

# Depression in the Elderly

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# **Polygeia**

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#### **Abstract**

We are living longer than ever before and according to current predictions this trend is set to continue. The socio-economic impact of population aging is predicted to triple by 2050 and if we are to tackle this emerging problem, action must be taken promptly. Late life depression (LLD) plays a pivotal role in aging and the aggravation of commonly encountered age-related challenges, including; loneliness, physical disability and Alzheimer's disease. We will evaluate epidemiologic studies that address correlation between depression and aforementioned areas and determine whether there is evidence of potential causality that may be informative in establishing new, world-leading policies in UK elderly care. Importantly, none of the interactions presents themselves in one single direction. However, generally speaking, loneliness and physical disability tend to precede depression whereas the interaction with Alzheimer's disease appears to be more bidirectional in nature. Therefore, we suggest that creating an environment in which elderly are more frequently exposed to social interaction may form a feasible starting point. This will not only prevent loneliness but also encourage more physical activity which may lead to a general healthier population with a reduced risk for developing age-related disorders such as Alzheimer's disease. This approach may be complemented by active screening programmes for LLD so potential health issues following from LLD can be prevented early-on in the disease course.

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#### 1. Introduction

Depression in elderly populations is a significant issue, presenting a set of unique challenges for screening, diagnosis and treatment. The prevalence of mental and neurological disorders among older adults exceeds 20 per cent, accounting for 6.6 per cent of all disability-adjusted life years (DALYs) in this age group<sup>1,2</sup>. Additionally, the global population is ageing rapidly. The number of people over the age of 60 is expected to increase from 900 million to 2 billion people by 2050<sup>1</sup>. As such, the burden of mental illness in elderly groups is projected to rise dramatically over the coming decades. While close to 10% of the world population is affected by mental health disorders, accounting for 30% of the global non-fatal disease burden, governments allocate an average of only 3% of healthcare budgets on mental health on average.<sup>3</sup> Although, mental health is the single largest category of healthcare expenditure in the UK, a large chunk of this is made up of dementia care<sup>4</sup>.

Despite high levels of depression, older adults are underdiagnosed, undertreated and less likely to receive specialised mental health care than their younger counterparts<sup>5-7</sup>. Depression in older adults frequently co-exists with physical conditions such as cardiovascular disease, and neurodegenerative conditions such as dementia<sup>8</sup>. Late life depression (LLD) has a bidirectional relationship with co-morbid physical illness. That is, older adults with physical conditions tend to have higher rates of depression, while depression can negatively influence outcomes of physical illness, such as hypertension, diabetes or lung disease<sup>1,7,9-11</sup>. In addition to creating a reduction in overall functioning, depression in the elderly increases the perception of poor health and increases utilisation of medical services and health care costs<sup>1,10,12</sup>. The close relationship between depression, dementia and physical illness makes epidemiological investigation challenging, and may mask the clinical presentation of depression<sup>6,8</sup>. Consequently, mental health illnesses are often under-recognised by health-care professionals and older people themselves<sup>1</sup>.

The loss of ability to live independently affects many older adults and is often a consequence of impaired mobility, chronic pain, disability or other mental or physical problems requiring long-term care<sup>1</sup>. Additionally, older people are more likely to experience significant life events such as bereavement or decline in socioeconomic status with retirement. The combination of these factors can lead to social isolation, and therefore loneliness and psychological distress. In some studies, prevalence and incidence of depression in the elderly is particularly high in medical settings, including residential care or nursing homes<sup>5,8</sup>. This may relate to both the higher rates of physical health conditions in these settings, as well as loss of high quality social and/or community interactions.

The relationship between loneliness, social isolation, and depression is of major importance in the UK, with increasing numbers of older adults living alone or otherwise lacking regular social interaction<sup>13</sup>. Overall, depression has been consistently associated with loneliness and social isolation in older adults, while sustained social engagement may be protective<sup>14-17</sup>.

Given the significant burden of LLD, in terms of both morbidity and financial costs, there is an urgent need to address this issue. The unique challenges presented by LLD also offer a number of potential avenues for intervention, by tailoring treatments to the specific needs of the elderly. This paper will further examine key elements of LLD and its relationships with social isolation, physical impairment and dementia in the form of Alzheimer's disease. Additionally, we seek to identify feasible avenues for efficacious and cost-effective interventions, at both individual and population-wide levels.

## 2. Loneliness and social isolation in old age

There are important differences between loneliness and social isolation, and the difference could be said to be psychological<sup>18</sup>. Social isolation refers to the objective number and frequency of social interactions, including a small social network, lack of social relationships, low levels of participation in social or community activities<sup>18</sup>, living alone, and/or lacking availability of social support from others<sup>19</sup>. Loneliness is the subjective experience of the objective social engagement<sup>19</sup>, such that living alone or having few social contacts does not automatically create a sense of perceived loneliness without the psychological impact<sup>16</sup>. This difference is important in deciphering the causal pathways through which depression can result from social isolation or loneliness.

# 2.1 Loneliness, social isolation, and the elderly

Loneliness and social isolation are becoming important problems in the UK. Factors such as divorce and the migration of relatives and friends have become more common, and rising life expectancy is increasing rates of disability, increasing the likelihood of reduced social networks and contact. Indeed, an estimated 2 million people in England over the age of 75 live alone, and more than 1 million reported going for over a month without speaking to a friend, neighbour, or family member<sup>20</sup>. In addition, almost a quarter of people aged over 65 do not go out socially at least once a month<sup>20</sup>. An ONS UK survey found that social isolation can lead to feelings of loneliness, which become increasingly common with age: over a third of those aged over 52 expressed feeling lonely some of the time or often, and this rose to over 45% for those aged over 80<sup>21</sup>. Other studies have since supplemented the evidence of an increased risk of loneliness with older age<sup>22</sup>.

