27-year time trends in dementia incidence in Europe and the US: the Alzheimer Cohorts Consortium

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Number of tables: 3

Number of figures: 4

Word count in abstract: 226

Word count in text body: 3,471

Reference Count: 34

Author Disclosures

Dr. Wolters reports no disclosures.

Dr. Chibnik reports no disclosures.

Dr. Waziry reports no disclosures.

Dr. Anderson is an independent scientific Non-Executive Director of Glaxosmithkline (GSK). GSK has no active research programmes of R&D on Alzheimer's or dementia therapies, and played no part in funding this research. Dr. Anderson holds shares in GSK and receives research funding support from GSK for work on pneumococcal vaccines and the development of antibiotic drug resistance. Dr. Anderson receives research funding (an unencumbered educational research grant) from Janssen (part of Johnson and Johnson) for the development of clinical trial simulators and mathematical models of disease progression. Janssen and Johnson and Johnson played no part in the writing of this manuscript or in the development of its content.

Dr. Berr reports no disclosures.

Dr. Beiser reports no disclosures.

Dr. Bis reports no disclosures.

Dr. Blacker reports no disclosures.

Dr. Bos reports no disclosures.

Dr. Brayne reports no disclosures.

Dr. Dartigues reports a grant from Roche, outside the submitted work.

Dr. Darweesh reports no disclosures.

Dr. Davis-Plourde reports no disclosures.

Dr. de Wolf is employed by Janssen Pharmaceuticals of Johnson & Johnson.

Dr. Debette reports no disclosures.

Dr. Dufouil reports no disclosures.

Dr. Fornage reports no disclosures.

Dr. Goudsmit reports no disclosures.

Dr. Grasset reports no disclosures.

Dr. Gudnason reports no disclosures.

Dr. Hadjichrysanthou reports no disclosures.

Dr. Helmer reports grants and personal fees from Roche, outside the submitted work.

Dr. M.A. Ikram reports no disclosures.

Dr. M.K. Ikram reports no disclosures.

Dr. Joas reports no disclosures.

Dr. Kern reports no disclosures.

Dr. Kuller reports no disclosures.

Dr. Launer reports no disclosures.

Dr. Lopez reports no disclosures.

Dr. Matthews reports no disclosures.

Dr. McRae-McKee reports no disclosures.

Dr. Meirelles reports no disclosures.

Dr. Mosley Jr. reports no disclosures.

Dr. Pase reports no disclosures.

Dr. Psaty reports service on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson.

Dr. Satizabal reports no disclosures.

Dr. Seshadri reports no disclosures.

Dr. Skoog reports grants from Swedish Research Council, grants from Swedish Council for Working Life and Social Research, grants from Swedish State ALF-agreement (ALF 716681) during the conduct of the study; personal fees from Takeda, outside the submitted work.

Dr. Stephan reports no disclosures.

Dr. Wetterberg reports no disclosures.

Dr. Wong reports no disclosures.

Dr. Zettergren reports no disclosures.

Dr. Hofman reports no disclosures.

ABSTRACT

Objective: To determine changes in the incidence of dementia between 1988 and 2015.

Methods: This analysis was performed in aggregated data from individuals >65 years in seven population-based cohort studies in the United States and Europe from the Alzheimer Cohort Consortium. First, we calculated age- and sex-specific incidence rates for all-cause dementia, and then defined non-overlapping 5-year epochs within each study to determine trends in incidence. Estimates of change per 10-year interval were pooled and results are presented combined and stratified by sex.

Results: Of 49,202 individuals, 4,253 (8.6%) developed dementia. The incidence rate of dementia increased with age, similarly for women and men, ranging from about 4 per 1,000 person years in individuals aged 65-69 years, to 65 per 1,000 person years for those aged 85-89 years. The incidence rate of dementia declined by 13% per calendar decade (95% CI: 7%-19%), consistently across studies, and somewhat more pronouncedly in men than in women (24% [95% CI 14%-32%] versus 8% [0%-15%]).

Conclusion: The incidence rate of dementia in Europe and North America has declined by 13% per decade over the past 25 years, consistently across studies. Incidence is similar for men and women, although declines were somewhat more profound in men. These observations call for sustained efforts to finding the causes for this decline, as well as determining their validity in geographically and ethnically diverse populations.

Introduction

At present, an estimated 47 million people worldwide are living with dementia, making it a leading cause of dependence and disability.[1-3] Because of a rapid aging of populations, the number of people living with dementia is projected to triple in the next 30 years, and the socioeconomic burden of dementia to increase accordingly. The projected burden of dementia could be alleviated if improvements in life conditions and healthcare over the last decades have decreased dementia risk. Indeed, recent studies in North America and Europe have reported a decline in the incidence of dementia over the last forty years, with possible reductions of 10% to 38% per decade, but estimates are inconsistent and often imprecise.[4-8]

Reliable assessment of time trends in the incidence of dementia calls for careful monitoring in the general population, in a consistent manner over a prolonged period of time. Population-based cohort studies have generally collected data on dementia incidence over decades, but few have been designed and powered to test for differences across calendar time. Consequently, individual studies lack the precision to quantify time trends in dementia incidence, leaving projections of the future burden of disease uncertain, with the range of reported reductions in time trends allowing for a variation of tens of millions new cases of dementia in the coming decades. Large heterogeneity, notably in the applied methodology of prior analysis of secular trends further hinders comparison and reliable prediction across populations.[6, 9] In a multinational collaboration, we aggregated data from available long-term population-based studies from Europe and the USA to study the trend in dementia incidence, and establish whether similar changes were observed in men and women.

Methods

Data sources and study population: the Alzheimer Cohorts Consortium: ACC

The ACC is composed of nine cohorts selected based on pre-determined criteria. Specifically, the included cohorts had to be prospective, population-based, have in-person exams, a span of at least 15 years of available follow-up and include at least 2,000 participants at baseline. In addition, many cohorts have data on genotype and extensive phenotyping, particularly of cardiovascular factors and acquisition of brain magnetic resonance imaging (MRI). The consortium includes the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, the Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study (CHS), the Cognitive Function and Ageing Studies (CFAS), the Framingham Heart Study (FHS), the Gothenburg population studies, the Personnes Agées QUID (PAQUID) study, the Rotterdam Study, and the Three-City Study (3C). More detailed information on the ACC has been published previously.[10]

Standard Protocol Approvals, Registrations, and Patient Consents

All the participating ACC studies were approved by their respective institutional review committees, and all subjects provided written informed consent.

