



# 21ST CENTURY EURODEM

Report of a JPND Working Group on Longitudinal Cohorts

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**JPND**  
research

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*This document is the final report from one of ten working groups commissioned by the EU Joint Programme – Neurodegenerative Disease Research (JPND) in 2014 through a peer-reviewed call for proposals. The working groups were established to address methodological challenges preventing current population- and disease-based cohorts being further exploited for ND research. All ten reports are listed below and are available to download on the JPND website by clicking on the website link at the bottom of this page:*

- **HD-REAdy (High-Dimensional Research in Alzheimer’s Disease)**  
*Coordinator: Professor M. Afran Ikram, Erasmus University Medical Centre, Rotterdam, Netherlands.*
- **Harmonization and innovation of cognitive, behavioural and functional assessment in neurodegenerative dementias**  
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- **NETCALS (Network of Cohort Assessment in ALS)**  
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- **21st Century EURODEM**  
*Coordinator: Professor Carol Brayne, University of Cambridge, Cambridge, UK*
- **Multi-centre cohort-studies in Lewy-body dementia: Challenges in harmonizing different clinical and biomarker protocols**  
*Coordinator: Professor Dag Aarsland, Stavanger University Hospital, Stavanger, Norway*
- **Developing a methodological framework for trials in presymptomatic neurodegenerative disease – the Presymptomatic Neurodegeneration Initiative (PreNI)**  
*Coordinator: Dr Jonathan Rohrer, University College London, London, UK*
- **BioLoC-PD: Harmonization of biomarker assessment in longitudinal cohort studies in Parkinson’s disease**  
*Coordinator: Professor Daniela Berg, Hertie-Institute for Clinical Brain Research and German Center for Neurodegenerative Diseases, Tübingen, Germany*
- **Dementia Outcome Measures: charting new territory**  
*Coordinator: Professor Gail Mountain, University of Sheffield, Sheffield, UK*
- **Body fluid biobanking of longitudinal cohorts in neurodegenerative diseases**  
*Coordinator: Dr Charlotte Teunissen, VU University Medical Centre, Amsterdam, Netherlands*
- **Realising the potential of cohort studies to determine the vascular contribution to neurodegeneration**  
*Coordinator: Professor Joanna Wardlaw, University of Edinburgh, Edinburgh, UK*

JPND Website link: <http://www.neurodegenerationresearch.eu/initiatives/jpnd-alignment-actions/longitudinal-cohorts/>

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## Summary

Our working group sought to explore how existing investment in population based studies focused on later life across Europe can be aligned to provide better descriptive data on neurodegenerative disorders in contemporary older Europeans. It also sought to establish measurement and methodological protocols to provide a resource for risk stratification, surveillance, pooling data and meta-analysis. The over-arching aim being to determine the potential for identification of individuals from population representative cohorts towards prevention of dementia (primary, secondary and tertiary prevention types), depending on the decrease of risk or expression of risk (clinical or biological) being expressed.

We have created a new consortium (EU-EPPiDem) responding to the recent JPND call to cohorts with an expression of interest submitted resulting in an invitation to full proposal. 21st Century EURODEM held three workshops focusing on the working group's aims and has produced a draft set of guidelines aimed at policy makers and researchers interested in contemporary populations with dementia. In addition, we have established a website ([www.eu-eppidem.eu](http://www.eu-eppidem.eu)) where the reports of the workshops will be available. The guidelines cover how population representative studies should be assessed, planned and (if feasible) integrated. Members of the consortium have published an overview of European cohort studies [6] and a synthesis of the comparative European studies which have published prevalence and incidence to date (in press, *Lancet Neurology*). In addition to our guidelines, workshop reports and continued discussions have led to a planned suite of papers on timely topics relevant to dementia epidemiology, both current and future.

## Introduction

This consortium includes the old and the new in terms of knowledge and data relevant to dementia epidemiology. The combination of investigators provides an unrivalled collaboration of internationally recognised epidemiologists and trialists all of whom are leading researchers focused on dementia from a public health perspective. It is this population and public health perspective that is so critically needed in a world where a strong focus of research is earlier translation from bench to clinic. The consortium includes the leaders of studies which incorporate both bench to individual and, across the critical challenging and oft neglected second translational gap, from individual to population. The reason this is so important is that, to some extent, all progress in achieving population health is dependent upon translation into actions or behaviours at the individual level or change through policy and legislation at the population and societal level.

