**Supplementary Material**

**A Systematic Review of Meta-Analyses that Evaluate Risk Factors for Dementia to Evaluate the Quantity, Quality, and Global Representativeness of Evidence**

METHODOLOGICAL DETAILS

*Search strategy*

 The following search strategy was used in PubMed/Medline: *(((((((("protective factors"[Mesh]) OR precipitating factors [MeSH Terms]) OR ((prevention and control[MeSH Terms]))) OR risk factors[MeSH Terms]) OR etiology[MeSH Terms]) OR epidemiology[MeSH Terms]))* ***AND*** *("dementia"[Mesh] OR "cognitive dysfunction"[Mesh] OR healthy brain OR brain health))* ***AND*** *systematic [sb].* The following search strategy was used in Cochrane Library: ***#1:*** *MeSH descriptor: [Dementia] explode all trees;* ***#2:*** *MeSH descriptor: [Mild Cognitive Impairment] explode all trees;* ***#3:*** *MeSH descriptor: [Causality] explode all trees;* ***#4:*** *MeSH descriptor: [Epidemiologic Factors] explode all trees;* ***#5:*** *#1 or #2;* ***#6:*** *#3 or #4;* ***#7:*** *#5 and #6 in Other Reviews*. The following search strategy was used in Global Index Medicus: *mh:("Alzheimer Disease" OR "Dementia, Vascular" OR "Dementia")) AND (mh:("Risk Factors" OR "Causality" OR "Epidemiologic Factors).*

*Data screening*

 Citations of all publications returned by thesearch strategies were screened for duplicates and remaining reviews screened in two further stages. At least two independent reviewers rated each article, inconsistencies in decisions on inclusion being resolved through discussion and consensus. Abstracts were screened for relevance and where there was insufficient information available for a decision, they were tentatively included. All remaining publications underwent full-text review for assessment against inclusion and exclusion criteria.

*Data extraction*

 Data extracted for potential meta-analysis and narrative review included: risk exposure measured at midlife (<65 years) or late-life (65+ years), dementia outcome (AD, VaD, and Any Dementia which, potentially included AD, VaD, dementia with Lewy bodies, frontotemporal dementia/Pick’s disease, alcohol related dementia, mixed and other dementias), study design (sample source, number of participants, observation period), sample characteristics (country, percentage female, average age of participants included in the review, age range, average years of education), risk factor reviewed, number of studies, measurement of dementia or cognition, unadjusted and adjusted estimates of association, hazard ratio (HR), relative risk (RR), beta, p-values with 95% confidence intervals (CI), and I2. From each article we extracted the number of individual studies included in each meta-analysis, and the specific study details to allow for evaluation of how many studies were included in multiple meta-analyses, as well as the continent/region in which the original data were collected (North America, Europe, Asia/Middle East, Australia/Oceana, Africa, Latin America).

