Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies

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Objective: Dementia has a multifactorial etiology, but the importance of individual health and lifestyle related risk factors is often uncertain or based on few studies. The goal of this paper is to identify the major modifiable risk factors for dementia as a first step in developing an effective preventive strategy and promoting healthy late life cognitive functioning.

Methods: A mixed-method approach combined findings from a systematic literature review and a Delphi consensus study. The literature search was conducted in PubMed and updated an earlier review by the United States National Institutes of Health from 2010. We reviewed the available evidence from observational epidemiological studies. The online Delphi study asked eight international experts to rank and weigh each risk factor for its importance for dementia prevention.

Results: Out of 3127 abstracts, 291 were included in the review. There was good agreement between modifiable risk factors identified in the literature review and risk factors named spontaneously by experts. After triangulation of both methods and re-weighting by experts, strongest support was found for depression, (midlife) hypertension, physical inactivity, diabetes, (midlife) obesity, hyperlipidemia, and smoking, while more research is needed for coronary heart disease, renal dysfunction, diet, and cognitive activity.

Conclusions: Findings provide good support for several somatic and lifestyle factors and will be used to inform the design of a new multicenter trial into dementia prevention. Copyright © 2014 John Wiley & Sons, Ltd.

Key words: epidemiology; risk factors; prevention; dementia; public health

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Introduction

The total number of people with dementia will increase because of the aging of the population (Ferri et al., 2005; Hebert et al., 2013), and so will associated care costs (Hurd et al., 2013), despite declining prevalence and incidence rates (Schrijvers et al., 2012; Matthews et al., 2013), making dementia a global public health
priority (World Health Organization, 2012). Identifying major determinants for dementia is important for understanding disease mechanisms and designing effective preventive strategies in the absence of curative treatment (Scalco and van Reekum, 2006).

Potentially modifiable risk factors for cognitive decline and dementia include depression, diabetes mellitus, smoking, vegetable intake, physical activity, and cognitive training (Plassman et al., 2010; Williams et al., 2010). A recent review suggested that seven major modifiable risk factors (diabetes mellitus, midlife hypertension, midlife obesity, smoking, depression, and cognitive and physical inactivity) account for about 50% of all cases of Alzheimer’s disease (AD) dementia (Barnes and Yaffe, 2011). Yet, the quality of evidence for several of these factors has been judged to be low because most evidence comes from observational studies (Plassman et al., 2010). In the absence of well-designed randomized controlled trials (RCTs) for most risk and protective factors, experts’ opinion about the evidence from observational studies might offer an alternative approach to weight the current evidence regarding a factor’s importance for primary prevention.

Therefore, the current study aimed (1) to update the evidence base regarding major risk factors for dementia in a systematic review and (2) to obtain a better balanced account of their (relative) importance for dementia prevention in a Delphi expert study (Dalkey and Helmer, 1963).

Methods

Phase 1: systematic review

Data sources and searches. PubMed was searched using the search strategy of a recent United States NIH report that evaluated all literature between 1984 and 27 October 2009 (Plassman et al., 2010; Williams et al., 2010). However, a more generic search term was used as to be more inclusive and potentially identifying novel risk factors studied only recently.

Study selection. Inclusion criteria were as follows: population-based sample, prospective design (cross-sectional and retrospective case–control studies were excluded), ≥200 participants, aged ≥45 years, ≥1 year follow-up, and published between 28 October 2009 and 5 December 2012. For the full search term, see Appendix 1 of the Supporting Information.

Data extraction. A single rater (S.K.) screened abstracts for broad suitability. Two investigators (K.D., J.L.M.) then extracted relevant information from full texts such as sample size, age range, follow-up period, outcome (e.g. dementia, cognitive impairment, cognitive decline), predictors, and association.

Quality assessment. Quality aspects of the included cohort studies were assessed with the 8-item Newcastle Ottawa Scale (Wells et al., 2000).