## Context

### *Why is there such a focus on dementia?*

Alzheimer's disease or dementia has become a global challenge. In 2010, nearly 36 million people in the world were affected by dementia, and the total number of people with dementia was projected to double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. The impact of the disorder in terms of human suffering and family burden is enormous. The global cost of dementia care in 2010 was estimated at \$604 billion, which corresponds to approximately 1% of global gross domestic product. The largest proportion of the cost ( 70%) was spent on informal, social, and direct medical care. The contexts in which our guidelines are aimed to be valuable will include governmental and international agencies, non governmental organisations, funding agencies, researchers in the field of brain ageing and dementia and those constituencies considering investment in new cohorts relevant to dementia, brain health and brain failure.

### *Why will the guidelines be useful?*

Population studies of dementia and associated conditions have been invaluable around the world. When robust, or indeed any, population data are not available, governments and constituencies interested in promoting awareness of dementia agonise about what estimates to base policy upon. They may rely on approximate estimates guided by expert opinion that will invariably lead to a mismatch of resourcing with that of true need. Rapidly changing sociocultural environments, migration and lifecourse experiences mean that governments cannot assume that needs remains stable. Ageing itself is changing and dementia now may not be the same as it was in the past, and cannot be assumed to remain the same as new generations age. Reliance on approaches such as risk stratification using novel methods e.g. amyloid imaging (PET), needs to be placed in the context of cost and appropriateness for populations. Societies need to invest in policies that will lead to greatest benefit to the population, avoiding social and gender inequality, which must involve integrating evidence on new approaches. This requires evaluation of new methods such as biomedical measurements (often developed in highly selective clinical populations) in the context of other potential approaches, assessing performance in population studies and modelling impact. This allows evaluation of the optimal balance of investment.

Life expectancy has seen dramatic increases globally in the last decades, with a significant proportion of this increase accounted for by primary prevention. The recent European studies reporting on dementia occurrence using stable diagnostic methods suggest a possible significant reduction [1-5]. Recent global interest in dementia from research and biological angles has led to a rapidly increasing armamentarium of investigative methods and associated changes in diagnostic criteria, not just for manifest dementia but also earlier prodromes. These criteria have followed the 'high tech' trend in medicine with additional biological measures being incorporated in new criteria that seek to define risk in people before clinical expression with the aim of better prediction for dementia. Such approaches are not without difficulties and the guidelines will assist policy makers and researchers who seek to understand what is required to carry out and interpret dementia related findings and how they might fit into the wider context.

## Terminology

**Prevalence:** the number of cases of a disease or condition in a given population.

**Incidence rate:** the number of new cases of a disease or condition that occur over a defined time in a given population.

**Cohort:** a well defined group of individuals who are followed up over time for occurrence of disease.

- Population representative:** a study where there is a known relationship between the population denominator and the study sample that can estimate the sampling bias and where all risk groups are included.
- Population derived:** a study with a known population denominator but where all risk groups may not be included in the final sample or where this cannot be determined.

## Methods

Background work leading up to the application included active contributions to the JPND process and work between the collaborators and beyond. These include outputs which are highly relevant [6-9]. The first workshop was focused on the cohorts and shared experience of investigators who have conducted population studies in the first wave of epidemiological dementia work in Europe and those with contemporary studies. Each study was described and discussed in relation to the aims of the working group. The studies described were CFAS I and II, Kungsholmen and SNAC-K, the Gothenburg studies, ZARADEM and ZARADEMP, the Rotterdam Study, Leila 75+, the 3C study, TILDA and the planned Rhineland study. Following the ground setting presentations, where discussions were necessarily broad, breakout groups then focused on two areas of interest which emerged: Descriptive Epidemiology and Mechanistic Analysis.

