Trends in the prevalence and incidence of dementia: a review of current evidence

Authors

Yu-Tzu Wu[1], Alexa S Beiser[2,16], Monique M B Breteler[3,4], Laura Fratiglioni[5], Catherine Helmer[6], Hugh C Hendrie[7], Hiroyuki Honda[8], M Arfan Ikram[9], Kenneth M Langa[10], Antonio Lobo[11], Fiona E Matthews[12,13], Tomoyuki Ohara[14,15], Karine Pérès[6], Chengxuan Qiu[5], Sudha Seshadri[16], Britt-Marie Sjölund[5,17], Ingmar Skoog[18], Carol Brayne[19]

Affiliations

[1.] REACH: The Centre for Research in Ageing and Cognitive Health, Department of Psychology, College of Life and Environmental Sciences, University of Exeter, Washington Singer Building, Perry Road, Exeter EX4 4QG, United Kingdom

[2.] Boston University School of Public Health, 72 East Concord St, B602 Boston, MA 02118, United States

[3.] German Center for Neurodegenerative diseases (DZNE), Population Health Sciences, Sigmund-Freud-Straße 27, 53127 Bonn, Germany

[4.] University of Bonn, Faculty of Medicine, Institute for Medical Biometry, Informatics and Epidemiology, Germany

[5.] Aging Research Center, Department of Neurobiology, Care Sciences and Society,

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This is the author's manuscript of the article published in final edited form as:
Wu, Y.-T., Beiser, A. S., Breteler, M. M. B., Fratiglioni, L., Helmer, C., Hendrie, H. C., … Brayne, C. (2017). The changing prevalence and incidence of dementia over time — current evidence. Nature Reviews Neurology, 13(6), 327. https://doi.org/10.1038/nrneurol.2017.63

Karolinska Institutet-Stockholm University, Gävlegatan 16, S-113 30, Stockholm, Sweden

[6.] INSERM, ISPED, Centre INSERM, U1219 - Bordeaux Population Health Research Center, Bordeaux, France

[7.] Department of Psychiatry, Indiana University School of Medicine, 410 West 10th Street, Indianapolis, IN 46202, United States

[8.] Department of Neuropathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

[9.] Department of Epidemiology, Erasmus University Medical Center, Wytemaweg 80, 3015 CN Rotterdam, The Netherlands

[10.] Department of Internal Medicine, Veterans Affairs Center for Clinical Management Research, Institute for Social Research, and Institute for Healthcare Policy and Innovation, University of Michigan, 2800 Plymouth Road, Ann Arbor, Michigan 48109-2800, US

[11.] Department of Psychiatry, Universidad de Zaragoza and Instituto de Investigación Sanitaria Aragón, Zaragoza. CIBERSAM, Madrid, Spain

[12.] MRC Biostatistics Unit, Institute of Public Health, Forvie Site, Cambridge Biomedical Campus, Cambridge CB2 0SR, United Kingdom

[13.] Institute of Health and Society, Newcastle University, Newcastle Upon Tyne, NE4 5PL, United Kingdom

[14.] Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University,

Fukuoka, Japan.

[15.] Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

[16.] Boston University School of Medicine, The Framingham Study, 72 East Concord St, B602 Boston, MA 02118, United States

[17.] Department of Health and Caring Sciences, Faculty of Health and Occupational Studies, University of Gävle, SE-801 76 Gävle, Sweden

[18.] Centre for Ageing and Health AgeCap, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Box 100, S-405 30, Gothenburg, Sweden

[19.] Department of Public Health and Primary Care, Cambridge Institute of Public Health, Forvie Site, University of Cambridge, School of Clinical Medicine, Cambridge Biomedical Campus, Cambridge CB2 0SR, United Kingdom

Corresponding author

Carol Brayne

Professor of Public Health Medicine

Department of Public Health and Primary Care

Cambridge Institute of Public Health, University of Cambridge

Forvie Site, School of Clinical Medicine, Cambridge Biomedical Campus

Cambridge CB2 0SR, United Kingdom

Email: carol.brayne@medschl.cam.ac.uk

Telephone: +44 1223 330321

Competing interests

YTW, AB, MMBB, LF, CH, HCH, HH, MAI, KML, AL, FEM, TO, KP, CQ, SS, BMS, IS and CB declare no competing interests

Abstract

Dementia, a syndrome of cognitive decline severe enough to interfere with daily functioning and independent living, has been the subject of increasing focus for policymakers, civil organisations and multidisciplinary researchers. A substantial body of the most recent descriptive epidemiological research on dementia is allowing investigation of how prevalence and incidence might be changing across time. To establish clear trends, such comparisons need to be based on population-based studies using similar diagnostic and research methods over time. This review synthesises findings from nine prevalence trend studies and five incidence trend studies from western European countries (Sweden, Spain, UK, the Netherlands and France), the US, Japan and Nigeria. These population-based studies, apart from the Japanese study, have reported stable or declining prevalence and incidence and evidence of both inconsistent and similar changes in men and women within and across countries. No single risk or protective factor has been identified to fully explain these trends, but major societal changes in western societies and improvement in factors potentially associated with risk and protecting such as living conditions, higher education attainment and wider availability of healthcare might have favourably influenced multiple factors related to physical, mental and cognitive health across the lifecourse and could be responsible for this reduced risk of dementia in later life. Analytical epidemiologic approaches combined with translational neuroscientific research may provide a unique opportunity to explore underlying

mechanisms of neuropathology and dementia in the general population. The findings from these studies provide robust evidence for developing fruitful avenues for prevention, diagnosis and treatment.

1. Introduction

1.1 General

Dementia has become an important issue in public health, economic, social and political domains as well as a popular research topic attracting major and increasing investment. Recent estimates from the World Alzheimer Report 2015 have suggested the global number of people with dementia is 46.8 million and is estimated to increase to 74.7 million by 2030 and 131.5 million by 2050.[1] In response to the potential dementia 'epidemic' and its consequent economic burden, the London G8 dementia summit in 2013 and the World Health Organisation Ministerial Conference in 2015 called for a global action against dementia and committed to the target of identifying a cure or disease-modifying therapy by 2025.[2] To date, a large proportion of dementia research has focused on neurological features, pathophysiological mechanisms and drug discovery in order to understand the causes, pathology and progress of dementia and defeat this 'one of greatest enemies of humanity'.[3] Although findings from the basic sciences have provided knowledge on dementia at the individual or biological level, a predominantly reductionist approach and focus on single mechanisms, do not suffice to understand the full spectrum of dementia in the general population and identify potential risk factors across different populations and life courses.[4] This can only be investigated fully through population-based epidemiological research.