Supplementary Table 1. Body of evidence for each risk factor

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Systematic reviews** |  |  | **Age group\*** |  |  | **Egger's *p*** |  |  |  |
| **Risk Factor** | **no.** | **author, year** | **Exposure measure** | **Outcome** | **RR** | ***I2*** | **n** | ***R*** | **N** |
|  |  |  |  |  |  |  |  |   |  |  |  |
| Education | 3 | Caamano-Isorna 2006 | Lower versus highest levels | AD | adj | 1.32 (1.09, 1.59) | absent | - | 9 | 0.25 | 36 |
|  | Xu 2015 | Low (<16 years) versus high (≥16 years) | AD | adj | 1.60 (1.32-1.94) | 57.0% | 0.00 | 14 | 0.39 |  |
|  | Xu 2016 | Lowest versus reference quartile | AD | adj | 1.78 (1.43, 2.22) | 36.0% | absent^ | 9 | 0.25 |  |
|  | Xu 2016 | Highest versus reference quartile | AD | adj | 0.44 (0.32, 0.60) | 41.5% | 0.018 | 10 | 0.28 |  |
|  | Caamano-Isorna 2006 | Lower versus highest levels | Any Dementia  | adj | 1.45 (1.16-1.81) | present | - | 10 | 0.28 |  |
|  | Xu 2016 | Lowest versus reference quartile | Any Dementia  | adj | 1.81 (1.59, 2.06) | 0.0% | absent^ | 14 | 0.39 |  |
|   | Xu 2016 | Highest versus reference quartile | Any Dementia  | adj | 0.59 (0.41, 0.87) | 77.4% | absent^ | 10 | 0.28 |   |
| Bilingualism | 1 | Mukadam 2017 | Bilingual versus mono-lingual | Any Dementia  | LL/**?** | 0.96 (0.74, 1.23) | 41.0% |  | 4 | 0.11 | 4 |
| **Lifestyle** |  |  |  |  |  |  |  |  |  |  |  |
| Alcohol | 4 | Anstey 2009 | Drinker versus non-drinkers | AD | LL | 0.66 (0.47, 0.94) | 0.0% | ~ | 2 | 0.08 | 25 |
|  |  | Peters 2008 | Drinker versus non-drinkers | AD | LL/? | 0.60 (0.41, 0.88)  | 55.1% | 0.48 | 8 | 0.32 |  |
|  |  | Xu 2015 | Ever versus never | AD | LL/**?** | 0.43 (0.17, 0.69) | 0.0% | 0.33 | 3 | 0.12 |  |
|  |  | Anstey 2009 | Heavy/excessive versus non-drinker | AD | LL | 0.92 (0.59, 1.45) | 0.0% | 0.22 | 3 | 0.12 |  |
|  |  | Xu 2015 | High versus low/none  | AD | LL/**?** | 0.96 (0.18, 1.74) | 78.8% | 0.56 | 3 | 0.12 |  |
|  |  | Anstey 2009 | Light to moderate versus non-drinker | AD | LL | 0.72 (0.61, 0.86) | 56.4% | 0.36 | 6 | 0.24 |  |
|  |  | Xu 2015 | Light-moderate consumption versus non-drinkers | AD | LL/**?** | 0.61 (0.54, 0.68) | 0.0% | 0.44 | 5 | 0.20 |  |
|  |  | Anstey 2009 | Drinker versus non-drinkers | Any Dementia  | LL | 0.66 (0.53, 0.82) | 0.0% | 0.87 | 3 | 0.12 |  |
|  |  | Cao 2016 | Drinking | Any Dementia  | ML/LL/**?** | 0.74 (0.55, 1.01) | 68.7% | - | 8 | 0.32 |  |
|  |  | Peters 2008 | Drinker versus non-drinkers | Any Dementia  | LL/**?** | 0.65 (0.54, 0.79)  | 33.2% | 0.89 | 3 | 0.12 |  |
|  |  | Anstey 2009 | Heavy/excessive versus non-drinker | Any Dementia  | LL | 1.04 (0.69, 1.56) | 0.0% | 0.40 | 2 | 0.08 |  |
|  |  | Anstey 2009 | Light to moderate versus non-drinker | Any Dementia  | LL | 0.74 (0.61, 0.91) | 52.6% | 0.63 | 4 | 0.16 |  |
|  |  | Peters 2008 | Drinker versus non-drinkers | VaD | LL/**?** | 0.83 (0.12, 5.57)  | 87.5% | ~ | 3 | 0.12 |  |
|  |  | Anstey 2009 | Heavy/excessive versus non-drinker | VaD | LL | 1.36 (0.68, 2.71) | 0.0% | ~ | 4 | 0.16 |  |
|  |   | Anstey 2009 | Light to moderate versus non-drinker | VaD | ? | 0.75 (0.57, 0.98) | 5.2% | 0.63 | 5 | 0.20 |  |
| Cognitive engagement | 2 | Xu 2015 | High participation in cognitive activity  | AD | **LL**/? | 0.53 (0.42, 0.63) | 90.5% | 0.00 | 5 | 0.63 | 8 |
|  | Yates 2016 | Intellectual activities (e.g., reading, writing studying)  | Any Dementia  | ? | 0.61 (0.42, 0.90) | 65.2% | ~ | 3 | 0.38 |  |
|   | Yates 2016 | Stimulating activities (including using computers)  | Any Dementia  | ? | 0.58 (0.46, 0.74) | 0.0% | ~ | 2 | 0.25 |  |
| Diet | 11 | Singh 2014 | Adherence to Mediterranean diet - highest versus lowest  | AD | LL | 0.64 (0.46, 0.89) | 0.0% | ~ | 2 | 0.02 | 90 |
|  |  | Xu 2015 | Caffeine/coffee drinking | AD | ML/**?** | 0.69 (0.47, 0.90) | 0.0% | 0.96 | 3 | 0.03 |
|  |  | Barranco 2007 | Coffee consumption versus non-consumption | AD | ? | 0.73 (0.54, 0.99)  | 0.0% | ~ | 2 | 0.02 |
|  |  | Kim 2015 | Coffee intake, highest versus lowest | AD | LL | 0.71 (0.52, 0.97) | 0.0% | ~ | 3 | 0.03 |
|  |  | Liu 2016 | Coffee intake, highest versus lowest | AD | ML/**LL** | 0.73 (0.55, 0.97)  | 0.0% | 0.80 | 4 | 0.04 |
|  |  | Wu 2016 | <1 cup per day versus 1-2 cups  | AD | LL | 0.71 (0.54, 0.94) | 0.0% | 0.98 | 3 | 0.03 |
|  |  | Xu 2015 | Fat, DHA | AD | LL/**?** | 0.76 (0.52, 1.11) | 68.3% | 0.04 | 4 | 0.04 |
|  |  | Xu 2015 | Fat, EPA | AD | ? | 0.96 (0.75, 1.16) | 0.0% | 0.25 | 3 | 0.03 |
|  |  | Wu 2015 | Fat, DHA/EPA highest versus lowest | AD | LL | 0.89 (0.74, 1.08) | 36.3% | 0.01 | 3 | 0.03 |
|  |  | Zhang 2016 | Fat, DHA, 0.1-g/d increment | AD | ML/**LL** | 0.63 (0.51, 0.76) | 94.6% | 0.10 | 3 | 0.03 |
|  |  | Zhang 2016 | Fat, EPA, 0.1-g/d increment | AD | ML/LL | 1.04 (0.85, 1.23) | 5.1% | 0.10 | 2 | 0.02 |
|  |  | Zhang 2016 | Fat, PUFA, 8-g/d increment | AD | ML/LL | 0.96 (0.65, 1.27) | 34.6% | - | 2 | 0.02 |
|  |  | Zhang 2016 | Fish, 1 serving/wk increment | AD | ML/**LL** | 0.93 (0.90, 0.95) | 74.8% | 0.174 | 5 | 0.06 |
|  |  | Xu 2015 | Fish intake | AD | LL/**?** | 0.66 (0.43, 0.90) | 64.7% | 0.54 | 6 | 0.07 |
|  |  | Wu 2015 | Fish intake, highest versus lowest  | AD | LL | 0.64 (0.44, 0.92) | 59.0% | 0.10 | 6 | 0.07 |
|  |  | Xu 2015 | Folate, high serum folate levels | AD | LL/? | 0.51 (0.29, 0.73) | 16.0% | 0.29 | 4 | 0.04 |
|  |  | Kim 2015 | Tea intake, highest versus lowest  | AD | LL | 1.12 (0.83, 1.50) | 0.0% | ~ | 3 | 0.03 |
|  |  | Xu 2015 | Vitamin C intake | AD | **LL**/? | 0.74 (0.55, 0.93) | 0.0% | 0.19 | 6 | 0.07 |
|  |  | Shen 2015 | Vitamin D deficiency (25(OH)D level < 50 nmol/L) | AD | LL/? | 1.21 (1.02, 1.41) | 0.0% | - | 2 | 0.02 |
|  |  | Xu 2015 | Vitamin E intake | AD | **LL**/? | 0.73 (0.62, 0.84) | 0.0% | 0.81 | 6 | 0.07 |
|  |  | Cao 2016 | Adherence to Mediterranean diet - highest versus lowest  | Any Dementia  | **LL**/? | 0.69 (0.57, 0.84) | 1.0% | - | 4 | 0.04 |
|  |  | Kim 2015 | Caffeine (coffee/tea), highest versus lowest  | Any Dementia  | LL | 1.13 (0.59, 2.16)  | 27.4% | ~ | 3 | 0.03 |
|  |  | Liu 2016 | Coffee intake, highest versus lowest  | Any Dementia  | ML/**LL**/? | 1.08 (0.81, 1.44) | 28.2% | 0.80 | 5 | 0.06 |
|  |  | Wu 2016 | <1 cup per day versus 1-2 cups  | Any Dementia  | LL | 0.78 (0.67, 0.91) | 10.0% | 0.98 | 6 | 0.07 |
|  |  |  | Fat, Unsaturated | Any Dementia  | LL | 0.84 (0.74, 0.95) | 0.0% | absent^ | 5 | 0.06 |
|  |  | Wu 2015 | Fat, DHA/EPA, highest versus lowest  | Any Dementia  | LL | 0.97 (0.85, 1.10) | 0.0% | 0.09 | 2 | 0.02 |
|  |  | Zhang 2016 | Fat, DHA, 0.1-g/d increment | Any Dementia  | ML/LL | 0.86 (0.76, 0.96) | 92.7% | 0.10 | 3 | 0.03 |
|  |  | Zhang 2016 | Fat, EPA, 0.1-g/d increment | Any Dementia  | LL | 1.02 (0.97, 1.07) | 76.3% | 0.10 | 2 | 0.02 |
|  |  | Zhang 2016 | Fat, PUFA - 8-g/d increment | Any Dementia  | ML/LL | 0.96 (0.71, 1.21) | 27.5% | 0.10 | 2 | 0.02 |
|  |  | Cao 2016 | Fish intake, highest versus lowest  | Any Dementia  | LL | 0.79 (0.59, 1.06) | 39.7% | - | 3 | 0.03 |
|  |  | Zhang 2016 | Fish, 1 serving/wk increment  | Any Dementia  | ML/LL | 0.95 ( 0.90, 0.99) | 63.4% | 0.31 | 4 | 0.04 |
|  |  | Wu 2015 | Fish intake, highest versus lowest  | Any Dementia  | LL | 0.84 (0.71, 1.01) | 29.1% | 0.05 | 5 | 0.06 |
|  |  | Cao 2016 | Fruit and vegetable intake, highest versus lowest | Any Dementia  | 0.46 (0.16, 1.32) | 78.3% | - | 2 | 0.02 |  |
|  |  | Jiang 2017 | Fruit and vegetable intake, highest versus lowest | Any Dementia  | ML/LL | 0.72 (0.58, 0.90) | 0.0% | ~ | 2 | 0.02 |  |
|  |  | Ma 2016 | Tea intake, drinkers versus non/rare-drinkers | Any Dementia  | ML/**LL** |  0.65 (0.33, 0.97) | 89.3% | 0.71 | 4 | 0.04 |
|  |  | Cao 2016 | Antioxidant intake | Any Dementia  | ML/**LL**/? | 0.87 (0.77, 0.98) | 36.2% | absent^ | 11 | 0.12 |
|  |  | Cao 2016 | Flavanoids intake | Any Dementia  | **LL**/? | 0.97 (0.65, 1.46) | 59.6% | absent^ | 3 | 0.03 |
|  |  | Cao 2016 | Vitamin B intake | Any Dementia  | **LL**/? | 0.72 (0.54, 0.96) | 41.6% | absent^ | 4 | 0.04 |
|  |  | Cao 2016 | Vitamin C intake | Any Dementia  | ML/**LL**/? | 0.89 (0.74, 1.06) | 24.0% | absent^ | 8 | 0.09 |
|  |  | Cao 2016 | Vitamin D intake | Any Dementia  | ML/**LL** | 1.52 (1.17, 1.98) | 45.3% | absent^ | 3 | 0.03 |
|  |  | Sommer 2017 | Vitamin D deficiency (25(OH)D level < 50 nmol/L) | Any Dementia  | **ML**/LL | 1.54 (1.19, 1.99) | 20.0% | ~ | 5 | 0.06 |
|  |   | Cao 2016 | Vitamin E intake | Any Dementia  | ML/**LL**/? | 0.80 (0.65, 0.98) | 33.6% | absent^ | 10 | 0.11 |
| Physical activity | 8 | Xu 2015 | High participation inleisure-time PA | AD | LL/**?** | 0.65 (0.46, 0.84)  | 81.0% | 0.09 | 10 | 0.29 | 35 |
|  |  | Daviglus 2011 | Higher versus lower PA | AD | ? | 0.72 (0.53, 0.98) |  - | - | 9 | 0.26 |  |
|  |  | Xu 2017 | Higher versus lower PA | AD | ML/**LL** | 0.80 (0.69, 0.94) | 0.0% | ~ | 8 | 0.23 |  |
|  |  | Xu 2017 | Highest versus lowest PA | AD | ML/**LL** | 0.74 (0.58, 0.94) | 46.3%   | ~ | 8 | 0.23 |  |
|  |  | Santos-Lozano 2016 | Higher versus lower PA | AD | ML/**LL** | 0.65 (0.55, 0.75)  | 39.3%   | 0.83 | 9 | 0.26 |  |
|  |  | Beckett 2015 | Highest versus lowest PA | AD | ML | 0.61 (0.52, 0.73) | 0.0% | 0.02 | 9 | 0.26 |  |
|  |  | Hamer 2009 | Highest versus lowest PA | AD | ML/**LL** | 0.55 (0.36, 0.84) | 79.5% | <0.01 | 6 | 0.17 |  |
|  |  | Santos-Lozano 2016 | Physically active (international guidelines: >150 min/week of MVPA) versus inactive | AD | LL | 0.60 (0.51, 0.71) | 5.6% | 0.34 | 5 | 0.14 |  |
|  |  | Xu 2017 | Higher versus lower PA | Any Dementia  | ML/**LL** | 0.79 (0.66, 0.93) | 51.2% | 0.26 | 15 | 0.43 |  |
|  |  | Blondell 2014 | Highest versus lowest PA | Any Dementia  | ML/**LL** | 0.86 (0.76, 0.97) | 66.0% | possible^ | 21 | 0.60 |  |
|  |  | Hamer 2009 | Highest versus lowest PA | Any Dementia  | ML/**LL** | 0.72 (0.60, 0.86) | 71.5% | <0.01 | 11 | 0.31 |  |
|  |  | Xu 2017 | Highest versus lowest PA | Any Dementia  | ML/**LL** | 0.73 (0.52, 0.87) | 44.1% | 0.26 | 15 | 0.43 |  |
|  |  | Aarsland 2010 | Higher versus lower PA | VaD | LL | 0.62 (0.42, 0.92) | 55.8% | some^ | 5 | 0.14 |  |
| Sleep | 3 | Bubu 2017 | Sleep disorder versus none | AD | ML/**LL** | 1.47 (1.28:1.69 | 66.9% | 0.79 | 6 | 0.46 | 13 |
|  |  | de Almondes 2016 | Clinical diagnosis of insomnia versus none | Any Dementia  | ML/**LL**/? | 1.53 (1.07, 2.18) | 82.0% | modest^ | 5 | 0.38 |  |
|  |   | Kim 2016 | Shorter versus longer duration | Any Dementia  | LL | 1.42 (1.15,1.77) | 2.87 | absent^ | 3 | 0.23 |   |
| Smoking | 6 | Anstey 2007 | Current versus former | AD | **LL**/? | 1.70 (1.25, 2.31) | 0.0% | 0.70 | 4 | 0.09 | 47 |
|  |  | Anstey 2007 | Current versus never | AD | **LL**/? | 1.79 (1.43, 2.23) | 0.0% | 0.89 | 4 | 0.09 |  |
|  |  | Zhong 2015 | Current versus never | AD | LL | 1.40 (1.13, 1.73) | 66.8% | <0.01 | 12 | 0.26 |  |
|  |  | Almeida 2002 | Current versus never/non-smokers | AD | ? | 1.99 (1.33, 2.98) | 56.5% | ~ | 7 | 0.15 |  |
|  |  | Peters 2008 | Current versus never/non-smokers | AD | ML/**LL**/? | 1.59 (1.15, 2.20)  | 69.9% | 0.19 | 8 | 0.17 |  |
|  |  | Almeida 2002 | Ever versus never | AD | ? | 1.10 (0.94, 1.29) | 93.5% | 0.53 | 7 | 0.15 |  |
|  |  | Zhong 2015 | Ever versus never | AD | LL | 1.12 (1.00, 1.26) | 55.9% | <0.01 | 23 | 0.49 |  |
|  |  | Peters 2008 | Former versus never | AD | ? | 0.99 (0.81, 1.23) | 46.8% | 0.79 | 8 | 0.17 |  |
|  |  | Xu 2015 | Former versus never | AD |  | 1.00 (0.92, 1.08) | 0.0% | 0.27 | 9 | 0.19 |  |
