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The effect of midlife risk factors on dementia in older age

Report

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Public Health
England



The effect of midlife risk factors on dementia in older age

Personal Social Services Research Unit
London School of Economics and Political Science

March 2017

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. We do this through world-class science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health, and are a distinct delivery organisation with operational autonomy to advise and support government, local authorities and the NHS in a professionally independent manner.

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Executive summary

Public Health England (PHE) commissioned the Personal Social Services Research Unit (PSSRU) at the London School of Economics and Political Science (LSE) to conduct a study on primary prevention of dementia. The aim of the study is to provide information to assist commissioners to make decisions about prioritisation of primary prevention measures relevant to dementia.

This report presents findings from a focused review of evidence, which formed a substantial part of the overall study. The review covers all types of dementia and in all age groups, subject to the availability of evidence. It focuses on recent literature on the relationship between changes in risk factor behaviours or conditions in midlife (ages 40 to 64) and onset of dementia later in life. The risk factors considered comprise: smoking, excessive drinking, high blood pressure, lack of physical activity and obesity, diabetes, depression and other common mental health conditions, social isolation and loneliness, and lifelong learning and cognitive stimulation.

For the risk factors which were considered in a recent systematic review (Norton et al. 2014) we searched for more recent systematic reviews or primary empirical studies published for any possible new evidence or more comprehensive reviews. For the risk factors not considered in that systematic review, we searched for relevant papers in the recent NICE review on midlife risk factors and dementia in older age (Lafortune et al., 2016; Lafortune, Kelly, and Cowan, 2014) and when necessary, conducted additional searches for papers published since 2000.

We have focused on papers reporting impact on dementia or Alzheimer's disease, except in the case of risk factors where we have found only papers reporting impact on cognitive impairment. We have concentrated on papers reporting quantitative findings on the relative risk or odds ratio of onset of dementia as between those experiencing and those not experiencing the risk.

We have found evidence that the following risk factors in mid-life are associated with an increased risk of dementia later in life:

- **physical inactivity** in mid-life is highly prevalent and increases the risk of all-cause dementia: people inactive in midlife have more than double the risk of dementia in old age than those who are physically active
- **current smoking** increases the risk of all-cause dementia: the risk of dementia in old age is slightly higher for smokers in midlife than for non-smokers, but past smoking is not associated with an increased all-cause dementia risk
- **diabetes** increases the risk of all-cause dementia; while the samples in several reviews include older people, there are some original studies specifically from

midlife which suggest that people with diabetes have around 2.5 times the risk of onset of dementia in old age

- **hypertension in mid-life** increases the risk of all-cause dementia: people with hypertension in midlife are at slightly greater risk of dementia in old age
- **obesity in mid-life** increases the risk of all-cause dementia: people who are obese have around 1.6 times the risk of onset of dementia in old age
- **depression** increases the risk of all-cause dementia; while the samples in several reviews include older people, there are studies specifically for midlife depression which suggest that people with depression in midlife are at slightly greater risk of dementia in old age
- **mental activities in mid-life** are associated with a lower risk of dementia in later life: for example, higher complexity of working with data among lower educated people in midlife can roughly halve the risk of dementia in old age

We have not found robust evidence that the following suggested risk factors in mid-life are associated with an increased risk of dementia later in life:

- **alcohol:** while heavy and chronic drinking results in specific dementia-type symptoms, there is a lack of robust evidence of a general effect on all-cause dementia
- **diet:** the evidence on diet as a risk factor for dementia is inconclusive and scarce
- **mental distress in mid-life:** the evidence for an impact on risk of dementia later in life is scarce and weak
- **social isolation and loneliness:** very few studies report the long-term effect of midlife social isolation or loneliness on risk of dementia in older age
- **air pollution and other environmental toxins (eg heavy metals such as lead and copper), drug abuse, sleep disturbances (such as short or fragmented sleep) and hormones** (eg low estrogens levels) have been suggested as possible midlife risk factors, but there is insufficient evidence to draw conclusions

It is important to recognise a number of key caveats. First, we have conducted a focused and not a systematic review. Second, we have concentrated on risk factors in mid-life. While factors in mid-life which are found to be associated with later onset of dementia may be causative, factors associated with dementia in old age may have a more complex relationship with dementia, with causation potentially running in either direction. Third, the risk factors we consider are correlated. Where an intervention relates to just one risk factor and does not extend to other risk factors with which it is correlated, use of unadjusted relative risk estimates would overstate the likely impact of the intervention: adjusted relative risk estimates should be used when assessing the likely impact on future dementia incidence.

Finally, reduction in some risk factors, for example smoking, affects mortality as well as dementia incidence. People who change behaviours in middle age may experience considerably improved life expectancy. It is, therefore, possible that while they may gain a reduced risk of onset of dementia at a given age, for example in their seventies, their lifetime risk of onset of dementia may rise and be higher than if they had not changed their behaviours.

Glossary for statistical terms in the report

Case-control study: compares non-randomised groups of individuals with differing outcomes, and looks back in time to see how the risk factors of the groups differed. A special case, a co-twin case-control study, compares twin pairs who share genetic factors and early environment but experience different outcomes (eg one twin has dementia, whereas the co-twin does not).

Cohort study: is a longitudinal study which follows up the same individuals over a period of time. A longitudinal approach enables collection of the same measures on several occasions over time (repeated measures).

Confidence interval (CI): is a range of values (interval) indicating the estimated variation around the estimated central value of an unknown population parameter. If the 95% confidence interval for a variable is shown as 10 to 20, for example, this means that the analysis has found that there is a 95% likelihood that the 'true' value of the variable lies between 10 and 20 and only a 5% probability that it lies outside that range.

Hazard ratio (HR): is the ratio of two hazard rates, the rate at which events happen. HR reflects how often a particular event happens in one group compared to how often it happens in another group, over time. If, for example, the annual incidence rate of dementia is 5% for one group and 10% for another group (eg those at higher risk), the HR is 0.5.

Odds ratio (OR): is the ratio of odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. If for example the odds of onset of dementia is 1:4 for one group and 1:3 for another group (e.g. those at higher risk), the OR is 1.333. [In a simple 2x2 group case the OR can be calculated as $OR = (a \times d)/(b \times c)$. a = number of exposed cases, b = number of exposed non-cases, c = number of unexposed cases, d = number of unexposed non-cases].

Relative risk (RR): is the ratio of the incidence rate in an exposed group divided by the incidence rate in an unexposed (or less exposed) comparison group. If, for example, the lifetime probability of experiencing onset of dementia is 20% for one group and 40% for another group (eg those at higher risk), the RR is 2.0. [In a 2x2 group, $RR = (a/(a+b))/(c/(c+d))$. a = number of exposed cases, b = number of exposed non-cases, c = number of unexposed cases, d = number of unexposed non-cases].

Introduction

Public Health England (PHE) commissioned the Personal Social Services Research Unit (PSSRU) at the London School of Economics and Political Science (LSE) to conduct a study on primary prevention of dementia. The aim of the study is to provide information to assist commissioners to make decisions about prioritisation of primary prevention measures relevant to dementia.

The study covers all types of dementia and in all age groups, subject to the availability of evidence. The risk factors for dementia considered in the study comprise: smoking, excessive drinking, high blood pressure, lack of physical activity and obesity, diabetes, depression and other common mental health conditions, social isolation and loneliness, and lifelong learning and cognitive stimulation. The focus is on risk factors in mid-life (ages 40 to 64). Although dementia is typically developed in very late life, the processes leading to precursory health problems often start in mid-life (1). While there is no cure for dementia, mid-life provides a window of opportunity for early intervention to reduce or modify the risk factors for dementia.

The original focus and outputs for this study were amended in view of the lack of evidence on the impact of primary prevention measures such as smoking cessation in mid-life on subsequent onset of dementia in old age. There are no evaluations of interventions which follow-up individuals for very many years to ascertain the proportions experiencing onset of dementia. Generally, follow-up periods in studies are short (less than one year) and cognitive performance or decline rather than diagnosis of dementia is used as an outcome (1), restricting the usefulness of the evidence for the purpose of this work. For this reason, the current work aims to provide information on the importance of different risk factors of dementia.

The outputs from this study following the changes to its focus are:

- a report summarising the evidence from studies of the impact on dementia incidence of changes in behaviours, eg smoking, or in conditions, eg loneliness, obesity or depression
- a report summarising barriers and facilitators to primary prevention of dementia and recommending next steps for rolling out implementation of interventions to reduce its prevalence

This report, which is the first of these two outputs, presents findings from our focused review of evidence. Because of the tight time schedule and the availability of recent comprehensive reviews on the topic (2–4), this study was not designed to carry out a new systematic review, but to use the existing high quality summaries as starting points and update searches of literature only when needed.