Phase 2: Delphi study—first round

The Delphi study was conducted among experts in dementia epidemiology and prevention. Inclusion criteria for experts were as follows: (1) associate professor or higher; (2) proven track record in the field; (3) board members of professional organizations for dementia research; and (4) leaders of prominent research groups. A dedicated website was constructed hosting an online survey, thereby blinding participants to contributions from other participants. Experts were provided with a link and unique access code, which allowed blinding of the moderator (S.K.) when processing participants’ responses. Twenty experts were invited, of which eight agreed (40% response rate), one initially agreed but did not complete the survey, four declined (two lack of time, two referred to colleague), and seven did not respond after three reminders. In the first round (February–March 2013), each participant freely named potential risk factors for all-type dementia in subjective order of importance and indicated potential interactions. Individual responses were then given a “rank score” (RS) (see Appendix 2 of the Supporting Information for the formula). Individual experts’ RS were then summed across experts for a factor’s total RS.

Phase 3: synthesis of information

Next, evidence was aggregated by compiling lists with the major modifiable risk factors from both the literature review (the number of encountered studies, consistency in direction of association, effect size) and the first Delphi round (risk factor’s total RS). The preliminary risk factor inventory included the highest-ranking factors from both methods.

Phase 4: Delphi study—second round

In the second round (June–September 2013), the same experts were provided with the results from the systematic review and the aggregated results of the first Delphi round. They were invited to comment on the
preliminary risk factor inventory. Experts then weighted the risk factors in order of importance for primary prevention of dementia by general practitioners. For this, they were given 100 points, which could be distributed across risk factors (more points = more important). Summation of these points yielded the final ranking and inventory of most important risk factors.

Results

Systematic review

The search returned 3127 abstracts, of which 320 (10.2%) were included for full-text scrutiny. Of these, 29 were excluded for different reasons (Figure 1). From all encountered risk factors (Appendix 3 of the Supporting Information), we identified the ones studied most extensively and calculated their consistency of association (Table 1). Several factors showed good (i.e. ≥80%) consistency: depression, diabetes, and smoking. While there was considerable overlap with factors reported in our reference reviews (Plassman et al., 2010; Barnes and Yaffe, 2011), some were not included before but seemed promising candidates: coronary heart disease, renal dysfunction, and inflammation. Quality assessment of 289 studies showed that all of these were of sufficient quality to include in our analyses (mean = 7.92, SD = 0.64, median = 8, range = 6–9). For two studies, sufficient information could be extracted on the basis of the abstract.

First Delphi round

Experts named 25 modifiable risk factors (Appendix 4 of the Supporting Information). Table 2 shows those with the highest RS. Also, 10 non-modifiable risk factors were named, with the highest RS for age, generic genetic effects, the apolipoprotein E (APOE) gene in particular, sex, and family history of dementia. No interaction between risk factors was named twice.

Figure 1  Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)—style flowchart of study selection and review.
In this round, experts assigned points (100 in total) to the modifiable risk factors that were most prominent in the review and first Delphi (see also Tables 1 and 2). Most points were given to depression, diabetes, cognitive activity, physical activity, and hypertension. Mediterranean diet, obesity in midlife, smoking, alcohol intake (low/moderate), and cholesterol/hyperlipidemia were considered relatively less important (Table 3).

Summary of major modifiable risk factors

Table 4 shows the final inventory based on the review, Delphi study, and the two reference reviews (Plassman et al., 2010; Barnes and Yaffe, 2011). Relative risks (RR) for dementia were extracted from existing meta-analyses.