|  |  | Zhong 2015 | Former versus never | AD | LL | 1.04 (0.96, 1.13) | 2.8% | <0.01 | 13 | 0.28 |  |
|  |  | Anstey 2007 | Current versus former | Any Dementia  | ML/**LL** | 1.30 (0.96, 1.77) | 0.0% | ~ | 2 | 0.04 |  |
|  |  | Anstey 2007 | Current versus never | Any Dementia  | **LL**/? | 1.27 (1.02, 1.60) | 0.0% | ~ | 2 | 0.04 |  |
|  |  | Zhong 2015 | Current versus never | Any Dementia  | ML/**LL** | 1.30 (1.18, 1.45) | 50.6% | <0.01 | 17 | 0.36 |  |
|  |  | Cao 2016 | Current versus never/non-smokers | Any Dementia  | **LL**/? | 1.43 (1.15, 1.77) | 57.4% | - | 9 | 0.19 |  |
|  |  | Peters 2008 | Current versus never/non-smokers | Any Dementia  | **LL**/? | 1.16 (0.90, 1.50) | 54.6% | 0.91 | 5 | 0.11 |  |
|  |  | Zhong 2015 | Ever versus never | Any Dementia  | ML/**LL** | 1.13 (1.05, 1.22) | 45.7% | <0.01 | 27 | 0.57 |  |
|  |  | Peters 2008 | Former versus never | Any Dementia  | ? | 0.90 (0.75, 1.07) | 46.8% | 0.091 | 5 | 0.11 |  |
|  |  | Zhong 2015 | Former versus never | Any Dementia  | ML/**LL** | 1.01 (0.96, 1.06) | 6.3% | <0.01 | 18 | 0.38 |  |
|  |  | Anstey 2007 | Current versus former | VaD | LL | 1.26 (0.60, 2.63) | 0.0% | ~ | 2 | 0.04 |  |
|  |  | Anstey 2007 | Current versus never | VaD | LL | 1.78 (1.28, 2.47) | 53.6% | ~ | 2 | 0.04 |  |
|  |  | Zhong 2015 | Current versus never | VaD | ML/**LL** | 1.38 (1.15, 1.66) | 27.2% | <0.01 | 5 | 0.11 |  |
|  |  | Peters 2008 | Current versus never/non-smokers | VaD | **LL**/? | 1.35 (0.90, 2.02) | 44.6% | 0.12 | 4 | 0.09 |  |
|  |  | Zhong 2015 | Ever versus never | VaD | ML/LL | 1.25(1.05, 1.47) | 38.3% | <0.01 | 8 | 0.17 |  |
|  |  | Peters 2008 | Former versus never | VaD | ? | 1.05 (0.72, 1.54) | 0.0% | 0.15 | 4 | 0.09 |  |
|  |  | Zhong 2015 | Former versus never | VaD | ML/**LL** | 0.97 (0.83, 1.13) | 0.0% | <0.01 | 5 | 0.11 |  |
| Social engagement | 1 | Kuiper 2015 | Less frequent social participation | Any Dementia  | LL | 1.41 (1.13, 1.75) | 31.0% | 0.08 | 6 | 0.50 | 12 |
|  | Kuiper 2015 | Less social contact | Any Dementia  | LL | 1.57 (1.32, 1.85) | 0.0% | 0.95 | 8 | 0.67 |  |
|  |  | Kuiper 2015 | Lonely versus not lonely | Any Dementia  | LL | 1.58 (1.19, 2.09 | 0.0% | 0.12 | 3 | 0.25 |  |
|  |  | Kuiper 2015 | Low satisfaction with social network | Any Dementia  | LL | 1.25 (0.96, 1.62) | 49.0% | 0.93 | 4 | 0.33 |  |
|  |   | Kuiper 2015 | Small network size  | Any Dementia  | LL | 1.17 (0.92, 1.48) | 64.0% | 0.14 | 5 | 0.42 |  |
| Stress | 1 | Xu 2015 | Yes versus no | AD | ML/? | 2.03 (1.48, 2.57) | 0.0% | 0.05 | 3 | 1.00 | 3 |
| **Medical** |   |   |   |   |   |   |   |  |  |  |   |
| Arthritis | 2 | Xu 2015 | History of arthritis (self-report)  | AD | LL/? | 0.63 (0.42, 0.84) | 0.0% | 0.83 | 2 | 0.40 | 5 |
|  |   | Ungprasert 2016 | Dementia patients with arthritis versus controls | Any Dementia | **ML**/? | 1.34 (0.93, 1.94) | 57.0% | absent^ | 3 | 0.60 |   |
| Atrial fibrillation | 4 | Kalantarian 2013 | Yes versus no (ECG, medical history, ICD-9, unclear) | AD | LL | 1.47 (0.92, 2.34) | 68.2% | ~ | 3 | 0.18 | 17 |
|  | Xu 2015 | Yes versus no (medical records, self-report health questionnaire) | AD | LL | 1.29 (0.97, 1.60) | 60.6% | 0.94 | 3 | 0.18 |  |
|  |  | Santegeli 2012 | Yes versus no (ECG study, ICD code, clinical exam, medical history, unclear) | Any Dementia | **LL**/? | 1.42 (1.17, 1.72) | 50.0% | 0.22 | 8 | 0.47 |  |
|  |  | Kwok 2011 | Yes versus no (ECG, ICD code, clinical exam, medical history, unclear) | Any Dementia | LL | 1.98 (1.43, 2.71)  | 75.0% | - | 14 | 0.82 |  |
|  |  | Kalantarian 2013 | Yes versus no (ECG, medical history, ICD-9, unclear) | Any Dementia | LL | 1.36 (1.19, 1.56) | 51.6% | 0.13 | 5 | 0.29 |  |
| Anxiety | 1 | Gulpers 2016 | Clinically relevant anxiety versus none | Any Dementia | LL | 1.61 (1.00, 2.58) | 59.4% | 0.88 | 6 | 1.00 | 6 |
| BMI | 6 | Anstey 2011 | Change (increase) continuous measures of BMI  | AD | LL | 0.72 (0.62, 0.84)  | 71.5% | ~ | 2 | 0.07 | 28 |
|  |  | Xu 2015 | High BMI (>28/30) in midlife versus normal | AD | ML/LL/**?** | 1.61 (1.11, 2.12)  | 69.2% | 0.11 | 6 | 0.21 |  |
|  |  | Xu 2015 | High BMI (>30/28/25, abdominal obesity, increase in BMI) in late-life | AD | **LL**/? | 0.80 (0.64, 0.97)  | 72.9% | 0.95 | 12 | 0.43 |  |
|  |  | Anstey 2011 | Obese versus normal | AD | **ML**/LL | 2.04 (1.59, 2.69) | 82.8% | ~ | 3 | 0.11 |  |
|  |  | Beydoun 2008 | Obese versus normal | AD | **ML**/LL | 1.80 (1.00, 3.29) |  - | <0.01 | 4 | 0.14 |  |
|  |  | Loef 2013 | Obese versus normal | AD | ML/**LL** | 1.98 (1.24, 3.14)  |  - | - | 4 | 0.14 |  |
|  |  | Meng 2014 | Obese versus normal | AD | ML | 1.88 (1.32, 2.69)  | 59.1% | 0.55 | 5 | 0.18 |  |
|  |  | Anstey 2011 | Obese versus not Obese | AD | LL | 1.46 (0.97, 2.21) | 42.3% | ~ | 2 | 0.07 |  |
|  |  | Anstey 2011 | Overweight versus normal | AD | **ML**/LL | 1.35 (1.19, 1.54) | 92.0% | ~ | 3 | 0.11 |  |
|  |  | Loef 2013 | Overweight versus normal | AD | ML/LL | 1.44 (0.96, 2.15)  |  - | - | 4 | 0.14 |  |
|  |  | Anstey 2011 | Underweight versus normal | AD | ML/**LL** | 1.96 (1.32, 2.92) | 69.1% | ~ | 3 | 0.11 |  |
|  |  | Anstey 2011 | Obese versus normal | Any Dementia | **ML**/LL | 1.64 (1.34, 2.00) | 0.0% | ~ | 3 | 0.11 |  |
|  |  | Beydoun 2008 | Obese versus normal | Any Dementia | ML/**LL** | 1.42 (0.93, 2.18) |  - | <0.01 | 4 | 0.14 |  |
|  |  | Loef 2013 | Obese versus normal | Any Dementia | ML/**LL** | 1.91 (1.41, 2.62)  | 53.0% | - | 5 | 0.18 |  |
|  |  | Pedditizi 2016 | Obese versus normal - midlife | Any Dementia | **ML**/LL | 1.41 (1.20, 1.65) | 0.0% | - | 4 | 0.14 |  |
|  |  | Pedditizi 2016 | Obese versus normal –late-life | Any Dementia | LL | 0.83 (0.74, 0.94)  | 0.0% | - | 4 | 0.14 |  |
|  |  | Anstey 2011 | Obese versus not Obese | Any Dementia | LL | 1.11 (0.80, 1.55)  | 80.9% | ~ | 2 | 0.07 |  |
|  |  | Anstey 2011 | Overweight versus normal | Any Dementia | **ML**/LL | 1.26 (1.10, 1.44)  | 61.7% | ~ | 3 | 0.11 |  |
|  |  | Beydoun 2008 | Overweight versus normal | Any Dementia | ML/**LL** | 0.88 (0.60, 1.27)  |  - | <0.01 | 4 | 0.14 |  |
|  |  | Loef 2013 | Overweight versus normal | Any Dementia | ML/**LL** | 1.34 (1.08, 1.66)  | 58.0% | - | 5 | 0.18 |  |
|  |  | Pedditizi 2016 | Overweight versus normal – late-life | Any Dementia | LL | 0.88 (0.76, 1.02)  | 53.0% | - | 5 | 0.18 |  |
|  |  | Pedditizi 2016 | Overweight versus normal -midlife | Any Dementia | **ML**/LL | 1.10 (0.99, 1.22)  | 0.0% | - | 4 | 0.14 |  |
|  |  | Beydoun 2008 | Underweight versus normal | Any Dementia | ML/LL | 1.36 (1.07, 1.73)  |  - | <0.01 | 2 | 0.07 |  |
|  |  | Beydoun 2008 | Obese versus normal | VaD | ML/**LL** | 1.73 (0.47, 6.31) |  - | <0.01 | 3 | 0.11 |  |
|  |   | Anstey 2011 | Overweight versus normal | VaD | ML/LL | 1.33 (1.02, 1.75)  | 82.3% | ~ | 2 | 0.07 |  |
| Cancer | 2 | Ma 2014 | History of cancer versus none (ICD code diagnosis)  | AD | LL | 0.63 (0.56, 0.72) | 0.0% | 0.28 | 5 | 0.71 | 7 |
|  |   | Xu 2015 | Yes versus no (Questionnaire/self-report, ASL-Mi1 tumour registry) | AD | **LL**/? | 0.65 (0.57, 0.73) | 6.7% | 0.81 | 6 | 0.86 |  |
| Carotid atherosclerosis | 1 | Xu 2015 | Yes versus no (carotid medina wall thickness) | AD |   | 1.65 (1.03, 2.26) | 31.1% | ~ | 2 | 1.00 | 2 |
| Cholesterol | 5 | Xu 2015  | Elevated serum total cholesterol level  | AD | ML**/LL**/? | 1.07 (0.89, 1.28) | 59.9% | 0.02 | 16 | 0.76 | 21 |
|  |  | Meng 2014 | High cholesterol (>6.5mmol/l) versus non-high | AD | ML | 1.72 (1.32, 2.24) | 8.5% | possible^ | 4 | 0.19 |  |
|  |  | Anstey 2017 | High cholesterol (>6.5mmol/l) versus non-high - midlife | AD | ML | 2.14 (1.33, 3.44) | 12.9% | ~ | 3 | 0.14 |  |
|  |  | Daviglus 2011 | Highest versus lowest quartile | AD | ? | 0.85 (0.65, 1.12) |  - | ~ | 3 | 0.14 |  |
|  |  | Anstey 2017 | Highest versus lowest quartile - Total cholesterol, late-life | AD | LL | 0.93 (0.69, 1.26) | 50.5% | 0.2768 | 4 | 0.19 |  |
|  |  | Anstey 2017 | Low HDL-C | AD | LL | 0.78 (0.54, 1.13) | 65.4% | ~ | 3 | 0.14 |  |
|  |  | Anstey 2008 | Second versus lowest quartile - total cholesterol | AD | LL | 0.85 (0.67, 1.10) | 40.1% | ~ | 3 | 0.14 |  |
|  |  | Anstey 2017 | Highest versus lowest quartile- total cholesterol | AD/dementia | ? | 1.82 (1.27, 2.60)  | 41.2% | 0.045 | 4 | 0.19 |  |
|  |  | Anstey 2017 | High cholesterol (>6.5mmol/l) versus non-high- midlife | Any Dementia | ? | 1.47 (0.96, 2.27) | 37.0% | ~ | 2 | 0.10 |  |
|  |  | Anstey 2017 | Highest versus lowest quartile- total cholesterol, late-life | Any Dementia | LL | 1.03 (0.74, 1.43) | 38.9% | ~ | 3 | 0.14 |  |
|  |  | Anstey 2017 | Low HDL-C | Any Dementia | LL | 1.06 (0.71, 1.56) | 0.0% | ~ | 2 | 0.10 |  |
|  |  | Anstey 2008 | Second versus lowest quartile - total cholesterol | Any Dementia | LL | 1.00 (0.81, 1.24)  | 0.0% | ~ | 3 | 0.14 |  |
|  |  | Anstey 2017 | High cholesterol (>6.5mmol/l) versus normal – late-life | VaD | LL | 0.96 (0.71, 1.30) | 0.0% | ~ | 2 | 0.10 |  |
|  |  | Anstey 2017 | Low HDL-C | VaD | LL | 1.13 (0.60, 2.14) | 0.0% | ~ | 2 | 0.10 |  |
|  |  | Anstey 2008 | Second versus lowest quartile - total cholesterol  | VaD | LL | 1.19 (0.65, 2.17)  | 34.5% | ~ | 2 | 0.10 |  |
| Depression | 3 | Cherbuin 2015 | Categorical clinical thresholds (>20/21 CES-D or equivalent) | AD | LL | 2.04 (1.40, 2.98)  | 54.9% | possible^ | 10 | 0.22 | 46 |
|  |  | Diniz 2013 | Continuous (mostly CES-D & variants) | AD | ? | 1.65 (1.42, 1.92) | 2.0% | absent^ | 17 | 0.37 |  |
|  |  | Xu 2015 | Continuous (self-reporting, CES-D, HAM, Questionnaire, DSM-IV, Diagnosis, CAMDEX, Neuropsychiatric interview, SCL-90) | AD | **LL**/? | 1.08 (1.04, 1.13) | 40.3% | 0.00 | 24 | 0.52 |  |
|  |  | Cherbuin 2015 | Continuous symptomology measures - CES-D, HAM, GDS, SCL-90, the NEO | AD | LL | 1.06 (1.02, 1.10) | 62.1% | possible^ | 10 | 0.22 |  |
|  |  | Cherbuin 2015 | Categorical clinical thresholds (>20/21 CES-D or equivalent) | Any Dementia | LL | 1.98 (1.50, 2.63) | 38.3% | possible^ | 11 | 0.24 |  |
|  |  | Cherbuin 2015 | Continuous - CES-D, HAM, GSM, SCL-90 | Any Dementia | LL | 1.05 (1.02, 1.08) | 63.1% | possible^ | 10 | 0.22 |  |
|  |  | Diniz 2013 | Continuous (mostly CES-D & variants) | Any Dementia | ? | 1.85 (1.67, 2.04)  | 0.0% | absent^ | 23 | 0.50 |  |
|  |  | Cherbuin 2015 | Categorical clinical thresholds (>20/21 CES-D or equivalent) | VaD | LL | 2.20 (0.87, 5.59 | 74.1% | possible^ | 3 | 0.07 |  |
|  |  | Cherbuin 2015 | Continuous - SCL90, GDS) | VaD | LL | 1.06 (0.92, 1.21) | 72.9% | possible^ | 2 | 0.04 |  |
|  |  | Diniz 2013 | Continuous (mostly CES-D & variants) | VaD | ? | 2.52 (1.77, 3.59) | 2.0% | absent^ | 5 | 0.11 |  |
| Diabetes | 8 | Meng 2014 | Any diabetes (Type I or II) | AD | **ML**/LL | 1.40 (1.25, 1.57) | 10.6% | - | 4 | 0.07 | 54 |
|  |  | Zhang 2017 | Any diabetes (Type I or II) | AD | ? | 1.53 (1.42, 1.63) | 18.5% | absent^ | 17 | 0.31 |  |
|  |  | Cheng 2012  | Type II diabetes (according to standard criteria) | AD | ML/**LL** | 1.54 (1.40, 1.70) | 71.7% | <0.01 | 18 | 0.33 |  |
|  |  | Lu 2009 | Type II diabetes (medical history, laboratory test, antidiabetic medications) | AD | LL | 1.39 (1.16, 1.66) | 0.0% | <0.01 | 8 | 0.15 |  |
|  |  | Xu 2015 | Type II diabetes (self-report, family report) | AD | ML/**LL** | 1.33 (1.14, 1.52) | 70.4% | 0.06 | 22 | 0.41 |  |
|  |  | Gudala 2013 | Type II diabetes (Self-reported, registry-based or antidiabetics use) | AD | ML/**LL** | 1.56 (1.41, 1.73) | 9.8% | 0.93 | 20 | 0.37 |  |
|  |  | Vagelatos 2013 | Type II diabetes, self-report and blood sampling | AD | ML/**LL** | 1.57 (1.41, 1.75) | 38.7% | 0.22 | 15 | 0.28 |  |