Descriptive epidemiology provides a context for public health interventions including resource allocations. It also supports development of simple models to predict future clinical, economic and social needs associated with neurodegenerative disease. Mechanistic analysis to disclose potential disease mechanisms for clinical outcomes has to take methodological and analytical consideration of both risk and resilience factors. The recent attempts to stratify risk in new 'prodromal' criteria imply mechanistic factors that have not been derived from robust empirical analyses and moreover are stratified for risk of a very restricted concept. In this regard, the current diagnosis of 'dementia' is too restrictive even before subclassification. This hampers mechanistic analyses for brain failure that may have numerous relevant mechanistic/pathological processes on going concurrently in any given individual. The work of the international biostatistical collaborative MELODEM (lead Dufouil) is well established to act as a source of knowledge in methodologies. Whilst analyses of pre-existing datasets, harmonised and merged into a single data structure has attractiveness and strong proponents, more traditional meta-analysis can be aided by a consistent methodological approach in the primary research cohorts themselves. Recent metaanalysis has been hampered by inconsistent and, at times, poor methodological quality. As a reaction to this the Cochrane Collaboration developed the STARD-Dem criteria for diagnostic studies in dementia – such an approach may be needed for observational cohort studies specific to the array of features associated with dementia cohorts [10].

To move the field forward, derivation of new exposures in the 'meaning' of old exposures is essential to maximise the investment in large studies without clinical diagnostic outcomes, but with well-measured cognition, particularly with regard to functional and social change. Finding larger samples for analysis may be possible through creating pooled datasets. This 'Big Data' revolution that offers so much does need to be led by epidemiologists with support from bioinformaticians and the biomedical community, rather than vice versa if maximum value is to be gained.

The intermediate workshop focused heavily on preparing the expression of interest for the JPND main call. The consortium developed several themes that the combined studies can tackle in a way which is unique globally. The workgroup creation through the current funding was critical to this ability. The emerging consortium settled on operational, topic and integrative approaches to the new call.

The second formal workshop was held close to the submission of the bid and part of the time was spent finalising its elements. However, we did retain the original programme content which brought together a wider group including those funded by the EU with intervention for prevention programmes. These are ground-breaking initiatives (MINDD, FINGER, HATICE) and our intention was to bring their experience to the cohorts in order to explore the implications and practicalities of introducing experimental approaches into existing cohorts. This topic was debated in a lively way with the outcome that there continues to be a strong justification for continuation of population representative observational cohorts, with the need for varying designs to test for change over time (dynamic cohorts as in the case of Rotterdam, and new independent sampling with fixed cohorts as in the case of CFAS and Stockholm studies). Some cohorts would be able to incorporate the experimental paradigm under the right circumstances, with careful consideration of participation in a variety of study types (risk stratification and pharma trials such as EPAD, multi-domain trials such as FINGER or MAPT). The interplay of high response rate and later attrition remains a key issue in discussions on population representation.

## AGREED GUIDELINES

### **Guidelines for the maximization of value of contemporary and future population representative studies to inform current policy, practice and research relevant to ageing societies. June 2015**

#### **1. Purpose**

Despite the undoubted strength of Europe following earlier investment in cohort studies of ageing populations, less so in recent times, it is clear that many unanswered questions remain and new questions emerge. Prominent amongst these is whether dementia is changing as our global population itself is shifting, whether clinical profiles of dementia and associated phenotypes are changing and will change further, whether the relationships between diagnosis and disability, dependence and survival as outcomes are changing and the interplay of relevant risk factors at earlier lifestages. Population representative cohorts are particularly important as they are uniquely able to address these questions in a way that can be compared across time and geography. There is a compelling need to maximise the value of existing data and argue for investment into studies that can address these questions at intermittent time periods, and across geographies and communities, most notably those in which there is little or no contemporary or even historical data. These guidelines are aimed at a wide range of audiences to inform and guide researchers entering the area. This includes helping those in different fields of dementia research understand what a population representative perspective is and why it is important and, critically, policy makers and funders who must make decisions about the balance of research funding available to existing and new work, across biomedical to policy relevant domains. These guidelines cover all elements of the evolution of the dementia syndrome, and also cognitive impairment which does not meet criteria for dementia (whether mild cognitive impairment (MCI) or the wider category of non demented cognitively impaired).

