LONGITUDINAL COHORT STUDIES IN NEURODEGENERATION RESEARCH

Report of the JPND Action Group

September 2013

JPND research

EU Joint Programme – Neurodegenerative Disease Research

Executive Summary

The purpose of this report is to recommend options for JPND action in the area of longitudinal cohort studies, spanning general population-based, targeted (preclinical) and disease-focused cohorts. These highlight where current member-led or EC-supported activities can be expanded or better exploited, or new activities identified, to progress European neurodegeneration research. These options are based on an analysis of opportunities presented by current European longitudinal cohort capability, as well as comparison with selected international studies. A series of potential and realisable actions are presented, spanning coordination, funding and policy areas.

Current research landscape

The Action Group drew extensively on two sources of information - the published JPND portfolio and a scoping exercise undertaken by the UK Alzheimer's Society, completed in Jan 2013 - to undertake an analysis of European longitudinal cohorts, supported by consideration of key international studies and those currently being established. Overall, 171 cohorts were considered. It is apparent that a wide range of longitudinal cohort studies exist, covering all age groups and a wide variety of risk factors (including those at societal level, modifiable lifestyle behaviours and biological pathways) and disease entities. However, the comparability of the cohorts varies considerably, according to the sampling methods, the intensity of investigation and consequent response rates. Within the different types of cohorts, ageing studies offer an opportunity to study the early disease stages and trajectories of neurodegenerative disorders, while there is also considerable scope for longitudinal studies set up for other purposes to be utilised for research in neurodegenerative diseases (ND) by adding additional cognitive, genetic or other measures. A number of major prospective disease-based cohorts have been established, notably in Alzheimer's Disease (AD) and Parkinson's Disease (PD), but also in less common conditions such as Amyotrophic lateral sclerosis (ALS) where networking and coordination become essential to gather sufficient cases for study.

Despite this richness in population studies, some gaps are apparent. For example, there is an under-representation of studies able to identify and then test the value of early diagnostic and prognostic markers of preclinical dementia in ND. Relatively few cohorts have been set up to look at intergenerational change in prevalence and incidence of ND, while cohorts that support research into the provision and outcomes of health and social care are also lacking. Some countries have no available descriptive epidemiological studies to inform policy planning. A notable discordance was observed in the relative intensity of research into ND which are now known to be scientifically inter-related, such as Motor Neuron Disease (MND) and Fronto Temporal Dementia (FTD), or PD and Lewy Body Disease (LBD). For example, few studies address the incidence or risk factors for LBD, a condition which affects up to 20% of people with dementia.

Opportunities and needs

Current population and disease-focused cohorts offer significant opportunity for advancing our understanding of the risks of developing neurodegenerative conditions and the influences on disease progression. Such cohorts also offer the prospect of providing platforms for prevention and intervention studies in the longer term. Nevertheless, this work has revealed that surprisingly little information is available on the natural biomedical history of ND despite a wealth of cohort activity across Europe. It therefore appears to be timely to take steps to improve and co-ordinate existing capability, given the opportunities offered by the recent evidence for convergence amongst risk factors and underlying pathologies across ND.

The key priority for furthering scientific progress at the European level should be to enhance the capabilities of existing studies, or linking related studies to address key questions through a synergistic approach. The

case for establishing new cohorts, aside from one or two well defined areas, is much harder to make. To deliver the required impact, a number of opportunities and challenges can be defined where action would be merited:

- There is an opportunity to bring together cohorts to achieve added value, primarily through large increases in sample size and hence the statistical power to look at interactions. One such example would be through the alignment of genetically enriched cohorts across Europe. However, the heterogeneity of studies and measures will require new conceptual approaches to allow data to be pooled, and methodological rigour needs to be promoted if linkage across studies is to be successfully achieved. Through such approaches detailed deep phenotyping can be analysed alongside larger more superficial studies to improve translation and meaning of findings.
- Coordination of datasets and/or bioresources could be promoted through the collection of a detailed inventory of the assessments and protocols used within studies. Minimum parameters should be defined regarding future data collection, use, and dissemination, whilst ensuring flexibility is retained to incorporate emerging approaches/technologies. The access to sample collections and data by external groups also needs to be encouraged to promote secondary analyses of population data. Account will need to be taken of other global efforts in this arena, such as the PAD2020 project.[1]
- Large Europe-wide population-based and longitudinal studies of at risk and disease populations should, where feasible, incorporate as much integrated and in-depth phenotyping as possible to link health, environmental and lifestyle data (including nutrition) to biological, clinical and behavioural outcome measures. This research should encompass the use of cerebrospinal fluid (CSF) and brain PET imaging studies and emerging technologies - such as 'omics' approaches, iPS cell line generation, molecular imaging etc - once the performance of these technologies is validated for this type of research.
- Many cohorts starting in midlife may provide an opportunity for identifying and testing potential characteristics of the preclinical and prodromal stages. These will have limited power unless sample size is very large. Studies should be encouraged that identify the early markers (cognitive, functional and behavioural) that herald the onset and progression of neurodegeneration. For these studies in particular, long term follow-up will be needed with the consequent need for investment in forward planning and stable systems to curate data and maintain contact with respondents.
- Developing a life-course approach. Given the long incubation/latency periods, aetiological approaches to late-life ND might particularly benefit from analysis of data prospectively collected from a young age. In addition, working across European countries offers possibilities to study cultural diversity which provides an additional opportunity for studies of gene-environment interaction as well as issues related to health service delivery.
- Well characterized cohorts offer the prospect for future prevention/intervention trials that in combination will have sufficient power to provide robust scientific data. Potentially very interesting information could be provided by combining intervention studies in other relevant fields, eg. anti-hypertensive, anti-diabetic, antidepressant, and cholesterol-lowering trials. It is notable in this respect that an accumulating body of evidence supports a relationship between Type 2 Diabetes and the development of AD and cognitive impairment. Understanding the mechanism underlying this

[1] PAD2020 (The Campaign to Prevent Alzheimer's Disease by 2020) is spearheading the International Database on Aging and Dementia [IDAD] Project. A standardized database structure will be used across approx. 20 large, well-phenotyped cohorts representing asymptomatic and at-risk participants through to those presenting with early-onset dementia across N America and Europe. This will be used to mine biological and genomic biomarkers, along with behavioural data, in order to develop methods for the early detection of AD, and putative interventions to prevent or delay the onset of dementia.

relationship will be crucial to assessing the potential for and the development of treatment/preventive strategies for cognitive impairment in both diabetic and non-diabetic populations to address a major risk factor for AD.

- Linkage of research subjects to medical and social service records and wider administrative data offers a powerful approach to enrich datasets, while harmonising clinical data in existing cohorts would facilitate cross-centre sharing. Resource and data quality, data protection and access will need to be addressed to ensure the value and appropriateness of research using these methods.
- The development of new ICT platforms is required to promote data capture and sharing and intensive data analysis as well as biostatistical methodologies that can maximise the value of diverse datasets. This is particularly needed to fully exploit the potential offered through the development of multimodal imaging packages, which also requires the supportive development of harmonized imaging protocols, software compatibility and data acquisition procedures and validation studies of imaging markers as outcome measures for intervention studies.

Recommendations for Delivery

It is recommended that JPND considers action in three domains. In all cases implementation should take account of ongoing activity in related European and global initiatives.

i) Coordination and development of best practice

A series of JPND workshops should be established to address the key challenges in the field, through providing a framework for exploiting and harmonizing existing or planned cohort studies, or as a basis for developing new research proposals. In essence these should focus on bringing together key cohorts and opinion leaders to develop solutions to the barriers to progress, and such workshops could be progressed with modest levels of funding provided on a competitive basis. It is suggested that a JPND Steering Group should be appointed to take responsibility for oversight of these activities. The goal would be to provide cohort researchers with a clear way forward, with topics to include:

- **preclinical (asymptomatic and presymptomatic) stages of ND:** defining the key methodological issues, tools and measures. To establish guidelines for dealing with multimodal imaging approaches and perspectives in molecular imaging, including software compatibility and minimum image and metadata for inclusion in image databanks.
- **cognition, behaviour & function:** to develop a consensus on methodologies to define cognitive, behavioural and functional change/decline/case/outcomes relevant to ND for population based cohort studies and disease cohorts.
- **data handling:** the integration of 'omics' technologies within the context of complex longitudinal data of differing types, the interpretation of data protection legislation and the handling and sharing of big data sets.
- **cohort alignment**: bringing cohorts together in selected areas where data pooling can realistically be achieved and is particularly beneficial (eg. rare ND).
- **clinical data linkage:** to convene studies with clear clinical linkage to identify how they might be exploited in prospective studies, areas where harmonisation might be achieved, best practice for data protection and storage, and dissemination issues and solutions.
- **exploiting intervention-studies of potential risk factors** (eg. hypertension, Type 2 diabetes etc): identification of how ongoing large trials can be used to adequately address risk of ND as an outcome.

ii) Calls for proposals

In parallel to the activities described above there should be calls for proposals centred on optimal strategies

to take advantage of the current longitudinal studies in a European framework. The calls should seek to establish cross-centre research programmes that:

- bring together well-characterised relevant cohort groups to harmonize, or make accessible, data to promote secondary analysis;
- add new measurements, sample collections or data sweeps that add significant value or provide linkage to other studies;
- establish novel assessment measures, taking advantage of new technologies, extending beyond the cognitive domain (ie. motor and perceptual function) that can be applied to the broad spectrum of ND;
- deliver methodological developments or enhancements to establish cohorts as intervention platforms;
- provide training programs to ensure good operational understanding of cohort study design, data analysis, interoperability and high quality standards of practice. There may be benefit to delaying initiation of training until greater JPND consensus on these issues is established.

iii) Data access policy:

- A JPND policy should be developed to help ensure that data from JPND funded research is open access. Alongside this, guidance should be developed on the use of both anonymised and sensitive data, which may have to be stored on secure servers with access approved by a data custodian using best safe haven practice. Ideally this framework should be implementable by JPND member organisations regarding their own national programmes, with recognition inbuilt that it may be hard for older established cohorts to be fully compliant.
- A study should be undertaken to scope the potential for establishing a European population data warehouse using ND as the model disease area. This should ideally involve the European Commission to ensure connectivity to existing EU-wide activities in this area, such as the eTRIKS[2] project to create a research informatics and analytics platform for use by IMI. The warehouse would store in a secure manner and make widely accessible data generated through genetic and other 'omics' studies, imaging etc, providing a resource to support nationally-funded studies and enhance cooperative research and impact.