|  |  | Chatterjee 2016 | Type II diabetes (according to standard criteria) | Any Dementia | ML/**LL** | *F:* 1.68 (1.64, 1.71)*M*: 1.61 (1.42, 1.83) | 0.0%37.6% | - | 14 | 0.26 |  |
|  |  | Cheng 2012  | Type II diabetes (according to standard criteria) | Any Dementia | ML/**LL** | 1.51 (1.31, 1.74) | 67.1% | <0.01 | 11 | 0.20 |  |
|  |  | Lu 2009 | Type II diabetes (medical history, laboratory test, antidiabetic medications) | Any Dementia | LL | 1.47 (1.25, 1.73) | 0.0% | 0.95 | 6 | 0.11 |  |
|  |  | Gudala 2013 | Type II diabetes (Self-reported, registry-based or antidiabetics use) | Any Dementia | ML/**LL** | 1.73 (1.65, 1.82) | 71.3% | 0.12 | 20 | 0.37 |  |
|  |  | Chatterjee 2016 | Type II diabetes (according to standard criteria) | VaD | LL | *F*: 2.34 (1.86, 2.94)*M:* 1.73 (1.61, 1.85) | 33.9%0.0% | - | 8 | 0.15 |  |
|  |  | Cheng 2012  | Type II diabetes (according to standard criteria) | VaD | ML/**LL** | 2.49 (2.09, 2.97) | 0.0% | 0.90 | 10 | 0.19 |  |
|  |  | Lu 2009 | Type II diabetes (medical history, laboratory test, antidiabetic medications) | VaD | **LL**/? | 2.38 (1.79, 3.18) | 0.0% | 0.42 | 9 | 0.17 |  |
|  |  | Gudala 2013 | Type II diabetes (Self-reported, registry-based or antidiabetics use) | VaD | LL | 2.27 (1.94, 2.66)  | 0.0% | 0.41 | 13 | 0.24 |  |
| Hearing loss | 1 | Ford 2017 | Hearing impairment versus none | Any Dementia | ML**/LL**/? | 1.38 (1.23-1.53) | 18.0% | - | 13 | 1.00 | 13 |
| Homocysteine | 3 | Xu 2015 | High total homocysteine levels | AD | ML**/LL**/? | 1.15 (1.09, 1.23) | 45.0% | 0.00 | 8 | 0.73 | 11 |
|  |  | Van Dam 2009 | Hyperhomocysteinemia  | AD | LL | 2.50 (1.38, 4.56) | 81.6% | ~ | 3 | 0.27 |  |
|  |   | Ho 2011 | High total homocysteine levels | Any Dementia | ML**/LL**/? | 1.34 (0.94, 1.91)  | 36.7% | ~ | 2 | 0.18 |  |
| Hormones  | 3 | Wang 2016 | High versus. normal levels of thyrotropin | AD | LL | 1.70 (1.18, 2.45) | 42.2% | 0.75 | 2 | 0.11 | 18 |
|  |  | Lv 2016 | Low plasma testosterone (in elderly men) | AD | ? | 1.48 (1.12, 1.96) | 47.2% | 0.15 | 7 | 0.39 |  |
|  |  | Wang 2016 | Low versus. normal levels of thyrotropin | AD | LL | 1.69 (1.31, 2.19) | 38.0% | 0.74 | 4 | 0.22 |  |
|  |  | Wang 2016 | Per SD increment in thyrotropin levels | AD | LL | 0.89 (0.78, 1.01) | 31.3% | 0.01 | 6 | 0.33 |  |
|  |  | Wu 2016 | High versus middle levels of thyroid-stimulating hormone | Any Dementia | LL | 1.14 (0.85, 1.54) | 0.0% | 0.48 | 2 | 0.11 |  |
|  |  | Wu 2016 | Low versus middle levels of thyroid-stimulating hormone | Any Dementia | LL | 1.50 (1.17, 1.92) | 0.00% | 0.25 | 4 | 0.22 |  |
|  |  | Wu 2016 | Per SD increment of free thyroxine | Any Dementia | LL | 1.08 (1.00, 1.17) | 48.5% | 0.62 | 4 | 0.22 |  |
|  |   | Wu 2016 | Per SD increment of thyroid-stimulating hormone | Any Dementia | LL | 0.91 (0.84, 0.99) | 0.0% | 0.97 | 5 | 0.28 |  |
| Hyper/hypotension | 5 | Meng 2014 | All combined - high SBP, DBP, hypertension | AD | **ML**/LL | 1.31 (1.01, 1.70) | 45.7% | - | 5 | 0.13 | 38 |
|  |  | Meng 2014 | High DBP | AD | **ML**/LL | 2.38 (1.34, 4.23) | 0.0% | - | 3 | 0.08 |  |
|  |  | Meng 2014 | High SBP  | AD | **ML**/LL | 1.77 (0.93, 3.37) | 0.0% | - | 3 | 0.08 |  |
|  |  | Xu 2015 | Higher SBP  | AD | ? | 1.02 (0.92, 1.13) | 68.7% | <0.01 | 28 | 0.74 |  |
|  |  | Power 2011 | History of hypertension | AD | ML/LL | 0.98 (0.80, 1.19)  | 41.8% | 0.69 | 12 | 0.32 |  |
|  |  | Guan 2011 | Hypertension versus none | AD | ML/**LL** | 1.01 (0.87, 1.18) | 37.2% | - | 9 | 0.24 |  |
|  |  | Meng 2014 | Hypertension versus none | AD | **ML**/LL | 1.10 (0.88, 1.37) | 48.6% | - | 2 | 0.05 |  |
|  |  | Xu 2015 | Lower DBP  | AD | LL/**?** | 1.14 (0.89, 1.39) | 60.0% | <0.01 | 6 | 0.16 |  |
|  |  | Power 2011 | Per 10mmHg DBP | AD | ML | 0.93 (0.84, 1.04) | 12.4% | 0.85 | 4 | 0.11 |  |
|  |  | Power 2011 | Per 10mmHg DBP | AD | LL | 0.94 (0.85, 1.04) | 14.0% | 0.45 | 5 | 0.13 |  |
|  |  | Power 2011 | Per 10mmHg increment SBP  | AD | ML | 0.95 (0.90, 1.00)  | 69.4% | ~ | 4 | 0.11 |  |
|  |  | Power 2011 | Per 10mmHg increment SBP  | AD | LL | 0.95 (0.91, 1.00) | 0.0% | 0.54 | 5 | 0.13 |  |
|  |  | Sharp 2011 | History of/current hypertension | VaD | ? | 1.59 (1.29, 1.95) | 37.4% | <0.01 | 6 | 0.16 |  |
| Inflammatory markers | 1 | Koyama 2013 | C-reactive protein | AD | LL | 1.36 (1.13, 1.63) | 40.3% | ~ | 3 | 0.75 | 4 |
|  | Koyama 2013 | Interleukin-6 | AD | LL | 1.15 (0.84, 1.59) | 0.0% | ~ | 4 | 1.00 |  |
|  | Koyama 2013 | C-reactive protein | Any Dementia | LL | 1.27 (1.00, 1.60) | 0.0% | ~ | 3 | 0.75 |  |
|   | Koyama 2013 | Interleukin-6 | Any Dementia | LL | 1.39 (1.08, 1.81) | 0.0% | ~ | 4 | 1.00 |  |
| Metabolic syndrome | 1 | Xu 2015 | NCEP ATP III criteria | AD | **LL**/? | 0.71 (0.49, 0.93) | 36.5% | 0.30 | 4 | 1.00 | 4 |
| Motor function | 1 | Kueper 2017 | Overall parkinsonism-presence versus absence | Any Dementia | **LL**/? | 3.05 (1.31, 7.07) | 66.0 | - | 2 | 0.20 | 10 |
|  |  | Kueper 2017 | Tremor-presence versus absence | Any Dementia | LL | 0.80 (0.31, 2.03) | 76.8 | - | 3 | 0.30 |  |
|  |   | Kueper 2017 | Gait velocity-slow versus fast | Any Dementia | LL | 1.94 (1.41 2.65) | 69.6 | - | 5 | 0.50 |   |
| Peripheral artery disease | 1 | Xu 2015 | Ankle to Brachial Index <0.9-11 | AD | LL/? | 1.68 (0.97, 2.38) | 0.0% | 0.51 | 2 | 1.00 | 2 |
| Renal disease | 1 | Xu 2015 | eGFR (MDRD), I/SCr, questionnaire | AD | LL/**?** | 1.13 (0.68, 1.59) | 0.0% | 0.67 | 3 | 1.00 | 3 |
| Serum uric acid | 1 | Du 2016 | Serum uric acid levels | AD | ? | 0.66 (0.52, 0.85) | 6.0% | low risk^ | 3 | 1.00 | 3 |
| Stroke | 1 | Xu 2015 | Self-reported history of stroke | AD | LL/**?** | 0.97 (0.71, 1.24)  | 40.9% | 0.03 | 9 | 1.00 | 9 |
| TBI | 3 | Xu 2015 | Head trauma with/without loss of consciousness | AD | LL/**?** | 1.18 (0.89, 1.47) | 7.5% | 0.16 | 6 | 0.40 | 15 |
|  |  | Li 2017 | Prior TBI | AD | **LL**/? | 1.24 (1.04, 1.49)  | 26.8 | 0.32 | 8 | 0.53 |  |
|  |  | Perry 2016 | Prior TBI | AD | ? | 0.95 (0.58, 1.54) | 51.4% | 0.83 | 7 | 0.47 |  |
|  |  | Li 2017 | Prior TBI | Any Dementia | ML/**LL**/? | 1.63 (1.33, 2.00) | 95.2% | 0.35 | 8 | 0.53 |  |
|  |  | Perry 2016 | Prior TBI | Any Dementia | ? | 1.34 (0.56, 3.18) | 78.8% | ~ | 3 | 0.20 |  |
| **Pharmacological** |   |   |   |   |   |   |   |  |  |  |   |
| Antacids | 1 | Virk 2015 | Aluminium containing antacids | AD | ? | 0.70 (0.30, 1.80) | 0.0% | ns | 2 | 1.00 | 2 |
|  |   | Virk 2015 | Antacid | AD | ? | 0.83 (0.39, 1.78) | 0.0% | ns | 2 | 1.00 |   |
| Antihypertensives | 6 | Chang-Quan 2011 | Antihypertensives | AD | ML/**LL**/? | 0.92 (0.79, 1.08) | 0.0% | 0.66 | 5 | 0.21 | 24 |
|  |  | Guan 2011 | Antihypertensives | AD | ML/LL | 0.92 (0.79, 1.08) | 0.0% | 0.66 | 5 | 0.21 |  |
|  |  | Xu 2015 | Antihypertensives | AD | LL/**?** | 0.71 (0.59, 0.83) | 52.7% | 0.36 | 5 | 0.21 |  |
|  |  | Xu 2017 | Antihypertensives | AD | LL | 0.83 (0.64, 1.07) | 40.5% | possible^ | 6 | 0.25 |  |
|  |  | Chang-Quan 2011 | Antihypertensives | Any Dementia | ML/**LL**/? | 0.84 (0.71, 0.99) | 0.0% | 0.27 | 4 | 0.17 |  |
|  |  | Levi 2013 | Antihypertensives | Any Dementia | LL | 0.82 (0.73, 0.94) | 79.3% | 0.12 | 7 | 0.29 |  |
|  |  | Xu 2017 | Antihypertensives | Any Dementia | LL | 0.86 (0.75, 0.99) | 73.4% | possible^ | 6 | 0.25 |  |
|  |  | Tully 2016 | Diuretics | Any Dementia | LL | 0.79 (0.70, 0.89) | 0.0% | 0.71 | 8 | 0.33 |  |
| Anti-inflammatories | 4 | Etminan 2003 | All NSAIDs | AD | ML/**LL** | 0.84 (0.54, 1.05) | 62.3% | 0.95 | 6 | 0.35 | 17 |
|  | Wang 2015 | All NSAIDS | AD | **LL**/? | 0.69 (0.56, 0.86) | 79.7% | 0.10 | 12 | 0.71 |
|  | Etminan 2003 | Aspirin | AD | ML/**LL** | 0.85 (0.71, 1.03) | 80.5% | 0.90 | 5 | 0.29 |
|  | Wang 2015 | Aspirin | AD | **LL**/? | 0.74 (0.57, 0.97) | 67.9% | - | 8 | 0.47 |
|  | Wang 2015 | Non-aspirin NSAIDs | AD | **LL**/? | 0.61 (0.43, 0.88) | 68.6% | 0.04 | 7 | 0.41 |
|  | Xu 2015 | NSAIDs | AD | LL/**?** | 0.67 (0.44, 0.90) | 65.8% | <0.01 | 9 | 0.53 |
|  | Szekely 2004 | NSAIDs - lifetime exposure | AD | ML/**LL**/? | 0.74 (0.62, 0.89) |  - | absent^ | 4 | 0.24 |
|  | Szekely 2004 | NSAIDs -exposure for 2 or more years | AD | ML/LL/? | 0.42 (0.26, 0.66) | 0.0% | ~ | 3 | 0.18 |
| Benzodiazepines | 1 | Islam 2016 | Benzodiazepine use versus none | Any Dementia | ? | 1.47 (1.28:1.69) | 0.0% | ~ | 2 | 0.67 | 3 |
| HRT | 3 | LeBlanc 2001 | Any use versus never use | AD | LL | 0.50 (0.30, 0.80) | 0.0% | ~ | 2 | 0.22 | 9 |
|  |  | O'Brien 2014 | Any use versus never use | AD | ? | 0.69 (0.48, 1.00) | 31.4% | 0.78 | 8 | 0.89 |  |
|  |  | Xu 2015  | Any use versus never use | AD | **LL**/? | 0.61 (0.46, 0.76) | 38.1 | <0.01 | 4 | 0.44 |  |
| Insulin sensitizers | 1 | Ye 2016 | Insulin-sensitizers versus non-insulin sensitizer | AD | ? | 0.90 (0.55, 1.45) |  - | ~ | 2 | 0.33 | 6 |
|  |  | Ye 2016 | Metformin versus non-insulin sensitizer | Any Dementia | ? | 0.78 (0.84, 0.95) | 55.1 | unobvious^ | 6 | 1.00 |  |
|  |  | Ye 2016 | Thiazolidinediones versus non-insulin sensitizer | Any Dementia | ? | 0.79 (0.82, 1.01) | 63.1 | unobvious^ | 6 | 1.00 |  |
|  |   | Ye 2016 | Insulin-sensitizers versus non-insulin sensitizer | Any Dementia | ? | 0.75 (0.56, 1.00) | 0 | ~ | 2 | 0.33 |   |
| Statins | 5 | Zhou 2007 | Any use versus non-user | AD | ? | 0.90 (0.65, 1.25)  | 0.0% | ~ | 3 | 0.14 | 22 |
|  |  | Xu 2015 | Current use versus never use | AD | LL/**?** | 0.59 (0.45, 0.73)  | 26.4% | 0.29 | 5 | 0.23 |  |
|  |  | Xu 2015 | Former versus never use | AD | ? | 1.28 (0.69, 3.24)  | 74.6% | ~ | 2 | 0.09 |  |
|  |  | Xu 2015 | Longer use versus never use  | AD | ? | 0.24 (0.07, 0.70)  | 0.0% | ~ | 2 | 0.09 |  |
|  |  | Richardson 2013 | Users versus non-users | AD | ML/**LL**/? | 0.79 (0.63, 0.99)  | 91.6% | 0.38 | 10 | 0.45 |  |
|  |  | Wong 2013 | Users versus non-users | AD | ? | 0.70 (0.60, 0.80)  | 18.2% | minimal^ | 13 | 0.59 |  |
|  |  | Zhou 2007 | Any use versus non-user | Any Dementia | ? | 0.77 (0.61, 0.96)  | 0.0% | 0.36 | 4 | 0.18 |  |
|  |  | Richardson 2013 | Users versus non-users | Any Dementia | ML/**LL**/? | 0.87 (0.82, 0.92)  | 34.4% | <0.01 | 10 | 0.45 |  |
|  |  | Swiger 2013 | Users versus non-users | Any Dementia | **ML**/LL/? | 0.71 (0.61, 0.82)  | 15.0% | - | 2 | 0.09 |  |
|  |  | Wong 2013 | Users versus non-users | Any Dementia | ? | 0.82 (0.69, 0.97) | 95.9% | minimal^ | 12 | 0.55 |  |
| **Environmental** |   |   |   |   |   |   |   |  |  |  |   |
| Pesticides | 2 | Yan 2016 | Pesticide exposure | AD | LL**/?** | 1.37 (1.08, 1.75) | 0.0% | 0.66 | 3 | 1.00 | 3 |
|   | 1 | Xu 2015 | Occupational exposure to pesticides | AD | LL**/?** | 1.26 (0.93, 1.59) | 5.4% | 0.78 | 3 | 1.00 |   |
| *Note. \*The primary age represented per pooled effect (RR) is indicated by bolded text; 'adj' denotes age-adjusted, (baseline age is not relevant to measures of self-reported educational attainment), 'ML' denotes midlife (baseline age<65), 'LL' denotes late-life (baseline age 65+) and '?' denotes unknown. 'RR' denotes risk ratio, which is the pooled risk estimate; 'M' denotes RR for males; 'F' denotes RR for females. '-' denotes not reported; '~' indicates there were too few studies to calculate Eggers p; ^ bias as indicated by visual inspection of funnel plot. Egger’s values are as reported in primary reviews, but not a recommended measure of bias when n<10.'n' is the number of primary studies included in the meta-analysis for each RR.'N' is the total number of unique primary studies for each risk factor.'R' denotes representativeness statistic, R = n/N.* |