There are several risk factors that can increase the vulnerability of the elderly to loneliness, including living alone or in a residential home, bereavement and widowhood, an inability or lack of opportunity, and/or poor health and functional status<sup>16,18,22</sup>. For instance, poor health has been associated with lower participation in organised social activity for nursing home residents<sup>23</sup>, and reduced social activity combined with functional impairments in older adults was associated with higher levels of depressive symptoms<sup>24</sup>. In particular, a meta-analysis conducted by Cole et al. found that bereavement was the most significant risk factor for depression in adults aged over 50, more than tripling the risk of depression, even compared to prior depressive symptoms<sup>25</sup>. Such adverse life events can also increase the need for social support, causing the personal impact of social isolation to be greater compared to younger groups experiencing the same level of social engagement but without these other risk factors<sup>19</sup>. Importantly, in addition to functional disability, loneliness was identified as a risk factor with the most potential for improvement in depressive outcomes amongst elderly groups<sup>26</sup>.

#### 2.2 Social isolation, loneliness, and depression.

Social isolation is known to have a link with the occurrence of depression in the elderly<sup>15,27</sup>, with a health risk comparable to factors such as smoking and obesity<sup>28</sup>. Conversely, social contact appears to have a key protective role against risk factors for depression by encouraging positive self-perception and a greater sense of control and independence<sup>29</sup>.

However, when social isolation and subjective loneliness are analysed as independent variables, the relationship between objective social disconnectedness and poor mental health is primarily mediated through subjective loneliness<sup>16,19</sup>. Furthermore, relationships with friends and community members seem to be more important in determining perceived loneliness than interactions with family, since they represented greater choice and autonomy over social engagement. Since older age tends to be associated with loss of friendship and community networks, advancing age can confer a particular risk of

loneliness. Importantly, subjective feelings of loneliness was identified as one of the three main risk factors for the development of depression in older adults across one three year study<sup>30</sup>, and had a significant positive correlation with the level of self-reported depressive symptoms in a cross-sectional study<sup>16</sup>. These relationships may start at younger ages: in the US, subjective reports of poor social support and quality of social relationships was associated with up to double the risk of depression between the lowest and highest quality levels across a wide range of ages, and continued to be a predictor of future risk up to 10 years later <sup>31</sup>. The study accounted for numerous potential confounders, providing evidence for a potential causal relationship<sup>31</sup>.

#### 2.3 Feedback cycles

Social isolation and loneliness may represent both a causal factor and an outcome of depression, leading to feedback loops. Individuals suffering from depression, compared to non-depressed individuals, tend to exhibit social skill deficits and are more likely to perceive negative outcomes from social activities and follow up social engagement with a series of self-critical though processes<sup>24</sup>. This can lead to a decline in the frequency of active social engagement, further reducing opportunities for positive social interactions and maintaining and intensifying depressive symptoms<sup>24</sup>. Amongst elderly groups in particular, functional and cognitive limitations may create perceived threats to personal and social competence. This may lead to the formation of both physical and mental barriers to social engagement and increased reason to engage in negative cognitions that can increase vulnerability to depression<sup>24</sup>.

This highlights the key role of health promotion strategies in breaking these cycles. For example, focusing on increasing motivation and ability for social interaction amongst those already exhibiting depressive symptoms, and in targeting resources towards prevention for elderly groups in general to avoid the onset of these feedback cycles.

#### 2.4 Community and residential care homes

The relationship between social isolation, loneliness, and depression is relevant in both communities and health settings. In particular although admission to a residential home can result in a greater frequency of objective social contact for an elderly individual, it can lead to low quality of engagements. In one study, admission to a nursing home led to self-reported contact with friends and family being reduced by around half, and signified a loss of proximity to social networks, local communities, and previous engagement in community or social activities<sup>32</sup>. This was linked to a reduction in an individual's sense of control and autonomy, creating risk factors for depression<sup>32</sup>. Indeed, depression amongst nursing home residents in the Netherlands was found to be particularly high<sup>33</sup>, demonstrating that a high frequency of low quality social contact alone cannot ameliorate the risk factors for depression in older age. Structural issues such as a high turnover of staff, and reliance on casually or temporally employed staff, can reduce the extent to which residents are able to form meaningful relationships with staff, whilst interactions between staff and residents tend to be predominantly task-orientated in nature<sup>34</sup>. Indeed, relationships with care workers can be central in the quality of life for elderly people<sup>34</sup>.

#### 2.5 Policy and health promotion implications

It is likely that there are substantial population-level benefits to recognising the critical role that social relationships and networks can play in the medical care of relationships, and thus, health services needs to also provide resources that enable individuals to improve the objective and perceived quality of social relationships<sup>32</sup>. Furthermore, social connectedness within social and community activities may play a role in preventative healthcare, since it can buffer the impact of stress and adverse life events<sup>19</sup>, and other risk factors of depression<sup>33</sup> in both objective and subjective measures. This can also improve general quality of life, since individuals with lower perceived loneliness tend to also have more active

coping strategies, greater self-esteem, and a greater sense of control<sup>34</sup>. This might include inquiring about perceived social relationships as part of appointments, services, or treatments for other conditions, as a key indicator for potential risk of depression in patients<sup>32</sup>, and thus a means of targeting preventative resources. Overall, since loneliness is such a complex subjective experience, often with complex causes, interventions must take into account such situational and individual factors<sup>21</sup>.