Methods

We took as the starting point for our search for evidence the findings of Norton and colleagues (4). For the seven risk factors which they considered, we searched for very recent systematic reviews or primary empirical studies published from January 2015 onwards for any possible new evidence, or more comprehensive reviews. Similar to Norton et al (4), a review was considered to be more comprehensive if it included a larger number of studies than any previous reviews and pooled them using an appropriate meta-analytic method.

For the risk factors which Norton and colleagues (4) did not consider - alcohol, diet, mental distress, social isolation and loneliness, and air pollution - we searched for relevant papers in the recent NICE review on mid-life risk factors and dementia in older age (3,5). When necessary we conducted additional searches for papers published since 2000. We also checked the World Alzheimer Report 2014 (6) for any relevant studies on mid-life risk factors and older age all-cause dementia which our search had not identified.

We searched for papers which reported as outcomes dementia or Alzheimer's disease or cognitive impairment. Our search terms included combinations of these outcome variables and risk factors, eg 'dementia and smoking' or 'Alzheimer's and diet'. We searched Ovid Medline, Pubmed, Psycinfo and Cochrane database. We excluded papers published before the dates mentioned above, papers in languages other than English, papers reporting changes to the brain rather than dementia, Alzheimer's or cognitive impairment, and papers with less than good quality and applicability, ie papers rated less than + or ++ in the NICE review 2 (5).

We have not included in this report all the papers we have found. This is because the aim of this study is not to report a systematic review, but to provide evidence of value to commissioners in making decisions about what primary prevention measures to commission. We have focused on papers reporting impact on dementia or Alzheimer's disease, except in the case of risk factors where we have found only papers reporting impact on cognitive impairment (using a dementia screening measure such as MMSE score cut-off).

We have concentrated on papers reporting quantitative findings on the relative risk or odds ratio of onset of dementia as between those experiencing and those not experiencing the risk, eg smokers compared to non-smokers. The reason is that a major purpose of the review is to provide evidence to incorporate in a tool to assist local commissioners and other stakeholders to prioritise primary prevention activity.

We report the evidence separately for each risk factor and show a summary of the key papers in Appendix Table 2. We also report evidence relating to combinations of risk factors. While most of the studies we found followed up people with and without an individual risk factor, for example comparing smokers and non-smokers, a few followed up people with and without a combination of risk factors. These latter studies reported the effect of the count of risk factors (not separating out each combination) (7), and/or used cognitive functioning as outcome (8 (also a wide age range from 24 to 74), 9), which made it difficult to use the findings in the present work.

The risk factors we are considering are correlated, as discussed in Norton et al (4) who report adjusted population-attributable risk estimates which take account of the correlation. We report both the relative risk estimates as presented in the papers and adjusted relative risk factors, where the adjustment is based on Norton et al. It is in general the adjusted estimates that are relevant for consideration of the likely impact of interventions.

If, for example, people with risk factor A are twice as likely to have risk factor B than those without risk factor A, relative risk estimates obtained by following up and comparing people with and without risk factor A will implicitly include the effect of their above-average probability of risk factor B. Yet interventions relating to risk factor A may generally not impact on risk factor B. For this reason, the adjusted relative risk estimates should generally be used when assessing the likely impact on future dementia incidence.

It is important to recognise that reduction in some risk factors, for example smoking, affects mortality as well as dementia incidence. People who stop smoking in middle age experience considerably improved life expectancy. It is therefore entirely possible that, while they may gain a reduced risk of onset of dementia at a given age, for example in their seventies, their lifetime risk of onset of dementia may be higher than if they had not given up smoking, because they survive to an age where dementia prevalence is higher. Analyses by Anstey et al (10) found that, while population-level reductions in smoking, sedentary lifestyle and obesity increase longevity and number of years lived without cognitive impairment, years lived with cognitive impairment may also increase.

Physical activity (PA)

Key findings:

- evidence that mid-life physical inactivity is highly prevalent and increases the risk of all-cause dementia (7,11). For the purpose of this paper we focus on a study which shows that mid-life leisure-time physical activity of at least 20 to 30 minutes at least twice a week is associated with a reduced risk of all-cause dementia (odds ratio, OR: 0.47, 95% confidence interval, CI: 0.25, 0.90) (11)
- 33% of the population in the UK are physically inactive while the population-attributable risk of Alzheimer's disease for physical inactivity is 21.8% (95% CI: 6.1, 37.7) (4)
- main caveats: most of the cohort studies look at physical activity in old age and dementia, using shorter than ten-year follow-ups

Barnes and Yaffe (2) refer to a systematic review by Hamer and Chida (12), which identified 16 prospective studies of the association between physical activity and dementia. The risks associated with inactivity (less than 20 minutes of vigorous activity on three or more days or 30 minutes of moderate activity on five or more days per week) have a relative risk, RR, of 1.39 (95% CI: 1.16, 1.66) for all-cause dementia. However, the review pools the results from samples of middle aged and older people. We, therefore, looked for studies specifically of mid-life physical activity in the NICE review (3,5). We excluded one study because of retrospective physical activity measure (asking people to recall how much physical activity they had undertaken many years earlier), one study that did not include dementia as an outcome, and two studies because of poor quality (according to NICE). We considered the two remaining relevant studies on leisure time physical activity.

In one of these two studies, Rovio and colleagues (11) studied leisure-time physical activity in mid-life (ages 39 to 64) that lasts at least 20 to 30 minutes and causes breathlessness and sweating at least twice a week and followed up all-cause dementia 21 years later (ages 65 to 79) in Finland (see Table 2 in appendix). They reported a protective effect of exercising on dementia (OR: 0.47, 95% CI: 0.25, 0.90), which was similar for both men (OR: 0.31, 95% CI: 0.09, 1.12) and women (OR: 0.43, 95% CI: 0.14, 1.28).

In a second study, Elwood and colleagues (7) investigated physical activity (walking two or more miles to work each day, or cycling ten or more miles to work each day, or 'vigorous' exercise described as a regular habit) among Welsh men in mid-life (ages 45 to 59), and followed up about 30 years later for all-cause dementia at ages 70 to 85. They reported a protective effect on dementia (OR: 0.41, 95% CI: 0.22, 0.77), which was fairly similar to what Rovio et al (11) found, but restricted to men only.

Both of these studies reported a high participation rate: 73% in Rovio et al (11) and 77% in Elwood et al (7). Moreover, Rovio et al (11) also used medical records data on all of those who participated in the baseline (baseline participation rate 97%), and received similar results (not reported in their paper). The studies, however, lack a precise definition of physical activity, in that they do not report whether the participants were physically active just in the last few weeks or months before baseline interview, or for several years before interview. Rovio et al (11) uses quite a conservative cut-off for physical activity (20 to 30 minutes at least twice a week) and they refer to some previous studies which also used this cut-off.

We also found some studies which specifically looked at work-related physical activity, but the association between such physical activity and dementia was reported to be weak (13,14). A recent study from Sweden (15) suggested that the association between mid-life physical inactivity and dementia may be only evident among obese people. Stronger associations between mid-life physical inactivity and dementia among overweight compared to normal weight, and also men compared to women were reported in a Finnish study (16) which used the same data as Rovio et al (11). They analysed physical activity in three categories and compared the low activity (a few times a year) to high activity (two to three times a week) and moderate activity (two to three times month to once a week).

We also found a recent study using Finnish twins, which reported physical activity from ages 24 to 60 and followed-up dementia deaths for 29 years (17). Persistent vigorous physical activity (measured on two occasions six years apart in mid-life) was associated with a lower risk of dementia death (hazard ratio, HR: 0.65; 95% CI: 0.43 – 0.98). Using samples of twins enables adjustment for genetic and early environmental effects. Twin-pairs discordant for physical activity showed a HR of 0.48 but wider confidence intervals (0.17 – 1.32). The paper investigates dementia deaths rather than actual dementia diagnosis, which may restrict the opportunities to compare the results to the other studies. However, it points to associations in the same direction as previous studies that used dementia diagnosis, ie that physical activity is associated with lower risk of dementia.

Physical activity appears to be the most promising mid-life approach to reduce the risk for dementia. Norton et al (4) estimated that, of the key risk factors which they considered (diabetes, hypertension, obesity, physical inactivity, depression, smoking and low educational attainment), physical inactivity had the highest prevalence (33%) and relative risk for Alzheimer's disease in the UK. Hence bearing the largest weight in population-attributable risk. According to Norton et al (4), the population-attributable risk for physical inactivity is 21.8% (95% CI: 6.1, 37.7), whereas for the two next biggest risk factors, low educational attainment and smoking, it was 12.2% (95% CI: 7.6, 16.9) and 10.6% (95% CI: 2.9, 19.4) respectively.