[2] eTRIKS Delivering European Translational Information & Knowledge Management Services www.imi.europa.eu/content/etriks

Full Report

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1. Introduction

The EU Joint Programme – Neurodegenerative Disease Research (JPND) is the largest global research initiative aimed at tackling the challenge of neurodegenerative diseases. JPND aims to increase coordinated investment between participating countries in research aimed at finding causes, developing cures, and identifying appropriate ways to care for those with neurodegenerative diseases.

This report to the JPND Management Board was prepared by a JPND Action Group with the following membership:

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- Catherine Moody (MRC UK)
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- Bruno Dubois (France, and JPND SAB)
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The following members of the JPND SAB also attended some of the Action Group meetings and provided helpful input: Professors Thomas Gasser (Chair), Martin Rossor (Deputy Chair) and Philip Scheltens.

The Action Group is grateful for the assistance of the following individuals during the preparation of this report: Javier Almazán, Enrique Alcalde, David Burn, Elizabeth Breeze, Enrica Cavedo, Teddy Cosco, Joanne Feeney, Giovanni Frisoni, Nicola Hart. We thank Alzheimer's Society UK for sharing their own portfolio analyses with us, also Brian Dickie from the UK MNDA and Kieran Breen from Parkinson's UK for other European portfolio information.

The report also took into consideration comments from 17 research experts from the wider JPND community during the final drafting stages. The input from these reviewers is gratefully acknowledged.

2. Glossary

Definitions of the terms used in this report relate to those developed for Alzheimer's disease (AD) [3] and are as follows:

i) **Preclinical:** Refers to the long asymptomatic stage between the earliest pathogenic events/brain lesions and the first appearance of specific cognitive or other changes. Two preclinical states can be demonstrated:

- **Asymptomatic at-risk state** – where there is, for example evidence of amyloidosis in the brain or CSF. In the absence of knowledge about the value of these biological changes to predict the further development of clinically manifest syndromes during an individual's lifespan, the asymptomatic phases should still be referred to as an 'at-risk' state.
- **Presymptomatic at-risk state** – applies to individuals who will develop the disease. Only ascertainable in families carrying rare autosomal dominant monogenic mutations.

[3] *Dubois et al. Lancet Neurology online publication Oct 11, 2010 www.thelancet.com/neurology*

ii) **Prodromal** or "predementia" stage: This term refers to the early symptomatic phase of disease.

iii) **Mild cognitive impairment (MCI)**: This term is usually applied to individuals who have an AD phenotype with measureable MCI in the absence of a significant effect on activities of daily living. The diagnostic label is applied if there is no disease to which MCI can be attributed.

iv) **Longitudinal cohort studies (LCS).** A broad definition of LCS was adopted, representing studies based on groups of people which include those that are truly population based (with or without institutional representation), volunteer studies, or those selected on the basis of some other characteristic such as a risk measure or occupation. Selection can also be on the basis of a specific disease or prodromal signs or risk factors for a disease. These people are then followed for a period of time (the study period) so that the sequence of exposure and outcome can be prospectively or retrospectively tracked, as well as trajectories of risk and evolution of endophenotypes with emergence of clinical syndromes over time.

3. Purpose

The purpose of this report is to recommend options for JPND action in the area of longitudinal cohort studies, spanning general population-based, targeted (preclinical) and disease-focused cohorts, whereby current member-led or EC-supported activities can be expanded or better exploited, or new activities identified, to progress European research on neurodegeneration. The options for JPND are based on an analysis of opportunities presented by current European longitudinal cohort capability by the Action Group and co-opted members, as well as comparison with selected international studies. They outline potential and realisable actions that span coordination, funding and policy areas, in line with the Terms of Reference below.

4. Remit and Terms of Reference

The main focus of the report is on longitudinal cohorts. We define longitudinal cohorts as large, long-term prospective studies that collect and follow up data from a population. Included are true population studies that attempt to reflect or represent whole populations. We also refer to examples of cohorts that are formed from specific groups of patients or individuals at-risk of developing neurodegenerative disorders.

The Terms of Reference for this exercise were as follows:

1. To take stock of current longitudinal cohorts, both population-based and disease-based, which are, or might be, placed to contribute to the study of age-related neurodegenerative disease (ND), at-risk groups and related early-onset examples, focusing on the JPND member countries but also taking account of large-scale international efforts. This encompasses both ND-based and general population studies of relevance.

2. To determine how we best add value to existing cohort investments, for example through:
    - increasing the accessibility / sharing of data.
    - increasing access and utility of cohort-associated biobanks.
    - generating detailed subphenotyping of existing cohorts which, if coordinated, can be cross linked to other cohorts (see below).

3. To identify opportunities for cross-cohort linkage, for example through methodological innovation and common analysis of measures (harmonization where possible, but other methods where not).

4. To identify gaps in the JPND portfolio of population studies and scope the requirements for further cohorts that might be considered in areas of unmet need (eg. basic epidemiological studies in countries with widely varying risk profiles such as vascular risk and alcohol exposures, rare/orphan NDs).
    - to scope the emerging scientific opportunities.
    - to investigate the interplay of biological determinants with environmental, social, economic and other factors in the determination of cognitive decline and behavioural and psychological symptoms.
    - to investigate the life-course risk profiles, asymptomatic specific disorders and early prodromal stages of ND.
    - the potential to nest future intervention studies within cohorts.
5. To provide a report and list of recommendations for action to JPND Management Board.

5. Current research landscape

5.1 Introduction

The major emphasis of the Action Group's assessment was on current research in Europe which is longitudinal, which either already focuses on neurodegenerative disorders or could be brought to bear on these disorders. For greater breadth, some disease based cohorts were included and some reference is also made to major non-European cohort studies. None of these analyses should be seen as comprehensive as this was not feasible with resources available. The Action Group recognizes that while broad coverage was achieved, it is inevitable that some studies will have been missed and thus escaped the Group's analysis.

Annex D provides a full list with web references, where available, of the 171 studies examined in the preparation of this report.

In undertaking this exercise the Action Group considered two broad categories of cohort:

- General population-based cohorts of people not selected on the basis of a ND diagnosis (spanning the life-course);
- Targeted & disease-focused cohorts: (spanning at-risk; presymptomatic, and manifest disorders);

and sought to:

i) establish the level of opportunity to promote research across these cohorts in order to strengthen their potential to answer questions relevant to neurodegenerative disorders;

ii) identify significant gaps that might require the instigation of completely new research;

iii) establish the potential to maximize the value of existing cohorts to carry out new research on existing data and bioresources, and through further follow up, using a variety of research methodologies, for example by
    - re-contacting participants;
    - combining data from different cohorts;
    - creating new bioresources; and
    - tracking health and social care records.

5.2 Background to the analyses

The Action Group drew extensively on two exercises to 'map' the existing profile of longitudinal cohorts of value to ND research:

- the published JPND portfolio, captured through a mapping exercise of studies funded through JPND members and accessible through a searchable database[4] ;
- a scoping exercise undertaken by the UK Alzheimer's Society, completed in Jan 2013, which focused on cohorts relevant to dementia with narrative capture of their designs and methodologies.

The JPND mapping exercise aimed to capture details of European research funding relevant to ND that was active on 1st January 2011. Only population cohorts of greater than 1000 participants were included, which will have excluded many of the smaller genetic or disease-based cohorts. 81 cohorts were identified through this exercise, with some relevant to more than one ND disorder. Around 60% of cohorts have 1,000–5,000 participants enrolled and over 25% have more than 15,000 participants. Most studies (51) were found to be prospective.

For the Alzheimer's Society mapping exercise a synthesis of 112 observational cohort studies in Europe was undertaken drawing on existing databases of ageing and AD cohorts, data from the JPND mapping exercise and further detailed searching. This exercise should not be seen as completely comprehensive.

To complete the picture, information on newer longitudinal cohorts or major disease-focused studies, some of which are being set up and others ongoing, within and outside Europe, was supplied by members of the Action Group from personal knowledge or contacts and through the suggestions of the reviewers. Here, key representative cohorts are identified, rather than a fully inclusive list.

5.3 General population cohorts

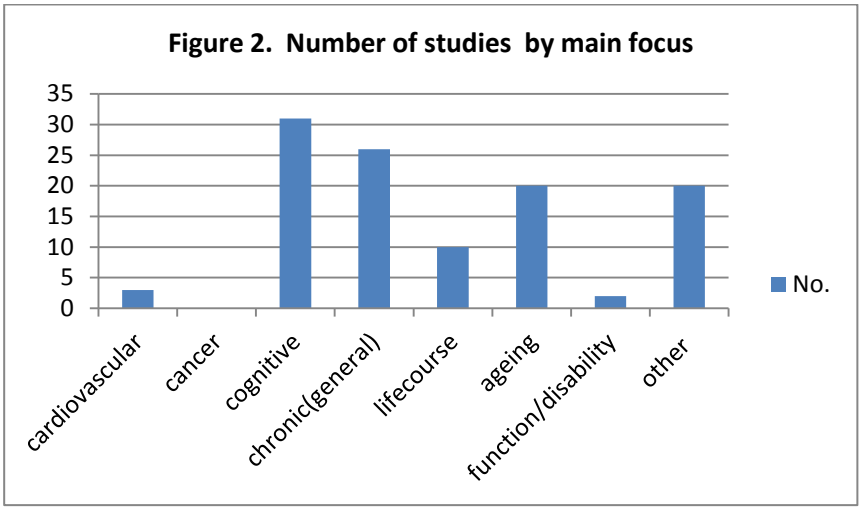
This section provides an overview of general population cohorts, more detail is contained in Annex A.

5.3.1 Longitudinal cohort studies

In Figure 2 below we provide an analysis of 112 European longitudinal cohorts on which information was compiled through the Alzheimer's Society mapping exercise, of which 31 were dementia focused and a further 20 were focused on ageing. These studies cover all age groups and a wide variety of risk factors including those at societal level, modifiable lifestyle behaviours and biological pathways. Around a half of these studies have DNA and many include cognitive function measures for those over age 50 even when not focused on dementia. Few examine the impact of health care or treatments or quality of life and there is very little investigation of urban, rural or environmental influences, ethnic factors and migration. Those in residential care are often excluded.