Cohorts

The present study included seven participating cohorts and data collection summaries are presented in Table 1, and include a total of 49,202 (minimum age of 65 at entry) of whom 4,253 had developed dementia to date. Cohort descriptions have been provided previously.[8] Briefly, the *Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study* is a sample drawn from the population-based Reykjavik Study cohort[11]. The original source population in the Reykjavik Study included a random sample of men and women born between 1907 and 1935 and living in Reykjavik in 1967. Between 2002 and 2006, 5,764 survivors of the original cohort were re-examined for the AGES-Reykjavik study. The *Cognitive Function and Ageing Studies (CFAS)* comprises two population-based studies among individuals aged 65 years and over living in the community, including those in institutions.[5] The original six-site study began in 1989 (MRC-CFAS; response 80%), however, interviewing began in 1991 for the three sites that were selected for the current comparison study. This comparison study, with independent sampling across three similar sites was initiated two decades later, with baseline interviewing undertaken from 2008-2010 (CFAS II; response 56%). For this analysis, the baseline and two-year follow-up data are included. The *Framingham Heart Study (FHS)* began in 1948 with the recruitment

of an original cohort of 5,209 men and women who were 28 to 62 years of age at entry.[12] In 1971, a second generation of study participants, including 5,124 children and spouses of children of the original cohort were enrolled.[13] The *Gothenburg population studies* consist of four studies among individuals representative of the Swedish population.[14, 15] These include Prospective Population Study of Women, a study of women which includes 1,462 women aged 38-60 who are followed since 1968; the Gothenburg H70 Birth Cohort Studies, which studies several birth cohorts of 70-year olds recruited from 1971 and onwards of which a cohort of 70-years olds enrolled in 2000 were included in this study; and the second H85 study, which started in 2009 with the enrolment of a birth cohort of 85-year olds. The *Personnes Agées QUID (PAQUID)* cohort is a population-based study in the southwest of France among 3,777 individuals aged 65 years or older recruited in 1988.[16] There have been twelve subsequent waves of data collection at 1, 3, 5, 8, 10, 13, 15, 17, 20, 22, 25 and 27 years after the baseline assessment. Due to changes in diagnoses over the first years of follow-up, for trends analysis, only data from the 8-year follow-up was included.[17] The *Rotterdam Study (RS)* is a prospective population-based cohort study comprising 14,926 subjects aged 45 years or older.[18] Baseline data of 7,983 participants were collected between 1990 and 1993 (response 78%), with subsequent cohort expansions in 2000 (3,011 individuals, 67%) and 2006 (3,236 individuals, 65%). Participants are interviewed at home and re-examined at a dedicated research center once every 4 years. In addition, the entire cohort is continuously under surveillance for disease outcomes through linkage of electronic medical records with the study database. The *Three-City Study (3C)* is a longitudinal population-based study of the relation between vascular diseases and dementia in persons aged 65 years and older.[19] Between 1999 and 2001, a total of 9 294 non-institutionalized persons were recruited from the electoral rolls of three French cities: Bordeaux (South-West), Dijon (North-East) and Montpellier (South-East). Extensive follow-up examinations were performed at home or in a dedicated research center every two years after the baseline assessment, comprising standardized questionnaires, clinical examinations, and detailed cognitive assessment. An overview of the study populations is presented in Table 1.

The Atherosclerosis Risk in Communities (ARIC) study and the Cardiovascular Health Study (CHS), which are also part of the ACC, were not included in these analyses as ARIC did not have sufficient follow-up at the time of these analyses, and the CHS had consistent data on long-term follow-up available in only a small subset of the (Pittsburgh) population only.

Assessment of Dementia and Alzheimer's Disease

Our primary outcome of interest is a diagnosis of all-cause dementia with a secondary outcome of clinical Alzheimer's Disease, where available. Dementia diagnostic criteria were consistent across the study period for each study, and are based on either Diagnostic and Statistical Manual – IIIR (DSM-IIIR) (CFAS, Gothenburg studies, PAQUID and the Rotterdam study) or DSM-IV (AGES, FHS and 3C). The National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria[20] for Alzheimer's disease diagnosis was used in all cohorts except CFAS and the Gothenburg studies, which did not have data on Alzheimer's diagnosis.

Statistical Analysis

Poisson regression was used to calculate 5-year incidence rates (IRs) and 95% confidence intervals. All models were adjusted for age at time of entry and sex, and the log of follow-up time was used as an offset variable with incidence rates presented for the middle age of each 5-year age group (e.g. for 65 to 69.9 age group we used the middle age of 67.5). A single participant was able to contribute to multiple age groups as long as that person is free from dementia at the start of the age-group category. A robust sandwich estimator was used to calculate the 95% confidence interval to control for the violation of the independence assumption[21]. Additionally, models for all-cause dementia were stratified by age and sex. Due to limited data and follow-up among men, the Gothenburg studies included only women for these analyses. For comparison between men and women, results from the sex-specific incidence rates were analysed across all cohorts using the "meta"-package (version 4.8-4) of the statistical software R, version 3.4.2 with heterogeneity across studies being assessed with an I^2 statistic.

Cohorts with sufficient follow-up data to create at least two epochs were included in the trends analysis. Cohort-specific, non-overlapping epochs were created in order to maximize the person-years available in each cohort, with two epochs in the Three-City study, three epochs in PAQUID, the Rotterdam Study and the Gothenburg studies, and four epochs in FHS. Cox proportional hazard regression models were used to calculate the 5-year cumulative hazards per epoch, and hazard ratios (HR) for all-cause dementia and Alzheimer's disease for each epoch relative to the first. In CFAS Bayesian full likelihood imputation models were used to adjust for study design of CFAS I.[22] All models were adjusted for age at entry of the epoch and sex, with the exception of the sex-stratified models, which were adjusted solely for age. Participants were included in an epoch if they were free of dementia at the beginning of the epoch, and censored at the end of five years, at their last visit, when lost to follow-up or at date of death, whichever came first. Similar to the incidence analyses, participants contributed to multiple epochs if they

were free of dementia at the beginning of the epoch and we utilized a robust sandwich estimator for the covariance structure to estimate the 95% confidence limits to account for non-independence[21]. To compare temporal trends across studies, we then calculated a hazard ratio per 10-year change in calendar time. This is interpreted as a change in 5-year hazard per decade advance in calendar time and was estimated using years from the median date of the referent first epoch to the median start date of each epoch, divided by ten and treated as a continuous variable in the model. This assumes the time trend is constant across the 25-year study period. Trends were meta-analysed across all cohorts, with heterogeneity across studies assessed with an I^2 statistic using the "meta"-package (version 4.8-4) of the statistical software R, version 3.4.2. To rule out any dominant effect of the largest studies on the pooled estimate, we performed sensitivity analyses in which we excluded one by one the studies with the largest weight until a minimum of three studies.

