

BMJ Open Secular trends in the incidence of dementia in high-income countries: a protocol of a systematic review and a planned meta-analysis

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To cite: Roehr S, Pabst A, Luck T, *et al*. Secular trends in the incidence of dementia in high-income countries: a protocol of a systematic review and a planned meta-analysis. *BMJ Open* 2017;**7**: e013630. doi:10.1136/bmjopen-2016-013630

► Prepublication history and additional material is available. To view please visit the journal (<http://dx.doi.org/10.1136/bmjopen-2016-013630>).

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Received 26 July 2016
Revised 23 November 2016
Accepted 17 January 2017



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ABSTRACT

Introduction: A global dementia epidemic is projected for the year 2050 with an ever-rising number of individuals living with the syndrome worldwide. However, increasingly, studies are emerging from high-income countries (HIC) that show a positive trend towards a possible decrease in dementia occurrence. Therefore, we aim to systematically summarise evidence regarding secular trends in the incidence of dementia in HIC.

Methods and analysis: We will conduct a systematic review of the literature on secular trends in dementia incidence in HIC according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statements. To do so, we will search the databases MEDLINE (PubMed interface), EMBASE (Ovid interface) and Web of Science (Web of Science interface), as well as the grey literature on unpublished studies. To be eligible, studies must have been published in English or German since 1990 and provide sufficient information on prespecified eligibility criteria regarding outcome measurement and methodological approach. Study selection, data extraction and risk of bias assessment will be performed independently by 2 reviewers. Disagreement will be resolved by discussion and/or the involvement of a third researcher. Data abstraction will include study and participant characteristics, outcomes and methodological aspects. Results will be described and discussed regarding methodology. Depending on the number of studies found and the heterogeneity between the studies, we plan to combine outcome data through meta-analysis in order to get pooled incidence measures.

Ethics and dissemination: No primary data will be collected; thus, ethical approval is not required. The results will be disseminated through a peer-reviewed publication and conference presentations.

PROSPERO registration number: CRD42016043232.

INTRODUCTION

Dementia was named as a public health priority by the WHO in 2012, mostly because of

Strengths and limitations of this study

- First systematic review to summarise current findings on time trends in the incidence of dementia in high-income countries.
- The review will critically discuss methodological peculiarities of studies on secular trends of dementia incidence.
- The review may guide future study on secular trends of dementia occurrence.
- It may not be feasible to pool estimates of dementia incidence due to study heterogeneity.

the rising number of people living with dementia.¹ Currently, there are over 47 million cases of dementia worldwide, and this number is estimated to rise to over 131 million by the year 2050.² What has been termed an impending dementia epidemic has already had a huge economic impact. In 2015, the global estimated expenditures for dementia amounted to US \$818 billion. In the UK, for example, this exceeded the combined healthcare costs of cancer, stroke and heart disease.³ Besides the huge impact on the societal level, dementia places a tremendous burden on affected individuals, their families and caregivers, often family members themselves, with severe negative effects on quality of life for all involved.^{4 5} This is mainly due to the progressive nature of the syndrome which involves mounting neurocognitive impairment and losses in basic functioning in daily life. Dementia demands a substantial need for care, often requiring institutionalisation.⁶ Finally, dementia is linked to increased mortality.⁷

The rapid increase in the number of people living with dementia is mainly attributed to increasing life expectancy with the largest gains in low-income and middle-income countries (LMIC), where individuals may benefit most from better access to

healthcare and nutrition. Globally, individuals over 60 years of age are the most rapid increasing segment of the population due to the combination of increasing longevity and declining birth rates.⁸

Although, from a global perspective, the projected increase in the number of people living with dementia is daunting, there is evidence of differential dementia occurrence with regard to geography and time. Recent estimates of dementia prevalence, that is, the percentage of a population that is affected by the syndrome, revealed an increase in LMIC between 2010 and 2015 (Asia: 3.9% vs 4.7%, Africa: 2.6% vs 4.6%), as opposed to that in high-income countries (HIC; Western Europe: 6.2% vs 5.9%, the Americas: 6.5% vs 6.4%).²

The possibility of a decrease in dementia occurrence in HIC has recently received attention. For example, Jones and Greene asked in the *New England Journal of Medicine*, ‘Is dementia in decline?’ referring to the results from the Framingham Heart Study (USA) on incidence estimates of dementia from over three decades.⁹ In that longitudinal study, Satizabal *et al*¹⁰ reported a 20% decrease in dementia incidence for each decade. Debating results from other epidemiological studies on change of dementia occurrence, Langa¹¹ also suggested an optimistic trend towards declining dementia risk. Furthermore, from a policy perspective with regard to dementia occurrence in Western Europe, Wu *et al*¹² provided a ‘positive and encouraging message in terms of a possible decrease in dementia occurrence’.

