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**Review** article

# Adult-onset hearing loss and incident cognitive impairment and dementia – A systematic review and meta-analysis of cohort studies



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## ABSTRACT

| Keywords:<br>Hearing loss<br>Dementia<br>Cognitive impairment<br>Meta-analysis<br>Moderators | <i>Background:</i> We comprehensively summarized the cohort evidence to date on adult-onset hearing loss as risk factor for incident cognitive impairment and dementia, and examined the evidence for dose-response, risk for various dementia subtypes, and other moderators. Previous meta-analyses were less comprehensive. <i>Methods:</i> We included cohort studies with participants without dementia and with hearing assessments at baseline, minimum 2 years follow-up and incident cognitive outcomes. We used random-effect models and subgroup and meta-regression on moderator analyses. <i>Results:</i> We identified fifty studies (N=1,548,754). Hearing loss (yes/no) was associated with incident dementia risk (HR=1.35 [95% CI = 1.26 - 1.45), mild cognitive impairment (MCI HR=1.29 [95% CI = 1.11 - 1.50]), cognitive decline not specified as MCI or dementia (HR=1.29 [95% CI = 1.17 - 1.42]), and Alzheimer's disease dementia (ADD, HR=1.56 [95% CI = 1.30 - 1.87]), but not with vascular dementia (HR, 1.30 [95% CI = 0.83 - 2.05]). Each 10-decibel worsening of hearing was associated with a 16% increase in dementia risk (95% CI = 1.07 - 1.27). The effect of hearing loss did not vary across potential moderators. <i>Conclusions:</i> Cohort studies consistently support that adult-onset hearing loss increases the risk of incident previous regiment of the previous and the previous of the previous advection of the previ |
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|  | cognitive decline, dementia, MCI, and ADD.  |

#### 1. Introduction

The World Health Organization estimates that 1.5 billion people worldwide are affected by hearing loss (Haile et al., 2021; McDaid et al., 2021), a number set to rise as the global population ages. The Lancet Commission on Dementia identified that hearing loss could be a modifiable risk factor for dementia (Livingston et al., 2017, 2020) as it is associated with increased risk of cognitive impairment (MCI) and accelerated cognitive decline (Bucholc et al., 2022). This raises the possibility that treatments like hearing aids could potentially prevent or delay dementia (Yeo et al., 2023). The causal pathways might involve reduced social interaction or accelerated brain pathology (Ray et al.,

2019). However, it is also possible that the observed association is not causal, but due to residual confounding from inadequately controlled factors like age or cardiovascular health.

Experimental evidence from randomized controlled trials is essential to establish causality, but the evidence to date has been limited and inconclusive. The ACHIEVE trial is the only large scale RCT with a cognitive outcome to date (Lin et al., 2023). ACHIEVE did not find evidence of benefit of hearing aid treatment on cognitive outcomes at three years in the whole sample, but a sub-sample of participants with higher baseline dementia risk did experience substantially reduced cognitive decline compared to those who received an educational intervention but no hearing aids.

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Previous systematic reviews and meta-analyses of epidemiological studies on this topic (Supplementary Table 1) have shown varied results, partly due to differences in methodology. These systematic review also included cross-sectional studies, which do not address the sequence in which hearing loss and cognitive decline happen (Lau et al., 2022; Loughrey et al., 2018), not setting a minimal follow-up duration for cohort studies (Ford et al., 2018; Lau et al., 2022; Wei et al., 2018; Yuan et al., 2018), and combining studies reporting varying effect size measures (hazard ratios (HR), odds ratios (OR), risk ratio (RR)) despite their methodological differences (Ford et al., 2018; Liang et al., 2021; Livingston et al., 2017; Loughrey et al., 2018; Wei et al., 2018; Yuan et al., 2018; Zheng et al., 2017). Dementia is an umbrella term for several diseases affecting cognition (WHO, 2018). The most common is Alzheimer's disease (ADD), a brain degenerative disease caused by amyloid plaques and tau tangles. The second most common is vascular dementia, resulting from decreased brain blood flow (Livingston et al., 2020). So far, few have investigated whether hearing loss is associated with specific dementia subtypes (Ford et al., 2018; Liang et al., 2021; Loughrey et al., 2018; Zheng et al., 2017). Moreover, recent interest and research has expanded the available literature in this area, which earlier meta-analyses may not have included.

In light of these uncertainties, our systematic review aims to provide a comprehensive analysis of the existing epidemiological evidence to date, guided by the Bradford Hill criteria (Bradford et al., 1965; Fedak et al., 2015). This is a set of nine principles to help assess whether an observed association may be due to a causal relationship. We focused on the following four principles: the strength of the association (strength criterion) and the presence of a dose-response relationship (dose/response criterion), where greater hearing loss potentially leads to a higher risk of dementia. We also assessed the consistency of the evidence across different methods, populations, and outcomes between studies (consistency criterion). We incorporated an extensive analysis on different variables from cognitive impairment to dementia subtypes, methods of hearing assessments from self-report to the gold standard of pure tone audiometry (PTA) (Ramkissoon, 2011; Santana et al., 2011); and other variables like follow-up duration, use of hearing aids in the sample, baseline age, and cardiovascular risk factors. Moreover, to establish a clear sequence of events where hearing loss precedes dementia (temporality criterion), we only included cohort studies if they excluded people who had dementia at baseline and followed them up for at least two years before cognitive outcome assessment.

### 2. Methods

The protocol of this is systematic review was pre-registered on the international prospective register of systematic reviews PROSPERO (registration number: CRD42016048835) and followed standard guidelines for conducting and reporting systematic reviews, including Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Page et al., 2021).

### 2.1. Data sources and search strategy

We searched the following electronic databases starting from their inception up to March 20th, 2023: PubMed, Ovid Embase, PsycINFO, Web of Science, The Cochrane Library, and The Centre for Reviews and Dissemination (CRD). We used the search terms: "dementia" or "cognitive decline" or "Alzheimer's disease" or "mild cognitive impairment" AND "hearing" or auditory or aural or "presbycusis".

## 2.2. Inclusion criteria

We applied the following inclusion criteria:

• Prospective or retrospective cohort studies with a minimum followup period of 2 years.

- At baseline:
  - No diagnosis of dementia (except for studies that included dementia at baseline for other research purposes, such as dementia prevalence, and removed these participants from the dementia risk analysis).
  - Determination of hearing loss conducted at baseline by clinical diagnosis, PTA, a speech-based hearing tests (speech in noise testing, whisper test), or a self-report hearing questionnaire.
- During follow-up:
  - Diagnosis of incident dementia or incident cognitive decline based on operationalized criteria or clinical diagnosis based on internationally recognized criteria, such as Diagnostic and Statistical Manual of Mental Disorders (DSM) or ICD.
  - The studies reported a measure of risk association between adultonset hearing and incident cognitive outcomes, adjusted at least by age.

## 2.3. Study selection

We exported the searches to Endnote and eliminated duplicates. Five authors - DP, LP, JS, R-CY, and SCG, independently screened the titles and abstract of retrieved articles, and evaluated the full text, to determine their eligibility for inclusion. Disagreements were resolved through discussion. We contacted the authors of five publications to obtain further details regarding eligibility criteria. Of these, four provided further information so their studies were included in the metaanalysis. One author did not respond, this study was not included.

#### 2.4. Data extraction and quality assessment

Four authors (DP, LP, JS, and R-CY) extracted data from each included paper using a data extraction excel form. Data were extracted on: number of participants at baseline, demographics (age, sex, education, country), methods of hearing assessment, proportion of population with hearing loss and hearing aid users, number of follow-up years, cognitive outcomes (dementia and its subtypes, MCI, or cognitive decline not specified as MCI or dementia), and adjustment variables in the models (age, sex, education, cardiovascular factors, and other factors). Disagreements were resolved through discussion.

Five authors (DP, LP, JS, R-CY, and SCG) independently assessed the quality of studies using the Mixed Methods Appraisal Tool (MMAT) diagnostics criteria (Nha Hong et al., 2018) (see Supplementary Table 3 for MMAT details for this study).

## 2.5. Data selection and synthesis

We selected only one effect measure per study in each subgroup, thereby avoiding the potential bias introduced by "double counting" study findings. When a study reported several effect measures, we prioritized outcomes that were maximally adjusted for co-variates, those with the longest follow-up period, and those based on PTA (rather than self-report or other methods). For studies presenting effect measures across different subgroups (e.g., participants with or without depression (Powell et al., 2022)), we combined these effect measures into an overall pooled estimate using random effects meta-analysis, and then this pooled estimate was integrated into the overall meta-analyses. Finally, the goal of our study was to assess the link between hearing loss and dementia, but there is evidence that treated hearing loss may not confer such risk; we therefore excluded from the main analysis studies with more than 50% hearing aid users (Yeo et al., 2023).

## 2.6. Statistical analysis

We used random-effects meta-analyses to calculate pooled estimates of association between hearing loss and incident cognitive outcomes and corresponding 95% confidence intervals. We used the  $I^2$  statistic to

describe heterogeneity between studies (Lin et al., 2020). We computed separate pooled estimates for the following effect measures: (1) HR, (2) OR, (3) RR because these measures are different in definition, computation, and interpretation (George et al., 2020). We computed separate pooled estimates for studies where hearing was categorized as normal hearing versus different degrees of hearing impairment, and those that categorized it per 10-decibels of hearing level [10-dB HL]. We meta-analyzed according to cognitive outcomes: (1) incident dementia, (2) incident MCI, (3) incident cognitive decline not specified as MCI or dementia (4) incident ADD, (5) incident VaD.

We conducted subgroup and moderator analyses comprising: mean age of the cohort participants at baseline ( $\geq$  65 and < 65 years, with the total age range among studies being 40–83 years), length of follow-up (2–6 years, > 6–10 years, and > 10 years), whether the findings were adjusted by (a) cardiovascular risk factors, (b) a measure of education or premorbid cognitive function, PTA vs non-PTA studies, and severity of hearing loss (mild and moderate-severe, as defined by each study). We conducted meta-regressions for continuous variables: average age at baseline, sex, and the length of follow-up in years.

We used visual inspection of funnel plots of study effect measures versus precision to assess evidence for publication bias on subgroups with at least 10 studies based on Cochrane Library's guidelines (Page et al., 2023). We reported Egger's test, with p < 0.05 for the slope coefficient indicating significant asymmetry. We used R software (version 4.3.1), and applied the function 'metagen' (package 'metafor' (Viechtbauer, 2010)) for meta-analyses and function 'metareg'(package 'meta' (Schwarzer, 2023)) for univariable meta-regression.

#### 3. Results

### 3.1. Study characteristics

We identified 50 studies in the systematic review (Table 1, Fig. 1 for PRISMA diagram and Supplementary Table 5 for PRISMA checklist). Most studies were prospective (37 out of 50, or 74%), and 24 studies were conducted in the US (48%), 10 in Europe, 5 in Australia, 11 in East Asia (Supplementary Table 2). Regarding determination of hearing, 24 (48%) studies used self-reported questionnaires, 15 (30%) studies used PTA and one used a screening audiometer (Lin et al., 2004), 9 used clinical diagnoses, and other less frequently used methods included the whispered voice test (2 studies, Heywood et al., 2017; Rolandi et al., 2020), and dichotic digits test (1 study, Stevenson et al., 2022).

Quality assessment using the MMAT (Nha Hong et al., 2018), was based on 5 indicators: (i) representativeness of the sample, (ii) appropriateness of outcome and exposure measurements, (iii) completeness of outcome data, (iv) accounting of confounding and (v) exposure occurrence during the study (details in Supplementary Table 3); 23 studies (46%) met at least four out of these quality criteria, while 12 studies (24%) met only two of the five criteria, and no study met less than two criteria (Supplementary Table 4).

Among the included studies, 39 studies reported the effect measures using HR, nine used OR, four used RR, four used HR in per 10-dB HL, one used OR and RR in per 10-dB HL, respectively. Incident dementia was reported as an outcome in 33 studies, cognitive decline in 16 studies, MCI in 3 (Heywood et al., 2017; Strutt et al., 2022; Vassilaki et al., 2019), Alzheimer's disease dementia (ADD) in 5 and Vascular dementia (VaD) in 3 (Golub et al., 2017; Hwang et al., 2020, 2022), with some studies reporting more than one outcome. We conducted separate meta-analyses for each combination of effect measure and cognitive outcome, with moderator analyses restricted to the 37 studies (excluding two studies with more than 50% hearing aids users; Bucholc et al., 2022; Marinelli et al., 2022) that reported HR as the effect measure for the association between hearing loss as a yes/no variable and any incident cognitive impairment.

## 3.2. Meta-analyses of incident cognitive outcomes

Presence of hearing loss as a dichotomic yes/no variable was associated with a range of incident cognitive outcomes (Table 2, Fig. 2) including increased hazard ratio of incident dementia (Table 2, HR = 1.35 [1.26–1.45], based on k = 30 studies), MCI (1.29 [1.11–1.50], k = 3, Heywood et al., 2017; Strutt et al., 2022; Vassilaki et al., 2019), cognitive decline not specified as MCI or dementia (1.29 [1.17–1.42], k = 9), and Alzheimer's disease (HR = 1.56 [1.30–1.87], k = 4), whilst the association with vascular dementia was not statistically significant (HR = 1.30 [0.83 – 2.05], k = 3, Golub et al., 2017; Hwang et al., 2020, 2022).

For studies that reported their findings as odds ratios (OR, Table 2) presence of hearing loss was associated with increased risk of MCI or dementia (OR = 1.42 [1.05 - 1.91], k = 5), whilst the association with dementia only was not statistically significant (OR = 1.52 [0.86-2.70], k = 3, Beason-Held et al., 2022; Brewster et al., 2021b; Byeon et al., 2021). Pooling of two studies that reported risk ratios for dementia did not reveal a statistically significant association (RR = 1.20 [0.67-2.16], k = 2, Table 2, Deal et al., 2019; Gates et al., 1996), and another isolated study did not find a statistically significant association for cognitive decline not specified as MCI or dementia (RR = 0.93 [0.63-1.37], k = 1, Schubert et al., 2019).

Two studies investigated how dementia risk changes with every 10 dB decrease in hearing ability, and found increased hazard ratios for dementia (HR = 1.16 [1.07–1.27], k = 2, Table 2, Fig. 3, Deal et al., 2017; Lin et al., 2011). Additionally, individual studies reported increased risk of incident cognitive impairment when using hazard ratios (HR = 1.07 [1.01–1.14], k = 1, Lin et al., 2013) and odds ratios (OR = 1.36 [1.21–1.53], k = 1, Sugiura et al., 2022) and dementia when using risk ratios (RR = 1.04 [1.00–1.09], k = 1, Myrstad et al., 2023). We found varying degrees of residual heterogeneity in these meta-analyses, ranging from 0% to 93% for different meta-analyses (Figs. 2 and 3).

## 3.3. Moderator analyses

We conducted moderator analyses on 37 studies that reported HR. None of the factors investigated moderated the relationship between hearing loss and any type of incident cognitive impairment, including the age at baseline of the study participants, the type of hearing assessment, the length of follow-up or whether the analysis was adjusted by a measure of baseline cognitive state or vascular factors (Fig. 4, Supplementary Figs. 1–6).

Regarding hearing severity, both mild (HR = 1.27 [95% CI: 1.05–1.53]) and moderate to severe hearing loss (HR =1.69 [95% CI: 1.29–2.22]) were associated with increased dementia risk, but the degree of hearing loss did not moderate the relationship between hearing loss and dementia risk (p = 0.09, Fig. 4, Supplementary Fig. 6).

Meta-regression analyses did not reveal any statistically significant effect of the number of follow-up years, the proportion of the sample who were female, or the average age of the sample at baseline (Table 3).

#### 3.4. Publication bias

We examined the publication bias by graphical analyses through funnel plots, which revealed dispersion of study findings but no evidence of systematic asymmetry on examination (Supplementary Fig. 7); Egger's test for publication bias was also not statistically significant for HR in the studies of dementia (p = 0.77, k = 30) and cognitive decline not specified as dementia or MCI (p = 0.12, k = 9), the remaining subgroups were excluded from the analysis of publication bias due to a small number of studies included.

| Table 1   |                |
|---|----------------|
| Characteristics of the studies included (in alphabetical order by | first author). |

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| First author & year Number of people at baseline |        | Drop-out      | Mean age           | Sex (number     | Education (level                     | Hearing                     | Number with | HA users at   | Follow-up             | Outcome               | Number who                      | Adju         | isted f      | actors       |              |   |
|--|--------|---------------|--------------------|-----------------|--------------------------------------|-----------------------------|-------------|---------------|-----------------------|-----------------------|---------------------------------|--------------|--------------|--------------|--------------|---|
|  |        | rate (%)      |                    | of females)     | or mean years)                       | assessment                  | baseline HL | baseline      | years                 | subtypes              | develops CD<br>(%)              | Α            | S            | E            | С            | 0 |
| Amieva et al. (2018)                             | 3588   | NR            | 75                 | 2075 (58%)      | 2344 school certificate              | self-report                 | 1289 (36%)  | 176 (14%)     | up to 25<br>years     | Dementia              | 876 (24%)                       | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ | ١ |
| Beason-Held et al.<br>(2022)                     | 1234   | NR            | 82                 | 463 (38%)       | NR                                   | ICD-9                       | NR          | NR            | 5 years               | ADD, VaD              | 357 (29%)                       | $\checkmark$ | $\checkmark$ |              |              | ۱ |
| Brenowitz et al.<br>(2019)                       | 1810   | NR            | 77                 | 938 (52%)       | 1438 high<br>school                  | РТА                         | 1344 (75%)  | 237 (18%)     | > 10  years           | Dementia              | 336 (19%)                       | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ | ۱ |
| Brewster et al.<br>(2021a,b)                     | 8529   | NR            | 74                 | 5412 (64%)      | 16 years                             | self-report                 | 2051 (24%)  | 1102<br>(54%) | 6 years<br>(mean)     | Dementia,<br>CD       | 498 (6%)                        | $\checkmark$ | $\checkmark$ | $\checkmark$ |              |   |
| Bucholc et al. (2022)                            | 4358   | NR            | 69                 | 2994 (69%)      | 16 years                             | self-report                 | 450 (10%)   | 313 (70%)     | 4 years               | MCI                   | 416 (10%)                       |              |              |              |              |   |
| Byeon et al. (2021)                              | 6520   | around<br>49% | 70                 | 3709 (57%)      | 1158 university                      | self-report                 | NR          | NR            | 6 years               | Dementia              | 245 (4%)                        |              |              |              | v            | 1 |
| Chen and Lu (2019)                               | 6309   | NR            | 83                 | 3112 (49%)      | 3179 >1 year education)              | self-report                 | 2562 (41%)  | NR            | 6 years               | CD                    | 1936 (31%)                      | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ | 1 |
| Chen (2021)                                      | 10341  | NR            | 79                 | 5093 (49%)      | 5041 literate                        | self-report                 | 995 (10%)   | NR            | 6 years<br>(median)   | CD                    | 2614 (25%)                      | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ | ۱ |
| Chern et al. (2022)                              | 206801 | NR            | 69                 | 117407<br>(57%) | NR                                   | ICD-9 and ICD-<br>10        | 56523 (57%) | 1265 (2%)     | 6 years<br>(mean)     | Dementia              | 8269 (4%)                       | $\checkmark$ | $\checkmark$ |              | $\checkmark$ | ۱ |
| Deal et al. (2019)                               | 154414 | NR            | 64                 | 74464 (48%)     | 124749 some college                  | ICD 9-CM                    | 77207 (50%) | NR            | up to 10<br>years     | Dementia              | 2499 (2%)                       | $\checkmark$ | $\checkmark$ |              | $\checkmark$ | ١ |
| Deal et al. (2017)                               | 1889   | NR            | 76                 | 996 (53%)       | 920 post-<br>secondary               | РТА                         | 1103 (58%)  | 240<br>(22%)  | 6 years               | Dementia              | 229 (12%)                       | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ | ۱ |
| Fischer et al. (2016)                            | 1884   | NR            | 67                 | 1113 (59%)      | 697 post-<br>secondary               | PTA                         | 826 (44%)   | NR            | 10 years              | CD                    | 187 (10%)                       | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ | ۱ |
| Ford et al. (2018)                               | 37898  | NR            | 73                 | 0               | NR                                   | ICD 8-10                    | 1420 (4%)   | NR            | 11 years<br>(mean)    | Dementia              | 6948 (18%)                      | $\checkmark$ |              |              | $\checkmark$ | ۱ |
| Fritze et al. (2016)                             | 154783 | NR            | NR                 | 92161 (60%)     | NR                                   | ICD-10                      | 70294 (45%) | NR            | 2–6 years             | Dementia              | 14602 (9%)                      |              |              |              | 1/           | ١ |
| Gates et al. (1996)                              | 1509   | NR            | 72                 | NR              | NR                                   | PTA                         | NR          | NR            | 6 years               | Dementia              | 41 (3%)                         | v            | v            |              | v            | , |
| Amin   | 15278  | NR            | 65                 | 8323 (55%)      | 2943 tertiary                        | self-reported               | NR          | NR            | 13 years              | Dementia              | 535 (4%)                        | Ň            |              |              |              |   |
| Gharbi-Meliani<br>et al. (2023)                  | 102/0  | THE .         | 00                 | 0020 (0070)     | education                            | sen reported                | 1410        |               | 10 years              | Dementia              | 000 (170)                       | v            | v            |              |              |   |
| Golub et al. (2017)                              | 1881   | NR            | 76                 | 1308 (70%)      | 10 years                             | self-reported               | 204 (11%)   | 75 (37%)      | 7 years<br>(mean)     | ADD, VaD              | 377 (20%)                       | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ | 1 |
| Gurgel et al. (2014)                             | 4463   | 2%            | 75                 | 2543 (57%)      | 13 years                             | self-reported               | 836 (19%)   | NR            | 5.8 years<br>(mean)   | Dementia              | 575 (13%)                       | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ | 1 |
| Heywood et al.<br>(2017)                         | 1515   | around<br>26% | >55                | 988 (65%)       | 658, <6 years education              | whispered<br>voice test     | 32 (2%)     | NR            | 3.8 years<br>(median) | CD, MCI               | 155 (MCI), 11<br>(1%, dementia) | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ | ۱ |
| Hong et al. (2016)                               | 1352   | NR            | NR                 | NR              | NR                                   | PTA                         | 303 (17%)   | NR            | 10 years              | CD                    | 167 (12%)                       |              |              |              |              |   |
| Hwang et al. (2020)                              | 2051   | 6%            | 79                 | 905 (44%)       | 14 years                             | self-reported               | 161 (8%)    | NR            | 8 years               | Dementia,<br>ADD, VaD | 321 (16%)                       | $\sqrt[v]{}$ | $\sqrt[v]{}$ | $\checkmark$ | v            | ۱ |
| Hwang et al. (2022)                              | 2254   | NR            | 75                 | 1704 (58%)      | 703 college<br>graduate              | self-reported               | 311 (11%)   | NR            | 8 years               | Dementia              | 307 (11%)                       | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ | ۱ |
| Karpa et al. (2010)                              | 2815   | 25%           | 67                 | 1597 (57%)      | NR                                   | PTA                         | 929 (33%)   | NR            | 5 years               | CD                    | 79 (3%)                         | 1/           | 1            |              |              |   |
| Kim et al. (2018)                                | 26950  | NR            | > 40               | 12180 (45%)     | NR                                   | ICD 10                      | 5390 (20%)  | NR            | 7.9 years<br>(mean)   | Dementia              | 1789 (7%)                       | $\sqrt[v]{}$ | v            |              | $\checkmark$ | ۱ |
| Kojima et al. (2022)                             | 53549  | NR            | 74                 | 29015 (54%)     | 26130, >10 vears education           | self-reported               | 4039 (8%)   | NR            | 6 years               | Dementia              | 6013 (11%)                      | $\checkmark$ | $\checkmark$ |              |              |   |
| Kuo et al. (2021)                                | 7562   | NR            | 41% > 80 years old | 4411 (58%)      | 1671, < high<br>school               | self-reported               | 1664 (22%)  | NR            | 4 years<br>(median)   | Dementia              | 1572 (21%)                      | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ | ۱ |
| Lavrencic et al.<br>(2022)                       | 155    | 37%           | 66                 | 96 (62%)        | 10 years (no<br>CD), 8 years<br>(CD) | previous<br>medical history | 32 (21%)    | NR            | 6.2 years<br>(mean)   | CD                    | 36 (23%)                        | $\checkmark$ |              |              |              |   |

