectionally but not longitudinally associated (Ganguli, Du, Dodge, Ratcliff, & Chang, 2006). When anxiety and depressive symptoms are investigated in relation to cognitive decline, they were found to be at their peak in the early phase of cognitive decline and then tapered out as cognitive decline progressed (Bierman, Comijs, Jonker, & Beekman, 2007). The authors proposed that as patients lost insight into their illness they also lost subjective awareness of their situation and hence experienced less distress.

Depression as a prodrome

The final hypothesis explaining the association between depression and cognitive decline/dementia is that depression is an early, prodromal sign of cognitive decline. The theory behind this hypothesis is that depression in the context of cognitive decline shares the same underlying neuropathology as dementia. Thus depression is thought to be a result of and an early sign of the dementing process (Panza et al., 2010). Support for this theory comes from studies that investigate cognitive profiles of patients with depressive symptoms and cognitive decline as well as studies investigating the temporal relationship between the two. Chronic depression over a three-year period was found more likely to predict cognitive profiles in keeping with sub-cortical impairment as opposed to global cognitive decline or isolated memory impairments. This pattern of impairment is indicative of white matter lesions that are also found in some dementias suggesting that chronic

depression in late life and dementia share a similar neuropathology (Comijs et al., 2004; Comijs, Jonker, Beekman, & Deeg, 2001). Further support for the 'prodrome' hypothesis comes from investigations into the temporal relationship and trajectory of depressive symptoms. A peak in incidence of depression, either side or very close to a diagnosis of dementia supports the 'prodrome' hypothesis (Heun, Kockler, & Ptok, 2002; Lenoir et al., 2011). In contrast to Ownby's (2006) meta-analysis results, several studies have found that late onset depression rather than chronic or depression earlier in the life course is associated with incident dementia (Heser et al., 2013). This is the case even when trajectories of depressive symptoms are followed over periods of up to 28 years (Singh-Manoux et al., 2017).

Temporal studies

Support for each of the three hypotheses has come in part from the use of longitudinal studies investigating the temporal nature of the relationship between cognitive decline and depression. There are a number of limitations with some of these studies. One potential problem with some previous studies is the use of screening tools or brief inventories of global cognition. Tools such as the mini mental state examination (MMSE) are widely used in studies (e.g. Bierman et al., 2007; Chi & Chou, 2000; Geerlings, 2000) to assess cognitive decline and dementia. However, the sensitivity of the MMSE has been called into question particularly when used to detect cognitive decline pre-dementia due to its ceiling effect (P. Chen et al., 2000). Another problem with the use of global measures of cognition is that decline is not necessarily uniform across the different cognitive domains. There are many different types of dementia all of which have different cognitive profiles of impairment. For example, Alzheimer's disease shows early impairments in memory, Lewy body dementia early impairments in executive functioning and normal pressure hydrocephalus deficits in attention (Lezak,

Howieson, Bigler, & Tranel, 2012). Thus, cognitive decline is not a uniform process and different domains of cognition may be affected differentially. It stands to reason that the relationship between depressive symptoms and different domains of cognitive function may also not be uniform. Screening tools or global measures of cognitive function fall short of adequately assessing the impact of depressive symptoms on different domains of cognitive decline pre-dementia. To get a more comprehensive understanding of how depressive symptoms may interact with different domains of cognition, the current study aimed to use four measures of cognition tapping into the domains of; memory, general intelligence, executive function and attention.

A more salient problem is investigating the temporal relationship in one direction (Panza et al., 2009). Only two previous studies have investigated the possibility of a bi-directional relationship between depressive symptoms and cognitive decline (Cui, Lyness, Tu, King, & Caine, 2007; Panza et al., 2009). These studies did not find evidence for a bi-directional relationship but they may have been limited by their sample sizes and measures of cognition. Aside from these two studies most of the previous longitudinal studies have used linear regression models to test an a priori hypothesis about the direction of the relationship between cognitive decline and depressive symptoms. This is the case for studies that have reported that depression is a risk factor (Dotson et al., 2010), psychological reaction (Vinkers et al., 2004) and prodome (Singh-Manoux et al., 2017) of cognitive decline. The problem with this is that the relationship between depressive symptoms and cognitive decline is only examined uni-directionally and we might not be seeing the whole picture. In other words, studies either ask: do depressive symptoms predict cognitive decline, or does cognitive decline predict depressive symptoms. If there is a dynamic bi-directional relationship between the two, one-directional regression models would always find support for a uni-directional relationship creating endless

debate. Not many studies have simultaneously investigated the bi-directional relationship between depressive symptoms and cognitive decline. At best longitudinal studies have controlled for baseline cognitive function in regression analyses. However, accounting for baseline cognitive function provides no information about the dynamic nature of the relationships studied. Cross-lagged analysis is a way of both accounting for cognition and simultaneously examining the bi-directional nature of a relationship between two variables and allows us to ask: does cognitive decline predict depressive symptoms; do depressive symptoms predict cognitive decline; or, is there a dynamic bidirectional relationship between the two as a function of time?

Aims

The aim of the current study was to examine the temporal relationship between depressive symptoms and cognitive decline, in a population sample of adults in mid to late life, in relation to the three hypotheses using a cross-lagged design. This design was used to investigate the reciprocal nature of the relationship between cognitive decline and depressive symptoms. If cognitive decline precedes depressive symptoms then this would provide support for the 'psychological reaction' hypothesis. If on the other hand depressive symptoms precede cognitive decline then the results would provide support for either the 'risk factor' or 'prodrome' hypotheses. If there is a dynamic bidirectional relationship between the two this might indicate several mechanisms at play. The second aim of the current study was to further tease apart the 'risk factor' and 'prodrome' hypotheses if there was found to be support for either of these in the first part of the study. If depressive symptoms are a risk factor for cognitive decline then, according to the 'vascular depression' hypothesis, this may be mediated by vascular risk factors. We aimed to test this by examining if the relationship between depressive symptoms and

cognitive decline was mediated by the known risk factors of vascular disease of high BMI, physical inactivity and higher levels of alcohol consumption.

3. Method

Study Design

The current study utilised a longitudinal population cohort design with a one-year follow-up period.

Recruitment: Participants were recruited via a media campaign and through leaflets advertising the study at GP practices and memory clinics located in South London.

Eligibility: Participants met inclusion criteria if they were aged 50 years or over, lived in the UK, had a working command of English, and access to the Internet via a computer. A pre-existing diagnosis of dementia was an exclusion criterion for the study.

Data collection: Data were collected as part of the PROTECT study. The PROTECT study is an on-going ten-year longitudinal study collecting data on cognitively healthy individuals aged 50 years and over. The primary research objective of PROTECT is to investigate the relationship between genes and cognitive function in the context of aging. Baseline data were collected between November 2015 and November 2016 and one-year follow-up data collected between November 2016 and November 2017. Data were collected via an on-line portal where participants were guided through a series of questionnaires and a battery of cognitive assessments. Researchers from the PROTECT team contacted participants at regular intervals to keep them up-to-date with the study and prompt them to log on to complete study related tasks as and when required.

Ethics: The PROTECT study received ethical approval from the London Bridge NHS Research Committee (Ref: 13/LO/1578).

Measures

Demographic, mental health and lifestyle measures: Demographic information including sex, age, marital status, ethnicity, employment and education details were collected at baseline. Measures of mood, anxiety, weight, levels of alcohol consumption and physical activity were collected at baseline and follow-up. Height was collected at baseline and was used with weight to calculate the body mass index (BMI) for each participant.

Mood was assessed with the PHQ-9 depression inventory (Kroenke, Spitzer, & Williams, 2001). This questionnaire has been found to be valid and reliable (Kroenke et al., 2001) and comprises of nine questions capturing depressive symptoms on a range of 0-27. Higher scores indicated more depressive symptoms.

Anxiety was assessed with the GAD-7 inventory (Spitzer, Kroenke, Williams, & Löwe, 2006). This questionnaire has been found to be valid and reliable (Spitzer et al., 2006) and comprises of seven questions capturing anxiety symptoms on a range of 0-21. Higher scores indicated more anxiety symptoms.

Alcohol consumption was assessed using one question asking about the frequency of alcohol use. Participants rated alcohol consumption on a five-point scale ranging from never to 4 or more times a week. Higher scores indicated a more frequent level of alcohol consumption.

Physical activity was assessed using one question that asked the participants to report how active they were taking into account both work and leisure. Participants scored themselves on a 4-point scale where higher scores indicted higher levels of physical activity.