The generalizability of the cohorts varies according to the sampling methods, the intensity of investigation and consequent response rates (which range from 5% to 90%). This is crucial in assessment of the value of cohorts to policy makers and the translation of findings for public health, but may not be so important for questions on specific hypotheses at an earlier stage of translation.

[4] www.neurodegenerationresearch.eu/search-our-database/



General population-based cohorts are available to cover the entire life-span, each with different attributes (see Annex A). There are also examples of other types of cohort collaboration that have been able to conduct analyses which bring data from longitudinal studies conducted at different lifestages together for specific study such as risk (eg. Falcon and HALcYON collaborations). Other examples include disease-specific areas, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) or at-risk studies, such as the Genetic Frontotemporal dementia Initiative (GENFI) which have no denominator population but are, rather, collections of recruited individuals from clinical settings and who are willing to take part in detailed studies.

5.3.2 Ageing studies – general comment

Studies on ageing also offer an opportunity to study ND and especially the early disease stages. With increasing attention to early life trajectories in cognition, biomarkers and endophenotypes it was considered valuable to look across the whole lifespan, particularly from adulthood. The Action Group identified 26 ageing studies over ages from 18 upwards that already do or could measure cognitive decline and other symptoms such as changes in motor function that are symptomatic of neurodegenerative conditions, offering an opportunity for JPND. However there has been varying investment in terms of biological measures. Careful attention to the sampling frames, tracking of attrition and measured variables, length of follow up and repeat measures could identify those studies with existing data which lend themselves to combined analysis (and in some cases possible harmonisation) in order to create lifecourse trajectories (as for example has recently been done in the area of blood pressure)[5]. Mid life cohorts may benefit from new and deeper phenotyping for stratification of risk and disease trajectories and more extensive follow up. Such work must include sufficient repeat measures over time to provide value for trajectory work. It should be considered whether new and baseline descriptive investment, followed by repeat measurement should include relatively neglected areas such as rural and ethnic populations, targeting different age groups. At least some attention should be paid to how studies' findings relate to general populations now and in the future, taking into account cohort and secular trends.

Outside Europe there are further major studies that offer an excellent opportunity for ND study, each with distinctive features, for example the Canadian Longitudinal Ageing Study which is recruiting individuals in mid life from the population for long term follow up, with baseline detailed questionnaires and biobanking, the Honolulu Asia Aging Study (participants selected from an earlier whole population cohort study focused

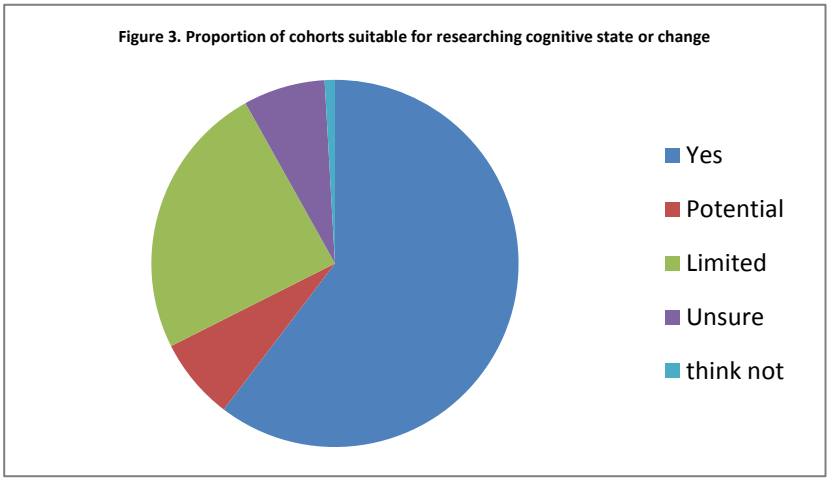
[5] Wu Y-T, Lee H-y, Norton S, Chen C, Chen H, et al. (2013) Prevalence Studies of Dementia in Mainland China, Hong Kong and Taiwan: A Systematic Review and Meta-Analysis. PLoS ONE 8(6): e66252. doi:10.1371/journal.pone.0066252

on cardiovascular disease with follow up and post-mortem examination), the US-based Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study (prediction of cognitive impairment from mid-life vascular risk factors in an mixed ethnic group with a range of measures) and the Health Aging and Body Composition study (Health ABC, USA) which is one of the relatively few studies with ethnic diversity and includes detailed phenotyping, biobanking and longer term follow up. Investment in dementia studies in China is increasing with at least one multicentre population based study ongoing (China Cognition and Aging Study, COAST). Any investment in Europe should take these global strengths into account, with linkage where valuable for the science.

5.3.3 Existing studies assessing evolution of neurodegenerative disorders including cognitive change

Thirty one of the European longitudinal studies were set up to look at cognitive change in healthy people, of which about two thirds were primarily concerned with risk factors while one third, while still based (sometimes loosely) on general populations , looked at the way in which neurodegeneration progresses (with some overlap of studies). Approximately 15% were particularly interested in how to measure cognition. No study was set up specifically to examine incidence of other neurodegenerative disorders, largely because such disorders are relatively infrequent. However, some studies have included neurodegenerative outcomes in their outputs as the measures need to include other disorders or because they do have considerable power, which demonstrates that this is feasible. The most obvious example in this is EPIC, which has examined motor neurone disease (MND/ALS) and PD.

Figure 3 shows an assessment of the distribution of the 112 studies that were analysed by their potential for researching cognitive change. This suggests that these cohorts might also lend themselves to the study of a wider range of neurodegenerative disorders – a decision would need to be determined by sample size, risk profiles and questions to be addressed as well as potential for common analysis with other cohorts with similar potential.



5.4 Targeted and Disease-based cohorts

The JPND research strategy notes that cohorts of particular patient groups with both rare (e.g. SCA, HD, Mendelian forms of common diseases) and more common ND are required. The Action Group found several prospective and large AD and PD studies. In Annex B examples of each type are listed. There are also several large studies of rare diseases such as MND and Creutzfeldt–Jakob disease (CJD), and some including Huntington's disease (HD). A few, new Frontotemporal lobar degeneration (FTLD) cohorts have also recently been established. Given recent attention to the role of Lewy Bodies as a contributor to dementia it is striking that there are no specific cohorts focused on this, although there are many focused on the emergence of Parkinson's disease and associated cognitive changes which go some way to addressing this gap.

To determine which cohorts would be suitable for targeting to look at-risk factors such as environment or social factors a careful analysis would be needed of the degree to which studies are engaged in relevant follow up, including follow up of memory clinic cohorts despite their lack of population generalizability.

5.4.1 Presymptomatic at-risk cohorts

Studies including people with a genetic risk for ND, for example family studies, are particularly useful for genetic studies. Population based and at-risk cohorts need to be differentiated. Across Europe there are eight clearly enabled multi-generational studies and six more with the potential to do so with scope for some limited links across generations in seven more studies. For example in Iceland, half the population has joined a genetic study (deCODE and Ages Reykjavik), based on combining the unique genetic database of 140 000 people with a dementia registry study, thus providing a unique background for searching for new genetic risk and also protective factors. Included in the study are the whole genome sequences of 2,500 people. A study diagnosing patients with dementia and assessing cognition in elderly people is being added to this project, providing a potential for genetic analyses. This is an interesting example of how projects can be combined to provide new results. Another interesting example of an at-risk cohort is the TREND study in Tübingen/Germany, which follows 1200 individuals aged above 50 years with prodromal clinical or genetic markers of neurodegenerative disorders like AD and PD.

Internationally perhaps the most well known risk factor study for non-communicable disorders is the US Framingham series. The prospective Dominantly Inherited Alzheimer Network (DIAN) is an international research partnership to study a rare dominantly inherited genetic form of AD and is enrolling the biological adult children of a parent with the mutated gene. Such individuals – who are clinically examined and have imaging and biomarker measurements taken - may or may not carry the gene themselves and may not have disease symptoms. The Michael J Fox Foundation- sponsored LRRK2-cohort study follows a similar strategy as DIAN, and contains US but also European groups. Overall this study encompasses more than 20 sites within North America, Europe, Middle East, and China, and examines participants prospectively with regard to clinical signs, biomarkers and neuroimaging.

5.4.2 Disease cohorts

Disease-focused cohorts are mostly patient-based. A few are population-based, i.e. either incidence- or prevalence cohorts followed longitudinally, but the majority are clinic-based. Across Europe, there are disease-based cohorts for all of the main ND disorders (see Annexes B and D). There are few major single centre disease studies. Generally such studies are multi-centred and this applies particularly to less common conditions where networking and coordination become essential to gather sufficient cases for study.

For the relatively common conditions of AD and PD some major international projects have been established. The successful and intensively phenotyped, biomarker-focused Alzheimer's Disease Neuroimaging Initiative (ADNI) study in the USA has led subsequently to ADNI-GO and ADNI II and there are international sister studies such as ADNI Japan and the Australian AIBL. There are also European ADNI-type initiatives including AddNeuroMed and NeuroGrid. Of particular interest is AIBL, which in addition to the biomarker search in common with these related studies, also aims to develop hypotheses about diet and lifestyle factors that might delay the onset of the disease.

An important development for AD is the International AD Research Portfolio (IADRP) supported by the US National Institute of Aging (NIA) in collaboration with the US Alzheimer's Association. IADRP makes publicly and internationally available a database that aims to capture the full spectrum of current AD research investments and resources. Launched in 2012, the database will enable research analyses and help avoid unnecessary duplication. Of relevance to JPND is that discussions are ongoing about whether IADRP capabilities should be extended to other ND.

Another important development for AD is the Innovative Medicines Initiative European Medical Informatics Framework (IMI EMIF) project, which includes plans to characterise AD cohorts, develop a conceptual framework for data pooling, an ICT platform and provide access to automated MRI analyses.

PD is fairly well represented in terms of cohort availability with more than 10 studies with more than 100 participants available across Europe. Several large national network projects have recently been set up, for example in Germany and in the UK. A recent development is the ambitious Parkinson's Progression Markers Initiative (PPMI) study. This international multi-centre study funded by the US Michael J Fox Foundation carries out biomarker assays of blood and CSF and detailed cognitive assessment as well as neuroimaging. This project involves several European centres.

In the case of Huntington's disease (HD), two major cohorts exist: Track HD and the European HD registry, while in SCA prospective studies such as RISCA and Euro-SCA are available. Two multi-site cohorts, in the UK (UCL) and Germany (Ulm) have also recently established on FTD. We were unable to identify larger, longitudinal studies focusing on DLB, although some of the larger dementia cohorts have included such patients (for example the VUMC Amsterdam Dementia Cohort includes 200 DLB patients).