Supplementary Table 2. Reasons for full-text exclusions

|  |  |  |
| --- | --- | --- |
|  | **Excluded articles** | **Reasons** |
| 1 | Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: recommendations and rationale. Ann Intern Med 2002; 137(10): 834-9. | Summative statement on methods for the meta-analysis of HRT & Dementia - sourced original article (LeBlanc 2017) |
| 2 | Adelman S, Blanchard M, Livingston G. A systematic review of the prevalence and covariates of dementia or relative cognitive impairment in the older African-Caribbean population in Britain. Int J Geriatr Psychiatry 2009; 24(7): 657-65. | A systematic review of reviews (reference list used in search) |
| 3 | Akinyemi RO, Mukaetova-Ladinska EB, Attems J, Ihara M, Kalaria RN. Vascular risk factors and neurodegeneration in ageing related dementias: Alzheimer's disease and vascular dementia. Curr Alzheimer Res 2013; 10(6): 642-53. | Cannot separate dementia outcomes from cognitive decline  |
| 4 | Altavilla R, Altamura C, Palazzo P, Buratti L, Silvestrini M, Vernieri F. Emerging Risk Factors for Dementia: The Role of Blood Pressure Variability. CNS Neurol Disord Drug Targets 2016; 15(6): 672-7. | Cognitive outcomes, tests and assessment of decline not clear, not definitive on what performance of MMSE is “worse” – ambiguous on how diagnostic tool was used |
| 5 | Anstey KJ, Cherbuin N, Herath PM. Development of a new method for assessing global risk of Alzheimer's disease for use in population health approaches to prevention. Prevention science: the official journal of the Society for Prevention Research 2013; 14(4): 411-21. | data incompatible, could not re-pool as unable to determine which HRs were originally pooled |
| 6 | Aravena Castro JM. La ocupación como factor protector de la demencia por enfermedad de alzheimer (Occupancy as protective factor of dementia due to Alzheimer's disease). Rev chil ter ocup 2014; 14(2): 149-59. | Did not employ meta-analytic methodology  |
| 7 | Aridi YS, Walker JL, Wright ORL. The Association between the Mediterranean Dietary Pattern and Cognitive Health: A Systematic Review. Nutrients 2017; 9(7). | Did not employ meta-analytic methodology  |
| 8 | Arvanitakis Z, Wilson RS, Bennett DA. Diabetes mellitus, dementia, and cognitive function in older persons. J Nutr Health Aging 2006; 10(4): 287-91. | Did not employ meta-analytic methodology  |
| 9 | Azad NA, Al Bugami M, Loy-English I. Gender differences in dementia risk factors. Gend Med 2007; 4(2): 120-9. | Did not employ meta-analytic methodology  |
| 10 | Bellou V, Belbasis L, Tzoulaki I, Middleton LT, Ioannidis JP, Evangelou E. Systematic evaluation of the associations between environmental risk factors and dementia: An umbrella review of systematic reviews and meta-analyses. Alzheimers Dement 2016. | Did not employ meta-analytic methodology  |
| 11 | Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006; 5(1): 64-74. | Did not employ meta-analytic methodology  |
| 12 | Billioti de Gage S, Pariente A, Begaud B. Impact of anesthesia on the cognitive functioning of the elderly. Expert Opin Drug Saf 2015; 14(5): 733-47. | Did not employ meta-analytic methodology  |
| 13 | Breteler MM, Bots ML, Ott A, Hofman A. Risk factors for vascular disease and dementia. Haemostasis 1998; 28(3-4): 167-73. | Did not employ meta-analytic methodology  |
| 14 | Burgener SC, Buettner L, Coen Buckwalter K, et al. Evidence supporting nutritional interventions for persons in early stage Alzheimer's disease (AD). J Nutr Health Aging 2008; 12(1): 18-21. | Did not employ meta-analytic methodology  |
| 15 | Campbell NL, Unverzagt F, LaMantia MA, Khan BA, Boustani MA. Risk factors for the progression of mild cognitive impairment to dementia. Clin Geriatr Med 2013; 29(4): 873-93. | Did not employ meta-analytic methodology  |
| 16 | Canevelli M, Lucchini F, Quarata F, Bruno G, Cesari M. Nutrition and Dementia: Evidence for Preventive Approaches? Nutrients 2016; 8(3): 144. | Did not employ meta-analytic methodology  |
| 17 | Cataldo JK, Prochaska JJ, Glantz SA. Cigarette smoking is a risk factor for Alzheimer's Disease: an analysis controlling for tobacco industry affiliation. J Alzheimers Dis 2010; 19(2): 465-80. | Did not employ meta-analytic methodology  |
| 18 | Cations M, Withall A, Low LF, Draper B. What is the role of modifiable environmental and lifestyle risk factors in young onset dementia? Eur J Epidemiol 2016; 31(2): 107-24. | Did not employ meta-analytic methodology  |
| 19 | Chui HC, Zheng L, Reed BR, Vinters HV, Mack WJ. Vascular risk factors and Alzheimer's disease: are these risk factors for plaques and tangles or for concomitant vascular pathology that increases the likelihood of dementia? An evidence-based review. Alzheimers Res Ther 2012; 4(1): 1. | Did not employ meta-analytic methodology  |
| 20 | Crichton GE, Bryan J, Murphy KJ. Dietary antioxidants, cognitive function and dementia--a systematic review. Plant foods for human nutrition (Dordrecht, Netherlands) 2013; 68(3): 279-92. | Did not employ meta-analytic methodology  |
| 21 | Crichton GE, Elias MF, Buckley JD, Murphy KJ, Bryan J, Frisardi V. Metabolic syndrome, cognitive performance, and dementia. J Alzheimers Dis 2012; 30 Suppl 2: S77-87. | Did not employ meta-analytic methodology  |
| 22 | Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. Diabetologia 2005; 48(12): 2460-9. | Did not employ meta-analytic methodology  |
| 23 | da Silva J, Goncalves-Pereira M, Xavier M, Mukaetova-Ladinska EB. Affective disorders and risk of developing dementia: systematic review. Br J Psychiatry 2013; 202(3): 177-86. | Did not employ meta-analytic methodology  |
| 24 | Deckers K, Camerino I, van Boxtel MP, et al. Dementia risk in renal dysfunction: A systematic review and meta-analysis of prospective studies. Neurology 2017; 88(2): 198-208. | Did not employ meta-analytic methodology  |
| 25 | Deckers K, van Boxtel MP, Schiepers OJ, et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. Int J Geriatr Psychiatry 2015; 30(3): 234-46. | Did not employ meta-analytic methodology  |
| 26 | Devi Bastida J, Puig Pomes N, Jofre Font S, Fetscher Eickhoff A. [Depression: A predictor of dementia]. Rev Esp Geriatr Gerontol 2016; 51(2): 112-8. | Did not employ meta-analytic methodology  |
| 27 | Dick SE, DeWitt DE, Anawalt BD. Postmenopausal hormone replacement therapy and major clinical outcomes: a focus on cardiovascular disease, osteoporosis, dementia, and breast and endometrial neoplasia. The American journal of managed care 2002; 8(1): 95-104; quiz 5-6. | Did not employ meta-analytic methodology  |
| 28 | Durazzo TC, Mattsson N, Weiner MW. Smoking and increased Alzheimer's disease risk: a review of potential mechanisms. Alzheimers Dement 2014; 10(3 Suppl): S122-45. | Did not employ meta-analytic methodology  |
| 29 | Duron E, Hanon O. Vascular risk factors, cognitive decline, and dementia. Vasc Health Risk Manag 2008; 4(2): 363-81. | Did not employ meta-analytic methodology  |
| 30 | Duron E, Hanon O. Hypertension, cognitive decline and dementia. Archives of cardiovascular diseases 2008; 101(3): 181-9. | Did not employ meta-analytic methodology  |
| 31 | Etgen T, Chonchol M, Forstl H, Sander D. Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. American journal of nephrology 2012; 35(5): 474-82. | Did not employ meta-analytic methodology  |
| 32 | Etgen T, Sander D, Bickel H, Forstl H. Mild cognitive impairment and dementia: the importance of modifiable risk factors. Dtsch Arztebl Int 2011; 108(44): 743-50. | Did not employ meta-analytic methodology  |
| 33 | Etgen T, Sander D, Bickel H, Sander K, Forstl H. Vitamin D deficiency, cognitive impairment and dementia: a systematic review and meta-analysis. Dement Geriatr Cogn Disord 2012; 33(5): 297-305. | Did not employ meta-analytic methodology  |
| 34 | Farina N, Isaac MGEKN, Clark AR, Rusted J, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. Cochrane Database of Systematic Reviews, 2012. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002854.pub3/abstract | Did not employ meta-analytic methodology  |
| 35 | Ferreira PC, Piai Kde A, Takayanagui AM, Segura-Munoz SI. Aluminum as a risk factor for Alzheimer's disease. Revista latino-americana de enfermagem 2008; 16(1): 151-7. | Did not employ meta-analytic methodology  |
| 36 | Fillit H, Nash DT, Rundek T, Zuckerman A. Cardiovascular risk factors and dementia. Am J Geriatr Pharmacother 2008; 6(2): 100-18. | Did not employ meta-analytic methodology  |
| 37 | Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry 2003; 74(7): 857-62. | Did not employ meta-analytic methodology  |
| 38 | Forlenza OV, Diniz BS, Stella F, Teixeira AL, Gattaz WF. Mild cognitive impairment. Part 1: clinical characteristics and predictors of dementia. Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999) 2013; 35(2): 178-85. | Did not employ meta-analytic methodology  |
| 39 | Fotuhi M, Mohassel P, Yaffe K. Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association. Nature clinical practice Neurology 2009; 5(3): 140-52. | Did not employ meta-analytic methodology  |
| 40 | Gates NJ, Sachdev PS, Fiatarone Singh MA, Valenzuela M. Cognitive and memory training in adults at risk of dementia: a systematic review. BMC Geriatr 2011; 11: 55. | Did not employ meta-analytic methodology  |
| 41 | Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke 2011; 42(9): 2672-713. | Did not employ meta-analytic methodology  |
| 42 | Gorospe EC, Dave JK. The risk of dementia with increased body mass index. Age Ageing 2007; 36(1): 23-9. | Did not employ meta-analytic methodology  |
| 43 | Guerchet M, Aboyans V, Nubukpo P, Lacroix P, Clement JP, Preux PM. Ankle-brachial index as a marker of cognitive impairment and dementia in general population. A systematic review. Atherosclerosis 2011; 216(2): 251-7. | Did not employ meta-analytic methodology  |
| 44 | Herbert CP. Cultural aspects of dementia. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques 2001; 28 Suppl 1: S77-82. | Did not employ meta-analytic methodology  |
| 45 | Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D. Risk factors associated with the onset and progression of Alzheimer's disease: A systematic review of the evidence. Neurotoxicology 2017; 61: 143-87. | Did not employ meta-analytic methodology  |
| 46 | Hinterberger M, Fischer P. Folate and Alzheimer: when time matters. J Neural Transm (Vienna) 2013; 120(1): 211-24. | Did not employ meta-analytic methodology  |
| 47 | Ilomaki J, Jokanovic N, Tan EC, Lonnroos E. Alcohol Consumption, Dementia and Cognitive Decline: An Overview of Systematic Reviews. Current clinical pharmacology 2015; 10(3): 204-12. | Did not employ meta-analytic methodology  |
| 48 | Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry 2000; 15(11): 983-91. | Did not employ meta-analytic methodology  |
| 49 | Julien J, Joubert S, Ferland MC, et al. Association of traumatic brain injury and Alzheimer disease onset: A systematic review. Ann Phys Rehabil Med 2017; 60(5): 347-56. | Did not employ meta-analytic methodology  |
| 50 | Killin LO, Starr JM, Shiue IJ, Russ TC. Environmental risk factors for dementia: a systematic review. BMC Geriatr 2016; 16(1): 175. | Did not employ meta-analytic methodology  |
| 51 | Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. Eur J Pharmacol 2008; 585(1): 97-108. | Did not employ meta-analytic methodology  |
| 52 | Kopf D, Frolich L. Risk of incident Alzheimer's disease in diabetic patients: a systematic review of prospective trials. J Alzheimers Dis 2009; 16(4): 677-85. | Did not employ meta-analytic methodology  |
| 53 | Lafortune L, Martin S, Kelly S, et al. Behavioural Risk Factors in Mid-Life Associated with Successful Ageing, Disability, Dementia and Frailty in Later Life: A Rapid Systematic Review. PloS one 2016; 11(2): e0144405. | Did not report results in full |
| 54 | Lee Y, Back JH, Kim J, et al. Systematic review of health behavioral risks and cognitive health in older adults. Int Psychogeriatr 2010; 22(2): 174-87. | Examined the clinical significance/usefulness of SMC for diagnosis of MCI/dementia – not as risk factor as primary outcome |
| 55 | Levine DA, Langa KM. Vascular cognitive impairment: disease mechanisms and therapeutic implications. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics 2011; 8(3): 361-73. | Findings only include population with herpes virus  |
| 56 | Li FJ, Shen L, Ji HF. Dietary intakes of vitamin E, vitamin C, and beta-carotene and risk of Alzheimer's disease: a meta-analysis. J Alzheimers Dis 2012; 31(2): 253-8. | Focused on RCTs |
| 57 | Loef M, von Stillfried N, Walach H. Zinc diet and Alzheimer's disease: a systematic review. Nutritional neuroscience 2012; 15(5): 2-12. | Focuses mostly on diagnostic entity and doesn’t summarise relationship between MCI and dementia clearly; reviewed the conceptual and clinical characteristics of MCI not focused on risk factors |
| 58 | Loef M, Walach H. Copper and iron in Alzheimer's disease: a systematic review and its dietary implications. The British journal of nutrition 2012; 107(1): 7-19. | Focuses on case-control studies only  |