Cognitive measures: Participants completed an on-line battery of four cognitive measures namely Paired Associate Learning, Verbal Reasoning, Spatial Working Memory and Digit Span. At each testing period participants attempted each measure three times and a total summary score was calculated based on the average of the three attempts. The four cognitive measures used in the battery were based on validated 'pen and paper' cognitive tests and adapted for on-line use by Owen et al. (2010). The online versions of the tests have been found to be valid (see cambridgebrainsciences.com) and reliable (Wesnes et al., 2017).

The Paired Associate Learning (PAL) test is a test of episodic memory and new learning. The PAL test has been found to be particularly sensitive to deficits seen in memory and learning in MCI (Fowler, Saling, Conway, Semple, & Louis, 2010) and the early stages of Alzheimer's disease (Bondi, Salmon, & Kasziak, 2009). The PAL task requires participants to learn digits, symbols or words in pairs and to later recall an item when one half of the pair is presented to them. In the adapted on-line version this was achieved by presenting a series of closed windows that were opened in sequence to reveal hidden objects, such as a ball. After all the windows had revealed their objects they were then closed again. Next the participant was presented with one of the objects and asked to identify the window in which that particular object had previously appeared. The first trial presented two windows and paired objects. If the objects and window locations were matched correctly then the subsequent trial increased the number of windows by one whereas if an error was made, then number of windows was decreased by one. After three incorrect trials the test was stopped and the final PAL score was calculated as the average number of object-location associations in the successfully completed trials. Higher scores indicated better learning.

The Verbal Reasoning (VR) test was based on Baddeley's Grammatical Reasoning test and is found to correlate well to general intelligence (Baddeley, 1968). The on-line adapted version asked participants to make decisions about the accuracy of a statement in relation to a picture. For example, a large square and a smaller circle were presented on the screen and the participant required to determine the accuracy of a statement such as, 'the circle is not smaller than the square'. The total VR score was calculated as the number of correct answers given in 180 seconds minus the number of errors made. Higher scores indicated better verbal reasoning.

The Spatial Working Memory (SWM) test used a self-ordered search task that is found to be sensitive to deficits in executive function (Owen, Downes, Sahakian, Polkey, & Robbins, 1990). In this test participants were presented with series of boxes and required to search through in order to find a hidden object (such as a star). Once the object had been found, the next series was presented and the participants once again required to find the hidden object whilst holding in mind that an object would not be hidden in the same place twice. The test was terminated after three errors and the final score was calculated as the mean number of boxes in successful trials. Higher scores indicated greater spatial working memory.

The Digit Span (DS) test measures attention (Lezak et al., 2012). In the on-line version of the test, participants were presented with a sequence of digits to recall. If the participant was able to recall the digits correctly then the subsequent sequence was one digit longer than the preceding one. If the participant recalled the digits incorrectly then the next trial was comprised of a series of digits that was one digit shorter than the preceding one. The final score was calculated as the mean number of digits in correctly completed trials. Higher scores indicated greater digit span.

Participants: Participants who completed the cognitive assessment battery at baseline and follow-up were included in the sample to assessing the temporal association between depressive symptoms and cognitive decline. To test the second hypothesis, that the relationship between depressive symptoms and cognitive decline is mediated by lifestyle, a sub-group of participants who were representative of the typical client group treated in Improving Access to Psychological Therapies (IAPT) services was created. The subgroup included participants who scored above threshold for mild depression (PHQ-9 score >5) and/or anxiety (GAD-7 >5). No upper threshold was used because although IAPT services were originally commissioned to treat people with mild to moderate levels of depression and/or anxiety, it is becoming increasing common for these services to treat complex clients including those with severe levels of depression and/or anxiety (Hepgul et al., 2016). Therefore, all participants who scored above the threshold for mild depression (PHQ-9 score >5) and/or anxiety (GAD-7 score >5) were included in the mediation analysis.

Data Analyses

Data Cleaning: Data cleaning took place in a two-step process. First, missing data was assessed. Little and Rubin (2002) propose that there are three distinct categories of missing data, namely; missing completely at random (MCAR), missing at random (MAR) and not missing at random (NMAR). In practice the pattern of missing data rarely neatly falls into one category and is instead a mix of all three in varying proportions (Graham, 2009). Missing data can be problematic in data analyses particularly if the pattern of missing data is more consistent with NMAR. When the pattern of missing data is correlated between variables it is said to be NMAR and is more likely to yield biased parameter estimates. Full information maximum likelihood (FIML) was used to handle missing data. FIML calculates the

parameter estimates based on all the available information rather than imputing or deleting cases. As such FIML is recommended as the preferred way of handling missing data (Schlomer, Bauman, & Card, 2010) and is the most robust method of dealing with missing data when data are NMAR.

Secondly, the assumptions of linear modelling were checked. Linear models are based on the assumptions of Normality. This is the assumption that the residuals come from a sampling distribution that is Normally distributed. To test for this assumption in large data sets it is recommended that the distributions be checked visually and considered in light of the values of skewness and kurtosis (Field, Miles, & Field, 2012). Histograms were plotted for each variable and inspected visually. Inspection of the histograms revealed that several of the variables deviated from Normality. One variable, depression at follow-up, was too skewed for a transformation to be feasible so the analysis was bootstrapped with 10000 bootstrap draws.

Cross-Lagged Panel Analysis: Cross-lagged panel analysis was used to assess the temporal relationship between depressive symptoms and cognitive decline. Cross-lagged panel analysis in longitudinal studies allows for the investigation of relationships between variables over time (Selig & Little, 2012). It allows for the examination of reciprocal effects and whether relationships between variables are bi- or uni- directional. When considering two variables, X and Y, which are correlated in a cross-sectional analysis no inferences can be made about whether X precedes Y or vice versa. If on the other hand X and Y are observed at two time points, X_1 and Y_1, and X_2 and Y_2 (subscripts denote time points 1 and 2) the variables can be autoregressed to assess the stability of the relationship over time. The cross-lagged panel model can be represented by the following two

regression equations, where the β represents the regression coefficient and e the error term:

$$X_2 = \beta_1 X_1 + \beta_2 Y_1 + e1$$

$$Y_2 = \beta_3 Y_1 + \beta_4 X_1 + e2$$

The two regression equations can be equally represented pictorially by the path diagram shown in Figure 1.

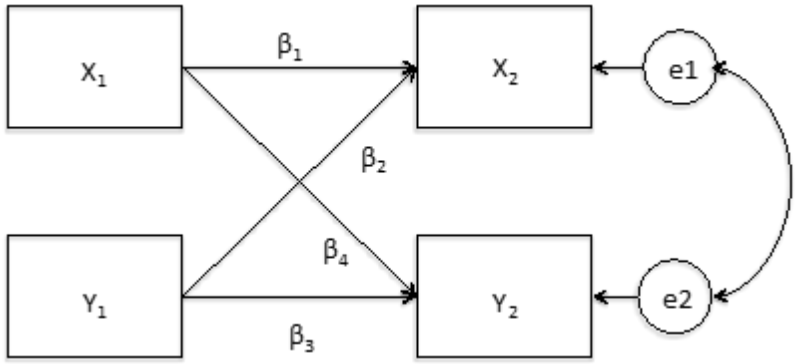

Figure 1 *Path diagram representing the variables X and Y in cross-lagged design over two time points*

In the cross-lagged model, X_2 is regressed on both X_1 and Y_1. In this way the shared variance explained by the correlation of the variables at time point one is controlled for. Thus, it can be assumed that, if the model is significant, Y_1 precedes X_2. The bidirectional nature of this is tested in the model by the second regression equation or in other words, regressing Y_2 on X_1 and Y_1. Thus, a model depicting a bidirectional relationship would include a significant path from X_1 to Y_2 as well as a significant path from Y_1 to X_2. A unidirectional relationship would by represented by only one of these paths being significant.

Mediation Analysis: Mediation analysis was used to test the second hypothesis, that the relationship between depression and cognitive decline is mediated by the lifestyle factors of physical activity, BMI and alcohol consumption. Lifestyle measures collected at follow-up were used in the analysis to allow for a temporal ordering of the variables in the mediation analysis.

In the simple mediation model *X* exerts an effect on *Y* through an intervening variable *M*. This simple mediation model can be represented by the following two equations where *a*, *b* and *c'* are the standardised regression coefficients and e is the error term:

$$M = aX + e_m$$

$$Y = bM + c'X + e_y$$

The two regression equations can be equally represented pictorially by the path diagram shown in figure 2.