Three recent reviews (18–20) also suggested physical (or leisure time) activities as among the most potentially effective lifestyle modifiers of later life dementia. Although the size of impact may be only moderate. The World Alzheimer Report, however, gives a more cautious summary of the effects of physical activity both in mid-life and old age (6). It cites only two studies focusing on mid-life leisure time physical activities, however, and does not carry out a meta-analysis. Yet, both of these two studies showed similar or even stronger association with dementia compared to the pooled estimate reported in Barnes and Yaffe (2). These two studies were also included in the NICE review (3,5), one of which is described in more detail above (11), and the other one excluded from this report because it used a retrospective measure of physical activity (21).

Alcohol

Key findings:

- the association between mid-life alcohol use and risk of all-cause dementia appears to be quadratic or J-shaped such that light to moderate use of alcohol is associated with the lowest risk of dementia. See Figure 1, NICE review (5) and World Alzheimer Report (6). Insufficient evidence restricts the conclusions. There is, however, evidence that heavy and chronic drinking results in specific dementia-type symptoms
- 9% of men and 4% of women in the UK show signs of alcohol dependency according to the NHS England (22)
- main caveats: insufficient evidence, mixed risk in the group of abstainers, issues around causality, selection and measuring drinking

The study by Norton et al. (2014), which is based on Barnes and Yaffe (2), did not include alcohol use on their list of major risk factors for dementia. Di Marco et al (20) and Baumgart et al (18) concluded that the evidence of effects of alcohol use on dementia is inconsistent. The World Alzheimer Report presents a meta-analysis on alcohol use and dementia, but pools the results from mid-life and old age (6). The NICE review (3,5) reported three original studies of mid-life alcohol use (7,23,24). Two of these studies were excluded from our review because they did not have dementia or cognitive impairment as an outcome.

A Finnish population-based study (24) had a good measure for alcohol consumption, and assessed also binge drinking and pass-outs. Moreover, alcohol consumption was measured repeatedly and participants were twins which made it possible to control for some causal mechanisms. The sample was aged 38+ years at the first and 44+ years at the second measurement occasion, and 65+ years at dementia screening. Cognitive impairment was based on a screening instrument which was similar to MMSE. The association was quadratic, so that both abstainers OR: 1.51 (95% CI: 1.04, 2.18) and heavy drinkers (> 7 drinks for women, > 14 for men) OR: 2.03 (95% CI: 1.17, 3.54) were more likely to develop cognitive impairment than light drinkers (>0 and ≤3 drinks per week). Moderate drinkers (> 3 and ≤7 drinks for women, > 3 and ≤14 drinks per week for men) did not differ from light drinkers (OR: 0.97; 95% CI: 0.58, 1.32).

The association between heavy drinking and cognitive impairment became even stronger when persistent alcohol consumption (on both measurement occasions) was taken into account. For heavy drinkers compared to light drinkers the OR was 2.23 (95% CI: 1.29, 3.86). Binge drinking (drinking more than five bottles of beer, one bottle of wine, half of a bottle of spirits, or an equivalent amount of other beverages on the one

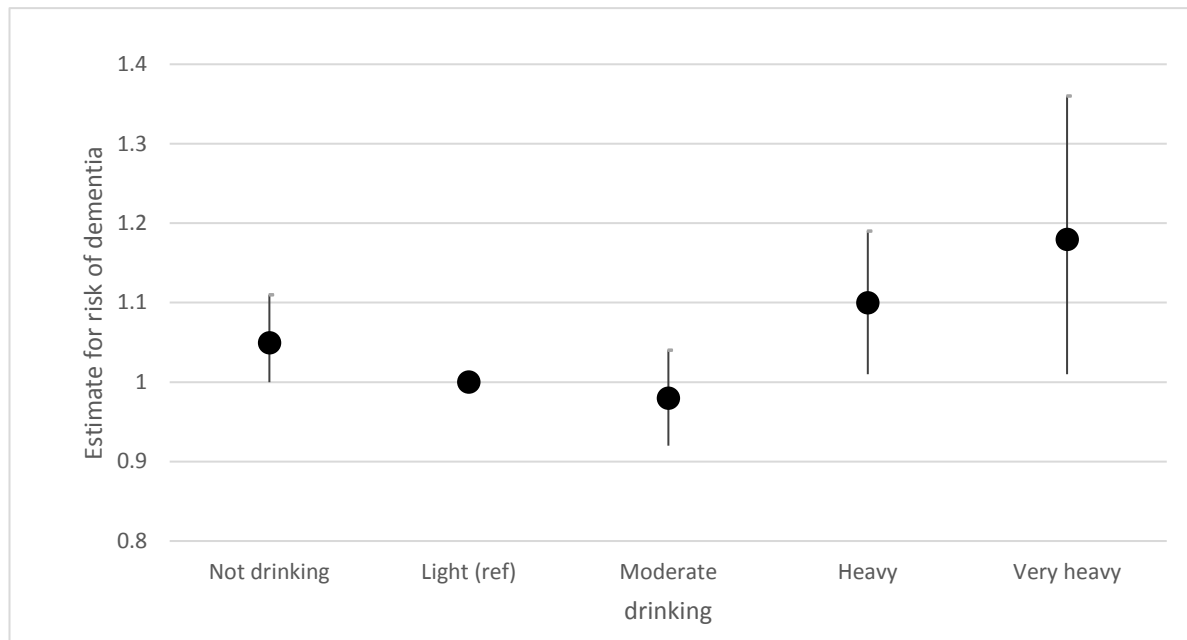
and same occasion at least monthly) reported at one time point (OR: 1.87; 95% CI: 1.04, 3.38) and at two time points (OR: 1.98; 95% CI: 1.05, 3.72) and pass-outs (3+ times/year vs. never (OR: 4.10; 95% CI: 1.54, 10.94) were also associated with cognitive impairment. The discordant twin analysis showed weaker associations between alcohol consumption and cognitive impairment, suggesting that the associations may not be fully causal, but partly determined by genetic and familial effects.

A recent paper (25) using the Swedish twin registry sample showed that compared to light drinking (>0 and ≤5 g/d), heavy (>12 and ≤ 24 g/d) and very heavy drinking (>24 g/d) in mid-life (ages 42 to 64) was associated with increased risk of dementia (HR: 1.10, 95%CI: 1.01, 1.19 and HR: 1.18, 95%CI: 1.01, 1.36, respectively). Figure 1 shows the estimated risk for different groups of alcohol consumption in this study. The study also showed that there was a protective effect of light wine drinking compared to never drinking wine or heavy drinking of wine. Beer and spirit drinking appeared to have a linear effect on dementia, with each unit increase in consumption raising the risk of dementia.

Discordant twin analysis showed that the twin consuming very heavy amounts of alcohol had almost five years shorter time to dementia onset compared to the co-twin who consumed light amounts (estimate = -4.76, SE = 2.01, p = .019). The risk of dementia diagnosis was higher in a member of the twin pair with moderate to heavy alcohol consumption (OR: 1.57, 95%CI: 1.04, 2.37). This association was even higher among monozygotic discordant pairs (OR: 3.07, 95%CI: 1.37, 6.86) than among dizygotic twins, which suggests that genetic and early life environmental factors do not explain the association.

It is difficult to be confident about the link between alcohol consumption in mid-life and onset of dementia later in life because of the non-linear J-shaped association between alcohol consumption and risk of dementia (see Figure 1), mixed risk in the group of abstainers, mixed results on trying to assess causality and difficulties in measuring drinking behaviours in surveys (reporting bias, selection) (6). However, chronic and heavy alcohol use involves serious health risks and can lead to dementia-type symptoms (alcohol-related brain damage due to nerve cell damages and tissue shrinkage, and vitamin B1 deficiency also known as Korsakoff's syndrome) (26).

Figure 1 Estimated relative risk (RR) of dementia among those reporting no, moderate, heavy and very heavy alcohol use compared to those reporting light alcohol use in mid-life.



Source: Handing et al. (25)

The 95% confidence interval is shown with a vertical line through the point estimate.

