Mortality rates in Alzheimer's disease and non-Alzheimer's dementias: a systematic review and meta-analysis

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Summary

Background People with dementia die prematurely. Identifying differences in mortality rates between different types of dementia might aid in the development of preventive interventions for the most vulnerable populations. The aim of this study was to compare the difference in mortality rates between individuals without dementia and individuals with various types of dementia.

Methods For this systematic review and meta-analysis, we did a systematic search of MEDLINE, PubMed, Embase, and Cochrane Library from inception to July 11, 2020, for cross-sectional or cohort studies that assessed mortality and survival-related outcomes among people with different types of dementia compared with people without dementia. Single-arm studies without comparison groups and autopsy studies or family studies that used a selected sample were excluded. The Newcastle-Ottawa Scale was used by two authors (D-JL and C-SC) independently to measure the methodological quality of included studies, and two authors (F-CY and P-TT) independently extracted data. We assessed differences in all-cause mortality rate and survival time from dementia diagnosis between individuals without dementia, individuals with Alzheimer's disease, and individuals with non-Alzheimer's disease dementias. The secondary outcomes were age at death and survival time from disease onset. Random-effects meta-analyses were done. Effect sizes included hazard ratios (HRs) and mean differences (MDs) with 95% CIs. Potential moderators, including age-associated moderators, were identified through meta-regression and subgroup analyses. This study is registered with PROSPERO, CRD42020198786.

Findings Our database search identified 11 973 records, and we included 78 eligible studies in our analyses, encompassing 63 125 individuals with dementia and 152 353 controls. Individuals with any type of dementia had a higher mortality rate than individuals without dementia (HR 5·90, 95% CI 3·53 to 9·86), and the HR for all-cause mortality was highest for Lewy body dementia (17·88, 5·87 to 54·46). After diagnosis, the mean survival time for people with Alzheimer's disease was 5·8 years (SD 2·0). Compared with people with Alzheimer's disease, a diagnosis of any non-Alzheimer's disease dementia was associated with a higher risk of all-cause mortality (HR 1·33, 1·21 to 1·46), a shorter survival time from diagnosis (MD –1·12 years, 95% CI –1·52 to –0·72), and a younger age at death (–1·76 years, –2·66 to –0·85). Survival time from disease onset was also shorter in people with non-Alzheimer's dementia, across types, compared with people with Alzheimer's disease, but the subgroup analysis revealed that this difference was only significant for vascular dementia (MD –1·27 years, –1·90 to –0·65) and dementia with Lewy bodies (MD –1·06 years, –1·68 to –0·44). The interactions between age and several survival-related outcomes were significant. 39 (50%) of the 78 included studies were rated as good quality, and large heterogeneity (I^2>75%) was observed for most of the study outcomes.

Interpretation Alzheimer's disease is the most common type of dementia and one of the major causes of mortality worldwide. However, the findings from the current study suggest that non-Alzheimer's disease dementias were associated with higher morality rates and shorter life expectancy than Alzheimer's disease. Developing tailored treatment and rehabilitation programmes for different types of dementia is important for mental health providers, patients, and their families.

Funding None.

Introduction

The prevalence of dementia, also classified as neurocognitive disorder,[1] has been increasing,[2] and is one of the major causes of disability and dependency among older people worldwide.[2] This results in high costs for health and social care systems,[3] and people with dementia face substantial health challenges and might have at least twice as high a mortality risk as people without dementia.[4,5]

Differences in mortality rates across different types of dementia might affect prevalence rates and health-care service needs. Previous studies addressing life expectancy and survival have largely focused on Alzheimer's disease.

Lancet Healthy Longev 2021; 2: e479–88

Published Online July 20, 2021 https://doi.org/10.1016/S2666-7568(21)00140-9

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Research in context

Evidence before this study

Alzheimer's disease is the most common form of dementia. Alzheimer's disease was the sixth leading cause of death in the USA and the fifth leading cause of death among US Americans aged 65 years and older in 2019. However, differences in mortality rates between different types of dementia remain unknow. Previous studies addressing life expectancy and survival have largely focused on Alzheimer's disease, but findings for other types of dementia have been inconsistent. Identifying differences in survival between different types of dementia might aid in the development of preventive interventions for these most vulnerable populations. To our knowledge, no meta-analyses have been done to examine mortality rates across different types of dementias compared with individuals without dementia.

We searched MEDLINE, PubMed, Embase, and Cochrane Library for studies done in humans from database inception until July 11, 2020, for studies published in English that provided sufficient data on survival or mortality parameters for any types of dementia versus individuals without dementia or any non-Alzheimer's types of dementia versus Alzheimer's disease. The search terms used were: ("mortality" OR "death" OR "survival") AND ("Alzheimer's disease" OR "Frontotemporal dementia" OR "Frontotemporal lobar degeneration" OR "behavioral variant frontotemporal dementia" OR "dementia with Lewy body" OR "Lewy body" OR "Lewy bodies" OR "Lewy" OR "dementia with Lewy bodies" OR "LBD" OR "Parkinson's disease dementia" OR "Parkinson's disease dementia" OR "vascular dementia" OR "Arteriosclerotic Dementia" OR "Dementia Multi-Infarct") AND ("normal cognition" OR "non-dementia" OR "control"). Specific database search terms are outlined in the appendix (p 170). We aimed to examine which type of dementia is associated with the highest mortality rate and the shortest survival.

Added value of this study

To our knowledge, this study is the first systematic review and meta-analysis to compare mortality rates and survival outcomes between people with Alzheimer's disease, people with non-Alzheimer's dementias, and people without dementia based on all the available published evidence.