(continued on next page)

Table 1 (continued)

| First author & year        | Number of             | Drop-out | Mean age  | Sex (number     | Education (level           | Hearing                     | Number with | HA users at   | Follow-up            | Outcome              | Number who         | Adju         | isted fa     | actors       |              |              |
|----------------------------|-----------------------|----------|-----------|-----------------|----------------------------|-----------------------------|-------------|---------------|----------------------|----------------------|--------------------|--------------|--------------|--------------|--------------|--------------|
|                            | people at<br>baseline | •        | of female | of females)     | f females) or mean years)  | assessment                  | baseline HL | baseline      | years                | subtypes             | develops CD<br>(%) | A            | S            | E            | С            | 0            |
| Lin et al. (2011)          | 639                   | NR       | NR        | 279 (44%)       | NR                         | РТА                         | 184 (3%)    | 58<br>(32%)   | 12 years<br>(median) | Dementia             | 58 (9%)            | $\checkmark$ | $\checkmark$ | $\checkmark$ |              |              |
| Lin et al. (2013)          | 1626                  | NR       | NR        | NR              | 967, $\geq$ some college   | РТА                         | 1162 (72%)  | 257 (22%)     | 6 years              | CD                   | 609 (38%)          | $\checkmark$ | $\checkmark$ | $\checkmark$ |              |              |
| Lin et al. (2004)          | 1333                  | NR       | 76        | 1333 (100%)     | NR                         | PTA Screening<br>audiometer | NR          | NR            | 4 years              | CD                   | 960 (72%)          | $\checkmark$ |              | $\checkmark$ |              |              |
| Luck et al. (2020)         | 3027                  | NR       | 80        | 1970 (65%)      | 329, higher education      | self-reported               | 924 (31%)   | NR            | 13 years             | Dementia             | 704 (23%)          | $\checkmark$ |              |              |              |              |
| Maharani et al.<br>(2020)  | 19618                 | NR       | 58        | 10871 (55%)     | 9675, > some college       | self-reported               | 2532 (13%)  | NR            | 18 years             | Dementia,<br>CD      | 951 (5%)           | $\checkmark$ | $\checkmark$ | $\checkmark$ |              |              |
| Marinelli et al.<br>(2022) | 1159                  | 3%       | 76        | 607 (52%)       | 886, <16 years             | РТА                         | 763 (64%)   | 492<br>(65%)  | 7 years              | Dementia             | 207 (18%)          | $\checkmark$ | $\checkmark$ | $\checkmark$ |              |              |
| Maruta et al. (2020)       | 2190                  | NR       | 79        | 1738 (79%)      | NR                         | self-reported               | 961 (21%)   | NR            | 8 years              | Dementia             | 1153 (53%)         |              |              |              |              |              |
| Mohammed et al.<br>(2022)  | 280                   | 5%       | 80        | 177 (63%)       | 144, $< 16$ years          | РТА                         | 121 (43%)   | NR            | 8 years<br>(mean)    | Dementia,<br>ADD     | 89 (32%)           | v            | ۲            | $\checkmark$ |              | ·            |
| Myrstad et al.<br>(2023)   | 7135                  | NR       | 57        | 3943 (55%)      | 1447, primary school only  | РТА                         | 1058 (15%)  | NR            | 22 years<br>(mean)   | Dementia,<br>ADD     | 1089 (15%)         | $\checkmark$ | $\checkmark$ | $\checkmark$ |              | $\checkmark$ |
| Osler et al. (2019)        | 658465                | NR       | 59        | 0 (0%)          | NR                         | РТА                         | 59834 (9%)  | NR            | 7 years<br>(mean)    | Dementia             | 9114 (1%)          | $\checkmark$ |              | $\checkmark$ |              | $\checkmark$ |
| Pabst et al. (2021)        | 3497                  | NR       | 80        | 2349 (67%)      | 1207, ${\geq}10$ years     | self-reported               | 1061 (30%)  | NR            | 7 years<br>(mean)    | Dementia             | 902 (26%)          | $\checkmark$ | $\checkmark$ | $\checkmark$ |              | $\checkmark$ |
| Powell et al. (2022)       | 2408                  | 7%       | 74        | 1072 (45%)      | 1136, ><br>secondary edu   | РТА                         | 1495 (62%)  | NR            | 8 years              | Dementia             | 223 (9%)           | $\checkmark$ | $\checkmark$ | $\checkmark$ |              | $\checkmark$ |
| Rolandi et al. (2020)      | 1100                  | NR       | 70–74     | 589<br>(54%)    | 617, <5 years              | whispered<br>voice test     | 139 (13%)   | NR            | 7 years              | Dementia             | 111 (10%)          | $\checkmark$ |              |              |              |              |
| Schubert et al.<br>(2019)  | 2556                  | NR       | 49        | 1401 (55%)      | 918, > 16 years            | РТА                         | 332 (13%)   | NR            | 10 years             | CD                   | 89 (4%)            | $\checkmark$ | $\checkmark$ | $\checkmark$ |              |              |
| Stevenson et al. (2022)    | 82039                 | NR       | 64        | 42772 (52%)     | 18160, no<br>secondary edu | digit triplets<br>test      | 14394 (18%) | 1844<br>(13%) | 10 years<br>(median) | Dementia             | 1285 (2%)          | $\checkmark$ | $\checkmark$ | $\checkmark$ |              | $\checkmark$ |
| Strutt et al. (2022)       | 529                   | 5%       | 79        | NR              | 12 years (mean)            | self-reported               | 397 (40%)   | 111<br>(28%)  | 6 years              | Dementia,<br>MCI, CD | 216 (40.8%)        | $\checkmark$ | $\checkmark$ | $\checkmark$ |              |              |
| Su et al. (2017)           | 8121                  | NR       | 69        | 3171<br>(39%)   | NR                         | Clinical<br>diagnosis       | 4108 (51%)  | NR            | up to 10<br>years    | Dementia             | 869 (11%)          | $\checkmark$ | $\checkmark$ |              |              | $\checkmark$ |
| Sugiura et al. (2022)      | 1193                  | NR       | 72        | 533 (45%)       | 494, $\leq$ 9 years        | PTA                         | 582 (49%)   | 6%            | up to 10<br>years    | CD                   | 525 (44%)          | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ | $\checkmark$ |
| Гаі СЈ et al. (2021)       | 1418                  | NR       | 74        | 558 (39%)       | 34, > college              | self-reported               | 709 (50%)   | 83 (12%)      | 9 years              | CD                   | 1018 (72%)         |              |              |              |              |              |
| Tai SY et al. (2021)       | 14900                 | NR       | 52        | 6933<br>(46.5%) | NR                         | ICD-9                       | 3725 (25%)  | NR            | 5 years<br>(mean)    | Dementia             | 442 (3%)           | v            | √            |              | v            | v            |
| Tomata et al. (2020)       | 9017                  | NR       | 72        | 4968 (55%)      | 4743, low<br>education     | self-reported               | 748 (8%)    | NR            | <16 years            | Dementia             | 1950 (22%)         | $\checkmark$ |              | $\checkmark$ |              |              |
| Vassilaki et al.<br>(2019) | 4812                  | 7%       | 74        | 2333 (49%)      | 14 years (mean)            | self-reported               | 981 (20%)   | NR            | 5 years<br>(mean)    | MCI and<br>Dementia  | 1032 (21%)         | $\checkmark$ | $\checkmark$ | $\checkmark$ |              |              |

Adjusted factors: A, age; S, Sex; E, education; C, cardiovascular factors; O, other factors not included in the four categories; ADD, Alzheimer's disease dementia; CD, cognitive decline; HA, Hearing aids; ICD, International Classification of Diseases; VaD, Vascular dementia; PTA, Pure-tone assessment; MCI, mild cognitive impairment; NR = Not reported. P, prospective design; R, retrospective design.

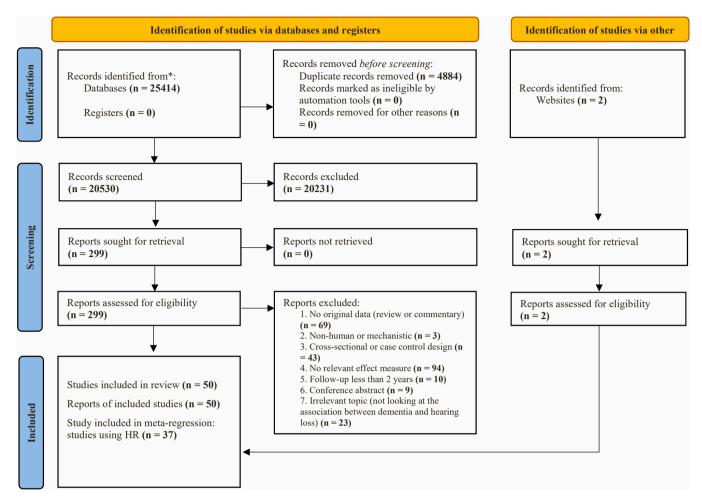


Fig. 1. PRISMA diagram.

| Table 2 |  |
|---------|--|
|---------|--|

Summary of effect sizes across cognitive outcomes.

| Outcome           | HL vs non-HL  | Per 10 dB   |             |             |
|-------------------|---------------|-------------|-------------|-------------|
|                   | HR            | OR          | RR          | HR          |
| Dementia          | 1.35          | 1.52        | 1.20        | 1.16        |
|                   | [1.26-1.45]   | [0.86-2.70] | [0.67-2.16] | [1.07-1.27] |
|                   | k = 30        | k=3         | k=2         | k = 2       |
| Cognitive decline | 1.29          | 1.42        | -           | -           |
| (not specified as | [1.17 - 1.42] | [1.05–1.91] |             |             |
| MCI or dementia)  | k = 9         | k = 5       |             |             |
| MCI               | 1.29          | -           | -           | -           |
|                   | [1.11 - 1.50] |             |             |             |
|                   | k=3           |             |             |             |
| ADD               | 1.56          | -           | -           | -           |
|                   | [1.30–1.87]   |             |             |             |
|                   | k=4           |             |             |             |
| VaD               | 1.30          | -           | -           | -           |
|                   | [0.83-2.05]   |             |             |             |
|                   | k=3           |             |             |             |

\* Numbers in bold indicate a significant outcome; ADD; Alzheimer's disease dementia; HL, hearing loss; HR, hazard ratio; MCI, mild cognitive impairment; OR, odds ratio; RR; risk ratio; VaD, vascular dementia. For clarity, cells with only 1 study have been omitted.

# 4. Discussion

This meta-analysis is the most extensive to date with fifty cohorts reporting on a total sample of 1,548,754 participants. We found that hearing loss as a yes-no variable was consistently associated to increase risk for a range of clinically relevant cognitive outcomes, including dementia, MCI and Alzheimer's disease, whilst the association with vascular dementia was not statistically significant. Only three studies (Beason-Held et al., 2022; Golub et al., 2017; Hwang et al., 2020) specifically looked at the association between hearing loss and vascular dementia, thus resulting in limited statistical power. Two of the three studies also adjusted for cardiovascular factors, which may have diluted the association (Golub et al., 2017; Hwang et al., 2020).

The magnitude of the increased risk for dementia that we report for hearing loss as a yes-no variable (1.35 [1.26–1.45], k = 30) is in line with previous meta-analyses (OR, 1.28 [1.02–1.59], k = 3) (Loughrey et al., 2018) and overlapping but on the lower end of the confidence interval of the effect reported by the 2017 Lancet commission (1.9 [1.4–2.7]; k = 3) (Livingston et al., 2017). These previous meta-analyses relied on a substantially smaller sample of studies, so the findings from our updated meta-analysis should be more robust.

Our findings provide support to the possibility of a causal relationship between adult-onset hearing loss and dementia. First, our results are overall consistent in that despite heterogeneity between studies in population, methodology, and type of incident cognitive outcome, most of the meta-analyses we conducted identified a statistically significant increase in risk across effect measures and cognitive outcomes, and even for those that were not significant, the magnitude of the effect consistently pointed towards risk increase (Figs. 2 and 3, Table 2).

Second, we found evidence of a dose-response relationship. Both mild hearing loss and moderate-severe hearing loss were associated with increasing dementia risk, although the difference in risk increase by degree of hearing loss was not statistically significant. We found a statistically significant association between every 10 dB decrease in hearing ability and increased dementia risks. Taken together, these findings