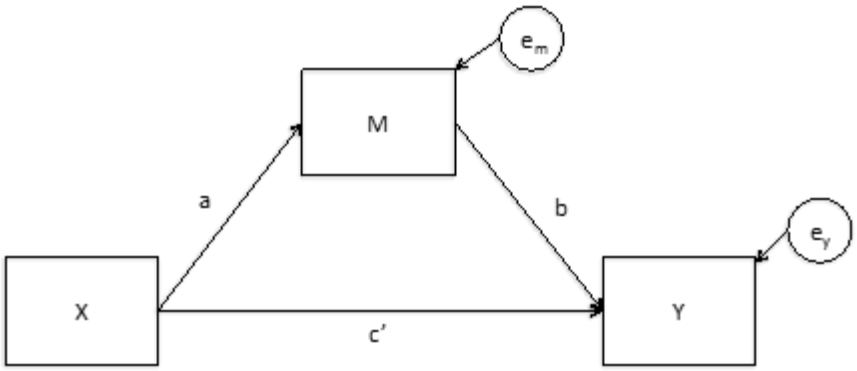

Figure 2 *Simple mediation model of the effect of X on Y via a third variable M*

Using path-tracing rules the direct, indirect and total effects of X on Y can be expressed as:

Direct effect = *c*'

Indirect effect = *ab*

Total effect = *ab* + *c*'

Baron and Kenny (1986) used these principles and logical inference to propose a three-step causal model to determine mediation. The first step involves regressing *Y* on *X* and if the mediating path (*c*) is found to be significant than mediation analysis is indicated and the subsequent two-steps can be performed. However, Hayes (2009) argues that it is not necessary for *c* to be significant to test a meditation model because if there are several mediating variables, indirect paths

can be both positive and negative summing to cancel out an overall significant relationship between predictor and outcome variable. Hayes (2009) recommends using a one-step bias corrected bootstrap method of mediation analysis. This method has a number of advantages. Firstly, the significance of the mediated indirect path (*ab*) as well as the total effect (*ab* + *c*') are explicitly tested. Secondly, multiple mediators and multiple outcome variables can be entreated into a single model and tested simultaneously. Thirdly, as all the paths are tested in one model the overall number of tests is reduced and therefore the type I error rate is also reduced. Fourthly, the method uses bootstrapping techniques so does not rely on assumptions regarding Normality of the sampling distribution, which are requirements of the linear model. The mediation analysis was run using 10000 bootstrap draws.

All analyses were performed using R programming language and the statistical programming environment provided by RStudio (2016) software version 1.1.419. The lavaan package for structural equation modelling (Rosseel, 2014) in R was used to run the cross-lag and mediation analyses.

4. Results

Participant flow: At baseline 24024 participants registered and completed the cognitive assessment battery. There was a high level of attrition (50.7%) between baseline and follow-up. Thus, 11855 completed the cognitive assessment battery at follow-up. Only participants who completed cognitive measures at both baseline and follow-up were included in the analyses. Of these participants 2577 participants reported clinical levels of depression and / or anxiety symptoms at baseline. The demographic characteristics of the sample are presented in Table 1.

Table 1 *Demographic characteristics of participants who completed the study at both time points and those who only participated at T1*

	Participants with data at T1 and T2 (N=11855)		Participants with data at T1 only (N=12169)			
	n	(%)	n	(%)	χ^2 (df)	*p*
Sex					13.20 (1)	<.001
Male	3120	(26.3)	3457	(28.4)*		
Female	8735	(73.7)	8712	(71.6)		
Age					28.88 (3)	<.001
50-59	4699	(39.6)	4111	(42.8)*		
60-69	5418	(45.7)	4113	(42.8)*		
70-79	1567	(13.2)	1238	(12.9)		
≥80	171	(1.4)	151	(1.6)		
Marital Status					13.95(6)	.030
Married	8070	(68.1)	6209	(66.1)*		
Civil partner	65	(0.5)	55	(0.6)		
Co-habiting	737	(6.2)	620	(6.6)		
Widowed	754	(6.4)	602	(6.4)		
Separated	192	(1.6)	181	(1.9)		
Divorced	1301	(11.0)	1145	(12.2)*		
Single	723	(6.1)	577	(6.1)		
Ethnicity					19.18(4)	.001
White	11658	(98.4)	9171	(97.7)*		
Mixed	64	(0.5)	67	(0.7)		
Asian	62	(0.5)	87	(0.9)*		
Black	26	(0.2)	34	(0.4)		
Other	32	(0.3)	30	(0.3)		
Employment					95.35(4)	<.001
Employed full-time	2264	(23.9)	2324	(19.1)*		
Employed part-time	1981	(15.9)	1547	(16.7)		
Self-employed	1226	(10.4)	1047	(10.8)		
Retired	6034	(51.0)	4466	(45.9)*		
Unemployed	337	(2.8)	340	(3.5)*		
Education					56.82 (1)	<.001
GCSE/A-Levels/Diploma	5497	(46.4)	5029	(51.6)*		
Degree	6374	(53.5)	4724	(48.4)*		

n=number of participants; X^2 Chi-square statistic; df =degrees of freedom; *p* =probability, *adjusted standardised residual significant at $p < .05$, T1 =time point 1, T2 =time point 2

The majority of the participants were female (73.7%), with a mean age of 62.0 years (*SD*=7.2), married (68.1%), white (98.4%), retired (51.0%) and educated to degree level (53.1%). There was a high level of attrition between time points one and two, with 12169 participants withdrawing from the study after baseline data collection. These two groups, participants with data at both time points and those only with data at time point one, were compared for differences in their demographic characteristics. There were some demographic differences between these two groups (Table 1). Participants with data at both time points, and thus those included in the present study, were significantly more likely to be female [χ^2 (1) = 13.2, p < .001], fall within the age group 60 to 69 years [χ^2 (3) = 28.9, p <.001], more likely to be married [χ^2 (6) = 14.0, p =.030], white [χ^2 (4) = 19.2, p =.001], in full time employment or retired [χ^2 (4) = 95.4, p < .001], and educated to degree level [χ^2 (1) = 56.8, p < .001] than their counterparts who only participated at the first time point. In addition, there were differences in mood and cognitive scores at baseline between those who completed the study at both time points and those who did not (Table 2). Those who remained in the study and thus contributed to data at both time points reported significantly lower levels of depressive symptoms at baseline than participants who withdrew from the study. In addition, those who remained in the study performed significantly better in all measures of cognition than those who withdrew.

Table 2 *Mean mood and cognition scores for participants who completed the study at both time points and those who only participated at T1*

	Participants with data at T1 and T2 (N=11855) Mean (SD)		Participants with data at T1 only (N=12169) Mean (SD)		*t*	*p*
Depressive symptoms						
PHQ-9	2.53	(3.02)	2.93	(3.54)	-8.50	<.001
Cognition						
PAL	4.52	(.75)	4.41	(.88)	8.61	<.001
VR	32.30	(9.06)	30.39	(9.62)	14.05	<.001
SWM	7.59	(2.22)	7.14	(2.70)	12.66	<.001
DS	7.39	(1.47)	7.11	(1.21)	11.54	<.001

PAL: Paired Associates Learning; VR: Verbal Reasoning; SWM: Spatial Working Memory; DS: Digit Span, *t*-test of mean differences, *p*=probability

Missing data ranged from 0% for the cognitive variables to 2.73% for total PHQ-9 depression score at time point one and 8.35% for depression score at time point two. Little's (1988) MCAR test indicated that the data were not missing completely at random [χ^2 (26) = 255.9, $p < .001$]. The FIML method was used to handle missing data.

Temporal relationship between depressive symptoms and cognitive decline

The cross-lagged path analysis was run in one model that included depression at both time points and all four cognitive variables. Table 3 summarises the mood and cognition scores at each time point.

Table 3 *Mean mood and cognition scores at baseline and follow-up (N=11855)*

	Time 1 Mean (SD)	Time 2 Mean (SD)
Depressive symptoms		
PHQ-9	2.53 (3.02)	2.60 (3.24)
Cognition		
PAL	4.52 (.75)	4.67 (.70)
VR	32.30 (9.06)	36.06 (9.53)
SWM	7.59 (2.22)	7.84 (1.94)
DS	7.39 (1.47)	7.57 (1.23)

PAL: Paired Associates Learning; VR: Verbal Reasoning; SWM: Spatial Working Memory; DS: Digit Span

For ease of presentation the model is presented in four separate diagrams. Figure 3 shows the cross-lagged relationship between depressive symptoms and PAL. There was a significant negative relationship between depressive symptoms and PAL (β = -.020, p = .015) at time point two with no significant association for the reciprocal relationship (β = .001, p = .978). That is, depressive symptoms at time one predicted a significant decline in PAL at time two but PAL at time point one did not predict depressive symptoms at time point 2.