Smoking

Key findings:

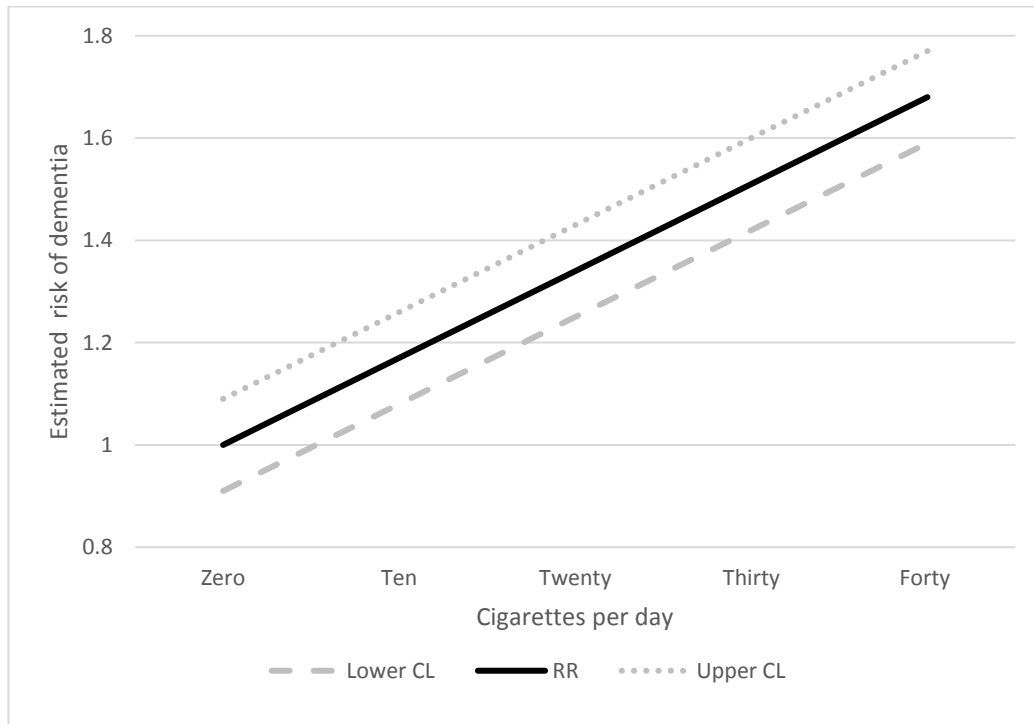
- evidence that current smoking increases the risk of all-cause dementia whereas past smoking is not associated with increased all-cause dementia risk: a recent review found an estimated RR of 1.30 (95% CI: 1.18, 1.45) for current smoking and risk of all-cause dementia (27). Past history of smoking was not associated with dementia
- about 20% of the adult population are current smokers in the UK while the population-attributable risk of Alzheimer's disease for smoking is 10.6% (95% CI: 2.9, 19.4) (4)
- main caveats: the history of smoking is difficult to study in surveys to establish when, and for how long, the behaviour change in mid-life is needed for dementia risk reduction in old age

Barnes and Yaffe (2) state that, while several earlier studies reported that smoking was associated with reduced risk of Alzheimer's disease, more recent studies have found the reverse. Barnes and Yaffe (2) refer to three separate meta-analyses with somewhat different findings. The World Alzheimer Report presents a meta-analysis of seven studies with weak effect of current vs never smoking on all-cause dementia (RR 1.20; 95% CI: 0.96, 1.44) and current smoking vs current non-smoking on all-cause dementia (RR: 1.28, 95% CI: 0.99, 1.60) (6).

We focused on a recent review of studies on the effect of smoking on all-cause dementia based on 37 papers published from 1999 onwards and using several subgroup and sensitivity analyses (27): see Table 2 in appendix. This review reported the relative risk of developing all-cause dementia for smokers to be 1.30 (95% CI: 1.18, 1.45). The paper also reports dose-response effects based on two empirical studies: the risk of dementia increased by 34% for every 20 cigarettes per day (RR: 1.34, 95% CI: 1.25, 1.43), illustrated in Figure 2. Past history of smoking was not associated with dementia. The risk of all-cause dementia did not differ between never smokers and former smokers (RR: 1.01, 95%CI: 0.96, 1.06).

Current smokers aged 65 to 75 years at baseline showed increased risk of all-cause dementia and AD compared to those aged over 75 or under 65 years, but the difference between these subgroups was not significant. Sex, study location, race and several key study characteristics, including sample size, mean duration of follow-up and loss to follow-up rate, did not systematically affect the result when comparing the RRs of all-cause dementia and AD for current, former and never smoking between the studies. The previous reviews considering multiple risk factors suggest moderate evidence of smoking as a risk factor for dementia (18,19).

Figure 2 Estimated increase in risk of dementia by number of cigarettes smoked per day.



Source: Zhong et al. (27).

RR = relative risk, Lower CL = Lower confidence limit (95%), Upper CL = Upper confidence limit (95%).

The World Alzheimer Report (6) highlights smoking as one of the key risk factors for dementia with moderate evidence, despite the rather meagre results in their meta-analysis. For example, the report cited five studies which compared dementia risk among current smokers and never smokers. Of these studies only two showed an effect of current smoking on dementia. The pooled RR for the five studies was 1.20 (95% CI: 0.96, 1.44). Although the effect was quite modest and confidence interval wide, the report emphasised the consistency of findings on the direction of the effects (6).

Diet

Key findings:

- the evidence of diet on risk of dementia is scarce and inconclusive
- main caveats: studies have concentrated on immediate health effects rather than long-term patterns from mid-life to older age

The evidence of the effects of diet on dementia is inconsistent (19). There have been few studies, which makes it difficult to establish the pattern of association. Norton et al (4) and Barnes and Yaffe (2) did not include diet in their list of major risk factors for dementia. The World Alzheimer Report (6) cites several studies on the associations between diet and dementia, all of them measuring diet in old people and not separating out the effect from mid-life, and some using cognitive decline rather than dementia as outcome. In the NICE review (3,5), seven studies looked at mid-life diet, but three of these studies were not relevant for our report because they used cognitive decline and not dementia as outcome.

Among the studies that were relevant, there was some indication that high saturated fat intake was associated with increased risk of dementia (28,29). However, this association seemed to follow a quadratic pattern, so that moderate fat intake was associated with the lowest risk of dementia, whereas no fat intake and high fat intake were associated with increased risk (30). The results for coffee and tea drinking, and fruit and vegetable consumption were inconclusive. A recent review on the effect of coffee, tea and caffeine consumption on dementia did not find any consistent pattern of association (31). Antioxidants intake also showed an inconsistent pattern.

A better approach than just paying attention to individual items of diet may be to look at diet as a whole. There are a number of recent reviews and interventions looking at healthy eating on dementia, eg Mediterranean diet (32), Mind diet (33) and Nordic diet (34). The basis of a Mediterranean diet (and these other approaches) is similar to that shown in the Eatwell Guide – the UK recommendations for healthy eating. However, as the impacts of dietary patterns on dementia have been investigated only with short follow-ups in these studies (6,18), the existing literature cannot establish the link between diet change in mid-life and dementia in later life. Studies need to use longer follow-ups and also consider the link through other risk factors, such as diabetes and obesity.

Diabetes

Key findings:

- evidence that diabetes (Type 1 or Type 2) increases the risk of all-cause dementia
- a large case-control study based on data from the Finnish national health insurance registry found an OR of 1.60, 95% CI: 1.34-1.84 (35) between mid-life diabetes and Alzheimer's disease
- a Swedish co-twin matched case-control study found an OR of 2.51 (95% CI: 1.10, 5.72) for the association between mid-life diabetes and all-cause dementia (36)
- the prevalence of diabetes is 5% in the UK, while the population-attributable risk of Alzheimer's disease for diabetes is 1.9% (95% CI: 0.8, 3.1) (4)
- main caveats: most studies focus on diabetes in older age only (which entails problems of possible reverse causation), very few looking at mid-life diabetes

Norton et al (4) report an RR of 1.46 (95% CI: 1.20-1.77) for the association between diabetes mellitus between ages 20 and 79 and AD. However, this estimate is drawn from a meta-analysis of 19 studies where most of the participants were 65+ with short follow-up (37). Barnes and Yaffe (2) use another review (38) which gives an estimate for all-cause dementia (RR: 1.47, 95% CI: 1.25, 1.73). This is, however, also restricted to people aged 60+.

The World Alzheimer Report review focuses on late-life diabetes (type I or type II) and dementia (6). It identifies three studies from mid-life, but because of small numbers does not provide a meta-analysis. The three studies cited in the report all used medical records as a source of information on the diagnosis. Their results suggest that the association between diabetes and dementia is possibly stronger when diabetes is evident already in mid-life compared to having diabetes in older age.