| miewa_2016<br>merework_2019<br>merework_2019<br>merework_2019<br>merework_2019<br>merework_2019<br>merework_2019<br>merework_2019<br>merework_2019<br>merework_2019<br>merework_2019<br>merework_2019<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_2018<br>merework_  | Study or<br>Subgroup  | HR                             | 95% CI                        | Hazard Ratio<br>IV, Fixed + Random, 95% C |
|---|---|--------------------------------|-------------------------------|---|
| renoviz, 2019 1.25 [1.01; 1.55]<br>renoviz, 2019 1.25 [1.01; 1.55]<br>renoviz, 2021 1.33 [0.98; 1.79]<br>renoviz, 2021 1.33 [0.98; 1.79]<br>renoviz, 2016 1.44 [1.45; 2.09]<br>renoviz, 2016 1.44 [1.45; 2.09]<br>renoviz, 2016 1.44 [1.45; 2.09]<br>renoviz, 2016 1.45 [1.45]<br>renoviz, 2016 1.45 [1.45]<br>renoviz, 2016 1.45 [1.45]<br>renoviz, 2017 1.45 [1.45]<br>renoviz, 2010 1.45 [1.45]<br>renoviz, 2010 1.45 [1.45]<br>renoviz, 2010 1.45 [1.45]<br>renoviz, 2010 1.45 [1.45]<br>renoviz, 2011 1.23 [1.45]<br>renoviz, 2011 1.23 [1.45]<br>renoviz, 2021 1.45 [1.45]<br>renoviz, 2022 1.45 [1.45]<br>renoviz, 2021 1.45 [1.45]<br>renoviz, 2020 1.45 [1.45]<br>renoviz, 2020 1.45 [1.45]<br>renoviz, 2021 1.45 [1.45]<br>renoviz, 2020 1.45 [1.45]<br>renoviz, 2021 1.45 [1.45]<br>renovi  | ubgroup = Dementia.HR   |                                |                               |   |
| yeon, 2021 0.33 (0.26, 3.3)<br>head, 2017 1.23 (0.26, 3.4)<br>head, 2017 1.23 (0.26, 1.70)<br>try 2016 1.14 (1.45, 2.09)<br>head, 2017 1.15 (0.27, 2.25)<br>head, 2017 1.15 (0.27, 2.25)<br>head, 2014 1.27 (1.03, 1.56)<br>wang, 2020 1.18 (0.28, 1.69)<br>wang, 2020 1.18 (0.28, 1.69)<br>wang, 2020 1.18 (0.28, 1.69)<br>wang, 2020 1.15 (0.28, 1.69)<br>wang, 2020 1.20 (0.71, 2.02)<br>wang, 2010 1.33 (1.31, 1.39)<br>val (aradom effect, 55% (1) (1.32 (1.47, 1.48))<br>wang, 2020 1.16 (0.20, 3.31)<br>wang, 2010 1.16 (0.21, 3.31)<br>wang, 2010 1.16 (0.21, 3.31)<br>wang, 2020 1.32 (1.29, -0.03), i = 55%<br>wang, 2020 1.34 (1.29, -0.03), i = 55%<br>wang, 2020 1.35 (0.23, -1.68, 1.77)<br>wang, 2020 1.36 (0.21, 0.21, 0.21)<br>wang, 2020 1.36 (0.21, 0.21, 0.21, 0.21)<br>wang, 2020 1.36 (0.21, 0.21, 0.21)<br>wang, 2020 1.36 (0.21, 0.21, 0.21)<br>wang, 2020 1.3  |   |                                |                               |   |
| hem_2022   1.33   (0.98): 1.78]     ord 2018   1.84   (1.94): 1.85]     ord 2018   1.99   (1.94): 1.85]     ord 2014   1.27   (1.31): 1.56]     wang_2020   1.18   (0.98): 1.78]     ord 2018   1.29   (1.94): 1.85]     m_2018   1.29   (1.94): 1.85]     m_2011   2.32   (1.94): 1.85]     m_2020   1.99   (1.94): 2.86]     owell_2022   1.87   (1.09): 2.86]     owell_2022   1.87   (1.02): 2.86]     owell_2022   1.99   (1.72): 2.86]     owell_2022   1.97   (1.92): 2.86]     owell_2022   1.99   (1.72): 2.86]     owell_2022   1.99   (1.72): 2.86]     owell_2022   1.97   (1.92): 2.86]     owell_2022   1.91   (1.31): 1.39]     otal (common effect, 95%; C)   1.35   (1.32): 1.87]     owell_2021   1.92   (1.31  |   |                                | [0.26: 3.31]                  |   |
| eal_2017 1 25 [0.89; 1.76]<br>rtzc_2016 1.44; 1.55]<br>rtzc_2016 1.44; 1.55]<br>rtzc_2016 1.44; 1.66; 1.77]<br>habri-Matani-Matani-Matani-2023 1.74 [1.45; 2.69]<br>wang_2023 1.53 [1.19; 1.56]<br>wang_2022 1.53 [1.19; 1.56]<br>gima_2022 1.53 [1.19; 1.56]<br>gima_2022 1.28 [1.19; 1.38]<br>or 2021 1.29 [1.06; 1.55]<br>gima_2022 1.28 [1.19; 1.38]<br>wang_2022 1.28 [1.19; 1.38]<br>wang_2022 1.28 [1.19; 1.38]<br>wang_2022 1.28 [1.19; 1.38]<br>wang_2022 1.29 [1.10; 1.55]<br>gima_2022 1.67 [1.09; 2.56]<br>startarized<br>2020 1.09 [0.95; 1.26]<br>thatus 2020 1.09 [1.11; 1.20]<br>assistal 2019 1.45 [1.20; 1.31; 1.31]<br>al_2021 1.3 [1.39 [1.13; 1.71]<br>assistal 2019 1.72 [1.20; 2.47]<br>that 2020 1.39 [1.3; 1.48]<br>uproup = Cloognitive decline.HR<br>hen_2021 [1.71; 1.40]<br>thatarani 2020 1.17 [1.36 [0.78; 4.39]<br>thatarani 2020 1.17 [1.36; 1.31]<br>thatarani 2020 1.16 [1.20; 1.31]<br>thatarani 2020 1.17 [1.36; 1.31]<br>thatarani 2020 1.16 [1.20; 1.31]<br>thatarani 2020 1.16 [1.20; 1.31]<br>thatarani 2020 1.16 [1.20; 1.31]<br>thatarani 2020 1.16 [1.30; 1.31]<br>thatarani 2020 1.16 [1.30; 1.31]<br>thatarani 2020 1.16 [1.30; 1.31]<br>thatarani 2020 1.16 [1.30; 1.31]<br>thatarani 2020 1.17 [1.36 [1.31; 2.62]<br>thatarani 2020 1.16 [1.30; 1.31]<br>thatarani 2020 [1.30 [1.30; 1.30]<br>thatarani 2020 [1.30 [1.30; 1.30]<br>thatarani 4.1555 [1.30]<br>thatarani 4.1555 [1.30]<br>thatarani 4  | Chern_2022  |                                |                               | L.  |
| <pre>titze_2016</pre>   | Deal_2017   |                                |                               |   |
| hard-Median, 2023<br>hard-Median, 2023<br>hard-Median, 2023<br>hard-Median, 2023<br>hard-Median, 2023<br>hard-Median, 2022<br>hard, 2020<br>hard-Median, 2022<br>hard-Median, 2022<br>hard, 2020<br>hard, 202   | Ford_2018   |                                |                               |   |
| blob_2017 160 [127:225]<br>wang_2020 1.8 [139]<br>m_2018 122 153 [118:156]<br>m_2018 122 153 [118:156]<br>m_2018 122 153 [118:156]<br>m_2018 122 153 [118:156]<br>m_2018 122 153 [118:156]<br>m_2019 122 153 [118:156]<br>m_2011 232 [132:407]<br>wang_2020 1.09 [0.95:125]<br>m_2011 232 [132:407]<br>wang_2020 1.09 [0.95:126]<br>bhamrad_2020 1.09 [0.95:126]<br>bhamrad_2020 1.09 [0.95:126]<br>bhamrad_2020 1.09 [0.95:126]<br>bhamrad_2020 1.09 [0.95:126]<br>bhamrad_2020 1.09 [0.95:126]<br>wang_2010 1.15 [0.98:134]<br>tabarad_2020 1.09 [0.95:126]<br>bhamrad_2022 1.67 [1.08:266]<br>wand_2020 1.20 [0.71:202]<br>terremon_2022 1.72 [1.56:189]<br>turd_2020 0.06 [0.82:266]<br>wang_2020 1.20 [0.71:202]<br>terremon_2022 1.72 [1.56:189]<br>turd_2020 0.120 [0.71:202]<br>terremon_2022 1.72 [1.56:189]<br>turd_2020 0.120 [1.10:1.13]<br>manual_2020 1.20 [0.71:202]<br>terremon_2022 1.72 [1.56:189]<br>turd_2020 0.120 [1.10:1.13]<br>manual_2020 1.20 [0.71:202]<br>terremon_2022 1.72 [1.56:189]<br>turd_2020 [1.10:1.13]<br>manual_2020 1.20 [0.71:202]<br>terremon_2022 1.72 [1.56:189]<br>turd_2020 [1.10:1.13]<br>manual_2020 1.20 [1.11:1.20]<br>tal.2011 1.20 [2.20]<br>turd_2020 [1.10:1.13]<br>tal.2011 1.12 [0.22:20]<br>turd_2020 [1.10:1.13]<br>tal.2011 1.12 [0.22:20]<br>turd_2020 [1.10:1.13]<br>tal.2011 1.15 [0.20:1.13]<br>tal.2012 [1.11:1.20]<br>tal.2012 [1.11:1.20]<br>tal.2014 [1.10:1.51]<br>tal.2014 [1.2014 [1.20:1.51]<br>tal.2014 [1.2014 [1.20:1.5   |   |                                |                               | 1   |
| urgel_2014 1.27 [103:156]<br>wwag_2022 1.53 [119:166]<br>wwag_2022 1.53 [119:166]<br>m_2018 2.22 1.53 [119:166]<br>m_2018 2.22 1.53 [119:166]<br>m_2019 2.22 1.59 [106:159]<br>wwag_2020 1.15 [0.98:1.29]<br>hard_aran_2020 1.15 [0.98:1.34]<br>hardaran_2020 1.09 [0.96:1.28]<br>hard_aran_2020 1.20 [0.17:2.28]<br>wwwg_2020 1.20 [0.17:2.28]<br>hard_aran_2020 1.20 [0.13:1.13:19]<br>aran_2020 1.22 [0.13:1.26:1.46]<br>hard_aran_2022 [0.13: [1.26:1.46]<br>hard_aran_2020 [0.32 [0.14:2.9] (P < 0.01) F < 75%<br>hard_aran_2020 [0.13: [1.26:1.46]<br>hard_aran_2020 [0.12 [0.62:2.02]<br>ara_20210 [1.15:1.50]<br>hard_aran_2020 [1.17:1.31]<br>hard_aran_2020 [1.17:1.31]<br>hard_aran_2020 [1.17:1.31]<br>hard_aran_2020 [1.17:1.31]<br>hard_aran_2020 [1.16:1.31]<br>hard_aran_2020 [1.16   |   |                                | [1.45; 2.09]                  | -   |
| wang_2020 1.18 [0.8:1.59]<br>m.2018 1.29 [1.06:1.59]<br>m.2018 1.29 [1.06:1.59]<br>m.2018 1.29 [1.06:1.59]<br>m.2018 1.29 [1.06:1.59]<br>m.2011 1.00 [0.55:1.20]<br>that anal_2020 1.09 [0.53:1.20]<br>that anal_2020 1.15 [1.10:1.130]<br>that anal_2020 1.29 [1.11:1.50]<br>that (anal_10:4:1.59]<br>that (anal_10:4:1.50]<br>that (anal_10:4:1.50]<br>that (anal_10   |   |                                | [1.27; 2.25]                  |   |
| wang_2022 1.53 [1.19:1.96]<br>gim_2018 1.29 [1.06:1.55]<br>gim_2021 1.28 [1.19:1.80]<br>gim_2022 1.28 [1.19:1.81]<br>gim_2022 1.28 [1.19:1.81]<br>m_2011 2.23 [1.32:407]<br>m_2011 2.23 [1.32:407]<br>handa_2020 1.09 [0.95:1.26]<br>handa_2020 1.09 [0.95:1.26]<br>handa_2020 1.09 [0.95:1.26]<br>handa_2020 1.09 [0.95:1.26]<br>handa_2020 1.09 [0.95:1.26]<br>handa_2020 1.09 [0.95:1.26]<br>handa_2020 1.09 [1.47:2.88]<br>dista_2021 1.16 [1.04:1.30]<br>well_2022 1.72 [1.56:1.89]<br>handa_2020 1.29 [1.17:1.20]<br>handa_2020 1.17 [1.26:2.47]<br>tasiaki_2016 1.42 [1.26:1.45]<br>isobic_2016 1.95% C1 1.35 [1.34:1.39]<br>tata (candom effect, 95% C0] 1.35 [1.34:1.45]<br>isobic_2016 1.90 [1.16:1.31]<br>han_2011 1.45 [1.08:1.44]<br>han_2021 1.45 [1.08:1.44]<br>han_2021 1.45 [1.08:1.44]<br>han_2021 1.45 [1.08:1.44]<br>han_2021 1.45 [1.08:1.44]<br>han_2020 1.17 [1.09:1.26]<br>handa_2020 1.17 [1.09:1.26]<br>handa_2020 1.17 [1.09:1.26]<br>handa_2020 1.16 [0.09.42:27]<br>handa_2020 1.17 [1.09:1.26]<br>handa_2020 1.16 [0.07:2.01]<br>handa_2020 1.17 [1.09:1.26]<br>handa_2020 1.16 [0.07:2.01]<br>handa_2020 1.20 [0.06:1.18]<br>handa_2020 1.20 [0.06:1.20]<br>handa_2020 1.30 [0.23:2.05]<br>handa_2020 1.30 [0.23:2.05]<br>handa_2020 1.30 [0.23:2.05]<br>handa_2021 1.15 [0.33:3.78]<br>handa_2020 2.26 [1.36:1.19]<br>handa_2022 2.26 [1.36:1.19]<br>handa_2020 1.30 [0.32:2.26]<br>handa_2020 2.26 [1.30:1.20]<br>handa_2020 1.30 [0.32:2.26]<br>handa_2020 2.26 [1.30:1.20]<br>handa_2020 1.30 [0.32:2.26]<br>handa_2021 1.15 [0.33:3.78]<br>handa_2021 1.15 [0.33:3.78]<br>handa_2021 1.15 [0.33:3.78]<br>handa_2031 1.15 [0.33:3.78]<br>handa_2031 1.15   |   |                                |                               |   |
| im 2018 129 [106:155]<br>join 2022 128 [119:138]<br>join 2022 128 [129:132:407]<br>join 2022 129 [129:145]<br>join 2022 129 [147:268]<br>join 2022 [149:13:148]<br>join 2020 129 [149:368]<br>join 2022 [264 = 11764, df = 29 [P = 001] F = 75%<br>tubgroup = Clicopnitive decline.HR<br>hen_2021 13 [148:177]<br>join [common effect, 95% C) 135 [131:139]<br>join [140:272]<br>join [common effect, 95% C) 129 [147:142]<br>tetrogenetry Tar <sup>1+</sup> 0.002; Cd <sup>2</sup> = 11764, df = 29 [P = 0.01] F = 75%<br>tubgroup = MCLHR<br>jeymod 2017 185 [0.78:429]<br>join [149:328]<br>join [140:320]<br>join [140:328]<br>join [140:328]<br>join [140:329]<br>join [140:328]<br>join [140:329]<br>join [140:   |   |                                |                               |   |
| uo. 2021 109 005; 125<br>1.201 1232<br>1.22 4 67<br>1.22 1132; 407<br>1.22 1132; 407<br>1.22 1132; 407<br>1.22 1132; 407<br>1.22 1132; 129<br>1.22 1133; 121<br>1.23 1133; 121<br>1.23 1133; 121<br>1.23 1133; 121<br>1.23 1133; 121<br>1.23 1133; 121<br>1.23 1134; 129<br>1.23 113; 121<br>1.23 113; 121<br>1.24 113; 121<br>1.25 1145;<br>1.25 1145;<br>1  | Kim_2018  | 1.29                           |                               | +   |
| in 2011 2.322 (1.32; 4.07)<br>Labaran, 2020 1.15 (0.96; 1.34)<br>Labaran, 2020 1.09 (0.95; 1.26)<br>Lohammed, 2022 1.67 (1.09; 2.66)<br>wowell, 2022 1.67 (1.09; 2.66)<br>wowell, 2022 1.67 (1.09; 2.66)<br>used 2022 1.72 (1.56; 1.69)<br>Labaran, 2020 0.71; 2.02]<br>tervenson, 2022 1.72 (1.56; 1.69)<br>Labaran, 2020 0.866 (0.28; 2.66)<br>u_2017 1.29 (1.31; 1.43)<br>analyzon 0.866 (0.28; 2.66)<br>u_2017 1.29 (1.31; 1.43)<br>contal, 2020 0.866 (0.28; 2.66)<br>u_2017 1.29 (1.31; 1.43)<br>contal, 2020 0.120 (0.12; 2.47)<br>contal, 2020 0.120 (0.12; 2.47)<br>contal, 2020 0.120 (1.14; 1.36)<br>Labaran, 2020 1.20 (1.14; 1.36)<br>Labaran, 2020 1.20 (1.14; 1.36)<br>Labaran, 2020 1.17 (1.09; 1.46)<br>Labaran, 2020 1.17 (1.09; 1.46)<br>Labaran, 2020 1.17 (1.09; 1.26)<br>chuber, 2016 1.90 (1.14; 1.36)<br>Labaran, 2020 1.17 (1.09; 1.26)<br>chuber, 2016 1.90 (1.14; 1.36)<br>Labaran, 2020 1.17 (1.09; 1.26)<br>chuber, 2016 1.91 (1.16; 1.26)<br>Labaran, 2020 1.17 (1.09; 1.26)<br>Labaran, 2020 1.16 (1.04; 1.47)<br>Labaran, 2020 1.17 (1.09; 1.26)<br>Labaran, 2020 1.16 (1.02; 1.31)<br>Labaran, 2020 1.16 (1.14; 1.47)<br>Labaran, 2020 1.16 (1.14; 1.47)<br>Labaran, 2020 1.16 (1.14; 1.47)<br>Labaran, 2020 1.17 (1.09; 1.26)<br>Labaran, 2020 1.16 (1.14; 1.47)<br>Labaran, 2020 1.17 (1.46; 1.48)<br>Labaran, 2020 1.16 (1.14; 1.47)<br>Labaran   | Kojima_2022   |                                | [1.19; 1.38]                  |   |
| und 2020 1:15 [0.98:1.34]<br>tarut 2020 1:09 [0.92:1.29]<br>tarut 2020 1:09 [0.92:1.29]<br>tarut 2020 1:09 [0.92:1.29]<br>tarut 2022 1:67 [1.09:2.66]<br>sker_2019 1:45 [1.02:2.66]<br>sker_2019 1:45 [1.02:2.66]<br>towel 2022 1:99 [1.47:2.68]<br>und 2020 1:20 [1.71:2.68]<br>und 2020 1:20 [1.71:2.68]<br>und 2020 1:20 [1.71:2.68]<br>und 2020 1:20 [1.71:1.50]<br>tassilasi 2019 1:72 [1.20:2.47]<br>total (cannon effect, 95% CI) 1:35 [1.26:1.45]<br>taster_2016 1:10 [1.72 [1.20:2.47]<br>total (cannon effect, 95% CI) 1:25 [1.71:1.31]<br>total (cannon effect, 95% CI) 1:25 [1.71:1.32]<br>total (cannon effect, 95% CI) 1:29 [1.71:1.42]<br>teterogenehy, Tar <sup>2</sup> = 0.07: Ch <sup>2</sup> = 1.94; d = 2(P = 0.05); P <sup>2</sup> = 53%:<br>ubgroup = MCIHR<br>tetorgenehy, Tar <sup>2</sup> = 0.07: Ch <sup>2</sup> = 1.94; d = 2(P = 0.05); P <sup>2</sup> = 0.55;<br>ubgroup = MDLR<br>total (cannon effect, 95% CI) 1:29 [1.71:1.50]<br>total (cannon effect, 95% CI) 1:29 [1.71:1.50]<br>total (cannon effect, 95% CI) 1:29 [1.71:1.50]<br>total (cannon effect, 95% CI) 1:20 [1.72:1.87]<br>tetorgenehy, Tar <sup>2</sup> = 0.01; P <sup>2</sup> = 0.20; P <sup>2</sup> = 0.57; P <sup>2</sup> = 0.55; P |   |                                |                               | F1  |
| tahārani, 2020<br>tohammad, 2022<br>tohammad, 2024<br>tohammad, 2022<br>tohammad, 2022<br>tohammad, 2022<br>tohammad, 2023<br>tohammad, 2024<br>tohammad, 2024<br>tohammad, 2025<br>tohammad, 2025<br>tohammad, 2025<br>tohammad, 2025<br>tohammad, 2025<br>tohammad, 202   |   |                                |                               | _   |
| lanuta_2020 109 0.65; 1.26]<br>sker_2019 1.45 10.02; 2.26]<br>sker_2019 1.45 10.22; 2.66]<br>sker_2019 1.45 10.24; 1.30]<br>towell_2022 199 1.45; 1.66]<br>sker_2010 0.72; 1.72 10.05; 2.66]<br>wint_2020 0.86 0.05; 2.66]<br>u_2017 129 1.33; 1.48]<br>u_2017 129 1.33; 1.48]<br>u_2017 129 1.33; 1.48]<br>u_2017 129 1.35; 1.44]<br>u_2017 129 1.35; 1.31; 1.49]<br>u_2017 129 1.35; 1.31; 1.49]<br>u_2017 1.25 1.32; 1.31; 1.49]<br>u_2017 1.25 1.31; 1.49]<br>u_2017 1.25 1.32; 1.41; 1.49]<br>u_2017 1.42 11.20; 2.47]<br>ubgroup = Clicognitive decline.HR<br>ham_2021 142 113; 2.61]<br>total (cannon effect, 95%; CI) 1.25 1.14; 1.38]<br>ubgroup = Clicognitive decline.HR<br>ham_2021 142 1142 113; 2.61]<br>ubgroup = Clicognitive decline.HR<br>ham_2021 145 1108; 1.94]<br>total (cannon effect, 95%; CI) 1.25 1.14; 1.38]<br>ubgroup = Clicognitive decline.HR<br>ham_2020 1.17; 1.09; 1.26<br>total (cannon effect, 95%; CI) 1.25 1.14; 1.34]<br>ubgroup = Clicognitive decline.HR<br>ham_2021 142 0.05; Ch <sup>2</sup> = 10, d = 2 (P = 0.05); P <sup>2</sup> = 53%;<br>ubgroup = Clicognitive decline.HR<br>ham_2021 1.12 0.62; 2.02]<br>total (cannon effect, 95%; CI) 1.25 1.14; 1.31]<br>ubgroup = MCI-HR<br>symood 2007 1 185 0.07; P <sup>2</sup> = 53%;<br>ubgroup = MCI-RR<br>total (candom effect, 95%; CI) 1.29 1.11; 1.50]<br>ubgroup = MCI-RR<br>total (candom effect, 95%; CI) 1.29 1.11; 1.50]<br>total (cannon effect, 95%; CI) 1.20 1.33; 2.05]<br>total (cannon effect, 95%; CI) 1.36 1.13; 2.62]<br>twogenety, Tau <sup>2</sup> = 0.01; R <sup>2</sup> = 2.0; P = 0.00; P <sup>2</sup> = 37%;<br>ubgroup = DD.HR<br>total (cannon effect, 95%; CI) 1.36 1.13; 2.62]<br>twogenety, Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 3.2; d = 4 (P = 0.00; P <sup>2</sup> = 37%;<br>ubgroup = Dementia.OR<br>eason_1 Hed_2022 2.25 1.66 1.161; 2.38]<br>total (cannon effect, 95%; CI) 1.55 1.63; 3.61]<br>twogenety, Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 3.2; d = 4 (P = 0.00; P <sup>2</sup> = 95%;<br>ubgroup = Clocognitive decline.OR<br>revester_2021 1.10 1.55 1.08; 3.61]<br>total (cannon effect, 95%; CI) 1.56 1.42; 1.72]<br>twogenety, Tau <sup>2</sup> = 0.00; Ch <sup>2</sup>  |   |                                | [0.92: 1.29]                  | -   |
| bohamined, 2022 1 67 (109; 2.56)<br>abst_2019 1 45 (102; 2.06)<br>abst_2021 1.16 (104; 1.30)<br>overlage 2022 199 (147; 2.88)<br>overlage 2022 199 (147; 2.88)<br>fund, 2020 0.86 0.28; 2.66)<br>u, 2017 129 (113; 1.48)<br>a, 2021 0 0 139 (113; 1.71)<br>a, 2021 0 139 (113; 1.71)<br>overlage 2042 2.47]<br>overlage 2042 2.44]<br>overlage 2042 1.44 2.42]<br>overlage 2042 1.45 (106; 2.48]<br>overlage 2.44]<br>overlage 2   |   |                                | [0.95; 1.26]                  | -   |
| abst_2021 1.16 [104;130]<br>word[.2022 1.99 [147; 2.86]<br>Joland_2020 1.20 [0.71; 2.02]<br>trut_2020 0.86 [0.28; 2.66]<br>Jut[.2020 0.86 [0.28; 2.72]<br>Jut[.2020 0.117 1.29 [P.400]; $r^2$ - 75%<br>Ubgroup = ClCogntive decline.HR<br>Hen_2021 1.17 1.09 [1.16; 1.58]<br>Jut[.2020 1.17 1.09 [1.17; 1.59]<br>Jut[.2020 1.17 1.09 [1.17; 1.59]<br>Jut[.2020 1.17 1.09 [1.16]<br>Jut[.2020 1.17 1.09 [1.16]<br>Jut[.2020 1.17 1.09 [1.17; 1.42]<br>detrogrammy. Tar <sup>1</sup> = 0.076. Ch <sup>2</sup> = 1.9.8, d = 8 (P = 0.03); $r^2$ = 5%.<br>Ubgroup = MCLAR<br>eywood_2017 1.85 [0.78; 4.39]<br>Jut[.2020 1.16 [0.67; 2.01]<br>Jut[.2020 1.16 [0.57]<br>Jut[.2020 1.16 [0.5   | Mohammed 2022   |                                |                               |   |
| owell_2022     1.99     [1.47, 2.68]       istoresco.2022     1.72     [1.56, 1.89]       istoresco.2022     1.72     [1.56, 1.89]       istoresco.2022     1.72     [1.56, 1.89]       istoresco.2022     1.72     [1.56, 1.89]       istoresco.2022     1.72     [1.06, 1.89]       istoresco.2022     1.72     [1.06, 1.45]       istoresco.2022     1.72     [1.07, 1.42]       istoresco.2022     Chi * 117.01, di * 29 (P < 0.01); * 7.5%   | Osler_2019  |                                |                               |   |
| boland_2020 1.20 [0.71: 2.02]<br>trut_2020 0.66 [0.28: 2.66]<br>u_2017 1.29 [1.31: 1.48]<br>ai_2021a 1.39 [1.31: 1.71]<br>orata_2020 1.29 [1.31: 1.50]<br>assilat_2019 1.72 [1.20: 2.47]<br>otal (common effect, 95% CI) 1.35 [1.31: 1.39]<br>otal (candom effect, 95% CI) 1.35 [1.31: 1.39]<br>otal (candom effect, 95% CI) 1.35 [1.31: 1.39]<br>trut_2021 1.40 [1.28: 1.59]<br>trut_2021 1.40 [1.28: 1.59]<br>trut_2021 1.40 [1.28: 1.59]<br>trut_2021 1.42 [1.28: 1.59]<br>trut_2020 1.17 [1.20: 2.47]<br>otal (candom effect, 95% CI) 1.25 [1.31: 1.39]<br>trut_2021 1.42 [1.28: 1.59]<br>trut_2020 1.17 [1.20: 2.47]<br>otal (candom effect, 95% CI) 1.25 [1.31: 1.29]<br>trut_2021 1.42 [1.28: 1.59]<br>trut_2020 1.17 [1.20: 1.27]<br>trut_2020 1.17 [1.20: 1.27]<br>trut_2020 1.17 [1.20: 1.27]<br>trut_2020 1.17 [1.20: 1.27]<br>trut_2020 1.12 [0.62: 2.02]<br>ai_2021b 1.16 [0.63: 2.20]<br>trut_2020 1.12 [0.62: 2.02]<br>trut_2020 1.12 [0.62: 2.02]<br>trut_2020 1.12 [0.63: 2.01]<br>trut_2020 1.12 [1.19: 1.31]<br>otal (candom effect, 95% CI) 1.29 [1.17: 1.42]<br>tetrogenety.Tau <sup>2</sup> = 0.076: CH <sup>2</sup> = 16.96, df = 8 (P = 0.03); P = 53%.<br>tubgroup = MCLHR<br>tetrogenety.Tau <sup>2</sup> = 0.076: CH <sup>2</sup> = 16.96, df = 8 (P = 0.03); P = 53%.<br>tubgroup = MCLHR<br>tetrogenety.Tau <sup>2</sup> = 0.076: CH <sup>2</sup> = 16.96, df = 8 (P = 0.03); P = 53%.<br>tubgroup = MCLHR<br>tetrogenety.Tau <sup>2</sup> = 0.076: CH <sup>2</sup> = 1.29 (P = 0.07); P = 0%.<br>ubgroup = ADD.HR<br>otal (candom effect, 95% CI) 1.28 [1.31; 2.62]<br>trut_2020 1.16 [1.11: 1.50]<br>tetrogenety.Tau <sup>2</sup> = 0.076: CH <sup>2</sup> = 2.16, df = 2 (P = 0.07); P = 37%.<br>ubgroup = VAD.HR<br>otal (candom effect, 95% CI) 1.42 [1.30; 1.37]<br>tetrogenety.Tau <sup>2</sup> = 0.076; CH <sup>2</sup> = 2.75, df = 2 (P = 0.07); P = 37%.<br>ubgroup = Dementia.OR<br>tetrogenety.Tau <sup>2</sup> = 0.076; CH <sup>2</sup> = 3.2, df = 2 (P = 0.07); P = 37%.<br>ubgroup = Clicognitive decline.OR<br>rewster_2021 1.05 [0.88; 1.26]<br>tetrogenety.Tau <sup>2</sup> = 0.070; CH <sup>2</sup> = 3.2, df = 2 (P < 0.01); P = 38%.<br>ubgroup = Dementia.RR<br>tetrogenety.Tau <sup>2</sup> = 0.070; CH <sup>2</sup> = 3.2, df = 4 (P < 0.01); P = 38%.<br>ubgroup = Clicognitive decline.OR<br>rewster_2021 1.125 [1.26; 1.24]<br>tetrogenety.Tau <sup>2</sup> = 0.070; CH <sup>2</sup>  |   |                                |                               | -   |
| isteresson_2022 1.72 [1.56; 1.89]<br>isteresson_2022 1.72 [1.66; 1.89]<br>$u_2017$ 1.29 [1.13; 1.48]<br>$i_2021a$ 1.39 [1.3; 1.71]<br>ornal_2020 1.29 [1.11; 1.50]<br>assiki_2019 1.72 [1.20; 2.47]<br>otal (common effect, 95%, C) 1.35 [1.3; 1.45]<br>isteregomety, Tau <sup>2</sup> = 0.2022, Ch <sup>2</sup> = 117.04, dr = 20 (P < 0.01); h <sup>2</sup> = 75%<br>ubgroup = CliCognitive decline.HR<br>hen_2021 1.45 [1.30; 1.45]<br>isteregomety, Tau <sup>2</sup> = 0.2022, Ch <sup>2</sup> = 117.04, dr = 20 (P < 0.01); h <sup>2</sup> = 75%<br>ubgroup = CliCognitive decline.HR<br>hen_2021 1.45 [1.30; 1.45]<br>isteregomety, Tau <sup>2</sup> = 0.2022, Ch <sup>2</sup> = 117.04, dr = 20 (P < 0.01); h <sup>2</sup> = 75%<br>ubgroup = CliCognitive decline.HR<br>hen_2021 1.45 [1.30; 1.47]<br>isteregomety, Tau <sup>2</sup> = 0.007; Ch <sup>2</sup> = 16.98, dt = 8 (P = 0.03); h <sup>2</sup> = 53%.<br>Ubgroup = A0076, Ch <sup>2</sup> = 16.98, dt = 8 (P = 0.03); h <sup>2</sup> = 53%.<br>ubgroup = MCLHR<br>leywood 2017 1.45 [0.47; 2.01]<br>assiki_2019 1.129 [1.11; 1.50]<br>isteregomety, Tau <sup>2</sup> = 0.007; Ch <sup>2</sup> = 16.98, dt = 8 (P = 0.03); h <sup>2</sup> = 53%.<br>ubgroup = MCLHR<br>leywood 2017 1.45 [1.30; 1.47]<br>assignet_2018 1.29 [1.11; 1.50]<br>isteregomety, Tau <sup>2</sup> = 0.07; h <sup>2</sup> = 0.67; h <sup>2</sup> = 0%.<br>ubgroup = ADD.HR<br>biolub_2017 1.45 [1.30; 1.47]<br>atteregomety, Tau <sup>2</sup> = 0.01, dt = 2 (P = 0.57; h <sup>2</sup> = 0%.<br>ubgroup = VaD.HR<br>biolub_2017 1.156 [1.30; 1.47]<br>atteregomety, Tau <sup>2</sup> = 0.01, dt = 2 (P = 0.57; h <sup>2</sup> = 0%.<br>ubgroup = VaD.HR<br>biolub_2017 1.156 [1.30; 1.47]<br>atteregomety, Tau <sup>2</sup> = 0.07; Ch <sup>2</sup> = 2.15, dt = 2 (P = 0.07); h <sup>2</sup> = 37%.<br>ubgroup = VaD.HR<br>biolub_2017 1.156 [1.30; 1.47]<br>atteregomety, Tau <sup>2</sup> = 0.07; Ch <sup>2</sup> = 1.27, dt = 2 (P = 0.07); h <sup>2</sup> = 37%.<br>ubgroup = Damentia.OR<br>aeson_held_2023 2.33 [1.90; 2.86]<br>atteregomety, Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 1.2, dt = 2 (P = 0.07); h <sup>2</sup> = 37%.<br>ubgroup = Damentia.OR<br>aeson_held_2023 2.23 [1.30; 1.42]<br>atteregomety, Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 3.2, dt = 4 (P < 0.07); h <sup>2</sup> = 37%.<br>ubgroup = Damentia.RR<br>tealgroup = Damentia.RR<br>tealgoregomety, Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 3.2, dt = 4 (P < 0.07); h <sup>2</sup> = 37%.<br>ubgroup = Damentia.RR<br>tealgoregomety, Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 3.2, dt = 4 (P < 0.07); h <sup>2</sup>                              |   |                                | [1.47; 2.68]                  |   |
| trut_2020 0.666 [0.28; 2.66]<br>u_2017 1.29 [1.3; 1.48]<br>ai_2021a 1.39 [1.13; 1.71]<br>ornals_2020 1.29 [1.11; 1.50]<br>assilati_2019 1.72 [1.20; 2.47]<br>otal (common effect, 95% CI) 1.35 [1.31; 1.39]<br>otal (common effect, 95% CI) 1.35 [1.31; 1.39]<br>otal (common effect, 95% CI) 1.35 [1.31; 1.39]<br>terrogenety.Tau <sup>2</sup> = 0.020; $Ch^2 = 117.04$ , $df = 20 (P < 0.01)$ ; $r^2 = 75\%$<br>ubgroup = Clocognitive decline.HR<br>hen_2021 1 4.42 [1.28; 1.58]<br>isoher_2016 1.90 [1.11; 3.26]<br>terrogenety.Tau <sup>2</sup> = 0.020; $Ch^2 = 117.04$ , $df = 20 (P < 0.01)$ ; $r^2 = 75\%$<br>ubgroup = Clocognitive decline.HR<br>hen_2021 1.445 [1.08; 1.94]<br>in_2013 1.244 [1.04; 1.47]<br>Isharani_2020 1.17 [1.09; 1.26]<br>chubert_2019 1.60 [0.94; 2.72]<br>trutt_2020 1.16 [1.02; 1.31]<br>otal (common effect, 95% CI) 1.25 [1.19; 1.31]<br>otal (common effect, 95% CI) 1.29 [1.17; 1.42]<br>terrogenety.Tau <sup>2</sup> = 0.076; $Ch^2 = 15.98$ , $df = 0.03$ ; $r^2 = 35\%$<br>ubgroup = MCLHR<br>eywood_2017 1.85 [0.76; 2.01]<br>assilat_2019 1.16 [0.67; 2.01]<br>assilat_2019 1.26 [1.30; 1.37]<br>ator and mether, 95% CI] 1.29 [1.11; 1.50]<br>ator and offect, 95% CI] 1.30 [0.33; 2.05]<br>ator and offect, 95% CI] 1.30 [0.33; 2.05]<br>ator and offect, 95% CI] 1.44 [1.09; 2.18]<br>band [common effect, 95% CI] 1.52 [0.36; 2.70]<br>ator and fert, 95% CI] 1.52 [0.36; 2.70]<br>ator and offect, 95% CI] 1.52 [0.36; 2.70]<br>ator and offect, 95% CI] 1.52 [0.36; 2.70]<br>ator and effect, 95% CI] 1.52 [0.36; 2.70]<br>ator and effect, 95% CI] 1.52 [0.36; 2.70]<br>ator and offect, 95% CI] 1.52 [0.36; 2.70]<br>ato  |   |                                |                               |   |
