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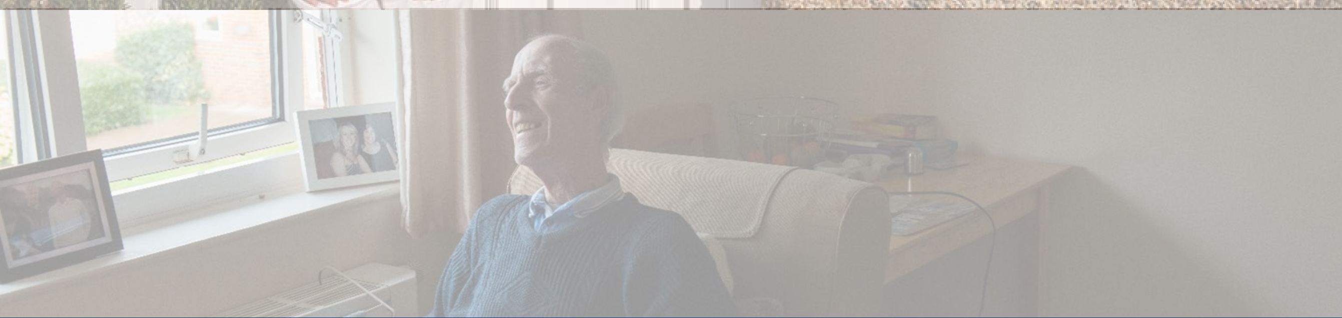
Scoping for a return-on-investment tool for dementia



Final Report

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Introduction

Dementia is an increasingly common condition in old age in England, as in other countries. The dementia prevalence rate increases with age, and so population ageing is adding to the number of people living with the condition and, in countries like England, also increasing the number of people who have unpaid caring roles. The number of people living with dementia is expected to increase considerably over the coming decades, even though there have been some changes which could reduce mid-life risks (and so slightly reduce incidence rates) (Matthews et al., 2016) and even though there is a lot of endeavour currently to find disease-modifying treatments (Alzheimer's Research UK, 2021).

Not surprisingly, supporting people who live with dementia has substantial resource impacts in both the health and social care sectors, and even larger impacts in terms of the costs of unpaid care (Wittenberg et al., 2019).

Evidence on earlier life risk factors for dementia has accumulated over recent years and is summarised well in the two versions of the Lancet Commission on Dementia (Livingston et al., 2017; 2020). Those authors estimated that 40% of dementia cases could be prevented or delayed by targeting twelve modifiable risk factors (with their weighted population attributable fractions in parentheses): hearing loss (8.2%), less education (7.1%), smoking (5.2%), depression (3.9%), social isolation (3.5%), traumatic brain injury (3.1%), air pollution (2.3%), hypertension (1.9%), physical inactivity (1.6%), diabetes (1.1%), excessive alcohol (0.8%) and obesity (0.7%). Many of these risk factors are obviously interconnected.

Some previous research has shown that mid-life interventions for hypertension, smoking cessation and hearing loss are cost-effective even when looking at their effects on dementia alone, and after factoring in that the (dementia-specific) 'pay-offs' will not be seen for many years (Mukadam et al., 2020). The same study found that mid-life diabetes prevention was effective but not cost-effective in relation to dementia prevention *alone*. Obviously, the economic case for each of these interventions is much stronger when all health benefits (both short- and long-term) are taken into account.

Awareness of dementia risk-reduction is low. According to the Dementia Attitudes Monitor (Alzheimer's Research UK, 2018), just a third of people (34%) are aware that there is anything that can be done to prevent dementia. Appetite is high: 73% of people would like to understand more about their own personal risk of developing dementia and 40% of people say they would adopt a healthier lifestyle to reduce their dementia risk. Consequently, there is opportunity to reduce the prevalence of dementia if we can support people to reduce their risk of developing dementia by making healthy choices across their life. This would require action, not just on the part of individuals but also at population/community level, since many of the risk factors are shaped by the social, economic and other contexts within which people work, study, socialise and relax.

One possible way to encourage such investment in risk-reduction would be to develop a return-on-investment (ROI) tool that would be available for commissioners and others to support informed decisions on where best to target their efforts and resources, and thereby help and encourage risk-reducing actions and behaviours. However, there has to date been insufficient evidence to develop such a tool. For background information, two of this report's authors were commissioned by Public Health England a few years ago to explore the feasibility of developing such a tool (Wittenberg et al., 2017). At that time, it was agreed by everyone that there were too many challenges, partly linked to insufficient evidence, and particularly the difficulty in identifying sufficiently precise quantitative parameters to support ROI calculations.

The research question posed to OPFPRU was whether recent research now provides sufficient evidence on the economic return to risk-reduction activities to support development of an ROI tool. The initial task was to review the available evidence relevant to England about which interventions targeting modifiable risk factors in dementia appear to be effective and cost-effective in preventing dementia. The purpose would be to analyse the strength of the evidence to determine whether it would subsequently be feasible to build an ROI tool to support local commissioning decisions around investing in reducing the risk of dementia.

The potential benefits gained through exploring whether this is feasible extend beyond dementia impacts to other long-term conditions. If it was feasible to produce a tool which encouraged further investment in dementia risk-reduction, there would be health benefits and cost savings (to health and social care sectors, and to individuals themselves) linked to a number of other conditions which would also be potentially preventable through many of the same modifiable risk factors.

This report presents findings from that review, focusing initially on three of the twelve known modifiable risk factors for dementia identified by the Lancet Commission.

Methods

As agreed with DHSC, our initial focus has been on three of the twelve known modifiable risk factors: low education, physical inactivity and hearing loss. We selected these three risk factors for initial scoping as, according to the evidence assembled by the Lancet Commission, they generally pertain to different points in the life-course: ‘early life’, ‘mid-life’ and ‘later life’, respectively. We looked at low education even though the original request from DHSC suggested to exclude it; the reasons were that it is still amenable to some degree of change (e.g., through lifelong learning), that it is closely linked with many other risk factors and because we had expertise in this area within OPFPRU, which made the review process faster. The Lancet Commission also suggest a 7.1% reduction in dementia prevalence if this ‘low education’ risk factor is eliminated (after accounting for associations with other risks). Eliminating ‘physical inactivity’ would reduce dementia risk by close to 2% (equivalent to more than 4000 new cases per year; Matthews et al., 2016), and has a strong socioeconomic gradient; we also have expertise in this area within OPFPRU (Katzmarzyk et al., 2022). We also chose to focus on it because it is one of the more challenging risk factors to specify and measure precisely. Hearing loss is the risk factor with the largest weighted population attributable fraction according to the Lancet Commission’s calculations (8.2%) and was selected partly for that reason and partly because it has had a rapidly accumulating evidence base since the earlier Wittenberg et al. work in 2017.