We identified 78 studies encompassing 63 125 individuals with dementia and 152 353 controls. We found that people with Lewy body dementia were associated with the highest all-cause mortality rate compared with individuals without dementia. The mean survival time was 7·6 years from Alzheimer's disease onset and 5·8 years from diagnosis. Compared with people with Alzheimer's disease, people with non-Alzheimer's dementias had higher mortality rates, shorter survival times from diagnosis, and younger ages at death. Although our meta-regression analyses identified several factors that moderated individual study findings, the change in point estimates of mortality rate was less than 10% when adjusted for potential moderators. Group differences between vascular dementia, Lewy body dementias, and frontotemporal lobe degeneration were not significant.

Implications of all the available evidence

Our findings suggest that Alzheimer's disease has the most favourable survival-related outcomes compared with non-Alzheimer's dementias, and Lewy body dementias have the highest mortality rates. Understanding differences in mortality between different types of dementia is important for both physicians and policy makers to develop tailored treatment and rehabilitation programmes and for patients and their families to facilitate future care planning. Future studies should explore risks and potential contributing factors affecting these differences between different types of dementia.

The life expectancy is about 7–10 years in individuals diagnosed with Alzheimer's disease in their 60s and early 70s,[6] but findings for other types of dementia have been inconsistent. For example, in some studies, people with vascular dementia were found to have a poorer prognosis and a shorter survival time after diagnosis than people with Alzheimer's disease,[7,8] whereas other studies have reported opposite findings.[9,10] People with Parkinson's disease dementia or dementia with Lewy bodies were found to have a three times higher risk of mortality compared with individuals without dementia,[11] and people with dementia with Lewy bodies have also been shown to have poorer health outcomes and higher mortality rates compared with people with Alzheimer's disease.[12–14] However, several studies have found little differences in mortality between different dementia types.[15,16]

Studies on non-Alzheimer's types of dementia have commonly used people with Alzheimer's disease as a reference group, and considerable uncertainty exists regarding mortality rates in non-Alzheimer's types of dementia compared with the individuals without dementia after controlling for confounders (eg, age and co-occurring medical conditions). Thus, a systematic review and meta-analysis might provide more robust evidence to inform treatment plans and advice to those affected. To our knowledge, there has been no meta-analysis focusing on mortality rates across different types of dementias compared with the general population. The aim of this study was to compare mortality rates and other survival-related outcomes among individuals without dementia, people with Alzheimer's disease, and people with non-Alzheimer's dementias using a meta-analysis to synthesise all available evidence.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (appendix pp 166–69).[17]

See Online for appendix

From June 27 to July 11, 2020, two authors (D-JL and C-SC) independently searched MEDLINE, PubMed, Embase, and Cochrane Library for studies done in humans and published in English from database inception until July 11, 2020. To ensure comprehensiveness, we examined the reference lists from retrieved articles for supplementary relevant studies. The study was approved by the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB: B-109–29).

The following eligibility criteria were applied: (1) cohort (prospective or retrospective) or cross-sectional studies reporting survival times from dementia diagnosis or onset, (2) studies with a baseline and follow-up evaluation, (3) studies with sufficient data on survival or mortality parameters for individuals with any type of dementia versus individuals without dementia or any non-Alzheimer's type of dementia versus individuals with Alzheimer's disease, (4) studies using well established criteria for the diagnosis of dementia (appendix p 6), and (5) peer-reviewed studies written in English.

Studies were excluded if they were: (1) single-arm studies without any comparison groups (eg, general population or individuals with Alzheimer's disease), (2) a selected sample from autopsy studies or family studies, precluding external generalisability, (3) review articles that did not provide original data, (4) case series or case reports, (5) conference or meeting abstracts, and (6) randomised controlled trials.

Outcomes

The main outcomes were the hazard ratio (HR) of all-cause mortality rate and mean difference (MD) in survival time from diagnosis. The survival time from diagnosis was the mean survival time (year) from diagnosis to death. The secondary outcomes were age at death and survival time from disease onset.

Data analysis

Two authors (D-JL and C-SC) independently used the Newcastle-Ottawa Scale (NOS) to assess the quality of each included study.[18] Disagreements were resolved through discussion with a third author (C-SL). Two authors (F-CY and P-TT) independently extracted data using a prespecified data extraction form. Disagreements were resolved through discussion with a third author (C-SL). Information extracted included patients' characteristics (number of participants, age, sex, baseline mean scores on the Mini-Mental State Examination [MMSE], data on co-occurring physical and mental illness, and medications), study characteristics (population, study design, year of publication, follow-up period, diagnostic criteria, and country), and data on the number of deaths, age at dementia diagnosis, age at disease onset, age at death, and survival time (year) from diagnosis and from disease onset. The present meta-analysis used summary estimates for analysis.

We first compared the HR for all-cause mortality of all dementia participants, across subtypes, with that of individuals without dementia, and then compared mortality risk and survival-related outcomes of individuals with non-Alzheimer's types of dementia with outcomes of individuals with Alzheimer's disease. We also did subgroup analyses to examine group differences in outcomes between vascular dementia, Lewy body dementia, frontotemporal degeneration, and Alzheimer's disease. The subtypes of Lewy body dementia included Parkinson's disease dementia, dementia with Lewy bodies, and Lewy body variant of Alzheimer's disease, and the subtypes of frontotemporal degeneration included behavioural variant frontotemporal dementia, progressive non-fluent aphasia, semantic dementia, progressive supranuclear palsy, and corticobasal degeneration. The subtypes of Lewy body dementia and of frontotemporal degeneration were compared with Alzheimer's disease for all outcomes, if at least two studies on the subtypes provided the data.

The pooled HR and MD with corresponding 95% CIs were calculated. If the HR of the Cox regression was not available in the original study, we estimated it using established methods.[19] A random-effects model was used to account for heterogeneity. If two or more studies shared a control sample, the size of this sample was divided equally between these studies. Heterogeneity was assessed using the I^2 statistic, and a value exceeding 75% implied a high heterogeneity.[20] Publication bias was assessed using funnel plot asymmetry and Egger's regression test.