| u_2017 1.29 [1.13; 1.48]<br>i_2021a 1.39 [1.3; 1.71]<br>ornal_2020 1.29 [1.11; 1.50]<br>assilat, 2019 1.72 [1.00; 2.47]<br>otal (common effect, 95% CI) 1.35 [1.31; 1.45]<br>tetrogenety; Tat <sup>2</sup> = 0.202; Ch <sup>2</sup> = 117.64, dr = 29 ( $P < 0.01$ ); $r^2 = 75\%$<br>ubgroup = Cl/Cognitive decline.HR<br>hen_2021 1.12 [1.02; 1.45]<br>isober_2016 1.90 [1.11; 3.26]<br>eywood 2017 2.30 [1.08; 4.91]<br>arpa_2010 1.45 [1.08; 1.94]<br>in_2013 1.24 [1.04; 1.47]<br>tharana_2020 1.17 [1.09; 1.26]<br>that arpa_2010 1.45 [1.08; 1.24]<br>arpa_2010 1.45 [1.08; 1.24]<br>in_2013 1.24 [1.04; 1.47]<br>tharana_2020 1.17 [1.09; 1.26]<br>that arpa_2010 1.45 [1.09; 1.21]<br>that arpa_2010 1.45 [1.09; 1.21]<br>that arpa_2010 1.45 [1.09; 1.21]<br>that arpa_2010 1.45 [1.09; 1.21]<br>that arpa_100 [1.12] [1.71; 1.21]<br>that arpa_2010 [1.12] [1.71; 1.21]<br>that arpa_2010 [1.12] [1.71; 1.21]<br>that arpa_2010 [1.12] [1.71; 1.21]<br>that arpa_2010 [1.15]<br>that [1.10] [1.21] [1.11; 1.50]<br>that [andom effect, 95% CI] [1.29 [1.11; 1.50]<br>that [andom effect, 95% CI] [1.28 [1.31; 1.62]<br>that [andom effect, 95% CI] [1.28 [1.31; 1.62]<br>that [andom effect, 95% CI] [1.56 [1.30; 1.87]<br>that [andom effect, 95% CI] [1.50 [1.53; 1.14]<br>that [andom effect, 95% CI] [1.50 [1.53; 1.14]<br>that [andom effect, 95% CI] [1.50 [1.53; 1.16]<br>that [andom effect, 95% CI] [1.50 [1.53; 1.16]<br>that [andom effect, 95% CI] [1.50 [1.52; 1.16]<br>that [andom effect, 95% CI] [1.50 [1.52; 1.16]<br>that [andom effect, 95% CI] [1.50 [1.42; 1.72]<br>that [andom effect, 95% CI] [1.52 [1.26; 1.51]<br>that [andom effect, 95% CI]   |   |                                |                               |   |
| a 2021a 1.39 (1.13.1.71)<br>ornata_2020 1.29 (1.11.1.50)<br>assibilit_2019 1.72 (1.20.2.47)<br>otal (common effect, 95% C) 1.35 (1.31.1.39)<br>otal (common effect, 95% C) 1.35 (1.31.1.39)<br>otal (common effect, 95% C) 1.35 (1.31.1.39)<br>therapoenetit_2012 ( $D^{*} = 120.4 d = 20 (P < 0.01); P^{*} = 75\%$<br>ubgroup = Clocognitive decline.HR<br>hen_2021 1.42 (1.28.1.58)<br>isolar_2016 1.42 (1.28.1.58)<br>isolar_2016 1.42 (1.28.1.58)<br>isolar_2016 1.42 (1.28.1.58)<br>isolar_2016 1.42 (1.28.1.58)<br>isolar_2017 2.30 (1.08.4.91)<br>arga_2010 1.45 (1.08.1.944)<br>in_2013 1.24 (1.04.1.47)<br>laharani_2020 1.17 (1.09.1.26)<br>chubert_2019 1.60 [0.94:2.72]<br>thut_2020 1.12 [0.62;2.02]<br>ai_2021b 1.16 [1.02.1.31]<br>otal (common effect, 95% C) 1.25 [1.9:1.31]<br>otal (common effect, 95% C) 1.29 [1.17.1.42]<br>tercognetit_7.11 = 0.0076. Cht <sup>a</sup> = 16.98. dt = 0 (P = 0.03); P = 3%.<br>ubgroup = MCLHR<br>leywood_2017 1.85 [0.78;4.39]<br>thut_2020 1.16 [0.67;2.01]<br>assilat_2019 [0.1.67]<br>assilat_2019 [0.1   | Su 2017   |                                |                               | -   |
| omala_2020 1.29 [1.11; 1.50]<br>sasiaki_2020 1.25 [1.20; 2.47]<br>total (common effect, 95%, C1) 1.35 [1.21; 1.45]<br>eterogenety, Tau <sup>2</sup> = 0.202; Ch <sup>2</sup> = 117.04, df = 29 ( $P < 0.01$ ); $P = 75\%$ .<br>tubgroup = CUcognitive decline.HR<br>hen_2021 1.42 [1.28; 1.59]<br>ischer_2016 1.90 [1.11; 3.26]<br>teywood_2017 2.30 [1.08; 4.91]<br>arpa_2010 1.45 [1.08; 1.94]<br>in_2013 1.24 [1.04; 1.47]<br>taharan_2020 1.17 [1.09; 1.26]<br>total (common effect, 95%, C1) 1.25 [1.19; 1.31]<br>otal (common effect, 95%, C1) 1.25 [1.19; 1.31]<br>otal (common effect, 95%, C1) 1.29 [1.17; 1.42]<br>eterogenety, Tau <sup>2</sup> = 0.0076; Ch <sup>2</sup> = 16.96, df = 8 ( $P = 0.03$ ); $P = 53\%$ .<br>tubgroup = MCLHR<br>teywood_2017 1.85 [0.78; 4.39]<br>total (common effect, 95%, C1) 1.29 [1.11; 1.50]<br>otal (common effect, 95%, C1) 1.29 [1.11; 1.50]<br>otal (common effect, 95%, C1) 1.29 [1.11; 1.50]<br>otal (common effect, 95%, C1) 1.56 [1.30; 1.67]<br>otal (common effect, 95%, C1) 1.52 [0.06; 2.70]<br>eterogenety, Tau <sup>2</sup> = 0.076?, Ch <sup>2</sup> = 2.0; df = 2 (P = 0.20); P = 37%.<br>ubgroup = Domentia.OR<br>eason_1 held_2023 2.33 [1:00; 2.86]<br>terogenety, Tau <sup>2</sup> = 0.076?, Ch <sup>2</sup> = 2.75, df = 2 (P = 0.01); P = 37%.<br>ubgroup = 0.0006; Ch <sup>2</sup> = 3.2, df = 2 (P = 0.01); P = 37%.<br>ubgroup = 0.0006; Ch <sup>2</sup> = 3.2, df = 2 (P < 0.01); P = 85%.<br>ubgroup = 0.0006; Ch <sup>2</sup> = 3.2, df = 2 (P < 0.01); P = 85%.<br>ubgroup = 0.0006; Ch <sup>2</sup> = 3.2, df = 2 (P < 0.01); P = 85%.<br>ubgroup = 0.0006; Ch <sup>2</sup> = 3.2, df = 2 (P < 0.01); P = 85%.<br>ubgroup = 0.0006; Ch <sup>2</sup> =  | Tai_2021a   | 1.39                           |                               | 1   |
| assibal; 2019 1.72 [1.20, 2.47]<br>total (common effect, 95% CI) 1.35 [1.31; 1.39]<br>total (random effect, 95% CI) 1.35 [1.26; 1.45]<br>tetrogenety: Tar <sup>2</sup> + 0.0202 Cn <sup>2</sup> = 171.04, df = 29 (P < 0.01); l <sup>2</sup> = 75%<br>tubgroup = Cl/cognitive decline.HR<br>then, 2021 [1.42 [1.26; 1.58]<br>tetrogenety: Tar <sup>2</sup> + 0.0202 Cn <sup>2</sup> = 171.04, df = 29 (P < 0.01); l <sup>2</sup> = 75%<br>tubgroup = Cl/cognitive decline.HR<br>then, 2021 [1.42 [1.26; 1.58]<br>tetrogenety: Tar <sup>2</sup> + 0.0202 Cn <sup>2</sup> = 17.17 [1.90; 2.20]<br>tetrogenety: Tar <sup>2</sup> + 0.0202 Cn <sup>2</sup> = 16.98, df = 8 (P = 0.03); l <sup>2</sup> = 53%<br>tubgroup = MCLHR<br>tetrogenety: Tar <sup>2</sup> + 0.076; Ch <sup>2</sup> = 16.98, df = 8 (P = 0.03); l <sup>2</sup> = 53%<br>tubgroup = MCLHR<br>tetrogenety: Tar <sup>2</sup> + 0.076; Cl <sup>3</sup> = 16.98, df = 8 (P = 0.03); l <sup>2</sup> = 0.5%<br>tubgroup = MCLHR<br>tetrogenety: Tar <sup>2</sup> + 0.076; Cl <sup>3</sup> = 16.98, df = 2 (P = 0.07); l <sup>2</sup> = 0.5%<br>tubgroup = MCLHR<br>tetrogenety: Tar <sup>2</sup> = 0.01, df = 2 (P = 0.07); l <sup>2</sup> = 0.5%<br>tubgroup = MCLHR<br>tetrogenety: Tar <sup>2</sup> = 0.01, df = 2 (P = 0.07); l <sup>2</sup> = 0.5%<br>tubgroup = MCLHR<br>tetrogenety: Tar <sup>2</sup> = 0.01, df = 2 (P = 0.07); l <sup>2</sup> = 0.5%<br>tubgroup = VaD.HR<br>total (common effect, 95% CI) 1.29 [1.11; 1.50]<br>etterogenety: Tar <sup>2</sup> = 0.01, df = 2 (P = 0.07); l <sup>2</sup> = 0.5%<br>tubgroup = VaD.HR<br>total (common effect, 95% CI) 1.36 [1.30; 1.87]<br>total (candom effect, 95% CI) 1.56 [1.30; 1.87]<br>total (candom effect, 95% CI) 1.56 [1.30; 1.67]<br>total (candom effect, 95% CI) 1.57 [1.36; 1.31]<br>total (candom effect, 95% CI) 1.52 [1.26; 1.84]<br>tetrogenety: Tar <sup>2</sup> = 0.050; l <sup>2</sup> = 2.95, df = 2.001; l <sup>2</sup> = 93%<br>tubgroup = Dementia.OR<br>tetrogenety: Tar <sup>2</sup> = 0.05% CI) 1.52 [1.26; 1.84]<br>total (candom effect, 95% CI) 1.52 [1.26; 1.84]<br>total (candom effect, 95% CI) 1.52 [1.26; 1.84]<br>tatl   | omata_2020  | 1.29                           | [1.11; 1.50]                  | +   |
| otal (random effect, 95% CI) 1.35 [1.26; 1.45]<br>eterogenety: Tau <sup>2</sup> = 0.0202: Ch <sup>2</sup> = 117.04, df = 29 ( $P < 0.01$ ); $l^2 = 75\%$<br>tubgroup = Cl/cognitive decline.HR<br>then, 2021 [1.42] [1.28; 1.58]<br>teroparticle of the second s  | /assilaki_2019  | 1.72                           | [1.20; 2.47]                  |   |
| eterogenethy: $Tau^2 = 0.0202$ : $Chi^2 = 117.04$ , $df = 29 (P < 0.01)$ ; $l^2 = 75%$<br>ubgroup = CUcognitive decline.HR<br>hen, 2021<br>(scher, 2016)<br>(scher, 2016)<br>(scher, 2016)<br>(scher, 2016)<br>(scher, 2017)<br>(scher, 2016)<br>(scher, 2016)<br>(scher, 2017)<br>(scher, 2016)<br>(scher, 2017)<br>(scher, 2016)<br>(scher, 2017)<br>(scher, 2016)<br>(scher, 2020)<br>(scher, 2021)<br>(scher, 2021)<br>(scher, 2021)<br>(scher, 2022)<br>(scher, 2021)<br>(scher, 2022)<br>(scher, 2021)<br>(scher, 2022)<br>(scher, 20  |   |                                |                               | 1   |
| ubgroup = Cl/cognitive decline.HR<br>hen_2021 142 [128; 158]<br>ischer_2016 150 [108; 4:91]<br>apa_2010 145 [108; 194]<br>in_2013 124 [104; 147]<br>isharan_2020 117 [109; 126]<br>chuber_2019 160 [0.94; 272]<br>inut_2020 117 [109; 126]<br>chuber_2019 160 [0.94; 272]<br>inut_2020 117 [120; 0.62; 202]<br>at [common effect, 95% CI] 1.25 [1:9; 1.31]<br>otal [common effect, 95% CI] 1.25 [1:9; 1.31]<br>otal [common effect, 95% CI] 1.25 [1:9; 1.31]<br>otal [common effect, 95% CI] 1.25 [1:17; 1.42]<br>eterogenety: Tau <sup>2</sup> = 0.000; Chr <sup>2</sup> = 16.98, df = 8 (P = 0.03); l <sup>2</sup> = 53%<br>ubgroup = MCLHR<br>eywood_2017 185 [0.78; 4.39]<br>itrut_2020 116 [0.67; 2.01]<br>otal [common effect, 95% CI] 1.29 [1:11; 1.50]<br>eterogenety: Tau <sup>2</sup> = 0.00; df = 2 (P = 0.67); l <sup>2</sup> = 0%<br>ubgroup = ADD.HR<br>obub_2017 185 [1.31; 2.62]<br>wang_2020 130 [0.92; 1.84]<br>itrut_2020 130 [0.92; 1.84]<br>itrut_2020 130 [0.92; 1.84]<br>itrut_2020 130 [0.92; 1.84]<br>itrut_2020 [1.0; 1.51]<br>otal [common effect, 95% CI] 1.56 [1.30; 1.87]<br>eterogenety: Tau <sup>2</sup> = 0.0; df = 3 (P = 0.57); l <sup>2</sup> = 0%<br>ubgroup = VaD.HR<br>otal [common effect, 95% CI] 1.56 [1.30; 1.87]<br>otal [common effect, 95% CI] 1.66 [1.16; 2.38]<br>otal [common effect, 95% CI] 1.30 [0.63; 2.05]<br>eterogenety: Tau <sup>2</sup> = 0.050; Chr <sup>2</sup> = 3.2, df = 2 (P = 0.07); l <sup>2</sup> = 37%<br>ubgroup = VaD.HR<br>otal [common effect, 95% CI] 1.40 [0.40; 1.81]<br>otal [common effect, 95% CI] 1.50 [0.88; 1.26]<br>iterogenety: Tau <sup>2</sup> = 0.050; Chr <sup>2</sup> = 3.2, df = 2 (P = 0.07); l <sup>2</sup> = 37%<br>ubgroup = Dementia.RR<br>eterogenety: Tau <sup>2</sup> = 0.070; Chr <sup>2</sup> = 2.75, df = 2 (P = 0.07); l <sup>2</sup> = 85%<br>ubgroup = Dementia.RR<br>eterogenety: Tau <sup>2</sup> = 0.070; Chr <sup>2</sup> = 2.75, df = 2 (P < 0.07); l <sup>2</sup> = 85%<br>ubgroup = Dementia.RR<br>eterogenety: Tau <sup>2</sup> = 0.070; Chr <sup>2</sup> = 3.2, 3.5, df = 4 (P < 0.07); l <sup>2</sup> = 85%<br>ubgroup = Dementia.RR<br>eterogenety: Tau <sup>2</sup> = 0.76; Chr <sup>2</sup> = 3.2, 3.5, df = 4 (P < 0.07); l <sup>2</sup> = 85%<br>ubgroup = Dementia.RR<br>eterogenety: Tau <sup>2</sup> = 0.76; Chr <sup>2</sup> = 3.2, 4.5, df = 4 (P < 0.07); l <sup>2</sup> = 85%  |   |                                |                               | 1   |
| hen. 2021 142 [128: 1.58]<br>ischer. 2016 190 [11: 3.26]<br>ischer. 2016 142 [1.08: 4.91]<br>anpa. 2010 145 [1.08: 1.94]<br>in. 2013 124 [1.04: 1.47]<br>italiarani. 2020 117 [1.09: 1.26]<br>chuberl. 2019 160 [0.94: 2.72]<br>ituit. 2020 112 [0.62: 2.02]<br>ai. 2021b 1.20 [1.17; 1.42]<br>eterogenety. Tau <sup>2</sup> = 0.007; Ch <sup>2</sup> = 16.98, df = 8 (P = 0.03); l <sup>2</sup> = 53%<br>ubgroup = MCLHR<br>eywood_2017 1.85 [0.78; 4.39]<br>tutt. 2020 1.16 [0.67; 2.01]<br>assikat_2019 1.29 [1.11; 1.50]<br>eterogenety. Tau <sup>2</sup> = 0.007; Ch <sup>2</sup> = 16.98, df = 8 (P = 0.03); l <sup>2</sup> = 53%<br>ubgroup = MCLHR<br>eywood_2017 1.85 [0.78; 4.39]<br>tutt. 2020 1.16 [0.67; 2.01]<br>assikat_2019 1.29 [1.11; 1.50]<br>eterogenety. Tau <sup>2</sup> = 0.051, df = 2 (P = 0.67); l <sup>2</sup> = 0%<br>ubgroup = ADD.HR<br>olub_2017 1.85 [1.31; 2.62]<br>wang_2020 1.30 [0.52; 1.84]<br>wang_2022 1.54 [1.04: 2.52]<br>otal (random effect, 95% CI) 1.56 [1.30; 1.87]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.56 [1.42; 1.72]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogenety: Tau <sup>2</sup> = 0.070; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Dementia.RR<br>teatogenety: Tau <sup>2</sup> = 0.070; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Dementia.RR<br>teatogenety: Tau <sup>2</sup> = 0.070; Ch <sup>2</sup> = 3   | teterogeneity: rau = 0.0202; Chi" = 117.  | u4, di = 29 (P <               | 0.01); 1 = 75%                |   |
| hen. 2021 142 [128: 1.58]<br>ischer. 2016 190 [11: 3.26]<br>ischer. 2016 142 [1.08: 4.91]<br>anpa. 2010 145 [1.08: 1.94]<br>in. 2013 124 [1.04: 1.47]<br>italiarani. 2020 117 [1.09: 1.26]<br>chuberl. 2019 160 [0.94: 2.72]<br>ituit. 2020 112 [0.62: 2.02]<br>ai. 2021b 1.20 [1.17; 1.42]<br>eterogenety. Tau <sup>2</sup> = 0.007; Ch <sup>2</sup> = 16.98, df = 8 (P = 0.03); l <sup>2</sup> = 53%<br>ubgroup = MCLHR<br>eywood_2017 1.85 [0.78; 4.39]<br>tutt. 2020 1.16 [0.67; 2.01]<br>assikat_2019 1.29 [1.11; 1.50]<br>eterogenety. Tau <sup>2</sup> = 0.007; Ch <sup>2</sup> = 16.98, df = 8 (P = 0.03); l <sup>2</sup> = 53%<br>ubgroup = MCLHR<br>eywood_2017 1.85 [0.78; 4.39]<br>tutt. 2020 1.16 [0.67; 2.01]<br>assikat_2019 1.29 [1.11; 1.50]<br>eterogenety. Tau <sup>2</sup> = 0.051, df = 2 (P = 0.67); l <sup>2</sup> = 0%<br>ubgroup = ADD.HR<br>olub_2017 1.85 [1.31; 2.62]<br>wang_2020 1.30 [0.52; 1.84]<br>wang_2022 1.54 [1.04: 2.52]<br>otal (random effect, 95% CI) 1.56 [1.30; 1.87]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.56 [1.42; 1.72]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogenety: Tau <sup>2</sup> = 0.070; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Dementia.RR<br>teatogenety: Tau <sup>2</sup> = 0.070; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Dementia.RR<br>teatogenety: Tau <sup>2</sup> = 0.070; Ch <sup>2</sup> = 3   | subgroup = CI/cognitive decline.HR  |                                |                               |   |
| ischer 2016 190 [1.11: 3.26]<br>ischer 2017 2.30 [1.68: 4.91]<br>anpa.2010 145 [1.08: 1.94]<br>in 2013 124 [1.04: 1.47]<br>tainsani 2020 1.17 [1.09: 1.26]<br>chubert_2019 1.60 [0.94: 2.72]<br>intuit 2020 1.12 [0.62: 2.02]<br>al 2021b 1.16 [1.02: 1.31]<br>otal (common effect, 95% CI) 1.25 [1.19: 1.31]<br>otal (common effect, 95% CI) 1.29 [1.17: 1.42]<br>tetrogenety: Tau" = 0.076; Ch" = 16.98, df = 8 (P = 0.03); P' = 53%<br>ubgroup = MCLHR<br>leywood_2017 1.85 [0.78; 4.39]<br>trutt_2020 1.16 [0.67; 2.01]<br>assilak_2019 0.Ch" = 16.98, df = 8 (P = 0.03); P' = 53%<br>ubgroup = MCLHR<br>leywood_2017 1.85 [0.78; 4.39]<br>trutt_2020 1.16 [0.67; 2.01]<br>assilak_2019 0.Ch" = 0.81, df = 2 (P = 0.67); P' = 0%<br>ubgroup = ADD.HR<br>blub_2017 1.85 [1.31; 2.62]<br>wang_2020 1.54 [1.09; 2.18]<br>wang_2020 1.54 [1.09; 2.18]<br>wang_2020 0.86 [0.46; 1.61]<br>wang_2020 0.86 [1.66; 1.36]<br>otal (common effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogenety: Tau" = 0, Ch" = 2.01, df = 2 (P = 0.57); P' = 0%<br>ubgroup = VaD.HR<br>blub_2017 1.84 [0.51; 3.51]<br>wang_2020 0.86 [1.46; 1.61]<br>otal (common effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogenety: Tau" = 0.069; Ch" = 3.2, df = 2 (P = 0.20); P' = 37%<br>ubgroup = Dementia.OR<br>aeson_Held_2023 2.33 [1.90; 2.86]<br>trewster_2021a 1.10 [0.90; 1.34]<br>yeon_2021 1.15 [0.33; 3.78]<br>otal (common effect, 95% CI) 1.52 [0.86; 2.70]<br>eterogenety: Tau" = 0.1927; Ch" = 32.95, df = 2 (P < 0.01); P' = 93%<br>ubgroup = Dementia.OR<br>aeson_Held_2023 2.37 [1.90; 2.86]<br>averncic 2022 2.87 [0.99; 8.34]<br>in 2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogenety: Tau" = 0.1927; Ch" = 32.95, df = 4 (P < 0.01); P' = 93%<br>ubgroup = Clrcognitive decline.OR<br>rewster_2021b [0.50; 1.42 [1.65; 1.81]<br>otal (common effect, 95% CI) 1.42 [1.65; 1.81]<br>averncic 2022 2.87 [0.99; 8.34]<br>in 2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.42 [1.65; 1.91]<br>eterogenety: Tau" = 0.1927; Ch" = 32.95, df = 4 (P < 0.01); P' = 93%<br>ubgroup = Dementia.RR<br>tead_2019 [1.52 [1.26; 1.84]<br>interogenety: Tau" = 0.1927; Ch" = 32.95, df = 4 (P < 0.01); P' = 38%<br>ubgrou   | Chen_2021   | 1.42                           | [1.28; 1.58]                  | ÷   |
| arpa_2010 1.45 [1.08: 1.94]<br>in_2013 1.24 [1.04: 1.47]<br>taharan_2020 1.17 [1.09: 1.26]<br>chubert_2019 1.60 [0.94: 2.72]<br>trutt_2020 1.12 [0.62: 2.02]<br>ai_2021b 1.16 [1.02: 1.31]<br>otal (common effect, 95% CI) 1.29 [1.17; 1.42]<br>terrogenery: Tau" = 0.070; Ch <sup>2</sup> = 16.98, dt = 8 (P = 0.03); t <sup>2</sup> = 53%<br>ubgroup = MCLHR<br>terrogenery: Tau" = 0.070; Ch <sup>2</sup> = 16.98, dt = 8 (P = 0.03); t <sup>2</sup> = 53%<br>ubgroup = MCLHR<br>terrogenery: Tau" = 0.070; Ch <sup>2</sup> = 16.98, dt = 8 (P = 0.03); t <sup>2</sup> = 53%<br>ubgroup = MCLHR<br>terrogenery: Tau" = 0.031, dt = 2 (P = 0.07); t <sup>2</sup> = 0%<br>ubgroup = ADD.HR<br>ioub_2017 1.85 [1.31; 2.62]<br>twang_2020 1.30 [0.92; 1.84]<br>wang_2020 1.30 [0.92; 1.84]<br>wang_2020 1.30 [0.92; 1.84]<br>wang_2020 1.30 [0.92; 1.84]<br>twang_2020 1.30 [0.92; 1.84]<br>ubgroup = ADD.HR<br>ioub_2017 1.85 [1.31; 2.62]<br>total (common effect, 95% CI) 1.56 [1.30; 1.87]<br>tetrogenery: Tau" = 0.Chi" = 2.01; dt = 2 (P = 0.57); t <sup>2</sup> = 0%<br>ubgroup = VaD.HR<br>ioub_2017 1.34 [0.51; 3.51]<br>wang_2020 0.86 [0.46; 1.61]<br>total (common effect, 95% CI) 1.56 [1.30; 1.87]<br>tetrogenery: Tau" = 0.069; Ch <sup>2</sup> = 2.07; dt = 2 (P = 0.20); t <sup>2</sup> = 37%<br>ubgroup = Dementia.OR<br>tetrogenery: Tau" = 0.069; Ch <sup>2</sup> = 3.2; dt = 2 (P = 0.07); t <sup>2</sup> = 0%<br>ubgroup = Dementia.OR<br>tetrogenery: Tau" = 0.069; Ch <sup>2</sup> = 3.2; dt = 2 (P < 0.01); t <sup>2</sup> = 93%<br>ubgroup = Clrcognitive decline.OR<br>terewster_2021a 1.10 [0.36; 1.26]<br>tetrogenery: Tau" = 0.1927; Ch <sup>2</sup> = 32.95, dt = 4 (P < 0.01); t <sup>2</sup> = 93%<br>ubgroup = Clrcognitive decline.OR<br>terewster_2021b 1.05 [0.88; 1.26]<br>tetrogenery: Tau" = 0.1927; Ch <sup>2</sup> = 32.95, dt = 4 (P < 0.01); t <sup>2</sup> = 93%<br>ubgroup = Clrcognitive decline.OR<br>terewster_2021b 1.05 [0.88; 1.26]<br>tetrogenery: Tau" = 0.1927; Ch <sup>2</sup> = 32.95, dt = 4 (P < 0.01); t <sup>2</sup> = 93%<br>ubgroup = Clrcognitive decline.OR<br>tetrogenery: Tau" = 0.1927; Ch <sup>2</sup> = 32.95, dt = 4 (P < 0.01); t <sup>2</sup> = 93%<br>ubgroup = Clrcognitive decline.OR<br>tetrogenery: Tau" = 0.1927; Ch <sup>2</sup> = 32.95, dt = 4 (P < 0.01); t <sup>2</sup> = 93%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.51]<br>total (common effect, 95% CI) 1.42 [1.05; 1.51]<br>to   | Fischer_2016  | 1.90                           | [1.11; 3.26]                  | - <del>-</del>                            |
| in $2013$ 1.24 [1.04; 1.47]<br>taharani.2020 1.17 [1.09; 1.26]<br>chuber.2019 1.60 [0.94; 2.72]<br>titutt.2020 1.12 [0.62; 2.02]<br>ai 2021b 1.16 [1.02; 1.31]<br>otal (common effect, 95% CI) 1.25 [1.19; 1.31]<br>otal (common effect, 95% CI) 1.29 [1.17; 1.42]<br>tetrospenty. Tau <sup>2</sup> = 0.070; Ch <sup>2</sup> = 16.98, df = 8 (P = 0.03); P <sup>2</sup> = 53%<br>ubgroup = MCLHR<br>teywood_2017 1.85 [0.78; 4.39]<br>titutt.2020 1.16 [0.67; 2.01]<br>assikat_2019 1.29 [1.10; 1.51]<br>otal (common effect, 95% CI) 1.29 [1.11; 1.50]<br>otal (common effect, 95% CI) 1.29 [1.11; 1.50]<br>otal (common effect, 95% CI) 1.29 [1.11; 1.50]<br>tetrospenty. Tau <sup>2</sup> = 0; Chi <sup>2</sup> = 0.81, df = 2 (P = 0.67); P <sup>2</sup> = 0%<br>ubgroup = ADD.HR<br>iolub_2017 1.85 [1.30; 1.87]<br>otal (common effect, 95% CI) 1.56 [1.30; 1.87]<br>otal (common effect, 95% CI) 1.56 [1.30; 1.87]<br>otal (common effect, 95% CI) 1.56 [1.30; 1.87]<br>otal (common effect, 95% CI) 1.66 [1.62; 2.88]<br>otal (common effect, 95% CI) 1.56 [1.30; 1.87]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.56 [1.42; 1.72]<br>tetrogenety: Tau <sup>2</sup> = 0.022; Ch <sup>2</sup> = 2.715, df = 2 (P < 0.01); P <sup>2</sup> = 93%<br>ubgroup = Clucognitive decline.OR<br>rewester 2021a 1.05 [0.88; 1.26]<br>tetrogenety: Tau <sup>2</sup> = 0.070; Ch <sup>2</sup> = 32.98, df = 4 (P < 0.01); P <sup>2</sup> = 83%<br>ubgroup = Dementia.RR<br>tead_2019 1.52 [1.26; 1.84]<br>atterogenety: Tau <sup>2</sup> = 0.075; Ch <sup>2</sup> = 32.98, df = 4 (P < 0.01); P <sup>2</sup> = 83%<br>ubgroup = Dementia.RR<br>tead_2019 1.52 [1.26; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.   |   |                                |                               |   |
| tability of the set o   |   |                                |                               |   |
| chuber 2019 1.60 $[0.94; 2.72]$<br>with 2020 1.12 $[0.62; 2.02]$<br>a) 2021b 1.16 $[1.02; 1.31]$<br>otal (random effect, 95% CI) 1.25 $[1.14; 1.42]$<br>eterogeneity: Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 16.98, df = 8 (P = 0.03); l <sup>2</sup> = 53%<br>ubgroup = MCI.HR<br>leywood_2017 1.85 $[0.78; 4.39]$<br>that 2020 1.16 $[0.67; 2.01]$<br>assikat_2019 1.29 $[1.10; 1.51]$<br>otal (random effect, 95% CI) 1.29 $[1.11; 1.50]$<br>otal (random effect, 95% CI) 1.29 $[1.11; 1.50]$<br>otal (random effect, 95% CI) 1.29 $[1.11; 1.50]$<br>eterogeneity: Tau <sup>2</sup> = 0.06; df = 0.67; l <sup>2</sup> = 0%<br>ubgroup = ADD.HR<br>iobub_2017 1.85 $[1.31; 2.62]$<br>wang_2020 1.54 $[1.09; 2.18]$<br>total (common effect, 95% CI) 1.56 $[1.30; 1.87]$<br>eterogeneity: Tau <sup>2</sup> = 0.06; df = 0.67); l <sup>2</sup> = 0%<br>ubgroup = VaD.HR<br>iobub_2017 1.84 $[0.51; 3.51]$<br>wang_2020 0.86 $[0.46; 1.61]$<br>wang_2020 0.86 $[0.46; 1.61]$<br>wang_2020 0.86 $[0.46; 1.61]$<br>into 1.30; 1.87]<br>eterogeneity: Tau <sup>2</sup> = 0.0696; Ch <sup>2</sup> = 3.2, df = 2 (P = 0.20); l <sup>2</sup> = 37%,<br>ubgroup = VaD.HR<br>iobub_2017 1.52 $[0.36; 2.70]$<br>eterogeneity: Tau <sup>2</sup> = 0.0696; Ch <sup>2</sup> = 3.2, df = 2 (P = 0.20); l <sup>2</sup> = 37%,<br>ubgroup = Dementia.OR<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 27; 15, df = 2 (P = 0.20); l <sup>2</sup> = 37%,<br>ubgroup = Clicognitive decline.OR<br>rewster_2021a 1.10 $[0.39; 3.38]$<br>otal (common effect, 95% CI) 1.52 $[0.86; 2.70]$<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32; df = 4 (P < 0.01); l <sup>2</sup> = 93%,<br>ubgroup = Clicognitive decline.OR<br>rewster_2021b $[1.52 [1.26; 1.81]$<br>otal (common effect, 95% CI) 1.45 $[1.42; 1.72]$<br>otal (common effect, 95% CI) 1.45 $[1.42; 1.72]$<br>otal (common effect, 95% CI) 1.46 $[1.42; 1.72]$<br>otal (common effect, 95% CI) 1.46 $[1.42; 1.72]$<br>otal (common effect, 95% CI) 1.42 $[1.05; 1.191]$<br>eterogeneity: Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 32.96, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>tead_2019 $[1.52 [1.26; 1.84]$<br>atterogeneity: Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 32.96, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>tead_2019 $[1.52 [1.26; 1.51]$<br>otal (common effect, 95% CI) 1.44 $[1.20; 1.73]$<br>otal (common effect, 95% C   |   |                                | [1.04; 1.47]                  |   |
| thut, 2020 1:12 [0.62; 2.02]<br>ai, 2021b 1:16 [1.02; 1.31]<br>otal (common effect, 95% CI) 1.25 [1.19; 1.31]<br>otal (random effect, 95% CI) 1.29 [1.17; 1.42]<br>terrogeneity: Tau" = 0.0076; Chi" = 16.98, df = 8 (P = 0.03); l" = 53%<br>ubgroup = MCLHR<br>terrogeneity: Tau" = 0.0076; Chi" = 15.98, df = 8 (P = 0.03); l" = 53%<br>ubgroup = MCLHR<br>terrogeneity: Tau" = 0.0076; Chi" = 12.9 [1.11; 1.50]<br>terrogeneity: Tau" = 0, Chi" = 0.61, df = 2 (P = 0.67); l" = 0%<br>ubgroup = ADD.HR<br>solub_2017 1.85 [1.31; 2.62]<br>twang_2020 1.30 [0.22; 1.84]<br>twang_2020 1.30 [0.22; 1.84]<br>twang_2020 1.30 [0.22; 1.84]<br>twang_2020 1.56 [1.30; 1.87]<br>otal (common effect, 95% CI) 1.50 [0.83; 2.05]<br>tetrogeneity: Tau" = 0.066; Chi" = 3.2; df = 2 (P = 0.20); l" = 37%<br>ubgroup = VaD.HR<br>otal (common effect, 95% CI) 1.40 [1.04; 1.89]<br>otal (common effect, 95% CI) 1.57 [0.36; 3.78]<br>otal (common effect, 95% CI) 1.57 [0.36; 3.78]<br>otal (common effect, 95% CI) 1.57 [0.36; 3.78]<br>otal (common effect, 95% CI) 1.57 [0.36; 2.70]<br>tetrogeneity: Tau" = 0.1927; Chi" = 22; 15, df = 2 (P < 0.01); l" = 93%<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.57 [0.36; 3.78]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>tetrogeneity: Tau" = 0.1927; Chi" = 32.95, df = 4 (P < 0.01); l" = 93%<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.05 [0.88; 1.26]<br>tetrogeneity: Tau" = 0.1927; Chi" = 32.95, df = 4 (P < 0.01); l" = 93%<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.05 [0.88; 1.26]<br>tetrogeneity: Tau" = 0.1927; Chi" = 32.95, df = 4 (P < 0.01); l" = 83%<br>ubgroup = Dementia.RR<br>tearogeneity: Tau" = 0.076; Chi" = 32.95, df = 4 (P < 0.01); l" = 83%<br>ubgroup = Dementia.RR<br>tearogeneity: Tau" = 0.076; Chi" = 32.95, df = 4 (P < 0   |   |                                |                               |   |