There are a number of well-established population based longitudinal studies of ALS/MND through a network of European Registers including Ireland (data on over 1800 patients over 20 years), Holland (1600 patients over 5 years) and Italy (>2000 patients over 10 years) [EURALS[6] and ENCALS [7]]. For CJD/ prion disease, as a result of CJD surveillance, large national cohorts are available in Europe, Japan, Australia, Canada and the US, and this provides an example of where studies have progressed in a timely way because data have been shared. At present there is no reliable means to detect those people who are at-risk of acquired or sporadic forms, though blood tests are under development.

5.5 Conclusions on current activity

- A strength of longitudinal approaches is their adaptability for different purposes, as outlined below.
    - There is clear scope for longitudinal studies set up for other purposes to be deployed for ND research through the addition of cognitive, genetic or other measures. An example is studies that have already been set up to study cognitive change. Other examples would be cohorts set up to examine risk within specific disorders (outside the scope of the review here) such as type 2 diabetes, across Europe.
    - Many population-based studies have collected blood and/or MRI markers at varying ages – this has been determined more by funding potential than by strategic approaches to discovery. The measures therefore are not necessarily specific for the underlying pathology or include measures which only become abnormal at later disease stages. To better understand the pathophysiology of disease, regular deep phenotyping of participants designed to track the earliest stages of potential change of specific biomarkers with long term tracking will be required.
    - Studies could be linked to advanced European health and social care systems to provide valuable insights into who seeks care, when and why, how individuals from different settings track through systems and factors such as institutionalization and mortality.
    - Linking to health and social care systems would also allow dedicated studies of the perspective of relatives and carers in relation to service support.

[6] www.orpha.net/consor/cgi-bin/ResearchTrials_Networks.php?lng=EN&data_id=81536&title=EURALS--consortium-europeen-de-la-sclerose-amyotrophique-laterale&search=Disease_Search_Simple

[7] www.encals.eu/center/irish-als-research-group/

- Some existing studies could be converted into intervention trials, provided sufficiently robust measures at the population level are available. Depending on the measures, either pilot or definitive trials could be possible. Trials exist which are either based on earlier cohorts, populations considered to be at-risk, or primary care recruitment. Three such studies are collaborating within the HATICE collaboration with EU funding which aims to test supported internet lifestyle change to reduce dementia risk. No large scale have yet been set up specifically to examine ND prevention, but subgroups from existing longitudinal studies could be designated for this purpose, as has happened for the Columbian PS1 and DIAN studies and is under development for CFAS II. AIBL, which has neuroimaging data available to researchers, has a physical activity prevention arm in groups considered to be at high risk.
- Few cohorts have been set up to look at intergenerational change in the prevalence and incidence of neurodegenerative disorders.

- From our analysis there is a striking gap in terms of a large difference in research intensity in the past two decades between ND which are now known to be scientifically inter-related, examples being MND and FTD; or PD and LBD. There are few studies available to determine incidence or risk factors for FTD and LBD. This may in part be due to the relatively recent availability of diagnostic criteria for these conditions, a required tool for disease specific surveys. Other reasons will include the low incidence and the competing interests of vascular dementia and AD. Research into prion disorders - which occur much less frequently than FTD or LBD - was stimulated by the requirement for concerted public health action.
- Changing boundaries on prodromal stage, severity and the disorders themselves has been and is likely to continue to be a major issue for any study that requires stability. To address this, some core features and measures within studies might be held steady to permit examination over long periods of time. The quality of cohorts could be increased further by better definition of the specific clinical phenotypes and standardization of core requirements to identify inclusion criteria. It is anticipated that in time, it will become possible to examine the inter-relationship between relatively rare disorders within the very largest cohorts as EPIC Europe, UK Biobank and the Rhineland Project, informed by methodological advances and modelling.
- Towards prevention trials, an enabling first step will be to identify and align registers of at-risk or genetically enriched cohorts across Europe. This might also provide an opportunity for collaboration with the USA. For disorder or prodromal studies the provenance of samples will be very important to capture, along with the context in which the research recruitment was undertaken (eg. the health service care system) as this will influence the interpretation of any outputs and also the way in which any cohorts can be used to understand particular disorders in the population. Further work will be required to establish which cohorts would be suitable to look at environmental or social risk factors in terms of risk mitigation or trials of potential compensatory mechanisms.
- Some of the work above, particular identification of at-risk groups and repeated endophenotyping has societal and policy implications. Such work needs to be underpinned by a parallel investment in ethical, social and legal implications and an ongoing dialogue with the public about the work and its implications.

6 Analysis of key opportunities/challenges/gaps

6.1 Genetics/ clinical/environmental risk factors

The major scientific challenges

- In order to understand the triggers for disease and the risk factors at different stages it is necessary to re-focus attention from end-stage disease and follow up cohorts of people who have yet to develop clinical symptoms
- The biochemical outcomes of neurodegeneration have not been sufficiently defined for each affected tissue (CNS, vasculature, endocrine or other). In-depth phenotyping (eg. protein expression, proteomic analyses in cerebrospinal fluid (CSF) and plasma will be required for both discovery science and clinical research.
- There is a particular need for CSF and plasma biomarker studies on CSF in cohorts where participants have preclinical stages of disease. There are no adequate biomarkers yet for types of dementia other than AD. In addition, there is a need to research potential, and value of, diagnostic biomarkers and biomarkers suitable to monitor disease progression.
- A fundamental challenge is the need to formulate possible causal processes from the broad base of current laboratory-based, observational clinical or population research knowledge. In the aetiological field, “initiators” versus “promoters” and their temporal correlates have not yet been differentiated, whereas this has been done for example in the field of cancer research. In doing so, attention must be given to the age profile of those with the disorder and likely relationship with age of the disorder itself. There is scope for the consensual development of statistical methods to analyse multiple end point, cause and consequence during the follow up of cohorts, as is happening with MELODEM, an international initiative co-ordinated in France to harmonize analytic approaches in longitudinal dementia research.
- Empirically based (non-speculative), biologically plausible and operationally testable causal hypotheses have to be identified for single ND entities or for specific groups of disorders, the likely age at which such causes operate and their potential for modification. These hypotheses should be tested on available data. There is a need to identify, worldwide, existing, statistically powerful data sets that are appropriate for testing gene/clinical/environmental interactions early in the life-course of cohort members. Such work needs to include attention to effect sizes and likely impact over prolonged time periods.
- The ND field has suffered from epidemiological research designs with low or insufficient discriminatory potential or high sensitivity to bias. Better classifications of outcomes/entities and methodological improvements (ie. latency analysis, competing risks control) are required to improve the quality of epidemiological study design. New studies will be more informative if there is detailed endophenotype characterisation of participants along the diagnostic pathway from asymptomatic to clinical outcome, including the oldest old as well as younger age groups.
- A major limitation of disease specific registers is that they rarely relate to a base population which limits their interpretability, although an exception would be registers for ALS/MND. Quality controls can be an issue when a case control comparison is made.
- A serious challenge that has not yet been addressed appropriately would be to make dispersed genetic information available in a linked format, and to develop a structured way to feed in new genetic information. Such a data source would ideally contain GWAS data on large cohorts and more detailed exome or genome sequencing data on smaller, better defined individuals. All ND should be included in order to be able to evaluate the extent to which one gene influences more than one trait.

- The fragmented approach to investment in this area has meant that there has not been a strategic investment in deep phenotyping of valuable cohorts. Rather, a responsive competitive approach has been adopted. Consideration should be made to identification of cohorts for investment with a strategic purpose, where the investment in deeper phenotyping then leads to common resources for analysis using appropriate methodologies.
- Research into ND is often done on atypical younger populations that have limited generalizability whereas policy and public health needs are in general for information about older people. The fact that most usual neurodegenerative disorders occur in the context of ageing is the most important gap here. Similarly, most neurodegenerative disorders occur in the context of other disease.
- For ND conditions, clinical presentation often does not match the underlying pathological diagnosis because of mixed disease. It is important to take this mixed pathology into account, for example the contribution of vascular changes. Younger patients, where a single disease is present, can serve as excellent models to study specific disease processes in isolation.
- A significant but relevant gap is that there are few cohorts of the oldest old. Such cohorts require special design with very frequent follow-up due to the attrition due to mortality, but can address the important and related issue of exceptional longevity.

Key opportunities

This exercise has revealed the major investment in cohorts across Europe. Key opportunities exist to achieve additional scientific impact by linking cohorts with comparable data across clinical measurements, risk factors, biosampling and imaging strands. In general this will require:

- National co-ordination and streamlining of cohort groups to facilitate Europe-wide studies
- Harmonisation of clinical data in existing cohorts, where possible, and integrated analytical approaches where not, to facilitate cross-centre data sharing.
- Standardisation of future in-depth phenotyping across studies, including, but not limited to, clinical phenotyping, the collection and use of biomaterials (CSF, blood, fibroblasts etc), imaging and cognitive assessment data, as well as increased availability of post-mortem analyses.
- Bio-banking.

Specific opportunities were defined as follows:

<u>New interpretation of existing data</u>

- Scope exists for new interpretation of well-established associations, for instance with specific vascular risk factors, e.g. hypotension, hypertension, type 2 diabetes, and with depression. Intervention studies in these areas could be examined for their potential for prevention of ND.
- There is also scope to explore potential overlaps between traditionally diagnosed disease groups Cohorts starting in midlife will provide an opportunity for identifying preclinical risk factors, or biomarkers.
- Across Europe there may be opportunities to study specific populations including the aggregation of family data where unique genetic predispositions or novel environmental exposures may contribute to risk or resilience in ND. Where the nature, quality, and access to data for cohort members exists countrywide, ie., from national health services, this may enhance the cohort value.
- Given the long incubation/latency periods, understanding the onset and progression of late-life

ND may benefit from the analysis of data prospectively collected at young age.

Enhancement of existing resources

- Cohorts gathered from memory clinics could be expanded with structured follow up, particularly if these are based within a health service context that allows generalizability to the source populations.
- Identification of disease registries and longitudinal cohorts sharing a proportion of their population bases is essential for aetiologic studies provided data on exposures can be obtained symmetrically for cases and controls from a third data source.
- Approaches to maximize value of existing data (eg. clinical information and biological variables such as genetics, biomarkers, imaging) should be explored. This could assess the relative merits of developing better methodology to meta-analyse such complicated datasets, or an approach of the 'data warehouse' type to provide a secure and structured source of all related information.