We completed several pre-planned subgroup and meta-regression analyses to examine potential moderators, namely, whether the study used a cohort versus non-cohort design; MMSE score; proportion of female participants; sample size; proportion of diabetes, hypertension, cerebrovascular accident, and cardiovascular disease; and NOS scores. Because age is an important risk factor of death, age needs to be considered a significant moderator for all the primary and secondary outcomes. Therefore, the effects of age-associated moderators were specifically examined, namely, age at onset and diagnosis and group differences in age at onset and diagnosis. For significant moderators, we calculated the proportion of change-in-estimate of the adjusted effect sizes against the raw effect sizes. When applicable, one-way sensitivity analyses were done by removing a single study at a time to determine the robustness of the findings.[21] We also calculated the risk ratio (RR) of all-cause mortality. The meta-regression and publication bias test was done when at least ten studies were available.[22] The threshold for statistical significance was set at a two-tailed $p<0·05$ for all analyses with the exception of $p<0·1$ for Egger's regression test. Analyses were done using Stata version 16.0. This study is registered with PROSPERO, CRD42020198786.

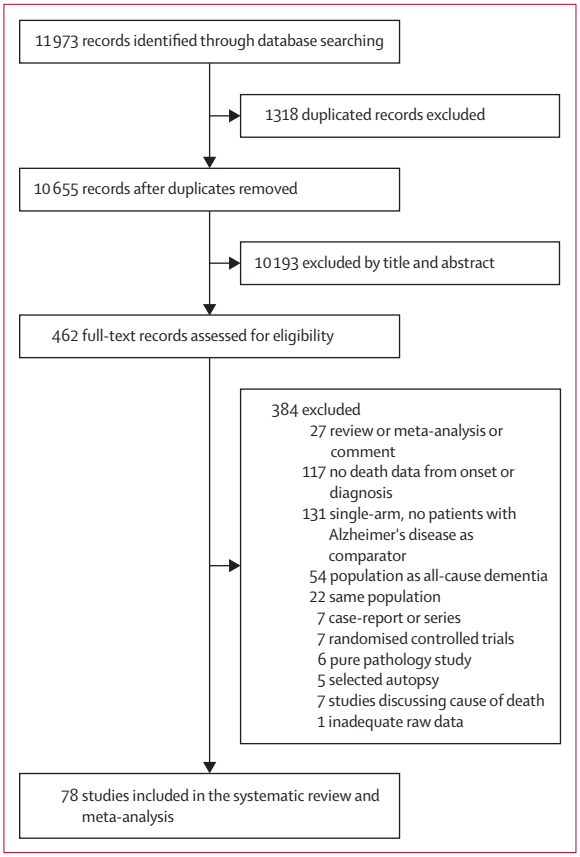

Figure 1: **Study selection**

	All dementia	AD	VaD	LBD	FTLD
Sample size	63 125	46 314	10 799	4474	1538
Age at onset, years	68·1 (7·0)	68·8 (6·7)	67·5 (7·2)	72·4 (3·2)	58·6 (2·5)
Age at diagnosis, years	72·7 (5·9)	74·2 (5·7)	73·5 (7·0)	74·5 (2·5)	64·2 (3·2)
Age at death, years	77·6 (5·3)	78·6 (5·1)	77·0 (6·9)	79·1 (2·4)	68·2 (3·2)
Survival from onset, years	7·3 (2·3)	7·6 (2·1)	6·5 (1·2)	6·8 (2·5)	7·6 (2·9)
Survival from diagnosis, years	4·8 (2·0)	5·8 (2·0)	3·2 (1·4)	4·7 (1·8)	4·9 (2·2)

Data are given in n or mean (SD). AD=Alzheimer's disease. FTLD=frontotemporal lobe degeneration. LBD=Lewy body dementia. VaD=vascular dementia.

Table 1: **Summarised clinical characteristics of the included dementia types**

Role of the funding source

There was no funding source for this study.

Results

The database search identified 11 973 studies (figure 1). After reviewing the titles and abstract, we excluded 11 511 studies that did not fulfil our inclusion criteria (appendix p 170). The remaining 462 studies were reviewed in full text, and 78 articles containing relevant data were included in our analysis (appendix p 6). The results of the primary and secondary outcomes are summarised in the appendix (p 19). We identified 15 control samples (n=152 353) and 173 dementia samples (n=63 125): 78 Alzheimer's disease samples (n=46 314), 27 vascular dementia samples (n=10 799), 48 Lewy body dementia samples (n=4474), and 20 frontotemporal degeneration samples (n=1538). There were four Lewy body dementia samples with unspecified subtype (n=326) and 15 unspecified frontotemporal degeneration samples (n=1296). Among the subtypes of Lewy body dementia, there were four studies on Parkinson's disease dementia (n=411), 28 studies on dementia with Lewy bodies (n=2794) and 12 studies on Lewy body variant of Alzheimer's disease (n=943). Among the subtypes of frontotemporal degeneration, there were two studies on behavioural variant frontotemporal dementia (n=176) and three studies on semantic dementia (n=64). We excluded studies on progressive non-fluent aphasia (n=27), progressive supranuclear palsy (n=44), and corticobasal degeneration (n=15) because there was only one available sample in these subtypes of frontotemporal degeneration.

In people with any dementia type, the mean age at disease onset was 68·1 (SD 7·0) years, and mean age was 72·7 (5·9) years (table 1). HR estimates indicated a higher mortality rate in people with any dementia type than in individuals without dementia (5·90, 95% CI 3·53–9·86; figure 2). Compared with individuals without dementia, Lewy body dementia was associated with the highest HR for mortality (17·88, 5·87–54·46), followed by frontotemporal degeneration (15·26, 4·34–53·69), vascular dementia (5·03, 1·63–15·51), and Alzheimer's disease (3·70, 1·99–6·88). Group differences in mortality risk between Alzheimer's disease, frontotemporal degeneration, Lewy body dementia, and vascular dementia were significant (p=0·04; appendix p 22).