Of the three included studies in the World Alzheimer's report, a US study on enrolled members of a health plan showed that diabetes in mid-life (age 40 to 44) was associated with dementia 30 years later (RR: 1.46; 95% CI: 1.19, 1.79) (39). A large Finnish case-control study based on national health insurance registry data showed that diabetes diagnosed at mid-life (age 40 to 64) was more strongly associated with Alzheimer's disease (OR 1.60, 95% CI: 1.34-1.84) than diabetes diagnosed in later life (age 65+) (OR 1.25, 95% CI: 1.16-1.36) (35), see Table 2 in appendix for a summary.

A Korean study, also based on the national health insurance registry, showed that mid-life (age 40 to 64) raised blood glucose levels or diagnosis of diabetes were associated with dementia when people were followed-up for 14 years (40). The association was

particularly strong with vascular dementia (HR: 2.3; 95% CI: 1.5 -3.3 for men, and HR: 3.0; 95% CI: 1.8 – 5.1 for women), and somewhat weaker with Alzheimer’s disease (HR: 1.6; 95% CI: 1.2 -2.1 for men and HR: 1.2; 95% CI: 0.8 – 1.7 for women). The paper does not report pooled results for all-cause dementia.

Our further search for studies specifically on mid-life diabetes found a review of 14 original studies which separated the effect of mid-life (age 45 to 65) and old age diabetes (66+) on dementia (41). This review gave a pooled median OR 2.2 for mid-life diabetes and 1.6 for old age diabetes (no CIs reported, but can be calculated from the extraction tables). The follow-up times vary between 25 and 35 years in the mid-life samples and two and 12 years in the older age samples.

A large Swedish twin study reported that mid-life diabetes (onset before age 65) increased risk of dementia (OR: 2.76, 95% CI: 1.97, 3.87), whereas the association between older age diabetes (onset at 65+) and dementia (after age 65) was somewhat weaker (OR: 1.63, 95% CI: 1.23, 2.16) (36), see Table 2 in appendix for a summary. The study looked at both Type I or Type II diabetes. The study also provided co-twin matched case-control results for the association with dementia of mid-life diabetes (OR: 2.51, 95% CI: 1.10, 5.72) and of older age diabetes (OR: 0.68, 95% CI: 0.30, 1.53).

The pattern of the weakening association when genetic factors and early environment were taken into account, suggests that the association between late-life diabetes and dementia in unmatched comparisons is likely to be caused by factors that affect both diabetes and dementia. Another Swedish study of women provided an HR of 1.95 (95% CI: 0.94, 4.05) for mid-life diabetes (ages 38 to 60) and all-cause dementia 34 years later (ages 72 to 94)(15). The participation rates for these two studies were 68% (36) and 70% (15).

Hypertension

Key findings:

- evidence that mid-life hypertension increases the risk of all-cause dementia (2,4). The estimate reported by Norton et al (4) is RR 1.61 (95% CI: 1.16, 2.24)
- the prevalence of hypertension is 12% in the UK, while the population-attributable risk of Alzheimer's disease for mid-life hypertension is 7.0% (95% CI: 1.9, 13.3) (4)
- main caveats: the association between hypertension and dementia changes with age Even though anti-hypertensive treatments are common in mid-life, we have not found any trials which have investigated the long-term effects on dementia

Norton et al (4) report an RR of 1.61 (95% CI: 1.16, 2.24) for the association between mid-life hypertension and AD. This is a pooled estimate of mid-life hypertension and older age dementia (AD and all cause), based on four studies (39,42–44) reviewed in Barnes and Yaffe (2). See Table 2 in appendix for a summary. See Appendix 1 in Barnes and Yaffe (2) for the final selection of studies and slightly different cut-offs of hypertension used for the pooled estimate.

This review showed that mid-life hypertension is more strongly associated with later life dementia than hypertension in older age. The World Alzheimer's Report cited five studies from mid-life (most of which were the same as used in the Barnes and Yaffe report) and stated that mid-life hypertension is a risk factor for all-cause dementia (6). The report also highlighted the lack of any trials which examined the impact on dementia of antihypertensive treatments in mid-life. In a review by Baumgart et al (18), mid-life hypertension was listed as one of the important risk factors for dementia, with moderate strength of evidence.

Obesity

Key findings:

- evidence that mid-life obesity increases the risk of all-cause dementia (2,4). The estimate of relative risk reported by Norton et al (4) and Barnes and Yaffe (2) is 1.60 (95% CI: 1.34, 1.92)
- the prevalence of obesity in the UK is 12%, while the population-attributable risk of Alzheimer's disease for mid-life obesity is 6.6% (95% CI: 3.9, 9.8) (4)
- main caveats: the role of obesity as a risk factor for dementia may depend on age of the individual and also the type of measure used for obesity

Norton et al (4) report an RR of 1.60 (95% CI: 1.34, 1.92) for the association between mid-life obesity and AD. This figure is based on a pooled estimate from six studies of obesity (BMI = 30+) measured in mid-life and taking both AD and all-cause dementia as an outcome (2, Appendix 3). See Table 2 in appendix for a summary. Similar to hypertension, obesity in older age shows a different pattern of association with dementia, with obesity in old age becoming more of a protective factor and underweight a risk factor for dementia (2,45). This suggests reverse causation due to weight loss during the preclinical phases of dementia, experienced as early as late 50s (46).

The World Alzheimer Report (6) refers critically to the previous evidence on obesity from mid-life, but does not carry out a new meta-analysis. The criticism was mostly targeted on a review (47) published two years before Barnes and Yaffe (2). The Anstey et al (47) review did not seem to include all available evidence, which may have led to overestimation of the pooled RR (6). Barnes and Yaffe (2) included a wider range of studies, some of them not used in the Anstey et al (47) review. The World Alzheimer Report review also points to recent evidence on the use of central obesity (eg waist-to-hip ratio) instead of BMI (6). Compared to BMI, central obesity appears to be more consistently associated with a higher risk of dementia. There are, however, not enough studies yet to draw a comprehensive conclusion. Mid-life obesity has been reported as an important risk factor for dementia, with moderate evidence in two other recent reviews on the risk factors (18,19).

Cholesterol

Key findings:

- the evidence of the effects of high cholesterol on dementia is not clear (see 6,18)
- main caveats: very few studies on the association of mid-life cholesterol and dementia available. Cholesterol may be a risk factor for dementia only at very high levels (not usual in current populations)

Norton et al (4), Barnes and Yaffe (2) and the NICE review (3,5) did not include cholesterol on their list of major risk factors for dementia. Only a few studies from mid-life are available and the evidence is generally inconsistent (6,18). The World Alzheimer Report (6) suggests that cholesterol may be a risk factor for dementia only at very high levels which are not usual for most populations today. There are some reports suggesting that long-term treatment of hyperlipidaemia might be beneficial in reducing dementia risk (6,19).

Depression

Key findings:

- there is some evidence that mid-life depression increases the risk of all-cause dementia (48), with HR: 1.19 (95% CI: 1.07, 1.32)
- the prevalence of depression is 14% in the adults in the UK, while the population-attributable risk of Alzheimer's disease for depression is 8.3% (95% CI: 5.5, 11.3) (4)
- main caveats: Most studies on the association between depression and dementia focus on older ages, although they collect data on lifetime episodes. Later life depression may be difficult to disentangle from preclinical symptoms of dementia and the order in which they occur may be uncertain

Norton et al (4) report an RR of 1.65 (95% CI: 1.42, 1.92) for the association between depression and AD. This figure is based on a meta-analysis of data from studies on lifetime depression (aged 50+) and dementia (49). Their report also provides a pooled estimate for all-cause dementia (RR: 1.85, 95% CI: 1.67, 2.04). The follow-up periods are relatively short, on average five years. The World Alzheimer's Report found little evidence on mid-life depression and did not carry out any meta-analysis on mid-life depression and dementia (6).

A search for studies separating mid-life depression from old age depression yielded one study by Barnes et al (48), see Table 2 in appendix. This study used a large cohort of Californians whose depression was measured at age 44 to 60 with a self-reported item and medical records. No information on antidepressant use was collected. The participation rate for the eligible sample in this study was 71%.

The study showed that all-cause dementia (measured from age 60 onwards and three years after the depression measurement) increased by approximately 20% for mid-life depressive symptoms only (at ages 40 to 55) (HR: 1.19, 95% CI: 1.07, 1.32), 70% for late-life symptoms only (ages 57 to 90) (HR: 1.72, 95% CI: 1.54, 1.92), and 80% for both (HR: 1.77, 95% CI: 1.52, 2.06). In line with the World Alzheimer Report review on studies in older age depression and dementia (6), these results suggest that the association between late old age depression and dementia is stronger than between mid-life or younger old age depression and dementia. This may be because of fluctuation of depressive symptoms and changes in diagnosis of depression over time, because the follow-up period was not long enough for the younger participants in the sample to reach the point of diagnosis of dementia, or because older age depression may be strongly associated with dementia, making it difficult to determine causal relationships.