To visualize the impact of changing incidence in dementia both globally and within Europe and the USA, we used data from the 2012 and 2015 World Alzheimer Reports to estimate how a decreasing trend in incidence would impact the expected number of new cases per year by 2040. We used the change in total cases/year between 2010 and 2015 and extrapolated that same change for each 5-year interval, taking into account the increasing population size and increasing longevity through to 2040, which resulted in similar projections as given in the 2012 report. We then estimated the effect of a continued decline in incidence on the total number of new dementia cases until 2040, assuming effect estimates for time trends from the present study.

All analyses were done separately by investigators responsible for each cohort. In order to ensure harmonization in analyses, each cohort received a detailed analysis plan, including statistical code in both SPSS (IBM Corp., Armonk, NY) and SAS (SAS Institute, Cary, NC).

Data availability statement

Framingham Study data are available through BioLINCC, where qualified researchers can apply for authorization to access (https://biolincc.nhlbi.nih.gov/studies/framcohort/?q=Framingham). Data of European cohorts are available upon request, after approval by the relevant institutional review boards, in keeping with informed consent and the national and EU data protection regulations. Request can be directed at the following contacts: for AGES, the Icelandic Heart Association (AGES_data_request@hjarta.is); for the Rotterdam Study, data manager Frank J.A. van Rooij (f.vanrooij@erasmusmc.nl); for CFAS, the national co-ordinator of the CFAS Collaboration Data Archive, Linda Barnes (leb22@medschl.cam.ac.uk); for 3C, the principle

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Results

Cohort characteristics, and demographics of participants in the analyses per cohort are presented in Table 1. Data on nearly 50,000 participants with 2 to 27 years of follow-up are included in this study. All the cohorts comprise more women than men with a mean relative frequency of 59%. Mean age at baseline of the first epoch was between 71 and 77 for all cohorts (Table 1).

A total of 49,202 participants were included in the incidence analyses and followed for a total of 256,805 person-years. A total of 4 253 incident cases of dementia were recorded in the data analysed for the included cohorts (Table 1). Across all cohorts, incidence rates by age group were consistent (Table 2). As expected, the incidence of dementia increased with age, from 1.6 to 8.6 per 1,000 person-years in the youngest age group (65-69 years), to between 42.2 and 97.0 per 1,000 person-years in the oldest age group (85-89 years). In general, the CFAS II cohort and the FHS had the lowest incidence rates and the Rotterdam Study observed the highest (Figure 1). This pattern was similar for the sex-specific results. When results were combined across cohorts, we saw little difference in incidence rates by age group, or between men and women (Figure 2).

We directly compared and analysed the 5-years hazard ratios per 10-year increment in calendar time between cohorts. This showed a consistent decrease in the 5-year cumulative hazard of all-cause dementia in all cohorts (Figure 3A; Table 3). Across studies, we saw a 13% (95% CI: 7-19%) decrease in all-cause dementia per decade since 1990. Patterns were similar, for clinical Alzheimer's disease (decrease per decade: 16% [8-24%]; Figure 3B). The decrease in 5-year cumulative hazard for all-cause dementia was larger in men than women, with a 24% decrease [14-33%] in men versus an 8% decrease [0-15%] in women, again with little heterogeneity across studies (I^2=0% and 5%, respectively) (Figure 3C and 3D). Results were broadly unaltered by stepwise excluding the three studies with the largest weight, with hazard ratios (95% CI) of 0.84 (0.78-0.92), 0.87 (0.77-0.97), and 0.82 (0.71-0.95), after exclusion of respectively CFAS, CFAS and RS, and CFAS, RS, and FHS.

Discussion

In this analysis of data from seven large cohort studies representing populations from six different countries, we show that the age-stratified incidence rates of dementia are consistent across cohorts and notably similar between men and women. When examining changes in the incidence rate over the past 25 years, we observe a decline of 13% per decade, again consistent across studies, but somewhat stronger for men compared to women. If we assume continuation of this trend in Europe and North America into the coming decades – although this was not the main objective of our study – it could imply that 15 million fewer people will develop dementia by 2040 in high-income countries, compared to widely quoted projections of the global burden of disease.[23] If the same continuous incidence reduction could be achieved worldwide, this could lead to a reduction in the expected incidence of dementia of up to 60 million new cases of dementia by 2040 (Figure 4).

Several of the cohorts within the ACC have previously published data on time trends in the incidence of dementia.[4, 5, 7, 8] The incidence trends described here are an important step towards consensus, with substantially greater precision arising from using consistent analytical techniques across cohorts. In addition, our analyses suggest that these time-trends in dementia incidence have occurred in both men and women. However, the effects of this decline in age-specific incidence will also depend on concurrent changes in life-expectancy.[24] Reductions in years spent with cognitive disability in the UK from 1991 to 2011,[5] and reductions in years lived with dementia in the USA over the last 30 years[7] raise hope that preventive efforts involving lifestyle and health care interventions against dementia can offset at least part of the growing burden of dementia with from global gains in life-expectancy.

The study has strengths and limitations. First and foremost, this analysis has greater precision derived from combining several large, long-term population-based cohorts that have strived to limit person attrition from the studies over many years. We have described methodological considerations for studying trends in the incidence of dementia previously[10]. It is important to note that despite inevitable differences in population demographics, genetic and lifestyle make-up, and ascertainment methods for dementia, incidence trends displayed relatively little heterogeneity across studies. Further, concurrent increases in life expectancy and increased awareness of dementia in the population may have led to underestimation of a downward trend arising from increased diagnosis efficiency.

As a first limitation, despite extensive efforts to limit attrition, differential dropout may have occurred when linkage to health records was not available. However, attrition that is constant over time is unlikely to affect secular trends. Second, while the definition of dementia as a syndrome has remained relatively constant, the definition and understanding of what should

be called Alzheimer's disease have shifted substantially over the past decades. In the absence of pathologically confirmed diagnoses in most cohort studies, it remains uncertain what pathological changes may underlie the observed trends. Third, calculating the effect of the observed trends on future dementia incidence relies on various assumptions that were beyond the scope of the current study to address entirely, and studies applying multistate modelling remain required for accurate projections in light of changing risk factor burden and mortality. Fourth, the application of consistent entry criteria helped guarantee valid assessment of incidence trends, but may have led to selection of a somewhat healthier population and consequently underestimation of absolute incidence rates. Finally, the choice to limit our analyses to population-based cohorts in order to get the most accurate measure of population incidence, has led to a study population containing only those of European ancestry living in either the United States or Europe, with a generalizability of our findings to no more than 16% of the world's total population. These analyses should therefore be expanded to include (future) population studies with more diverse populations both within the United States and around the globe.