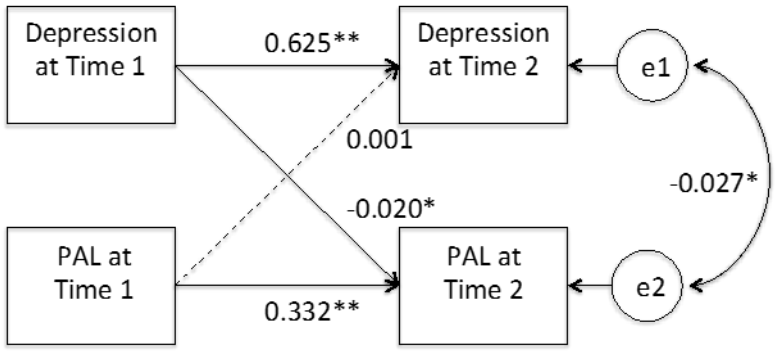

Figure 3 *Cross-lagged relationship between depression and PAL shown with standardised regression coefficients. Solid lines indicate significant positive paths, and dotted lines indicate non-significant paths. * p <0.05, ** p <0.001*

Figure 4 shows the cross-lagged relationship between depressive symptoms and VR. There was a significant negative relationship between depressive symptoms and VR (β = -.043, p = .014) at time point two but no significant association for the reciprocal relationship (β = .002, p = .850). That is, depressive symptoms at time point one predicted a significant decline in VR at time point two, but VR at time point one did not predict depressive symptoms at time point two.

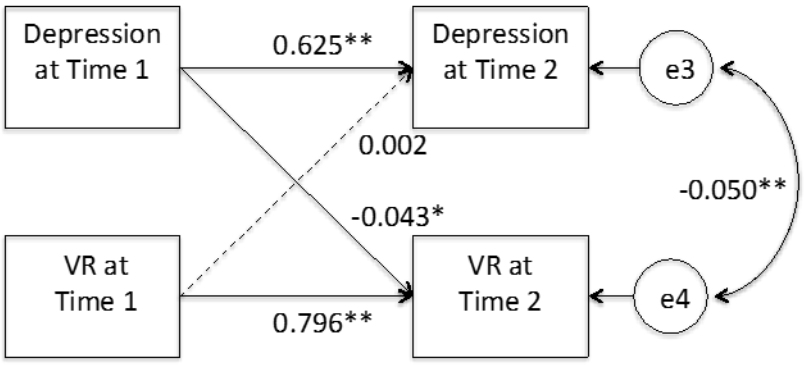

Figure 4 *Cross-lagged relationship between depression and VR shown with standardised regression coefficients. Solid lines indicate significant positive paths and dotted lines indicate non-significant paths. * p <0.05, ** p <0.001*

Figure 5 shows the cross-lagged relationship between depressive symptoms and SWM. There was a significant negative relationship between depressive symptoms and SWM (β = -.043, p < .001) at time point two as well as a significant negative relationship between SWM at time point one and depressive symptoms at time point two (β = -.031, p < .001). In other words, the relationship between depressive symptoms and SWM was reciprocal. Depressive symptoms at time point one predicted a significant decline in SWM at time point two and lower levels of SWM at time point one predicted significantly higher levels of depressive symptoms at time point two.

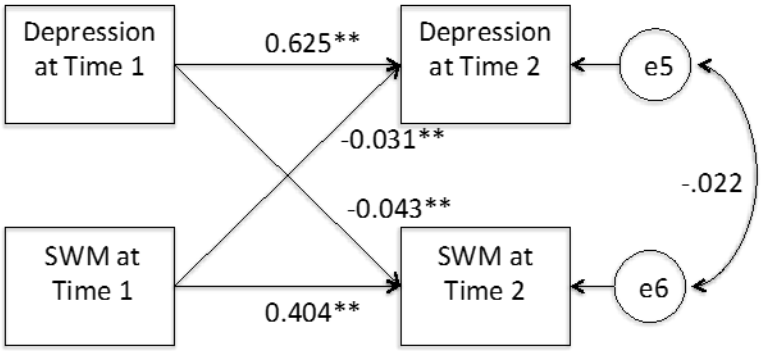

Figure 5 *Cross-lagged relationship between depression and SWM shown with standardised regression coefficients. Solid lines indicate significant positive paths and dotted lines indicate non-significant paths. * p <0.05, ** p <0.001*

Figure 6 shows the cross-lagged relationship between depressive symptoms and DS. There was a significant negative relationship between depressive symptoms and DS (β = -.029, p < .001) at time point two as well as a significant negative relationship between DS at time point one and depressive symptoms at time point two (β = -.025, p = .002). In other words, the relationship between depressive symptoms and DS was reciprocal. Depressive symptoms at time point one predicted a significant decline in DS at time point two and shorter DS at time point one predicted significantly higher levels of depressive symptoms at time point two.

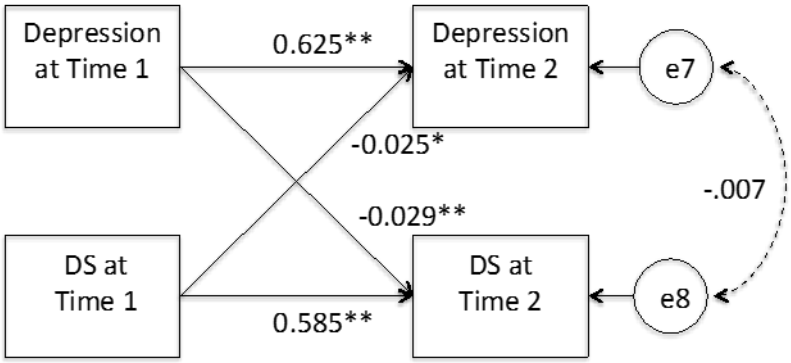

Figure 6 *Cross-lagged relationship between depression and DS shown with standardised regression coefficients. Solid lines indicate significant positive paths and dotted lines indicate non-significant paths. * p <0.05, ** p <0.001*

The temporal relationship between depressive symptoms and PAL and VR was uni-directional. That is, depressive symptoms at time point one predicted significant decrease in PAL and VR at time point two. However, there was no relationship between VR and PAL at time point one and depressive symptoms at time point two. The temporal relationship between depressive symptoms and SWM, and depressive symptoms and DS was bi-directional. That is, depressive symptoms at time point one predicted a decrease in SWM and DS as well as lower levels of SWM and shorter DS at baseline predicting higher depressive symptoms at time point two.

Is the relationship between depression and cognitive decline mediated by lifestyle factors?

Demographic characteristics: The clinical subgroup sample consisted of 2577 participants. The demographic characteristics are presented in Table 4. The majority of the participants who were included in the mediation analysis were female (77.4%), with a mean age of 60.6 years (*SD*=7.1), married (62.6%), white (98.1%), retired (40.7%) and educated to degree level (50.8%). Mental health, lifestyle

factors as well as missing data for each variable is presented in Table 5. Most participants had levels of depression and anxiety that fell in the mild range (64.3% and 67.0% respectively). Over half (57.3%) of the sample consumed alcohol at least twice a week. Over half (54.9%) the sample self-reported to being fairly active and 39.7% of the sample had a BMI that fell in the 'normal' range. Missing data ranged from 0% for the cognitive variables, depression and anxiety scores to 11.3% for the physical activity variable.

Table 4 *Demographic characteristics of participants included in the mediation analysis*

	n	%
Sex		
Male	582	22.6
Female	1995	77.4
Age		
50-59	1396	54.2
60-69	899	34.9
70-79	255	9.9
≥80	27	1.0
Marital Status		
Married	1614	62.6
Civil partner	12	0.5
Co-habiting	207	8.0
Widowed	144	5.6
Separated	66	2.6
Divorced	336	13.0
Single	198	7.7
Ethnicity		
White	2527	98.1
Mixed	19	0.7
Asian	16	0.6
Black	6	0.2
Other	9	0.3
Employment		
Employed full-time	603	23.4
Employed part-time	503	19.5
Self-employed	296	11.5
Retired	1048	40.7
Unemployed	127	4.9
Education		
GCSE/A-Levels/Diploma	1268	49.2
Degree	1309	50.8

Table 5 *Mental health and lifestyle factors of participants included in the mediation analysis*

	n	(%)
Depression		
None/Minimal	490	19.0
Mild	1658	64.3
Moderate	337	13.1
Moderately Severe	68	2.6
Severe	24	0.9
Missing	0	0
Anxiety		
Mild	1727	67.0
Moderate	682	26.5
Moderately Severe	120	4.7
Severe	48	1.9
Missing	0	0
Alcohol Intake		
Never	219	8.6
Monthly or less	393	15.4
2-4 times a month	481	18.8
2-3 times a week	733	28.6
4 or more times a week	734	28.7
Missing	17	0.7
Physical Activity		
Not at all active	35	1.4
Not very active	498	19.3
Fairly active	1416	54.9
Very active	336	13.0
Missing	292	11.3
BMI		
Underweight	38	1.5
Normal	1022	39.7
Overweight	752	29.2
Obese	374	14.5
Very obese	227	8.8
Missing	164	6.4

The mediation analysis was run in one model that included depression at time point one, all three mediators and all four cognitive variables. The goodness of fit indices indicated that the proposed mediation model did not fit the data well [χ^2 (3) = 9.4, p = .002]. The mediation model is presented below. For clarity the model is presented in four separate diagrams.