#### **2. Basic orientation - why population representation?**

##### *2.1 What are population representative cohort studies and what have they been traditionally 'used' for?*

The definition of a population representative cohort study is a complex undertaking. Here the distinction between population derived or population representative is crucial. The term population derived can refer to any sample where the original sampling frame is a population, no matter how unrepresentative that

population might be at recruitment and in follow-up. A cohort study recruiting from a population but with very low responses and no linkage to that population denominator would be population derived, rather than population representative. A cohort study of 'volunteers' can be population representative as long as knowledge of the recruitment from the original complete population is known, and the relationship between the volunteer cohort and this complete population can therefore be determined. A population representative study is thus one where the recruitment is conducted from a known population base. This can take a variety of approaches such as random or purposeful sampling from geographical areas or other defined clusters. The key here is that the provenance of the sample recruited is known and the findings from the study can be mapped back in a robust statistical manner, with appropriate acknowledgment of potential bounds of uncertainty, to the original population. Ideally some information on the unseen population should be available – this might be in the form of knowledge about responses from particular areas of socioeconomic level. Whilst many cohorts are population derived few are population representative. Full exploration of the impact on generalisability of research findings is rare, with most papers findings highly generalisable from one setting to another. The dementia field includes abundant examples of such thinking, related to the enthusiasm of particular constituencies about the rapid translation of their findings beyond the populations in which the evidence was generated. Sometimes this will be robust, sometimes not. From a public health perspective this lack of awareness of the provenance and generalisability of evidence is critically important and likely to be an underlying factor in the frequent lack of repeatability of findings or reduction in effect observed in research which attempts to implement earlier promising findings. Definition of the original population sampling frame, who is in and who is not in (important for hard to reach populations), response rates and attrition are further critical areas of importance in assessing the value of research for generalisability and population meaning.

There have been many volunteer cohorts across the lifecourse but relatively few have robust links to their original sampling frame, so although such studies have provided the bulk of our knowledge about risk factors and the evolution of dementia within the cohort, they provide less evidence for translation of those risk factors' meaning into whole populations. On the other hand representative cohorts can suffer from higher attrition rates than volunteer cohorts which, if they are not taken into account using appropriate methods, can lead to biased findings on incidence rates and associations. The need for representative populations has been neglected, particularly since the genomic and biomarker revolutions where convenience samples are often used, without much attention paid to selection biases. However, this does not mean population representation has lost importance, as evidenced by the poor ratings of almost all studies of biomarkers for the early detection of dementia [11]. A new approach to educating our policy makers and researchers is needed, as well as further robust research within epidemiology. Response rates in many areas are going down and this too is an area of concern. The meaning of population and the relationship between personalised and collective requires new scrutiny, enormously important in the field of dementia research and public health, as decisions are made about balance of investment for current and future populations. Finally, there is a need in population descriptive work to consider what groups are missed and underrepresented, even where studies have been conducted to be population representative. This includes socio-economic status needed in relation to inequality such as: immigrant groups, prisoners, travellers and ethnicity.

## 2.2 *What is the meaning of a diagnosis in different settings and why does this matter?*

Dementia is a syndrome or label with a long history. Since diagnostic criteria were introduced these have moved from discursive texts to more specific symptom and sign lists. The introduction of subtypes such as Alzheimer's disease has been followed with recognition of other neuropathologies such as Lewy Bodies, frontal-temporal dementia etc. The extent to which diagnosis differs as the outcome measure from a cohort study is crucial to understanding the relationship between that outcome and the potential of the study to provide insights into realistic changes seen outside the study setting. The more the diagnosis is similar to that seen in the general

population using existing sources, the more likely the cohort study is to be able to answer questions about the relationships seen within a population. However if the existing sources are biased or inaccurate (as is the case in dementia) then it is essential that the issue around diagnostic ascertainment is decided prior to the start of the study itself. Diagnostic creep is a concern for all cohort studies as the field of knowledge about the diagnosis moves during the course of the cohort study. It is essential that the same symptoms give the same diagnoses for person number 1 and person number 1000. The more invasive and less typical the diagnostic ascertainment's the more likely that heterogeneity in diagnosis is removed, but at the cost of increased participant burden, selection bias into the diagnostic phases and movement away from the relationship between the routine outcome and the study outcome. These are not one size fits all diagnoses and researchers need to be aware of the potential benefits and limitations of each method prior to the beginning of the cohort study. However once started, it is essential that consistency of the measurements is maintained.