A main challenge in finding a cause of declining temporal trends in dementia is that there have been many concurrent changes over time in possible key risk factors, including lifestyle education and health interventions such as blood pressure control and antithrombotic medication. While none of these have been specifically intended to halt cognitive decline, decades of cardiovascular risk management have likely had substantial effects on brain health, supported by reduction of small-vessel disease on brain imaging in more recent years.[8] The challenge remains to identify the critical causal factors among a variety of interventions influencing blood pressure, cholesterol, and inflammation that may have contributed to the decrease. Improved access and provision of education is another major change over the past century that could explain decreasing dementia incidence rates over time.[25]

Contrasting reports on the incidence of dementia have emerged recently from Japan,[26] China,[27] and Nigeria,[28] showing stable, or even increasing incidence rates. Similarly, in multi-ethnic populations in the USA declines have been seen in some,[29] but not all studies.[30] Against the backdrop of the large expected increases in dementia burden, particularly in Asia and Africa,[23] these observations temper the optimism for low to middle income countries, and render it all the more necessary to unravel the causes underlying the trends seen in this present study. Comparison with other geographical regions may well aid in pinpointing similar or discordant trends. Overall increased ethnic and geographic diversity within the ACC and the wider research community is therefore an important ongoing goal.

The development we see now in the epidemiology of dementia is somewhat reminiscent of the first report of a decline in mortality from coronary heart disease in 1964.[31] If history has taught us anything in that respect, it is the need for prolonged, consistent surveillance of disease and associated factors to enable the future modelling of trends and the identification of causes.[9, 31] Similar to heart disease[31], we should caution that the rise on a global scale of obesity,[32] diabetes,[33] and hypertension,[34] may reverse trends in dementia over the coming decades. As such, continued surveillance for dementia in the population-based studies within the ACC provides the framework for further investigation of potential causes of the declining time-trend in dementia incidence.

In conclusion, the incidence of dementia in Europe and North America is very similar among men and women and has declined by 13% per decade over the past three decades. Identification of the underlying causes is vital to sustain and possibly enhance these trends in the face of changing risk factor profiles. It is essential to achieve equal reductions in areas of the world where projected increases in dementia burden are steep, and improvements in incidence thus far absent.

Funding

The present study was supported by an unrestricted grant from Janssen Prevention Center, Leiden, The Netherlands

Funding for individual Cohorts

Age, Gene/Environment Susceptibility (AGES). This study is supported by National Institute of Aging contracts (N01-AG-12100 and HHSN271201200022C) with contributions from the National Eye Institute, National Institute on Deafness and Other Communication Disorders, and the National Heart, Lung and Blood Institute, the National Institute of Aging Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament).

Cognitive Function and Ageing Studies (CFAS): Medical Research Council (MRC) CFAS I was funded by the MRC (Research Grant: G9901400) and the National Health Service (NHS). CFAS II has been supported by the UK Medical Research Council (Research Grant:G06010220) and received additional support from the National Institute for Health Research (NIHR), comprehensive clinical research networks in West Anglia, Nottingham City and Nottinghamshire County NHS Primary Care trusts and the dementias and neurodegenerative disease research Network (DeNDRoN) in Newcastle.

Framingham Heart Study (FHS). This work was supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (contracts N01-HC-25195 and HHSN268201500001I). This study was also supported by grants from the National Institute on Aging: (AG054076, U01-AG049505, and AG008122, R01AG049607, AG033193, AG033040, AG052409, AG59421) and the National Institute of Neurological Disorders and Stroke (R01-NS017950, NS100605).

The Gothenburg study. This study was supported by grants from The Swedish Research Council 2012-5041, 2015-02830, 2013-8717, Swedish Research Council for Health, Working Life and Wellfare (no 2001-2646, 2003-0234, 2004-0150, 2006-0020, 2008-1229, 2012-1138, 2004-0145, 2006-0596, 2008-1111, 2010-0870, 2013-1202, 2001-2849, 2005-0762, 2008-1210, 2013-2300, 2013-2496, Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse, Hjärnfonden, Swedish State Support for Clinical Research (ALF Västra Götalandsregionen), the Swedish state under the agreement between the Swedish Government and the county councils, the ALF-agreement (ALFGBG-813921, ALFGBG-65930, ALF-GBG-716681), The Alzheimer's Association Zenith Award (ZEN-01-3151), The Alzheimer's Association Stephanie B. Overstreet Scholars (IIRG-00-2159), Alzheimer's Association (IIRG-03-6168), The Alzheimer's Association (IIRG-09-131338), Eivind och Elsa K:son Sylvans stiftelse, Stiftelsen Söderström-

Königska Sjukhemmet, Stiftelsen för Gamla Tjänarinnor, Handlanden Hjalmar Svenssons Forskningsfond, Stiftelsen Professor Bror Gadelius' Minnesfond, Swedish Alzheimer foundation.

PAQUID. The PAQUID cohort was supported by IPSEN France, NOVARTIS Pharma France, and the CNSA (Caisse Nationale de Solidarité et d'Autonomie). The research presented in this manuscript is original. The contents of this article are solely the responsibility of the authors. IPSEN, NOVARTIS and the CNSA did not fund this specific study. The funders had no role in the collection, management, analysis, or interpretation of the data and had no role in the preparation, review or approval of the manuscript.

The Rotterdam Study. This study is supported by the Erasmus Medical Centre and Erasmus University Rotterdam, The Netherlands Organization for Scientific Research (NWO), The Netherlands Organization for Health Research and Development (ZonMW), the Research Institute for Diseases in the Elderly (RIDE), The Netherlands Genomics Initiative, the Ministry of Education, Culture and Science, the Ministry of Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. This research was further supported by funding from the European Union Seventh Framework Program (FP7/2007e2013) under grant agreement no. 601055, VPH-Dare@IT (FP7-ICT-2011-9e601055); and funding from the European Union's Horizon 2020 research and innovation program under grant agreement no. 667375 (Co-STREAM) and under grant agreement no. 678543 (European Research Council (ERC) funded project: ORACLE). None of the funding organizations or sponsors were involved in study design, in collection, analysis, and interpretation of data, in writing of the report, or in the decision to submit the article for publication.

The Three-City Study is conducted under a partnership agreement between INSERM, Bordeaux school of public health (ISPED) of the University of Bordeaux, and Sanofi-Aventis. The "Fondation pour la Recherche Médicale" funded the preparation and initiation of the study. The Three-City Study is also supported by the "Caisse Nationale Maladie des Travailleurs Salariés", "Direction Générale de la Santé", "Mutuelle Générale de l'Education Nationale", "Institut de la Longévité", "Conseils Régionaux of Aquitaine and Bourgogne", "Fondation de France", and Ministry of Research-INSERM Programme "Cohortes et collections de données biologiques," French National Research Agency COGINUT ANR-06-PNRA-005 and COGICARE ANR Longvie (LVIE-003-01), the "Fondation Plan Alzheimer" (FCS 2009-2012), and the" Caisse Nationale pour la Solidarité et l'Autonomie".