| ai $2021b$ 1.16 [1.02; 1.31]<br>otal (common effect, 95% CI) 1.25 [1.49; 1.31]<br>otal (random effect, 95% CI) 1.29 [1.47; 1.42]<br>eterogeneity: Tau <sup>2</sup> = 0.0076; Ch <sup>2</sup> = 16.98, df = 8 (P = 0.03; l <sup>2</sup> = 53%,<br>Ubgroup = MCI-HR<br>leywood 2017 1.85 [0.78; 4.39]<br>intit_2020 1.16 [0.67; 2.01]<br>assikat_2019 1.29 [1.10; 1.51]<br>otal (common effect, 95% CI) 1.29 [1.11; 1.50]<br>otal (common effect, 95% CI) 1.29 [1.11; 1.50]<br>eterogeneity: Tau <sup>2</sup> = 0, Ch <sup>2</sup> = 0.61, df = 2 (P = 0.67); l <sup>2</sup> = 0%<br>ubgroup = ADD.HR<br>blub_2017 1.85 [1.31; 2.62]<br>wang_2020 1.54 [1.09; 2.18]<br>total (common effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogeneity: Tau <sup>2</sup> = 0, Ch <sup>2</sup> = 2.01, df = 3 (P = 0.57); l <sup>2</sup> = 0%<br>ubgroup = ADD.HR<br>blub_2017 1.56 [1.30; 1.87]<br>eterogeneity: Tau <sup>2</sup> = 0, Ch <sup>2</sup> = 2.01, df = 3 (P = 0.57); l <sup>2</sup> = 0%<br>ubgroup = VaD.HR<br>blub_2017 1.34 [0.51; 3.51]<br>wang_2020 0.86 [0.46; 1.61]<br>wang_2020 0.86 [0.46; 1.61]<br>wang_2021 1.50 [0.33; 2.05]<br>eterogeneity: Tau <sup>2</sup> = 0.0696; Ch <sup>2</sup> = 3.2, df = 2 (P = 0.20); l <sup>2</sup> = 37%,<br>ubgroup = Dementia.OR<br>eason_Heid_2023 2.33 [1.90; 2.86]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.0192; Ch <sup>2</sup> = 27; 15, df = 2 (P < 0.01); l <sup>2</sup> = 93%,<br>ubgroup = Cl'cognitive decline.OR<br>rewster_2021b [0.65; 1.82]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 32.96, df = 4 (P < 0.01); l <sup>2</sup> = 83%,<br>ubgroup = Dementia.RR<br>etargoneity: Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 32.96, df = 4 (P < 0.01); l <sup>2</sup> = 83%,<br>ubgroup = Dementia.RR<br>etargoneity: Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 32.96, df = 4 (P < 0.01); l <sup>2</sup> = 83%,<br>ubgroup = Dementia.RR<br>etargoneity: Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 32.96, df = 4 (P < 0.01); l  | Strutt_2020   |                                |                               |   |
| otal (random effect, 95% CI) 1.29 $[1.17; 1.42]$<br>eterogenety: Tau <sup>2</sup> = 0.0076; Ch <sup>2</sup> = 16.98, df = 8 (P = 0.03); l <sup>2</sup> = 53%,<br>ubgroup = MCLHR<br>leywood 2017 1.85 $[0.78; 4.39]$<br>trutt 2020 1.16 $[0.67; 2.01]$<br>sasiaki_2019 1.129 $[1.10; 1.51]$<br>otal (common effect, 95% CI) 1.29 $[1.11; 1.50]$<br>otal (common effect, 95% CI) 1.29 $[1.11; 1.50]$<br>eterogenety: Tau <sup>2</sup> = 0.0:1, df = 2 (P = 0.67); l <sup>2</sup> = 0%<br>ubgroup = ADD.HR<br>iobub_2017 1.85 $[1.31; 2.62]$<br>wang_2022 1.54 $[1.09; 2.18]$<br>total (common effect, 95% CI) 1.56 $[1.30; 1.87]$<br>eterogenety: Tau <sup>2</sup> = 0.0:6; l = 2.0; l = 0.57); l <sup>2</sup> = 0%<br>ubgroup = VaD.HR<br>iobub_2017 1.84 $[0.51; 3.51]$<br>wang_2022 1.54 $[1.09; 2.18]$<br>total (common effect, 95% CI) 1.56 $[1.30; 1.87]$<br>eterogenety: Tau <sup>2</sup> = 0.0:60; ch <sup>2</sup> = 3.2, df = 2 (P = 0.20); l <sup>2</sup> = 37%<br>ubgroup = VaD.HR<br>iobub_2017 1.34 $[0.51; 3.51]$<br>wang_2020 0.86 $[0.46; 1.61]$<br>wang_2020 1.30 $[1.40; [1.44; 1.89]$<br>otal (cammon effect, 95% CI) 1.57 $[1.36; 1.81]$<br>otal (cammon effect, 95% CI) 1.50 $[0.88; 1.26]$<br>otal (cammon effect, 95% CI) 1.57 $[1.36; 1.81]$<br>otal (cammon effect, 95% CI) 1.48 $[1.42; 1.72]$<br>otal (cammon effect, 95% CI) 1.48 $[1.42; 1.72]$<br>otal (cammon effect, 95% CI) 1.48 $[1.42; 1.72]$<br>otal (cammon effect, 95% CI) 1.42 $[1.05; 1.91]$<br>eterogenety: Tau <sup>2</sup> = 0.070; Ch <sup>2</sup> = 32.96, df = 4 (P < 0.01); l <sup>2</sup> = 38%<br>ubgroup = Dementia.RR<br>tead_2019 $[1.52 [1.26; 1.84]$<br>otal (cammon effect, 95% CI) 1.44 $[1.20; 1.73]$<br>otal (cammon effect, 95% CI) 1.44 $[1.20; 1.73]$<br>otal (cammon effect, 95% CI) 1.44 $[1.20; 1.73]$   | ai_2021b  | 1.16                           |                               | -   |
| eterogenety: Tau <sup>2</sup> = 0.0076; Chi <sup>2</sup> = 16.98, dt = 8 (P = 0.03); l <sup>2</sup> = 53%<br>ubgroup = M0LHR<br>leywood 2017 1.85 [0.78; 4.39]<br>initial 2019 1.29 [1.10; 1.51]<br>otal (common effect, 95% Cl) 1.29 [1.11; 1.50]<br>eterogenety: Tau <sup>2</sup> = 0.05% Cl) 1.29 [1.11; 1.50]<br>eterogenety: Tau <sup>2</sup> = 0.05% Cl) 1.29 [1.11; 1.50]<br>eterogenety: Tau <sup>2</sup> = 0.05% Cl) 1.56 [1.30; 1.87]<br>otal (common effect, 95% Cl) 1.56 [1.30; 1.87]<br>otal (common effect, 95% Cl) 1.56 [1.30; 1.87]<br>otal (random effect, 95% Cl) 1.66 [1.30; 1.87]<br>otal (random effect, 95% Cl) 1.66 [1.30; 1.87]<br>eterogenety: Tau <sup>2</sup> = 0.06%; Ch <sup>2</sup> = 2.01, df = 2 (P = 0.07); l <sup>2</sup> = 0%<br>ubgroup = VaD.HR<br>blub_2017 1.34 [0.51; 3.51]<br>wang_2020 0.0.86 [0.46; 1.61]<br>otal (random effect, 95% Cl) 1.40 [1.44; 1.89]<br>otal (random effect, 95% Cl) 1.40 [1.44; 1.89]<br>otal (common effect, 95% Cl) 1.40 [1.44; 1.89]<br>otal (common effect, 95% Cl) 1.57 [1.36; 1.81]<br>otal (common effect, 95% Cl) 1.57 [1.36; 1.81]<br>otal (common effect, 95% Cl) 1.57 [1.36; 3.78]<br>otal (common effect, 95% Cl) 1.57 [1.36; 1.81]<br>otal (common effect, 95% Cl) 1.57 [1.36; 1.81]<br>otal (common effect, 95% Cl) 1.57 [1.36; 1.81]<br>otal (common effect, 95% Cl) 1.52 [0.68; 2.70]<br>eterogenety: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 27.15, df = 2 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b [1.50 [0.88; 1.26]<br>then_2019 [1.52 [1.26; 1.84]<br>averenc; 2022 2.87 [0.99; 8.34]<br>in 2004 [1.42; 1.72]<br>otal (random effect, 95% Cl) 1.42 [1.05; 1.91]<br>eterogenety: Tau <sup>2</sup> = 0.195% Cl) 1.42 [1.05; 1.91]<br>eterogenety: Tau <sup>2</sup> = 0.197; Chi <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 83%<br>ubgroup = Dementia.RR<br>tealogenetis, Tau <sup>2</sup> = 0.076; Chi <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 83%<br>ubgroup = Dementia.RR<br>tealogenetis, Tau <sup>2</sup> = 0.076; Chi <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 83%  | otal (common effect, 95% CI)  |                                |                               | •   |
| ubgroup = MCLHR<br>leywood_2017 1.85 [0.78:4.39]<br>tintl_2020 1.16 [0.67:2.01]<br>assikal_2019 1.29 [1.11:1.50]<br>otal (cammon effect, 95% CI) 1.29 [1.11:1.50]<br>eterogenety: Tau <sup>2</sup> = 0. Ch <sup>2</sup> = 0.81, df = 2 ( $P = 0.67$ ); $P^2 = 0\%$<br>ubgroup = ADD.HR<br>otal (cammon effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogenety: Tau <sup>2</sup> = 0. Ch <sup>2</sup> = 2.01, df = 2 ( $P = 0.67$ ); $P^2 = 0\%$<br>ubgroup = ADD.HR<br>otal (cammon effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogenety: Tau <sup>2</sup> = 0. Ch <sup>2</sup> = 2.01, df = 3 ( $P = 0.57$ ); $P^2 = 0\%$<br>ubgroup = VaD.HR<br>otal (cammon effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogenety: Tau <sup>2</sup> = 0. Ch <sup>2</sup> = 2.01, df = 3 ( $P = 0.57$ ); $P^2 = 0\%$<br>ubgroup = VaD.HR<br>otal (cammon effect, 95% CI) 1.40 [1.44; 1.88]<br>otal (cammon effect, 95% CI) 1.40 [1.44; 1.88]<br>otal (cammon effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (cammon effect, 95% CI) 1.52 [0.85; 2.70]<br>eterogenety: Tau <sup>2</sup> = 0.0996, Ch <sup>2</sup> = 3.2, df = 2 ( $P = 0.01$ ); $P^2 = 93\%$<br>ubgroup = Dementia.OR<br>eterogenety: Tau <sup>2</sup> = 0.0996, Ch <sup>2</sup> = 3.2, df = 2 ( $P < 0.01$ ); $P^2 = 93\%$<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.55 [0.85; 2.70]<br>eterogenety: Tau <sup>2</sup> = 0.095% CI) 1.42 [1.05; 1.81]<br>otal (cammon effect, 95% CI) 1.42 [1.05; 1.81]<br>otal (cammon effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogenety: Tau <sup>2</sup> = 0.070?, Ch <sup>2</sup> = 3.29.5, df = 4 ( $P < 0.01$ ); $P^2 = 93\%$<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.55 [1.85; 2.70]<br>otal (cammon effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogenety: Tau <sup>2</sup> = 0.070?, Ch <sup>2</sup> = 3.29.5, df = 4 ( $P < 0.01$ ); $P^2 = 38\%$<br>ubgroup = Dementia.RR<br>tead_2019 1.52 [1.26; 1.84]<br>attes_1996 0.82 [0.45; 1.51]<br>otal (cammon effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (cammon effect, 95% CI) 1.44 [1.20; 1.73]  | Total (random effect, 95% CI)   |                                | [1.17; 1.42]                  | •   |
| leywood 2017 1.85 [0.78; 4.39]<br>trut 2020 1.16 [0.67; 2.01]<br>assilak 2019 1.29 [1.10; 1.51]<br>otal (common effect, 95% CI) 1.29 [1.11; 1.50]<br>eterogeneity: Tau <sup>2</sup> = 0.61, df = 2 ( $P = 0.67$ ); $I^2 = 0\%$<br>ubgroup = ADD.HR<br>olub 2017 1.85 [1.31; 2.62]<br>wang_2020 1.30 [0.92; 1.84]<br>wang_2022 1.54 [1.09; 2.18]<br>total (common effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogeneity: Tau <sup>2</sup> = 0.0th <sup>2</sup> = 2.01, df = 3 ( $P = 0.57$ ); $I^2 = 0\%$<br>ubgroup = VaD.HR<br>olul (common effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogeneity: Tau <sup>2</sup> = 0.0th <sup>2</sup> = 2.01, df = 3 ( $P = 0.57$ ); $I^2 = 0\%$<br>ubgroup = VaD.HR<br>olul (common effect, 95% CI) 1.30 [0.43; 2.05]<br>eterogeneity: Tau <sup>2</sup> = 0.0th <sup>2</sup> = 2.01, df = 3 ( $P = 0.57$ ); $I^2 = 0\%$<br>ubgroup = VaD.HR<br>olul (common effect, 95% CI) 1.30 [0.43; 2.05]<br>eterogeneity: Tau <sup>2</sup> = 0.0506; Ch <sup>2</sup> = 3.2, df = 2 ( $P = 0.20$ ); $I^2 = 37\%$<br>ubgroup = Dementia.OR<br>eterogeneity: Tau <sup>2</sup> = 0.0596; Ch <sup>2</sup> = 3.2, df = 2 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Dementia.OR<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 27.15, df = 2 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Cl'cognitive decline.OR<br>rewster 2021b 1.05 [0.88; 1.26]<br>then 2019 1.90 [1.65; 1.81]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Cl'cognitive decline.OR<br>rewster 2021b 1.05 [0.88; 1.26]<br>then 2019 1.90 [1.66; 1.12]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Cl'cognitive decline.OR<br>rewster 2021b 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.075; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 83\%$<br>ubgroup = Dementia.RR<br>tealogeneity: Tau <sup>2</sup> = 0.075; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 83\%$<br>ubgroup = Dementia.RR<br>tealge_2019 1.52 [1.26; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.7  | Heterogeneity: Tau" = 0.0076; Chi" = 16.9   | 8, df = 8 (P = 0.0             | J3); 1° = 53%                 |   |
| leywood 2017 1.85 [0.78; 4.39]<br>trut 2020 1.16 [0.67; 2.01]<br>assilak 2019 1.29 [1.10; 1.51]<br>otal (common effect, 95% CI) 1.29 [1.11; 1.50]<br>eterogeneity: Tau <sup>2</sup> = 0.61, df = 2 ( $P = 0.67$ ); $I^2 = 0\%$<br>ubgroup = ADD.HR<br>olub 2017 1.85 [1.31; 2.62]<br>wang_2020 1.30 [0.92; 1.84]<br>wang_2022 1.54 [1.09; 2.18]<br>total (common effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogeneity: Tau <sup>2</sup> = 0.0th <sup>2</sup> = 2.01, df = 3 ( $P = 0.57$ ); $I^2 = 0\%$<br>ubgroup = VaD.HR<br>olul (common effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogeneity: Tau <sup>2</sup> = 0.0th <sup>2</sup> = 2.01, df = 3 ( $P = 0.57$ ); $I^2 = 0\%$<br>ubgroup = VaD.HR<br>olul (common effect, 95% CI) 1.30 [0.43; 2.05]<br>eterogeneity: Tau <sup>2</sup> = 0.0th <sup>2</sup> = 2.01, df = 3 ( $P = 0.57$ ); $I^2 = 0\%$<br>ubgroup = VaD.HR<br>olul (common effect, 95% CI) 1.30 [0.43; 2.05]<br>eterogeneity: Tau <sup>2</sup> = 0.0506; Ch <sup>2</sup> = 3.2, df = 2 ( $P = 0.20$ ); $I^2 = 37\%$<br>ubgroup = Dementia.OR<br>eterogeneity: Tau <sup>2</sup> = 0.0596; Ch <sup>2</sup> = 3.2, df = 2 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Dementia.OR<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 27.15, df = 2 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Cl'cognitive decline.OR<br>rewster 2021b 1.05 [0.88; 1.26]<br>then 2019 1.90 [1.65; 1.81]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Cl'cognitive decline.OR<br>rewster 2021b 1.05 [0.88; 1.26]<br>then 2019 1.90 [1.66; 1.12]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Cl'cognitive decline.OR<br>rewster 2021b 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.075; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 83\%$<br>ubgroup = Dementia.RR<br>tealogeneity: Tau <sup>2</sup> = 0.075; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 83\%$<br>ubgroup = Dementia.RR<br>tealge_2019 1.52 [1.26; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.7  | subgroup = MCI.HR   |                                |                               |   |
| assibility 2019 1.29 [1.10; 1.51]<br>otal (common effect, 95% CI) 1.29 [1.11; 1.50]<br>eterogeneity: Tau <sup>2</sup> = 0.81, df = 2 ( $P = 0.67$ ); $I^2 = 0\%$<br>ubgroup = ADD.HR<br>blub_2017 1.85 [1.31; 2.62]<br>wang_2020 1.30 [0.92; 1.84]<br>wang_2022 1.54 [1.09; 2.18]<br>total (common effect, 95% CI) 1.56 [1.30; 1.87]<br>otal (crandom effect, 95% CI) 1.30 [0.43; 2.05]<br>eterogeneity: Tau <sup>2</sup> = 0.069; Ch <sup>2</sup> = 3.2, df = 2 ( $P = 0.20$ ); $I^2 = 37\%$<br>ubgroup = VaD.HR<br>otal (common effect, 95% CI) 1.30 [0.43; 2.05]<br>eterogeneity: Tau <sup>2</sup> = 0.069; Ch <sup>2</sup> = 3.2, df = 2 ( $P = 0.20$ ); $I^2 = 37\%$<br>ubgroup = Dementia.OR<br>eterogeneity: Tau <sup>2</sup> = 0.195% CI) 1.52 [0.86; 2.70]<br>otal (common effect, 95% CI) 1.52 [0.86; 2.70]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 27:15, df = 2 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Cl'cognitive decline.OR<br>rewster 2021b 1.05 [0.88; 1.26]<br>then 2019 1.90 [1.69; 2.14]<br>in 2004 1.38 [0.99; 2.00]<br>otal (crandom effect, 95% CI) 1.42 [1.05; 1.31]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Cl'cognitive decline.OR<br>rewster 2021b 1.05 [0.88; 1.26]<br>then 2019 1.90 [1.69; 2.14]<br>in 2004 1.38 [0.99; 2.00]<br>otal (crandom effect, 95% CI) 1.42 [1.05; 1.31]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 83\%$<br>ubgroup = Cl'cognitive decline.OR<br>rewster 2021b 1.42 [1.05; 1.31]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 83\%$<br>ubgroup = Dementia.RR<br>tealogeneity: Tau <sup>2</sup> = 0.195% CI) 1.42 [1.26; 1.84]<br>atales_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [0.57; 2.16]  | Heywood_2017  | 1.85                           | [0.78; 4.39]                  | - <u>+</u>                                |
| otal (common effect, 95% CI) 1.29 [1.11; 1.50]<br>otal (radiom effect, 95% CI) 1.29 [1.11; 1.50]<br>eterogeneity: Tau <sup>2</sup> = 0, Ch <sup>2</sup> = 0.81, df = 2 (P = 0.67); I <sup>2</sup> = 0%<br>ubgroup = ADD.HR<br>otalb 2017 185 [1.31; 2.62]<br>twang_2020 1.30 [0.92; 1.84]<br>wang_2020 1.54 [1.09; 2.18]<br>otal (common effect, 95% CI) 1.56 [1.30; 1.87]<br>otal (common effect, 95% CI) 1.30 [0.83; 2.05]<br>eterogeneity: Tau <sup>2</sup> = 0.096; Ch <sup>2</sup> = 3.2, df = 2 (P = 0.20); I <sup>2</sup> = 37%<br>ubgroup = Dementia.OR<br>eason_Heid_2023 2.33 [1.90; 2.86]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.56 [1.42; 1.72]<br>eterogeneity: Tau <sup>2</sup> = 0.096; Ch <sup>2</sup> = 3.2, df = 2 (P < 0.01); I <sup>2</sup> = 93%<br>ubgroup = Dementia.OR<br>eason_Heid_2023 2.37 [1.90; 2.86]<br>total (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.56 [1.42; 1.72]<br>eterogeneity: Tau <sup>2</sup> = 0.152; Ch <sup>2</sup> = 3.29, df = 4 (P < 0.01); I <sup>2</sup> = 93%<br>ubgroup = D(Lognitive decline.OR<br>rewster_2021b 1.09 [0.65; 1.20]<br>otal (common effect, 95% CI) 1.56 [1.42; 1.72]<br>otal (common effect, 95% CI) 1.56 [1.42; 1.72]<br>otal (common effect, 95% CI) 1.56 [1.42; 1.72]<br>otal (common effect, 95% CI) 1.52 [1.26; 1.84]<br>atterogeneity: Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); I <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>tealcomentia: Check (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>ota   | Strutt_2020   |                                |                               | - <del></del>                             |
| otal (random effect, 95% CI) 1.29 [1.11; 1.50]<br>eterogenesity: Tau <sup>2</sup> = 0.81, df = 2 ( $P = 0.67$ ); $I^2 = 0\%$<br>ubgroup = ADD.HR<br>iolub 2017 1.85 [1.31; 2.62]<br>iwang_2020 1.30 [0.92; 1.84]<br>iwang_2022 1.54 [1.09; 2.18]<br>ionammed_2022 1.54 [1.09; 2.18]<br>ionammed_2022 1.54 [1.09; 2.18]<br>ionammed_2022 1.56 [1.30; 1.87]<br>eterogenesity: Tau <sup>2</sup> = 0.0th <sup>2</sup> = 2.01, df = 3 ( $P = 0.57$ ); $I^2 = 0\%$<br>ubgroup = VaD.HR<br>iolub_2017 1.34 [0.51; 3.51]<br>iwang_2020 0.86 [0.46; 1.61]<br>iwang_2020 0.86 [0.46; 1.61]<br>iwang_2020 0.86 [0.46; 1.61]<br>iwang_2020 0.86 [0.46; 1.61]<br>ivang_2020 0.86 [0.46; 1.61]<br>ivang_2020 0.86 [0.46; 1.61]<br>ivang_2020 0.86 [0.46; 1.61]<br>ivang_2020 0.86 [0.46; 1.61]<br>ivang_2021 1.30 [0.83; 2.05]<br>eterogenesity: Tau <sup>2</sup> = 0.0696; Ch <sup>2</sup> = 3.2, df = 2 ( $P = 0.20$ ); $I^2 = 37\%$<br>ubgroup = Dementia.OR<br>eterogenesity: Tau <sup>2</sup> = 0.0696; Ch <sup>2</sup> = 3.2, df = 2 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Cl'cognitive decline.OR<br>rewster_2021b 1.52 [0.36; 2.70]<br>eterogenesity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Cl'cognitive decline.OR<br>rewster_2021b 1.05 [0.88; 1.26]<br>iterogenesity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 93\%$<br>ubgroup = Cl'cognitive decline.OR<br>rewster_2021b 1.35 [0.56; 1.82]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogenesity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ); $I^2 = 83\%$<br>ubgroup = Dementia.RR<br>tead_2019 1.52 [1.26; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [1.65; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [0.57; 2.16]   |   |                                |                               | 11  |
| eterogenety: $Tau^2 = 0$ ; $Cht^2 = 0.81$ , $df = 2$ ( $P = 0.67$ ); $P^2 = 0\%$<br>ubgroup = ADD.HR<br>biolub_2017 1.85 [1.31; 2.62]<br>wang_2020 1.30 [0.92; 1.84]<br>wang_2022 1.54 [1.04; 2.52]<br>otal (common effect, 95% CI) 1.56 [1.30; 1.87]<br>otal (common effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogenety: $Tau^2 = 0$ , $Cht^2 = 2.01$ , $df = 3$ ( $P = 0.57$ ); $P^2 = 0\%$<br>ubgroup = VaD.HR<br>olub_2017 1.34 [0.51; 3.51]<br>otal (common effect, 95% CI) 1.40 [1.04; 1.89]<br>otal (common effect, 95% CI) 1.40 [1.04; 1.89]<br>otal (common effect, 95% CI) 1.40 [1.04; 1.89]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.57 [0.36; 2.70]<br>eterogenety: $Tau^2 = 0.099$ ; $Cht^2 = 32$ , $df = 2$ ( $P = 0.20$ ); $P^2 = 37\%$<br>ubgroup = Dementia.OR<br>eason_Heid_2023 2.33 [1.90; 2.86]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.56 [1.42; 2.72]<br>eterogenety: $Tau^2 = 0.1927$ ; $Cht^2 = 32.95$ , $df = 4$ ( $P < 0.01$ ); $P^2 = 93\%$<br>ubgroup = Clicognitive decline.OR<br>rewster_2021b 1.09 [0.66; 1.26]<br>then_2019 1.09 [0.66; 1.26]<br>then_2019 1.95 [1.26; 1.84]<br>averncic_2022 2.87 [0.99; 8.34]<br>or 204 3.38 [0.59; 2.00]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogenety: $Tau^2 = 0.0767$ ; $Cht^2 = 32.95$ , $df = 4$ ( $P < 0.01$ ); $P^2 = 83\%$<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>attes_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]  |   |                                |                               | I   |
| ubgroup = ADD.HR<br>joiub_2017 1.85 [1.31; 2.62]<br>joiub_2017 1.85 [1.31; 2.62]<br>joint_2020 1.30 [0.92; 1.84]<br>juang_2020 1.54 [1.09; 2.18]<br>joint (common effect, 95% CI) 1.56 [1.30; 1.87]<br>otal (common effect, 95% CI) 1.56 [1.30; 1.87]<br>ubgroup = VaD.HR<br>joiub_2017 1.34 [0.51; 3.51]<br>juang_2020 0.86 [0.46; 1.61]<br>juang_2020 0.83; 2.05]<br>elerogenety; Tau <sup>2</sup> = 0.096; Ch <sup>2</sup> = 3.2, df = 2 (P = 0.20); l <sup>2</sup> = 37%<br>ubgroup = Dementia.OR<br>eason_Held_2023 2.33 [1.90; 2.86]<br>juang_2016 1.09 [0.66; 1.82]<br>juang_2016 1.42; [1.05; 1.91]<br>elerogenety; Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 93%,<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b [1.52 [1.26; 1.84]<br>juang_2016 1.09 [0.65; 1.82]<br>juang_2016 1.42; [1.05; 1.91]<br>elerogenety; Tau <sup>2</sup> = 0.0767; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 83%<br>ubgroup = Dementia.RR<br>lead_2019 [1.52 [1.26; 1.84]<br>juang_2019 [1.52 [1.26; 1.84]<br>juang_2019 [1.52 [1.26; 1.51]<br>juang_2016 [1.62]<br>juang_2016 [1.62]<br>j   | Heterogeneity: $Tau^2 = 0$ ; $Chi^2 = 0.81$ , df = 1                                      | 2 (P = 0.67); I <sup>2</sup> = | = 0%                          | T   |
| biolub_2017 1.85 [1.31; 2.62]<br>wang_2020 1.30 [0.52; 1.84]<br>wang_2022 1.54 [1.09; 2.18]<br>tohammed_2022 1.54 [1.09; 2.18]<br>tohammed_2022 1.56 [1.30; 1.87]<br>otal (common effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogeneity: Tau" = 0. Chi" = 2.01, df = 3 ( $P = 0.57$ ); $f^2 = 0\%$<br>ubgroup = VaD.HR<br>biolub_2017 1.34 [0.51; 3.51]<br>wang_2020 0.86 [0.46; 1.61]<br>wang_2020 0.86 [0.46; 1.61]<br>wang_2020 0.86 [0.46; 1.61]<br>wang_2020 0.86 [0.46; 1.61]<br>otal (common effect, 95% CI) 1.40 [1.44; 1.89]<br>otal (common effect, 95% CI) 1.30 [0.83; 2.05]<br>eterogeneity: Tau" = 0.066; Chi" = 3.2, df = 2 ( $P = 0.20$ ); $f^2 = 37\%$<br>ubgroup = Domentia.OR<br>eason_Hold_2023 2.33 [1.90; 2.86]<br>rewster_2021a 1.10 [0.90; 1.34]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.52 [0.36; 2.70]<br>eterogeneity: Tau" = 0.1927; Chi" = 27.15, df = 2 ( $P < 0.01$ ); $f^2 = 93\%$<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.05 [0.88; 1.26]<br>then_2019 1.90 [1.66; 1.82]<br>averenc; 2022 2.87 [0.99; 8.34]<br>in 2004 1.38 [0.99; 8.00]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau" = 0.0767; Chi" = 32.95, df = 4 ( $P < 0.01$ ); $f^2 = 83\%$<br>ubgroup = Dementia.RR<br>teatogeneits, Tau" = 0.0767; Chi" = 32.95, df = 4 ( $P < 0.01$ ); $f^2 = 83\%$<br>ubgroup = Dementia.RR<br>teatogeneits, Tau" = 0.0767; Chi" = 32.95, df = 4 ( $P < 0.01$ ); $f^2 = 83\%$  |   |                                |                               |   |
| $\begin{aligned} & \text{vang} (2020) & 1.30 & [0.92; 1.84] \\ & \text{vang} (2022) & 1.54 & [1.04; 2.52] \\ & \text{toharmed} (2022) & 1.62 & [1.04; 2.52] \\ & \text{total (common effect, 95% CI)} & 1.56 & [1.30; 1.87] \\ & \text{eterogeneity: Tau" = 0. Chr2 = 2.01, df = 3 (P = 0.57); I2 = 0% \\ & \text{ubgroup = VaD.HR} \\ & \text{olub} (2017) & 1.34 & [0.51; 3.51] \\ & \text{wang} (2020) & 0.86 & [0.46; 1.61] \\ & \text{wang} (2022) & 1.66 & [1.16; 2.38] \\ & \text{otal (common effect, 95% CI)} & 1.40 & [1.04; 1.89] \\ & \text{otal (common effect, 95% CI)} & 1.40 & [1.04; 1.89] \\ & \text{otal (common effect, 95\% CI)} & 1.30 & [0.33; 2.05] \\ & \text{eterogeneity: Tau" = 0.0696; Chr2 = 3.2, df = 2 (P = 0.20); I2 = 37% \\ & \text{ubgroup = Dementia.OR} \\ & \text{eason} (Hed (2023) & 2.33 & [1.90; 2.86] \\ & \text{otal (common effect, 95\% CI)} & 1.57 & [1.36; 1.81] \\ & \text{otal (common effect, 95\% CI)} & 1.52 & [0.86; 2.70] \\ & \text{eterogeneity: Tau" = 0.1927; Chr2 = 27.15, df = 2 (P < 0.01); I2 = 93\% \\ & \text{ubgroup = Cl'cognitive decline.OR} \\ & \text{rewster} (2021) & 1.90 & [0.66; 1.82] \\ & \text{varrencic} (2022) & 2.87 & [0.99; 8.34] \\ & \text{ing adom of fect, 95\% CI)} & 1.52 & [1.26; 1.81] \\ & \text{otal (common effect, 95\% CI)} & 1.43 & [1.05; 1.91] \\ & \text{eterogeneity: Tau" = 0.0767; Chr2 = 32.95, df = 4 (P < 0.01); I2 = 88\% \\ \\ & \text{ubgroup = Dementia.RR} \\ & \text{talegrouneity: Tau" = 0.0767; Chr2 = 32.95, Chr = 4 (P < 0.01); I2 = 88\% \\ \\ & \text{ubgroup = Dementia.RR} \\ & \text{talegrouneity: Tau" = 0.0767; Chr2 = 32.95, Chr = 4 (P < 0.01); I2 = 88\% \\ \\ & \text{ubgroup = Dementia.RR} \\ & \text{talegrouneity: Tau" = 0.0767; Chr2 = 32.95, Chr = 4 (P < 0.01); I2 = 88\% \\ \\ & \text{ubgroup = Dementia.RR} \\ & \text{talegrouneity: Tau" = 0.0767; Chr = 32.95, Chr = 4 (P < 0.01); I2 = 88\% \\ \\ & \text{ubgroup = Dementia.RR} \\ & \text{talegrouneity: Tau" = 0.0767; Chr = 32.95, Chr = 4 (P < 0.01); I2 = 88\% \\ \\ & \text{ubgroup = Dementia.RR} \\ & \text{talegrouneity: Tau" = 0.0767; Chr = 32.95, Chr = 4 (P < 0.01); I2 = 88\% \\ \\ & \text{ubgroup = Dementia.RR} \\ & talegrouneity: Tau" = 0.0767; Chr = 32.95, Chr = 4 (P < 0.01); I2 = 88\% $  |   | 1 95                           | [4 24: 2 62]                  |   |