Specifically, our research questions were:

1. What, in summary, is the state of evidence on these three risk factors for dementia, and what are the underlying mechanisms of action?

2. What is the state of evidence on interventions to address these risk factors?

We employed the following methods to address these questions:

1. We rapidly scoped the available evidence that confirms these risk factors (affecting incidence of dementia) and the underlying mechanisms of action.

2. We rapidly scoped the literature on interventions to address these risk factors, either targeted on individuals or on communities/populations (although the distinction is sometimes difficult). The aim was to identify interventions that are effective in changing behaviour. (A recent systematic review helpfully identified relevant community/population intervention designs: changing the physical/food environment, mass media programmes, reducing financial barriers or increasing resources, whole community approaches, and legislative changes (Walsh et al., 2022).)

Results

We report our findings for each of the three risk factors in turn. For each, we describe the background, mode of action, possible interventions and some implications of our findings.

Low Education

Background

Epidemiological and longitudinal research, as well as systematic reviews, provide strong evidence for the role of cognitive activity in dementia prevention: a number of studies have demonstrated that participation in cognitively stimulating activities across the lifespan is associated with reduced incident dementia in later life (Bosma et al. 2002, Crowe et al. 2003, Scarmeas et al., 2001; Wilson et al., 2013). Large-scale epidemiological studies have also indicated that high levels of education and occupational complexity, as well as cognitively stimulating leisure activities, are protective against dementia (Valenzuela and Sachdev 2006). Education level, in particular, is a widely acknowledged protective factor for dementia and cognitive decline. While evidence for the protective effects of education has been mixed (Alley, Suthers and Crimmins, 2007; van Dijk et al., 2008), a recent systematic review on the life-course determinants of ‘cognitive reserve’ (CR) concluded that the evidence for the protective effects of education on cognition in the face of a number of brain burden measures was consistent (Chapko et al., 2017). (CR is commonly defined as the hypothesised capacity of the brain to cope with brain damage in order to minimise the clinical symptoms of that damage (Stern, 2009).) More recent research (Kremen, 2019) suggests that education is most important in early life (up to age 20 years) and that apparent later life effects may be due to people with higher cognitive functioning seeking out further education and cognitively stimulating activities.

Mode of Action

Cognitive reserve is the concept of protection against the clinical manifestation of acquired and progressive disease processes in the brain. There is a growing body of literature that points to an important role played by CR in moderating the expression of progressive and often multiple disease processes in dementia (Chapko et al., 2017). The protective effects of an individual’s degree of engagement in cognitive activities throughout the lifespan can be characterised as CR, and measures of cognitive enrichment, such as education level, level of occupational complexity and participation in cognitively stimulating leisure activities, are frequently used as proxy measures of CR (Valenzuela and Sachdev, 2006). Epidemiological research suggests that CR not only protects against dementia (primary prevention), but also helps to maximise performance in prodromal populations and in those with established dementia (secondary and tertiary prevention) (see Stern (2009, 2012) for literature overviews).

The concept of cognitive reserve was proposed following the observation that the severity of neuropathological symptoms did not always correlate with brain damage severity (Solé-Padullés et al., 2009). For instance, post-mortem examinations have found high rates of Alzheimer's disease neurodegeneration in individuals who did not display neurocognitive clinical symptoms of the disease (Katzman et al., 1988). The theory of CR posits that this may be due to the buffering effect of protective factors, such as education and lifestyle.

The mechanisms underlying the association between cognitive activity and effects on cognition are not clearly understood (Marioni et al., 2012, Wilson et al., 2013). Two proposed mechanisms to explain how cognitive activity protects brain function from neuropathology include disease modification and compensation. Disease modification suggests a decreased risk for developing neuropathology (primary prevention), or a slower rate of the expression of pathology (secondary prevention), while compensation indicates a better ability to cope with underlying brain damage (secondary and tertiary prevention) (Marioni et al., 2012). Addressing the mechanisms of cognitive change across the lifespan, Craik and Bialystok (2006) propose a framework whereby crystallised and fluid abilities are viewed as two interactive systems. Representations of the world (crystallised schema that evolve through education/cognitive enrichment) are selected based on needs and desires, and in turn, these representations demonstrate control (fluid ability) through their influence on further selection of schema-relevant information across the lifespan. Under this framework, CR proxy measures such as education may reflect a representational system, while fluid abilities may reflect a cognitive control system. This highlights the potential role of higher-order cognitive control processes in CR (e.g., executive function) (Tucker and Stern, 2011). From this perspective, both cognitive enrichment (education across the lifespan) and cognitive control (fluid cognitive abilities such as executive function and processing speed) can be viewed as two arms of CR that have a reciprocal relationship.

Findings from the Framingham Heart Study suggest another potential mechanism of protection (Satizabal et al., 2016). Over three decades, these authors observed trends toward higher educational level and a parallel trend toward a lower prevalence of most vascular risk factors for dementia (excluding obesity and diabetes, which both tend to increase over time). It may be the case that people with more education look after their vascular health better than people with less education, but further research is needed.

Interventions

Education

A systematic review and meta-analysis by Meng and D'Arcy (2012) – covering 69 studies in meta-analysis and 66 studies in narrative synthesis – supports the association between higher levels of education and prevalence and incidence of dementia. Prevalence and incidence studies with pooled odds ratios (ORs) of 2.61 (indicating those with low education were 1.61 times more likely to have dementia than those with high education) and 1.88 (indicating those with low education were 0.88 times more likely to develop dementia than those with high levels of education) respectively, showed low education increased the risk of dementia. Heterogeneity and sensitivity tests confirmed the evidence. Generally, study characteristics had no effect on conclusions. Qualitative analyses also showed the protective effects of higher education levels on developing dementia and with clinical disease onset hastening a decline in cognition and function, and greater brain pathology. In this review, education was generally limited to formal education in early life (primary and secondary education) so conclusions cannot be drawn in relation to the protective effects of education into adulthood.

A meta-analysis of prospective cohort studies evaluated the dose-response relationship between education and dementia: dementia risk was reduced by 7% per year increase in education (Xu et al., 2016). In this review, years of education ranged from 0 to greater than or equal to 17 years, so again it is difficult to draw conclusions in relation to later life education. (However, 17 years does suggest education in early adulthood at least.) Similarly, a more recent systematic review and meta-analysis investigated the dose-response relationship between education and dementia (Maccora et al., 2020): each year of education reduced risk by 8% for Alzheimer's disease (AD) and 7% for any dementia. Furthermore, results indicated an increased risk for low education of 45% for any dementia and 85% for AD, although definitions of low education were heterogeneous, ranging from 0 to 12 years. The authors concluded that, while evidence of an association between low education and dementia incidence is robust, inconsistency in the definition, measurement and operationalisation of education hinders translation of this evidence into practical policy recommendations to reduce dementia risk.