Second Delphi round

In this round, experts assigned points (100 in total) to the modifiable risk factors that were most prominent in the review and first Delphi (see also Tables 1 and 2). Most points were given to depression, diabetes,
Depression. In our review, depression increased the risk of cognitive decline or dementia in 19 out of 21 studies (Boyle et al., 2010; Dotson et al., 2010; Greendale et al., 2010; Johansson et al., 2010; Peters et al., 2010; Ritchie et al., 2010; Rosenberg et al., 2010; Saczynski et al., 2010; Sander et al., 2010; Bielak et al., 2011; Goveas et al., 2011; Kim et al., 2011b; Köhler et al., 2011; Lenoir et al., 2011; Li et al., 2011; Mejia-Arango and Gutierrez, 2011; Potvin et al., 2011; Unverzagt et al., 2011b; Royall et al., 2012). Two studies found no association (90% consistency; Chodosh et al., 2010; Jajodia and Borders, 2011). Experts rated depression as the most important risk factor in the second Delphi round. Recent meta-analyses report a 90% higher risk for AD (Ownby et al., 2006), or 85% higher risk for all-type dementia (Diniz et al., 2013). Whether depression is a causal risk factor or a vulnerability marker is controversial (Butters et al., 2008). Next to neurodegeneration, cerebrovascular pathology might be involved (Butters et al., 2008; Köhler et al., 2011), which is in line with the notion of a 2.5 times increased risk for vascular dementia (Diniz et al., 2013).

Diabetes. Nineteen studies reported on diabetes, of which 17 found an increased effect (Alonso et al., 2009; Abbatecola et al., 2010; Crowe et al., 2010; Rastas et al., 2010; Reitz et al., 2010b; Ritchie et al., 2010; Yen et al., 2010; Cheng et al., 2011; Christman et al., 2011; Kimm et al., 2011; Mejia-Arango and Gutierrez, 2011; Ohara et al., 2011; Ronnemaa et al., 2011; Wessels et al., 2011; Creavin et al., 2012; Gaussiain et al., 2012; Wang et al., 2012). Two studies found no association (89% consistency; Euser et al., 2010; van Vliet et al., 2010). Experts ranked diabetes as the second most important risk factor in both Delphi rounds. In a meta-analysis of six prospective studies, diabetes carried a 47% increased risk of dementia (Lu et al., 2009). The pathological mechanisms linking diabetes to cognitive decline and dementia are

Table 4 Effects of modifiable risk factors for dementia based on all available evidence from Delphi expert survey and systematic reviews

<table>
<thead>
<tr>
<th></th>
<th>Delphi ranking Round 1</th>
<th>Delphi ranking Round 2</th>
<th>Consistency of association</th>
<th>Consistency of association</th>
<th>Included in review of Barnes and Yaffe (2011)</th>
<th>Relative risk extracted from existing meta-analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>4</td>
<td>1</td>
<td>21</td>
<td>90%</td>
<td>X</td>
<td>1.85 (Diniz et al., 2013)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2</td>
<td>2</td>
<td>19</td>
<td>89%</td>
<td>X</td>
<td>1.47 (Lu et al., 2009)</td>
</tr>
<tr>
<td>Cognitive activity</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>100%</td>
<td>8</td>
<td>0.38 (Anstey et al., 2013)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>71%</td>
<td>15</td>
<td>X 1.39 (Hamer and Chida, 2009)</td>
</tr>
<tr>
<td>(Midlife)</td>
<td>1</td>
<td>5</td>
<td>21</td>
<td>76%</td>
<td>40</td>
<td>X 1.61 (Barnes and Yaffe, 2011)</td>
</tr>
<tr>
<td>Diet</td>
<td>10</td>
<td>6</td>
<td>5</td>
<td>60%</td>
<td>7</td>
<td>— 0.60 (Psaltopoulou et al., 2013)</td>
</tr>
<tr>
<td>(Midlife)</td>
<td>6</td>
<td>7</td>
<td>14</td>
<td>50%</td>
<td>17</td>
<td>X 1.60 (Barnes and Yaffe, 2011)</td>
</tr>
<tr>
<td>Smoking</td>
<td>11</td>
<td>8</td>
<td>13</td>
<td>77%</td>
<td>27</td>
<td>X 1.59 (Peters et al., 2008)</td>
</tr>
<tr>
<td>Low/ moderate alcohol</td>
<td>7</td>
<td>9</td>
<td>3</td>
<td>33%</td>
<td>10</td>
<td>— 0.74 (Anstey et al., 2009)</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>80%</td>
<td>15</td>
<td>— 1.54 (Anstey et al., 2013)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>—</td>
<td>11</td>
<td>10</td>
<td>80%</td>
<td>10</td>
<td>— 1.36 (Kalantarian et al., 2013)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>—</td>
<td>—</td>
<td>9</td>
<td>100%</td>
<td>9</td>
<td>— 1.39 (Etgen et al., 2012)</td>
</tr>
<tr>
<td>Low</td>
<td>—</td>
<td>—</td>
<td>5</td>
<td>80%</td>
<td>11</td>
<td>—</td>
</tr>
<tr>
<td>unsaturated fat</td>
<td>—</td>
<td>—</td>
<td>5</td>
<td>60%</td>
<td>5</td>
<td>— 1.45 (Koyama et al., 2013)</td>
</tr>
</tbody>
</table>