| $\begin{aligned} & \text{van}_{2} 2022 & 1.54 & [1.09; 2.18] \\ & \text{toharmed}_{2} 2022 & 1.62 & [1.04; 2.52] \\ & \text{otal} (common effect, 95\% CI) & 1.56 & [1.30; 1.87] \\ & \text{otal} (random effect, 95\% CI) & 1.56 & [1.30; 1.87] \\ & \text{ubgroup} = VaD.HR \\ & \text{olub}_{2} 2017 & 1.34 & [0.51; 3.51] \\ & \text{wan}_{2} 2020 & 0.86 & [0.46; 1.61] \\ & \text{wan}_{2} 2020 & 0.86 & [1.16; 2.38] \\ & \text{otal} (common effect, 95\% CI) & 1.30 & [0.43; 2.05] \\ & \text{eterogeneity} \cdot Tau' = 0.066; Ch' = 2.(P = 0.20); l' = 37\% \\ & \text{ubgroup} = Dementia.OR \\ & \text{eason}_{1} Hed _{2} 2023 & [1.57 & [1.36; 1.81] \\ & \text{otal} (common effect, 95\% CI) & 1.57 & [1.36; 1.81] \\ & \text{otal} (common effect, 95\% CI) & 1.57 & [1.36; 1.81] \\ & \text{otal} (common effect, 95\% CI) & 1.57 & [1.36; 1.81] \\ & \text{otal} (common effect, 95\% CI) & 1.57 & [1.36; 1.81] \\ & \text{otal} (common effect, 95\% CI) & 1.57 & [1.36; 1.81] \\ & \text{otal} (common effect, 95\% CI) & 1.57 & [1.36; 1.26] \\ & \text{otal} (common effect, 95\% CI) & 1.57 & [1.36; 1.26] \\ & \text{otal} (common effect, 95\% CI) & 1.56 & [1.42; 1.72] \\ & \text{otal} (common effect, 95\% CI) & 1.56 & [1.42; 1.72] \\ & \text{otal} (common effect, 95\% CI) & 1.42 & [1.05; 1.84] \\ & \text{averenc}_{2} 2022 & 2.87 & [0.99; 8.34] \\ & \text{in}_{2} 2004 & [1.38 & [0.95; 2.00] \\ & \text{otal} (common effect, 95\% CI) & 1.42 & [1.05; 1.81] \\ & \text{eterogeneity} Tau' = 0.0767; Ch' = 32.95, dt = 4 (P < 0.01); t' = 83\% \\ \\ & \text{ubgroup} = Dementia.RR \\ & \text{teatogeneity} Tau' = 0.0767; Ch' = 32.95, dt = 4 (P < 0.01); t' = 83\% \\ & \text{ubgroup} = Dementia.RR \\ & \text{teatogeneit}_{1} Tau' = 0.0767; Ch' = 32.95, dt = 4 (P < 0.01); t' = 83\% \\ & \text{ubgroup} = Dementia.RR \\ & \text{teatogeneit}_{2} Tau' = 0.0767; Ch' = 32.95, dt = 4 (P < 0.01); t' = 83\% \\ & \text{ubgroup} = Dementia.RR \\ & \text{teatogeneit}_{2} Tau' = 0.0767; Ch' = 32.95, dt = 4 (P < 0.01); t' = 83\% \\ & \text{ubgroup} = Dementia.RR \\ & \text{teatogeneit}_{2} Tau' = 0.0767; Ch' = 32.95, dt = 4 (P < 0.01); t' = 83\% \\ & \text{ubgroup} = Dementia.RR \\ & \text{tal} (condom effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{tal} (condom effect, 95\% CI) & 1.44 & [1.20; 1.73$  |   |                                |                               |   |
| tohammed_2022<br>total (common effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogenety: Tau <sup>2</sup> = 0.06; 2.01, df = 3 (P = 0.57); I <sup>2</sup> = 0%<br>ubgroup = VaD.HR<br>total (common effect, 95% CI) 1.40 [1.44; 1.85]<br>total (common effect, 95% CI) 1.40 [1.44; 1.85]<br>total (common effect, 95% CI) 1.40 [1.44; 1.85]<br>total (common effect, 95% CI) 1.40 [1.04; 1.85]<br>total (common effect, 95% CI) 1.40 [1.04; 1.85]<br>total (common effect, 95% CI) 1.57 [1.36; 1.81]<br>total (common effect, 95% CI) 1.52 [0.86; 2.70]<br>eterogenety: Tau <sup>2</sup> = 0.066; Ch <sup>2</sup> = 3.2; 1.52 [0.86; 2.70]<br>eterogenety: Tau <sup>2</sup> = 0.056; Ch <sup>2</sup> = 3.2; 1.52 [0.86; 2.70]<br>eterogenety: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 27; 15, df = 2 (P < 0.01); I <sup>2</sup> = 93%<br>ubgroup = Cl'cognitive decline.OR<br>rewster_2021b 1.95 [0.86; 1.26]<br>total (common effect, 95% CI) 1.52 [0.86; 2.70]<br>eterogenety: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32; 15, df = 2 (P < 0.01); I <sup>2</sup> = 93%<br>ubgroup = Cl'cognitive decline.OR<br>rewster_2021b 1.05 [0.88; 1.26]<br>then_2019 1.90 [1.69; 1.42]<br>avrencic_2022 2.87 [0.98; 8.34]<br>in_2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.52 [1.26; 1.81]<br>otal (common effect, 95% CI) 1.52 [1.26; 1.84]<br>aterogenety: Tau <sup>2</sup> = 0.075; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); I <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>total (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common e   |   |                                |                               |   |
| otal (common effect, 95% CI) 1.56 [1.30; 1.87]<br>otal (random effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogeneity: Tau <sup>2</sup> = 0, Ch <sup>2</sup> = 2.01, df = 3 (P = 0.57); l <sup>2</sup> = 0%<br>ubgroup = VaD.HR<br>olub_2017 1.34 [0.51; 3.51]<br>wang_2020 0.86 [0.46; 1.61]<br>otal (common effect, 95% CI) 1.40 [1.44; 1.89]<br>otal (common effect, 95% CI) 1.30 [0.83; 2.05]<br>eterogeneity: Tau <sup>2</sup> = 0.696; Ch <sup>2</sup> = 3.2, df = 2 (P = 0.20); l <sup>2</sup> = 37%<br>ubgroup = Dementia.OR<br>eason_Held_2023 2.33 [1.90; 2.86]<br>rewster_2021a 1.10 [0.96; 2.76]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.52 [0.66; 2.70]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 27.15, df = 2 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.90 [1.68; 2.14]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 83%<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.95 [1.62; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.0767; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 83%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>aterogeneity: Tau <sup>2</sup> = 0.0767; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 83%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44  |   |                                |                               |   |
| otal (random effect, 95% CI) 1.56 [1.30; 1.87]<br>eterogenety: Tau <sup>2</sup> = 0.201, df = 3 (P = 0.57); I <sup>2</sup> = 0%<br>ubgroup = VaD.HR<br>iolub 2017 1.34 [0.51; 3.51]<br>iwang_2020 0.86 [0.46; 1.61]<br>iwang_2020 0.95% CI) 1.56 [1.42; 1.72]<br>iwang_2020 0.82 [0.45; 1.51]<br>iwang_2020 0.82 [0.4   | otal (common effect, 95% CI)  |                                |                               |   |
| ubgroup = VaD.HR<br>joidub_2017 1.34 [0.51; 3.51]<br>wang_2020 0.86 [0.46; 1.61]<br>wang_2022 1.66 [1.16; 2.38]<br>otal (common effect, 95% CI) 1.40 [1.04; 1.89]<br>otal (random effect, 95% CI) 1.30 [0.83; 2.05]<br>eterogenety: Tau <sup>2</sup> = 0.0696. Ch <sup>2</sup> = 3.2, df = 2 (P < 0.20); l <sup>2</sup> = 37%<br>ubgroup = Dementia.OR<br>eason_Heid_2023 2.33 [1.90; 2.86]<br>rewster_2021a 1.10 [0.90; 1.34]<br>yeon_2021 1.15 [0.35; 3.78]<br>otal (common effect, 95% CI) 1.52 [0.86; 2.70]<br>eterogenety: Tau <sup>2</sup> = 0.1927, Ch <sup>2</sup> = 27.15, df = 2 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.05 [0.88; 1.26]<br>then_2019 1.90 [1.65; 1.82]<br>avrencic 2022 2.87 [0.99: 8.34]<br>in_2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogenety: Tau <sup>2</sup> = 0.077; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [1.26; 1.51]<br>otal (common effect, 95% CI) 1.42 [1.26; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [0.67; 2.16]   | otal (random effect, 95% CI)  |                                | [1.30; 1.87]                  | -   |
| bolub_2017 1.34 [0.51; 3.51]<br>wang_2020 0.86 [0.46; 1.61]<br>wang_2022 1.66 [1.16; 2.38]<br>otal (common effect, 95% CI) 1.40 [1.04; 1.89]<br>otal (random offect, 95% CI) 1.30 [0.83; 2.05]<br>eterogenety: $Tau^2 = 0.096$ ; $Ch^2 = 3.2$ , $df = 2$ ( $P = 0.20$ ); $l^2 = 3.7\%$<br>ubgroup = Dementia.OR<br>eason_Held_2023 2.33 [1.90; 2.86]<br>rewster_2021a 1.15 [0.35; 3.78]<br>otal (common effect, 95% CI) 1.52 [0.86; 2.70]<br>eterogenety: $Tau^2 = 0.1927$ ; $Ch^2 = 27.15$ , $df = 2$ ( $P < 0.01$ ); $l^2 = 93\%$<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.05 [0.88; 1.26]<br>then_2019 1.90 [1.66; 1.82]<br>avrencic_2022 2.87 [0.99; 8.34]<br>in_2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogenety: $Tau^2 = 0.0757$ ; $Ch^2 = 32.95$ , $df = 4$ ( $P < 0.01$ ); $l^2 = 88\%$<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [1.65; 1.91]<br>eterogenety: Tau' = 0.0757; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ; $l^2 = 88\%$<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.42 [1.20; 7:71]<br>otal (common effect, 95% CI) 1.42 [0.67; 2.16]  | leterogeneity: Tau <sup>2</sup> = 0; Chi <sup>2</sup> = 2.01, df =                        | 3 (P = 0.57); I <sup>2</sup> = | = 0%                          |   |
| bolub_2017 1.34 [0.51; 3.51]<br>wang_2020 0.86 [0.46; 1.61]<br>wang_2022 1.66 [1.16; 2.38]<br>otal (common effect, 95% CI) 1.40 [1.04; 1.89]<br>otal (random offect, 95% CI) 1.30 [0.83; 2.05]<br>eterogenety: $Tau^2 = 0.096$ ; $Ch^2 = 3.2$ , $df = 2$ ( $P = 0.20$ ); $l^2 = 3.7\%$<br>ubgroup = Dementia.OR<br>eason_Held_2023 2.33 [1.90; 2.86]<br>rewster_2021a 1.15 [0.35; 3.78]<br>otal (common effect, 95% CI) 1.52 [0.86; 2.70]<br>eterogenety: $Tau^2 = 0.1927$ ; $Ch^2 = 27.15$ , $df = 2$ ( $P < 0.01$ ); $l^2 = 93\%$<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.05 [0.88; 1.26]<br>then_2019 1.90 [1.66; 1.82]<br>avrencic_2022 2.87 [0.99; 8.34]<br>in_2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogenety: $Tau^2 = 0.0757$ ; $Ch^2 = 32.95$ , $df = 4$ ( $P < 0.01$ ); $l^2 = 88\%$<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [1.65; 1.91]<br>eterogenety: Tau' = 0.0757; Ch <sup>2</sup> = 32.95, df = 4 ( $P < 0.01$ ; $l^2 = 88\%$<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.42 [1.20; 7:71]<br>otal (common effect, 95% CI) 1.42 [0.67; 2.16]  | ubgroup = VaD.HR  |                                |                               |   |
| $\begin{aligned} & \text{wang} (2020) & 0.86 & [0.46; 1.61] \\ & \text{wang} (2022) & 1.66 & [1.16; 2.38] \\ & \text{otal} (common effect, 95\% CI) & 1.40 & [1.04; 1.89] \\ & \text{otal} (random effect, 95\% CI) & 1.30 & [0.83; 2.05] \\ & \text{eterogeneity} : Tau' = 0.0996, Chi2 = 3.2, df = 2 (P = 0.20); I' = 37\% \\ & \text{ubgroup = Dementia.OR} \\ & \text{eason_Heid} (2023) & 2.33 & [1.90; 2.86] \\ & \text{rewster} (2021a) & 1.10 & [0.90; 1.34] \\ & \text{yeon} (2021a) & 1.15 & [0.35; 3.78] \\ & \text{otal} (common effect, 95\% CI) & 1.57 & [1.36; 1.81] \\ & \text{otal} (common effect, 95\% CI) & 1.57 & [1.36; 1.81] \\ & \text{otal} (common effect, 95\% CI) & 1.52 & [0.36; 2.70] \\ & \text{eterogeneity} : Tau' = 0.1927, Chi^2 = 27.15, df = 2 (P < 0.01); I' = 93\% \\ & \text{ubgroup = Clicognitive decline.OR} \\ & \text{rewster} (2021b) & 1.90 & [1.65; 1.82] \\ & \text{averencic} (2022) & 2.87 & [0.99; 8.34] \\ & \text{ing} (2016) & 1.09 & [0.65; 1.82] \\ & \text{averencic} (2022) & 2.87 & [0.99; 8.34] \\ & \text{otal} (common effect, 95\% CI) & 1.52 & [1.26; 1.84] \\ & \text{otal} (random effect, 95\% CI) & 1.52 & [1.26; 1.84] \\ & \text{otal} (common effect, 95\% CI) & 1.52 & [1.26; 1.84] \\ & \text{atgeroup = Dementia.RR} \\ \\ & \text{tealgroup = Dementia.RR} \\ \\ & \text{talges} (1996) & 0.82 & [0.45; 1.51] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & 1.44 & [1.20; 1.73] \\ & \text{otal} (common effect, 95\% CI) & $   | Solub_2017  |                                | [0.51; 3.51]                  |   |
| wang_2022   1.66   [1.6; 2.38]     otal (common effect, 95% CI)   1.40   [1.44; 1.89]     otal (random effect, 95% CI)   1.30   [0.83; 2.05]     eterogeneity: Tau <sup>2</sup> = 0.0696; Ch <sup>2</sup> = 3.2, df = 2 (P = 0.20; l <sup>2</sup> = 3.7%   Ubgroup = Domentia.OR     eason_Held_2023   2.33   [1.90; 2.86]     rewster_2021a   1.10   [0.33; 3.78]     otal (common effect, 95% CI)   1.57   [0.36; 2.70]     otal (common effect, 95% CI)   1.57   [0.36; 2.70]     otal (common effect, 95% CI)   1.50   [0.88; 1.26]     otal (common effect, 95% CI)   1.05   [0.88; 1.26]     then, 2019   1.90   [1.66; 1.82]     otal (common effect, 95% CI)   1.42   [1.05; 1.91]     eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 93%.   Ubgroup = Cl/cognitive decline.OR     rewster_2018   1.05   [0.88; 1.26]   ####################################   | lwang_2020  |                                | [0.46; 1.61]                  |   |
| otal (random effect, 95% CI) 1.30 [0.83; 2.05]<br>eterogeneity: Tau <sup>2</sup> = 0.0696; Ch <sup>2</sup> = 3.2, df = 2 (P = 0.20); l <sup>2</sup> = 3.7%<br>ubgroup = Dementia.OR<br>eeson_Heid 2023 2.33 [1.90; 2.86]<br>rewster 2021a 1.10 [0.90; 1.34]<br>yeon_2021 1.15 [0.35; 3.78]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.52 [0.86; 2.70]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 27.15, df = 2 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Cl/cognitive decline.OR<br>rewster 2021b 1.05 [0.88; 1.26]<br>then 2019 1.90 [1.66; 1.82]<br>avrencic 2022 2.87 [0.99: 8.34]<br>in 2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.075; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.42 [1.26; 7.21]  | lwang_2022  |                                |                               | 1.  |
| eterogeneity: Tau <sup>2</sup> = 0.0696; Chi <sup>2</sup> = 3.2, df = 2 (P = 0.20); l <sup>2</sup> = 37%<br>ubgroup = Dementia.OR<br>eason_Held_2023 2.33 [1.90; 2.86]<br>rewster_2021a 1.10 [0.90; 1.34]<br>yeon_2021 1.15 [0.36; 3.78]<br>otal (common effect, 95% Cl) 1.57 [1.36; 1.81]<br>otal (random effect, 95% Cl) 1.52 [0.36; 2.70]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Chi <sup>2</sup> = 27.15, df = 2 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.95 [0.88; 1.26]<br>hem_2019 1.90 [0.65; 1.82]<br>avrencic_2022 2.87 [0.99; 8.34]<br>in; 2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% Cl) 1.56 [1.42; 1.72]<br>otal (random effect, 95% Cl) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.0767; Chi <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ates 1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% Cl) 1.44 [1.20; 1.73]<br>otal (common effect, 95% Cl) 1.44 [1.20; 1.73]<br>otal (common effect, 95% Cl) 1.44 [1.20; 1.73]<br>otal (common effect, 95% Cl) 1.42 [1.26; 1.64]<br>ates 1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% Cl) 1.44 [1.20; 1.73]<br>otal (common effect, 95% Cl) 1.44 [1.20; 1.73]   |   |                                |                               | <b>◆</b>                                  |
| ubgroup = Dementia.OR<br>eason_Hold_2023 2.33 [1.90; 2.86]<br>rewster_2021a 1.10 [0.90; 1.34]<br>yeon_2021 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (common effect, 95% CI) 1.52 [0.68; 2.70]<br>eterogenety: Tau" = 0.1927, Ch <sup>2</sup> = 27.15, df = 2 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.05 [0.88; 1.26]<br>then_2019 1.90 [1.66; 2.14]<br>org_2016 1.09 [0.65; 1.82]<br>avrencic_2022 2.87 [0.99; 8.34]<br>in_2004 1.38 [0.99; 8.34]<br>in_2004 1.38 [0.99; 8.34]<br>in_2004 1.38 [0.99; 8.10]<br>otal (random effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogenety: Tau" = 0.0767; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 83%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]  | leterogeneity: $Tau^2 = 0.0696$ : $Chi^2 = 3.2$   |                                | [0.63; 2.05]<br>$  ^2 = 37\%$ |   |
| eason_heid_2023 2.33 [1.90; 2.86]<br>rewster_2021a 1.10 [0.90; 1.34]<br>yeon_2021 1.15 [0.35; 3.78]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (random effect, 95% CI) 1.52 [0.86; 2.70]<br>eterospenety: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 27.15, df = 2 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.05 [0.88; 1.26]<br>then_2019 1.09 [0.65; 1.82]<br>averencic_2022 2.87 [0.99; 8.34]<br>in_2004 1.38 [0.99; 8.20]<br>otal (common effect, 95% CI) 1.56 [1.42; 1.72]<br>otal (random effect, 95% CI) 1.42 [1.05; 1.91]<br>eterospenety: Tau <sup>2</sup> = 0.0767; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 83%<br>ubgroup = Dementia.RR<br>teat_2019 1.52 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]  |   | - (. 0.20)                     |                               |   |
| rewster 2021a 1.10 [0.90; 1.34]<br>yeon 2021 1.15 [0.35; 3.78]<br>otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (random effect, 95% CI) 1.52 [0.36; 2.70]<br>eterogeneity: Tau' = 0.1927, Chi <sup>#</sup> = 27.15, di = 2 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Cl/cognitive decline.OR<br>rewster 2021b 1.09 [0.68; 1.26]<br>hen_2019 1.90 [1.69; 2.14]<br>otal (random effect, 95% CI) 1.56 [1.42; 1.72]<br>otal (random effect, 95% CI) 1.52 [1.26; 1.84]<br>ategen eterster 2025 and a 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ategen = 0.057; Chi <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>teal_2019 0.52 [1.26; 1.84]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]  | ubgroup = Dementia.OR   | 0.00                           | 14.00.0.00                    |   |
| yeon_2021 1.15 [0.35; 3.78]<br>otal (common effect, 95% Cl) 1.57 [1.36; 1.81]<br>otal (random effect, 95% Cl) 1.52 [0.86; 2.70]<br>eterospenetry. Tau <sup>2</sup> = 0.1927. Ch <sup>2</sup> = 27.15, df = 2 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Cl/cognitive decline.OR<br>rewster_2021b 1.05 [0.88; 1.26]<br>then_2019 1.09 [0.65; 1.82]<br>avrencic_2022 2.87 [0.99; 8.34]<br>mi_2004 1.38 [0.99; 8.34]<br>mi_2004 1.38 [0.99; 8.34]<br>otal (random effect, 95% Cl) 1.42 [1.05; 1.91]<br>eterospenetry. Tau <sup>2</sup> = 0.0767; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>attes_1996 6ffect, 95% Cl) 1.44 [1.20; 1.73]<br>otal (common effect, 95% Cl) 1.44 [1.20; 1.73]<br>otal (common effect, 95% Cl) 1.44 [1.20; 1.73]   |   |                                |                               |   |
| otal (common effect, 95% CI) 1.57 [1.36; 1.81]<br>otal (radiom effect, 95% CI) 1.52 [0.86; 2.70]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Ch <sup>2</sup> = 27.15, df = 2 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Cl/cognitive decline.OR<br>reverser_2021 0 [1.05 [0.88; 1.26]<br>then_2019 1.90 [1.69; 2.14]<br>org_2016 1.09 [0.65; 1.82]<br>avrencic_2022 2.87 [0.99; 8.34]<br>avrencic_2022 2.87 [0.99; 8.34]<br>avrencic_2022 2.87 [0.99; 8.34]<br>avrencic_2022 2.87 [0.99; 8.34]<br>avrencic_2022 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.56 [1.42; 1.72]<br>otal (radiom effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.076; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.14]   |   |                                |                               |   |
| otal (random effect, 95% CI) 1.52 [0.86; 2.70]<br>eterogeneity: Tau <sup>2</sup> = 0.1927; Chi <sup>2</sup> = 27.15; df = 2 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Cl/cognitive decline.OR<br>revester_2021b 1.05 [0.88; 1.26]<br>hen_2019 1.90 [1.66; 2.14]<br>avrencic_2022 2.87 [0.99; 8.34]<br>in; 2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.0767; Chi <sup>2</sup> = 32.95; df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ates_1996 6.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]   | otal (common effect, 95% CI)  |                                |                               |   |
| eterogenetity: Tau <sup>2</sup> = 0.1927; Chi <sup>2</sup> = 27.15, df = 2 (P < 0.01); l <sup>2</sup> = 93%<br>ubgroup = Cl/cognitive decline.OR<br>revester_2021 = 0.105 [0.88; 1.26]<br>then_2019 = 1.00 [0.65; 1.82]<br>avrencic_2022 2.87 [0.99; 8.34]<br>in_2004 [0.95% Cl] 1.56 [1.42; 1.72]<br>otal (common effect, 95% Cl] 1.56 [1.42; 1.72]<br>otal (condon effect, 95% Cl] 1.42 [1.05; 1.91]<br>eterogenety: Tau <sup>2</sup> = 0.076; Chi <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ates_1996 0.82 [0.45; 1.51]<br>otal (condon effect, 95% Cl] 1.44 [1.20; 1.73]<br>otal (condon effect, 95% Cl] 1.42 [0.67; 2.16]   | otal (random effect, 95% CI)  |                                |                               |   |
| rewster 2021b 1.05 [0.88; 1.26]<br>then 2019 1.90 [1.69; 2.14]<br>long_2016 1.09 [0.65; 1.82]<br>avrencic_2022 2.87 [0.99; 8.34]<br>in 2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.42 [1.55; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.0767; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>etal_2019 1.52 [1.26; 1.84]<br>attes_1990 effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]  |   |                                |                               |   |
| rewster 2021b 1.05 [0.88; 1.26]<br>then 2019 1.90 [1.69; 2.14]<br>long_2016 1.09 [0.65; 1.82]<br>avrencic_2022 2.87 [0.99; 8.34]<br>in 2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.42 [1.55; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.0767; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>etal_2019 1.52 [1.26; 1.84]<br>attes_1990 effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]  | ubaroup = Cl/cognitive decline OP   |                                |                               |   |
| html, 2019   1.90   [1.69; 2.14]     averacic, 2022   2.87   [0.99; 8.34]     in, 2004   1.38   [0.95; 2.00]     otal (common effect, 95% CI)   1.56   [1.42; 1.72]     otal (random effect, 95% CI)   1.42   [1.05; 1.91]     eterogenerity: Tau" = 0.0767; Chi² = 32.95; dt = 4 (P < 0.01); i² = 88%  | Brewster_2021b  | 1.05                           | [0.88; 1.26]                  |   |
| long_2016 1.09 [0.65; 1.82]<br>avrencic_2022 2.87 [0.99; 8.34]<br>in 2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% CI) 1.56 [1.42; 1.72]<br>otal (common effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.0767; Ch <sup>2</sup> = 32.95, df = 4 (P < 0.01); I <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>ates_1990 6.082 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.42 [0.57; 2.16]  | Chen_2019   |                                |                               | [] <b></b>                                |
| avrencic_2022 2.87 [0.99; 8.34]   in_2004 1.38 [0.95; 2.00]   otal (common effect, 95% CI) 1.56 [1.42; 1.72]   otal (random effect, 95% CI) 1.42 [1.05; 1.91]   etarogeneity: Tau <sup>2</sup> = 0.0767; Chi <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 88% ubgroup = Dementia.RR   etales_1996 0.82 [0.45; 1.51]   otal (common effect, 95% CI) 1.44 [1.20; 1.73]   otal (common effect, 95% CI) 1.20 [0.67; 2.16]  | long_2016   |                                |                               |   |
| in_2004 1.38 [0.95; 2.00]<br>otal (common effect, 95% Cl) 1.56 [1.42; 1.72]<br>otal (random effect, 95% Cl) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.0767; Chi <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>teal_2019 1.52 [1.26; 1.84]<br>iates_1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% Cl) 1.44 [1.20; 1.73]<br>otal (common effect, 95% Cl) 1.20 [0.67; 2.16]   | avrencic_2022   | 2.87                           | [0.99; 8.34]                  |   |
| otal (random effect, 95% CI) 1.42 [1.05; 1.91]<br>eterogeneity: Tau <sup>2</sup> = 0.0767; Chi <sup>2</sup> = 32.95, df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>eael 2019 1.52 [1.26; 1.84]<br>iates 1996 0.82 [0.45; 1.51]<br>otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (common effect, 95% CI) 1.20 [0.67; 2.16]  | .in_2004  |                                | [0.95; 2.00]                  |   |
| eterogeneity: Tau <sup>2</sup> = 0.0767; Chi <sup>2</sup> = 32.95; df = 4 (P < 0.01); l <sup>2</sup> = 88%<br>ubgroup = Dementia.RR<br>eal_2019   | otal (common effect, 95% CI)  |                                |                               | •   |
| ubgroup = Dementia.RR<br>leal_2019  | Total (random effect, 95% Cl)<br>determined are 2 = 0.0767; Chi <sup>2</sup> = 32.0       |                                |                               | •   |
| leal_2019     1.52     [1.26; 1.84]       sates_1996     0.82     [0.45; 1.51]       otal (common effect, 95% CI)     1.44     [1.20; 1.73]       otal (random effect, 95% CI)     1.20     [0.67; 2.16]  | reterogeneity: rau* = 0.0767; Chi* = 32.9   | o, di = 4 (P < 0.0             | JT); I <sup>-</sup> = 88%     |   |
| iates_1996     0.82     [0.45; 1.51]       otal (common effect, 95% CI)     1.44     [1.20; 1.73]       otal (condmon effect, 95% CI)     1.20     [0.67; 2.16]   |   |                                |                               |   |
| otal (common effect, 95% CI) 1.44 [1.20; 1.73]<br>otal (random effect, 95% CI) 1.20 [0.67; 2.16]  |   |                                |                               | -   |
| otal (random effect, 95% CI) 1.20 [0.67; 2.16]  | Deal_2019   |                                | 10.45: 1.511                  |   |
|   | Deal_2019<br>Gates_1996   |                                |                               |   |
| ororogonomy, ruo = 0.1010, orii = 0.00, or = 1 (r = 0.00), r = 7270   | Deal_2019<br>Sates_1996<br>Total (common effect, 95% CI)                                  | 1.44                           | [1.20; 1.73]                  |   |
|   | Deal_2019<br>Sates_1996<br>Total (common effect, 95% CI)<br>Total (random effect, 95% CI) | 1.44<br>1.20                   | [1.20; 1.73]<br>[0.67; 2.16]  | -   |
|   | Deal_2019<br>Gates_1996<br>Fotal (common effect, 95% CI)<br>Fotal (random effect, 95% CI) | 1.44<br>1.20                   | [1.20; 1.73]<br>[0.67; 2.16]  | -   |