Cognitive interventions

A systematic review of randomised controlled trials (RCTs) and clinical studies (Reijnders et al. 2013) found that cognitive training can be effective in improving various aspects of objective cognitive functioning: memory performance, executive functioning, processing speed, attention, fluid intelligence and subjective cognitive performance. Whether the effects of cognitive interventions generalise to improvement in everyday life activities is still unresolved and needs to be addressed more explicitly in future research, although that is of less relevance when considering the impact on later development of dementia. Comparing different intervention studies is difficult because of the variety of different interventions that have been evaluated, as well as the variety of outcome measures employed in those studies.

Another systematic review of RCTs, non-randomised controlled trials and uncontrolled clinical trials (that included effect size analysis) aimed to evaluate the effect of cognitive training in individuals with mild cognitive impairment (MCI) considered to be at risk of developing dementia (Gates et al., 2011). Cognitive training interventions included both cognitive exercises and memory strategies. Results of effect size analysis on ten studies (five RCTs) showed moderate effects on memory outcomes. Cognitive exercises (relative effect sizes ranged from 0.10-1.21) may lead to greater benefits than memory strategies (relative effect sizes ranged from 0.88—1.18) on memory.

Appendix 1 provides further details on these interventions. Due to the heterogeneity of interventions included in these reviews, meta-analysis was not possible. Consequently, it is difficult to quantitatively summarise with confidence the effect of such interventions. In addition, it is not possible to directly infer an effect on dementia incidence or prevalence based on these interventions.

Strengths and weaknesses of the evidence

A strength of the evidence is that there are consistent reports from systematic reviews of the protective effects of education in relation to dementia. However, there is inconsistency across studies with regard to what constitutes low education, with definitions ranging from 0 to 12 years, depending on the study. From the perspective of dementia risk-reduction, variations in definition and measurement of what constitutes 'low education' would make it difficult to use this evidence to generate a ROI tool.

Besides inconsistency in the measurement of education, a further limitation of the evidence is that it stems from analyses of observational data. This is because experimental methods (RCTs) have usually been considered inappropriate, impossible or inadequate approaches to address this type of epidemiological research question.

A final limitation is that the studies included in the reviews that we examined did not clearly assess the effects of education beyond early adulthood. One of the reviews grouped education beyond 17 years as '17+ years', making it impossible to look at effects of continued education into later life.

Policy implications

There is consistent evidence from systematic reviews for the protective effects of education (at least up to and including early adulthood) with regards to dementia risk. This supports recent findings (Kremen et al., 2019) suggesting that education is most important in early life (up to age 20 years), and that apparent later life effects may be due (in part or in full) to people with higher cognitive functioning seeking out further education and cognitively stimulating activities. However, because the reviews summarised in this report did not assess the effects of education beyond early adulthood, they are unable to further inform this finding.

Primary and secondary education are mandatory in the UK and so any 'intervention' in this area would need to focus on uptake (i.e., remove any barriers to education) and adherence (i.e., reduce school absences) and quality, and also on post-compulsory education. Reducing dementia risk for the greatest number of people would imply policy that addressed inequity in relation to school attendance and drop-out, quality of education in schools and access to higher education.

Although the evidence is not as clear regarding the benefits of continuing formal education into adulthood, reducing barriers to accessing educational opportunities across the lifespan may be effective in encouraging people to stay cognitively active into and throughout adulthood. Such barriers may include lack of availability of appropriate, attractive courses, issues with accessibility (e.g., courses offered only in specific institutions or at times that are inconvenient) and cost to participants. Another potential barrier is a lack of motivation to continue with lifelong learning: research suggests that attitudes to lifelong learning usually develop early in school careers, suggesting that investment in early life education translates to better outcomes throughout the life-course (OECD 2021).

Physical inactivity

Background

The benefits of physical activity are well-documented. Physical activity is defined as 'any bodily movement produced by skeletal muscles that results in energy expenditure' (Caspersen et al., 1985). Exercise on the other hand is "a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness" (Caspersen et al., 1985). Physical activity is reported to have strong associations with reduced risk of cognitive decline and dementia (Aarsland et al., 2010; Blondell et al., 2014; Iso-Markku et al., 2022). Randomised trials of exercise and physical activity interventions are less conclusive (Hogervorst, 2012; Brasure et al., 2018), the latter concluding that evidence was "insufficient to draw conclusions about the effectiveness of aerobic training, resistance training, or tai chi for improving cognition … evidence regarding effects on dementia prevention was insufficient for all physical activity interventions". The Lancet Commission's analyses of dementia prevention identified physical inactivity as a risk factor in later life (from age 65 onwards), although recommended action from at least mid-adulthood (Livingston et al., 2020). Recommendations are that adults with normal cognition should aim to reduce their risk of cognitive decline through exercise (Blondell et al., 2014; World Health Organization, 2019; Alty et al., 2020).

For adults aged 65 and over, the World Health Organization (WHO) recommends physical activity of 150 minutes of moderate aerobic activity per week (World Health Organization, 2019). Uptake remains below the recommendation for the majority of the population (Boulton et al., 2020). Keeping active becomes more challenging as people age, and the effects of physical activity highly depend on adherence and sustained promotion to increase uptake (Rivera-Torres et al., 2019). There are multiple levels of influences that motivate older adults to be active and/or participate in physical activities. These could be intrapersonal/individual (e.g., socio-demographic characteristics, psychological characteristics, cultural expectations and individual preferences), interpersonal/relationships (e.g., support, social benefits), environmental (e.g., access to facilities, community features, transport services, urban safety) and organisational (e.g., engagement levels, lack of policy regulations) (Bethancourt et al., 2014; Boulton et al., 2017).

Interventions should focus on mid-life implementation as this is the period when neurodegeneration could develop (Livingston et al., 2020). The 2020 Lancet Commission recommended sustaining moderate to vigorous physical activity in mid-life (45-65 years) and possibly later life (aged 65 and over) (Livingston et al., 2020). As physical activity tends to decline with age, interventions should focus on the promotion of physical activity and identify behaviour change problems and techniques on how to resolve them. Exergaming as an approach to undertaking physical activity has increased in popularity over recent years. Exergames are active video games which combine gameplay with physical exercise and may also incorporate types of virtual reality simulations (Stanmore et al., 2019). Stanmore et al (2017) reviewed exergames which focus on both physical exercises and cognitively demanding tasks with cognitive outcomes and report their meta-analyses found exergames significantly improved global cognition. More research into exergaming is clearly required before we can conclude anything about effectiveness in prevention of dementia.