aN Number of studies based on “Mediterranean diet” and “unhealthy diet.”

bMediterranean diet.

cMeta-analysis on Mediterranean diet.

dMeta-analysis on atrial fibrillation.

eMeta-analysis based on pooled effect for C-reactive protein.
not fully understood but might include metabolic, vascular, and inflammatory processes. Insulin deficiency is linked to the metabolism of the AD pathology including amyloid beta and tau (Qiu and Folstein, 2006; Park, 2011).

**Cognitive activity.** From four studies on high cognitive activity (Marquie et al., 2010; Valenzuela et al., 2011; Sattler et al., 2012; Wilson et al., 2012), all found a decreased risk (100% consistency). Experts rated cognitive inactivity as the third most important factor. Pooled effect sizes of two large prospective studies suggest a 62% lower risk of AD in older adults who engage in cognitive stimulating leisure activities (Anstey et al., 2013). Yet, another large prospective study found no support (Eriksson Sorman et al., 2014). Engagement in cognitively stimulating activities has generally been associated with a reduced risk for cognitive decline (Marquie et al., 2010; Wilson et al., 2012), mild cognitive impairment (MCI) (Sattler et al., 2012), and dementia (Valenzuela et al., 2011; Sattler et al., 2012). However, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial found no effect of cognitive training on dementia risk after 5 years (Unverzagt et al., 2012). Cognitive activity may delay cognitive decline by increasing an individual’s cognitive reserve (Sattler et al., 2012).

**Physical activity.** Out of seven studies on low physical activity, five found an increased risk (Angevaren et al., 2010; Jedrzewski et al., 2010; Kim et al., 2011a; Buchman et al., 2012; Gelber et al., 2012), whereas two studies found no association (71% consistency; Sattler et al., 2011; Ku et al., 2012). Experts rated (high) physical activity as the fourth most important factor. Physical inactivity increased the risk of developing dementia in a meta-analysis of 14 prospective studies by 39% (Hamer and Chida, 2009). However, another report found insufficient evidence supporting an association between physical inactivity and dementia (Plassman et al., 2010). Definition of the optimal dose of physical activity is difficult, because studies rarely include measures of both frequency and intensity of exercise. Some studies have shown that physical activity might influence cognition by counteracting vascular risk factors such as hypertension, diabetes, and obesity (Hughes and Ganguli, 2009; Angevaren et al., 2010), whereas a large body of animal research has demonstrated that physical activity may directly affect the brain, independent from its cardioprotective effects (Voss et al., 2013).

**Hypertension.** Out of 21 studies, five focusing on mid-life hypertension, 13 on late-life hypertension, and three examined both. Seven studies into midlife hypertension found an increased risk (Alonso et al., 2009; Launer et al., 2010; Debette et al., 2011; Kimm et al., 2011; Ninomiya et al., 2011; Ronnemaa et al., 2011; Creavin et al., 2012), whereas one study found no association (88% consistency; Joas et al., 2012). For late-life, 12 studies found an increased risk (Bermejo-Pareja et al., 2010; Reitz et al., 2010b; Hajjar et al., 2011; Kimm et al., 2011; Mejia-Arango and Gutierrez, 2011; Ninomiya et al., 2011; Ogunniyi et al., 2011; Ronnemaa et al., 2011; Unverzagt et al., 2011a; Yang et al., 2011; Murray et al., 2012; Thorvaldsson et al., 2012), two a decreased risk (Rastas et al., 2010; Benetos et al., 2012), and two no association (75% consistency; Johnson et al., 2010; van Vliet et al., 2010; Debette et al., 2011). Experts ranked hypertension as the fifth most important factor. Midlife hypertension is associated with a 61% increased risk of developing dementia (Barnes and Yaffe, 2011). Two meta-analyses from 2011 found no association between hypertension and risk of AD (Guan et al., 2011; Power et al., 2011b), but they combined studies into midlife and late-life hypertension (Qiu, 2012). A meta-analysis of nine placebo controlled trials showed positive effects of blood pressure-lowering therapies, although interventions were not started in midlife (Staessen et al., 2011). Possible mechanisms include atherosclerosis, white matter lesions, increased neuritic plaques and tangles, and atrophy (Hughes and Ganguli, 2009).