Population-based studies on dementia epidemiology were initiated from the 1980s onwards in order to assess policy development.[5] These investigations started with prevalence (the percentage of dementia in the general population) before moving on, in longitudinal results, to incidence. A reasonable number of prevalence and incidence studies were carried out in western European countries and results from these studies contributed to the European Studies of Dementia (EURODEM) reports,[6,7] which synthesised epidemiological measures across European countries with a substantial impact on policy and research. This pan-European collaboration has been reconvened to bring together expertise from old and new population-based cohorts and research resources to update dementia epidemiology for contemporary older European populations.[8] In the US, several nationwide and regional cohorts of older people have included measures of cognitive function since the mid-1960s but the diagnosis of dementia is less often included over time in these cohorts.[9] Nationwide estimates on prevalence have been based on results from widely varying localities with the higher estimate used for extrapolation to the total population in the US.[10] In addition to western Europe and the US, a small number of epidemiological investigations have been conducted in Australia, Canada, Japan, China, Taiwan and other regions between the late 1980s and the early 1990s.[11] Initially and up to 2000, there was a lack of data from low and middle income countries but now there are many active studies in such societies.[1] These studies have provided evidence on population metrics for dementia widely used for policy and

lobbying for awareness and resources.

Since the early studies, new generational cohorts becoming old have experienced marked changes in living conditions, lifestyle, access to prevention and chronic disease during their lifetimes. Such changes could influence dementia occurrence across generations as they can influence substrate and the substances of the dementia syndrome (the brain and its processes).

1.2 Challenges of investigating trends in dementia occurrence

Although descriptive population-based studies of dementia have been conducted for well over 30 years, testing for changes across time in its prevalence or incidence through such studies have only emerged more recently. Despite estimates derived from statistical modelling and systematic reviews,[1,10,11] comparable data on prevalence and incidence over time have been limited because studies have inconsistent and changing methodologies. There have been substantial changes in diagnostic criteria proposed and accepted during these decades as well as dramatic changes in policy practice and public recognition of dementia. Different sets of criteria have been long known to identify very different groups of dementia cases.[13] Any difference in approach to diagnosis will similarly affect prevalence and incidence estimates in individual studies. Given these have been conducted with diverse diagnostic methods, different contexts and time points comparability even across geography has been challenging,

yet along across time. These changes in diagnostic boundaries occurring in parallel with increasing awareness among the public and professionals has led to earlier diagnosis.[14] Conducting a consensus diagnosis, even with standardised data collection and the use of the same diagnostic criteria, can still be affected by changes in clinicians' perception of diagnostic thresholds and criteria over time even when using the same diagnostic criteria.[15,16] Alzheimer's type dementia is a clinically diagnosed subtype of dementia which can be made with variable level of investigation, now including imaging (most intensively with the exclusion of vascular pathologies and inclusion of Pittsburgh compound B (PIB) positive individuals). Whatever the intensity of investigation this clinical diagnosis is still based on an assumption – that the pathology 'causing this dementia' is Alzheimer's type, but ultimately this remains heavily influenced by clinical judgement, available information on medical records and characteristics of study population, particularly in population-based studies. Thus, dementia remains a 'clinical syndrome' with emphasis on cognitive and functional states. Subtype analysis is even more difficult that the syndromic diagnosis to hold steady across time in order to provide any valid comparison of prevalence or incidence of subtypes.

A vital need in examining changes in dementia across time is to reduce the influence of changes in diagnostic standards, as well as other methodological variation across time. In other words, it is essential to hold research methods and diagnostic approaches steady and

therefore primary evidence has to be based on population-based studies with consistent study designs and measurement methods over time. Our earlier policy view focused on trends in dementia occurrence and summarised findings from five western European studies using consistent research methods across two time points in well-defined areas.[12] Here we incorporate new population-based studies on dementia prevalence and incidence trends and synthesise current evidence across the globe. We investigate variations in study designs and methodologies across individual studies and classify primary and secondary evidence based on their research methods.

2. Primary evidence from population-based studies

Primary evidence testing for changes in dementia occurrence across time included 14 population-based studies using sufficiently similar study methods at all time points in well-defined geographical areas for robust comparison. There were nine prevalence studies and five incidence studies from the US, Western Europe, Japan and Nigeria. Two Swedish studies[17,18] were excluded from the analysis. One investigated much early prevalence and incidence trends from 1947-1957 and 1957-1972.[17] This study was excluded as the results might be less relevant to contemporary older populations. The other focused on short term prevalence trends in very old populations aged 85 years or over in Umea, rural Sweden.[18] The study cohorts were not sampled independently and the analysis did not take the overlapping of

the study population into account. In addition, medical records were used to support dementia diagnosis and this might lead to bias due to changes in diagnostic boundaries. One Japanese study[19] investigating prevalence trends between 1980 and 2000 was not included in primary evidence because the screening for dementia was based on self-reported cognitive problems rather than objective cognitive testing, and clinical diagnosis was only applied to those who reported their cognitive problems. This approach could lead to biased prevalence estimates because of the marked change in awareness of dementia in the population as a medical diagnostic entity in the recent era. There have been two reports from the Hisayama study in Japan.[20,21] One investigated prevalence trends in the general population while the other focused on an autopsy subsample, which was not representative of the older population in the study area. The former[20] was selected for this analysis. One study from China compared prevalence and incidence trends in dementia but used different diagnostic criteria at the two time points.[22] This study was excluded.

Studies focusing only on Alzheimer's disease[23,24] and cognitive impairment[25,26] were excluded as the definitions and diagnostic methods are likely to be even more heterogeneous across time and studies. Those using medical records, healthcare administrative databases, systematic reviews and meta-analyses will be described briefly in the latter part of this review.

2.1 Prevalence trends

Nine studies have investigated prevalence trends in Western European countries,[16,27-31] the US[32,33] and Japan.[20] Table 1 summarises study designs and methodologies of the nine prevalence trend studies. The earliest cohort was in the Gothenburg study (1976-1977)[27] and the most recently reported cohort is in the Health and Retirement Study (HRS, 2012).[33] The Cognitive Function and Ageing Studies (CFAS), Zaragoza study and Indianapolis-Ibadan Dementia Project (IIDP) had similar designs recruiting two independent cohorts across two time points in defined geographical areas.[30-32] The French study focused on farmers living in the Bordeaux area and only included this specific occupational group for cohort comparison.[16] HRS is a dynamic cohort, enrolling new cohorts every six years in order to have a representative sample of older adults in the US.[33] Nordanstig study[28] and Stockholm study[29] compared regional prevalence in a nationwide cohort (Sweden National study on Aging and Care, SNAC) to earlier studies in the same localities (Nordanstig Project and Kungsholmen Project). The Gothenburg study[27] focused on comparing age-specific prevalence at age 70 and 75 over three decades using random samples of local populations. The only study from East Asia, the Hisayama study,[20] included all residents aged 65 and above in the study area at four time points. Zaragoza, CFAS, IIDP and two Bordeaux studies all experienced considerable drops in response rate.[30-32] To address potential selection bias due to this differential response rate, a wide range of sensitivity analyses was carried out in CFAS and the two Bordeaux

studies and revealed limited impacts on the results. Despite reduction in response rate, the Zaragoza study used sampling strategy to take into account non-response population and therefore the estimates are considered to be representative to the whole older population in the study area.