Mode of action

Regular physical activity contributes to healthier vascular health. It improves gait speed, endurance, functional mobility, lower extremity strength, falls and balance. It also leads to improvement in carrying out IADLs such as light housework, preparing meals or taking medication, and basic ADLs such as bathing, eating and dressing (Alty et al., 2020).

There is also considerable evidence that physical activity has social benefits and positive psychological impacts (Stock et al., 2012). Exercise acts as a mechanism to improving psychological factors, such as positive attitudes to ageing, positive self-perceptions, better mood, social engagement and mental stimulation, which then leads to larger improvement in cognitive functioning (Stock et al., 2012). This consequently impacts cognitive performance (Stock et al., 2012). In a Cochrane review *focusing on people living with dementia* (Forbes et al., 2008), structured physical activity was found to have positive influence on cognition and ability to undertake ADLs. Aerobic exercise as an intervention also shows promising benefits. It plays a key role in the beneficial effect of physical activity (World Health Organization, 2019). With sufficient intensity, it can lead to improved cognitive performance compared with other exercises (Hogervorst, 2012; Stock et al., 2012), but it would not be sufficient on its own. If combined with resistance and strength exercise, it can lead to improvement in cognition levels (Hogervorst, 2012; Stock et al., 2012).

Differences in uptake of physical activities in older people are exacerbated by health inequalities (Ige-Elegbede et al., 2019; Livingston et al., 2020). This includes non-modifiable risk factors, such as age, sex, ethnicity and education level (Blondell et al., 2014; Ige-Elegbede et al., 2019) and socioeconomic status (Picorelli et al., 2014). Higher levels of income, education and socioeconomic status are generally associated with higher levels of physical activity (Picorelli et al., 2014). Economically disadvantaged individuals are less likely to engage with exercise interventions, particularly group activities, as they are perceived as costly. This was also the case for older adults from ethnic minorities living in less affluent areas, where barriers to participate in physical activities included inadequate physical activity facilities, unsafe walking paths and limited access to open green space (Ige-Elegbede et al., 2019).

Interventions

There have been studies of the effectiveness of physical activity in reducing the risk of cognitive decline and dementia. With regular attendance, older people can engage in higher intensity exercises in order to have the highest levels of protection (Potter et al., 2011; Alty et al., 2020). Exercise is effective in reducing falls in older adults (Rimland et al., 2016), but most older adults do not regularly participate in sufficient levels of physical activity (Boulton et al., 2020).

Physical activity should not be confused with physical exercise. Physical exercise is defined as ‘planned, structured, and repetitive’ (Caspersen et al., 1985), with an objective of improving or maintaining physical fitness (Bowes et al., 2018). Whilst older people benefit from engaging in more physical activities, participating in exercises is also effective. Its effects in delaying the onset of dementia overlap with those for cardiovascular diseases (Stock et al., 2012) and, therefore, engaging in physical exercise can maintain cognitive abilities into old age. There are also benefits from functional activity, such as climbing stairs, sitting and standing (Rimland et al., 2016), although walking as an exercise on its own is not effective at reducing falls. The Prevention of Falls Network Europe (ProFaNE) (Lamb et al., 2009) provides a helpful taxonomy of different types of exercises commonly included in falls prevention interventions (Table 1).

Table 1: ProFANE taxonomy of exercises

Type	Description	Example
Gait, balance, and functional training	*Gait training*: correction of walking technique, changes of pace, level, and direction *Balance training*: transfer of body weight from one part of the body to another *Functional training*: training stimulus and task specificity	Heel and toe raises, ball exercises, foot eye coordination, standing on unstable surface, walking in line, reactive games, knee bends, calf raises, walking
Strength/resistance	Weight training, i.e., contracting the muscles against a resistance to overload and bring about a training effect in the muscular system	Weight training with free weights, bands, or resistance equipment, functional training with added weight (i.e., weighted shopping bags), Pilates resistance exercises, cable pulleys
Flexibility	Stretching exercises practiced and progressed to restore of maintain optimal range of movement to joints	Static stretches (e.g., hamstring, calf, chest stretch)
3 D	Constant movement in a controlled, fluid, repetitive way through all 3 spatial planes or dimensions	Tai Chi, Qigong, dance
General physical activity	Any bodily movement produced by skeletal muscle contraction resulting in a substantial increase in energy expenditure	Walking, swimming, cycling
Endurance	Aimed at cardiovascular conditioning and is aerobic in nature	Treadmill walking, rowing machines, continuous marching during exercise class, jogging
Other	Other exercises not described above	

Source: (Lamb et al., 2009)

Settings should also be examined since the physiological and psychological impact of physical exercise could be different. This is primarily influenced by the features (e.g., type of exercise, intensity and duration, group interaction, etc.) and the interactions between the individual and their environment (Stock et al., 2012). For instance, a treadmill intervention set in a laboratory could lead to similar physical movements and effects to a group walking intervention set in a local park. However, the psychological effects may vary due to the different environmental settings of the interventions.

The systematic review by Brasure et al. (2018) identified 32 eligible randomised trials which compared a physical activity intervention with an inactive control, 16 of which had low to moderate risk of bias. Most trials had 6-month follow-up; some 1- or 2-year follow-up. They report that "evidence was insufficient to draw conclusions about effectiveness of aerobic training, resistance training, or tai chi for improving cognition". There was low-strength evidence that multicomponent physical activity interventions had no effect on cognitive function and that a multi-domain intervention comprising physical activity, diet and cognitive training improved several cognitive outcomes. They conclude that "evidence regarding effects on dementia prevention was insufficient for all physical activity interventions".

Strengths and weaknesses of the evidence

In terms of the strengths and weakness of the evidence, there is inconsistency in the evidence about the quantitative impact of physical activity interventions in delaying the onset of dementia. One reason is that physical activity is very difficult to measure precisely.

Second, it is unclear to what extent physical activity reduces the risk of dementia due to variation in the population examined (for example, healthy people, community-dwelling older people with or without some developing health or care needs, and so on) and the outcomes measured.

Aarsland et al. (2010) presented a case-control meta-analysis of vascular dementia or no dementia including five cohort studies with 10,108 control subjects without dementia and 374 individuals with vascular dementia. They reported an OR of 0.62 (95% CI 0.42–0.92) for being more active or exercising. This is obviously suggestive of protective effects of activity, but the retrospective case-control methodology does not allow us to draw strong conclusions. The authors also do not draw clear distinctions between exercise and physical activity, making interpretation problematic.