**Diet.** Out of the three studies, two associated a healthy dietary pattern with a lower risk (Gu et al., 2010b; Shatenstein et al., 2012). One study found no association (67% consistency; Gelber et al., 2012). Experts rated healthy diet (i.e. Mediterranean diet) as the sixth most important factor.

Regarding the Mediterranean diet, one study found no association (Cherbuin and Anstey, 2012) and another study showed a protective association (Gu et al., 2010a). A Mediterranean diet is characterized by (1) a high consumption of olive oil, fruits, vegetables, nuts, seeds, beans, and fish; (2) a moderate consumption of wine or dairy products such as cheese or yogurt; and (3) a low consumption of meat (Gu et al., 2010a; Cherbuin and Anstey, 2012). Adherence might protect against dementia (Psaltopoulou et al., 2013). A recent systematic review of 12 studies (11 observational studies and one RCT) found that higher adherence was associated with less cognitive decline and a reduced risk of AD, but not MCI (Lourida et al., 2013).
Obesity. Fourteen studies reported on obesity, of which six focused on midlife obesity and eight on late-life obesity. Midlife obesity increased the risk in four studies (Dahl et al., 2010; Hassing et al., 2010; Debette et al., 2011; Xu et al., 2011), whereas two found no association (67% consistency; Gustafson et al., 2009; Gelber et al., 2012). In late-life, three studies found an increased risk (Reitz et al., 2010b; Kerwin et al., 2011; Luchsinger et al., 2012), two studies found a decreased risk (Forti et al., 2010; Power et al., 2011a), and three studies found no association (38% consistency; Abbatecola et al., 2010; Forti et al., 2010; van Vliet et al., 2010; Power et al., 2011a; Dolcos et al., 2012). Experts ranked midlife obesity as the seventh most important factor. In meta-analyses, midlife obesity has been associated with a 60% increased risk of dementia (Barnes and Yaffe, 2011). Overweight and obesity are interrelated and have effects on other risk factors such as hypertension, diabetes, and hyperlipidemia (Gustafson, 2006). Adiposity may influence brain health through different biological mechanisms including inflammatory cytokines (Gustafson, 2006; Whitmer, 2007).

Smoking. Thirteen studies reported on smoking. Ten studies found an increased risk (Alonso et al., 2009; Collins et al., 2009; Reitz et al., 2010b; Rusanen et al., 2010; Chen et al., 2011; Rusanen et al., 2011; Zhou et al., 2011; Gelber et al., 2012; Sabia et al., 2012; Weuve et al., 2012), one study suggested that (current and past) smoking may be a protective factor for cognitive decline (Wang et al., 2010a), whereas two studies found no association (77% consistency; Caselli et al., 2011; Gausson et al., 2012). Experts rated smoking as the eighth most important one. In a meta-analysis of 8 prospective studies, current smoking was associated with a 59% increased risk of AD (Peters et al., 2008). Smoking is a catalyst in the process of cognitive decline, although the exact mechanisms are still unknown. Smoking might have (indirect) effects on several vascular, inflammatory, and degenerative processes (e.g. oxidative stress; Collins et al., 2009; Rusanen et al., 2011) including atherosclerosis (HHS, 2004).