| 59 | Loef M, Walach H. Fruit, vegetables and prevention of cognitive decline or dementia: a systematic review of cohort studies. J Nutr Health Aging 2012; 16(7): 626-30. | Focuses on cognitive impairment, not MCI or dementia |
| 60 | Loef M, Walach H. The omega-6/omega-3 ratio and dementia or cognitive decline: a systematic review on human studies and biological evidence. Journal of nutrition in gerontology and geriatrics 2013; 32(1): 1-23. | Focuses on cognitive impairment, not MCI or dementia; Selective search and included only pertinent articles – non-Systematic, “selective literature search” |
| 61 | Lourida I, Soni M, Thompson-Coon J, et al. Mediterranean diet, cognitive function, and dementia: a systematic review. Epidemiology 2013; 24(4): 479-89. | Incompatible results, insufficient prospective studies  |
| 62 | Ma J, Zhang W, Wang HF, et al. Peripheral Blood Adipokines and Insulin Levels in Patients with Alzheimer's Disease: A Replication Study and Meta-Analysis. Curr Alzheimer Res 2016; 13(3): 223-33. | Meta-analysis of RCTs |
| 63 | Maki PM. A systematic review of clinical trials of hormone therapy on cognitive function: effects of age at initiation and progestin use. Ann N Y Acad Sci 2005; 1052: 182-97. | No dates for searches – cannot replicate |
| 64 | Mawanda F, Wallace R. Can infections cause Alzheimer's disease? Epidemiol Rev 2013; 35: 161-80. | No dates for the searches – non-replicable |
| 65 | McGeer PL, Schulzer M, McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. Neurology 1996; 47(2): 425-32. | No description of search methodology – cannot qualify as systematic review |
| 66 | Mendonca MD, Alves L, Bugalho P. From Subjective Cognitive Complaints to Dementia: Who is at Risk?: A Systematic Review. Am J Alzheimers Dis Other Demen 2016; 31(2): 105-14. | No description of search methods or inclusion exclusion criteria, non-systematic “review of the relevant literature” |
| 67 | Meng X, D'Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: A systematic review with meta-analyses and qualitative analyses. PLoS One 2012; 7(6): e38268,  | Education is used as a proxy measure for cognitive reserve |
| 68 | Mitchell AJ. The clinical significance of subjective memory complaints in the diagnosis of mild cognitive impairment and dementia: a meta-analysis. Int J Geriatr Psychiatry 2008; 23(11): 1191-202. | No reference to methodology of systematic or comprehensive search and no description of search methods |
| 69 | Muangpaisan W, Brayne C, Alzheimer's Society Vascular Dementia Systematic Review G. Systematic review of statins for the prevention of vascular dementia or dementia. Geriatr Gerontol Int 2010; 10(2): 199-208. | No reference to methodology that proves to be systematic; ARD only |
| 70 | Naismith SL, Glozier N, Burke D, Carter PE, Scott E, Hickie IB. Early intervention for cognitive decline: is there a role for multiple medical or behavioural interventions? Early intervention in psychiatry 2009; 3(1): 19-27. | No search dates, non-replicable |
| 71 | Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Archives of general psychiatry 2006; 63(5): 530-8. | No search dates, non-replicable |
| 72 | Patterson C, Feightner J, Garcia A, MacKnight C. General risk factors for dementia: a systematic evidence review. Alzheimers Dement 2007; 3(4): 341-7. | No search dates, non-replicable |
| 73 | Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol 2009; 8(11): 1006-18. | No stated inclusion or exclusion criteria, no method of appraisal of studies described, no search dates |
| 74 | Perez L, Heim L, Sherzai A, Jaceldo-Siegl K, Sherzai A. Nutrition and vascular dementia. J Nutr Health Aging 2012; 16(4): 319-24. | Non-systematic review – stated in introduction |
| 75 | Peters R. Blood pressure, smoking and alcohol use, association with vascular dementia. Experimental gerontology 2012; 47(11): 865-72. | Non-systematic, just a literature review; “selected epidemiological studies… were included in their report” not clear include/exclude criteria or if only selected studies were reviewed, no description of data synthesis  |
| 76 | Peters R, Booth A, Peters J. A systematic review of calcium channel blocker use and cognitive decline/dementia in the elderly. J Hypertens 2014; 32(10): 1945-57; discussion 57-8. | Not a comprehensive search and no description of search methods |
| 77 | Piazza-Gardner AK, Gaffud TJ, Barry AE. The impact of alcohol on Alzheimer's disease: a systematic review. Aging Ment Health 2013; 17(2): 133-46. | Not a comprehensive search and no description of search methods |
| 78 | Plassman BL, Williams JW, Jr., Burke JR, Holsinger T, Benjamin S. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. Ann Intern Med 2010; 153(3): 182-93. | Not a comprehensive search and no description of search methods, literature review |
| 79 | Power MC, Weuve J, Sharrett AR, Blacker D, Gottesman RF. Statins, cognition, and dementiasystematic review and methodological commentary. Nat Rev Neurol 2015; 11(4): 220-9. | Not a comprehensive search and no description of search methods, not a systematic review |
| 80 | Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. Biological psychiatry 2010; 67(6): 505-12. | Not a comprehensive search and no description of search methods, not a systematic review  |
| 81 | Purnell C, Gao S, Callahan CM, Hendrie HC. Cardiovascular risk factors and incident Alzheimer disease: a systematic review of the literature. Alzheimer Dis Assoc Disord 2009; 23(1): 1-10. | Not a comprehensive search and no description of search methods, not a systematic review, literature review |
| 82 | Ritchie K, Polge C, de Roquefeuil G, Djakovic M, Ledesert B. Impact of anesthesia on the cognitive functioning of the elderly. Int Psychogeriatr 1997; 9(3): 309-26. | Not a comprehensive search and no description of search methods, not a systematic review, literature review  |
| 83 | Rojas-Fernandez CH, Moorhouse P. Current concepts in vascular cognitive impairment and pharmacotherapeutic implications. The Annals of pharmacotherapy 2009; 43(7): 1310-23. | Not a comprehensive search and no description of search methods; Not a systematic review - a statement |
| 84 | Sachdeva A, Chandra M, Choudhary M, Dayal P, Anand KS. Alcohol-Related Dementia and Neurocognitive Impairment: A Review Study. International journal of high risk behaviors & addiction 2016; 5(3): e27976. | Not a systematic review |
| 85 | Sajeev G, Weuve J, Jackson JW, et al. Late-life Cognitive Activity and Dementia: A Systematic Review and Bias Analysis. Epidemiology 2016; 27(5): 732-42. | Not a systematic review, just summative paper of existing research |
| 86 | Santibanez M, Bolumar F, Garcia AM. Occupational risk factors in Alzheimer's disease: a review assessing the quality of published epidemiological studies. Occupational and environmental medicine 2007; 64(11): 723-32. | Not clear if included case control and or cross sectional studies, no data on included studies - they did not extract study details for their included studies |
| 87 | Savva GM, Stephan BC. Epidemiological studies of the effect of stroke on incident dementia: a systematic review. Stroke 2010; 41(1): e41-6. | Not fully systematic, and focus is on concept not prevention or risk |
| 88 | Seifan A, Schelke M, Obeng-Aduasare Y, Isaacson R. Early Life Epidemiology of Alzheimer's Disease--A Critical Review. Neuroepidemiology 2015; 45(4): 237-54. | Not looking at culture as a predictor of risk; Not a comprehensive search and no description of search methods - a critical review |
| 89 | Seitz DP, Shah PS, Herrmann N, Beyene J, Siddiqui N. Exposure to general anesthesia and risk of Alzheimer's disease: a systematic review and meta-analysis. BMC Geriatr 2011; 11: 83. | Not systematic review |
| 90 | Shah K, Qureshi SU, Johnson M, Parikh N, Schulz PE, Kunik ME. Does use of antihypertensive drugs affect the incidence or progression of dementia? A systematic review. Am J Geriatr Pharmacother 2009; 7(5): 250-61. | Not systematic review |
| 91 | Sharp ES, Gatz M. Relationship between education and dementia: an updated systematic review. Alzheimer Dis Assoc Disord 2011; 25(4): 289-304. | Not systematic review |
| 92 | Shively S, Scher AI, Perl DP, Diaz-Arrastia R. Dementia resulting from traumatic brain injury: what is the pathology? Arch Neurol 2012; 69(10): 1245-51. | Not systematic review |
| 93 | Skoog I, Gustafson D. HRT and dementia. Journal of epidemiology and biostatistics 1999; 4(3): 227-51; discussion 52. | Not systematic review |
| 94 | Solfrizzi V, Custodero C, Lozupone M, et al. Relationships of Dietary Patterns, Foods, and Micro- and Macronutrients with Alzheimer's Disease and Late-Life Cognitive Disorders: A Systematic Review. J Alzheimers Dis 2017; 59(3): 815-49. | Not systematic review |
| 95 | Song J, Lee WT, Park KA, Lee JE. Association between risk factors for vascular dementia and adiponectin. Biomed Res Int 2014; 2014: 261672. | Not systematic review |
| 96 | Steel AJ, Eslick GD. Herpes Viruses Increase the Risk of Alzheimer's Disease: A Meta-Analysis. J Alzheimers Dis 2015; 47(2): 351-64. | Not systematic review form abstract– inaccessible pdf (tried DSS, article reach) |
| 97 | Stephen R, Hongisto K, Solomon A, Lonnroos E. Physical Activity and Alzheimer's Disease: A Systematic Review. J Gerontol A Biol Sci Med Sci 2017; 72(6): 733-9. | Not systematic review- summative paper of existing research  |
| 98 | Sydenham E, Dangour AD, Lim W-S. Omega 3 fatty acid for the prevention of cognitive decline and dementia. Cochrane Database of Systematic Reviews, 2012. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005379.pub3/abstract | Only case-control studies included – criteria searched for case control and cohort studies but no eligible cohort studies found |
| 99 | Then FS, Luck T, Luppa M, et al. Systematic review of the effect of the psychosocial working environment on cognition and dementia. Occupational and environmental medicine 2014; 71(5): 358-65. | Only herpes has more than one cohort. Not possible to work out which 3 studies are cohorts with herpes results to recalculate pooled ratio |
| 100 | Twamley EW, Ropacki SA, Bondi MW. Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. J Int Neuropsychol Soc 2006; 12(5): 707-35. | Overview of systematic reviews (used reference list for search) |
| 101 | Udompanich S, Lip GY, Apostolakis S, Lane DA. Atrial fibrillation as a risk factor for cognitive impairment: a semi-systematic review. Qjm 2013; 106(9): 795-802. | Reported findings from another systematic review (Xu 2015) |
| 102 | van der Velpen IF, Feleus S, Bertens AS, Sabayan B. Hemodynamic and serum cardiac markers and risk of cognitive impairment and dementia. Alzheimers Dement 2016. | Review of only case controls  |
| 103 | Verdoux H, Lagnaoui R, Begaud B. Is benzodiazepine use a risk factor for cognitive decline and dementia? A literature review of epidemiological studies. Psychol Med 2005; 35(3): 307-15. | Review of only RCTS  |
| 104 | Wang HX, Xu W, Pei JJ. Leisure activities, cognition and dementia. Biochimica et biophysica acta 2012; 1822(3): 482-91. | Review of RCTs (exclusion criteria) |
| 105 | Williams JW, Plassman BL, Burke J, Benjamin S. Preventing Alzheimer's disease and cognitive decline. Evidence report/technology assessment 2010; (193): 1-727. | Review of RCTs only  |
| 106 | Wu B, Fillenbaum GG, Plassman BL, Guo L. Association Between Oral Health and Cognitive Status: A Systematic Review. Journal of the American Geriatrics Society 2016; 64(4): 739-51. | Review of unconfounded trails (RCTs)  |
| 107 | Xu W, Wang H, Wan Y, et al. Alcohol consumption and dementia risk: a dose-response meta-analysis of prospective studies. Eur J Epidemiol 2017; 32(1): 31-42. | Selection ambiguous “primarily based on being longitudinal studies”; study designs not clear |
| 108 | Yang C-W, Fuh J-L. Exposure to general anesthesia and the risk of dementia. J Pain Res 2015; 8: 711-8. | Semi-systematic review |
| 109 | Young J, Angevaren M, Rusted J, Tabet N. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. Cochrane Database of Systematic Reviews, 2015. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005381.pub4/abstract | Stroke population |
| 110 | Yue J, Dong BR, Lin X, Yang M, Wu HM, Wu T. Huperzine A for mild cognitive impairment. Cochrane Database of Systematic Reviews, 2012. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008827.pub2/abstract | Study designs not clear |
| 111 | Yusufov M, Weyandt LL, Piryatinsky I. Alzheimer's disease and diet: a systematic review. Int J Neurosci 2017; 127(2): 161-75. | Unclear how studies were selected |
| 112 | Zhong G, Wang Y, Zhang Y, Zhao Y. Association between Benzodiazepine Use and Dementia: A Meta-Analysis. PloS One 2015; 10(5): e0127836. | Young onset dementia to be excluded (as discussed when formulating exclusion criteria) |
| 113 | Siervo M, Harrison SL, Jagger C, Robinson L, Stephan BC. Metabolic syndrome and longitudinal changes in cognitive function: A systematic review and meta-analysis. J Alzheimers Dis 2014; 41(1): 151-61.  | Outcome is not dementia, only cognitive decline |

Supplementary Table 3.