The presence of many risk factors for loneliness specific to old age highlights potential avenues for intervention that are tailored to the specific needs of the elderly. Over half of older adults with depression experience their first onset in later life<sup>35</sup>, and in one community-based study, the increase in depressive symptoms with advancing age amongst those aged 75 and over was primarily attributable to age-related changes in risk factors. Therefore, there needs to be more focus on prevention efforts at these older ages. Indeed, evidence suggests that when evidence-based psychological therapies are combined with treatments that use community resources to address the practical problems faced by elderly individuals, there is a greater positive impact on depressive outcomes compared to using either approach in isolation<sup>36</sup>.

A more generalized strategy may include forms of psycho-, cognitive, and behavioural therapy that tackle emotional and cognitive perceptions about social and inter-personal relationships; these are effective in targeting behavioural and social engagement problems<sup>31</sup>, as well as acute and long-term depression<sup>37</sup>, particularly in patients experiencing high levels of loneliness<sup>38</sup>. This can be tailored to elderly groups. In particular, since these programmes cannot physically prevent many risk factors arising in older age, they may benefit from enabling older adults to better adapt to common lifestyle changes. Accessibility of treatment is also important<sup>24</sup>, and requires a consideration of treatment within the home and accessing those with physical disability or cognitive impairment, often the most at risk individuals<sup>18</sup>. Furthermore, these programmes also need to be supplemented with those that increase the opportunity and accessibility of social engagement amongst elderly communities, as well as combating common stereotypes about ageing and social engagement<sup>24</sup>.

To illustrate this, befriending schemes have been found to be one of the most effective services for combating both social isolation and perceived loneliness, particularly in combination with other programmes<sup>20</sup>. Through these schemes, volunteers or employees visit elderly individuals within their homes or at community venues, provide social, emotional, and practical support. In another strategy, a 10-year review of a telephone support programme for older adults found that suicide rates were lower than expected, suggesting a reduction in severe depression in relation to the programme<sup>39</sup>. In the US and Canada, 'gatekeeper' programmes have been effective – people such as postal or delivery workers were identified to be well placed at noticing older people at risk, who can then be linked with appropriate support services<sup>40</sup>.

Interventions tailored to risk factors associated with admission to a residential care home might include the organisation of family-orientated events and activities within residential units, and encouraging engagement with the wider community. Given the importance of relationships between care workers and residents, residential units should place greater emphasis on communication skills and developing relational and meaningful interactions<sup>34</sup>. Residential care homes also require a shift to an emphasis placed on quality of life indicators over quality of care<sup>18</sup>.

It is clear that older adults require greater provision and access to services, support, and opportunities that enable them to build and maintain positive and high quality social relationships. Since 'the magnitude of effect is sizeable, the prevalence of poor quality social relationships is high, and the population – level morbidity of major depressive disorder is among the highest of any condition<sup>31</sup>, these

factors represent important targets for health and public health officials. Services need to be high quality and sustainable since patchy and unreliable access to a service can have a particularly negative effect<sup>20</sup>. There is a growing need for health and social care public services to provide greater support in funding, providing, and implementing these services to the elderly, which often over-rely on the voluntary or third sector. This is particularly pertinent since preventative services have the potential to reduce the burden on more costly health and social care services.

# 3. Interactions between late-life depression and comorbid medical conditions

Comorbidity is defined as the presence of more than one distinct condition in an individual<sup>1</sup>, which tends to be the norm, rather than the exception in later life. This is a consequence of the various changes (physiological, psychological and social) associated with ageing, and is connected with worse health outcomes, more complex clinical management, and increased health care costs; it should thus represent a priority to healthcare professionals and policy makers alike<sup>41</sup>. In recent years, our understanding of the complex, bidirectional relationship between LLD and comorbid health conditions has become well-established in the literature. However, we are yet to see a conversion of this knowledge into any significant widespread healthcare reforms, which have the potential to both greatly improve health outcomes in the elderly population and achieve substantial financial savings in the middle to long-term. This chapter will consider the interrelationships between LLD and other comorbid medical conditions, their burdens to healthcare and the economy, and some core concepts which should guide the next steps in their management.

#### 3.1 How do comorbid medical conditions influence depression in older adults?

Historically, medical illness has tended to mask symptoms of depression in older adults; in the 1970s and 80s healthcare professionals considered negative mood and other now widely accepted hallmarks of clinical depression as an inconsequential adjunct to other medical conditions<sup>42</sup>. This established a precedent for the under-diagnosis and under-treatment of depression in older adults<sup>42</sup>. Whilst the understanding of LLD as a significant public health burden gained tract towards the end of the last century, the complex and intertwined presentation of symptoms of LLD and comorbid medical conditions means depression in the elderly remains underdiagnosed and undertreated<sup>24</sup>. Undertreatment of depression leads to a reduced quality of life, ability to self-care and social interaction, as well as increase health care use<sup>12,43,44</sup>. Consequently, there is an urgent need for more precise and thorough diagnostic procedures (focussing on differential symptomatic presentation) if we are to fully understand the true burden of LLD and better manage its consequences.

Rates of depression are significantly higher in individuals with other medical conditions than those with no comorbidity<sup>24</sup>. In particular, stroke, chronic obstructive pulmonary disease (COPD), cardiac disease and diabetes are associated with particularly high incidences of depression<sup>45-47</sup>. For example, approximately 20-25% of patients with cardiac diseases also have a diagnosis of major depressive disorder (MDD), with a further 20-25% experiencing depressive symptoms but below the diagnosis threshold<sup>48</sup>. Comorbid depression in cardiovascular disease (CVD) is associated with higher rates of rehospitalisation, disability and mortality, and a slower recovery and increased healthcare costs<sup>49</sup>. The mechanisms underpinning the connection between heart disease and depression remain unclear; suggestions include shared genetic predispositions, poor adherence to treatment and lifestyle recommendation, and dysfunction in bodily systems thought to play a role in the pathologies of both depression and CVD<sup>46</sup>. The high incidence of CVD in the elderly population and its high rates of comorbid depression (both diagnosed and subthreshold) represents a significant public health burden; tackling this threat promises to improve both quality of life and healthcare expenditure.