Figure 7 shows the mediation model for depression and PAL. The bootstrap results indicated that BMI (point estimate >.001, 95% bias corrected CI =.001, -.001), physical activity (point estimate >.001, 95% bias corrected CI =-.001, .002), and alcohol consumption (point estimate >.001, 95% bias corrected CI = -.004, .002) were not significant mediators in the relationship between depression and PAL. In addition, the total effect of depression on PAL was also non-significant (point estimate = -.004, 95% bias corrected CI = -.012, .004).

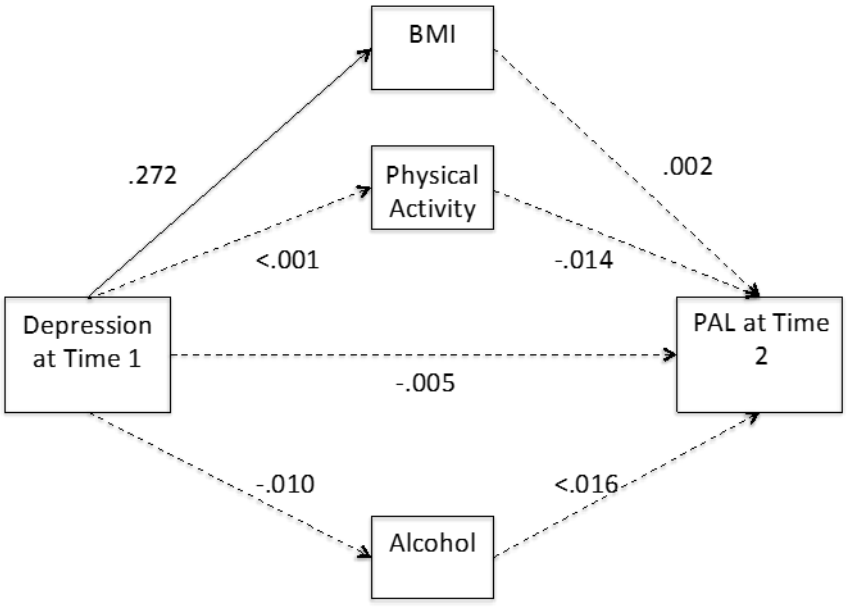

Figure 7 *Mediation model for depression and PAL shown with standardised regression coefficients. Solid lines represent significant paths, dotted lines represent non-significant paths.*

Figure 8 shows the mediation model for depression and VR. The bootstrap results indicated that BMI (point estimate >.001, 95% bias corrected CI = -.004, .002), physical activity (point estimate = -.012, 95% bias corrected CI =-.034, .005), and alcohol consumption (point estimate = -.003, 95% bias corrected CI = -.012, .001) were not significant mediators in the relationship between depression and SWM. In addition, the total effect of depression on VR was also non-significant (point estimate = -.034, 95% bias corrected CI = -.152, .084).

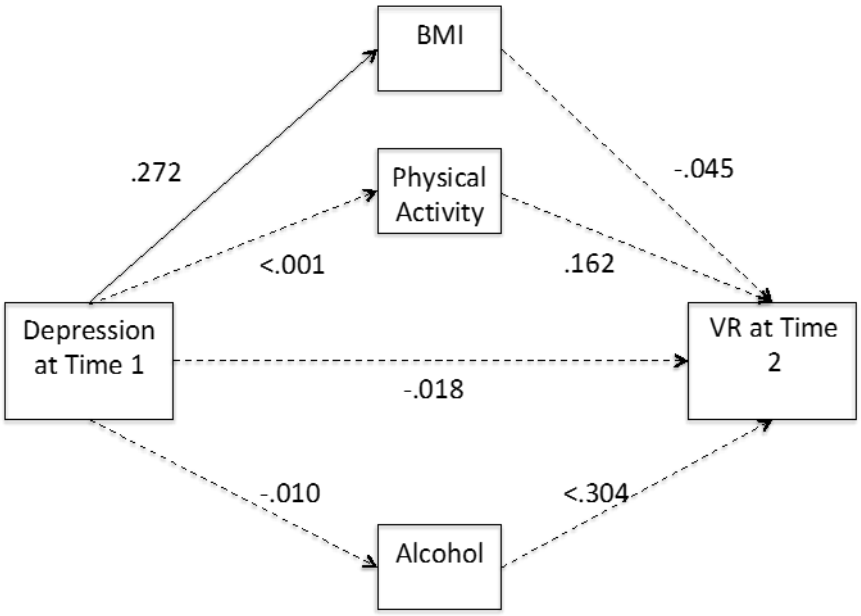

Figure 8 *Mediation model for depression and VR shown with standardised regression coefficients. Solid lines represent significant paths, dotted lines represent non-significant paths.*

Figure 9 shows the mediation model for depression and SWM. The bootstrap results indicated that BMI (point estimate >.001, 95% bias corrected CI = -.001, .009), physical activity (point estimate = -.001, 95% bias corrected CI =-.002, .001), and alcohol consumption (point estimate >.001, 95% bias corrected CI = -.001, .001) were not significant mediators in the relationship between depression

and SWM. In addition, the total effect of depression on SWM was also non-significant (point estimate = -.008, 95% bias corrected CI = -.014, .029).

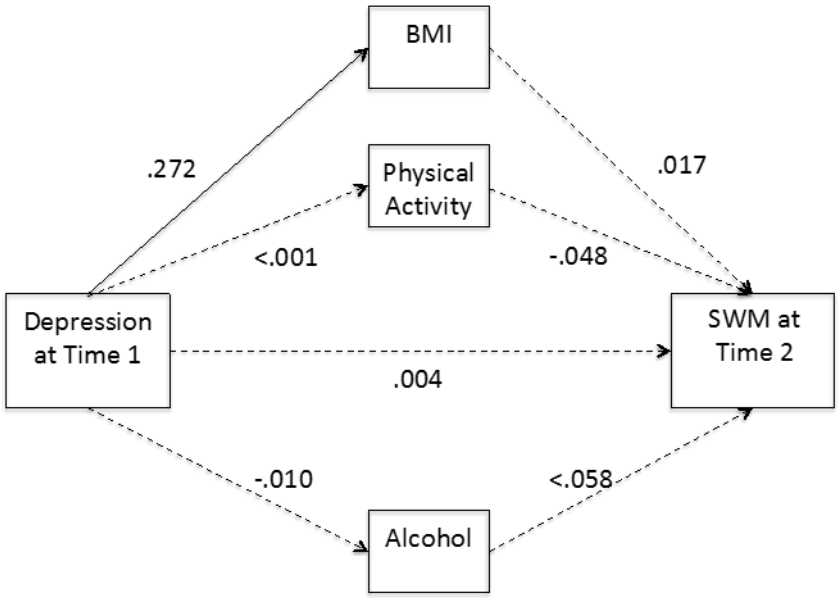

Figure 9 *Mediation model for depression and SWM shown with standardised regression coefficients. Solid lines represent significant paths, dotted lines represent non-significant paths.*

Figure 10 shows the mediation model for depression and DS. The bootstrap results indicated that BMI (point estimate >.001, 95% bias corrected CI = -.001, .001), physical activity (point estimate >.001, 95% bias corrected CI =-.003, .003), and alcohol consumption (point estimate =-.001, 95% bias corrected CI = -.002, .001) were not significant mediators in the relationship between depression and DS. In addition, the total effect of depression on DS was also non-significant (point estimate = -.019, 95% bias corrected CI = -.014, .098).