Alcohol consumption. Three studies reported on alcohol consumption. One found that low-to-moderate alcohol reduced the risk (Weyerer et al., 2011), while another study did not confirm this (Lobo et al., 2010). The remaining study suggested that daily drinking was associated with an increased risk of dementia (Zhou et al., 2011). Experts ranked low-to-moderate alcohol consumption as the ninth most important factor of dementia. A meta-analysis of 7 prospective studies found a 26% reduced risk in low-to-moderate drinkers (Anstey et al., 2009). A putative protective effect has been linked to cardiovascular (e.g. lowering of cholesterol, reducing blood pressure, blood clotting, and ischemic attacks) and anti-amyloidogenic effects of wine flavonoids (Commmenges et al., 2000; Agarwal, 2002). On the other hand, chronic alcohol abuse is associated with a number of brain-related diseases such as the Wernicke–Korsakoff’s syndrome, alcoholic dementia, stroke, and cerebellar degeneration (Zahr et al., 2011). Alcohol-related brain damage can be caused by neurotoxicity, nutritional deficiency, neuro-inflammation, and changes in neurotransmitter systems (Zahr et al., 2011).

Cholesterol/hyperlipidemia. Ten studies reported on high cholesterol levels, of which eight found an increased risk (Alonso et al., 2009; Reitz et al., 2010a; Reitz et al., 2010b; Reynolds et al., 2010; Zuliani et al., 2010; Beydoun et al., 2011; Song et al., 2012; van den Kommer et al., 2012), and two studies found no association (80% consistency; Mielke et al., 2010; van Vliet et al., 2010). Experts ranked high cholesterol as the 10th most important factor. A meta-analysis of prospective studies from 2008 implied that high midlife total serum cholesterol increases the risk of dementia (Anstey et al., 2008), whereas late-life cholesterol does not (Tan et al., 2003; Reitz et al., 2004). A recent meta-analysis of five prospective studies reported a 54% increased risk in older adults with high levels of serum cholesterol (Anstey et al., 2013). There are several putative mechanisms linking cholesterol and dementia. High levels of brain cholesterol accelerate AD progression by influencing the beta-amyloid metabolism and neurofibrillary tangle formation (Burns and Duff, 2002; Reid et al., 2007).

Coronary heart disease. Eight studies of 10 found an increased risk in people with coronary heart disease (Bunch et al., 2010; Eriksson et al., 2010; Bunch et al., 2011; Chen et al., 2011; Dublin et al., 2011; Unverzagt et al., 2011a; Hjelm et al., 2012; Kerola et al., 2012), and two studies found no association (80% consistency; Reitz et al., 2010b; Marengoni et al., 2011). Experts did not name coronary heart disease in the first Delphi round, and only one expert suggested to include it in the second round. Several forms of heart disease have been related to cognitive decline (Justin et al., 2013), with atrial fibrillation being studied most extensively (Kwok et al., 2011; Santangeli et al., 2012; Kalantarian et al., 2013). A meta-analysis of 7 prospective studies found a 36%
higher risk for AD in people with atrial fibrillation (Kalantarian et al., 2013). A large cohort study reported an association between atherosclerosis and dementia (van Oijen et al., 2007). The association between heart disease and dementia could be (partly) due to shared risk factors (e.g. hypertension, diabetes, high cholesterol levels, smoking, obesity), leading to vascular insufficiency, reduced cerebral blood flow, and ischemic brain lesions (Justin et al., 2013; Kalantarian et al., 2013).

Renal dysfunction. All nine studies on renal dysfunction encountered in the review found an increased risk (100% consistency; Khatiri et al., 2009; Jassal et al., 2010; Wang et al., 2010b; Barzilay et al., 2011; Helmer et al., 2011; Kurella Tamura et al., 2011; Sasaki et al., 2011; Feng et al., 2012; Sajjad et al., 2012). Experts did not name renal dysfunction in first or second Delphi round. Other considered it a new candidate risk factor (Bugnicourt et al., 2013). A meta-analysis of longitudinal studies in patients with chronic kidney disease found a 39% increased risk for cognitive impairment (Etgen et al., 2012). The underlying mechanisms have not been elucidated, but anemia and cerebral small vessel disease might play a role (Ikram et al., 2008).