Infrastructure for the **CHARGE** Consortium is supported in part by National Heart, Lung and Blood Institute (HL105756) and for the neurology working group by National Institutes of Aging (AG033193, AG049505, AG059421 and AG058589).

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Table 1: Demographics and Characteristics of cohorts

Study	PAQUID	Rotterdam Study	Framingham Heart Study	Gothenburg Studies	CFAS I	CFAS II	Three-City Study	AGES, Reykjavik
Country	France	Netherlands	USA	Sweden	UK	UK	France	Iceland
Sample Size	2,960	10,235	2,596	1,168	6,441	11,788	8,250	5,764
Dementia follow-up, y	27	25	25	23	2	2	13.5	6
Mean age, y	75.3	71.4	72.1	76.1	76.4	76.0	74.0	77.0
Women, %	58.0%	58.0%	59.2%	100%	61.6%	56.1%	61.3%	57.7%
Caucasian ethnicity, %	[a]	98.6%	100%	[a]	99.1%	97.2%	100%	100%
Person-Years	19,314	74,517	29,906	6,368	12,850	25,319	64,561	23,970
Incident dementia	578	766	685	145	261	390	951	477
Incident AD	455	521	540	[a]	[a]	[a]	653	150

[a] Data not collected

Table 2: Incidence rates (per 1000 persons) by cohort, age groups and sex

	PAQUID	Rotterdam Study	Framingham Heart Study	Gothenburg Studies	CFAS I	CFAS II	Three-City Study	AGES Reykjavik
Sample Size	4498	10235	1986	1168	6441	11788	12845	5135
Person-Years	18513	74517	20615	6368	12850	25319	53808	22386
Incident Dementia	491	766	592	145	261	390	634	369
Age Groups								
65-69	3.2 (1.8-5.5)	5.7 (4.0-8.1)	1.6 (0.6-4.5)	N/A	8.6 (5.2-14.2)	5.0 (3.0-8.7)	2.0 (0.1-0.3)	4.5 (2.7-6.5)
70-74	5.9 (3.6-9.3)	19.5 (15.7-22.4)	9.7 (7.1-13.3)	8.0 (5.4-11.8)	11.0 (6.8-17.7)	8.2 (5.4-12.6)	6.3 (0.5-0.8)	7.9 (6.4-9.5)
75-79	26.5 (22.2-31.5)	37.2 (31.3-44.3)	17.9 (1.4-2.2)	18.6 (10.2-33.6)	18.6 (11.7-29.4)	16.4 (11.4-23.6)	12.8 (1.3-1.5)	15.7 (13.4-18.1)
80-84	43.6 (37.6-50.6)	58.3 (48.3-70.4)	41.0(3.5-48.4)	43.2 (29.6-62.9)	41.2 (29.3-57.9)	32.1 (23.4-44.1)	23.1 (2.0-2.7)	37.3 (33.3-41.5)
85-89	73.1 (62.3-85.9)	97.0 (76.9-122.2)	67.9 (56.5-81.5)	73.3 (27.1-200.9)	56.3 (38.9-81.4)	42.2 (28.3-62.7)	48.2 (4.0-5.8)	66.3 (56.3-76.8)
				Men Only				
Sample Size	1826	4296	782	N/A	2279	5575	4834	2177
Person-Years	7491	30849	7685	N/A	4533	11961	19626	9177
Incident Dementia	158	271	188	N/A	95	173	214	155
Age Groups								
65-69	5.1 (2.6-9.8)	7.3 (4.3-12.5)	3.4 (1.5-7.3)	N/A	10.9 (5.7-20.6)	5.4 (2.6-11.3)	2.3 (0.1-0.5)	4.1 (1.5-7.2)
70-74	7.5 (4.0-14.0)	19.2 (14.0-26.4)	7.8 (5.1-11.8)	N/A	14.8 (8.0-27.5)	10.1 (5.8-17.6)	7.0 (0.5-1.0)	7.0 (4.9-9.3)
75-79	25.6 (19.3-33.9)	43.5 (33.1-57.2)	22.6 (17.6-29.0)	N/A	22.0 (8.1-59.2)	13.6 (7.0-26.6)	11.8 (0.9-1.5)	16.8 (13.3-20.6)
80-84	31.2 (23.3-41.8)	57.1 (41.8-78.0)	25.0 (18.7-33.2)	N/A	47.3 (27.6-81.2)	22.3 (12.4-38.9)	19.3 (1.5-2.6)	39.8 (33.1-46.4)
85-89	58.7 (42.7-80.5)	118.9 (76.5-184.8)	73.6 (57.0-95.1)	N/A	70.4 (35.8-138.3)	37.7 (22.4-63.4)	49.0 (3.5-6.9)	62.1 (45.1-76.2)
				Women Only				
Sample Size	2672	5939	1204	1168	4163	6914	8011	2958
Person-Years	11022	43668	12930	6368	8317	14787	33183	13209
Incident Dementia	333	495	404	145	166	300	420	214
Age Groups								
65-69	1.6 (0.6-4.5)	4.6 (2.9-7.4)	1.7 (0.6-4.6)	N/A	6.4 (3.0-13.7)	4.7 (2.1-10.2)	1.8 (0.1-0.4)	4.7 (2.4-7.3)
70-74	4.4 (2.0-9.4)	19.7 (14.6-26.4)	9.2 (6.5-13.0)	8.0 (5.4-11.8)	7.9 (3.8-16.2)	6.1 (3.0-12.4)	5.7 (0.4-0.8)	8.5 (6.5-10.7)

75-79	27.1 (21.6-33.9)	33.4 (26.6-41.9)	17.8 (14.2-22.3)	18.6 (10.2-33.6)	17.5 (10.5-29.2)	16.8 (10.6-26.8)	13.4 (1.1-1.6)	14.9 (11.9-18.0)
80-84	50.7 (42.7-60.1)	58.6 (46.2-74.4)	41.0 (34.8-48.4)	43.2 (29.6-62.9)	37.6 (24.6-57.3)	39.3 (26.7-57.6)	29.0 (2.1-3.0)	35.8 (30.8-41.2)
85-89	80.3 (66.7-96.6)	89.2 (68.0-116.9)	67.9 (56.4-81.6)	73.3 (27.1-200.9)	50.6 (32.6-78.5)	45.8 (30.0-69.9)	47.8 (3.8-6.0)	68.8 (57.3-83.7)