Factors contributing to such a potential decline have not been fully identified, but rising levels of education, greater wealth and successful management of cardiovascular diseases might most likely be driving factors in such trends.^{9–11} Successful pharmacotherapy and other therapies to treat cardiovascular diseases were introduced in the early 1990s leading to a significant reduction of, for example, stroke which is one established risk factor for dementia.¹³

Investigating secular trends, that is, the occurrence of a disease over a prolonged period in a specific population, issues a unique challenge in terms of study methodology.^{11 12} One approach would be to compare dementia occurrence between at least two cohorts with significant time intervals in between using the exact same research methods. Another approach is to conduct longitudinal comparisons of the same cohort. However, differing response rates, the choice of time intervals between cohorts, the length of follow-up periods and instability in diagnostic criteria are only a few of the factors that might influence such results leaving evidence on secular trends uncertain.

Objectives

Our projected systematic review and planned meta-analysis aims to provide an overview of current studies on secular trends in the incidence of dementia in HIC with attention to methodological aspects. We

understand our systematic review to be an extension and update to the policy paper by Wu *et al*.¹² The authors reported on five studies of trends in dementia occurrence (four studies on prevalence, one study on incidence).¹² However, their review does not include studies conducted in HIC outside of Western Europe or studies published after 2013. After the publication of the policy paper by Wu *et al*,¹² at least three new studies on trends in dementia occurrence in HIC have been published.^{10 14 15}

We aim to focus on secular trends in dementia incidence only, that is, the number of new cases in a population within a confined period of time. The scope on incidence was chosen because potential changes in dementia occurrence may mainly be driven by primary prevention as a result of the improvement of modifiable risk factors.¹⁶

Depending on the number of studies and the quality of results reported, we aim to synthesise and combine incidence data through meta-analysis and estimate age-specific and gender-specific (cumulative) incidence rates of dementia. To do so, we plan to systematically identify and assess current literature on secular trends in dementia incidence from HIC, and to conduct subgroup analyses to isolate sources of heterogeneity between studies.