In people with Alzheimer's disease, the mean age at disease onset was 68·8 (6·7) years, and the mean age at diagnosis was 74·2 (5·7) years. Compared with Alzheimer's disease, non-Alzheimer's dementias, across types, were associated with a higher HR for mortality (HR 1·33, 95% CI 1·21–1·46; figure 3), whereas the differences between vascular dementia, Lewy body dementia, and frontotemporal degeneration were not significant (group difference: p=0·31; appendix p 24). Among the subtypes of Lewy body dementia, dementia with Lewy bodies was associated with the highest HR for mortality compared with Alzheimer's disease (1·54, 1·23–1·93; figure 3). Frontotemporal degeneration and its subtypes were not associated with a higher HR for mortality compared with Alzheimer's disease. The forest plots showing the primary and secondary outcomes are shown in the appendix (pp 21–75).

The mean survival time from Alzheimer's disease onset was 7·6 years (2·1) and the mean survival time from diagnosis was 5·8 years (2·0). The survival time after diagnosis was shorter in people with any non-Alzheimer's dementia than in people with Alzheimer's disease (MD –1·12 years, 95% CI –1·52 to –0·72; figure 4). However,

the mean difference in survival time from diagnosis compared with Alzheimer's disease was similar for vascular dementia (–1·33, –2·16 to –0·51), Lewy body dementia (–1·01,–1·53 to –0·50), and frontotemporal degeneration (–1·01, –1·95 to–0·08; group difference: p=0·80; figure 4). Among the subtypes of Lewy body dementia, Parkinson's disease dementia was associated with the shortest survival time from diagnosis compared with the Alzheimer's disease reference (–3·81; –5·26 to –2·37), but data were only available from two studies (n=83). Among the subtypes of frontotemporal degeneration, there was only one cohort study on behavioural variant frontotemporal dementia and one cohort study on semantic dementia available.

Survival time from disease onset in people with any non-Alzheimer's dementia was shorter than survival time in those with Alzheimer's disease (MD –0·85, 95% CI –1·4 to –0·25; appendix p 56); however, this difference could not be replicated for each individual dementia subtype (only vascular dementia and dementia with Lewy bodies showed a significantly shorter survival time from disease onset than Alzheimer's disease [appendix pp 57–64], maybe because of the small sample sizes).

In the Alzheimer's disease group, the mean age at death was 78·6 years (5·1; table 1). The mean age at death in people with any non-Alzheimer's dementia was lower than that of people with Alzheimer's disease (MD –1·76, 95% CI –2·67 to –0·85; figure 5). Compared with people with Alzheimer's disease, people with frontotemporal degeneration had the lowest mean age at death, whereas people with vascular dementia did not show a significantly younger age at death (significant group differences between vascular dementia, Lewy body dementia, frontotemporal degeneration: p=0·03). All of the subtypes of Lewy body dementia and frontotemporal degeneration were associated with a younger age at death compared with Alzheimer's disease. Furthermore, people with semantic dementia (MD –6·04, –10·69 to –1·39) had the youngest age at death compared with Alzheimer's disease, although there were only two semantic dementia cohorts available (n=17; figure 5).

The results of meta-regression and subgroup analyses are reported in the appendix (pp 76–107) and summarised in table 2. For HR and RR outcomes of all-cause mortality, all changes in point estimates were less than 10% when adjusted for potential confounders. When adjusting for NOS scores, effect sizes of the comparisons of mean survival time from diagnosis between frontotemporal degeneration and Alzheimer's disease changed from –1·02 (95% CI –1·95 to –0·10) to –1·17 (–1·72 to –0·02) with a change-in-estimate of 14·7% (0·15 of 1·02). Age was a significant moderator in four comparisons between non-Alzheimer's dementia types and Alzheimer's disease, with more than 10% of change-in-estimate. Comparing the outcome for the age at death betweendementia with Lewy bodies and Alzheimer's disease, the effect size changed from –1·61 (–2·80 to –0·42) to –1·34 (–2·45 to –0·23) with a change-in-estimate of 16·8% (0·27/1·61) when adjusted for differences in age at onset, and the effect size was changed from –1·61 (–2·80 to –0·42) to –1·99 (–3·35 to –0·64) with a change-in-estimate of 23·6% (0·38/1·61) when adjusted for difference in age at diagnosis. Comparing the outcome for age at death between non-Alzheimer's dementia (a group of non-specified Lewy body dementia, Parkinson's disease dementia, and dementia with Lewy bodies) and Alzheimer's disease, the effect size was changed from –1·74 (–2·81 to –0·66) to –1·21 (–2·51 to 0·07) with a change-in-estimate of 30·5% (0·53/1·74) when adjusted for difference in age at onset; and the effect size was changed from –1·74 (–2·81 to –0·66) to –1·97 (–3·25 to –0·70) with a change-in-estimate of 13·2% (0·23/1·74) when adjusted for difference in age at diagnosis. Sex was a significant moderator in the comparison of RR outcomes for all-cause mortality between vascular dementia and Alzheimer's disease (effect size changed from 1·28 [1·13 to 1·45] to 1·22 [1·05 to 1·42]; change-in-estimate: 4·7% [0·06/1·28]) and in the age of death between non-Alzheimer's disease dementia and

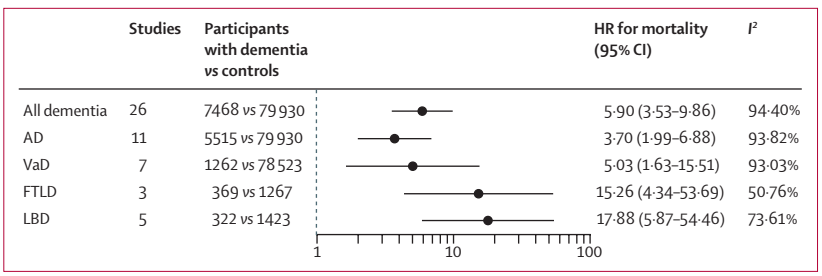

Figure 2: **HR of mortality for people with dementia versus controls**
AD=Alzheimer's disease. FTLD=frontotemporal lobe degeneration. HR=hazard ratio. LBD=Lewy body dementia. VaD=vascular dementia.