A meta-analysis (Blondell et al., 2014) of longitudinal observational studies found an association between higher levels of physical activity and reduced risk of both cognitive decline (RR 0.65, 95% CI 0.55-0.76) and dementia (RR 0.86, 95% CI 0.76-0.97). Individuals with higher levels of physical activity, when compared to those with lower levels, were at reduced risk. Although it is always hard to interpret data from observational studies, the authors of this review argue that a case can be made for a causal interpretation.

The review by Iso-Markku et al. (2022) of physical activity focused on cohort and case-control studies to identify if physical activity was protective of dementia, reporting inverse associations between activity levels and incidence of dementia even in studies with follow-up periods of over 20 years. They addressed dose-response relationships and found significant relationships between how much activity was done and dementia incidence. This is clearly promising evidence from a well-conducted review that physical activity is a potentially modifiable protective mid-life factor for dementia, but it remains observational rather than based on intervention studies.

The Brasure et al. (2018) review has the strength that it focuses on intervention trials of activity/exercise. However, evidence regarding effects on dementia prevention was insufficient for all interventions. As they point out, the quality of the evidence and the risk of bias of the included studies is such that they have to caution about the strength of the evidence. Many of the studies included were small, did not follow up participants for very long, and cognition was not the primary outcome in many cases. The type, frequency, intensity, and duration of the physical activity interventions varied greatly, hampering the degree to which strong conclusions could be drawn.

Although not looking at mid-life dementia prevention, it is interesting to note that a partial meta-analysis by Potter et al. (2011) of 13 RCTs concluded that physical activity interventions improve physical function in older people who already have dementia. Three of six trials that reported walking as an outcome found an improvement (timed walks, statistically significant improvement in speed 0.06 m/s, 95% CI 0.01, 0.1), as did four of the five trials reporting timed get up and go tests (TUG test, reduction in TUG with the intervention -1.39 s, 95% CI -2.59, 0.19). Evidence for an effect on quality of life was limited (QoL, at 3-months an intention to treat analysis showed an improvement of 5.9 points in intervention participants, and a decline of 16.6 points in control participants). A later meta-analysis by Lee et al. (2016) also concluded that physical activity programmes for people living with dementia were very effective in improving physical capability (1.05 (high effect size, 95% CI: 0.03 to 0.73)) and ADLs (0.73 (slightly high effect size, 95% CI: 0.23 to 1.23)), and also showed a small effect size in cognitive function (0.46 (medium effect size, 95% CI: 0.26 to 0.66)) and psychological states (0.39 (lower than the medium effect size, 95% CI: 0.01 to 0.77).

Appendix 2 details the most relevant studies.

Policy implications

The reviews of physical activity and exercise considered here tend to suggest that physical activity and exercise are potentially modifiable protective mid-life factors for dementia. Nonetheless, there is still a gap on improving the development and delivery of physical exercise interventions.

There are multiple influences on participation in physical activity and that, while much of the focus has been on behaviour change, we need to think more holistically to ensure that not only individual, but other considerations are addressed, including interpersonal factors, perceived environment, community or organisational factors, and policy levels (Boulton, 2017). Older people may have lower confidence in their ability to engage in physical activities due to their physical fitness and health status, which then affects their motivation (Bethancourt et al., 2014; Rivera-Torres et al., 2019; Bosco et al., 2022). For instance, a qualitative study (Bethancourt et al., 2014) found that older people are motivated to maintain a daily physical activity regime in order to stay for their favourite sports or for keeping up with their grandchildren. On another note, having existing morbidities and physical impairments could negatively impact the quality and level of participation on physical activities (Bosco et al., 2022). Older people with better motor control and coordination (Rivera-Torres et al., 2019) are likely to feel more confident in adhering to exercise interventions. Awareness of physical limitations is also translated into fear of falling (Bethancourt et al., 2014; Finnegan et al., 2015). This, therefore, affects older people’s self-efficacy because they may recognise their vulnerability and potentially reduced capacity to recover from a fall if they do not exercise.

Individual preferences are also a factor. Some older adults do not like engaging in physical activity because they are intimidated by group activities (Bethancourt et al., 2014). Social discomfort in participating in physical activities plays a big role in this (Kelly et al., 2016), as there is a likelihood to be self-conscious when performing group exercises in front of other people. Others prefer other types of physical activities (e.g., dance) as opposed to exercising in a gym (Bethancourt et al., 2014; Ige-Elegbede et al., 2019). There is some evidence, however, that others are keener to join group exercises because of its social benefits.

Physical activity engagement can be determined by attitude or health status for some participants, but, for the majority, it is about it being enjoyable, sociable, affordable, accessible, flexible and seasonal. Both motivated and unmotivated older adults need to have a range of appropriately labelled, appealing and accessible activities to choose from when thinking about engaging in physical activity. Policy makers and practitioners need to ensure that their offers of activity sessions are easy to access and easy to remain involved in. Reviews suggest that identifying behaviour change techniques (BCTs) can positively impact levels of physical activity (Williams and French, 2011; French et al., 2014; Ahmed et al., 2023). Goal setting (French et al., 2014), action planning (Williams and French, 2011) and implementation of motivational tools, such as self-monitoring and feedback (McGarrigle and Todd, 2020), are some of the approaches that result in positive association with physical activity. This may include community-based interventions that encourage older adults to “move more and sit less” (Swan et al., 2022) in their own homes or access to exercise programmes in community centres (Bethancourt et al., 2014).

Further research should focus on improving interventions and identifying the optimal physical activity modalities, particularly in terms of frequency, intensity and duration. More research is also needed on how best to organise the delivery of interventions, how to maximise uptake and adherence to activity or exercise programmes, and the cost-effectiveness of programmes. Consideration of how a population shift approach to increasing physical activity levels, rather than focus on higher risk subgroups, should also be considered (Rose, 2001).

Hearing Loss

Background

Dementia and hearing loss are highly prevalent neurological conditions in older adults. It is estimated that approximately 11 million people in the UK have hearing loss, 8 million of whom are aged 60 and over (Hearing Link Services, 2022). A growing body of literature suggests that the two conditions are inter-related and that hearing loss may be a risk factor for the development of dementia in older adults. A systematic review carried out in 2017 found that hearing loss is associated with a higher incidence of dementia in older adults (Thomson et al., 2017), and as already noted, the 2020 edition of the Lancet Commission found that hearing loss is the leading modifiable dementia risk factor with a weighted population attributable fraction of 8.2% (Livingston et al., 2020; Marinelli et al., 2022). There appears to be a dose-dependent relationship, with greater unassisted hearing loss associated with more severe dementia. People with mild, moderate or severe hearing loss are, respectively, nearly two, three or five imes more likely to develop dementia than those with no hearing loss (Lin et al., 2011).