Fig. 2. Meta-analysis of the association between hearing loss as a yes/no variable and dementia, MCI, cognitive decline not specified as dementia or MCI, Alzheimer's disease dementia, and vascular dementia.

are consistent with a dose response between degree of hearing loss and dementia risk.

Third, our meta-analysis supported an appropriate temporal sequence between hearing loss and dementia by excluding studies with participants who already had dementia at baseline, and excluding studies with less than two-year follow-up between hearing loss and subsequent dementia. However, dementia has a long prodrome of several years so reverse causality cannot be completely excluded. To further investigate this issue, we tested whether length of study followup was associated with the magnitude of the association between hearing loss and dementia, but found no statistically significant effect.

Additionally, there is separate evidence that treating hearing loss with hearing aids may mitigate this association. A meta-analysis on the effects of hearing aids and cochlear implants on the risk of future dementia found that hearing aid use was associated with 19% reduction in long-term incidence of cognitive decline relatively to uncorrected hearing (Yeo et al., 2023). There is one large-scale randomized trial, ACHIEVE, which has investigated the effect of hearing intervention on reducing cognitive decline in older adults. ACHIEVE randomized 977 people aged 70-84 years to hearing aids or an educational health intervention. No effect of hearing intervention on reducing cognitive decline was seen in the total cohort, but a substantial 48% reduction in cognitive decline was observed in a cohort of participants who had been recruited from a long-running population-based cohort and who had more baseline risk factors for cognitive decline and dementia (Lin et al., 2023; Livingston and Costafreda, 2023). This was a pre-planned but secondary analysis, and we therefore need to see if further RCTs to replicate this effect in people at higher risk for dementia.