Most studies had two-stage designs, including a screening (potential cases identification) and a diagnostic (detailed examination and application of clinical criteria) phase while one-stage design (diagnosis only) was used in Gothenburg study, Nordanstig study, HRS, the second cohorts of Stockholm study and CFAS. Clinical diagnoses were mainly based on the Diagnostic and Statistical Manual of Mental Disorders, third edition revised (DSM-III-R).[34] Algorithmic diagnosis in CFAS and algorithmic historical criteria used in Gothenburg study were also similar to DSM-III-R. In addition to clinical diagnosis, the Bordeaux farmer study used an algorithm approach based on Mini-Mental State Examination (MMSE)[35] and Instrument Activity of Daily Living (IADL)[36] scores to identify potential dementia cases. The diagnosis in HRS was based on a 27-point cognitive test or a proxy assessment if the participant was not able to complete the interview.[33] The assessment tool was conducted through phone or face to face interview and was validated in a HRS sub-sample (the Aging, Demographics, and Memory Study (ADAMS)), showing a 78% concordance with clinical diagnosis.[37]

Although these studies attempted to implement the same diagnostic methods over time, changes in subjective clinical opinion cannot be ruled out as a major factor which might influence case identification and prevalence estimates. To address this issue, Nordanstig and Stockholm study used the same physicians to make diagnoses in the two cohorts. IIDP used a clinical consensus process with the same basic group of clinicians conducting diagnoses in the two cohorts. CFAS and Gothenburg carried out algorithmic diagnosis using a structured psychiatric interview to avoid variation in subjective opinions across clinicians. Three studies[20,29,31] had small changes in study designs and methodologies. To ensure these changes had minimum impact on prevalence estimates, the new measurements used in these three studies were tested and validated before being used on their later cohorts.

Figure 1 reports the ratios of prevalence estimates in new over old cohorts by total population, men and women. If prevalence estimates remain the same across two cohorts, the ratio is 1.0; if estimates are lower in new compared to old cohorts, the ratio is smaller than 1.0. Most studies reported stable or declining prevalence over time and this is in contrast to the projected increase. The three Swedish studies generally reported stable prevalence in the total population with wide confidence intervals apart from the Stockholm study. CFAS reports a 23% reduction over two decades in prevalence observed by expected total study population in

England[31] and HRS suggests a 26% decrease in the US older population over 12 years.[33] The Bordeaux farmer study found a 40% decline in prevalence using the algorithmic diagnosis but an over two-fold increase in clinical diagnosis.[16] The Nordanstig study and Zaragoza study did not report significant reductions in the total population, but over 50% decreases in men.[28,30] Given increase in longevity of people with dementia[29], these results may suggest an actual decline in age-specific risk of dementia.

2.2 Incidence trends

Five studies investigated incidence trends in Western Europe,[38-40] the US[41,42] and Nigeria[41] (Table 2). IIDP has reported trends in two samples: one was for African Americans in Indianapolis, US, and the other was for a Yoruba population in Ibadan, Nigeria.[41] The Bordeaux incidence study used the same reference cohort as the prevalence study but mainly focused on incidence in urban residents.[39] Two studies have reported both prevalence and incidence trends within the same study cohorts.[31,32,40,41]

Three studies measured incidence in two independent cohorts, while the analyses of the Rotterdam study[38] were based on non-overlapping sub-cohorts, and the analyses of the Framingham Heart study (FHS)[42] were based on dynamic cohorts. The study population of Rotterdam study included all residents aged 60-90 in the study area in the 1990 cohort and a

non-overlapping sample of all who since aged or moved into that age range and study area in the 2000 cohort. FHS combined the data from the Original and Off-spring cohorts and divided them into four epochs to compare incidence across these periods. The follow-up periods and intervals varied across studies, with a range from 2 years in CFAS[40] to 5 years over a 30 year period in FHS.[42] To address differential response rate and potential impact of missing data, several sensitivity models were tested in Bordeaux study and CFAS.

Two studies used algorithmic diagnosis. Bordeaux study[39] used MMSE[35] and IADL[36] scores to define dementia cases, while CFAS[40] was based on a differential diagnosis derived from a structured psychiatric interview. The Bordeaux study also included clinical diagnosis but different clinical criteria were applied to the two cohorts so this was not used to assess temporal trends. The other three studies used clinical diagnosis based on DSM-III-R, ICD-10 or DSM-IV.[34,43,44]

Ratios of incidence between new and old cohorts are presented in Figure 2. Despite different study designs and methods, all studies suggest a potential decrease in incidence in the total population across cohorts and time periods. However, in the Bordeaux study this was mainly driven by an effect in women, whereas in CFAS the significant reduction was confined to men. In FHS, the substantial reduction in women occurred earlier and was sustained in the three

epochs but in men only appeared in the last epoch. IIDP suggests a reduced incidence in African Americans over 10 years with an indication of a 20% reduction in Nigerian cohorts which did not achieve statistical significance. In the Bordeaux study, the results of clinical diagnosis differed from algorithm diagnosis with the latter showing a decreasing incidence.[39]

3. Secondary evidence from other types of studies

Secondary evidence on dementia trends included studies using medical records, healthcare and insurance administrative databases, systematic reviews and meta-analyses as these types of research are not able to control for potential changes in diagnostic methods, subjective clinical opinions and public awareness. Several studies from Western Europe and North America have reported prevalence or incidence trends based on the analyses of medical records and healthcare administrative databases. These studies tend to cover large populations and be based on their contact with medical services or outpatients over time. These analyses have mainly focused on short-term trends and advanced analytical strategies have been required to estimate prevalence or incidence rates over continuous time periods and overlapping study populations. Bias in ascertainment and change in diagnostic practice across clinical settings cannot be addressed in these analyses and this is likely to result in findings which are challenging to interpret. Some studies in this class have suggested stable or reduced trends in annual prevalence or incidence rates of dementia diagnosis[25,45-49] and others have

reported significant increases in prevalence or incidence trends.[49-54]

Due to lack of comparable data, prevalence trends outside western countries mainly rely on systematic reviews and meta-analyses, which aggregate estimates across individual studies by the year of investigation. Systematic reviews of large number of prevalence studies in East Asian countries have suggested the increasing prevalence trends in Japan,[55] Korea,[56] Hong Kong,[57] Taiwan,[58] and China,[59,60] but for China the increase loses significance when controlling for methodological factors including changes in diagnostic criteria.[1,61,62] In addition, preliminary results from the Chinese Longitudinal Healthy Longevity Surveys, a dynamic cohort across 22 provinces in China, have in fact reported stable prevalence of cognitive impairment (measured by MMSE) between 1998 and 2011.[63] Although it remains unclear whether any change in East Asia could be attributed to heterogeneity of design and implementation or potential differences between high and low income countries, eastern and western societal contexts, different results from primary investigation and systematic reviews may, once again, underline the substantial impact of changes in diagnostic methods and social contexts on prevalence estimates over time.