As well as the outcome, descriptive epidemiology needs to consider or measure trends in risk factors associated with dementia, e.g. prevalence of smoking. The outcome should also not be dependent on what DSM-V and other clinical criteria considers as dementia as these are usually restricted to clinical diagnosis and consensus judgement rather than with empirical data. This brings into focus the recent prominence of biomarkers as diagnostic entities with only minimal evidence, at present, to support their use for such purposes. Different approaches to defining caseness for dementia can seriously hamper comparing data across time and cross-sectionally between, for example, geographies – in this regard capturing social, functional and cognitive outcomes and avoiding medical categorisations can overcome such inconsistencies. While prospective cohort studies which applied consistent measurement of outcomes are of greatest value, cross-sectional studies are still valuable as long as they accurately capture a valid denominator.

Accurate knowledge of incidence and prevalence of dementia or other neurodegenerative clinical outcomes is required with the emphasis on precision to mitigate measurement error as far as possible. Predictions can then be tested with real outcome data as it emerges and models improved. Taking a consistent approach to measurement allows trends in incidence and prevalence to be monitored using, for instance, sentinel clinical centres across Europe collecting a minimum core data set or longitudinal assessment from extant cohorts. These would need to consider non-cognitive influences on morbidity in dementia, e.g. social, physical and economic factors as well as the traditional cognitive approaches.

Studies also allow for stratification and risk assessment so that individuals might be offered trial participation, with appropriate consent procedures. These developments and the associated societal interest have had a profound impact on clinical services whereby biomarker salience in diagnostic pathways is becoming the norm with little evidence of real clinical value as yet. This has an impact on awareness and behaviour in relation to seeking help when concerned about memory problems, where in the absence of any disease course modifying interventions – avoidance (by people at risk) of testing may actually predominate over seeking help. The new diagnostic criteria have effectively changed the boundaries of the dementia syndrome, and it is important to have studies that can examine the impact of such changes and also their meaning. One example is that we do not know what the association and progression of the newer diagnostic criteria are in relation to disability and loss of independence. In addition, different cultural settings have different meanings. The findings from the bench can be translated to the individual within population studies and then straight out to their meaning for particular populations. Risk stratification and appropriate policy can only be integrated through such approaches allowing the balance of personalised approaches to be brought together with societal action. This is achieved through primary analysis, and then integrated analysis across cohorts in a manner which recognises the richness of individual cohorts.



In all this research those interested in public health must retain the question how relevant is this to the societal concern? In other words, if a new diagnosis of pre-clinical Alzheimer's disease leads to an epidemic of a diagnosis but one which has a benign prognosis, what does this mean for societal burden of dementia?

### 2.3 *What is the role and value of population representative studies in primary, secondary and tertiary prevention?*

Setting the agenda. The answer to this question hinges on what the research gaps are in dementia research. While the research agenda is heavily influenced by interested researchers in clinical and biomedical fields, it is also determined by funders, politicians, interested groups such as pharma, diagnostics and technological innovation leaders, charities and the media. These constituencies use epidemiological evidence to justify the particular activities but rarely give much thought to whether their promotional work actually maps onto the population evidence noted above. One activity that attempts to counterbalance these perspectives is the James Lind Alliance. This is a UK based exercise on what the more general public see as research priorities. The James Lind Alliance is one in which the people, and much wider audience than general in terms of who drives the pattern of research funding and decision making, have a chance to pitch their perception on the questions unanswered by research. In the dementia focused exercise, responses were distilled and synthesised into answerable questions, the literature searched on whether robust evidence exists. If not, these uncertainties were confirmed and a process of prioritisation using established methodology followed. This process was conducted for primary, secondary and tertiary prevention with the public and wider professional and institutional groupings. Over 4,000 individual questions were submitted and all the questions were framed in terms of the public health prevention model [12]. A public health research approach would aim to meet these uncertainties.

## 3. **Prevention**

### 3.1 *Primary Prevention*

Primary prevention is upstream prevention of a disorder or disease occurring, most clearly illustrated by the avoidance of smoking and reducing the risk of lung cancer almost to zero. If modifiable biomarkers are identified for risk factors for the development of dementia and this will reduce risk of developing dementia, this would meet the definition of primary prevention. However, if biomarkers are a marker of the earliest pathological manifestations in the development of a later clearcut condition, such as cervical dysplasia, this is not primary but secondary prevention (see below). The definition of primary prevention therefore depends on the perspective. From a pragmatic and clinical perspective, primary prevention refers to any intervention in persons with no symptoms or signs of cognitive impairment which change their known natural history of cognitive decline towards dementia. Primary prevention initiatives, such as in the case of dementia reduction in smoking, can be targeted towards whole populations, communities or individual level ranging from legislation to community designs encouraging optimal lifestyles, to individual health education. Primary prevention can also be targeted at specific high risk populations, sometimes based on clinical characteristics.