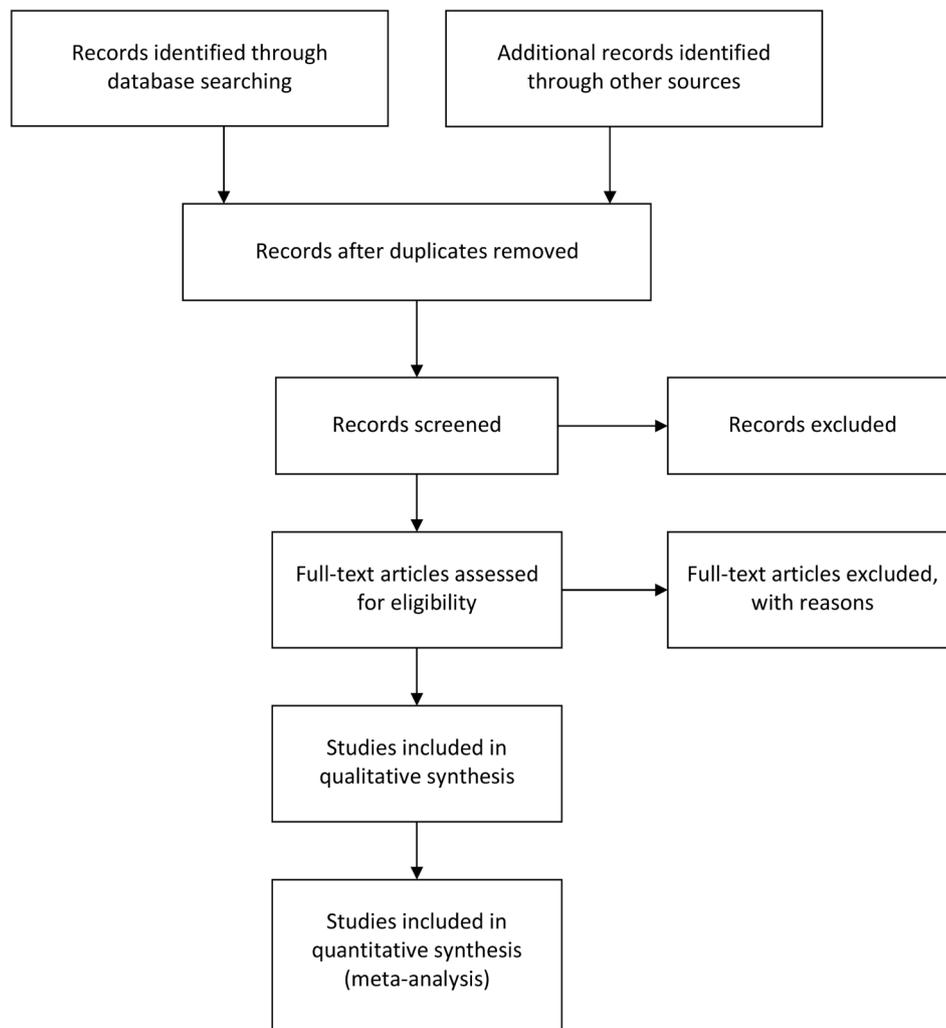
Methods and analysis

This protocol outlines our strategy to conduct a systematic review of cohort studies on secular trends in the incidence of dementia in HIC informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statements.^{17 18} We will adopt the four-phase PRISMA flow diagram (figure 1). The protocol itself is based on the PRISMA for systematic review protocols (PRISMA-P) guidelines.^{19 20}

Eligibility criteria

We will search for recent results from *observational studies* (study design criteria) conducted in *population-based or community-based samples* (setting criteria) reporting the *incidence of late-onset dementia* (outcome criteria) in at least *two different time points using comparable methods* (design criteria). We intend to only consider late-onset dementia, as young-onset dementia is relatively rare and might be driven by other underlying factors less subject to secular trends.²¹ Therefore, we will only include studies with participants who are *at least 60 years old* (participant criteria). We will only consider studies from HIC based on the World Bank classification.²² We do not set a minimum time interval for reported incidence rates of dementia in order to consider all such conducted studies. Finally, we will only include studies for which a detailed reporting of applied methods is available in order to be able to evaluate individual study quality and methodological differences between studies. We restrict

Figure 1 Flow diagram of the planned study selection process adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.



publications to the languages English and German. We will consider articles published since 1990.

Information sources and search strategy

Extensive literature searches will be performed by SR and AP in the databases MEDLINE (PubMed interface), EMBASE (OVID interface) and Web of Science (Web of Science interface). Search terms include a combination of (1) dementia, (2) Alzheimer's disease, (3) time, (4) trend, (6) secular, (7) change, (8) incidence, (9) epidemiology and (10) cohort. The draft of our explicit search strategy for MEDLINE is provided in online supplementary appendix 1. If feasible, medical subject headings (MeSH) will be used as search terms. The finalised MEDLINE search strategy will be adapted to the syntax and subject headings specifications of the other databases.

Furthermore, we will hand search the references of the identified literature for more potentially relevant studies to ensure literature saturation. Finally, we will conduct a grey literature search to consider unpublished studies (eg, conference abstracts) using Google and Google Scholar with the search terms named above. If

applicable and necessary, we will try to gather any other non-published data by contacting the researchers directly.

Data management

References and data will be managed using the Review Manager (RevMan) software package, version 5.3 (by the Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). RevMan is specifically designed for managing and analysing data in reviews applicable from bibliographical management to data synthesis. If sufficient, additional data analysis and meta-analysis will be performed using Stata V.13.1 SE (StataCorp LP, College Station, Texas, USA).