Mental distress

Key findings:

- the evidence on mental distress is similar to that for depression but scarce: the association from mid-life mental distress to old age dementia is weak, probably due to fluctuation and other measurement issues over time
- main caveats: different measures are used in different studies, which make it difficult to triangulate findings between studies. It is also important to note that several mental distress items overlap with depression

Mental distress was not included as a dementia risk factor in Norton et al (4) or Barnes and Yaffe (2). The NICE review (3,5) cited one study using depression and anxiety scores from mid-life which showed that mental distress was associated with dementia (OR: 1.35, 95% CI: 1.01, 1.80) (50). The association was stronger among those who were younger at baseline with OR of 2.44 (95% CI: 1.18, 5.05) for 30 to 44 years old, compared to OR of 1.24 (95% CI: 0.91, 1.69) for 45 to 60 year olds.

The World Alzheimer Report (6) cited a paper on mid-life anxiety in a sample of Welsh men (48 to 67 years) at baseline, who were followed up for dementia 17 years later (51). Higher anxiety (31st-95th centile on the Spielberger State Trait Anxiety Inventory) was associated with dementia (OR: 2.37; 95% CI: 0.98, 5.71).

A further search for recent papers found one study on 'hopelessness' in mid-life and dementia in older age. This paper reported that each step on the five-level hopelessness scale increased cognitive impairment (OR: 1.30, 95% CI: 1.11, 1.51) and Alzheimer's disease (OR: 1.37, 95% CI: 1.05, 1.78) (52). The associations remained significant after adjustment for depressive feelings and for hopelessness at baseline. Unlike the level of hopelessness score at baseline, the changes in hopelessness scores between mid-life and follow-up were not systematically related to cognitive impairment.

In another paper (53), the effect of mid-life distress (eg feelings of irritability, tension, nervousness, fear, anxiety or sleep disturbances) and psychosocial stressors (eg divorce, widowhood, work problems and illness in relative) on dementia was assessed in Swedish women. The number of psychosocial stressors at age 38 to 60 was associated with higher incidence of all-cause dementia (HR: 1.15, 96%CI: 1.04, 1.27). The number of psychosocial stressors (HR: 1.17, 95% CI: 1.03, 1.33) and long-standing distress (1968–1974–1980) (HR: 1.58, 95% CI: 1.03, 2.45) were independently associated with AD (but the paper does not show the associations with all-cause dementia).

The same research group published another paper focusing specifically on mid-life distress in the same sample of Swedish women (54). They found that later risk of dementia was higher among those who reported frequent and constant stress at the three measurement points: at age 38 to 60 (HR: 1.60, 95% CI: 1.10, 2.34), at age 44 to 66 (HR: 1.65, 95% CI: 1.12, 2.41) and age 50 to 72 (HR: 1.60, 95% CI: 1.01, 2.52). Reporting stress at one, two or three examinations was related to a sequentially higher dementia risk. Compared to women reporting no stress, hazard ratios for incident dementia were 1.10 (95% CI: 0.71, 1.71) for reporting frequent and constant stress at one examination, 1.73 (95% CI: 1.01, 2.95) for reporting stress at two examinations and 2.51 (95% CI: 1.33, 4.77) for stress at all three examinations.

Social isolation and loneliness

Key findings:

- there is no robust estimate of the impact on dementia of mid-life social isolation or loneliness
- main caveats: although there are papers looking at social isolation and/or loneliness and dementia in old age, very few studies report the long-term effects from mid-life to older age

Neither Norton et al (4) nor Barnes and Yaffe (2) included social isolation or loneliness as a dementia risk factor. One study (55) cited in the NICE review (3,5) looked at the association between social network size in mid-life and impaired cognition in older age. Each additional person in the network decreased the odds of having MMSE score lower than 27 (OR = .84, $p = .01$). Reviewed also in the NICE review, Kåreholt et al (56) found that social activities in mid-life were not associated with cognitive impairment (MMSE) in older age.

There are a number of studies looking at the concurrent association between social engagement, isolation or loneliness and dementia or cognitive functioning in older age. For instance, the World Alzheimer Report included some studies on social engagement measured in old age (6). A review by Fratiglioni et al (57) reported the links between older age social and leisure activities and dementia, with follow-up times varying between one and eight years.

An English study used social engagement independently and together with educational level and occupational complexity to measure cognitive lifestyle and risk of dementia (58). However, social engagement was measured only in older age. Because of these limitations, these studies cannot disentangle the long-term effects of social participation in mid-life. The search for more recent studies did not provide any new relevant papers on the topic. The evidence of social engagement on dementia has been previously reported to be unclear (18).

Life-long learning and mental activities

Key findings:

- there are various studies on the impact on dementia of different types of learning activities. They generally suggest an association between mid-life mental activities and lower risk of dementia in later life, some of it explained by initial educational level
- there is evidence that higher complexity of working with data among lower educated people in mid-life can reduce the risk of dementia (RR: 0.52, 95% CI: 0.29, 0.95) (59)
- main caveats: a range of different measures used which makes it difficult to compare the findings of the studies

Norton et al (4) and Barnes and Yaffe (2) report low education and cognitive inactivity to be among the strongest risk factors for Alzheimer's and all-cause dementia. However, their measures focused on formal education attended mainly before adulthood and cognitive interventions in old age, and therefore are not relevant when looking at the mid-life modifiable risk factors.

In two previous reviews on risk factors, the evidence concerning learning and mental activities was considered to be inconsistent (see 18,19). Our literature search found a number of papers, but most of them focus on short-term effects of learning activities (eg cognitive stimulation among people who already have cognitive impairment). However, there were some original studies specifically looking at mid-life mental activities.

Kåreholt et al (56) cited in the NICE review (3,5) showed that free-time political and mental activities in mid-life were associated with less cognitive impairment (MMSE) in older age among Swedish people. This paper reports a non-linear relationship between participation in these activities and cognitive impairment (MMSE).

A US study cited in the World Alzheimer Report (6) used a small sample of male twins to look at their leisure activities in mid-life (ages 40 to 50) and dementia in old age (from 63+) (60). A wide range of activities was considered including reading, studying, home chores and hobbies, family visits, clubs, following media and going to concerts, movies, theatre or museums. The study found an association between leisure activities, especially those related to social aspects, and reduced risk of dementia, when genetic, early life environment and occupational demands were adjusted in discordant twin-pair analysis (for monozygotic discordant twin-pairs OR: 0.70; 95% CI: 0.53 – 0.19).

Another stream of literature investigates occupational complexity and later life dementia. Occupational complexity relates to the amount of cognitive demand arising from interaction with things (eg operating, manipulating or handling things), people (eg

servicing, supervising or speaking with people) and data (eg computing, analysing or compiling data) in an individual's daily job, and is a different measure from occupational status. Adjustment for education and occupational status seems to weaken the association with onset of dementia, suggesting that occupational complexity may be partly overlapping with educational and occupational level, possibly acting as a mediator on the pathway to dementia. However, it is an important factor to take into account, as work forms a central part of mid-life time use and environment. Like occupational status, it has limitations in assessing careers of people with unusual jobs, homemakers and unemployed people.

There have been studies using data on twins in assessing the association between occupational complexity and dementia. One of these studies was an American twin registry study on WWII veterans (61). This study showed that working in occupations with lower complexity in terms of dealing with data was associated with a higher risk of dementia in a case-control setting (HR: 1.12; 95% CI 1.01, 1.23) and in twin-pairs discordant for dementia (HR: 1.41; 95% CI: 1.02, 1.94). The paper also showed that other job characteristics, such as mathematical, language and reasoning development in each specific job, were associated with lower risk of dementia. All these effects remained after adjusting for formal education. Occupational complexity with people and things was not associated with dementia risk.

Another twin registry study including Swedish men and women showed that those who have been working in occupations requiring high complexity in terms of working with people had a lower risk of developing dementia in case-control analysis (OR: 0.86; 95% CI: 0.76, 0.98) and in twin pairs discordant for dementia (OR: 0.47; 95% CI: 0.25, 0.88) (62). These associations were found when controlling for education. Complexity with data also showed a trend of lowered risk of developing dementia, but the association was weaker and generally not significant.