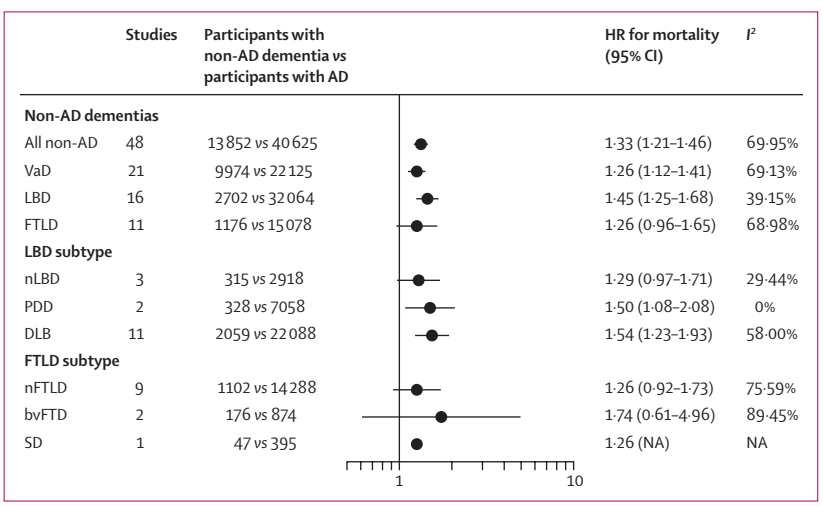

Figure 3: **HR of mortality for people with non-AD dementia versus AD**
AD=Alzheimer's disease. bvFTD=behavioral variant frontotemporal dementia. DLB=dementia with Lewy bodies. FTLD=frontotemporal lobe degeneration. HR=hazard ratio. LBD=Lewy body dementia. NA=not applicable. nFTLD=not specified frontotemporal lobe degeneration. nLBD=not specified Lewy body dementia. PDD=Parkinson's disease dementia. SD=semantic dementia. VaD=vascular dementia.

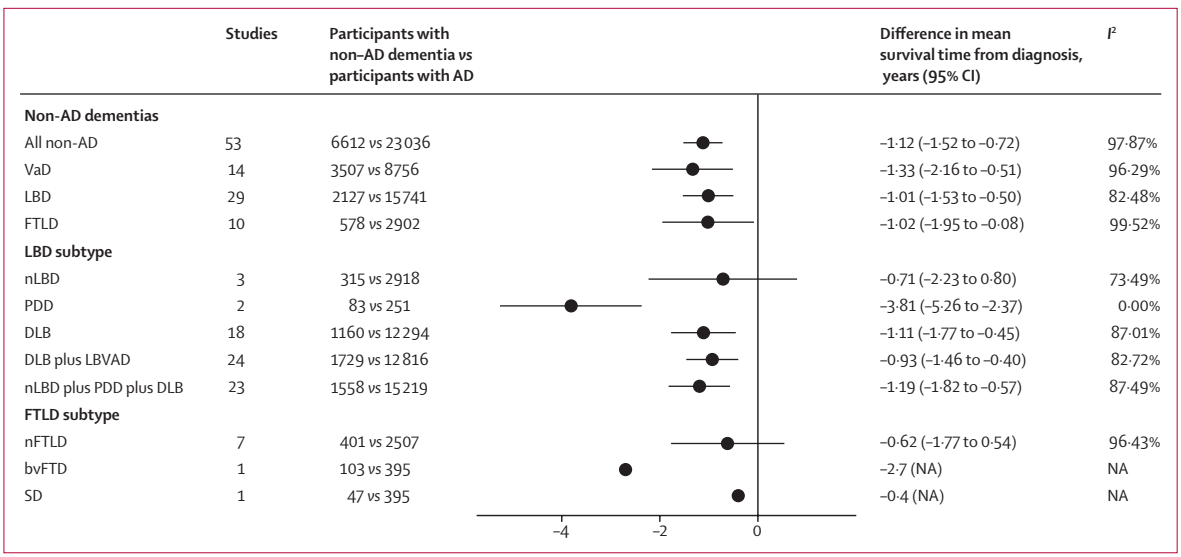

Figure 4: **Differences in survival time from diagnosis for people with non-AD dementia versus AD**
AD=Alzheimer's disease. bvFTD=behavioral variant frontotemporal dementia. DLB=dementia with Lewy bodies. FTLD=frontotemporal lobe degeneration. LBD=Lewy body dementia. LBVAD=Lewy body variant of Alzheimer's disease. NA=not applicable. nFTLD=not specified frontotemporal lobe degeneration. nLBD=not specified Lewy body dementia. PDD=Parkinson's disease dementia. SD=semantic dementia. VaD=vascular dementia.