Selection process

Two reviewers, namely SR and AP, will independently identify potentially eligible articles by screening all titles and abstracts of the hits from the databases. At this stage, articles will be classified as relevant, irrelevant or uncertain. Articles classified as irrelevant will be excluded and reasons for that decision will be given. For articles judged relevant or uncertain, full texts will be

obtained. Then a full-text analysis will be undertaken, again independently by the two reviewers, to finally estimate study eligibility based on the previously established criteria. Any discrepancies in each stage of the study selection process will be resolved by discussion between the two reviewers. In cases of disagreement about particular articles, a third opinion from a senior researcher (TL/SGR-H) will be obtained.

Data collection process and data items

A standardised data abstraction form will be used to extract information on study characteristics, participant characteristics, relevant outcomes and methodology. A pilot version of the data extraction form (see online supplementary appendix 2) will be tested independently by two reviewers (SR and AP) on a subsample of the included studies to ensure that all relevant information is covered. A discussion of the first extraction experience will follow and any emerging issues will be corrected in the finalised form.

Data from each study will be collected independently and in duplicate by SR and AP. Whether data abstraction is reliable will be tested on a random sample. If necessary, modifications may be made and, in cases of disagreement, a third researcher (TL/SGR-H) will be involved. If any data cannot be clearly extracted, the study authors will be contacted.

In particular, we seek to extract the following variables: (1) study characteristics (eg, author, year of publication, country, study, study year(s), time interval between examinations, design, setting, sample size(s), response rate(s), person time), (2) participants' characteristics (eg, age, gender), (3) measurements (eg, incidence measure, adjustment/control of confounders, subgroup analyses) and (4) methodological aspects (eg, approach to dementia diagnosis, inclusion/exclusion criteria, study limitations).

Outcomes and prioritisation

The main outcome considered is the change of dementia incidence over time. If necessary, estimates of outcome data will be transformed and synthesised to report the (cumulative) incidence rate of dementia over a given time period.

Risk of bias in individual studies

We will assess and report on the methodological risk of bias of included studies using the framework proposed by Hoy *et al.*²³ The tool consists of 10 items addressing two domains of internal (measurement error, statistical analysis) and external (selection, non-response) validity and provides a summary risk of bias assessment. Each item is judged as being at 'high' or 'low' risk of bias. The summary item is based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) and Cochrane approaches.^{24 25} The overall inter-rater agreement of the tool was reported to be high, with a κ statistic of 0.82. We will make

adaptations to the Hoy *et al* tool to apply to incidence studies. Where appropriate, we will further adapt the guidelines of the Cochrane Consumers and Communication Review Group to evaluate the handling of incomplete outcome data (eg, dropouts and withdrawal) for studies comparing the same cohort over time.²⁶

Two authors (SR and AP) will independently assess the risk of bias of included studies, with any disagreement resolved by discussion to reach consensus. We will contact study authors for additional information about the included studies, or for clarification of the study methods as required. We will report a justification for our judgement for each item in a risk of bias table.

Strategy for data synthesis

Data synthesis

We will both provide a narrative synthesis and, if appropriate, conduct a quantitative meta-analysis using funnel and forest plots, and pooled statistics. To do so, we will extract and pool outcome data from the selected studies to identify similarities and critical differences in clinical assessments, study design, and the methodological and statistical approach.

Both cross-sectional comparisons of two independent cohorts assessed with the same survey over time, and longitudinal comparisons of the same cohort will be included in the synthesis. Studies that report incidence rates of dementia from multiple waves of the same survey conducted in different years will be considered as separate studies in the meta-analysis.

We will use RevMan for implementing the characteristics of studies, preparing the review, and building the tables and plots. In addition, meta-analysis regression in Stata will be used to test for the effect of different sets of covariates on dementia incidence (Review Manager (RevMan) [Computer program], 2014).

Assessment of heterogeneity

We will inspect and test for heterogeneity in study characteristics using forest plots and statistics such as χ^2 tests (significance level a priori set at $p < 0.1$) and I^2 values for pairwise meta-analysis. According to the Cochrane Handbook, we suppose a moderate level of heterogeneity between studies for I^2 values ranging from 30% to 60%.²⁷ If I^2 exceeds 60% for the pooled analysis, we will explore sources of heterogeneity in subgroups of studies. Depending on the observed heterogeneity, we will decide to use fixed-effect, random-effect or mixed-effect models to estimate the overall incidence rate and to quantify the uncertainty of that estimate.²⁸

Sensitivity/subgroup analyses

Given that we will be able to include a sufficient number of studies, we will perform additional analyses in order to check the robustness of our analytical approach. If data are sufficiently available, we aim to repeat the meta-analysis including only studies of considerable

quality (ie, low risk of selection bias, low risk of non-response bias).