4. Current evidence on dementia trends

There is emerging evidence from population-based studies that have recently investigated

changes in dementia occurrence using different approaches. Since changes in diagnostic methods, knowledge and public awareness all influence identification of who meets and does not meet study diagnostic criteria for dementia, true prevalence and incidence trends must be based on population-based studies using similar research methods across different time periods. This review includes nine prevalence studies and five incidence studies from Western Europe, the US, Japan and Nigeria. Many of these recent studies report decreases in response rates as well as change in the diagnostic boundaries that clinicians use when making consensus diagnosis which are likely to impact results. But despite different study designs, methodologies and settings across individual studies, the primary evidence generally shows stabilising or decreasing prevalence and incidence. This is different from the mixed findings reported from secondary evidence, which have been based on the analysis of healthcare administrative databases, medical records, systematic reviews and meta-analyses. Different results between clinical and algorithmic diagnoses in the two Bordeaux studies[16,39] further emphasise the impact of changes in diagnostic boundaries and their substantial impact on prevalence and incidence estimates over time. Dementia diagnosis as well as diagnosis of other disorders is contextual, changing across time and geographies. As noted in our earlier review,[12] it is vital that any comparison should not rely on an overview of reported numbers but needs to include careful appraisals of methodologies and study contexts.

4.1 Potential explanations leading to changes in dementia occurrence in some western countries

Although this study did not investigate mortality trends in people with dementia, a recent review has only identified four survival studies with limited information.[64] Dementia has been associated with increased mortality and this difference in death rates between people with and without dementia may have changed over time. Given the overall mortality in the general population in most countries has declined over time, stable or decreasing prevalence trends are likely to indicate a decline of varying sizes in the incidence.

New generations entering old age seem to be healthier and to have lower risk of developing dementia compared to earlier generations. Improvement of brain health, in terms of larger brain volume, less brain atrophy and cerebral small vessel disease, has been reported in the more recent cohort of the Rotterdam study.[38] Although several possible reasons have been suggested to explain these encouraging findings,[12,65] only four studies[33,39,42,66] have identified the key factors associated with decreasing incidence trends (Table 3). The possible explanatory factors vary across American, French and Dutch cohorts. Measure of educational level explained varying amounts of the declining incidence trends by up to 6% in FHS cohorts and nearly 10% in French cohorts and in HRS controlling for education along with other socioeconomic factors explained 10% decrease in prevalence. In the Rotterdam study, the

percentage of preventable dementia cases related to low education remained similar over two decades and this suggest education still had a large effect on dementia occurrence in the more recent Dutch cohort.[66] Although the proportion of preventable cases due to smoking partly explained changes in the more recent Dutch cohort, smoking did not explain declining incidence in the American and French cohorts. These studies report both rising and reducing chronic diseases associated with dementia such as stroke, heart disease, hypertension and diabetes. These only explain a limited proportion of the observed reduction in incidence and prevalence although there would be unknown time-lags. Most treatments such as anti-hypertension, anti-depressants and statins have only been widely prescribed since the 1960s. Improving treatments for cardiovascular diseases and other chronic conditions might change the risk of developing dementia in later life and these may have further impact in the future.[48,67] Other lifestyle factors, such as changes in diet and physical activity, have been suggested to be possible reasons for declining incidence but there is currently a lack of primary evidence to confirm such hypotheses and these patterns are changing again in each successive generation.

A sex difference has been found in some prevalence and incidence trend studies (Table 4). Three European studies have reported decreasing prevalence trends in men[28,30,31] with mixed results for women. In incidence studies, mixed findings in men and women have been

reported in the Rotterdam study and IIDP (no difference)[38,41], CFAS (decline in men)[40], the Bordeaux study and FHS (greater or earlier decrease in women).[39,42] Life expectancy at age 60 is a good marker of overall health status of older people in 1990, 2000 and 2012.[68] Although women had longer life expectancy at age 60 with a persistent gap over time and across countries, men in these western countries generally had greater increase in life expectancy over the most recent two decades. Decline in smoking, improvement in prevention and treatments for cardiovascular diseases may have had a larger impact on health and life expectancy in men than in women. Such major risk changes might be important in the observed sex difference in brain health and dementia occurrence.

Although the reasons for stable or decreasing time trends are still unclear, any reduction in dementia occurrence is unlikely to be caused by a single risk factor. Societal changes in western societies after the two World Wars and improvement of living conditions have led to enhanced general health as well as cognitive development and reserve across the lifecourse.[69] Population level investments on infrastructures, education, health service and social welfare may have substantially improved multiple dimensions of physical, mental and cognitive health since early life with a consequence of mitigated risk of dementia in later life. For example, education level has been related to increase in cognitive reserve.[70] Recent studies have reported a positive relationship with cognitive performance but not rates of decline.[71]

Recent generations reaching older age have had more years of statutory education which may be associated with greater cognitive reserve and may in turn partly explain later dementia onset. Such impact on incidence trends can only be observed over decades. Addressing factors related to social disadvantage and health inequality may play an important role in cognitive health over the lifecourse.

4.2 Dementia trends in other regions

There is a lack of primary evidence outside Western Europe and the US. Although systematic review/meta-analysis is a possible approach to synthesise evidence on dementia epidemiology in low and middle income countries, any analyses of secular trends are unlikely to be robust if variations in methodologies and population characteristics have not been taken into account.[12] Since secondary evidence is not sufficient to inform understanding of true dementia trends, the discussion here only focuses on comparable primary evidence (Japan and Nigeria).

Two studies beyond western Europe and the US, from Japan and Nigeria, have reported different trends in dementia occurrence. The Hisayama study reports an increasing prevalence trend between 1985 and 2005 and the autopsy subsample further suggests a higher prevalence in 2012.[20,21] However, the analysis of the autopsy subsample did not take into account age and potential selection bias. Another Japanese study, which was excluded from this review due to

particular screening approaches that do not reflect whole populations, investigated prevalence in all residents in Diasen-Cho area and also report an increasing prevalence across three time points (1980, 1990 and 2000).[19] In contrast, stable incidence was found in the Nigerian cohorts.[41] The incidence rate in the 2001 cohort was slightly lower than the 1992 cohort with overlapping confidence intervals.

It is difficult to provide a unifying explanation for these different results as these countries have very different economic development, political, social and cultural backgrounds and pace of change over the past few decades. Figure 3 shows life expectancy at birth, an important indicator of general health in society, in all the countries with a prevalence or incidence trend study. Changes in life expectancy have been associated with substantial impact of societal factors and may also indicate different determinants of cognitive health across generations.[72] Different generations and populations experience various life events, health status and disease profiles and trends in dementia prevalence and incidence may reflect complex interactions of these factors. Japan and Nigeria have dramatically different profiles compared to the western countries over the last century. The dramatic impact of wars on life expectancy can indicate extremely deprived living conditions, interruption of education and lack of health care in early life of the study cohorts. Life expectancy in Japan was lower than western countries in the first half of the 20th century and then increased dramatically in the

1960s. Although life expectancy in Nigeria has increased by 30 years over the last century, there is still a 20-year gap between Nigeria and other countries. Historical or future dementia trends outside western countries are even less predictable because the interplay of lifecourse health, protective and risk factors varies so hugely across different social contexts.