One Swedish study looked at life-long cognitive reserve in relation to childhood school grades, qualifications and occupational complexity (63). All-cause dementia risk was lower among individuals with higher childhood school grades (HR: 0.79, 95% CI: 0.68, 0.93) and was lower among individuals in data-complex occupations (HR: 0.77, 95% CI: 0.64, 0.92). Occupational complexity relating to people and things was not associated with dementia. Professional/university education predicted lower risk of dementia in minimally adjusted models (HR: 0.74, 95% CI: 0.60, 0.91), although the effect faded with adjustment for occupational complexity. The lowest risk was found in the group with both higher childhood school performance and high occupational complexity with data (HR: 0.61, 95% CI: 0.50, 0.75). The authors concluded that high occupational complexity could not compensate for the effect of low childhood grades, because dementia risk was reduced in those with higher school grades, irrespective of occupational complexity.

Another study also from Sweden showed a lower dementia risk among those with higher data-related complexity of work (RR: 0.85, 95% CI: 0.75,0.95) and among those with higher people-related complexity of work (RR: 0.88, 95% CI: 0.80, 0.97) (59). Adjusting for education led to similar results, although they were no longer statistically significant. The highest degrees of complexity of work with data that involves analysing, coordinating, and synthesizing data were associated with lower dementia risk even among lower educated subjects (RR: 0.52, 95% CI: 0.29, 0.95). See Table 2 in appendix. No gender differences were detected.

A Canadian study on occupational complexity found that the higher levels of complexity in relation to people and things had a protective effect on dementia, but only when the principal work career including this level of complexity lasted a longer time (for this they divided the length of principal work lasting less than 23 vs. 23+ years) (64). Initial unadjusted models showed several protective effects of occupational complexity, but after adjusting for various factors including education, health-related behaviours and health, the associations weakened considerably and disappeared for occupational complexity related to data.

A recent systematic review of psychosocial work environment on cognition and dementia in later life (65) included four of the studies reported above (59,61,62,64). The review did not carry out a meta-analysis on the results, but drew conclusions based on a narrative analysis that work complexity related to data and, to some extent, work complexity related to people are associated with the risk of dementia in later life. The associations may be partly due to reverse causality: people may select into occupations requiring more data or people complexity because of their initial higher cognition. The associations with dementia tend to weaken or even disappear when adjustment is made for education or earlier life cognition. Some of the effects remained after adjusting for earlier educational attainment, however, suggesting a potential independent or mediating effect of occupational complexity.

Studies have also looked at older age at retirement and longer work careers as potential promoters of better cognitive functioning and reduced risk of dementia. Although there is some indication of reduced risk of dementia related to longer work careers, the studies point to the difficulty of disentangling causality and selection bias in this association (see 66). As the focus is on people already entering old age, the topic is outside the scope of this review which is specifically focusing on mid-life factors.

There are also papers discussing the role of life-long bilingualism as one of the potential factors contributing to cognitive reserve and postponing cognitive decline (67). However, the findings are not consistent and there are various underlying mechanisms which are not well understood (see for critical comments 68,69).

Other

A number of other risk factors, such as air pollution, heavy metals, drug abuse, sleep and hormones, have been suggested in various sources as risk factors for dementia, but there is insufficient evidence to draw conclusions in these areas (see 18, 70–73).

Multi-component approach

Key findings:

- a higher number of risk factors is associated with increased risk of dementia (7, 39)
- main caveats: very little is known about which combination of risk factors has the largest effect on dementia risk. The potential of biomarkers, genetic factors and psychosocial factors (such as social interactions and mental distress) as part of combined effects are not fully known

Although not many papers currently report the impact of a multi-component approach in mid-life on dementia in later life, this is an area which is attracting increasing attention. For instance, Andrieu and colleagues (1) suggested that trials should include multi-domain interventions and use biomarkers or genetic information. This may make it possible to provide targeted programmes which are better suited to specific subgroups of people. For example, one variant of apolipoprotein gene (APOE e4 allele) increases the risk of dementia, but it may also modify the effect of a number of risk factors for dementia (74). Compared to those without this allele, those with e4 allele have a higher risk of developing dementia which may be amplified by unhealthy lifestyles. That is, e4-carriers may be more vulnerable to environmental risk factors. The evidence is, however, inconsistent (75) and more research is needed. Genetic information may also help to tackle the issues of causality in cohort studies (76).

The multi-component approach has thus far looked at whether there is an association between the number of risk factors and onset of dementia. For example, Elwood et al (7) showed that there was a significant trend of decreasing risk of dementia when healthy lifestyles increased from 0 to 5 (including not smoking, normal weight, fruit and vegetable consumption, regular activity and light to moderate drinking). However, the confidence intervals around the findings on how much each additional healthy lifestyle reduced the risk of dementia were wide, probably due to small numbers in each subgroup.

A composite score of cardiovascular risk factors (cholesterol, hypertension, diabetes and smoking) in mid-life was found to have a dose-response association with dementia (39). Compared with those having no risk factors, the risk for dementia increased from 1.27 for people having one risk factor to 2.37 (95% CI: 1.10, 5.10) for people having all four risk factors. The study did not separate out which combinations of the risk factors would have the strongest effect.

Norton et al (4) looked at the interrelationship between the risk factors in estimating the risk of dementia. This approach aims to adjust for the combined effects, but does not study the effect of each possible combination of risk factors. The approach is useful when looking at the risk factors in isolation (as many studies do not adjust for all possible other health-related behaviours). More studies are needed to shed light on which specific combinations of health-related behaviours would be most powerful in reducing dementia risk.

There have been some interesting recent developments in measuring multi-component risk: Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score (77), Lifestyle for Brain Health (LIBRA) score (78) or chronic stress assessment (79) are examples of some new measures. A number of interventions, such as the Grey Matters study and FINGER study, focusing on multiple modifiable mid-life factors are already reporting promising results in alleviating cognitive decline and may in the future provide evidence on dementia reduction (see 80,81). A good summary of trials which include health-related behaviours can be found in Andrieu et al (1).

None of these trials, however, has as yet used dementia as an outcome, but they may do this in the future when follow-up periods are long enough. They, also, often focus only on a specific cluster of risk factors (eg cardiovascular factors), restricting the opportunity to understand the interplay between biological and psycho-social risks in old age health.

Conclusion

We have conducted and presented the findings from a focused review of the evidence on the links between dementia and a number of potential risk factors. We have concentrated on studies published since 2014 for the risk factors considered by Barnes and Yaffe (2) and Norton et al (4), and on systematic reviews published since 2000 for risk factors suggested by Public Health England but not covered by Barnes and Yaffe (2) or Norton et al (4). We have looked in particular for findings on relative risk (RR), odds ratios (OR) or hazard ratios (HR) that could be used to model the impact on future incidence and prevalence of dementia of changes in the numbers of people with the risk factors in mid-life.

We have found evidence that the following risk factors in mid-life are associated with an increased risk of dementia later in life (see Appendix Table 2 for a summary of the characteristics of the studies):

Physical inactivity in mid-life is highly prevalent and increases the risk of all-cause dementia (OR: 2.13, 95% CI: 1.11, 4.00).

Current smoking increases the risk of all-cause dementia (RR: 1.30, 95% CI: 1.18, 1.45), whereas past smoking is not associated with increased all-cause dementia risk.

Diabetes increases the risk of all-cause dementia; while the samples in several reviews include older people, there are some original studies specifically from mid-life (OR: 2.51, 95% CI: 1.10, 5.72).

Hypertension in mid-life increases the risk of all-cause dementia (RR 1.61, 95% CI: 1.16, 2.24).

Obesity in mid-life increases the risk of all-cause dementia (RR 1.60, 95% CI: 1.34, 1.92).

Depression increases the risk of all-cause dementia; while the samples in several reviews include older people, there are studies specifically for mid-life depression (HR: 1.19, 95% CI: 1.07, 1.32).

Mental activities in mid-life are associated with a lower risk of dementia in later life. For example, higher complexity of working with data among lower educated people in mid-life can reduce the risk for dementia (RR: 1.92, 95% CI: 1.05, 3.45).

We have not found robust evidence that the following suggested risk factors in mid-life are associated with an increased risk of dementia later in life:

Alcohol: while heavy and chronic drinking results in specific dementia-type symptoms, there is a lack of robust evidence of a general effect on all-cause dementia.

Diet: the evidence on diet as a risk factor for dementia is inconclusive and scarce.

Mental distress in mid-life: the evidence for an impact on risk of dementia later in life is scarce and weak.

Social isolation/loneliness: very few studies report the long-term effect of mid-life social isolation or loneliness on risk of dementia in to older age.