Table 3: Change in incidence per decade (HR, 95% CI) by study and sex

	PAQUID	Rotterdam Study	Framingham Heart Study	Gothenburg Studies[a]	CFAS I/II	3 Cities	Meta-Analysis (random-effects)
All cause dementia	0.75 (0.60-0.94)	0.82 (0.73-0.93)	0.93 (0.79-1.11)	0.84 (0.60-1.18)	0·93 (0.82-1.05)	0.90 (0.71-1.13)	0.87 (0.81-0.93)
Alzheimer's Disease	0.70 (0.55-0.89)	0.85 (0.74-0.98)	0.85 (0.71-1.03)			0.95 (0.72-1.25)	0.84 (0.76-0.92)
Sex							
Men	0.60 (0.39-0.91)	0.78 (0.63-0.97)	0.86 (0.64-1.16)	N/A	0.78 (0.63-0.97)	0.67 (0.45-1.00)	0.76 (0.67-0.86)
Women	0.82 (0.63-1.07)	0.84 (0.72-0.97)	0.97 (0.78-1.20)	0.84 (0.60-1.18)	1.02 (0.86-1.19)	1.04 (0.78-1.37)	0.92 (0.85-1.00)

[a] Includes only women

Figure 1.

Title: Incidence rates of dementia, stratified by cohort and age group

Figure 2.

Title: Incidence rates of dementia by age group, comparing men vs. women

Figure 3.

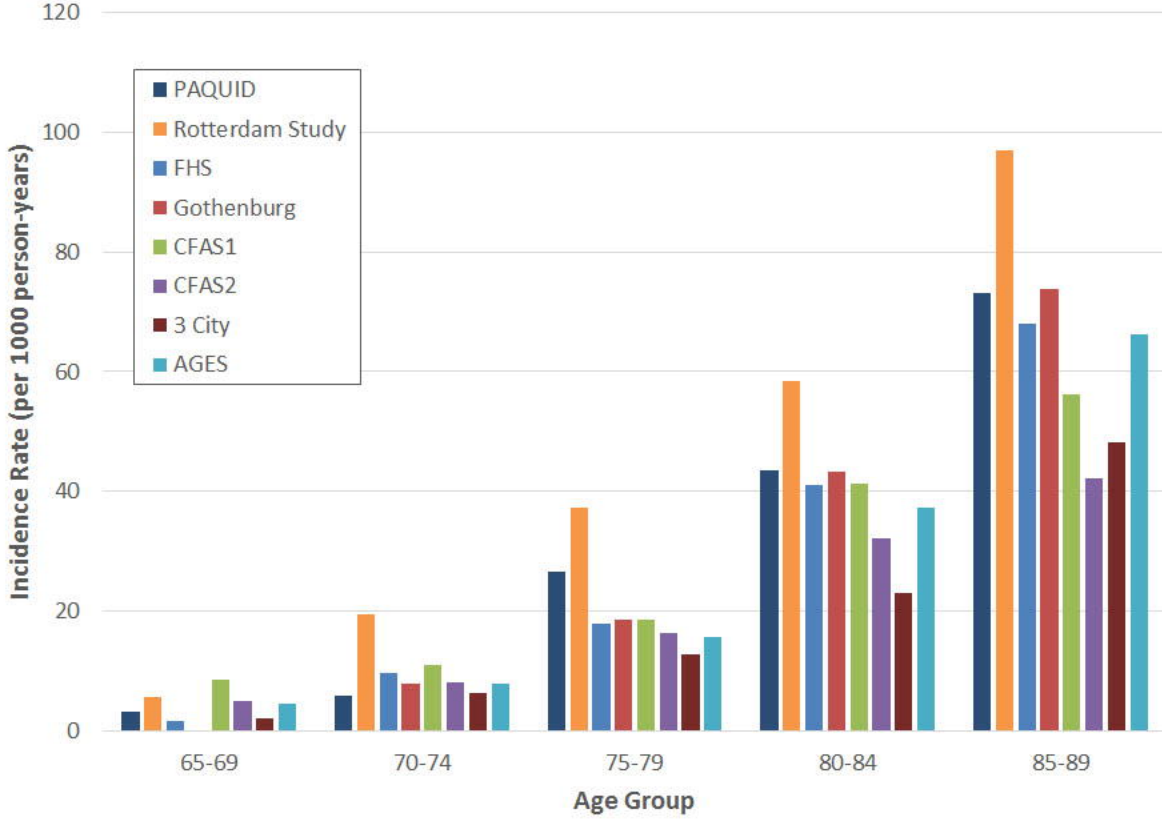
Title: Trends in the incidence of dementia