As well as the putative biological factors linking medical conditions to the emergence of comorbid depression, experiences related to these conditions can precipitate a depressive reaction in patients  $^{50-52}$ . Such experiences include disability -and by extension, reduced social interaction-, chronic pain, sensory loss and the demands and stress associated with managing the condition). Furthermore, accompanying medications (including commonly prescribed agents such as  $\beta$ -blockers, calcium antagonists and benzodiazepines) used to treat comorbid conditions can contribute to the emergence of depression and complicate treatment of the latter  $^{24}$ .

#### 3.2 How does depression influence comorbid medical conditions in older adults?

Depression can worsen the prognosis of comorbid illnesses. For example, appetite disturbance secondary to depression is a key cause of weight loss in older adults, contributing to failure to thrive<sup>8</sup>. Furthermore, depression can increase the severity of physical disability and the attendant reduction in motivation contributes to poor adherence to both drug regimens and rehabilitation programmes. These factors, alongside an accompanying increase in self-neglect and social isolation, establish a vicious cycle that ultimately leads to increased health costs<sup>24,53</sup>.

Whilst we remain uncertain of the causal biological mechanisms responsible for some of the interrelationships between depression and comorbid medical conditions, their existence underscores the importance of adequate and timely treatment of depression to minimise adverse effects on these comorbid conditions.

#### 3.3 Policy and health promotion implications

It is apparent from the evidence presented herein that the interaction between depression and comorbid medical illnesses in older adults is bidirectional and self-perpetuating, whereby physical illness increases susceptibility to depression, and depression worsens prognosis of the comorbid condition.

Depression in older adults is distinct from depression in young adults with respect to various factors (aetiology, presentation, prognosis, protective factors, etc<sup>24</sup>) and the common occurrence of comorbid medical conditions is a key distinguishing factor. These differences emphasise the need for a bespoke approach to managing LLD. Whilst 'across the board' approaches to healthcare may appear superficially economical, carefully planned and specific approaches can often yield positive health and financial returns.

Effective psychological and drug treatments exist for the treatment of depression in older adults, but in order to improve health incomes and cost savings, efforts must be made to 1) improve diagnosis of depression to prevent under-treatment and its consequences, and 2) integrate depression diagnostic screening and treatment into commonplace treatment of medical illness in older adults.

In structuring a programme for diagnosing LLD in older patients with physical illnesses, we should look to analogous systems, such as 'Depression Care for People with Cancer' (DCPC). MDD is a common complication of cancer, yet its treatment remains inadequate because of difficulties in 1) identifying those patients suffering from comorbid depression and 2) ensuring these patients are treated effectively. The DCPC model involves a screening programme with a linked treatment programme and has been shown in several multi-centre randomised control trials to achieve better patient outcomes in a cost-effective manner. There is potential for the design of a similar model specific to the elderly, where older adults presenting with a physical illness deemed to be at significant risk of comorbid depression should undergo mandatory depression screening, with a subsequent accessible treatment link available as part of collaborative care delivery. A recent report from the Independent Cancer Taskforce ("Achieving World-Class Cancer Outcomes: a Strategy for England 2015-2020") recommends an

integrated approach to comorbid MDD and cancer, illustrating the impressive policy tractability of this healthcare approach<sup>54</sup>.

Momentum for the integration of physical and mental health services continues to grow, a consequence of an increasing understanding of the coexistence of mental and physical illness<sup>55</sup> and of an ever-expanding body evidence demonstrating poorer patient outcomes and greater care costs when comorbid mental illnesses are concerned<sup>56</sup>. In early 2016, a King's Fund report ("Bringing Together Physical and Mental Health: A New Frontier for Integrated Care" <sup>57</sup>) discusses the case for integration of mental and physical health services, which had been championed previously by the NHS Five Year Forward View in 2014. Integration of different aspects of the NHS (for example, primary and secondary care) has been in the pipeline for a while, but this was the first time real impetus for integration between mental and physical health services had been put across. Emphasis is placed on the importance of tackling cultural mind-sets that reinforce division, the integration of organisational and payment services, and the need for strong leadership and willingness at both a clinical and board level<sup>58</sup>. The challenge is immense, but an innovative and engaged approach has the potential to finally offer an integrated NHS which is beneficial for health outcomes and the economy alike<sup>57</sup>.

# 4. Depression and Alzheimer's disease

Alzheimer's disease (AD) is an age associated form of dementia (the leading cause of death in England and Wales in 2015<sup>59</sup>) that poses a rising threat to the aging world population<sup>60-62</sup>. Therefore, it is essential to give a more in-depth appreciation of AD and depression as comorbidities in old age.

Dementia and depression are both heterogeneous in nature<sup>63,64</sup>, which means they often present themselves as syndromes rather than well-defined disorders<sup>65</sup>. Both syndromes share common features (even leading to occasional misdiagnoses of depression with cognitive impairment, termed pseudodementia<sup>66</sup>). This leads to exclusion of depressed patients in dementia studies and vice versa, resulting in a lack of co-occurrence studies<sup>67</sup>. Since AD is the predominant form of dementia in western societies, making up 50-70% of all cases<sup>64,68</sup>, we decided to focus on studies looking at Depression and Alzheimer's disease to help reduce this heterogeneity. As pure AD makes up roughly 43% of all cases, and is only diagnosed with 100% certainty after death, it is likely that a number of AD studies have considered individuals with mixed dementia<sup>63,69</sup>. Furthermore, mainly early AD and prodromal mild cognitive impairment (MCI) are of interest as late stage AD is accompanied by generalized degeneration of the brain, making direction of a correlation impossible to determine.