Areas for action

- Certain hypotheses can be pursued with single cohorts but integration of datasets across cohorts would add value through enabling identification of risks that arise for example from the interaction of genetic, clinical and environmental factors. There are too few models of such integration for ND within Europe at present. For successful integration of data from new fieldwork, prior agreement on standardization and harmonization across new measurement in existing cohorts and any new cohorts will be necessary.
- There will be opportunities:
  - to study specific populations where unique genetic predispositions or novel environmental exposures are identified within existent cohorts in order to examine interaction or interplay between risk factors.
  - to explore opportunities for collaboration with disease specific cohorts that are now known to be ND-relevant e.g. cardiovascular disease, type 2 diabetes, obesity/metabolic syndrome, depression from a risk factor and prevention point of view. A family aggregation approach could complement this work.
- Consent for brain donation (and brain banking) should be promoted in well characterized cohorts with linked clinical histories to enable rigorous phenotypic standardization.

6.2 Cognition, behaviour and function

The major scientific challenges

The key questions outlined below for the area of cognition, behaviour and function cannot be fully separated from the work on risk factors, in part because risk factors are shared between subclinical and clinical disease progression. For instance, while not systematically confirmed, the APoE4 allele has been reported as a risk factor for MCI, for AD, for LBD, for dementia in PD and interacting with PrPN for late-onset sporadic CJD, as well as for conversion from mild clinical impairment to AD. Additionally there is a need for measures of motor function for some cohort work across the range of ND, but in particular for PD and MND.

The key questions that apply to this area are as follows:

- New methodological and conceptual approaches and solutions are needed to address the difficulties of operationalizing cognitive, functional and behavioural endpoints and diagnosis across

studies. Existing methodologies that were mainly developed in other research areas do not readily translate to the area of cognitive function. New and ideally harmonized measures need to be developed to allow sharing of data between cohorts, while common indices that measure change, and address issues of specificity and sensitivity in relation to future outcomes need to be developed for application across cohorts in different care settings.

- Identifying the early markers (cognitive, functional sequences of impairment and behavioural changes) that herald the onset of neurodegeneration, for example by signalling cognitive decline. New tools are needed which exploit the possibility to assess subtle changes, for example processing speed (motor, perceptual, cognitive domain), including the increasing use of computerized assessment which is in need of validation and standardization. Their use should be integrated with use of standard ND biomarkers.
- If it is feasible, cognitive/behavioural markers of diagnosis should be distinguished from those of progression/prognosis.
- Cognitive reserve: there is a need to identify the impact and underlying biological substrate of potentially modifiable risk and protective factors including psychosocial, environmental, lifestyle [exercise, diet, alcohol, education, depression, loneliness & isolation] factors that might influence onset and progression of the ND process, at all stages of life.
- Identifying the biophysical factors (eg. frailty, hypertension, cholesterol, vascular risk, type 2 diabetes) that can influence onset and progression of dementia, and the major influencing factors.

Key Opportunities

- To develop common indices, measures and approaches that include cognitive, functional and behavioural assessment that can be applied across cohorts to increase the power and likelihood of being able to answer one of the 'big research questions'. An example would be the development of a frailty index that can be used across cohorts in the testing of the relationship between frailty and the emergence of cognitive decline. Other examples would be a common index for prodromal and dementia stages that could be validated and applied across cohorts.
- To harmonize the cognitive and behavioural measurement tools/batteries used in the different cohorts in order to permit correlations/comparisons between studies, populations, stages or periods of time across an expanded dataset. Methodological and biostatistical work can help to create integrated analyses of existing datasets where there is cohort heterogeneity.
- Additions can be made to studies lacking particular measures in order to be able to compare performance within and between populations.
- The relationship between type 2 diabetes and cognitive decline might be examined through adding an ND element to the assessment of outcomes in diabetes or cardiovascular risk cohorts that are not currently 'ND focused'.

Areas for action

The advantage of longitudinal cohorts that extend across the life span or from mid-life is that they provide the unique potential to uncover very early markers of disease onset. If data can be shared, it will open the door for very early population-based interventions that could prevent the onset of dementia or delay its clinical expression. Immediate priorities are:

- To address methodological barriers to the sharing of behavioural and cognitive data and endpoints. This will allow data-sets to be linked and expand ND research opportunities.
- To develop a consensus on methodologies to define cognitive, behavioural and functional change/decline/case/outcomes relevant to ND for population-based cohort studies.

6.3 Imaging

Annex C provides an overview of the imaging data available from existing longitudinal and other cohort studies that are relevant for ND research. The NISALS network[8] is an example of an existing ND-specific initiative where research centres collaborate with a focus on neuroimaging in ALS and MND.

The major scientific challenges

- In the 20th century the collection of imaging data in cohort studies has been somewhat limited for obvious reasons (cost, availability of large scale imaging facilities, radiation in the pre-MRI era). The situation is rapidly changing. In clinical longitudinal studies in at-risk or early stage ND disorders imaging is now invariably included with the aim to improve early and preclinical diagnosis and to assess the contribution of additional factors (i.e. brain reserve, vascular damage) to ND. The challenge of scanning large cohorts of the population (population imaging) has been already taken by a few studies (Rotterdam Study, Three Cities, Ages-Reykjavík Study, SHIP study), and is part of several newly initiated large scale projects (UK Biobank, German National Cohort, Rhineland Study, Maastricht Study, CamCAN).
- The fast technological advances in this area have led to comprehensive multimodal MRI imaging packages allowing the in vivo study of structural and functional brain status. These approaches are based on quantitative analysis of imaging data, which are intensive in terms of acquisition and data analysis. This is now the standard for any imaging study.
- Quantitative data analysis requires the availability of large dataset from well-phenotyped populations. A major challenge in terms of data linkage is the development of technological tools allowing acquisition independent data pooling. The limits of these developments are related to issues of data acquisition harmonization.
- Molecular imaging with positron emitting tracers (PET) is starting to play an important role in ND, in particular for AD. While cost and radiation issues may limit the application in population studies, longitudinal investigations of early and presymptomatic/at-risk groups are becoming one of the major scientific challenges in this area. Other imaging technologies such as MEG and spectral EEG have the potential for increased use in cohort studies.
- Development of computer aided diagnostics requires large scale population based reference data, rather than databases of “normal people”. These should cover state of the art multimodal imaging protocols. The acquisition of large scale innovative imaging data may conflict with the requirements of prospective cohort studies (identical protocols over time).
- While harmonization and standardization of imaging protocols across studies may enhance pooling and comparability between and across studies, the fast developments in imaging technology and image acquisition limit the desirability of “freezing” protocols, although some form of common core for comparison across time is necessary.
- A further challenge in these extensive phenotyping studies is the uptake and response, as the intensity leads to increasingly biased population uptake, favouring the younger, less complicated and more socially advantaged respondents. Research outputs will be enhanced if such factors can be addressed through examination of respondent profiles against population based studies on similar populations (integration of approaches).

[8] http://nedigs05.nedig.uni-jena.de/nisals/index.php?page=nisals

Key opportunities

- Harmonization of acquisition procedures allowing data pooling from clinical scanning studies.
- Definition of minimum imaging protocol standards for population imaging studies to enhance the possibility of data pooling and sharing across population studies without restricting development.
- Development of ICT platforms for data sharing and intensive data analysis and technologies for sharing across different scanning software programmes.
- Development of high through put generic data analytic tools and pipelines for image data analysis that are robust across different imaging acquisition protocols, data formats etc.
- Development of incentive schemes to encourage actual data sharing.
- Development of harmonized imaging protocols for additional ND diseases in the early, at-risk and presymptomatic stages within ongoing longitudinal studies (PD, MND).
- Development of molecular imaging protocols within ongoing studies in the early, at-risk and presymptomatic stages of ND disorders.
- Validation studies of imaging markers as outcome measures for intervention studies, both pharmacological and non pharmacological.

Areas for action

For imaging, further action is needed to:

- Harmonize acquisition procedures to allow data pooling from clinical scanning studies, and where not possible approaches to combined analysis which do not require full harmonization.
- Define the minimum imaging protocol standards for population imaging studies to enhance the possibility of data pooling and sharing across population studies without restricting development
- Develop ICT platforms for data sharing and intensive data analysis.

6.4 Biobank/tissue resources

The Major Scientific Challenges

- Samples are of limited use unless they are linked to the clinical history of the donors, and ideally are also linked to other markers including imaging, neuropsychology, and markers of clinical follow up.
- The level of access to sample collections by external groups remains variable.
- Further standardization of protocols is needed to allow for robust analysis and comparison of biosamples across sites/studies - for example variability in CSF sampling and the collection of brain material needs to be minimized, while protocols need to support the possibility of analysis through emerging molecular technologies (for example the analysis of transcriptomes, exosomes, proteomes etc).
- It will be necessary to develop and implement new software and technologies to improve the capture and sharing of bioresource information. This will be highly important for the success of future work.
- For translation to large studies it is important to avoid premature translation so full and rigorous interrogation of novel measures could be worked up in first pilots before being rolled out to large numbers of ‘bandwagon’ studies. This might enhance the value of investment in new biomarkers and save valuable research capacity.

Key Opportunities

There is scope to provide information for existing cohorts relevant to ND in a central and freely accessible place on:

- the nature of biosamples available - DNA, blood, CSF, brain, cell lines.
- the quality of the resources (technologies, storage, data linkage).
- the accessibility of such collections
- the number and type of patients included.

Other possibilities that could add significant value to existing cohorts include:

- Creating a 'biobank' (DNA, plasma, CSF, imaging data) based on key population cohorts , such as 'European ADNI', AdNeuroMed etc, for example, as is planned for the JPND BIOMARK APD/EMIF-AD projects for AD and PD research.
- Establish a multicentre brain banking platform for ND, based on the examples of the UK Brain Bank Network and BrainNet Europe consortium.
- The incorporation of next generation technologies, for example genotyping, epigenetic analysis, iPSC-resources etc.

Areas for action

- To function effectively, bioresource collections require sustainable, core support at the European or national level.
- Access for external groups to samples and data from existing collections needs to be encouraged, as this will facilitate secondary analyses.
- EU-wide networking resources such as the BBMRI should be encouraged to create a catalogue of European Biobanks for ND research.
- Harmonization/ standardization of technologies, annotation and storage is needed to enable sharing of bio-resources - for example through comparing/optimising techniques for imaging and biofluid markers from sampling to analysis.
- Take account of the JPND-funded BIOMARKAPD study in which SOPs are being created for pre-and post-analytical handling of biomarkers in AD and PD and standardization issues are being addressed.