Quality Assessment

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***Study*** | ***1. Was an 'a prior' design provided?*** | ***2. Was there duplicate study selection and data extraction?*** | ***3. Was a comprehensive literature search performed?*** | ***4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?*** | ***5. Was a list of studies (included/excluded) provided?*** | ***6. Were the characteristics of the included studies provided?*** | ***7. Was the scientific quality of the included studies assessed and documented?*** | ***8.Was the scientific quality of the included studies used appropriately in formulating the conclusions?*** | ***9. Were the methods used to combine the findings of the studies appropriate?*** | ***10. Was the likelihood of publications bias assessed?*** | ***11. Was the conflict of interest stated?*** |
| Aarsland 2010 | n | y | n | y | y | y | y | y | y | y | y |
| Almeida 2002  | n | y | y | y | n | y | y | y | y | na | n |
| Anstey 2007  | n | y | y | y | y | y | c | c | y | na | Y |
| Anstey 2008  | n | y | y | y | y | y | y | y | y | y | n |
| Anstey 2009 | n | y | y | y | n | y | c | y | y | n | n |
| Anstey 2011 | n | y | y | y | n | y | y | y | y | y | y |
| Anstey 2017 | y | y | y | y | n | y | y | y | y | y | y |
| Barranco 2007 | n | c | y | y | n | n | c | y | y | na | n |
| Becket 2015 | n | n | n | y | n | y | n | n | y | n | y |
| Beydoun 2008 | n | n | y | y | n | y | y | y | y | y | y |
| Blondell 2014 | y | y | y | n | y | y | y | y | y | y | y |
| Chang-Quan 2011 | y | y | y | y | n | y | y | y | y | y | y |
| Chatterjee 2016 | n | y | n | y | n | y | y | y | y | n | y |
| Cheng 2012 | n | y | y | y | n | y | y | y | y | y | n |
| Cherbuin 2015 | n | y | y | y | n | y | y | y | y | y | y |
| Daviglus 2011 | y | y | y | n | y | y | c | y | y | y | y |
| de Almondes 2016 | n | y | y | y | n | y | y | y | y | y | y |
| Diniz 2013 | n | y | y | y | n | y | y | y | y | y | y |
| Du 2016 | n | y | y | y | n | n | y | y | y | y | y |
| Etminan 2003 | n | y | y | y | n | y | c | y | y | y | y |
| Guan 2011 | n | y | y | y | n | y | y | y | y | n | y |
| Gudala et al 2013 | n | y | y | y | n | y | y | y | y | y | y |
| Hamer 2009 | n | y | y | y | n | y | y | y | y | y | y |
| Ho 2011 | n | y | y | y | n | y | n | c | y | y | n |
| Jansen 2015 | n | n | y | n | n | n | y | y | y | n | y |
| Jiang 2017 | n | y | n | y | n | y | y | y | y | y | y |
| Kalantarian 2013 | n | n | y | y | n | y | y | y | y | y | n |
| Kim 2015 | n | y | y | n | n | y | y | y | y | y | y |
| Koyama 2013 | n | y | y | y | n | y | y | y | y | y | n |
| Kuiper 2015 | n | y | y | y | n | y | y | y | y | y | y |
| Kwok 2011 | n | y | y | y | n | y | y | y | y | n | y |
| LeBlanc 2001 | n | n | y | y | n | y | y | n | y | y | n |
| Levi 2013 | n | y | y | y | n | y | n | c | y | y | y |
| Li 2017 | n | n | y | y | n | y | y | y | y | y | n |
| Liu 2016 | n | y | y | y | n | y | n | c | y | y | n |
| Loef 2013 | n | n | y | y | n | y | n | y | y | y | n |
| Low 2013 | n | y | y | y | n | y | na | y | y | n | n |
| Lu 2009 | n | y | y | y | n | y | na | y | y | y | y |
| Lv 2013 | n | y | y | y | n | y | y | y | y | y | y |
| Ma 2014 | n | y | n | y | n | y | y | y | y | y | n |
| Ma 2016 | n | y | y | y | y | y | y | y | y | y | n |
| Meng 2014 | n | n | y | y | n | y | y | y | y | y | y |
| O'Brien 2014 | n | y | y | n | n | y | na | y | y | y | n |
| Pedditizi 2016 | y | y | y | y | y | y | y | y | y | n | y |
| Perry 2016 | y | y | n | y | n | y | n | n | y | y | y |
| Peters 2008 (Alcohol) | n | y | y | y | y | y | y | y | y | y | n |
| Peters 2008 (Smoking) | n | y | y | y | n | y | y | y | y | y | y |
| Power 2011 | n | y | y | y | n | y | na | y | y | y | n |
| Quinn 2011 | y | y | y | y | n | y | y | y | y | y | y |
| Richardson 2013 | n | y | y | y | n | y | y | y | n | n | y |
| Santangeli 2012 | n | y | y | y | n | y | y | y | y | y | n |
| Santos-Lozano 2016 | n | na | y | y | n | y | y | y | y | y | n |
| Sharp 2011 | n | y | y | y | n | y | na | y | y | n | y |
| Shen 2015 | n | y | n | y | n | y | n | n | y | n | y |
| Singh 2014 | y | y | y | y | n | y | y | y | y | y | n |
| Sommer 2017 | y | y | y | y | n | y | y | y | y | n | y |
| Swiger 2013 | y | y | y | y | n | y | y | y | y | n | y |
| Szekely 2004 | n | y | y | y | y | y | n | y | y | y | n |
| Tully, 2016 | y | y | y | y | y | y | y | y | y | y | y |
| Ungprasert 2016 | n | y | y | n | n | y | y | y | y | y | y |
| Vagelatos 2013 | n | n | y | y | n | y | c | y | y | y | n |
| Van Dam 2009 | n | n | y | n | y | y | y | y | n | n | Y |
| Virk 2015 | n | y | y | y | n | y | y | y | y | y | n |
| Wang 2015 | n | y | y | n | n | y | y | y | y | y | y |
| Wang 2016 | n | y | y | n | y | y | y | y | y | y | y |
| Wijarnpreecha 2016 | n | y | y | n | n | n | y | y | y | y | y |
| Wong 2013 | n | y | y | n | n | y | y | y | y | y | y |
| Wu 2015 | n | y | y | y | y | y | y | y | y | y | y |
| Wu 2016 | n | y | y | n | n | y | y | y | y | y | y |
| Xu 2015 | n | y | y | y | y | y | y | y | y | y | y |
| Yates 2016 | n | y | y | y | n | n | y | y | y | y | y |
| Zhang 2016 | n | y | y | n | y | y | y | y | y | y | y |
| Zhang 2017 | n | y | y | n | n | y | y | y | y | y | y |
| Zhong 2015 (Smoking) | n | y | y | n | n | y | y | y | y | y | n |
| Zhou 2007 | n | c | y | y | n | n | c | y | y | y | n |
| Zhou 2015 | n | y | y | n | n | y | y | y | y | y | n |
| *Note. n, no; y, yes, c, cannot tell; na, not applicable.* |  |  |  |  |