In contrast to dementia, the heterogeneity between depressive syndromes is hardly reduced in the same way since diagnoses are always made in a more subjective neuropsychological fashion and there are currently no accepted diagnostic biological markers to stratify subtypes of depression<sup>70</sup>.

In looking for causality, it is important to distinguish three possibilities which are generally considered and are not necessarily mutually exclusive. Depression may be:

- A consequence of the patient being diagnosed with AD and now has the prospect of severe cognitive decline
- An early sign of AD onset and therefore a symptom of the actual disease
- An independent risk factor for the development of AD

All of these options will be considered individually.

## 4.1 Depression as consequence of psychological burden after Alzheimer's disease diagnosis

Although depression is a frequent comorbidity of AD, with an occurrence of 17-51% <sup>71-73</sup>, no systematic studies have focussed on the psychological burden of AD diagnosis for the patient and evidence tends to be anecdotal. AD is lethal in 100% of cases, with a median survival rate of 5 years <sup>74</sup>; in this respect, depressive rates may be expected to be close to those seen in other terminal illnesses like cancer, where the rate of depression lies between 4-17% <sup>75,76</sup>. However, this may not be completely translational, as the prospect of cognitive decline from a relatively healthy state of mind is a distinct characteristic. Furthermore, the fact that depression has been viewed as both a risk factor and early symptom of AD will always be a major confounder in providing answers to this question.

# 4.2 Depression as a symptom of early Alzheimer's disease

The reason for viewing depression as a prodromal sign of AD<sup>77</sup> comes mainly from the temporal overlap between LLD (45-65 years of age) and the earliest clinical diagnosis of sporadic AD (>65 years of age) (for a comprehensive overview see Panza at al<sup>78</sup>). Strikingly, a study by Steffens et al.<sup>79</sup> demonstrated that the risk for AD declines when the interval between depression and disease onset widens above 2 years. Within these two years (a period where various early onset signs develop), the correlation between depression and AD onset is strikingly increased and is therefore suggestive of depression as a prodromal symptom of the disease.

## 4.3 Depression as a risk factor for the development Alzheimer's disease

Although there seems to be an increased risk of developing dementia when an individual has suffered from depressive episodes –independent of their genetic risk<sup>80</sup>-, there appears to be more to the story than just a one-way interaction.

A meta-analysis conducted by A.F. Jorm<sup>77</sup> of 5 studies in 2001 found that the relative risk for dementia (AD) onset is 2.01 or 1.87 dependent on the employed study design. These numbers were later replicated by Ownby et al.<sup>81</sup>. A much larger meta-analysis conducted in 2013 by Diniz et al.<sup>82</sup> made a considerably clearer distinction between dementia subtypes and found that people who suffered from late-age depression were 1.67 times more likely to develop AD than unaffected individuals.

Interestingly, two studies by Alexopoulos et al.<sup>35</sup> and Kral et al.<sup>83</sup> showed independently that development of AD is most likely when a patient suffered from cognitive impairment during depressive episodes (in the form of previously mentioned pseudodementia). This indicates that a person may already have to be at an increased risk (by a potential third factor) to develop AD following a depressive episode. In this case depression in old age could be viewed as a red flag indicating that someone may need more rigorous monitoring for AD development.

# 4.4 Policy and health promotion implications

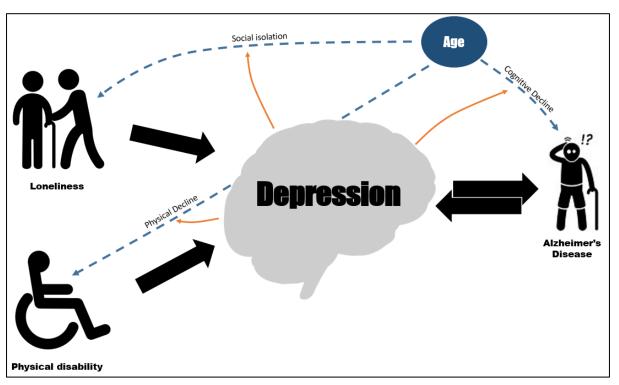
Although the exact mechanism by which depression may contribute to AD remains elusive, D.E. Barnes calculated the population attributable risk (PAR) and potential reduced number of AD cases by ameliorating the depressed state of AD diagnosed individuals<sup>84</sup>. She found that more than 10% of all AD cases were attributed to depression and that a reduction of LLD rates by 25% could lead to a reduction of more than 800,000 AD cases worldwide.

Taken together, these data indicate that treating depression may have a significant impact not only on the well-being of the elderly, but that it may also ameliorate their risk of AD-related cognitive decline<sup>85</sup>.

#### 5. Conclusion

This review has highlighted the importance of a holistic approach to tackling depression in the elderly. The interactions between cognitive, physical, psychological, and social faculties in old age are highly complex and require further research to explore their complexities. However, acknowledging the interactions explored within the current evidence base can enable UK policies and approaches to have greater impact on tackling these issues.

Figure 1 provides a summary of the reviewed interactions between aging and depression and highlights the interactions that are found at various levels. It highlights how various aspects of ageing can induce a vicious cycle for an individual and may affect faculties across many domains.



**Figure 1**| **Interactions between old age and depression.** Although depression rarely appears to be a causal factor in agerelated disability, it has been well documented to trigger and/or aggravate age-related mental and physical decline. Therefore, depression is a central factor in the development of age related disorders and should be considered as a pivotal engagement point for shaping policy around elderly care.