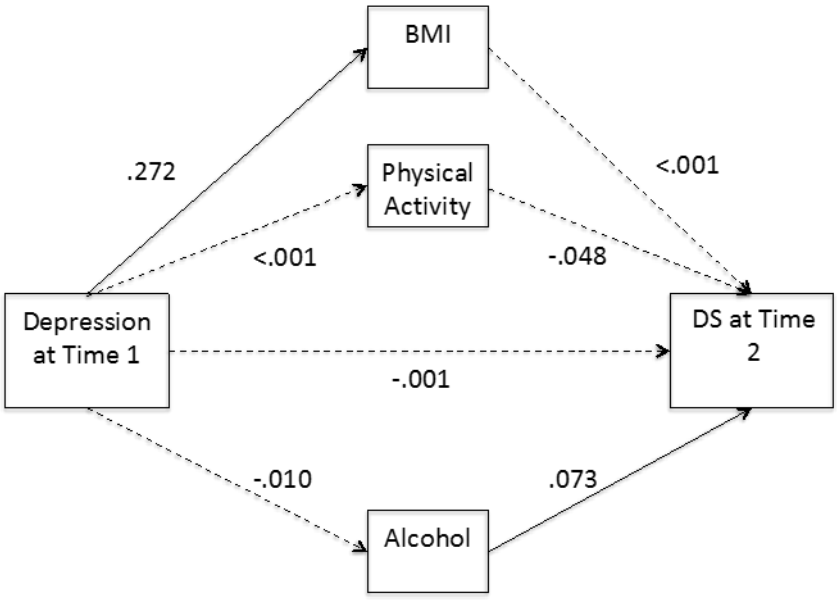

Figure 10 *Mediation model for depression and DS shown with standardised regression coefficients. Solid lines represent significant paths, dotted lines represent non-significant paths.*

5. Discussion

Summary of results

Cross-lagged analysis found that depressive symptoms predicted a decrease in new learning, verbal reasoning, spatial working memory and digit span. In addition, in the case of spatial working memory and digit span the analysis found the relationship to be bi-directional. That is, lower spatial working memory and a shorter digit span also predicted depressive symptoms. The meditation analysis found that for the subset of participants who reported clinical levels of anxiety and or depression that there was no total effect of depression and lifestyle factors on cognition.

Interpretation of results

This research study aimed to examine the temporal relationship between depressive symptoms and cognitive decline in relation to three hypotheses that are currently subject to debate in the research literature. The three hypotheses in question were: depressive symptoms are a psychological reaction to cognitive decline; depressive symptoms are a risk factor for cognitive decline; and depressive symptoms are a prodrome of cognitive decline. For all four cognitive measures (new learning, verbal reasoning, spatial working memory and digit span) higher depressive symptomatology predicted poorer cognitive performance. Indicating that depressive symptoms could either be a risk factor for or prodrome of cognitive decline. However, it should be noted that due to the level of attrition and the very small effect sizes of the relationships reported here the generalisability and clinical relevance are yet to be determined. To further tease apart the risk factor and prodrome hypotheses, mediation analysis was conducted. The results from the mediation analysis did not find support for the 'risk factor' hypothesis in that there was no evidence that the relation between clinical levels of depression and cognitive decline was mediated by health related behaviours. There are several possible explanations for these findings.

Firstly, it is possible that depressive symptoms are not a risk factor for cognitive decline via the vascular route and that another mechanism is at play. One possible causal mechanism for depression and cognitive decline is that of the interaction of motivational deficits often found in depression and perceived failure. People with depression are more likely to attend to negative stimuli in their environment (Roiser, Elliott, & Sahakian, 2012).When this is in the form of negative feedback from cognitive tasks (i.e. participant gets a item wrong in a cognitive battery), the perceived failure is more likely to be catastrophically interpreted. This, added with motivational deficits in people with depression, has been proposed as an

explanation of poor performance in subsequent tasks of cognition (Elliott et al., 1996). Another, explanation for the current findings is that the effect sizes of the associations in question were very small and thus the mediation analysis was underpowered. Given that the total effect between depressive symptoms and the mediators on cognition were all non-significant suggests that the subsample may have been too small for an effect to be detected. As the results from the present study were not able to provide support either way for the mediating effect of lifestyle factors future studies could use either larger sample sizes or longer follow-up periods.

Depressive symptoms at follow up were predicted by lower levels of spatial working memory and shorter digit span at baseline but not new learning or verbal reasoning. This gives partial support for the 'psychological reaction' hypothesis. The different findings for the spatial working memory and digit span tests compared to new learning and verbal reasoning, may be explained by the two former domains being aspects of executive functioning. This is in keeping with the results reported by Vinkers and colleagues (2004) who, as well as using a global screening tool, also used the Stroop test (Stroop, 1935), a validated measure of executive function (Lezak et al., 2012), as one of their measures of cognitive function. The study found that depressive symptoms increased with impaired performance on this task. Executive function is the aspect of cognition that allows for individuals to attend to, plan, organise and carry out tasks (Lezak et al., 2012). Deficits in this domain, even if only minimal, can potentially have consequences for an individual's capacity to care for themselves and engage in autonomous, meaningful behaviours (Lezak et al., 2012). Unlike some other domains of cognitive function, impairments of executive function are difficult for an individual to independently circumnavigate. For example, when there is a decline in memory if an individual's executive function is unimpaired then they would be able to employ executive functioning skills to plan

strategies to help compensate for their declining memory. If on the other hand, there were deficits in executive function no other aspect of cognition would be able to help with organising a compensatory strategy. For these reasons it may be the case that a even a minimal decline in this aspect of cognition is the most evident in an individual's experience of daily life, impacts the most on their sense of independence and therefore is experienced as particularly distressing.

One novel finding of the current study was that of the temporal relationship between depressive symptoms and spatial working memory, and depressive symptoms and digit span being bi-directional. Two previous studies (Cui et al., 2007; Panza et al., 2009) assessed the temporal relationship between depressive symptoms and cognitive decline for the possibility of bi-directional relationships. Contrary to the present findings, neither of the previous studies found evidence in support of a bi-directional relationship between depressive symptoms and cognition. However, this is possibly due to study design. The Cui et al. (2007) study did not find evidence of a bi-directional relationship between executive function and depressive symptoms over a two-year follow-up period in a geriatric sample of 709 participants. However, the sample size used by Cui et al. (2007) was much smaller than that used in the current study and therefore may have been underpowered to detect an effect. Panza and colleagues (2009) assessed the bi-directional temporal relationship between depressive symptoms using a measure of global cognitive function and episodic memory. This study found a uni-directional relationship between depressive symptoms and cognitive decline after a three and half year follow-up period. However, Panza et al., (2009) may not have found evidence of a bi-directional relationship because measures of executive function were not included in their study.

Strengths and limitations

A strength of the current study was the use of cross-lag analysis which allowed for the simultaneous examination of potential bi-directional relationships between depressive symptoms and cognitive decline. To the best of the authors' knowledge, this is the first study to find evidence that the relationship between some aspects of cognitive function and depressive symptoms is dynamic and bi-directional. Study designs that account for the possibility for there to be a bi-directional relationship between depressive symptoms and cognitive decline should at least be considered in future studies of depressive symptoms and cognitive decline. However, cross-lag analysis is not without limitations. One limitation is that the cross-lag design does not allow for modelling of change within individuals (Collins, 2006). Individuals are often on different trajectories of change in a given variable over time. Cross-lag panel designs only model the differences between individuals over time. An alternative design is the latent curve model that explicitly models trajectories across individuals time over multiple time points (Preacher, Wichman, MacCallum, & Briggs, 2008). However, this is only applicable for study designs with data from more than two time points and thus in terms of the present study the cross-lag design was the most appropriate.

Another strength of the current study was in its use of a very large population cohort sample allowing the detection of small effects. However, one limitation of using very large population cohorts, and one that must be considered here, is the level of attrition. Attrition between baseline and one-year follow-up was slightly over 50%. Therefore the possibility that the results presented here are biased must be considered. The sample of participants who completed cognitive measures at both time points were more likely to be married and have attained higher educational degrees than those who withdrew from the study. Both of these

variables are in themselves independent predictors of better cognitive function in old age (Helmer et al., 1999; Xu et al., 2016). In addition to these demographic differences, there were also differences in mood state and overall cognitive performance between the two groups. Those who remained in the study had less depressive symptoms and performed better in all tests of cognitive function than those who did not continue with the study. Another related point are the findings from a systematic review and meta-analysis of attrition in longitudinal cohort studies which found that age and cognitive decline were significant predictors of attrition (Chatfield, Brayne, & Matthews, 2005). It is possible that those who chose not to take part at time point two not only had lower cognitive performance at baseline but they may have also experienced the greatest cognitive decline in the follow-up period. This suggests that the sample analysed here might be biased towards representing a population that has better mood and higher overall cognitive function.

Implications for further research

Future research may focus on repeating the mediation analysis with a longer time period or larger sample size, as the results from the present study were inconclusive. Repeating the analysis with a larger sample may allow for the detection of a small effect size that the current study was not able to detect.

There are implications for further investigation of the dynamic bi-directional relationship between depressive symptoms and executive function and attention as this finding raises several questions. Is this pattern of relationship between depressive symptoms and cognitive function the same in clinical populations? Does the dynamic nature of the relationship between executive function and attention accelerate decline in these domains of cognitive function? The PROTECT study is well placed to answer these questions with its on-going data collection over the next

few years. In addition, as there will be multiple time points, latent growth curve modelling may be used to examine these questions.