Mode of action

The mechanisms underlying the association between hearing loss and dementia are unclear. Elucidating the causal pathway is challenging for several reasons: the existing research focuses on correlations; the wide variability and subjectivity in how cognition and dementia are assessed; and the limited methods of assessing hearing loss in epidemiological studies. There are a number of possible mechanisms (further outlined below) which have been proposed for the relationship between hearing loss and dementia. They are not mutually exclusive and decline in one pathway may affect other relationships (Chern and Golub, 2019). It has also been suggested that both dementia and hearing loss may share a common cause but do not interact with or cause each other (Griffiths et al., 2020). For example, there are several common risk factors for both dementia and hearing loss, mostly commonly vascular in nature (Ray et al., 2019).

Depletion of cognitive reserve

Individuals with hearing loss experience greater cognitive load, making them more susceptible to exhausting their cognitive reserve. Studies have demonstrated that individuals with hearing loss dedicate more neural resources to facilitate auditory processing at the expense of other cognitive processes, such as working memory (Griffiths et al., 2020).

Social isolation

Hearing loss makes communication difficult for older adults, leading them to withdraw from social environments and potentially increasing social isolation. Several longitudinal epidemiological and neuropathological studies have demonstrated that poor social networks and isolation increase the risk of incident dementia after adjusting for potentially confounding variables (Livingston et al., 2020; Rafnesson et al., 2020; Kuiper et al., 2015). Auditory deprivation creates an impoverished environment, particularly with the diminishment of speech and language input, that negatively affects brain structure and function.

Changes in brain structure and function

Hearing impairment is linked to accelerated brain atrophy of whole brain and regional volume reduction of the right temporal lobe. Chronic hearing loss leads to reduced activation of the central auditory pathway, dysfunction of the auditory-limbic pathway and deafferentation-induced atrophy of frontal lobe (Rutherford et al., 2018). Hearing loss has also been linked to atrophy of the hippocampus (Armstrong et al., 2019). Central auditory processing requires the brain to make sense out of the sounds received by the cochlea. This process is vulnerable to neurodegeneration and there is evidence to suggest that central auditory processing may be affected early in the course of mild cognitive impairment (Idrizbegovic et al., 2011).

Interventions

Hearing loss is generally considered to be a modifiable risk factor which can be improved by amplification (hearing aids or amplification devices) or cochlear implants which work by converting sound into electrical signals that directly stimulate the auditory nerve. Cochlear implants are only given to people with severe hearing loss, of which there are around 20,000 in the UK (Cullington, 2022). The overall goal of amplification is to aid the restoration of auditory input from impaired peripheral hearing and serve as a tool to help manage the presence of background or competing noise for communication and comfort. The scientific and clinical communities have begun to recognise the potential benefit of hearing loss management particularly for neuropsychiatric conditions like depression and dementia (Powell et al., 2021).

To date, only one systematic review and meta-analysis has been published investigating the association of hearing aids and cochlear implants with incident dementia. This review included 31 studies (25 observational, and six trials) involving just over 137,000 participants. Meta-analysis of eight studies with a follow-up duration ranging from 2 to 25 years and adjusted for age, gender, socioeconomic and comorbidity confounders found a 19% decrease in the hazard of cognitive decline amongst people using hearing aids. However, none of the studies included in this meta-analysis included patients using cochlear implants. Additional meta-analysis of eleven studies showed a significant 3% improvement in short-term (3 to 12 months) cognitive test scores after the use of hearing restorative devices, both hearing aids and cochlear implants. However, when analysed across different types of test to assess cognition, some tests remained significant and others did not (Yeo et al., 2022).

A recently published study analysed data from 437,704 people in the UK Biobank cohort (Jiang et al., 2023). It reported a 42% increased risk of dementia in people with uncorrected hearing loss compared to no hearing loss, but no increased risk in people who corrected their hearing loss with hearing aids. Findings were similar for all-cause dementia and different sub-types. The attributable risk proportion of dementia for hearing loss was estimated to be 29·6%.

Interventions to encourage hearing aid use

Only 30% of the 6.7 million people in the UK thought to benefit from hearing aids wear them (Hearing Link Services, 2022). This is due to a range of factors such as ill-fitting devices, delay in diagnosis and social stigma (Hearing Loss Academy UK, 2023). A Cochrane review (last search date 2016) included 37 RCTs (4,129 participants) of interventions providing self-management support which included information, practice and experience at listening or communicating, or changing how the service was delivered (Brennan-Jones et al., 2017). The range of interventions that have been tested is relatively limited and the quality of evidence (according to GRADE) was judged low or very low. Intervention content across the different trials included: post-fitting adjustments and/or telephone conversation, differences in the way the aids were fitted (i.e., ears fitted together or separately), group or home-based education sessions, behavioural counselling sessions, LACE (Listening And Communication Enhancement), video feedback, relaxation, self-help manual, teleconsultation, auditory training or rehab, speech training, psychosocial exercises and communication strategies. Low to very low-quality evidence supports the use of self-management support and complex interventions combining self-management support and delivery system design in adult auditory rehabilitation. Barriers to the use of hearing aids are more often associated with difficulties using them or stigma, and so improving people's knowledge through education and advice may not be sufficient for individuals who are not new users of hearing aids (Aazh et al., 2015).

Strengths and weaknesses of the evidence

Controlled hearing intervention studies of long-term cognitive outcomes are challenging, and thus the evidence for the impact of hearing interventions is primarily from observational studies as opposed to more robust evidence from RCTs (Dawes, 2019). However, the recent systematic review synthesising this evidence is of good quality (Yeo et al., 2022). Further, high-quality, studies are required to determine the benefit of hearing interventions on long-term cognitive outcomes.

The evidence about how to effectively encourage people with hearing loss to wear hearing aids is low quality due to small studies and little evidence of longer term (>1 year) effects. Further research is required to understand the most effective types of intervention and what they should target (e.g., psychosocial needs).

Policy implications

The strong evidence for the association between hearing loss and dementia demonstrates that hearing loss is an appropriate risk factor to target. Evidence suggests that use of hearing aids can reduce dementia risk and cognitive decline, but a significant challenge remains in increasing the use of hearing aids. One approach to address this could be to focus person-centred interventions on specific groups such as those with ill-fitting devices or newly diagnosed hearing loss where interventions may be most effective. In order to strengthen the evidence base for the impact of reducing hearing loss on cognitive decline, more controlled studies are required and further research into the effectiveness of cochlear implants for patients with the most severe hearing loss.