Population health surveillance, routine data and knowledge from volunteer cohort studies or population derived studies (cf representative) contribute to models about which risk factors have the greatest prevalence and potential for societal and service action. However, without longitudinal data on risk from population representative studies for given populations the true potential for prevention cannot be known.

Many countries are now seeking to include brain health in their health promotion messaging. Many individuals are now actively engaging in what they perceive to be risk reducing activities such as physical and cognitive

activity. Trials are important in this area to inform what can be done in whole populations, with which types of societal and individual interventions. Clinical conditions which constitute dementia risk are already being used in the UK health system as a loose programme ('Health Checks' now include dementia as an outcome for people with higher risk through conditions such as diabetes and stroke).

Primary prevention research: knowledge of whole populations informs trials, their designs and their implementation. Population studies can assist in the evaluation of primary prevention strategies through modelling and natural experiments (such as cohort changes). Estimation of treatment effects can be calculated using population data [13, 14], population studies can inform primary prevention through adoption of interventions and quasi-experimental designs can be considered, such as for instance, the regression discontinuity design, which allows for estimation of treatment effects without the need for randomisation. Different risk factors for dementia exert a different effect throughout the lifecourse, with potential cohort effects depending on population characteristics, cultural context and era in which data was collected. Future prevention programs should cover the full spectrum of primary prevention, from targeted at risk groups to the whole population. Specific attention should be paid to cohort effects influencing the observational data on which future interventions will be based.

### 3.2 *Secondary Prevention*

Secondary prevention is early detection of a disease process in which the natural history is understood and well known. Biomarkers (CSF, Imaging) and early clinical signs (such as neuropsychology or psychomotor disturbance) have the potential to be the measures that provide such detection. The marker needs to be extremely well understood, its relationship to the disorder in question must be very close such that individuals (of particular age, sex etc) with particular metrics can be given their prognosis with reasonable bounds of uncertainty. If biomarkers which can be obtained in a non or minimally invasive way with sufficiently good test characteristics in the general population become available and there are effective treatments for that particular disease, the clinical outcome such that early detection changes natural history positively, it is conceivable that these could also be used for selecting the right target population for a secondary prevention programme. Secondary prevention programmes can be opportunistically delivered, as is the case with much cardiovascular and diabetes risk identification, or through systematic programmes of screening for particular populations. Population data on natural history for biomarkers, their evolution and relationships to outcomes of relevance to populations in which a disorder occurs, are critical to progress the field of secondary prevention. This requires unselected populations to be studied using the proposed measures on a repeated basis (after they have been validated in more selected clinical populations) to see how well those who progress to develop a disorder within a population setting are identified by the proposed test or combinations of tests. Policy for secondary prevention programmes must be based on robust evidence and internationally accepted guidelines for such screenings have been well described through the World Health Organisation, the US Preventive Task Force work and the UK's National Screening Committee [15-17]. Population based studies, including cohort trials, are essential for knowledge about how secondary prevention should be implemented once preliminary trials have been conducted. Population evidence is crucial in the design of the research and the policy development in this area.

### 3.3 *Tertiary Prevention, including end of life*

Tertiary prevention is the mitigation of a disorder once present. This means that for those people who have presented to health and social care relevant, evidenced possibilities can be offered. The evidence base for this is largely developed through trials in clinical and other settings such as care homes. This includes end of life research about a dignified and compassionate approach to end of life care and decision making. Population studies are relevant here as clinical settings do not capture the population as it is in society. Individuals come

and go from clinical services and are then not followed up and primary care practitioners will not necessarily see those who are well supported in their communities. Research needs to describe the whole population, not just those seen in particular settings in order to understand the reality of dementia in populations. Applying costings based on those seen in services to all people with dementia does not take into account the range of need and may well be severely impacted by the selections of the characteristics of the individuals into the studies. The complete picture of the costs of dementia may therefore be inaccurately estimated. Such research informs policy development in an important and unique way, which is relevant to work such as the UK's NICE assessments (and similar ones elsewhere in Europe and beyond). Population studies provide a background and potentially a resource in which research aimed at tertiary prevention can be developed. Trials which work with this kind of approach are more likely to be relevant to the ultimate aim of all health research – to improve lived lives for the population.