The longitudinal data on cardiovascular risk factors in Hisayama cohorts may provide some insight into potential mechanisms between chronic conditions and dementia trends within the Japanese context. The Hisayama study has investigated dementia prevalence in older people as well as vascular diseases in middle age cohorts. Since the mid-1980s, the prevalence of hypertension, stroke and smoking has declined, along with increasing prevalence of diabetes, hypercholesterolemia and obesity.[73] Increasing prevalence trends of dementia might be related to changes in lifestyle factors including western diets and physical inactivity and rising obesity, metabolic syndrome and diabetes.[20,74] However, an earlier analysis shows that these factors were not associated with an increased risk of all-type dementia after a 7-year follow-up. A subtype analysis only found a significant association between diabetes and vascular dementia, for which prevalence appeared stable across time.[20,75] In more recent analyses of the 15-year follow-up, diabetes was related to increased risk of all type dementia and Alzheimer disease but not vascular dementia.[76] Growing recognition of mixed dementia will make interpretation of any subtype changes across time even more challenging. Until

deeper phenotyping, both in life and after death, is conducted which is consistent across time the detail of neurobiological changes in risk and clinical manifestation of dementia itself will be unknown.

The four studies from the Netherlands, the US and Japan have shown somewhat different trends in vascular diseases, metabolic syndrome and dementia.[20,38,41,42] Although population ageing and the increasing burden of non-communicable diseases and dementia are important challenges across the world, the impact of chronic diseases on dementia trends may vary across different contexts with uncertain and long time-lags. Forecasts for dementia burden need to take into account these different contexts of health profiles, deprivation and social environments in countries and regions rather than focusing on the potential impact of single risk factors.

4.3 Neuroscience and epidemiology

Current neuroscience research has largely invested in mechanistic research for treatments alongside searches for potential biomarkers for diagnosis of dementia subtypes, now preceding any clinical signs, and monitoring of treatment efficacy in highly selected clinical samples.[77] However, it is notable that existing population-based studies in the older age groups have repeatedly shown serious inconsistency between cognitive performance and

degree of neuropathology, as well as considerable overlap of pathological features in people with and without dementia.[78,79] The new techniques for defining brain pathology and 'normal' function must be grounded through research within contemporary populations in order to understand the underlying neurobiology of the population changes that the studies presented here indicate. Observational risk factor analysis can only go so far and it needs to be accompanied by deep phenotyping which can be mapped back to populations. Further work is needed to understand the neuroscience of the gender-related differences and it is also clear that new cohorts in different populations such as migrants, aborigines and disadvantaged sectors of society will be needed.[80,81]

The concept of population-based studies should be incorporated in future neuropathological research in dementia. Results from small, clinically based samples by definition have limited generalisability and considerable potential bias due to highly selective recruitment. In particular those who are socially disadvantaged are less likely to take part in such research. Given changes in population brain health, potential of analytical epidemiologic approaches and integration of neuroscience with population-based epidemiological studies (neuroscientific epidemiological approaches) is vitally important and provides society with a key opportunity to understand brain health, neurobiology and neuropathology in the general population in order to support better prevention, care and cure of dementia.

5. Conclusions

Recent descriptive epidemiological studies have reported prevalence and incidence trends in dementia. Although these studies have minimised the impact of changing diagnostic criteria and study methods on prevalence and incidence estimates, declining response rates in recent cohorts remain a major challenge for future research. There is a strengthening evidence base that dementia, age for age, is declining in some countries and the number of people with dementia can remain stable despite population ageing.[31,33] It is possible that substantial reduction in dementia risk for whole populations can balance out growing numbers of older people. Identifying contributing factors relevant to particular countries and regions should become a major priority as the findings will have important implications on health and social policies in relation to dementia prevention and risk reduction.

Although no single factor has been identified to fully explain these changes, reduction in absolute inequalities including improvement in living conditions, better access to education and healthcare systems are likely to have influenced multiple risk and protective factors across the lifecourse related to physical, mental and cognitive health and thus reduced risk of dementia in later life. There is an important message to all in society about the long term action to address factors that determine both healthy and unhealthy ageing and to make

further efforts to reduce inequalities within and across nations in expectation of health with age including dementia. Only an integrated approach incorporating lifecourse health bringing many disciplines underpinned by neuroscience and population-based epidemiological studies can provide the sufficiently robust evidence required to understand these changes.

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Tables

Table 1 Study designs and methodologies of the dementia prevalence studies

Study names	Study population	Study designs	Diagnostic methods	Major changes	Response to changes
Gothenburg study,[27] Sweden	Samples of people aged 70 and 75 in Gothenburg *C1*: 1976-77 (N=707, R=79%) *C2*: 2000-01 (N=579, R=66%) *C3*: 2005-06 (N=753, R=63%)	One-stage (diagnosis)	Clinical diagnosis (Historical criteria, similar to DSM-III-R)	(1) Subjective clinical opinion	
Nordanstig study,[28] Sweden	Samples of people aged 78+ in Nordanstig *C1*: 1995-1998 (N=303, R=90%) *C2*: 2001-2003 (N=384, R=77%)	One-stage (diagnosis)	Clinical diagnosis (DSM-III-R)	(1) Subjective clinical opinion	Same physicians conducted diagnosis to reduce subjective clinical opinions
Stockholm study,[29] Sweden	Samples of people aged 75+ in Kungsholmen, Stockholm *C1*: 1987-1989 (N=1700, R=72%) *C2*: 2001-2004 (N=1575, R=73%)	*C1*: Two-stage (screening + diagnosis) *C2*: One-stage (diagnosis)	Clinical diagnosis (DSM-III-R)	(1) Study designs (2) Subjective clinical opinions	Same physicians conducted diagnosis to reduce subjective clinical opinions
Zaragoza study,[30] Spain	Samples of people aged 65+ in Zaragoza *C1*: 1987-89 (N=1080, R=95%) *C2*: 1994-96 (N=3715, R*=64%)	Two-stage (screening + diagnosis)	Clinical diagnosis (DSM-III-R)	(1) Response rate (2) Subjective clinical opinion	Suggested refusals might not affect the results
Cognitive Function and Ageing Study (CFAS),[31] UK	Samples of people aged 65+ in England (Newcastle, Nottingham, Cambridgeshire) *C1*: 1991-94 (N=7635, R=80%) *C2*: 2008-11 (N=7796, R=56%)	*C1*: Two-stage (screening + diagnosis) *C2*: One-stage (diagnosis)	Algorithmic diagnosis (GMS-AGECAT, similar to DSM-III-R)	(1) Study design (2) Response rate	One-stage interview was validated in the C1 follow-up. Sensitivity analysis was used to address low response rate in C2.
Bordeaux farmer study,[16] France	Samples of farmers aged 65+ in Bordeaux *C1*: 1988-89 (N=595, R=69%) *C2*: 2007-08 (N=906, R=52%)	Two-stage (screening + diagnosis)	Clinical diagnosis (DSM-III-R) Algorithmic diagnosis (MMSE+IADL)	(1) Subjective clinical opinions (2) Response rate	Same physicians conducted consensus diagnosis. Sensitivity analysis was used to address low response rate.