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| Supplementary Table 4. Publications included  |
| **No.** | **Included articles** |
| 1 | Aarsland D, Sardahaee FS, Anderssen S, Ballard C, Alzheimer's Society Systematic Review g. Is physical activity a potential preventive factor for vascular dementia? A systematic review. Aging Ment Health 2010; 14(4): 386-95. |
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| 3 | Anstey KJ, Ashby-Mitchell K, Peters R. Updating the Evidence on the Association between Serum Cholesterol and Risk ofLate-Life Dementia: Review andMeta-Analysis. J Alzheimers Dis 2017; 56(1): 215-28. |
| 4 | Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obes Rev 2011; 12(5): e426-37. |
| 5 | Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. Am J Geriatr Psychiatry 2008; 16(5): 343-54. |
| 6 | Anstey KJ, Mack HA, Cherbuin N. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. Am J Geriatr Psychiatry 2009; 17(7): 542-55. |
| 7 | Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol 2007; 166(4): 367-78. |
| 8 | Barranco Quintana JL, Allam MF, Serrano Del Castillo A, Fernandez-Crehuet Navajas R. Alzheimer's disease and coffee: a quantitative review. Neurol Res 2007; 29(1): 91-5. |
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| 13 | Caamano-Isorna F, Corral M, Montes-Martinez A, Takkouche B. Education and dementia: a meta-analytic study. Neuroepidemiology 2006; 26(4): 226-32. |
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| 15 | Chang-Quan H, Hui W, Chao-Min W, et al. The association of antihypertensive medication use with risk of cognitive decline and dementia: a meta-analysis of longitudinal studies. International journal of clinical practice 2011; 65(12): 1295-305. |
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| 17 | Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J 2012; 42(5): 484-91. |
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| 19 | Daviglus ML, Plassman BL, Pirzada A, et al. Risk factors and preventive interventions for Alzheimer disease: state of the science. Arch Neurol 2011; 68(9): 1185-90. |
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| **Supplementary Table 5.** Corrected Covered Area (% CCA) Measure |  |
| Risk Factor | Systematic reviews | n | N | CCA (%) |
|   | no. | author, year |  |   |   |
| **Demographics** |   |   |  |   |   |
| Education | 3 | Caamano-Isorna 2006 | 9 | 36 | 9 |
|  |  | Xu 2015 | 14 |  |  |
|  |  | Xu 2016 | 9 |  |  |
|  |  | Xu 2016 | 10 |  |  |
|  |  | Caamano- Isorna 2006 | 6 |  |  |
|  |  | Xu 2016 | 14 |  |  |
|  |   | Xu 2016 | 10 |   |   |
| Bilingualism | 1 | Mukadam 2017 | 4 | 4 | 0 |
| **Lifestyle** |  |  |  |  |  |
| Alcohol | 4 | Anstey 2009 | 2 | 25 | 7 |
|  |  | Peters 2008 | 8 |  |
|  |  | Xu 2015 | 3 |  |
|  |  | Anstey 2009 | 3 |  |
|  |  | Xu 2015 | 3 |  |
|  |  | Anstey 2009 | 6 |  |
|  |  | Xu 2015 | 5 |  |
|  |  | Anstey 2009 | 3 |  |
|  |  | Cao 2016 | 8 |  |
|  |  | Peters 2008 | 3 |  |
|  |  | Anstey 2009 | 2 |  |
|  |  | Anstey 2009 | 4 |  |
|  |  | Peters 2008 | 3 |  |
|  |  | Anstey 2009 | 4 |  |
|  |   | Anstey 2009 | 5 |   |
| Cognitive engagement | 2 | Xu 2015 | 5 | 8 | 6 |
|  | Yates 2016 | 3 |  |
|  |   | Yates 2016 | 2 |   |
| Diet | 11 | Singh 2014 | 2 | 90 | 0 |
|  |  | Xu 2015 | 3 |  |
|  |  | Barranco 2007 | 2 |  |
|  |  | Kim 2015 | 3 |  |
|  |  | Liu 2016 | 4 |  |
|  |  | Wu 2016 | 3 |  |
|  |  | Xu 2015 | 4 |  |
|  |  | Xu 2015 | 3 |  |
|  |  | Wu 2015 | 3 |  |
|  |  | Zhang 2016 | 3 |  |
|  |  | Zhang 2016 | 2 |  |
|  |  | Zhang 2016 | 2 |  |
|  |  | Zhang 2016 | 5 |  |
|  |  | Xu 2015 | 6 |  |
|  |  | Wu 2015 | 6 |  |
|  |  | Xu 2015 | 4 |  |
|  |  | Kim 2015 | 3 |  |
|  |  | Xu 2015 | 6 |  |
|  |  | Shen 2015 | 2 |  |
|  |  | Xu 2015 | 6 |  |
|  |  | Cao 2016 | 4 |  |
|  |  | Kim 2015 | 3 |  |
|  |  | Liu 2016 | 5 |  |
|  |  | Wu 2016 | 6 |  |
|  |  |  | 5 |  |
|  |  | Wu 2015 | 2 |  |
|  |  | Zhang 2016 | 3 |  |
|  |  | Zhang 2016 | 2 |  |
|  |  | Zhang 2016 | 2 |  |
|  |  | Cao 2016 | 3 |  |
|  |  | Zhang 2016 | 4 |  |
|  |  | Wu 2015 | 5 |  |
|  |  | Cao 2016 | 2 |  |
|  |  | Jiang 2017 | 2 |  |
|  |  | Ma 2016 | 4 |  |
|  |  | Cao 2016 | 11 |  |
|  |  | Cao 2016 | 3 |  |
|  |  | Cao 2016 | 4 |  |
|  |  | Cao 2016 | 8 |  |
|  |  | Cao 2016 | 3 |  |
|  |  | Sommer2017 | 5 |  |
|  |   | Cao 2016 | 10 |   |
| Physical activity | 8 | Xu 2015 | 10 | 35 | 22 |
|  | Daviglus 2011 | 9 |  |
|  | Xu 2017 | 8 |  |
|  | Xu 2017 | 8 |  |
|  |  | Santos-Lozano 2016 | 9 |  |
|  |  | Beckett 2015 | 9 |  |
|  |  | Hamer 2009 | 6 |  |
|  |  | Santos-Lozano 2016 | 5 |  |
|  |  | Xu 2017 | 15 |  |
|  |  | Blondell 2014 | 21 |  |
|  |  | Hamer 2009 | 11 |  |
|  |  | Xu 2017 | 15 |  |
|  |  | Aarsland 2010 | 5 |   |
| Sleep | 3 | Bubu 2017 | 6 | 13 | 4 |
|  |  | de Almondes 2016 | 5 |  |  |
|  |   | Kim 2016 | 3 |   |   |
| Smoking | 6 | Anstey 2007 | 4 | 47 | 11 |
|  |  | Anstey 2007 | 4 |  |
|  |  | Zhong 2015 | 12 |  |
|  |  | Almeida 2002 | 7 |  |
|  |  | Peters 2008 | 8 |  |
|  |  | Almeida 2002 | 7 |  |
|  |  | Zhong 2015 | 23 |  |
|  |  | Peters 2008 | 8 |  |
|  |  | Xu 2015 | 9 |  |
|  |  | Zhong 2015 | 13 |  |
|  |  | Anstey 2007 | 2 |  |
|  |  | Anstey 2007 | 2 |  |
|  |  | Zhong 2015 | 17 |  |
|  |  | Cao 2016 | 9 |  |
|  |  | Peters 2008 | 5 |  |
|  |  | Zhong 2015 | 27 |  |
|  |  | Peters 2008 | 5 |  |
|  |  | Zhong 2015 | 18 |  |
|  |  | Anstey 2007 | 2 |  |
|  |  | Anstey 2007 | 2 |  |
|  |  | Zhong 2015 | 5 |  |
|  |  | Peters 2008 | 4 |  |
|  |  | Zhong 2015 | 8 |  |
|  |  | Peters 2008 | 4 |  |
|  |  | Zhong 2015 | 5 |   |
| Social engagement | 1 | Kuiper 2015 | 6 | 12 | 15 |
|  | Kuiper 2015 | 8 |  |
|  |  | Kuiper 2015 | 3 |  |
|  |  | Kuiper 2015 | 4 |  |
|  |   | Kuiper 2015 | 5 |   |
| Stress | 1 | Xu 2015 | 3 | 3 | 0 |
| **Medical** |   |   |   |   |  |
| Arthritis | 2 | Xu 2015 | 2 | 5 | 0 |
|  |   | Ungprasert 2016 | 3 |   |   |
| Atrial fibrillation | 4 | Kalantarian 2013 | 3 | 17 | 0 |
|  | Xu 2015 | 3 |  |
|  |  | Santegeli 2012 | 8 |  |
|  |  | Kwok 2011 | 14 |  |
|  |  | Kalantarian 2013 | 5 |   |
| Anxiety | 1 | Gulpers 2016 | 6 | 6 | 0 |
| BMI | 6 | Anstey 2011 | 2 | 28 | 7 |
|  |  | Xu 2015 | 6 |  |
|  |  | Xu 2015 | 12 |  |
|  |  | Anstey 2011 | 3 |  |
|  |  | Beydoun 2008 | 4 |  |
|  |  | Loef 2013 | 4 |  |
|  |  | Meng 2014 | 5 |  |
|  |  | Anstey 2011 | 2 |  |
|  |  | Anstey 2011 | 3 |  |
|  |  | Loef 2013 | 4 |  |
|  |  | Anstey 2011 | 3 |  |
|  |  | Anstey 2011 | 3 |  |
|  |  | Beydoun 2008 | 4 |  |
|  |  | Loef 2013 | 5 |  |
|  |  | Pedditizi 2016 | 4 |  |
|  |  | Pedditizi 2016 | 4 |  |
|  |  | Anstey 2011 | 2 |  |
|  |  | Anstey 2011 | 3 |  |
|  |  | Beydoun 2008 | 4 |  |
|  |  | Loef 2013 | 5 |  |
|  |  | Pedditizi 2016 | 5 |  |
|  |  | Pedditizi 2016 | 4 |  |
|  |  | Beydoun 2008 | 2 |  |
|  |  | Beydoun 2008 | 3 |  |
|  |   | Anstey 2011 | 2 |   |
| Cancer | 2 | Ma 2014 | 5 | 7 | 57 |
|  |   | Xu 2015 | 6 |   |
| Carotid atherosclerosis | 1 | Xu 2015 | 2 | 2 | 0 |
| Cholesterol | 5 | Xu 2015  | 16 | 21 | 11 |
|  |  | Meng 2014 | 4 |  |
|  |  | Anstey 2017 | 3 |  |
|  |  | Daviglus 2011 | 3 |  |
|  |  | Anstey 2017 | 4 |  |
|  |  | Anstey 2017 | 3 |  |
|  |  | Anstey 2008 | 3 |  |
|  |  | Anstey 2017 | 4 |  |
|  |  | Anstey 2017 | 2 |  |
|  |  | Anstey 2017 | 3 |  |
|  |  | Anstey 2017 | 2 |  |
|  |  | Anstey 2008 | 3 |  |
|  |  | Anstey 2017 | 2 |  |
|  |  | Anstey 2017 | 2 |  |
|  |  | Anstey 2008 | 2 |   |
| Depression | 3 | Cherbuin 2015 | 10 | 46 | 15 |
|  |  | Diniz 2013 | 17 |  |
|  |  | Xu 2015 | 24 |  |
|  |  | Cherbuin 2015 | 10 |  |
|  |  | Cherbuin 2015 | 11 |  |
|  |  | Cherbuin 2015 | 10 |  |
|  |  | Diniz 2013 | 23 |  |
|  |  | Cherbuin 2015 | 3 |  |
|  |  | Cherbuin 2015 | 2 |  |
|  |  | Diniz 2013 | 5 |   |
| Diabetes | 8 | Meng 2014 | 4 | 54 | 18 |
|  |  | Zhang 2017 | 17 |  |
|  |  | Cheng 2012  | 18 |  |
|  |  | Lu 2009 | 8 |  |
|  |  | Xu 2015 | 22 |  |
|  |  | Gudala 2013 | 20 |  |
|  |  | Vagelatos 2013 | 15 |  |
|  |  | Chatterjee 2016 | 14 |  |
|  |  | Cheng 2012  | 11 |  |
|  |  | Lu 2009 | 6 |  |
|  |  | Gudala 2013 | 20 |  |
|  |  | Chatterjee 2016 | 8 |  |
|  |  | Cheng 2012  | 10 |  |
|  |  | Lu 2009 | 9 |  |
|  |  | Gudala 2013 | 13 |   |
| Hearing loss | 1 | Ford 2017 | 13 | 13 | 0 |
| Homocysteine | 3 | Xu 2015 | 8 | 11 | 9 |
|  |  | Van Dam 2009 | 3 |  |
|  |   | Ho 2011 | 2 |   |
| Hormones  | 3 | Wang 2016 | 2 | 18 | 6 |
|  |  | Lv 2016 | 7 |  |
|  |  | Wang 2016 | 4 |  |
|  |  | Wang 2016 | 6 |  |
|  |  | Wu 2016 | 2 |  |
|  |  | Wu 2016 | 4 |  |
|  |  | Wu 2016 | 4 |  |
|  |   | Wu 2016 | 5 |   |
| Hyper/hypotension | 5 | Meng 2014 | 5 | 38 | 13 |
|  |  | Meng 2014 | 3 |  |
|  |  | Meng 2014 | 3 |  |
|  |  | Xu 2015 | 28 |  |
|  |  | Power 2011 | 12 |  |
|  |  | Guan 2011 | 9 |  |
|  |  | Meng 2014 | 2 |  |
|  |  | Xu 2015 | 6 |  |
|  |  | Power 2011 | 4 |  |
|  |  | Power 2011 | 5 |  |
|  |  | Power 2011 | 4 |  |
|  |  | Power 2011 | 5 |  |
|  |  | Sharp 2011 | 6 |   |
| Inflammatory markers | 1 | Koyama 2013 | 3 | 4 | 0 |
|  | Koyama 2013 | 4 |  |
|  |  | Koyama 2013 | 3 |  |
|  |   | Koyama 2013 | 4 |   |
| Metabolic syndrome | 1 | Xu 2015 | 4 | 4 | 0 |
| Motor function | 1 | Kueper 2017 | 2 | 10 | 0 |
|  |  | Kueper 2017 | 3 |  |  |
|  |   | Kueper 2017 | 5 |   |  |
| Peripheral artery disease | 1 | Xu 2015 | 2 | 2 | 0 |
| Renal Disease | 1 | Xu 2015 | 3 | 3 | 0 |
| Serum uric acid | 1 | Du 2016 | 3 | 3 | 0 |
| Stroke | 2 | Xu 2015 | 9 | 10 | 30 |
|  |   | Zhou 2015 | 4 |   |   |
| TBI | 3 | Xu 2015 | 6 | 15 | 24 |
|  |  | Li 2017 | 8 |  |
|  |  | Perry 2016 | 7 |  |
|  |  | Li 2017 | 8 |  |
|  |  | Perry 2016 | 3 |   |
| **Pharmacological** |   |   |   |  |
| Antacids | 1 | Virk 2015 | 2 | 2 | 0 |
|  |   | Virk 2015 | 2 |   |   |
| Antihypertensives | 6 | Chang-Quan 2011 | 5 | 24 | 12 |
|  |  | Guan 2011 | 5 |  |
|  |  | Xu 2015 | 5 |  |
|  |  | Xu 2017 | 6 |  |
|  |  | Chang-Quan 2011 | 4 |  |
|  |  | Levi 2013 | 7 |  |
|  |  | Xu 2017 | 6 |  |
|  |  | Tully 2016 | 8 |   |
| Anti-inflammatories | 4 | Etminan 2003 | 6 | 17 | 29 |
|  |  | Wang 2015 | 12 |  |
|  |  | Etminan 2003 | 5 |  |
|  |  | Wang 2015 | 8 |  |
|  |  | Wang 2015 | 7 |  |
|  |  | Xu 2015 | 9 |  |
|  |  | Szekely 2004 | 4 |  |
|  |  | Szekely 2004 | 3 |   |
| Benzodiazepines | 1 | Islam 2016 | 2 | 3 | 0 |
| HRT | 3 | LeBlanc 2001 | 2 | 9 | 28 |
|  |  | O'Brien 2014 | 8 |  |
|  |  | Xu 2015  | 4 |   |
| Insulin sensitizers | 1 | Ye 2016 | 2 | 6 | 28 |
|  |  | Ye 2016 | 6 |  |  |
|  |  | Ye 2016 | 6 |  |  |
|  |   | Ye 2016 | 2 |   |   |
| Statins | 5 | Zhou 2007 | 3 | 22 | 17 |
|  |  | Xu 2015 | 5 |  |
|  |  | Xu 2015 | 2 |  |
|  |  | Xu 2015 | 2 |  |
|  |  | Richardson 2013 | 10 |  |
|  |  | Wong 2013 | 13 |  |
|  |  | Zhou 2007 | 4 |  |
|  |  | Richardson 2013 | 10 |  |
|  |  | Swiger 2013 | 2 |  |
|  |  | Wong 2013 | 12 |   |
| **Environmental** |   |   |   |  |
| Pesticides | 2 | Yan 2016 | 3 | 3 | 100 |
|   |   | Xu 2015 | 3 |   |   |
| Note. CCA as calculated as per Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol 2014; 67(4): 368-75. |

**PRISMA 2009 Checklist**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | 1 |
| **ABSTRACT**  |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | 2 |
| **INTRODUCTION**  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | 4-5 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 4-5 |
| **METHODS**  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | 5 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 6 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 5 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | 5 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | 6 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | 6-7 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | 6-7 |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 9 |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | 9 |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | 9 |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | 7-9 |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | n.a. |
| **RESULTS**  |  |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | 10 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | 27-32; Supplementary Table 1. |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | 11; Supplementary Table 3. |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | 15-16; 27-32; Supplementary Table 1. |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | 15-16, 27-32; Supplementary Table 1. |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | 11 |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | n.a. |
| **DISCUSSION**  |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | 17-18 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | 17-18 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 19-18 |
| **FUNDING**  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | 20 |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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