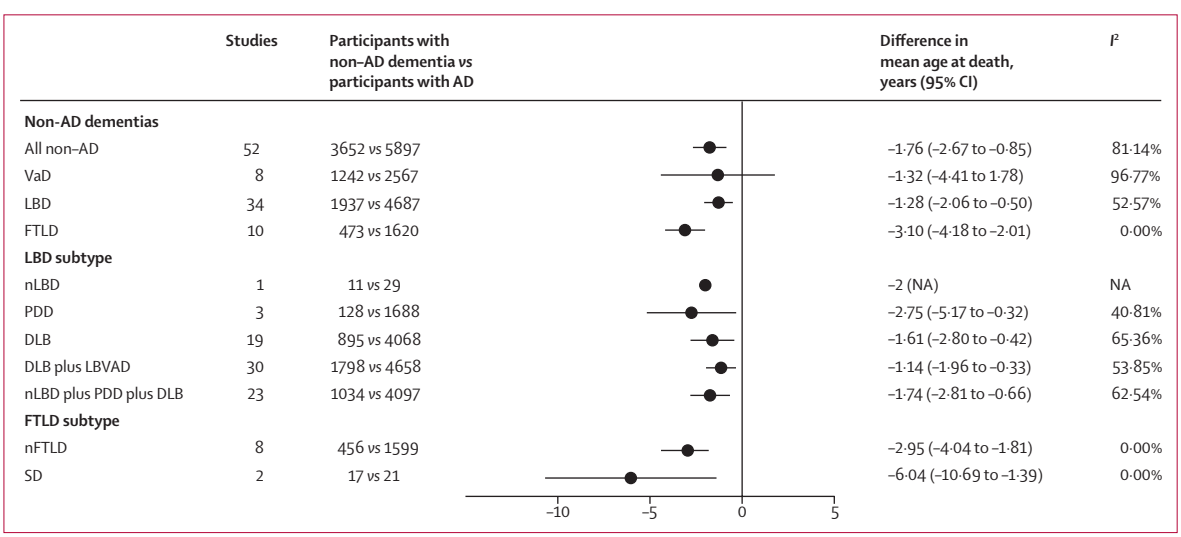

Figure 5: **Differences in age at death for people with non-AD dementia versus AD**
AD=Alzheimer's disease. bvFTD=behavioral variant frontotemporal dementia. DLB=dementia with Lewy bodies. FTLD=frontotemporal lobe degeneration. LBD=Lewy body dementia. LBVAD=Lewy body variant of Alzheimer's disease. NA=not applicable. nFTLD=not specified frontotemporal lobe degeneration. nLBD=not specified Lewy body dementia. PDD=Parkinson's disease dementia. SD=semantic dementia. VaD=vascular dementia.

Alzheimer's disease (effect size changed from –1·75 [–2·66 to –0·85] to –1·75 [–2·54 to –0·96]; change-in-estimate: 0% [0·0/1·75; table 2). The subgroup analyses revealed that the survival time from diagnosis was not significant for dementia with Lewy bodies compared with Alzheimer's disease and neither was it for a group of dementia with Lewy bodies and Lewy body variant of Alzheimer's disease compared with Alzheimer's disease in the cross-sectional studies (appendix pp 93–94).

Sensitivity analyses removing a single study at a time suggested that our study findings were robust (appendix pp 108–136). The funnel plots and Egger's tests detected several small-study effects (appendix pp 137–165). We found larger effect sizes for smaller studies in HR (non-Alzheimer's *vs* Alzheimer's disease on appendix p 138; vascular dementia *vs* Alzheimer's disease on appendix p 139; Lewy body dementia *vs* Alzheimer's disease on appendix p 140), RR (all dementia *vs* controls on appendix p 143; Lewy body dementia *vs* Alzheimer's disease on appendix p 146), and of age at death (frontotemporal degeneration *vs* Alzheimer's disease on appendix p 162). Publication bias and small-study effects

	Outcome	Moderator	Effect size (95% CI)	Adjusted effect size (95% CI)	Change-in-estimate
Dementia *vs* controls	Hazard ratio	Newcastle-Ottawa Scale	5·90 (3·53 to 9·86)	5·95 (4·00 to 8·84)	0·8%
LBD *vs* AD	Hazard ratio	Newcastle-Ottawa Scale	1·46 (1·26 to 1·68)	1·54 (1·36 to 1·75)	6·2%
VaD *vs* AD	Risk ratio	Difference in female proportion	1·28 (1·13 to 1·45)	1·22 (1·05 to 1·42)	4·7%
FTLD *vs* AD	Risk ratio	Follow-up year	1·22 (0·96 to 1·55)	1·24 (1·00 to 1·53)	1·6%
Non-AD *vs* AD	Survival from diagnosis	Difference in age at diagnosis	−1·12 (−1·52 to −0·72)	−1·21 (−1·64 to −0·79)	8·4%
FTLD *vs* AD	Survival from diagnosis	Sample size	−1·02 (−1·95 to −0·10)	−1·06 (−1·83 to −0·29)	3·9%
FTLD *vs* AD	Survival from diagnosis	Difference in sample size	−1·02 (−1·95 to −0·10)	−1·04 (−1·78 to −0·31)	2·0%
FTLD *vs* AD	Survival from diagnosis	Newcastle-Ottawa Scale	−1·02 (−1·95 to −0·10)	−1·17 (−1·72 to −0·02)	14·7%
DLB plus LBVAD *vs* AD	Survival from diagnosis	Age at diagnosis	−0·93 (−1·46 to −0·40)	−0·97 (−1·55 to −0·39)	4·3%
Non-AD *vs* AD	Age at death	Female proportion	−1·76 (−2·66 to −0·85)	−1·75 (−2·54 to −0·96)	0%
Non-AD *vs* AD	Age at death	Age at onset	−1·76 (−2·66 to −0·85)	−1·80 (−2·60 to −1·01)	2·9%
Non-AD *vs* AD	Age at death	Difference in age at onset	−1·76 (−2·66 to −0·85)	−1·83 (−2·45 to −1·21)	4·6%
Non-AD *vs* AD	Age at death	Difference in age at diagnosis	−1·76 (−2·66 to −0·85)	−1·86 (−2·79 to −0·93)	6·3%
LBD *vs* AD	Age at death	Difference in age at onset	−1·28 (−2·06 to −0·50)	−1·16 (−1·92 to −0·39)	9·4%
LBD *vs* AD	Age at death	Newcastle-Ottawa Scale	−1·28 (−2·06 to −0·50)	−1·39 (−2·13 to −0·66)	8·6%
DLB *vs* AD	Age at death	Difference in age at onset	−1·61 (−2·80 to −0·42)	−1·34 (−2·45 to −0·23)	16·8%
DLB *vs* AD	Age at death	Difference in age at diagnosis	−1·61 (−2·80 to −0·42)	−1·99 (−3·35 to −0·64)	23·6%
DLB plus LBVAD *vs* AD	Age at death	Difference in age at onset	−1·14 (−1·96 to −0·33)	−1·15 (−1·92 to −0·39)	0·9%
nLBD plus PDD plus DLB *vs* AD	Age at death	Difference in age at onset	−1·74 (−2·81 to −0·66)	−1·21 (−2·51 to 0·07)	30·5%
nLBD plus PDD plus DLB *vs* AD	Age at death	Difference in age at diagnosis	−1·74 (−2·81 to −0·66)	−1·97 (−3·25 to −0·70)	13·2%