6.5 Access to health and social care records/data

Health care and social services are paramount for people who live with ND, with the main users of these services being the elderly. In Europe, the development of health services largely preceded that of social services, with the social services generating the main expenditure due to ND. Recent trends in social service development for the elderly in pioneering EU countries include the systematic design of IT-framed, administratively- and professionally-rooted processes (codes, terms, classifications) aimed at definition of national models. ND patient cohorts may constitute an invaluable resource for comparative scientific research that takes into account disability, local needs and social features. Data can be tailored to immediate development goals because ND are the primary cause of severe disability among the elderly. For these types of study the availability of service data and data linkage is essential.

The advantage of data linkage is that information can be retrieved directly and does not rely on re-contacting individuals or the necessity for interview; however not all routine records are well maintained which means that this will need to be checked for any cohort study. The most common linkage is to death records but other health-related linkages contain information on hospitalisations, prescriptions, family doctor records, and national insurance claims. Some also use national registers for income, records, school

attainment, migration, and military conscription. Only 14 cohorts in our survey clearly mention use of social services, including long-term care.

The trend towards increased access to shared data that originated with genomics and proteomics is progressively expanding within the EU to include clinical, health and social services data. The IMI EMIF project will, for AD, be a flagship activity that will pool existing data based on a robust informatics framework. Access to electronic clinical records, which are available nationwide in some European countries for some ND, will enable verification that diagnostic criteria are fulfilled and opens up multiple research possibilities. Another EMIF project, EMIF-AD, will enable linkage between research cohorts and electronic health registries.

While the organization of healthcare in Europe allows for the linkage of research subjects to medical and social service records that should facilitate a longitudinal approach and the provision of rich datasets, problems relating to resource quality and access may limit what can be achieved. In addition, a number of practical, policy, governance and ethics issues need to be addressed before cohort data can routinely and effectively be combined across Europe.

Major scientific challenges

- Personal, cultural, institutional, and administrative issues: There may be differing attitudes of legal data owners or differences in willingness to share incomplete or unconsolidated data.
- Linkages for data completion or new data acquisition, for instance for use of services by persons alive, may require individual consent and this can be problematic particularly for ND where cognition can be affected. Regulations may restrict access to the full data set.
- Barriers to interoperability: these barriers may arise from differences in computing systems and the use of different storage formats. For example, problems can arise when new databases result from the linkage of databases and personal identification numbers are substituted by serial individual numbers, which need resolution on a case-by-case basis.
- Identification: The ability to identify a respondent is an issue at the heart of data protection and ethics, particularly if the data is of a sensitive nature. However, using multiple data streams with different respondents in each as would be the case with combining cohort data is an advantage in terms of minimizing the risk of identification compared to working on a single cohort. Ongoing work in EU collaborative studies is addressing such concerns through the development of robust methods for testing which should be rolled out if promising.
- Once data are stored within the EU, data protection policies for individual countries should carry over to another EU country. The issues around storage (and sharing) of data for studies between EU and non-EU countries will require joint discussions between the different data protection agencies to arrive at a solution.
- In health and social care research, the attribution of service needs to ND among the elderly can be difficult because of combined morbidities in which ND attribution is extremely difficult. Existing research may be based around factors such as multimorbidity and disability rather than specific ND diagnoses.

Key Opportunities

- The integration of emerging molecular and information technologies - there are currently several huge cohorts being initiated in Europe where this integration is being considered/undertaken
- Increasing the focus on preclinical identification, which is currently relatively under-represented in the EU portfolio. This should encompass combined investigation modalities and multiple biomarkers along

with detailed outcome measurement to define populations at varying risk across the life-course. Such approaches are not coordinated in the EU despite much potential. Studies with a short duration to follow up did not appear to have linkage(s) to clinical data. Studies reporting clinical linkages generally recruited young participants, i.e. <40 years, although a few recruited individuals at birth or when very old (>85).

- Working across European countries offers possibilities to study geographical and cultural diversity which provides an additional opportunity for studies of gene-environment interaction, though also highlights the need to consider varied diagnostic approaches. Capacity building would be necessary for cohorts to be set up in countries without existing studies.
- There is considerable expertise on governance issues in relation to clinical records and data that could be called upon to inform ND research, for example, from research using cancer registries and the public health observatories.
- The potential to examine different models of care and support in identified cohorts, at-risk of or with particular disorders, is worth considering.

Areas for action

- Cohort studies capture enormous ranges and amounts of data which makes it crucial to adopt or develop new software and data handling technologies, such as cloud computing and also to put measures in place to mitigate concerns over data security. The ND field needs to integrate experts with these skills.
- Linkage of research participants to clinical and post-mortem records should be encouraged as a powerful approach to enrich datasets, coupled to the resource to make such data available to the research community.
- Nomenclature should be harmonized and standardized in order to create data platforms, which will also require agreement on research governance and ethics issues. Where this is inefficient given the scale of the task, integrated and combined analytical approaches can be considered.
- Emerging technologies should be integrated across cohorts where possible, as is being done for newer studies.
- The value of existing work and outputs is poorly integrated into population 'meaning' and attention to modelling, simulation and potential impact could add considerable value and be developed for the whole lifecourse.
- Expertise on governance and ethics issues is available from population research into non-ND conditions and scope exists for adaptation as appropriate for ND research.

7. Conclusions

Research using health and social care records can been seen as contributing in a variety of ways to societies tackling the challenges of neurodegenerative disorders. There is a need to understand the nature of the disorders themselves and their evolution over the life-course using the new measures. This could be seen as descriptive epidemiology, including molecular and multi-modal deep phenotyping. It is clear that revisions of diagnostic criteria, the meaning of particular new markers, their repeatability and whether they are important to clinical expression all need to be tested in robust and unbiased cohorts to understand their value in different contexts. Then there is the work on relationship of risk and early tracking to evolution and expression of the disorders, with the potential to adapt such studies for testing interventions (basic prevention and screening). Finally conducting the natural history studies in the cohorts of established patients provides the base for work on prognostication, the value of biomarkers in this process

and their interrelation with any intervention – such work is always bounded by the use of diagnostic criteria in the selection of the cases so there is an inherent limitation vis a vis unselected cohorts.

Our assessment of the existing state in Europe is thus that current population and disease-focused cohorts offer significant opportunity for advancing our understanding of the risks of developing neurodegenerative conditions and the influences on disease progression. They also offer the prospect of providing platforms for prevention and intervention studies in the longer term. Surprisingly little information is available on the natural biomedical history of ND despite a wealth of cohort activity across Europe. Much of the disease-specific work is not population based and this has resulted, geographically and for many ethnic groups, in major knowledge gaps in terms of prevalence, incidence, and natural history. It appears to be timely to take steps to improve and co-ordinate existing capability, given the opportunities offered by the new scientific realization of convergence amongst risk factors and underlying pathologies across ND.

Scientific progress could be best enabled by enhancing the capabilities of existing studies, or through linking related studies to address key questions through a synergistic approach. However, the case for establishing entirely new cohorts, aside from one or two well defined areas, is much harder to make.

To deliver the required impact, a number of opportunities and challenges can be defined where action would be merited:

- There is an opportunity to bring together cohorts to achieve added value, primarily through large increases in sample size and hence the statistical power to look at interactions. One such example would be through the alignment of genetically enriched cohorts across Europe. However, the heterogeneity of studies and measures will require new conceptual and methodological approaches to allow data to be pooled.
- Coordination regarding datasets / bioresources could be promoted through the collection of a detailed inventory of the assessments and protocols used within studies. Minimum parameters should be defined regarding future data collection, use and dissemination, whilst ensuring flexibility is retained to incorporate emerging approaches/technologies. The access to sample collections and data by external groups also needs to be encouraged to promote secondary analyses of population data. Account will need to be taken of other global efforts in this arena such as the PAD2020 project[9].
- Large Europe-wide population-based and longitudinal studies of populations should incorporate integrated and in-depth multi-modal phenotyping that links clinical and lifestyle data including nutrition to biological and behavioural measures. This should encompass the use of emerging technologies - such as 'omics' approaches, iPS cell line generation, molecular imaging etc - once validated. Linkage to wider international activity might also provide opportunities for increasing study power and innovative approaches in selected areas.
- Increasing the focus on preclinical/prodromal identification. Many cohorts starting in midlife provide an obvious opportunity for elucidating the characteristics of the pre-symptomatic/ prodromal stage, although will have limited power for even more common ND unless sample size is very large. Studies should be encouraged that identify the early markers (cognitive, functional and behavioural) that herald the onset and progression of neurodegeneration.
- Linkage of research subjects to medical records is a powerful approach to enrich datasets, and harmonising clinical data in existing cohorts would facilitate cross-centre sharing. However, the problems relating to resource quality, data protection and access need addressing. Methodological rigour also needs to be promoted if linkage across studies is to be successfully achieved. This will be a major undertaking for ND that could usefully benefit from the experience of existing initiatives

[9] See footnote 1

on data harmonization such as the Integrative Analysis of Longitudinal Studies on Aging (IALSA) network in the USA[10] and the UK Healthy Ageing across the Life Course study (HALCyon).[11]

- The development of new ICT platforms is required to promote data capture, sharing and intensive data analysis. This is particularly needed to fully exploit the potential offered through the development of multimodal imaging packages, which also requires the supportive development of harmonized imaging protocols and data acquisition procedures and validation studies of imaging markers as outcome measures for intervention studies.
- Well characterized cohorts offer the prospect for future prevention/intervention trials that in combination will have sufficient power to provide robust scientific data. Potentially very interesting information could be provided by combining intervention studies in other relevant fields, ie. anti-hypertensive, anti-diabetic, antidepressant, and cholesterol-lowering trials.
- The relationship of risk trajectories of the other non-communicable disorders to neurodegenerative outcomes can be explored using existing cohorts. A particular example is type 2 Diabetes which is increasing in prevalence in all age groups but most particularly in older people; it has an accumulating body of evidence that supports a relationship with cognitive impairment, vascular pathology and AD; the mechanism underlying this relationship is crucial to developing treatment/preventive strategies for cognitive impairment in both diabetic and non-diabetic populations and to address a major risk factor for AD.
- The development of a life-course approach would be beneficial. For example, given the long incubation/latency periods, aetiological approaches to late-life ND might particularly benefit from analysis of data prospectively collected at a young age.
- Working across European countries offers possibilities to study cultural diversity which provides an additional opportunity for studies of gene-environment integration study, as well as opportunities to compare and evaluate methods for health service delivery for ND, the cost of care models, different approaches to care pathways and caregiver burden. Currently there is an under-representation of cohorts that support research into the provision and outcomes of health and social care including the costs of care and outcomes that relate to caregivers.
- A translational population modelling and simulation approach to integrate and incorporate new findings is desirable as this would allow faster pull through and assessment of ongoing research to allow more strategic considerations of the value of new findings. This could help avert repetition of large investment in approaches which have little likelihood of major population or patient benefit
- The cohort analysis revealed that there are opportunities to gain further knowledge within existing diagnostic groupings for disorders such as LBD for natural history and prognostication within current clinical definitions.
- Current definitions of neurodegenerative disorders are likely to change with increasing knowledge of overlap, gene and biopathological studies. There is a need to test potential early diagnostic and prognostic markers in unselected populations in order to ascertain value for clinical use. Some existing cohorts provide such potential settings and opportunity for follow up for appropriate outcomes, including some of the rarer disorders.