Clinical implications

Due to the bi-directional nature of the relationship between depressive symptoms and decline in executive function and attention it is likely that there is a vicious cycle of depressive symptoms predicting cognitive decline and cognitive decline predicting distress. Thus deficits in the domains of executive function and attention may be particularly vulnerable to an accelerated decline in cognitive function due to the impact of the dynamic bi-directional relationship between the two. In neurological disorders, which have neuropsychological profiles that typically show early deficits in executive functioning and attention, treatments for depressive symptoms may serve to slow the rate of cognitive decline. This would be particularly relevant to conditions such as Lewy body dementia, Parkinson's disease and Normal Pressure Hydrocephalus. Even in the early stages of Parkinson's disease there are found to be subtle deficits in executive function and attention indicative of anterior subcortical atrophy which worsen with disease progression (Lezak et al., 2012). At present the National Institute for Health and Care Excellence (NICE) only recommends pharmacological interventions to treat Parkinson's disease (NICE, 2017). Treating depressive symptoms early in the course of certain diseases may be relevant with regards to treating the neurological aspects of the disease. However, further research is needed to show the validity and effectiveness of such interventions.

Conclusion

Depressive symptoms predicted decreases in all four measures of cognitive function providing support for the 'risk factor' or 'prodrome' hypotheses. Mediation analysis did not find support for the 'risk factor' hypothesis although this cannot be ruled out as the may have been underpowered or there may be other causal mechanisms at play. In addition, in the cognitive domains of spatial working memory and digit span there was evidence for the 'psychological reaction' hypothesis. The temporal relationship between depressive symptoms and spatial working memory digit span was bi-directional. Future studies should look to investigate the stability of this pattern of results over time with latent growth curve modelling. There are clinical implications for patient populations with cognitive profiles showing executive dysfunction. Although this needs to be investigated it is possible that treating depressive symptoms in these populations could slow the progression of cognitive decline.

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PART 3: CRITICAL APPRAISAL

1. Introduction

This critical appraisal includes reflections from the empirical study as well as the literature review. The reflections from the empirical study focus on some of the challenges of working on an external project with secondary data as well as on the process of preparing the data. The reflections on the literature review focus mainly on the time consuming nature of completing a systematic literature review and the development of innovative new tools that have the potential to speed up this process up in the future.

2. Reflections on working on an external project with secondary data

One challenge I faced in my project was that of working mainly by myself. I was working on an external project with secondary data. In addition, I had chosen to learn a new programming language and statistical package. At times I was completely overwhelmed by the tasks at hand and struggled with my confidence in my abilities to complete the project.

The PROTECT study team were a team of busy professionals who although very willing had little time to supervise a DClinPsy thesis. It was at times frustrating when emails would go unanswered by the team. Often times I was unsure how many times I could send the same email asking the same questions without being perceived as annoying. I think not having any face-to-face contact or regular meetings with the PROTECT team meant my questions were perhaps not seen as pressing. However, I did make one connection within the PROTECT team that turned out to be invaluable resource. Having even one person within the team who would reply to emails and respond to queries was an immense help and helped me to feel a bit more linked into the project and supported. I realised that maintaining

this connection to the team was very important both in terms of completing my project and also with lessening my feelings of isolation.

Working with secondary data meant that I had no control over how or what data was collected. One instance where this was problematic was regarding the information collected about alcohol consumption. The study had included some, but not all the questions, from the Alcohol Use Disorders Identification Test (AUDIT) (Saunders, Asland, Babor, De La Fuente, & Grant, 1993). The AUDIT is a ten-item questionnaire that assesses drinking behaviours and has been designed to specifically pick up any hazardous drinking behaviours. The questions the study team had chosen meant that only people who reported having a drink more than 4 times a week went on to answer questions on the volume of alcohol they were consuming. This meant that people who potentially consumed hazardous amounts of alcohol over fewer days would not be captured. To me this did not seem like a useful way of collecting the data on alcohol consumption because information on binge drinking would not be collected. Binge drinking is a significant problem in the UK with some studies finding that approximately one third of men and one fifth of women binge drinking at least once a week (Sproston & Primatesta, 2004). In addition, binge drinking is associated with lower levels of education and socio-economic status whereas more frequent drinking is associated with higher levels of education and socio-economic status (Huckle, You, & Casswell, 2010). Therefore, the study was potentially only identifying hazardous levels of drinking in people who had higher levels of education and were from a higher socio-economic status. For these reasons, I thought, only collecting the data about volume of alcohol consumption from people who reported to drinking more than four times a week was creating a bias in the data. This potential bias in the data made it difficult to know how to use the data that the study had collected. If I used all the questions from the AUDIT then the data would be biased and have questionable validity. If I used fewer

questions from the AUDIT then I would be losing information and it would not really be a measure of hazardous drinking. I decided it was better to lose information than to use a variable that was potentially biased and decided to use only one question from the AUDIT as my measure of alcohol consumption.

I chose to analysis my data using the 'R' programming language. I knew I had to learn a new statistical package because SPSS, the package I was already familiar with, did not have had the functionality needed for my analyses. There were a few reasons I chose to use R. For starters R is an open source resource, which means that it is free for anyone to download and use but also anyone can write and upload public packages. These things in combination make R a very powerful resource. However, there were a few downsides with using R. At the time of completing my thesis UCL did not formally support R, which meant I did not have an expert to take any technical queries to. In addition, I was not aware of any other students in my cohort who were using R, which meant I did not have peer support. However, I did find some R courses run by UCL that were very good and an R user amongst the UCL course staff who was very helpful and open to questions. I also, found some useful on-line forums, on-line tutorials and a useful textbook on R (Beaujean, 2014). One thing I was surprised about was how easy to read some of the R-related papers were. The way R works is that members of the on-line community write and contribute to R packages. R packages are essentially little bundles of code that allow you carry out a function very simply using one command instead of painstakingly writing commands for each step. In my analyses one of the packages I used was the lavaan package (Rosseel, 2014). This is a package that allows the analysis of structural equations using a few commands. The authors of most packages also publish a paper describing and providing instructions on the use of their package. Yves Rosseel, the author of lavaan published his lavaan paper in *The Journal of Statistical Software.* At first, and as someone with a background

primarily in psychology, I was a little apprehensive about reading a paper published in *The Journal of Statistical Software.* However, contrary to my expectations and much to my surprise the paper was very clearly written and I found it accessible. It proved to be a valuable resource in navigating R and my analyses. I soon realised that if I had an R question that was not answered in the 'help' function of the programme then the associated package papers were very useful and generally easy to read. Once I had found out how to access information on packages and which resources to check when I needed to trouble shoot a problem, R was a very intuitive package to use. With just a few lines of code I found I could run quite complicated analysis and the ability to save R-script files meant it was very easy to re-run or refine analysis.

3. Reflections on preparing the data

One of my biggest challenges that I faced on this project and one that I had not fully envisaged at the start was the amount of time it would take for me to prepare and clean the data. The data arrived in six different excel spreadsheets organised by category of variable. That is, one spreadsheet contained all the demographic details, one contained all the medical information, one all the data about smoking and exercise, one all the mental health questionnaires and two separate spreadsheets contained the data related to cognition. Receiving it in this way was very overwhelming not least because my skills in excel were, at that point, limited. Even opening the spreadsheets to look at the variables at times proved challenging. There were too many data points for Excel to handle efficiently so the programme would often freeze or unexpectedly shut down. For example, one spreadsheet contained over 70 000 rows of data and would continually crash if I tried to manipulate any of the variables. Before I even cleaned the data I needed to combine some of the spreadsheets. This was a time consuming and complicated

task and hindered by Excel shutting down if it had too many commands running at the same time. On several occasions when Excel quit suddenly and I would lose work that had been unsaved. I quickly learned to save the files every ten minutes or so.

A lot of the data was quite ‘dirty’ and took a lot of processing until it was in a form that was usable. For example, one of the variables I created to use in the empirical study was that of body mass index (BMI). To create this one variable was fiddly and extremely time consuming and involved the following steps (interspersed with much time spent ‘Googling’ each step):

(1) The PROTECT Study had collected the data in the Imperial format. However, when the data was extracted and imported into Excel it was input into a single cell. That is, where a participant reported they were, for example, five feet seven inches this was represented in one cell in Excel as ‘5.7’. Where the first digit referred to the number of feet and the second digit the number of inches. So the first procedure was to separate the data into two cells.

(2) Once the numbers were separated, a column representing the height in total inches was calculated using the formula, ([number of feet]*12)+[number of inches] or (5*12)+7 as per the example above.

(3) Next the result of this calculation was multiplied by 0.0254 to convert the participant’s height in inches to height in metres.

(4) A similar process was undertaken for the weight, which had been obtained in stones and pounds and also input into one Excel cell.

(5) Lastly dividing the weight in kilograms by the height in metres squared created the new variable of BMI.