Unsaturated fat intake. Five studies reported on unsaturated fat intake. Four studies found a decreased risk (Gao et al., 2011; Lopez et al., 2011; Naqvi et al., 2011; Samieri et al., 2011), whereas one study found an increased risk (80% consistency; Cherbuin and Anstey, 2012). Experts did not name fat intake as a specific risk factor. Observational studies suggest that higher intake of omega-3 polyunsaturated fatty acids may be associated with a reduced risk of dementia (Morris et al., 2003; Devore et al., 2009; Sydenham et al., 2012). A meta-analysis of 10 RCTs found no effect in healthy individuals or patients with AD, but some support for improved memory, attention, and processing speed in those with cognitive impairment no dementia (Mazereeuw et al., 2012).

Inflammation. Five studies reported on serum inflammatory markers. Three studies found a positive association (Mooijaart et al., 2011; Dlugaj et al., 2012; Jenny et al., 2012), whereas two studies found no association (60% consistency; Laurin et al., 2009; Gallacher et al., 2010). Different markers of inflammation, for example, C-reactive protein (Laurin et al., 2009; Gallacher et al., 2010; Mooijaart et al., 2011; Dlugaj et al., 2012; Jenny et al., 2012) or interleukin-6 (Gallacher et al., 2010; Mooijaart et al., 2011; Dlugaj et al., 2012; Jenny et al., 2012), make comparisons of individual studies difficult. Inflammation was not named by experts in the Delphi study. Inflammation has been linked to the pathogenesis of dementia (McGeer and McGeer, 2010). A meta-analysis of observational studies found that high C-reactive protein levels increase dementia risk by 45%, while a 32% increased risk was found for higher interleukin-6 levels (Koyama et al., 2013). Inflammation might also be a mediator or moderator of the effect of other risk factors, including metabolic changes (Yaffe et al., 2004).

Discussion

This study weighted the evidence for major dementia risk factors by conducting a systematic literature review on the evidence from epidemiological studies, followed by expert consensus in a Delphi study. Support was found for several somatic and lifestyle factors: depression, (midlife) hypertension, physical inactivity, diabetes, (midlife) obesity, hyperlipidemia, and smoking. In addition, some risk factors were identified that need further validation (few studies, inconsistent results): coronary heart disease, renal dysfunction, diet, and cognitive activity. Modifiable risk factors have been estimated to account for 50% of the prevalence of AD dementia (Barnes and Yaffe, 2011). Evidence mostly comes from observational studies (Plassman et al., 2010; Barnes and Yaffe, 2011), which are subject to methodological limitations such as exposure and outcome misclassification, selection, and confounding, leading to uncertainty regarding their importance. Our approach of adding experts’ opinions to the findings of a systematic review, enriched by existing meta-analyses, make a strong case for targeting these factors in dementia prevention trials.

There is still considerable low public awareness that dementia risk may depend to some extent on modifiable lifestyle factors (Farrow, 2008). This has important consequences: persons-at-risk do not seek help, they receive insufficient and inaccurate care and support from their social environment, and dementia is stigmatized (Ferri et al., 2005). The present findings could inform the design of prevention programs or training curricula for health care providers. Recently, the Alzheimer’s Association and Centers for Disease Control and Prevention developed such an initiative (Alzheimer’s Association and Centers for Disease Control and Prevention, 2013; The Lancet Neurology,
Findings hopefully stimulate further research into the identified candidate risk factors.