When directing policy, it is important to understand that there is no typical type of older person: many continue to live a socially active and engaging life, and the objective extent of their social activity is not uniformly related to their experiences of loneliness. Thus, in the full consideration of the mental health challenges faced by an ageing population, it is important to take a nuanced approach and consider the multitude of factors relevant at older age, both for physical and mental health. Despite the potential for higher initial costs, a tailored approach will result in a higher overall efficacy, thereby keeping people healthy and productive for longer. This sustainability is ultimately what is needed in a future where the amount of people over 65 estimated to be larger than people under 16<sup>86</sup>.

This review proposes community-based schemes such as the befriending and gatekeeper examples explored in other areas in order to improve high quality social and community interactions to reduce risk of depression, as well as providing an environment where the elderly as less isolated and can be identified if at risk of both mental or physical conditions. This increased social control and identification

of risk factors amongst these groups is important in tackling the under-diagnosis and under-treatment of mental illness within these groups, improving reach of cognitive behavioural therapies and lifestyle changes. Organizing community based activities is also crucial in this plan of action, as it gives people an extra incentive to socialize within their community. Physical proximity is not to be underestimated in light of age-related immobility, therefore we propose that projects are funded locally and are budgeted by local councils.

We further propose that the government should be stimulated to arrange active screening programmes comparable to the DCPC in cancer treatment. These preventive measures will allow society to tackle problems early on and estimated to reduce healthcare cost in the long-term. Integrated healthcare is pivotal in this matter as screening programmes for physical illness often neglect screening for commonly found mental comorbidities which have been well-documented in scientific literature.

Finally, our research implies that in order for the UK to be the world-leading authority in dementia care - as was claimed early last year in the Prime Minister's 'Challenge on Dementia 2020'87 - it is essential that we tackle depression in the elderly, drawing on some of the policies suggested herein.

### 6. References

- 1 World Health Organization. *Mental health and older adults fact sheet,* <a href="http://www.who.int/mediacentre/factsheets/fs381/en/">http://www.who.int/mediacentre/factsheets/fs381/en/</a> (2016).
- Prince, M. J. et al. The burden of disease in older people and implications for health policy and practice. *The Lancet* **385**, 549-562, doi:10.1016/S0140-6736(14)61347-7 (2015).
- 3 Chisholm, D. *et al.* Scaling-up treatment of depression and anxiety: a global return on investment analysis. *The Lancet* **3**, 415-424, doi:doi:10.1016/S2215-0366(16)30024-4 (2016).
- 4 Trust, N. NHS spending on the top three disease categories in England., <a href="http://www.nuffieldtrust.org.uk/data-and-charts/nhs-spending-top-three-disease-categories-england">http://www.nuffieldtrust.org.uk/data-and-charts/nhs-spending-top-three-disease-categories-england</a> (2014).
- Polyakova, M. *et al.* Prevalence of minor depression in elderly persons with and without mild cognitive impairment: a systematic review. *J Affect Disord* **152-154**, 28-38, doi:10.1016/j.jad.2013.09.016 (2014).
- Lebowitz, B. D. *et al.* Diagnosis and Treatment of Depression in Late Life: Consensus Statement Update. *JAMA* **278**, 1186-1190, doi:10.1001/jama.1997.03550140078045 (1997).
- Fiske, A., Wetherell, J. L. & Gatz, M. Depression in older adults. *Annual Review of Clinical Psychology* **5**, 363-389 (2009).
- 8 Chew-Graham, C., Baldwin, R. & Burns, A. (Cambridge University Press, Cambridge, 2008).
- 9 Krishnan, K. R. R. Biological risk factors in late life depression. *Biological Psychiatry* **52**, 185-192, doi:10.1016/S0006-3223(02)01349-5 (2002).
- 10 Krishnan, K. R. R. *et al.* Comorbidity of depression with other medical diseases in the elderly. *Biological Psychiatry* **52**, 559-588, doi:10.1016/S0006-3223(02)01472-5 (2002).
- 11 Blazer, D. G. in *J. Gerontol. Ser. A-Biol. Sci. Med. Sci.* Vol. 58 249-265 (2003).
- 12 Katon, W. J. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biological psychiatry* **54**, 216-226 (2003).
- 13 QI, W. To Investigate IF MOAP-1 Deficiency decreases susceptibility to Brain damage after Cerebral Ischemia, (2013).
- Aylaz, R., Akturk, U., Erci, B., Ozturk, H. & Aslan, H. Relationship between depression and loneliness in elderly and examination of influential factors. *Arch Gerontol Geriatr* **55**, 548-554, doi:10.1016/j.archger.2012.03.006 (2012).
- 15 Capurso, A. *et al.* Depression in old age: a diagnostic and therapeutic challenge. *Recenti Progressi in Medicina* **98**, 43-52 (2007).
- Singh, A. & Misra, N. Loneliness, depression, and sociability in old age. *Indian Journal of Psychiatry* **18**, 51-55 (2009).
- Green, B. H. *et al.* Risk factors for depression in elderly people: A prospective study. *Acta Psychiatrica Scandinavica* **86**, 213-217 (1992).
- Grenade, L. & Boldy, D. Social isolation and loneliness among older people: issues and future challenges in community and residential settings. *Australian Health Review* **32**, 468-478 (2008).
- 19 Cornwell, E. Y. & Waite, L. J. Social disconnectedness, perceived isolation, and health among older adults. *Journal of health and social behavior* **50**, 31-48 (2009).
- 20 AgeUK. Evidence Review: Loneliness in Later Life, London, <a href="http://www.ageuk.org.uk/Documents/EN-GB/For-professionals/Research/Age%20UK%20Evidence%20Review%20on%20Loneliness%20July%202014.pdf?dtrk=true">http://www.ageuk.org.uk/Documents/EN-GB/For-professionals/Research/Age%20UK%20Evidence%20Review%20on%20Loneliness%20July%202014.pdf?dtrk=true</a> (2014).
- 21 Beaumont. (ed Office for National Statistics) (London, 2013).