[10] www.ilifespan.org/?q=IALSA

[11] www.halcyon.ac.uk/?q=cohorts

8. Recommendations for Delivery

It is recommended that JPND considers action in three domains. In all cases implementation should take account of ongoing activity in related European and global initiatives.

i) Coordination and development of best practice

A series of JPND workshops should be established to address the key challenges in the field, through providing a framework for exploiting and harmonizing existing or planned cohort studies, or as a basis for developing new research proposals. In essence these should focus on bringing together key cohorts and opinion leaders to develop solutions to the barriers to progress, and such workshops could be progressed with modest levels of funding provided on a competitive basis. It is suggested that a JPND Steering Group should be appointed to take responsibility for oversight of these activities. The goal would be to provide cohort researchers with a clear way forward, with topics to include:

- **preclinical (asymptomatic and presymptomatic) stages of ND:** defining the key methodological issues, tools and measures. To establish guidelines for dealing with multimodal imaging approaches and perspectives in molecular imaging , including software compatibility and minimum image and metadata for inclusion in image databanks.
- **cognition, behaviour & function:** to develop a consensus on methodologies to define cognitive, behavioural and functional change/decline/case/outcomes relevant to ND for population based cohort studies and disease cohorts.
- **data handling:** the integration of 'omics' technologies within the context of complex longitudinal data of differing types, the interpretation of data protection legislation and the handling and sharing of big data sets.
- **cohort alignment**: bringing cohorts together in selected areas where data pooling can realistically be achieved and is particularly beneficial (eg. rare ND).
- **clinical data linkage:** to convene studies with clear clinical linkage to identify how they might be exploited in prospective studies, areas where harmonisation might be achieved, best practice for data protection and storage, and dissemination issues and solutions.
- **exploiting intervention-studies of potential risk factors** (eg. hypertension, Type 2 diabetes etc): identification of how ongoing large trials can be used to adequately address risk of ND as an outcome.

ii) Calls for proposals

In parallel to the activities described above there should be calls for proposals centred on optimal strategies to take advantage of the current longitudinal studies in a European framework. The calls should seek to establish cross-centre research programmes that:

- bring together well-characterised relevant cohort groups to harmonize, or make accessible, data to promote secondary analysis;
- add new measurements, sample collections or data sweeps that add significant value or provide linkage to other studies;
- establish novel assessment measures, taking advantage of new technologies, extending beyond the cognitive domain (ie. motor and perceptual function) that can be applied to the broad spectrum of ND;
- deliver methodological developments or enhancements to establish cohorts as intervention platforms;
- provide training programs to ensure good operational understanding of cohort study design, data analysis, interoperability and high quality standards of practice. There may be benefit to delaying

initiation of training until greater JPND consensus on these issues is established.

These activities could be enhanced by the establishment of a JPND Neurodegeneration Cohort Cooperative Initiative to strategically exploit cohort studies going forward and link with intervention trials. NDCCI could provide a central administrative function, emphasizing collaborative working, with partnership and data-sharing (where appropriate or other methods where not) and focusing on issues relating to integrated analysis, and opportunities for collaboration and intervention. Such a Cooperative could also be used to assess the need for new work/studies in underserved populations that offer significant new opportunity. It should ideally incorporate a methodological subgroup.

iii) Data access policy:

- A JPND policy should be developed to help ensure that data from JPND funded research is open access. Alongside this, guidance should be developed on the use of both anonymised and sensitive data, which may have to be stored on secure servers with access approved by a data custodian using best safe haven practice. Ideally this framework should be implementable by JPND member organisations regarding their own national programmes, with recognition inbuilt that it may be hard for older established cohorts to be fully compliant.
- A study should be undertaken to scope the potential for establishing a European population data warehouse using ND as the model disease area. This should ideally involve the European Commission to ensure connectivity to existing EU-wide activities in this area, such as the eTRIKS[12] project to create a research informatics and analytics platform for use by IMI. The warehouse would store in a secure manner and make widely accessible data generated through genetic and other 'omics' studies, imaging etc, providing a resource to support nationally-funded studies and enhance cooperative research and impact.

- End –

[12] eTRIKS Delivering European Translational Information & Knowledge Management Services www.imi.europa.eu/content/etriks

Annex A
Analysis of longitudinal cohort studies

Longitudinal Cohort studies are those are based on groups of people which can be truly population based, volunteer, or selected on the basis of some other characteristic such as a risk measure or occupation. Selection can also be on the basis of a specific disease or prodromal signs or risk factors for a disease. These people are then followed for a period of time (the study period) so that the sequence of exposure and outcome can be tracked. Usually they are prospective, i.e. a set of measurements or characteristics made at the start of the time period (baseline measurements) or to then measure evolving exposures and sequelae as time passes. Some use routine data and linkage, others use data collected much earlier and reconstruct a cohort.

A synthesis of observational cohort studies in Europe has been undertaken which drew on existing databases and thorough searching (although not comprehensive due to the timeframe of the exercise). Out of 112 European cohorts, 31 were dementia focused and a further 20 on ageing. These studies cover all age groups and a wide variety of risk factors including those at societal level, modifiable lifestyle behaviours and biological pathways. Of these around a half are recorded as having DNA available. Many studies do include cognitive function measures, even when not focused on dementia. Measurement of cognitive function under 50 years of age is uncommon. Few examine the impact of health care or treatments or quality of life. There is little investigation of urban, rural, or environmental influences. Ethnic minorities and migrants are very underrepresented. Those in residential care are often excluded. The generalizability of the cohorts varies according to the sampling methods, the intensity of investigation and consequent response rates. These range from 5% to 90%. This is crucial in assessment of the value of cohorts to policy makers and the translation of findings for public health, but may not be so important for questions which are about specific hypotheses at an earlier stage of translation.

Longitudinal Cohort studies-key features

The main strength of longitudinal cohort studies is that they allow the investigation of the sequence of events such that it can be seen whether a hypothesised outcome does follow on from the hypothesised risk factor or exposure. Although by no means always possible to establish cause and consequence in longitudinal studies, especially if events and circumstances overlap and recur, it is more likely in cross-sectional studies that one cannot distinguish the direction of effect, e.g. did depression lead to low physical activity or vice versa? Other advantages of the longitudinal studies are that multiple effects of a single exposure can be traced. Rare exposures can be studied if one can identify a sufficiently large group of people with that exposure at the start. Longitudinal studies can also facilitate the pursuit of life course studies, i.e. improving understanding of the way in which events and circumstances accumulating over one's lifetime can explain health outcomes better than exposures at one point of time.
Disadvantages of longitudinal cohorts are:

- their expense – the main components being identification of the sample, setting up the instruments, person time in collecting data repeatedly, keeping track of participants, equipment for collection and analysis of biological or physical measurements, person time in analysis
- attrition – apart from deaths and migration people drop out of the follow-up and in many cohorts this percentage is substantial and biased
- advances in causative theory which may require knowledge of an exposure or intermediary variable that was not measured in a historic cohort

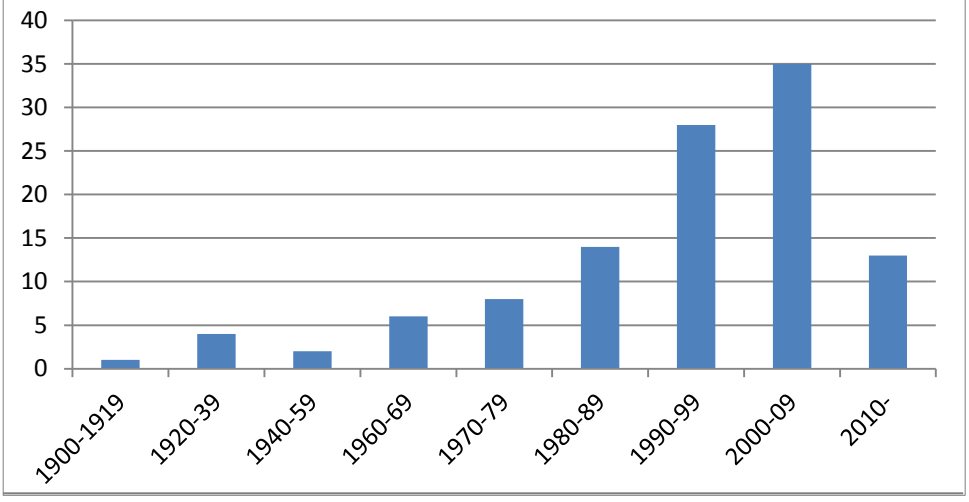
Aim of the scoping

To research into existing European longitudinal observational cohort studies to investigate their focus, with the potential for relevance to neurodegeneration in the future and any major gaps. This report outlines the key characteristics of European longitudinal cohorts discovered to date and identifies, where possible, gaps such as in populations recruited, population relevance and relevant risk factors for neurodegeneration.

Period that research on cohort began

Out of the 112 cohorts in Europe identified to date, the oldest data refers to 1911 (Hertfordshire Ageing Study- HAS). There has been a steady rise in the number of cohorts initiated particularly in the last decades of the last century and the first of this.