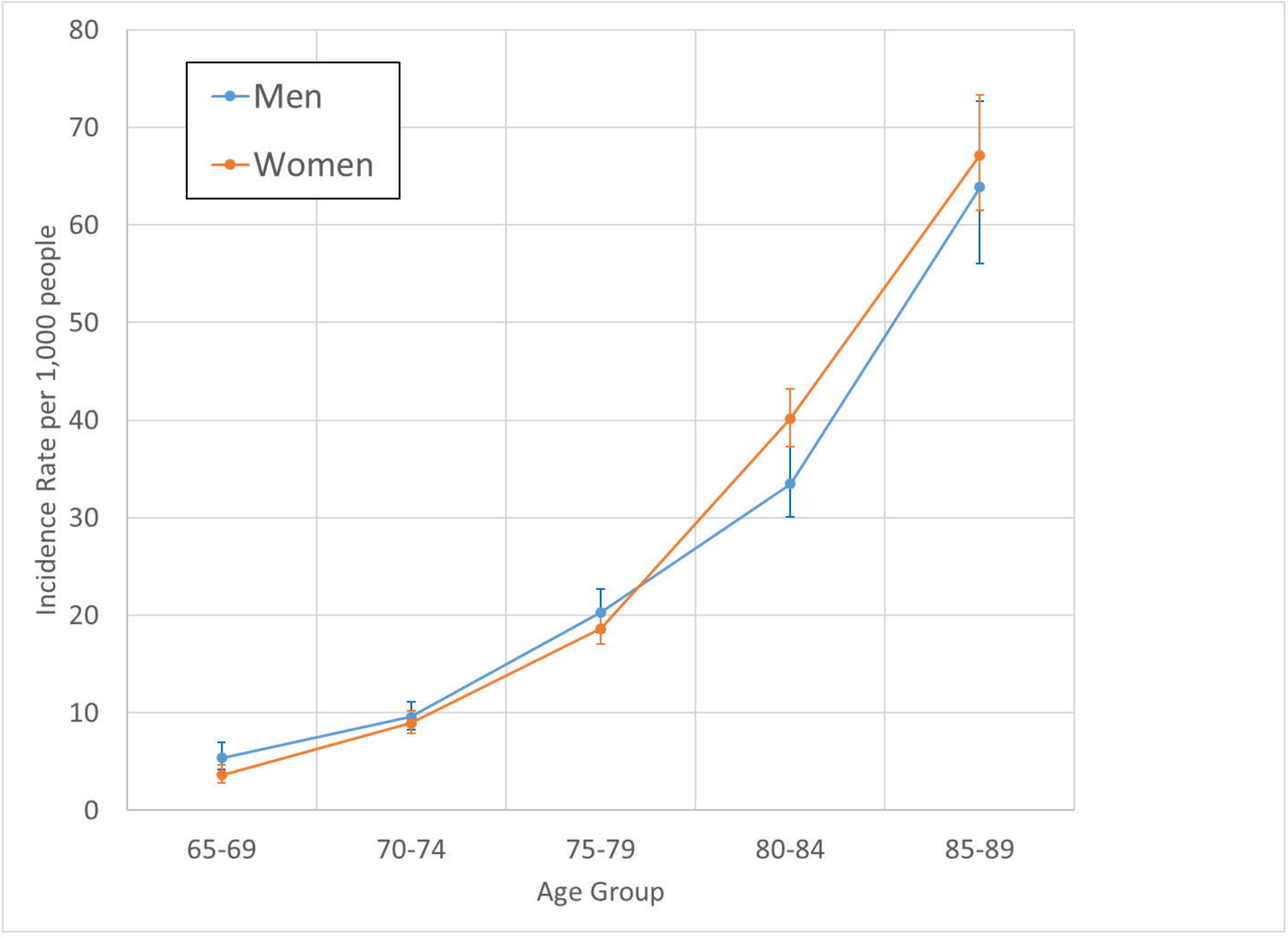
Caption: The forest plots represent the incidence trend for (a) all-cause dementia, (b) Alzheimer's disease, (c) all-cause dementia in men, and (d) all-cause dementia in women, expressed as a hazard ratio per 10-year advance in calendar time. This hazard ratio was calculated to compare temporal trends across studies, and can be interpreted as a change in the 5-year hazard per decade advance in calendar time.

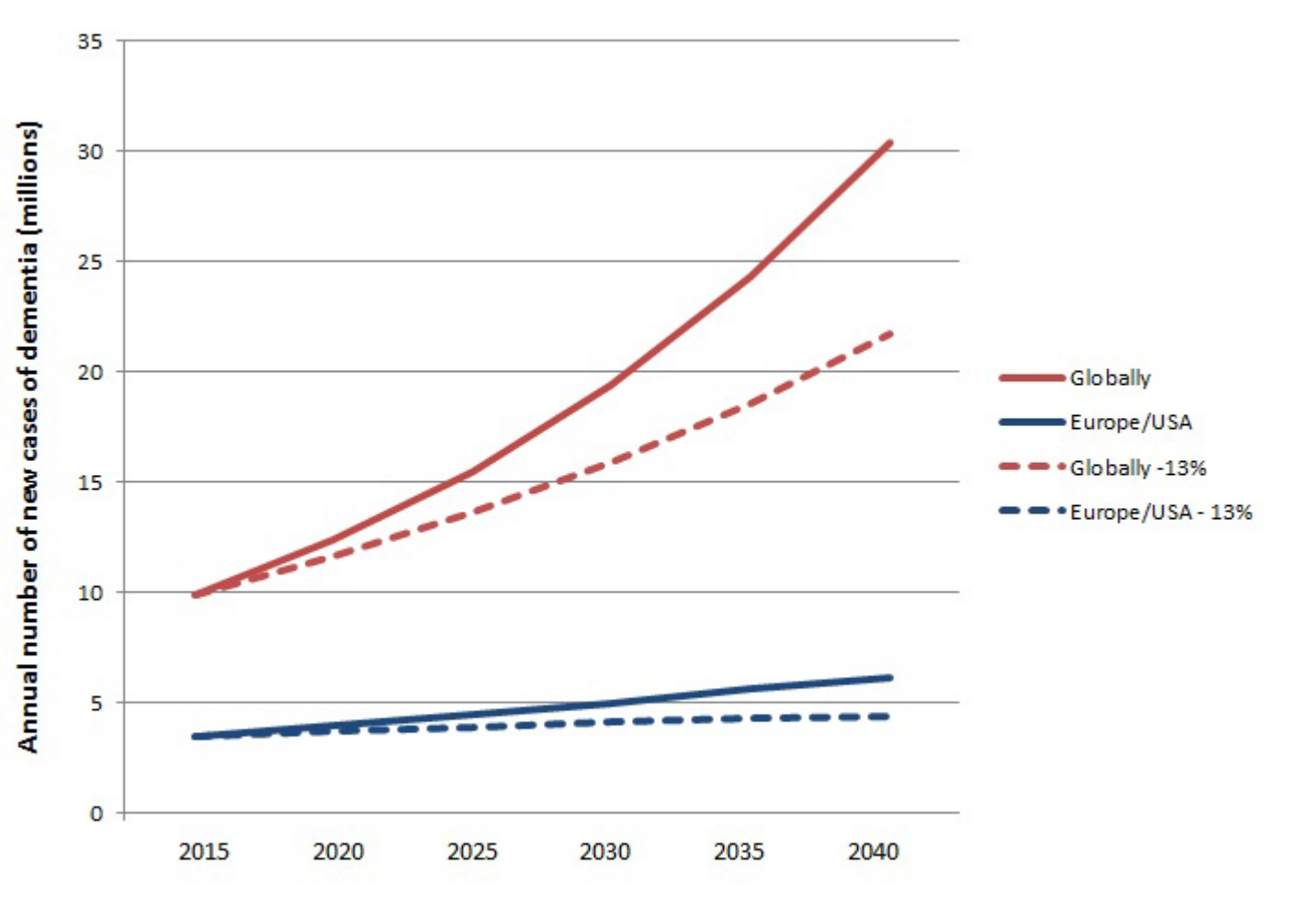
Figure 4.