Air pollution, heavy metals, drug abuse, sleep and hormones have been suggested as possible risk factors, but there is insufficient evidence to draw conclusions.

It is important to recognise that:

- we have conducted a focused and not a systematic review. The aim of this study was not to conduct a systematic review but to provide evidence of value to commissioners in making decisions about what primary prevention measures to commission
- we have concentrated on risk factors in mid-life. While factors in mid-life which are found to be associated with later onset of dementia may be causative, factors associated with dementia in old age may have a more complex relationship with dementia, with causation potentially running in either direction
- the risk factors we consider are correlated. Where an intervention relates to just one risk factor and does not extend to other risk factors with which it is correlated, use of unadjusted relative risk estimates would overstate the likely impact of the intervention: adjusted relative risk estimates should be used when assessing the likely impact on future dementia incidence
- reduction in some risk factors, for example, smoking affects mortality as well as dementia incidence. People who change behaviours in middle age may experience considerably improved life expectancy. It is therefore possible that, while they may gain a reduced risk of onset of dementia at a given age, for example in their seventies, their lifetime risk of onset of dementia may rise and be higher than if they had not changed their behaviours

Areas for future research

Further studies are required to examine the impact on incidence of dementia of life-style changes in mid-life. The studies should follow up a cohort of people in mid-life recording at regular intervals the amount of physical exercise they undertake, the amount of alcohol they consume and other possible risk factors. They should then continue to follow up the cohort into late old age, recording at regular intervals their cognitive function, onset of dementia and quality of life. Such studies, however, are complex, of very long duration and costly.

The association between the different risk factors needs to be studied in greater detail to explore the impact of changes in combinations of risk factors. It will be important to understand the impact on incidence of dementia in old age of changes at different ages in different combinations of risk factors.

A number of potential risk factors have been studied very little. For example, social isolation and loneliness, even though there is a wealth of evidence for the effect of social interaction and support on well-being and general level of cognition in older age. Research is warranted on the impact on incidence of dementia of these potential risk factors.

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Appendix 1: Search strategy

The search for evidence on the associations between the mid-life risk factors and dementia followed the steps below.

1. We used the findings of Norton and colleagues (4) based on the Barnes and Yaffe review of risk factors (2). For the seven risk factors which they considered we searched for very recent systematic reviews or primary empirical studies published from January 2015 onwards for any possible new evidence or more comprehensive reviews. Following Norton et al (4), we considered a review to be more comprehensive if it included a larger number of studies than any previous reviews and pooled them using an appropriate meta-analytic method.
2. For the risk factors which Norton et al (4) did not consider - alcohol, diet, mental distress, social isolation and loneliness, and air pollution, we searched for relevant papers in the recent NICE review on midlife risk factors and dementia in older age (3,5) and, when necessary, conducted additional searches for papers published since 2000. We also checked the World Alzheimer's Report 2014 (6) for any relevant studies on midlife risk factors and older age all-cause dementia which our search had not identified. For the search strategy and search terms used in these previous reports, please see (2), (3), (4), (5) and (6).

Search strategy for new papers published between January 2015 and May 2016

We selected the papers showing new evidence or more comprehensive reviews than published in Norton et al (4) based on Barnes and Yaffe (2), NICE review (3, 5) or World Alzheimer Report (6). The review was considered to be more comprehensive if it included a larger number of studies than any previous reviews and pooled them using an appropriate meta-analytic method, the same criterion as in (4). For new evidence which has not been a focus in the previous reports (eg social isolation, mental distress), we searched all papers published from 2000 to May 2016.

For more comprehensive reports, we covered the time between January 2015 and May 2016 (to update the searches done in the previous reports by Barnes and Yaffe, NICE and World Alzheimer Report). We searched the main data bases also used in the NICE review: MEDLINE, EMBASE PsycINFO, Cochrane and organisational databases. The search terms listed in the NICE review were used and for the risk factors not included in NICE, the terms used are listed in Appendix table 1.

Table 1 shows the numbers of new studies found and how many of them were included in this report. The most frequent reasons for excluding studies were: that they did not use a relevant age group for baseline risk factors (ages 40 to 64) or for outcome measures (ages 65+); they did not include at least one midlife risk factor and/or dementia in old age as outcome; they did use data collected in non-OECD countries; or they did not report a usable estimate of the risk (RRs, ORs or HRs for the associations). All the studies we found that fulfilled these criteria were of good quality.

Appendix Table 1 Additional literature searched on the associations between midlife risk factors and dementia

Midlife risk factor	Time period	Search words for the risk factor(s)	Electronic search for title and abstract screening	Full text screening	Included in the report
Physical inactivity	2015-16	See NICE (3,5)	72	3	0
Alcohol	2015-16	See NICE (3,5)	12	2	1
Smoking	2015-16	See NICE (3,5)	66	4	1
Diet	2015-16	See NICE (3,5)	95	3	3
Diabetes	2000-16	See NICE (3,5)	525	5	1
Hypertension	2015-16	See NICE (3,5)	115	6	0
Obesity	2015-16	See NICE (3,5)	121	2	0
Cholesterol	2015-16	See World Alzheimer Report (6)	46	4	0
Depression and mental distress	2000-16	Depression, depressive symptoms, mental distress	985	25	4
Social isolation and loneliness	2000-16	Social isolation, social contacts, loneliness	70	3	0
Life-long learning and mental activities	2000-16	Mental activities, leisure activities, occupational complexity	111	14	10
Other factors	2000-16	Sleep, drugs, toxins, heavy metals, pollution, hormones	379	5	0

Appendix Table 2: Key evidence on risk factors for dementia

Risk factor/source	Definition/measure of exposure	Outcome	Type of study	Estimate/ 95% CI
Physical inactivity Rovio, 2005	Midlife physical activity: self-report on at least 20–30 minutes and causes breathlessness and sweating at least twice a week (reversed scale)	All-cause dementia	Original study, population-based cohort (CAIDE) <i>n</i> = 1,449	OR 2.13 1.11 – 4.00
Smoking Zhong, 2015	Current smoking	All-cause dementia	Meta-analysis of 37 original studies <i>n</i> = 960,280	RR 1.30 1.18 - 1.45
Diabetes Xu, 2009	Midlife diabetes (type I or type II) from inpatient registry and self- and informant-reported history of diabetes diagnosis ^a	All-cause dementia	Original study, co-twin matched case-control, <i>n</i> of pairs = 4,274, of which 210 discordant in dementia	OR 2.51 1.10 - 5.72
Diabetes Toppanen, 2013	Midlife diabetes (type I or type II) based on reimbursed diabetes medication in the National Prescription Register and Special Reimbursement Register ^b	Alzheimer's disease	Original study with age, sex and region of residence case-control <i>n</i> of pairs = 28,093	OR 1.60 1.34 - 1.84
Hypertension Barnes & Yaffe, 2013	Midlife hypertension: blood pressure measure cut-off, medication and self-report ^c	All-cause dementia	Meta-analysis of four original studies <i>n</i> = 29,287	RR 1.61 1.16 – 2.24
Obesity Barnes & Yaffe, 2013	Midlife obesity: BMI≥30	All-cause dementia	Meta-analysis of six original studies <i>n</i> = 24,247	RR 1.60 1.34 – 1.92
Depression Barnes, 2012	Midlife depression: self-report binary question (“Do you often feel unhappy or depressed?”) and medical records ^d	All-cause dementia	Original study, population-based cohort <i>n</i> = 13,535	HR 1.19 1.07 – 1.32
Low occupational complexity Karp, 2009	Classification of lifetime main occupation according to the highest degree of complexity of work with data ^e (reversed scale)	All-cause dementia	Original study, population-based cohort <i>n</i> = 931	RR 1.92 1.05 - 3.45 for low educated group

^a (ICD-7 codes 260, ICD-8 and -9 codes 250); ^b Diabetes diagnosed on the basis of fasting capillary blood glucose concentration (SII reimbursement criterion cut-off is 7.0 mmol/L) or 2-h glucose concentration if an oral glucose tolerance test has been performed (cut-off 11.1mmol/L); ^c varying cut-offs SBP ≥ 140 mm Hg in two studies and SBP ≥ 160 mm Hg in two studies. One study used information on medication and self-report of diagnosis, in addition to a cut-off; ^d on ICD-9 diagnostic codes 296.2 (major depressive disorder), 296.3 (recurrent major depressive disorder), 298.0 (depressive type psychosis), 300.4 (dysthymic disorder) and 311.0 (depressive disorder not elsewhere classified); ^e Analysing, coordinating, and synthesizing data.