Health and Retirement Study (HRS)[33], US	Nationwide samples of people aged 65+ in US *C1*: 2000 (N=10546, R=88%) *C2*: 2012 (N=10516, R=89%)	One-stage (diagnosis)	Algorithmic diagnosis (Phone or facce to face interview using a 27-item cognitive test or proxy assessment +IADL)	(1) Study design (increased face to face interview in C2 and reduced phone interview and proxy assessment)	
Indianapolis-Ibadan Dementia Project (IIDP),[32] US	Samples of African-American aged 70+ in Indianapolis *C1*: 1992 (N=1500, R*=86%) *C2*: 2001 (N=1892, R=44%)	Two-stage (screening + diagnosis)	Clinical diagnosis (DSM-III-R, ICD-10)	(1) A clinical consensus process involving clinicians from both sites (2) Response rate	Same basic group of clinicians from both sites conducted the consensus process
Hisayama Study,[20] Japan	All residents aged 65+ in Hisayama town *C1*: 1985 (N=2457, R=95%) *C2*: 1992 (N=1189, R=97%) *C3*: 1998 (N=1437, R=100%) *C4*: 2005 (N=1566, R=92%)	Two-stage (screening + diagnosis)	Clinical diagnosis (DSM-III/DSM-III-R)	(1) Screening and diagnostic methods (2) Subjective clinical opinion	Changes in methodologies were validated in cohorts.

C1/C2/C3/C4: Cohort 1/Cohort 2/Cohort 3/Cohort 4; R: Response rate; R*: Response rate from the original cohorts including younger age groups (ZARADEMP-I (age 60+) and IIDP (age 65+))

Table 2 Study designs and methodologies of the dementia incidence studies

Study names	Study population	Follow-up	Study designs	Diagnostic methods	Major changes	Response to changes
Rotterdam Study,[38] the Netherlands	All residents aged 60-90 in Ommoord district *C1*: 1990 (N=5727, R=73%) *C2*: 2000 (N=1769, R=67%)	3-4 years until 2007	Two-stage (screening + diagnosis)	Clinical diagnosis (DSM-III-R)	(1) Subjective clinical opinion	
Bordeaux Study,[39] France	Samples of people aged 65+ in urban Bordeaux *C1*: 1988-89 (N=1469, R=60%) *C2*: 1999-2000 (N=2104, R=39%)	Every 2-3 years for 10 years	Two-stage (screening + diagnosis)	Clinical diagnosis (DSM-III-R/-IV) Algorithmic diagnosis (MMSE + IADL)	(1) Diagnostic criteria (2) Response rate	Algorithmic diagnosis was used to compare with clinical diagnosis. Sensitivity models were conducted to address differential response rate
Cognitive Function and Ageing Study (CFAS),[40] UK	Samples of people aged 65+ in England (Newcastle, Nottingham, Cambridgeshire) *C1*: 1991-94 (N=7635, R=80%) *C2*: 2008-11 (N=7796, R=56%)	2 years	*C1*: Two-stage (screening + diagnosis) *C2*: One-stage (diagnosis)	Algorithmic diagnosis (GMS-AGECAT, similar to DSM-III-R)	(1) Study design (2) Response rate	Imputation was used to address study design issue in C1. Sensitivity models were conducted to test the impact of missing data.
Indianapolis-Ibadan Dementia Project (IIDP),[41] US and Nigeria	Samples of African-American aged 70+ in Indianapolis *C1*: 1992 (N=1440, R*=86%) *C2*: 2001 (N=1835, R=44%) Samples of Yoruba aged 70+ in Ibadan, Nigeria *C1*: 1992 (N=1174, R*=98%) *C2*: 2001 (N=1895, R=100%)	Every 2-3 years until 2009	Two-stage (screening + diagnosis)	Clinical diagnosis (DSM-III-R, ICD-10)	(1) A clinical consensus process involving clinicians from both sites (2) Response rate	Same basic group of clinicians from both sites conducted the consensus process
Framingham Heart Study (FHS),[42] US	Longitudinal cohorts of people aged 60+ in Framingham *E1*: 1977-83 (N=2457) *E2*: 1986-91 (N=2135) *E3*: 1992-98 (N=2333) *E4*: 2004-08 (N=2090)	5 years	Two-stage (screening + diagnosis)	Clinical diagnosis (DSM-IV)	(1) Subjective clinical opinion	

C1/C2: Cohort 1/Cohort 2; E1/E2/E3/E4: Epoch 1/2/3/4; R: Response rate; R*: Response rate from the original cohorts including younger age groups (IIDP (age 65+))

Table 3 Potential factors related to decreasing trends in dementia: results from Bordeaux study, Framingham Heart study, Health and Retirement Study and Rotterdam study

Common risk/protective factors included in the investigations	Analytical methods	Study	Results
- Education - Smoking - Hypertension - Cardiovascular disease - Diabetes - BMI - Cholesterol levels	Adjusted for different factors to test whether the decreasing incidence/prevalence was attenuated	Bordeaux study,[39] France	Education and vascular factors had a small effect but the decreasing trends remain significant.
		Framingham Heart Study,[42] US	No significant effect of all investigated factors (<10% changes in the trend)
		Health and Retirement Study,[33] US	Education, cardiovascular factors and BMI attenuated by up to 12% but the decreasing prevalence remain significant.
	Calculated population attributable risk (PAR)* for different factors in the two cohorts	Rotterdam study,[66] the Netherlands	- Reduced PAR: smoking, cholesterol - Similar PAR: education, cardiovascular diseases - Increased PAR: diabetes, hypertension

* Population attributable risk (PAR): the proportion of dementia cases that could be prevented if risk factors were removed.