In terms of limitations, our systematic literature search identified a large number of studies, but these were heterogeneous in samples, methods of assessment of hearing and cognitive outcomes, duration of follow-up and methods of analysis. We addressed this heterogeneity by conducting separate meta-analyses depending on cognitive outcomes and effect measures, and by conducting extensive moderator analyses. We identified moderate to substantial residual heterogeneity in the meta-analyses (Figs. 2 and 3), but found no evidence that any of the potential moderating factors (the type of hearing assessments, the length of follow-up year, adjustment on cardiovascular risk factors, premorbid cognitive function, the severity of hearing loss, the age group of participants at baseline, and when age and gender proportion at baseline) had a statistically significant effect on the magnitude of the association or explained a significant amount of the heterogeneity. It is possible that this residual heterogeneity could be explained through other moderating or confounding factors that were not included in our analyses or adequately reported by the primary studies.

In conclusion, this meta-analysis of cohort studies provided compelling evidence across diverse study settings and designs of adultonset hearing loss being a robust and consistent independent risk factor for dementia. Adult-onset hearing loss is also potentially treatable, most often with hearing aids. Our findings suggest that this treatment may also reduce dementia risk.

#### Authors' contributions

Sergi Costafreda Gonzalez, Gill Livingston, Anne Schilder conceptualized and designed the study. Rumana Omar and Menelaos Pavlou wrote the statistical analysis plan and checked the main results. Ruan-Ching Yu, Danielle Proctor, Janvi Soni, Liam Pikett, and Sergi Costafreda Gonzalez prepared (searching, screening, retrieving, and maintaining the research data) and scored the included articles. Ruan-Ching Yu analysed the data, visualised the results, interpreted the results and wrote up the original draft. Sergi Costafreda Gonzalez, Gill Livingston, Anne Schilder, Danielle Proctor, Janvi Soni, Liam Pikett, Glyn Lewis, Doris Bamiou, Rishi Mandavia, Rumana Omar, Menelaos Pavlou, Frank Lin, and Adele Goman reviewed, and edited the manuscript.

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| Study  | HR                             | 95% CI       | Hazard Ratio<br>IV, Fixed + Random, 95% CI |
|--|--------------------------------|--------------|--|
| Deal_2017  | 1.14                           | [1.03; 1.26] |  |
| Lin_2011   | 1.24                           | [1.04; 1.48] |  |
| Total (common effect, 95% Cl)                                      | <b>1.16</b>                    | [1.07; 1.27] |  |
| Total (random effect, 95% Cl)                                      | <b>1.16</b>                    | [1.07; 1.27] |  |
| Heterogeneity: Tau <sup>2</sup> = 0; Chi <sup>2</sup> = 0.67, df = | = 1 (P = 0.41); I <sup>2</sup> | = 0%         |  |
|  |                                |              | 0.8 1 1.25                                 |



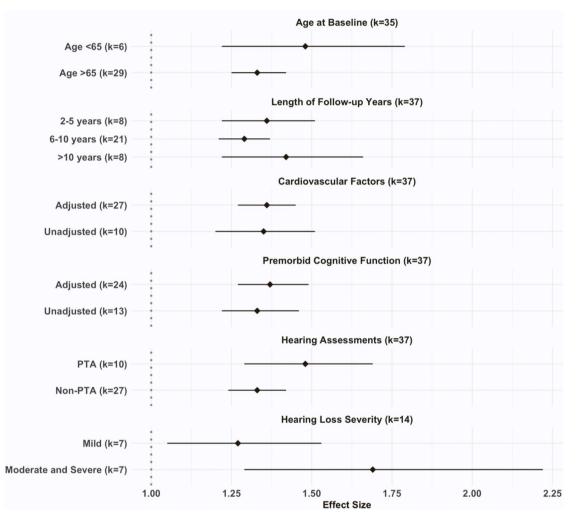


Fig. 4. Moderator analyses of the association between adult-onset hearing loss and any incident cognitive outcome (studies reporting HR, k=37).

| Table | 3 |
|-------|---|
|-------|---|

Meta-regression analyses of the association between adult-onset hearing loss and any incident cognitive outcomes (studies reporting HR, k=37) results.

| Moderator                      | Number<br>Studies | Estimate [95% CI]         | p-<br>value | $I^2$ |
|--------------------------------|-------------------|---------------------------|-------------|-------|
| Proportion of Sample<br>Female | 37                | -0.333<br>[-0.675,0.008]  | 0.0558      | 63%   |
| Age at baseline                | 33                | -0.007 [-0.014,<br>0.002] | 0.1114      | 68%   |
| Follow-up years                | 37                | -0.004 [-0.017,<br>0.009] | 0.5520      | 70%   |

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## **Declaration of Competing Interest**

None of the authors have any financial or other conflicts of interest to disclose.

## Data Availability

Data will be made available on request.

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We would like to thank the authors of the included studies for

contributing their original work.

### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2024.102346.

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