AD=Alzheimer's disease. FTLD=frontotemporal lobe degeneration. LBD=Lewy body dementia. LBVAD=Lewy body variant of Alzheimer's disease. nLBD=not specified Lewy body dementia. NOS=Newcastle-Ottawa Scale. VaD=vascular dementia.

Table 2: **Summarised findings of meta–regression analyses**

were not found in the outcomes of survival time from onset and diagnosis.

Discussion

This meta-analysis compared the mortality rate and survival outcomes between individuals with Alzheimer's disease, with non-Alzheimer's dementias, and without dementia on the basis of all the available published evidence. The main findings are that people living with dementia showed a 5·90 times larger HR for all-cause mortality rate compared with individuals without dementia, and the HR for all-cause mortality increased to 17·88 in people living with Lewy body dementia. With respect to the risk posed by different types of dementia, people living with non-Alzheimer's dementia (all types grouped together) showed a 1·33 times greater HR for all-cause mortality and a 1·12 year shorter survival after diagnosis compared with people with Alzheimer's disease, but there were no significant differences between the vascular dementia, Lewy body dementia, and frontotemporal degeneration subgroups. In brief, although Alzheimer's disease is the most common type of dementia and has been reported to be one of the leading causes of mortality, it has better survival outcomes than non-Alzheimer's dementias.

To date, most studies addressing mortality risk in people with dementia focused on individuals with Alzheimer's disease versus individuals without dementia. Our study found that people living with Alzheimer's disease had a 3·70 times larger HR for all-cause mortality compared with individuals without dementia, indicating that Alzheimer's disease contributed to a shortened life expectancy. We further found that people living with Lewy body dementia had a 17·88 times greater HR for all-cause mortality compared with individuals without dementia and a 1·45 times greater HR for all-cause mortality compared with individuals with Alzheimer's disease. The subtypes of Lewy body dementia (Parkinson's disease dementia and dementia with Lewy bodies) were also associated with higher HRs for all-cause mortality against the Alzheimer's disease reference, which strengthens the evidence of a poor prognostic profile in these neurodegenerative conditions. A previous meta-analysis indicated that the RR for all-cause mortality was 2·2 in people with Parkinson's disease versus people without dementia, and the subgroup analysis showed that people with Parkinson's disease dementia had a particularly high risk of mortality compared to people without dementia (RR 3·78, 95% CI 2·06–6·92).[23] A population-based cohort study suggested that part of the increased mortality risk in patients with Parkinson's disease can be ascribed to their increased risk of developing dementia.[24] Yet another previous study showed that the survival advantage of Alzheimer's

disease over dementia with Lewy bodies persisted after adjusting for age at onset, gender, comorbidity, and cognitive function.[13] It has been reported that people with Alzheimer's disease had a better prognosis than people with dementia with Lewy bodies.[12] Moreover, psychosis is more common in people with dementia with Lewy bodies than in people with Alzheimer's disease, resulting in increased mortality risk.[12] Compared with people with Alzheimer's disease, people with dementia with Lewy bodies are reported to have an accelerated cognitive decline, more comorbid conditions, greater health-care service use, and poorer quality of life, which leads to a higher mortality rate.[14,25–28] Consequently, Lewy body dementia (including Parkinson's disease dementia and dementia with Lewy bodies) was associated with a higher mortality rate and greater reduction in life expectancy compared with Alzheimer's disease.

We found that compared with people with Alzheimer's disease, people living with vascular dementia had a 1·26 times larger HR for all-cause mortality and a 1·33 year shorter survival time after diagnosis, whereas there were no significant differences in age at death. An increased occurrence of vascular risk factors[28] and higher rates of circulatory-associated death[29] have been implicated in the increased mortality risk and reduced life-span survival time in vascular dementia compared with Alzheimer's disease.[30] The high frequency of mortality from circulatory system diseases in vascular dementia might reflect that vascular dementia is part of a general cardiovascular disease.