Title: Projected incidence of dementia in millions

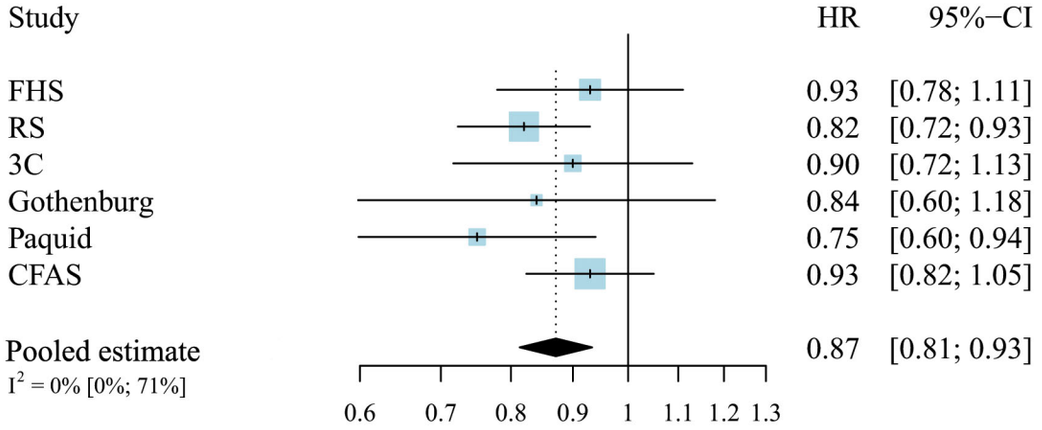
Caption: Projected incidence of dementia on the basis of current rates (solid lines) and projected incidence of dementia assuming continuation of a decreasing trend (dashed lines). Current rates are based on estimates from the 2012 World Alzheimer Report, which at the time estimated that 682 million new cases would occur over the 2010-2050 period.


120
100
80
60
40
20
0
Incidence Rate (per 1000 person-years)
PAQUID
Rotterdam Study
FHS
Gothenburg
CFAS1
CFAS2
3 City
AGES
65-69
70-74
75-79
80-84
85-89
Age Group


Men
Women
Incidence Rate per 1,000 people
0
10
20
30
40
50
60
70
80
65-69
70-74
75-79
80-84
85-89
Age Group

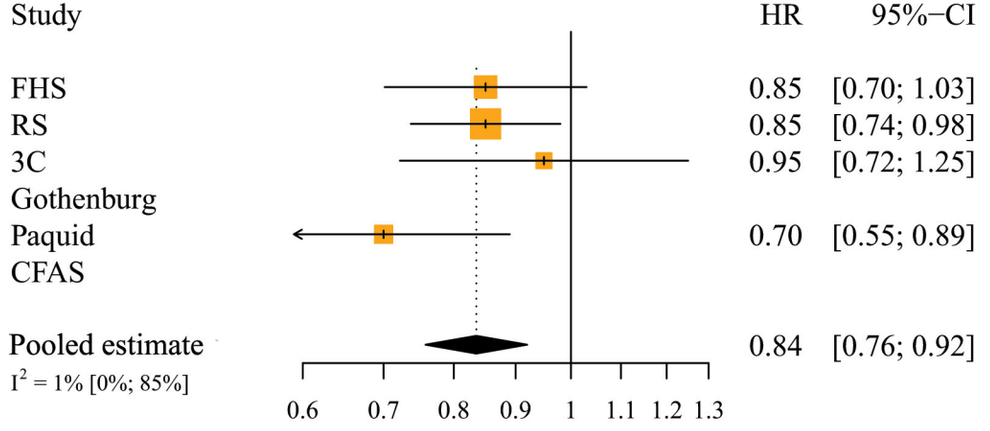

Annual number of new cases of dementia (millions)
35
30
25
20
15
10
5
0
2015
2020
2025
2030
2035
2040
Globally
Europe/USA
Globally -13%
Europe/USA - 13%

All-cause dementia



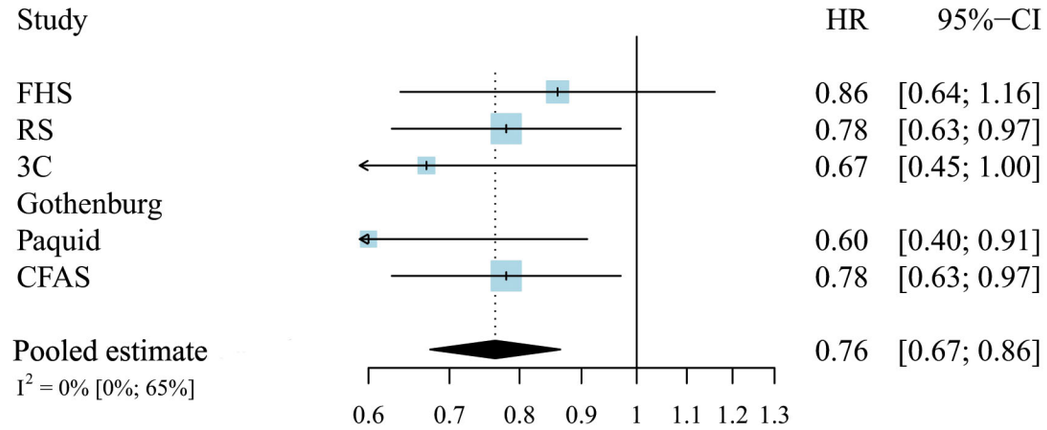
A

Alzheimer's disease



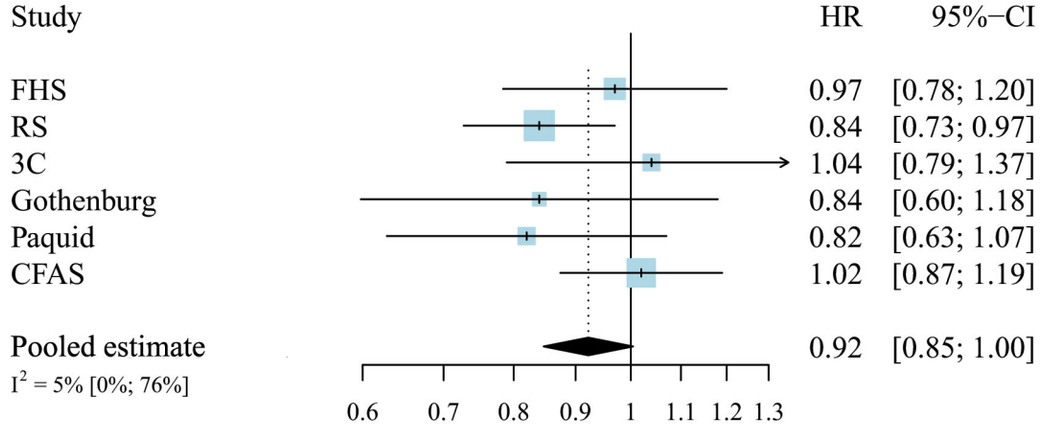
B

All-cause dementia in men only



C

All-cause dementia in women only



D