Conclusion

The aim of this OPFPRU study was to explore whether there is sufficient evidence on the economic return to risk-reduction activities to support development of a return-on-investment (ROI) tool. Such a tool could support local commissioning decisions around investing in dementia risk-reduction.

In essence, building an ROI tool would require the following six steps:

1. *Risk factor for dementia*: What is the risk factor? And what is the mechanism of action linking it to dementia?
2. *Intervention*: What action will reduce this risk?
3. *Risk-reduction*: What is the (quantitative) association between the intervention and reduced risk?
4. *Investment*: What is the (comprehensive) cost of delivering the intervention?
5. *Pay-off*: What are the health, quality of life and resource impacts of the intervention in terms of reducing the incidence or prevalence of dementia?
6. *Return on investment*: What, finally, is the relationship between investment and pay-off?

Our task was to examine the available evidence relevant to England about which interventions targeting modifiable risk factors for dementia appear to be effective and cost-effective in preventing later-life dementia. In that way we would be able to assess the strength of the evidence needed to build an ROI tool.

Our work to date has looked at evidence relating to the first two of the above six steps, concentrating initially on three of the twelve known modifiable risk factors: low education, physical inactivity and hearing loss. We sought to explain each risk factor and its specific mechanisms of action in relation to dementia, and to summarise evidence on interventions that have been shown to reduce the risk. We have highlighted the strengths and weaknesses of the available evidence on the effectiveness of interventions.

What does this work to date tell us about the feasibility of an ROI tool? Whilst it is encouraging to see the accelerating accumulation of evidence on these three risk factors – particularly in relation to hearing loss, which had received relatively little attention until publication of the Lancet Commission (Livingston et al., 2017) – there are still many challenges.

First, no single study has yet examined the full pathway from receipt of an intervention to incidence of dementia (some decades later). This is unsurprising, given the difficulties of conducting such a study, but it then means that any ROI tool would need to be built by piecing together evidence from different studies covering the six steps above. This requires studies to employ common inclusion criteria for individuals, similar definitions or specifications for risk factors and interventions, and measures of outcomes and costs that can be linked. Interventions that target specific subpopulations (such as to encourage participation in exercise programmes by people with weight problems or from particular cultural groups) are certainly relevant, but evaluations of them are not sufficient to build an ROI tool. Robust linkages between studies are essential for such a tool.

Another challenge is the difficulty in specifying some of the risk factors with sufficient precision. For example, our review of the evidence relating to ‘low education’ found inconsistency in the definition, measurement and operationalisation of education. Definitions of what constitutes ‘low education’ range from 0 to 12 years across studies.

It is also not always possible to specify the intervention with enough precision to calculate a cost or to make the links to other studies that look at longer-term changes in dementia incidence. For example, with variations in the meaning of physical inactivity, it is not surprising that there are variations in what needs to be done to address it. A related problem is that the quality of evidence is sometimes low or only short-term, as we found when looking at evidence on ways to encourage people with hearing loss to wear hearing aids. The heterogeneity of outcome measures and samples, added to the heterogeneity of interventions makes it hard to conduct the kinds of meta-analysis usually needed to avoid over-reliance on single studies. As we commented earlier, there is a need for more controlled studies to strengthen the evidence base. It should be noted that this challenge of lack of precision may be less of an issue for some of the nine modifiable risk factors for dementia that we have *not* looked at so far, such as interventions to address hypertension, smoking or diabetes.

There is variance – often considerable – around every association in the six steps. The cumulative effect would make an ROI tool very imprecise. This uncertainty stems in part from the challenges noted above but is also driven by the substantial time lags between intervention and impact on dementia incidence and prevalence, and thence on costs (and savings). There are many potential future developments that would affect both those impacts and the scale and distribution of savings.

Although not necessarily impacting on the feasibility of an ROI tool, it should also be noted that both the costs of some interventions and the savings from reduced or delayed dementia incidence will be spread across numerous budgets and sectors (public and private). This will have implications for the distribution of incentives. Among other effects, slowing down the speed of cognitive decline or reducing dementia incidence rates will shift the cost balance from taxpayers to individuals and families (including carers).

A second consideration is that interventions for some risk factors will increase life expectancy because of their non-dementia effects (such as interventions for hypertension, excessive alcohol consumption, smoking or diabetes), which could have the effect of *increasing* the number of people living with dementia, given the steep gradient between age and dementia prevalence rate.

With recent progress, and the ambition to make *further* progress, on disease-modifying treatments (DMTs), it is possible that analyses conducted now of the impacts of interventions to address risk factors will be out-of-date well before we reach the years when the interventions would be expected to have an impact on dementia incidence.

Our overarching conclusion is that it is not currently feasible to develop a return-on-investment tool for dementia prevention. As more evidence accumulates on the effects of the various factors on dementia, on the effectiveness and cost of interventions to reduce those risks, and on any actions needed to incentivise people to engage with those interventions or to encourage policy makers to adopt community-level risk-reduction strategies, then development of a robust tool will become more likely. However, there will always be inherent difficulties such as the long time-interval between interventions and their impacts on dementia incidence, the multiple budgets that could be involved (both in funding interventions and in experiencing savings) and the associated need for a range of stakeholders to agree how to coordinate their investments and other actions. Those difficulties are not insurmountable, but they add further complexity.

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Appendix 1. Education and Dementia Risk

Author / Date	Type of study	Sample	Intervention and/or Outcomes	Measures	Results	Effect size	Conclusion
Meng & D'Arcy 2012	Meta-analysis of 69 studies & Narrative synthesis of 66 studies (cross-sectional, case control or cohort studies)	The studies covered 437,477 subjects. (characteristics not specified)	Dementia prevalence and incidence	Education: years of study; level of study (dichotomised into high/low) Cognition scores: DSM criteria for diagnosis of AD or VaD	Robust evidence that a high level education in early life is related with a significant reduction both in the prevalence and incidence of dementia.	Prevalence studies: Pooled OR (any dementia) 2.61 (95%CI 2.21-3.07) Pooled OR (AD) 2.62 (95%CI 2.06-3.33) Pooled OR VaD 2.11 (95%CI 1.40-3.19) Pooled OR (unspecified dementia) 2.79 (95%CI 2.13-3.66) Incidence studies: Pooled OR (any dementia) 1.88 (95%CI 1.51-2.34) Pooled OR (AD) 1.82 (95%CI 1.36-2.44) Pooled OR VaD 2.75 (95%CI 2.20-3.45) Pooled OR (unspecified dementia) 1.48 (95%CI 1.17-1.86)	This systematic review and meta-analyses covering a wide range of observational studies and diverse settings provides robust support for the association between high level education in early life and reduced prevalence & incidence of dementia.
Xu 2016	Meta-analysis (16 studies) and narrative synthesis (24 studies) of prospective cohort studies	Study population representative of general population	Relative risk (RR) of dementia	Education: years	Dementia risk decreased by 7% for per year increase in education (years of education ranged from 0 to greater than or equal to 17 years)	RR=0.93 (95%CI 0.92-0.94)	This is a meaningful study which not only further confirmed but also quantified the dose-response relation between educational attainment and dementia.