In our study, frontotemporal degeneration was associated with a reduced life expectancy but not with an increased mortality rate compared with Alzheimer's disease, although a higher mortality rate was observed when compared with individuals without dementia. A study published in 2021 reported that motor symptoms were associated with reduced survival in patients with frontotemporal degeneration, including parkinsonism, dystonia, and apraxia.[31] Besides, rapid eating and dysphagia are common in patients with frontotemporal degeneration, and these symptoms might increase the risk of choking, aspiration pneumonia, and mortality.[32] Importantly, people with frontotemporal degeneration might have a younger age at onset and diagnosis than people with Alzheimer's disease, and thereby the mortality rate after diagnosis might be attenuated during the follow-up period. For example, Gerritsen and colleagues[33] studied people with young-onset dementia who experienced their first symptoms before the age of 65 years and reported a longer survival time for people with frontotemporal degeneration than for people with Alzheimer's disease. To date, studies investigating the survival outcomes of frontotemporal degeneration and its subtypes are scarce. The comparison of mortality rate between frontotemporal degeneration is debated.

Thus, for survival time from diagnosis, age at diagnosis might be a moderator; for survival time from onset, age at onset might be the moderator. Our study indeed found significant interactions between age and several survival-related outcomes. However, the interaction effects were only observed for particular types of non-Alzheimer's dementias compared with Alzheimer's disease. Moreover, most of the adjusted effect sizes on these outcomes had less than 10% of change-in-estimates. Importantly, the findings of mortality rate (HR and RR) were robust for all non-Alzheimer's dementias versus Alzheimer's disease, without significant age-related moderator effects. Furthermore, we did not find any small-study effects for the outcomes of survival time from onset and diagnosis. However, the interactions between age and mortality were significant for Lewy body dementia and its subtypes; the adjusted effect sizes for age at death had significant changes in point estimate when adjusted for age at onset or diagnosis (range 0·9–30·5%). Therefore, age at onset and diagnosis might play an important role in the difference in survival time between Lewy body dementia (or its subtypes) and Alzheimer's disease.

This study has several limitations. First, the sample size and the number of eligible studies for some subtypes of Lewy body dementia and frontotemporal degeneration were limited; therefore, we could not detect a difference though a significant difference might have existed for some comparisons. Second, heterogeneity was high in most analyses. We addressed this issue by using random-effects meta-analysis models as well as meta-regression and subgroup analyses. To further reduce heterogeneity, we did not include single-arm studies, and all the effect sizes were calculated against individuals without dementia or Alzheimer's disease reference groups. We also estimated the adjusted effect sizes and the proportion of change in point estimates for the significant moderators. Third, the data on age at onset and survival time from disease onset might be subject to recall bias. Fourth, we examined the mortality rate and survival time at a single point of clinical diagnosis, and some cases of dementia might be underdiagnosed or diagnosed late. A single cutoff of mortality on a particular date might lose information about when patients die over time. Local variation in practice groups (in terms of diagnosis) might add uncertainty to our estimates. Further studies could pool the prevalence and incidence data or infer the survival differences between Alzheimer's disease and non-Alzheimer's dementia. Fifth, in clinical studies, the diagnosis of dementia was based on clinical assessment, which lacks specificity. Patients with dementia might have co-pathologies of Alzheimer's disease, Lewy bodies, or vascular lesions. Finally, we only included peer-reviewed studies published in English. Therefore, our analyses did not include grey literature (eg, government reports) that might report vital statistics on dementia mortality.

In this systematic review and meta-analysis, we comprehensively compared non-Alzheimer's dementias with Alzheimer's disease and with individuals without dementia. Non-Alzheimer's dementias were associated

with higher mortality rates and shorter life expectancy than Alzheimer's disease. Most of all, Alzheimer's disease appeared to have the most favourable survival-related outcomes, and Lewy body dementia appeared to have the highest mortality rates. Higher mortality rates might also imply a higher likelihood of morbidity and disability. Discovering potential sources of divergence in mortality risks for distinct dementia types is important both for physicians and policy makers to develop tailored treatment and rehabilitation programmes for different types of dementia, and for patients and their families to facilitate future care planning. Further epidemiological research is warranted to investigate the specific risk factors of early mortality at different levels of morbidity across different types of dementia.

Contributors

C-SL and C-SC led the conception and design of the study. T-YC and T-CY led the data collection and quality assessment. C-SL, D-JL, C-CP, and C-SC did the statistical analysis, interpreted the data, and wrote and revised the Article. F-CY, P-TT, AFC, BS, TT, CM, JIS, JR, RS, TKR, Y-KT, C-KT, and C-LY contributed to study design, assisted in data interpretation, and revised the Article. All authors revised and approved the final version of the Article. All authors had full access to all the data reported in the study. C-SL and C-SC accessed and verified the data. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Our study is based on published data, and all data are retrieved from original papers. Therefore, there are no primary data to be shared. The data supporting the findings of our study are available within this Article and the appendix. The statistical plan and code for analyses are available on request from the corresponding author without any access criteria.

Acknowledgments

This work was not funded. BS is supported by a Clinical Lectureship (ICA-CL-2017–03–001) jointly funded by Health Education England and the UK National Institute for Health Research (NIHR). BS is part-funded by the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust. BS also holds active grants with the Medical Research Council (and the GCRF global multimorbidity seed-funding call) and Guy's & St Thomas' Charity (GSTT). The views expressed are those of the author(s) and not necessarily those of the (partner organisation), the NHS, NIHR, Department of Health and Social Care, MRC, or GSTT. RS is part-funded by the NIHR Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King's College London; and the NIHR Applied Research Collaboration South London (NIHR South London) at King's College Hospital NHS Foundation Trust. TKR has received research support from Brain Canada, Brain and Behavior Research Foundation, BrightFocus Foundation, Canada Foundation for Innovation, Canada Research Chair, Canadian Institutes of Health Research, Centre for Aging and Brain Health Innovation, National Institutes of Health, Ontario Ministry of Health and Long-Term Care, Ontario Ministry of Research and Innovation, and the Weston Brain Institute. TKR also received in-kind equipment support for an investigator-initiated study from Magstim, and in-kind research accounts from Scientific Brain Training Pro.

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