It is also noteworthy that experts did not agree on possible interactions between risk factors. Several commented on the scarcity of data available to make an “educated guess”. It is becoming increasingly clear that AD and other common types of dementia show a mixed pathology (MRC-CFAS, 2001; Bennett et al., 2013; Provenzano et al., 2013). Risk factors are unlikely to occur in isolation, but might interact in a synergistic or antagonistic way, or form clusters (e.g. metabolic syndrome). Obviously, more research into the etiological complexity of dementia using advanced statistical methods is needed to obtain a better view of the interrelated action of risk factors. Ongoing and planned dementia prevention initiatives will explore optimal target populations, intervention strategies, and outcome measures that are important for future multi-national clinical trials on dementia prevention. Three large multi-domain dementia prevention studies are ongoing (Prevention of Dementia by Intensive Vascular Care (preDIVA), Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), Multidomain Alzheimer Preventive trails (MAPT); Gillette-Guyonnet et al., 2009; Richard et al., 2009; Kivipelto et al., 2013), and together form the European Dementia Prevention Initiative (EDPI; Richard et al., 2012). This initiative developed a new RCT, the Healthy Aging Through Internet Counseling in the Elderly (HATICE) to investigate whether cognitive decline or new cardiovascular disease can be prevented (Richard et al., 2012).

The focus of these intervention studies is on older adults (>60 years), while some risk factors show most effect in middle-aged persons (e.g. hypertension, obesity). Identification of midlife modifiable risk factors is crucial in order to intervene at an early stage of the disease process. The In-MINDD (Innovative Midlife Intervention for Dementia Deterrence) project aims to decrease dementia risk and/or delay its onset through lifestyle interventions in midlife. The current findings will then be used to inform the design of a European multicenter trial into dementia prevention in individuals aged 40 to 60 years as part of the In-MINDD project.

The primary strength of our study is the use of both quantitative and qualitative information to identify dementia risk and protective factors. This allowed for cross-validation and triangulation of the findings in order to arrive at what appears as current best evidence. In addition, we compared and pooled our findings with the results and from recent meta-analyses and systematic reviews to arrive at a final risk inventory. Second, our broad search term yielded more results, and we therefore identified some candidate risk factors (e.g. renal dysfunction) that were not included in previous reviews (Plassman et al., 2010; Barnes and Yaffe, 2011).

Still our study has several limitations. First, we focused only on observational studies because of the nature of this study and research project. For some of the identified factors (e.g. diet, cognitive activity, physical activity), good evidence comes from RCTs (see Appendix 5 of the Supporting Information). We realize that by excluding RCT, valuable information was lost, and thereby causality between predictors and outcome cannot directly be demonstrated. Second, many of the risk factors encountered are interrelated (e.g. diabetes and obesity). Therefore, it is not possible to state that reduction of a certain risk factor could lead to a lower disease incidence because of that specific factor. Well-designed RCTs are needed to assess the effect of risk factor reduction strategies on dementia incidence, ideally targeting multiple modifiable risk factors and assessing possible interactions as well as age-dependent effects. Third, by restricting observational studies to those with a follow-up >1 year we excluded studies showing promising short-term results. Fourth, the majority of evidence for our findings (both systematic review and Delphi consensus study) reflects sources from the Western (mostly Caucasian) population, with little evidence from literature as applied to Asians, Blacks, and other minorities. Fifth, various measures were used across studies to define cognitive change (e.g. Mini-Mental State Examination (MMSE) score of 23 or less, 3 points change in MMSE score, incident MCI; Folstein et al., 1975; Graham et al., 1997; Petersen et al., 1999), making direct comparisons of findings difficult. Sixth, the present findings must be interpreted with caution because of the existence of publication bias. Finally, it would have been desirable to have more participants in the Delphi exercise. However, we considered the quality of the panel at least as important as quantity.

In summary, there is good support from both the literature and experts’ opinions on the role of several modifiable risk and preventive factors for cognitive decline and dementia. These findings flag several important targets for dementia prevention through interventions starting in midlife.

Conflict of interest

None declared.
Key points

- Dementia is an important public health problem in our aging society
- Dementia has a multifactorial etiology, but the validity and relative importance of risk factors are often uncertain or based on few studies
- The systematic review and expert consensus found good support for the following prevention targets: depression, (midlife) hypertension, physical inactivity, diabetes, (midlife) obesity, hyperlipidemia, and smoking
- Candidate risk factors that need further study are coronary heart disease, renal dysfunction, diet, and cognitive activity

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