#### 4. Guidance on understanding existing data

In order to conduct truly informative combined analysis with cohort data for the purposes of addressing the areas noted above the following areas must be well understood. Quality of reporting in these areas is highly variable, but it is increasingly recommended by journals that this is improved. The most recent of these dedicated to Neurology (STROND) is soon to be published in European Journal of Epidemiology.

**Table 1: Checklist for evaluation of population relevance**

|   |
|---|
| ✓ Original purpose  |
| ✓ Details of sampling frame, how generated, how up to date, patterns of migration, care settings.   |
| ✓ Approach to participants, opt-in, opt-out, incentives and exhortations.   |
| ✓ What did the consent process involve?   |
| ✓ Response.   |
| ✓ Where were people interviewed, what were they offered, what was the uptake of different offerings?  |
| ✓ What type of person did the interviews, was clinical examination involved?  |
| ✓ Reasons for refusal within the study – gate keepers and proxies, individual refusal, items, interviews abandoned. Ability to characterise the non-responders at the population/geographical level.            |
| ✓ Attrition details (moving, death).  |
| ✓ Information on those who did not take part – complete, partial and if partial what characterises this?  |
| ✓ Measures collected – origin of questions, validation if available against what gold standard, whether coding and by design missingness exists.  |
| ✓ Do the measures include sufficient basic sociodemographic perspectives to provide contextual information for assessment of interpretation and generalisability?   |
| ✓ Who collected the data?   |
| ✓ Was the respondent interviewed alone?   |
| ✓ Has there been stability of questions and measures across time? If not, how have questions changed and what is the potential implications of that change?   |
| ✓ If biological are they appropriate to the questions being addressed, including the way they were taken and who by, how were they handled immediately and shipped to storage, stored, extracted, and analysed? |
| ✓ How have problematic areas such as different IADL and ADL for men and women through cultural  |

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| disability been explored?  |
| ✓ Have any or all of these factors been examined in any outputs to date? If yes, is it only to say these might introduce bias or limitations or is there further exploration to test which way the bias might go and how large it might be?  |
| ✓ Have the findings been contextualised using all this information to assess what the true value of the outputs are – this means for that population, in relation to other known non independent risk factors (moving beyond salami publishing) – and what the potential for population impact is (i.e. meaningful effect sizes rather than p values). |

#### 4.2 Commentary

Most studies will not be able to meet the highest standards in all of these but some attempt is warranted, and any findings presented without sensitivity analyses to explore the impact of inevitable imperfection of studies should be treated with caution as the study will not be able to fully contribute to synthesised approaches. There are some questions that can be answered without going through this challenging listing but these will be divorced from true populations and thus their meaning for policy and future populations will be unclear.

### 5. Guidance on repurposing and establishing new cohorts to address the areas above

It is clear that new cohorts are urgently needed for those geographical areas and social groups either using data decades out of date or with no existing data. Some cohorts will have the potential to incorporate an experimental approach or be able to be used to evaluate geographical changes. This needs a range of implications and considerations for which new guidelines need development.

All the elements of the checklist above (Table 1) should be integrated into the design and collection of data at each sweep. Additionally and depending on context, detailed consideration of how inequalities and hard to reach communities are being included with particular design features appropriate to culture and setting (this will include gender and location of study being conducted for some communities). Our core recommended template is shown in the table below.