Table 4 Studies reporting sex difference in prevalence and incidence trends

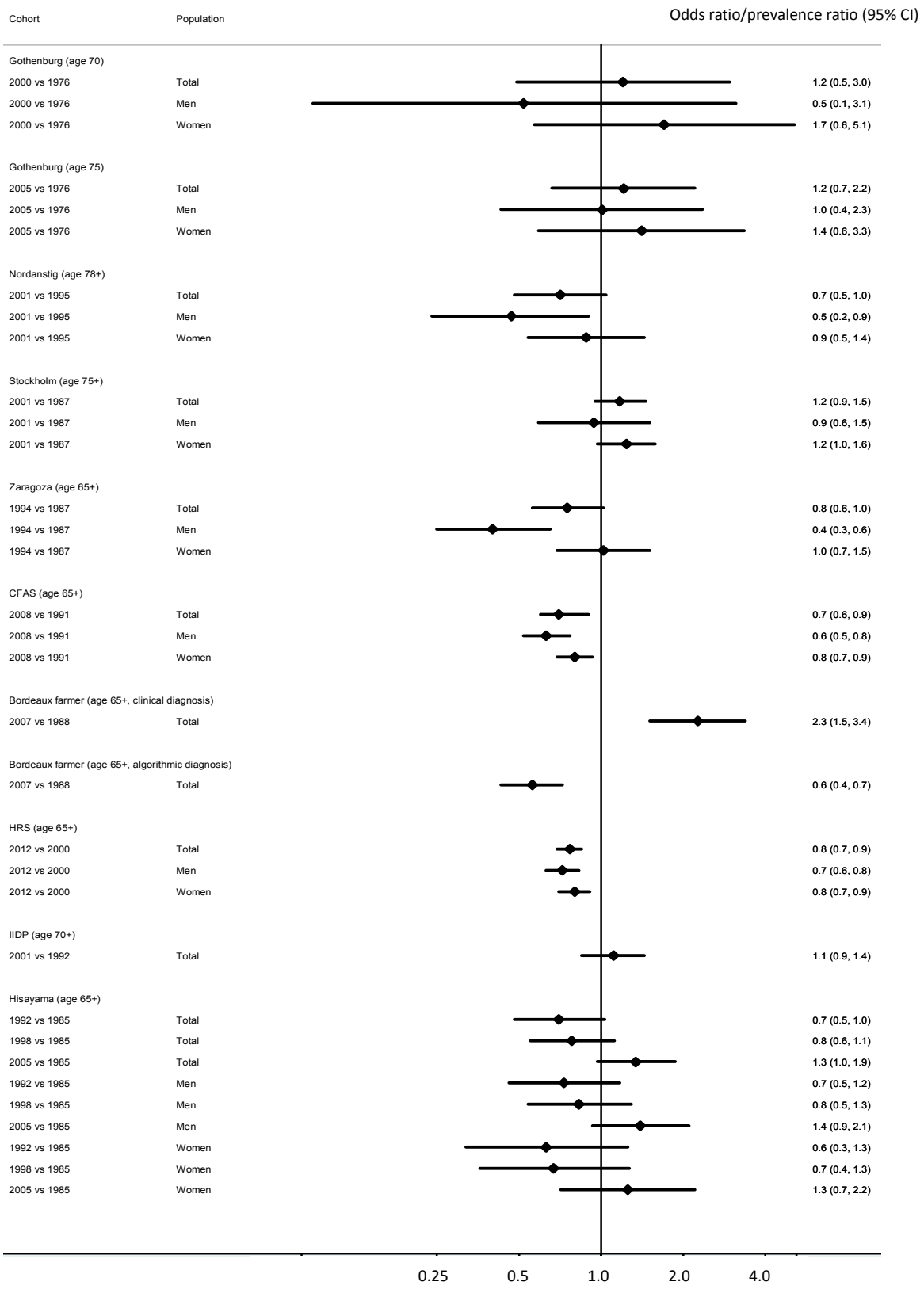
Study	Prevalence trends		Incidence trends		Life expectancy at age 60 in years					
	Men	Women	Men	Women	Men			Women		
					1990	2000	2012	1990	2000	2012
UK: CFAS (2008 vs 1991)	↓*	↓*	↓*	→	18	20	22	22	23	25
Spain: Zaragoza (1994 vs 1987)	↓*	→	-	-	19	21	22	24	25	27
Sweden: Nordanstig (2001 vs 1995)	↓*	→	-	-	19	21	23	23	24	25
France: Bordeaux (1999 vs 1988)	-	-	→	↓*	20	20	23	25	26	27
US: FHS (2005 vs 1985)	-	-	↓	↓*	19	20	21	23	23	24

↓ Decrease; → Stable

*Decreasing trends achieved statistical significance; life expectancy at age 60 was based on the World Health Organisation data

CFAS: Cognitive Function and Ageing Study; FHS: Framingham Heart Study; Stockholm study, Rotterdam study, Bordeaux farmer study, Health and Retirement study, Indianapolis-Ibadan Dementia Project (IIDP) and Hisayama study did not report any difference.

Figure 1 Odds ratio and prevalence ratio reported from the eight prevalence trend studies of dementia



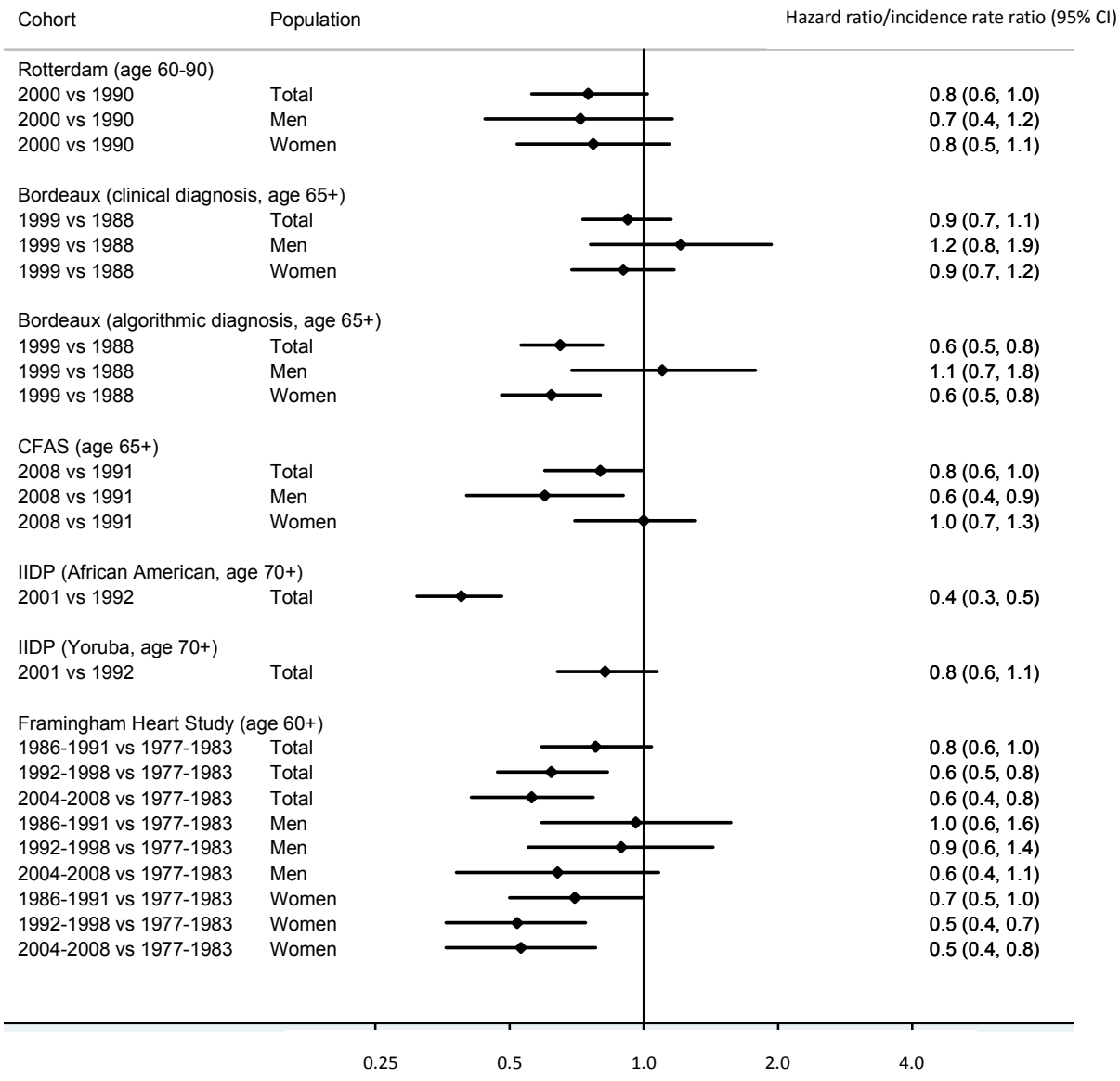
[1.] The figure reports the ratios of prevalence estimates and 95% confidence intervals in new over old cohorts by total population, men and women. If prevalence estimates remain the same across two cohorts, the ratio is 1.0; if