Further, we will perform subgroup analyses based on individual characteristics (age, gender, region/country) and observation period (eg, 3-year, 5-year and 10-year time lags) to identify possible sources of heterogeneity. Meta-regression will be used to examine and test differences in the incidence rates related to age, gender and region.

Meta-bias

If a sufficient number of studies can be included in the meta-analysis, we will use graphical (eg, funnel plots) and statistical (eg, Egger tests) methods to explore the presence of small-study effects, which are indicative of possible publication bias.^{29 30}

Confidence in cumulative evidence

We will assess the quality of the supporting evidence of each included study by using the GRADE methodology.²⁵ This allows for the assignment of four grades of evidence (high, moderate, low, very low quality) to five different domains: limitations (risk of bias), imprecision, inconsistency, indirectness and publication bias. We will use the GRADEpro online software tool from the Cochrane collaboration (GRADEpro V.3.6; available from <http://grade.pro.org>) to import results of statistical analyses from RevMan and export a summary of the findings table back into the RevMan file. We will provide a table in our systematic review summarising the quality assessment of included publications.

Amendments

In the event of protocol amendments, we will provide the date of each amendment, describe the change and give the rationale for it.

Ethics and dissemination

Since we are not collecting primary data, ethical approval is not required.

The results of the systematic review and planned meta-analysis are intended to be published in a peer-reviewed international journal. Moreover, results may be presented at conferences and meetings relevant to the field.

DISCUSSION

The systematic review and planned meta-analysis will provide a comprehensive overview of the evidence of current secular trends in the incidence of dementia in HIC. Second, we aim to provide a critical discussion of the methodological peculiarities of studies on secular trends in the light of the methodology used in the included studies.

If there is further evidence of a decrease of dementia incidence, this could have implications for policymakers. In particular, it would strengthen the public health

strategy to further promote primary prevention of dementia.¹ This is supported by studies on risk factor reduction with regard to Alzheimer's disease (AD). For example, Norton *et al*¹⁶ have demonstrated that one-third of the worldwide AD cases could be attributed to potentially modifiable risk factors, that is, access to education, physical activity, smoking, midlife hypertension, midlife obesity, diabetes and depression. Modification of such lifestyle factors in consideration of the whole lifespan may have the largest effect on dementia occurrence. It might also have implications for public health strategies in LMIC where it is projected that the number of people living with dementia will most dramatically increase over the next three decades.²

The results of the systematic review may be limited by study design. If the reviewed articles prove too heterogeneous, a meta-analysis may not be feasible, and hence, a summarising statement of the evidence of secular trends in dementia incidence would be impossible.

Studies on secular trends in dementia incidence represent an emerging research area, as it is only recently that enough cohorts on the epidemiology of dementia have been followed long enough to enable such estimates. Subsequently, one would expect a growth in the literature on secular trend estimates for dementia that could shed more light on future developments. Our systematic review might direct such future studies by contributing to the gathered knowledge.

Acknowledgements The authors acknowledge support from the German Research Foundation (DFG) and Universität Leipzig within the programme of Open Access Publishing.

Contributors SR and AP are the guarantors of the systematic review. SR and AP drafted the manuscript. All authors contributed to the conception and design of the review. SR, AP and TL developed the search strategy. AP and SR developed the methodological approach. TL and SGR-H critically revised the protocol for important intellectual content. All authors approved the final version of the manuscript.

Funding This work will be published in affiliation with the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe; funded by the German Federal Ministry of Education and Research grants: 01G1431 and 01G10714) and the Study on Needs, Health Service Use, Costs and Health-related Quality of Life in a large Sample of Oldest-old Primary Care Patients (85+) (AgeQualiDe; funded by the German Federal Ministry of Education and Research grant: 01GY1322A).

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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