- Savikko, N., Routasalo, P., Tilvis, R. S., Strandberg, T. E. & Pitkälä, K. Predictors and subjective causes of loneliness in an aged population. *Archives of gerontology and geriatrics* **41**, 223-233 (2005).
- Bajekal, M. & Prior, G. Care homes and their residents. (Stationery Office, 2002).
- Fiske, A., Wetherell, J. L. & Gatz, M. Depression in older adults. *Annual review of clinical psychology* **5**, 363 (2009).
- Cole, M. G. & Dendukuri, N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *American Journal of Psychiatry* **160**, 1147-1156 (2003).
- van't Veer-Tazelaar, P. J. N. *et al.* Depression in old age (75+), the PIKO study. *Journal of affective disorders* **106**, 295-299 (2008).
- Gourion, D. [Events of life and links with severe depression at different ages]. *L'Encephale* **35**, S250-256 (2009).
- House, J. S. Social isolation kills, but how and why? *Psychosomatic medicine* **63**, 273-274 (2001).
- Hansson, R. O. & Carpenter, B. N. *Relationships in old age: Coping with the challenge of transition*. (Guilford Press, 1994).
- Green, B. *et al.* Risk factors for depression in elderly people: a prospective study. *Acta Psychiatrica Scandinavica* **86**, 213-217 (1992).
- Teo, A. R., Choi, H. & Valenstein, M. Social relationships and depression: ten-year follow-up from a nationally representative study. *PloS one* **8**, e62396 (2013).
- Port, C. L. *et al.* Resident contact with family and friends following nursing home admission. *The Gerontologist* **41**, 589-596 (2001).
- Jongenelis, K. *et al.* Prevalence and risk indicators of depression in elderly nursing home patients: the AGED study. *Journal of affective disorders* **83**, 135-142 (2004).
- Marquis, R. Quality in aged care: a question of relational ethics? *Australasian Journal on Ageing* **21**, 25-29 (2002).
- Alexopoulos, G. S., Meyers, B. S., Young, R. C., Mattis, S. & Kakuma, T. The course of geriatric depression with" reversible dementia": a controlled study. *American Journal of Psychiatry* **150**, 1693-1693 (1993).
- Areán, P. A. *et al.* Treatment of depression in low-income older adults. *Psychology and Aging* **20**, 601 (2005).
- Cuijpers, P. *et al.* Interpersonal psychotherapy for depression: a meta-analysis. *American Journal of Psychiatry* (2011).
- Masi, C. M., Chen, H.-Y., Hawkley, L. C. & Cacioppo, J. T. A meta-analysis of interventions to reduce loneliness. *Personality and Social Psychology Review* (2010).
- De Leo, D., Buono, M. D. & Dwyer, J. Suicide among the elderly: the long-term impact of a telephone support and assessment intervention in northern Italy. *The British Journal of Psychiatry* **181**, 226-229 (2002).
- 40 Findlay, R. A. Interventions to reduce social isolation amongst older people: where is the evidence? *Ageing and Society* **23**, 647-658 (2003).
- Valderas, J. M., Starfield, B., Sibbald, B., Salisbury, C. & Roland, M. Defining comorbidity: implications for understanding health and health services. *The Annals of Family Medicine* **7**, 357-363 (2009).
- Lebowitz, B. D. *et al.* Diagnosis and treatment of depression in late life: consensus statement update. *Jama* **278**, 1186-1190 (1997).
- 43 Unützer, J. Late-life depression. *New England Journal of Medicine* **357**, 2269-2276 (2007).
- DiMatteo, M. R., Lepper, H. S. & Croghan, T. W. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of internal medicine* **160**, 2101-2107 (2000).
- 45 MacHale, S. Managing depression in physical illness. *Advances in psychiatric treatment* **8**, 297-305 (2002).