Maccora 2020	Meta-analysis of 65 studies (58 cohort studies, 6 case control studies, and 1 RCT)	Population based sample that were cognitively healthy at baseline	Documented diagnosis of any type of dementia	Education: years, level	Reduced risks of 8% for AD and 7% for any dementia for each year of education from continuous; and an 85% increased risk of AD and 45% increased risk of any dementia for those with low education from dichotomous Operationalisations.	AD and education years (continuous operationalisation): OR=0.92 (95%CI 0.88-0.96) Any dementia and education years (continuous operationalisation): OR=0.93 (95%CI 0.91-0.94) AD and low education (dichotomous operationalisation): OR=1.85 (95%cCI 1.56-2.18) Any dementia and low education (dichotomous operationalisation): OR=1.45 (95%CI 1.29-1.63)	While the evidence for an effect of education on dementia risk is robust and appears to withstand heterogeneity in study contexts, it could be strengthened to provide practical policy recommendations for dementia prevention if consensus were achieved on ways to define, measure and operationalise (low) education.
Reijinders 2013	Systematic review of 35 RCTs and clinical studies	Healthy older adults and those with mild cognitive impairment	Intervention: a range of intervention modalities (e.g. computer-based training; multi-factorial training programmes; educational courses) Outcome: Cognitive functioning; Most studies used memory performance as the primary outcome measure.	Range of different measures of memory performance, executive functioning, processing speed, attention, fluid intelligence, and subjective cognitive performance	The results show evidence that cognitive training can be effective in improving various aspects of objective cognitive functioning; memory performance, executive functioning, processing speed, attention, fluid intelligence, and subjective cognitive performance. A critical comparison between different intervention	-	From these data it can be concluded that there is very little evidence for generalization effects to overall cognitive functioning and daily life situations. The issue whether the effects of cognitive interventions generalize to improvement in everyday life activities

					studies is difficult because of the heterogeneity of the intervention programs and the chosen outcome measures.		still needs to be addressed more explicitly in future research.
Gates 2011	Systematic review and effect size analysis on 10 studies (5 RCTs)	People with mild cognitive impairment	Interventions included computerised cognitive exercise (9 studies) and pen & paper tasks (1 study). Mix of single- and multiple-domain training. Interventions also included memory strategies (both written and verbal) Outcomes: cognitive function. Variability in type (e.g. memory, attention, executive function, speed, global cognition).	Range of different measure of cognitive functioning.	Moderate-sized effects were found on memory performance and global cognitive measures in a majority of studies, with computer-based cognitive exercise studies exhibiting an increased frequency of stronger effect sizes, and enhanced generalization of benefits, compared to memory strategy training.	Cognitive exercises: relative effect sizes ranged from 0.10-1.21 Memory strategies: relative effect sizes ranged from 0.88—1.18	This review suggests cognitive exercise may be effective at enhancing cognitive outcomes, but several limitations have been identified which precludes firm conclusions.

Appendix 2. Physical Activity and Dementia Risk

Author/s, Date	Type of study	Sample	Interventions and Outcomes	Measures	Results	Effect size	Conclusion
Aarsland et al. 2010	Meta-analysis	24 longitudinal studies including 10,108 non-demented control subjects and 374 individuals with vascular dementia	Physical exercise and cognitive decline	Vascular dementia or no dementia; number and intensity of various physical activities performed during a week, 'moderate-high' exercise (three or more times per week, at least as intense as walking) or 'low' (all other physical activity)	Five studies reported on the association between physical exercise and cognitive decline, not excluding vascular cognitive impairment. Four of these studies reported that cognition was positively associated with physical activity. In two of these, the effect was significant in women only. In one study, no such association was found.	OR 0.62 (95% CI 0.42–0.92)	There is evidence supporting the hypothesis that physical activity is likely to prevent the development of VaD, and should be highlighted as part of secondary prevention programmes in people at risk for cerebrovascular disease
Blondell et al., 2014	Meta-analysis	21 cohorts on physical activity and cognitive decline 26 on physical activity and dementia	Physical activity and cognitive decline	Cognition scores: MMSE, 3MS Physical activity indicators: self-reported questionnaire	Participants with higher levels of physical activity, when compared to those with lower levels, are at reduced risk	Cognitive decline RR 0.65, 95% CI 0.55-0.76 Dementia RR 0.86, 95% CI 0.76-0.97	Longitudinal observational studies show an association between higher levels of physical activity and a reduced risk of cognitive decline and dementia
Brassure et al., 2018	Meta-analysis	16 RCTs	Aerobic training, resistance training, tai chi, physical activity with diet, and physical activity with a cognitive component And cognitive decline	Cognitive function	Evidence was insufficient to draw conclusions about the effectiveness of aerobic training, resistance training, or tai chi for improving cognition. Low-strength evidence showed that multicomponent physical		Evidence that short-term, single-component physical activity interventions promote cognitive function and prevent cognitive decline or dementia in older adults is largely insufficient. A multidomain intervention showed a delay in cognitive

					activity interventions had no effect on cognitive function. Low-strength evidence showed that a multidomain intervention comprising physical activity, diet, and cognitive training improved several cognitive outcomes.		decline (low-strength evidence).
Iso-Markku et al., 2022	Meta-analysis	58 studies w/ participants for all- cause dementia, Alzheimer's disease and vascular dementia outcomes	Physical activity and all-cause dementia, Alzheimer's disease, or vascular dementia	Physical activity levels	There are inverse associations between activity levels and incidence of dementia.	PA was associated with a decreased risk of all- cause dementia (pooled relative risk 0.80, 95% CI 0.77 to 0.84, n=257 983), Alzheimer's disease (0.86, 95% CI 0.80 to 0.93, n=128 261) and vascular dementia (0.79, 95% CI 0.66 to 0.95, n=33 870), even in longer follow- ups (≥20 years) for all- cause dementia and Alzheimer's disease	PA was associated with lower incidence of all- cause dementia and Alzheimer's disease, even in longer follow-ups, supporting PA as a modifiable protective lifestyle factor, even after reducing the effects of reverse causation

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