**Table 2: Guidelines for undertaking new cohort studies**

|   |
|---|
| <b>Design of study:</b>   |
| Knowledge of the population denominator, in as much detail as allowed prior to sampling (and usually consent).  |
| Ability to understand reasons for refusal from all participants (again as much detail as can be allowed within ethical considerations).   |
| Options for levels of participation (clinic visit, home visit, internet response, informants, note response) to increase participation rates.   |
| Considerations of enticements or remuneration for participants.   |
| Covering sociodemographic features and migration within and across regions and countries.   |
| Special undertakings for hard to reach populations. Capacity and consent and how to maximise response.  |
| Interval of change, how much and how often?   |
| <b>Measurements:</b>  |
| Core elements that can be compared across all new studies are the key here, such as gender, age, social-economic circumstances, chronic diseases, functional impairments, interactions with care givers |

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| (both formal and informal), cognitive testing (at least broad). Main aspects must have been measured (and reported on) in exactly the same way from at least one other European study to provide anchoring of measurements over time. This anchoring can be different studies (e.g. measurement of education is the same as UK Census, whereas functional impairment is the same as another study) but exact replication is the key. |
| Measuring risk and compensatory factors across the lifecourse, including vascular history and status along with other relevant medical conditions.   |
| Measuring regular medications, interactions with health services and care. Potential to measure easily accessible biological material (hair or nails collected appropriately) Questionnaires online or in person, in clinics or combinations.  |
| Potential for computerised testing in addition to existing and well understood testing procedures (not instead of an anchoring measure). Subsets with deeper phenotyping, deeper risk/protection data collection. Random subsets with known linkage. Not just opportunistic, but designed.   |

## 6. Guidelines on research expertise requirements

### 6.1 Skill requirements for cohorts

Undertaking a new cohort study requires a multi-disciplinary team all committed to getting the highest response rate possible based on the decisions taken, whatever the sample size chosen. The more the study has inclusion criteria based on the outcome measures, the less the response rate from the complete population will become. Studies require expertise in public health, statistics, general practice, specialist medical areas, study co-ordinators, interview trainers (if appropriate), professions skilled in communication, computer programmers (if applicable), ethics and data experts. Many skills associated with the setting up or following of a cohort study are not discipline specific and therefore not taught through usual channels.

### 6.2 Capacity building for the future

As stated above, the core skills needed for undertaking cohort studies are rarely taught in any formal arena. Years of expertise and knowledge has been collected by the leading researchers around Europe who are at the forefront of this research goal. Capacity building at the moment relies on these research groups to fund, and train, new researchers to be the next generation of population based researchers, funding does not always allow for such a transition. It takes years for a study to reach maturity from study initiation, mostly without core capacity involvement reliant on single leaders bringing together committed teams over prolonged periods. Few outside these communities appreciate the detailed issues outlined here, which is likely to be responsible for considerable future wasted investment in research avenues that have not been properly scrutinised and evaluated for population relevance and potential for benefit.

Training basic scientists and policy makers to be able to critically (but fairly) appraise evidence from all sources gives additional capacity to the community in terms of understanding population health.

## 7. How to use these guidelines

7.1 *For funders* – read and think about what the balance of your funding is and training for such skills. Long-term vision required not only for new cohorts, but in particular for future prevention trials.

7.2 *Policy maker* – read and apply to evidence provided to you which appears to be compelling, where did it come from?

- 7.3 Journal editors and reviewers - read and think about what you publish, much research is not contextualised and its value is limited because such careful considerations are not made, reviewers are not trained in this and should also take note. This will lead to higher quality publications and greater use of the excellent guidelines on publication standards (STARdem, STROND).
- 7.4 Steward of a cohort which might be population representative – think about whether you could address some of the areas where your study is weaker as there are often other sources of information that can help with contextual value, think before you overplay your results without consideration of impact;
- 7.5 Cohort investigator hopefuls, applying for funds - Advise against new cohorts unless very clear what this new cohort adds to existing cohorts; Only new era perhaps not a strong enough argument to start a new cohort. Very clear research questions required. Some sort of statistical power analysis for the main research questions of the cohort is required (as opposed to just collecting as much data as possible to fill a biobank). Aim for (inter)national collaboration to start few major cohorts, rather than multiple smaller cohorts. Focus on research questions. Measure parameters for these specific research questions in depth, rather than measuring a very broad range of parameters, but nothing in depth.
- 7.6 Other dementia researchers of a non-population representative cohort or if you work in primary, secondary and tertiary care - Don't aim to translate data of a non-representative sample to a wider population. Aim for proof of concept analyses in highly selected populations. Secondary or tertiary prevention. Never lose the scope of your cohort: highly selected, limited external validity. Look at your study through the lens of this guidance and see whether you can meet any of the elements.
- 7.7 Members of the public or a charity - question received statements about the evidence, ask where it came from and how appropriate it is for the challenges that society grapples with.

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