- 46 Blazer, D. G. Depression in late life: review and commentary. *Focus* **7**, 118-136 (2009).
- Evans, D. L. *et al.* Mood disorders in the medically ill: scientific review and recommendations. *Biological psychiatry* **58**, 175-189 (2005).
- 48 Carney, R. M. & Freedland, K. E. Depression, mortality, and medical morbidity in patients with coronary heart disease. *Biological psychiatry* **54**, 241-247 (2003).
- Krishnan, K. R. R. et al. Comorbidity of depression with other medical diseases in the elderly. Biological psychiatry **52**, 559-588 (2002).
- Djernes, J. K. Prevalence and predictors of depression in populations of elderly: a review. *Acta Psychiatrica Scandinavica* **113**, 372-387 (2006).
- Vink, D., Aartsen, M. J. & Schoevers, R. A. Risk factors for anxiety and depression in the elderly: a review. *Journal of affective disorders* **106**, 29-44 (2008).
- Rovner, B. W. & Casten, R. J. Preventing late-life depression in age-related macular degeneration. *The American journal of geriatric psychiatry* **16**, 454-459 (2008).
- Dhondt, T. D., Beekman, A. T., Deeg, D. J. & van Tilburg, W. latrogenic depression in the elderly. Social psychiatry and psychiatric epidemiology **37**, 393-398 (2002).
- 54 CRUK. ACHIEVING WORLD-CLASS CANCER OUTCOMES; A STRATEGY FOR ENGLAND 2015-2020. Report of the independent cancer taskforce (2015).
- Barnett, K. *et al.* Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet* **380**, 37-43 (2012).
- Naylor, C. et al. Long-term conditions and mental health: the cost of co-morbidities. (The King's Fund, 2012).
- 57 Chris Naylor, P. D., Shilpa Ross, Matthew Honeyman, James Thompson, Helen Gilburt. Bringing together physical and mental health: A new frontier for integrated care. *The King's Fund Report* (2016).
- 58 Wilkinson, P. (2016).
- statistics, O. f. n. h. *Deaths registered in England and Wales (Series DR): 2015*, <a href="https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregisteredinenglandandwalesseriesdr/2015">https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregisteredinenglandandwalesseriesdr/2015</a>> (2016).
- Prince, M. et al. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimer's & Dementia 9, 63-75. e62 (2013).
- Winblad, B. *et al.* Defeating Alzheimer's disease and other dementias: a priority for European science and society. *The Lancet Neurology* **15**, 455-532 (2016).
- Ferri, C. P. *et al.* Global prevalence of dementia: a Delphi consensus study. *The lancet* **366**, 2112-2117 (2006).
- Jellinger, K. A. & Attems, J. Prevalence of dementia disorders in the oldest-old: an autopsy study. *Acta neuropathologica* **119**, 421-433 (2010).
- 64 Graves, A. *et al.* Prevalence of dementia and its subtypes in the Japanese American population of King County, Washington state The Kame Project. *American journal of epidemiology* **144**, 760-771 (1996).
- 65 Small, G. & Jarvik, L. The dementia syndrome. *The Lancet* **320**, 1443-1446 (1982).
- 66 Wells, C. E. Pseudodementia. *Am J Psychiatry* **136**, 895-900 (1979).
- Korczyn, A. D. & Halperin, I. Depression and dementia. *Journal of the Neurological Sciences* **283**, 139-142, doi:http://dx.doi.org/10.1016/j.jns.2009.02.346 (2009).
- Reitz, C., Brayne, C. & Mayeux, R. Epidemiology of Alzheimer disease. *Nat Rev Neurol* **7**, 137-152, doi:http://www.nature.com/nrneurol/journal/v7/n3/suppinfo/nrneurol.2011.2 S1.html (2011).
- McKhann, G. M. *et al.* The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia* **7**, 263-269, doi:http://dx.doi.org/10.1016/j.jalz.2011.03.005 (2011).

- Domenici, E. *et al.* Plasma protein biomarkers for depression and schizophrenia by multi analyte profiling of case-control collections. *PLoS one* **5**, e9166 (2010).
- Lyketsos, C. G. *et al.* Major and minor depression in Alzheimer's disease: prevalence and impact. *Journal of Neuropsychiatry and Clinical Neurosciences* **9**, 556-561 (1997).
- Migliorelli, R., Teson, A., Sabe, L. & Petracchi, M. Prevalence and correlates of dysthymia and major depression among patients with Alzheimer's disease. *The American journal of psychiatry* **152**, 37 (1995).
- Wragg, R. E. & Jeste, D. V. Overview of depression and psychosis in Alzheimer's disease. *Am J Psychiatry* **146**, 577-587 (1989).
- Mölsä, P. K., Marttila, R. & Rinne, U. Survival and cause of death in Alzheimer's disease and multi-infarct dementia. *Acta Neurologica Scandinavica* **74**, 103-107 (1986).
- Breitbart, W. *et al.* Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer. *Jama* **284**, 2907-2911 (2000).
- Reeve, J., Lloyd-Williams, M. & Dowrick, C. Depression in terminal illness: the need for primary care-specific research. *Family practice* **24**, 263-268 (2007).
- Jorm, A. F. History of depression as a risk factor for dementia: an updated review. *Australian and New Zealand Journal of Psychiatry* **35**, 776-781 (2001).
- Panza, F. *et al.* Late-Life Depression, Mild Cognitive Impairment, and Dementia: Possible Continuum? *The American Journal of Geriatric Psychiatry* **18**, 98-116, doi:http://dx.doi.org/10.1097/JGP.0b013e3181b0fa13 (2010).
- 79 Steffens, D. C. *et al.* A twin study of late-onset depression and apolipoprotein E ε4 as risk factors for alzheimer's disease. *Biological Psychiatry* **41**, 851-856, doi:http://dx.doi.org/10.1016/S0006-3223(96)00247-8 (1997).
- Van Duijn, C. *et al.* Interaction between genetic and environmental risk factors for Alzheimer's disease: A reanalysis of case-control studies. *Genetic Epidemiology* **11**, 539-551 (1994).
- Ownby, R. L., Crocco, E., Acevedo, A., John, V. & Loewenstein, D. Depression and Risk for Alzheimer Disease: Systematic Review, Meta-analysis, and Metaregression Analysis. *Archives of general psychiatry* **63**, 530-538, doi:10.1001/archpsyc.63.5.530 (2006).
- Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A. & Reynolds, C. F. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *The British Journal of Psychiatry* **202**, 329-335, doi:10.1192/bjp.bp.112.118307 (2013).
- Kral, V. A. & Emery, O. B. Long-term follow-up of depressive pseudodementia of the aged. *The Canadian Journal of Psychiatry/La Revue canadienne de psychiatrie* (1989).
- Barnes, D. E. & Yaffe, K. The Projected Impact of Risk Factor Reduction on Alzheimer's Disease Prevalence. *Lancet neurology* **10**, 819-828, doi:10.1016/S1474-4422(11)70072-2 (2011).
- Potter, G. G. & Steffens, D. C. Contribution of depression to cognitive impairment and dementia in older adults. *The neurologist* **13**, 105-117 (2007).
- Rutherford, T. & Socio, A. Population ageing: statistics. *House of Commons library (Standard not. Retrieved Jan 2, 2013, from: www. parliament. uk/topics/PopulationArchive* (2012).
- 87 Health, D. o. (Department of Health London, UK, 2015).