estimates are higher in new compared to old cohorts, the ratio is greater than 1.0.

[2.] HRS and Gothenburg study: unadjusted; IIDP: adjusted for age; Nordanstig, Zaragoza, Bordeaux farmer and Hisayama study: adjusted for age and sex; Stockholm study: adjusted for age, sex and education; CFAS: adjusted for age, sex, area and deprivation;

[3.] Bordeaux farmer study: clinical diagnosis was conducted by neuropsychologists using DSM-IIIR criteria; algorithmic diagnosis was based on cognitive and functional ability tests.

Figure 2 Hazard ratio and incidence rate ratio from the five incidence trend studies of dementia

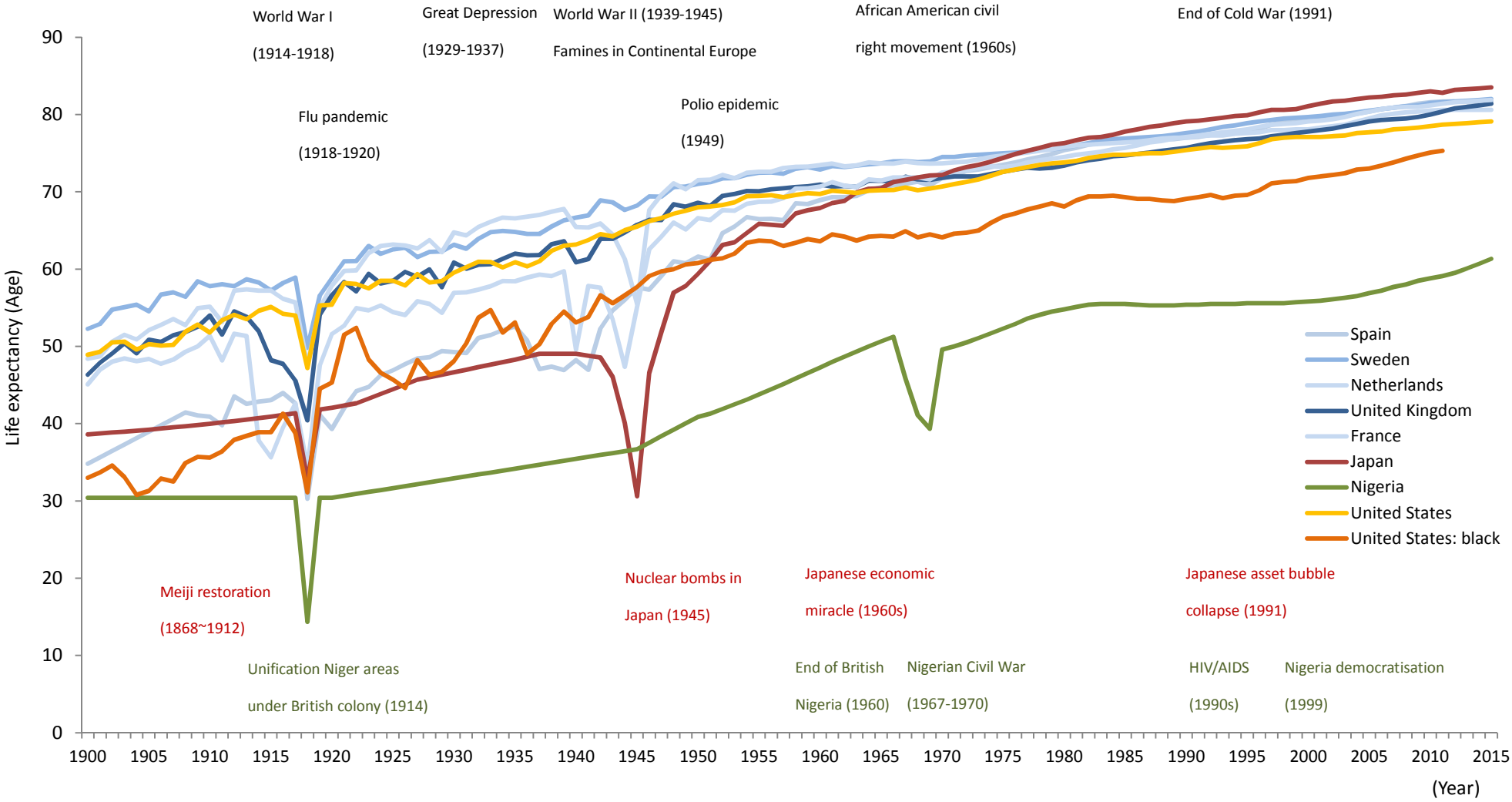


[1.] The figure reports the ratios of incidence estimates and 95% confidence intervals in new over old cohorts by total population, men and women. If incidence estimates remain the same across two cohorts, the ratio is 1.0; if estimates are higher in new compared to old cohorts, the ratio is greater than 1.0.

[2.] Rotterdam study, IIDP and Bordeaux study: adjusted for age; Framingham Heart study: adjusted for age and sex; CFAS: adjusted for age, sex, area and deprivation

[3.] Bordeaux study: clinical diagnosis was conducted by neuropsychologists and neurologists using DSM-IIIR and DSM-V criteria; algorithmic diagnosis was based on cognitive and functional ability tests

Figure 3 Life expectancy at birth in all the study countries



* Country-level life expectancy was based on the UN data and life expectancy in African Americans was based on the National Center for Health Statistics, US