In addition, I also found there were sometimes problems in the way I had separated the digits in the first instance. Unbeknownst to me at the time, when you use the 'Text to Columns' (which allows you to separate data from one cell into multiple cells) function in Excel it changes the format of the data from 'numeric' to 'general'. This was problematic because when the data was in the 'general' format Excel did not recognise '.' as missing data. So, when some of the later calculations were done I got some very spurious results (e.g. one participant appeared to have a BMI of 2801 which after conferring with Google I understood was not possible). As a fairly basic Excel user it took me quite a lot of time unpicking my formula and going back through the steps to find the source of errors. Being able to trace my steps backwards and unpick my formula was a strategy I refined throughout the data preparing process.

As mentioned above the data came in six different spreadsheets. Each spreadsheet contained raw data some of which required complicated formula to create a useful variable. My initial approach was to, once the variables had been created, I would remove the formula from the cells and just keep the numeric values as this helped lessen the amount of times Excel would 'unexpectedly quit'. However, the problem with this was that if I had not kept the formulas in the cells when I encountered an error it was quite difficult to retrace my steps and unpick what I had done to find the source of the error. I soon learned to keep very detailed records of the formulas I had used, what they did and why I had used them for each variable.

Another problem with using secondary data is I had little awareness of how the data had been input by the participants. This lack of knowledge about the data entry process turned out to be problematic in some situations. In the process of creating composite scores to form new variables I would often have to add several columns of data together. For example, I needed to combine two columns of data to create

the ‘smoking’ variable (this variable was not used in the final analyses due to the low numbers of people who smoked). Information was contained in two different columns representing two different questions. One column contained the answers to the question: Do you smoke [0=No, 1=Yes] (Q1) and the other column contained the answers to the question: How many cigarettes a day do you smoke [insert number] (Q2). To create a composite score for the ‘smoking’ variable I needed to add these two columns of data together but I had to be careful to differentiate between missing data and an item not entered because it did not apply. In the example of creating the ‘smoking’ variable, if a participant had answered ‘No’ to question 1 (i.e. they did not smoke and entered in the column as ‘0’) then the second question would also be unanswered because it did not apply (this was entered in the column as ‘.’). However, this was also how missing data was recorded. That is, if the participant had skipped both Q1 and Q2 they would be recorded in both columns as ‘.’ Therefore summing both the columns meant it would not be possible to tell if the data was missing because it did not apply or because the participant had not entered the data. To try and overcome this problem, I created a new column variable by using a logic function. The logic function instructed the programme to check the cell containing the answer to Q1 and if that cell was ‘0’ (i.e. the participant had recorded that they did not smoke) then to enter a ‘0’ in the new column and if the answer to Q1 was not ‘0’ then the function was instructed to look in the cell containing the answer to Q2 and enter that number into the new column. This logic function allowed me to differentiate between genuinely missing data and data not entered because it did not apply. One way I used to check if I had created new variables correctly was by looking at the column sum of the new variables. If I had created the new ‘smoking’ variable correctly then the column sum of the new variable should equal the column sum of the Q2 column. However, I found there was a discrepancy of 4 between the two columns. Initially I thought there was an error in excel or somehow the formula had been corrupted in a

couple of the cells. After several hours of investigation and checking it turned out to be an error in the data. In other words, it was human error or a error in the way the data collection had been set up in the first instance. Two participants had answered that they did not smoke and then gone on to enter a number for how many cigarettes a day they did smoke. In had not occurred to me that the discrepancy in the column sums was a problem with the way the data had been entered or collected in the first place. My first thoughts were to try and find the problem in the formula or in the excel spreadsheet. Having spent half a day trying to find 'my mistake' I realised it would have been useful to 'play' around with a dummy version of the on-line questionnaire to see what the questions looked like on screen and if it was even possible to enter certain combinations of answers.

After much trial, error and 'Googling' I managed to create a useable spreadsheet that I could import into R. Along the way I also learned a few strategies that helped me organise my work. By the end of the process I was keeping detailed notes of all the functions/formulas I had used. In this way if I needed to I could easily re-trace my steps in the event of an error. I also learned to check my formula using spot checks and summing columns and not to rule out the possibility of an error in the data (rather than focusing on finding an error in my formula) when trying to find the source of discrepancies.

4. Reflections on the literature review

The literature review search process was the most time consuming part of my entire thesis. My search results came up with in the region of 30 000 hits and even after removing duplicates there were over 20 000 titles and abstracts to sort through. Looking through the titles and abstracts of this many articles was incredibly time intensive. I would often try and squeeze in an hour or two on this task on the

commute to and from placement. At these times of day and being in the environment of a packed commuter train I wondered how much my human tiredness and distractibility would be impacting on the accuracy of the searching process. Just doing the search, sifting through the titles and abstracts and reviewing the full texts took me the best part of four months to complete.

During this period I came across a Technology Entertainment and Design (TED) talk that was using artificial intelligence (AI) to innovatively assist the legal research process (https://www.ted.com/talks/andrew_arruda_the_world_s_first_ai_legal_assistant). The legal research process is a process –not dissimilar to conducting the initial stages of a systematic literature review – that sifts through case law to find any cases relevant to the legal question at hand. Arruda identified that because this process is so time intensive and therefore expensive it puts recourse to legal advice out of the reach of many people. Arrunda teamed up with a computer scientist to try and make the law more accessible by creating an AI legal assistance. They named the AI legal assistant 'Ross'. It is reported that Ross can read over a million pages of legal case law in under a second finding anything it needs in minutes. In addition, as Ross is AI it uses neural networks and deep reinforcement learning to 'learn' how to better perform the task each time it's run. Using AI takes the time out of the legal research process and allows lawyers to focus on advising clients rather than spending hours and hours reading case law. I could see the parallels between conducting a systematic literature search and the legal research process which prompted me to research if there was anything similar being developed for academia.

My research took me to the Iris.AI website (https://the.iris.ai). Iris.Ai is described on their website as a young artificial intelligence that is being developed to assist in academic research. AI has many potential uses in the field of research

and currently two tools are being developed by the Iris.Ai team. One is that of an AI search engine and the other is as an AI research assistant not dissimilar to Ross. Currently Iris.Ai has access to all the open source research papers. There is a search feature, where you enter the name of a paper, and Iris.Ai is able to search and organise all the records available to it by using keywords. This feature of keyword searching is similar to current search functions available through databases such as Embase, which also organises and searches through papers using keywords. What is different is, in addition to this, Iris.AI can organise research papers according to 'concept'. The concept is generated by Iris.Ai and takes into account the context of the paper. Like the legal assistant, Iris.Ai runs on neural networks so therefore it is able to incorporate feedback to 'learn' how to make a more accurate concept. This is very different to the algorithmic-based search rules that the traditional databases use. These algorithmic based search engines use rules based criteria to search through literature regardless of the context of the paper. On the other hand Iris.Ai can potentially use context as well to keep search results down. Using AI in this way is quite a new initiative so currently the search function is limited. However, one thing that makes AI very powerful is its ability to learn and develop with exposure to content or training. The Iris.Ai website has a feature where anyone can 'train' the AI. In the training section researchers are invited to read an abstract and identify five keywords that the abstract covers. Iris.Ai then uses this feedback to progressively refine its search abilities.

The second tool that is being developed by the Iris.Ai team is that of a research assistant. This tool is under development and is currently in the beta-testing phase. The tool allows for the incorporation of external databases so could potentially connect to Embase and PsycInfo. The researcher then writes a problem statement as a starting point for the 'exploration' phase. The next stage is an iterative process that helps to narrow down the results. As with the search feature

because the tool uses neural networks and reinforcement learning this process becomes more refined with time and feedback. The tool can also suggest topics for inclusion and exclusion based on the original problem statement. The Iris.Ai team state that the tool can handle up to 20 000 documents and is able narrow this down to a short reading list in 10% of the time it would take to do this using traditional methods. My curiosity led me to contacting the developers of the tool and they have invited me to beta test this new tool on a subsample of my literature search results. I am aiming to test this in the near future and am excited by the potential time savings of such a tool.

Currently the time taken for researchers to complete systematic literature reviews is considerable. Ideally two researchers are needed to reach consensus in many of the steps of the process like the manual study selection. Within this process researchers often add in extra sources of bias for example by only including journal articles published in English. If systematic literature reviews or meta-analyses could be completed in a fraction of the time with higher levels of accuracy irrespective of language of publication it could have potential implications for the pace of research and the research process as a whole. Incorporating AI into the research process is still in the very early stages of development but the potential implications for this are huge. In the future there could quite possibly be a research search engine where the question of interest such as ‘is there an elevated risk of incident dementia conferred by living alone?’ could be entered. AI could search and ‘read’ all the relevant studies, extract the data and calculate a pooled effect size and give you an answer almost instantaneously.

5. References

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