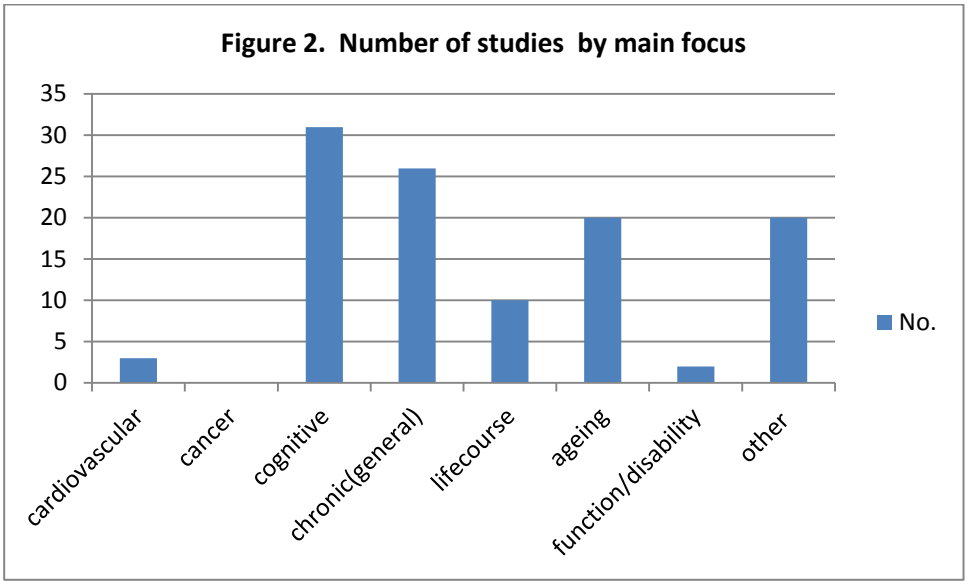
Figure 1 Number cohorts by period data collection started



Prime reported purpose of the cohorts.

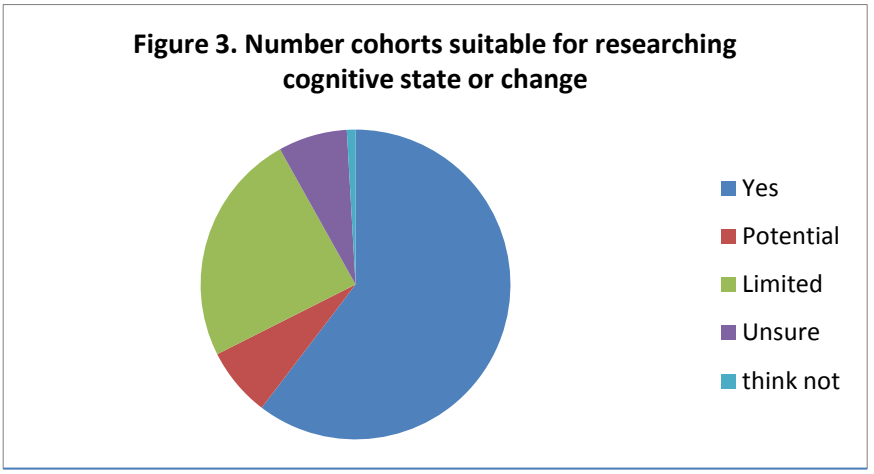
The studies had stated aims and these are defined in Box 1 and the distribution given in Figure 2. Many studies have included cognitive function, but many have also included them later as the cohort reached a particular age or in recognition of the policy interest in dementia. Very few cohorts have been set up to examine neurodegenerative disorders from the outset although several have done so (e.g. EPIC – originally set up to examine Cancer across Europe now examines conditions such as ALS and PD).

Box 1: Categories of prime purpose		
Category	**Definition**	**Example**
Cardio-vascular	Research into cardiovascular disease, including stroke, heart attack, angina, high blood pressure, and other heart conditions. Any individual study did not necessarily cover all forms of cardiovascular disease	Caerphillly, Aragon Workers
Cancer	Research into at least some forms of cancer	None (though Million Women's study and EPIC Norfolk could be placed here)
Cognitive	Looking at cognitive functioning or clinical condition in the broadest sense– dementia most commonly the cognitve focus but not necessarily	Cognitive Function and Ageing Studies (CFAS I & II), Minho Integrative database (MIND) on ageing (Minho); Italian Project on Epidemiology of Alzheimer's Disease (IPREA), Aberdeen Birth Cohorts of 1921 and 1936 (ABC), Lothian Birth Cohorts on 1921 and 1936 (LBC), Aberdeen Children of the Nineteen Fifties (ACONF)
Chronic (general)	Interest in not just one family of disease but groups of conditions that tend to be chronic, e.g. musculoskeletal and cardiovascular and cancer studies	ERGO-onderzoek Rotterdam (the Rotterdam Study); Whitehall II (though cardiovascular a large part), Lifelines; MoBa Norway
Lifecourse	Aim to study people from birth to death charting circumstances, events, behaviour and attitudes	National Survey of Health and Development (NSHD), also known as the Lifelong Health & Ageing Study or the 1946 cohort), Hertfordshire Ageing Study (HAS), also known as the Hertfordshire Cohort Studies, North Finland birth cohorts
Ageing	Focussing particularly on changes with growing older	Gothenburg cohorts H70,SHARE, ELSA, Italian Longitudinal Study of Ageing (ILSA);
Function/Disability	The research looks at what people can and cannot do, either physically or mentally, with disease a secondary consideration	PAQUID, Zaragosa cohort
Other	The research may be looking at a particular group of people, e.g. women or have aims that are not primarily health related but include relevant health information or at intergenerational differences in genetic and other data	Cohort of Norway (CONOR), Million Women's Study; patterns of multimorbidity In Primary care (multicare) Generation Scotland's Scottish Family Health Study



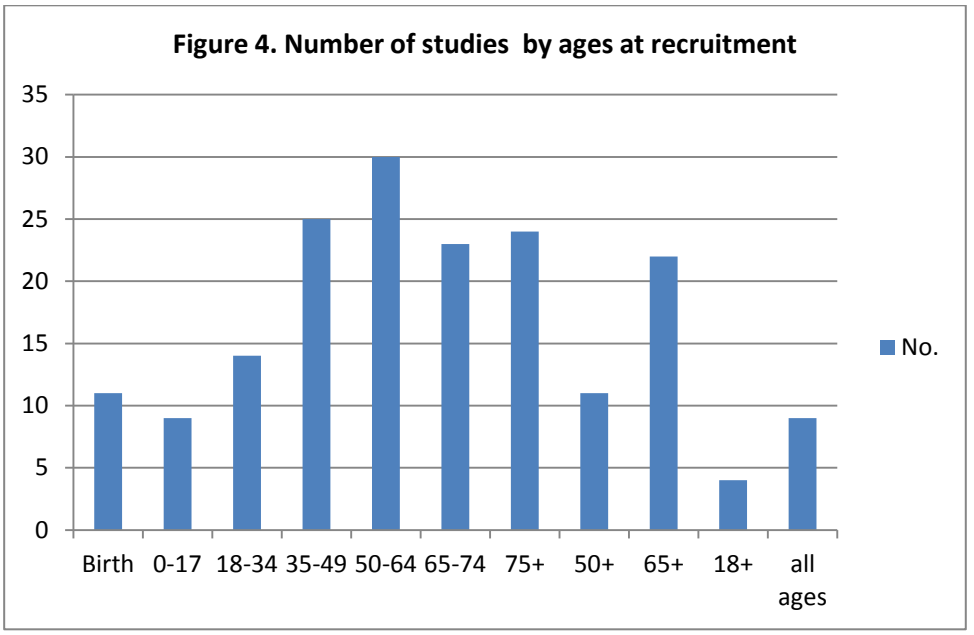
Of 31 studies set up to look at cognitive change about two thirds were primarily concerned with risk factors while one third looked at the way in which neurodegeneration progresses (with some overlap of studies) and one sixth were particularly interested in how to measure cognition.

Figure 3 shows an assessment of the distribution of studies by their potential for researching cognitive change (although all can be used at the minimum for either a snapshot or mortality analysis linked to cognitive function or disease). These cohorts might also lend themselves to the study of a wider range of neurodegenerative disorders which would be determined by sample size, risk profiles and questions to be addressed.



Ages studied

Figure 4 shows the distribution by age categories at selection of sample – some studies selecting people from more than one age group.



Out of the cohorts identified, five birth cohorts have followed people continuously from birth into adulthood of which the UK's 1946 birth cohort (NSHD) is one of the best known. Apart from NSHD there are four birth cohorts in the UK for children born respectively in 1958, 1970, 2000, and 2014 that have good characterisation from repeat assessment visits.

A further eight studies were established as cohorts when the participants were middle or advanced age but took advantage of records or surveys that had been made during the participants' childhood to reconstruct the cohort. These studies are good for looking at key factors in early life for which adults may have faulty memories or a lack of knowledge when asked decades later. However, they tend to leave a lacuna about a substantial part of a person's lifetime.

Studies with focus on cardiovascular diseases or with an interest in onset of diseases that become common in late middle age picked up cohorts across working age(see Figure 4) –some were occupationally based, e.g. the Whitehall II study , the Aragon Workers Health Study and the GAZEL study. There are cohorts with a broad remit to monitor population health, which cover a wide age range, e.g. Biohealth Norway, KORA studies in Germany, the Rotterdam Study, and Cohort Health 2000 in Finland. The Doetinchem Cohort Study also comes into this group looking at 'ageing' through working age and beyond. There are also a suite of new studies with very large numbers which are in their early stages or at recruitment phase such as the German National Cohort (and the Rhineland Study) and UK Biobank.

The cohorts with a focus on ageing usually cover a population aged around 50 and over at the start of the project, e.g the EPIC studies in Europe with 500,000 participants in total at baseline, the family of surveys stemming from the Health and Retirement Study (HRS) in the USA (The English Longitudinal Study of Ageing – ELSA – and the Surveys of Health Ageing and Retirement in Europe – SHARE; the Irish Longitudinal Study of Ageing –TILDA; the Northern Ireland study being planned - NICOLA). The Longitudinal Ageing Study of Amsterdam (LASA) started at ages 55 as did the Swedish Panel Survey of Ageing and the Elderly (PSAE). Other 'ageing' studies start at an older age. The Italian Longitudinal Study of Ageing (ILSA) covered ages 65-84 at baseline while Cohort Seniors (PAQUID) in France covered those aged 65 and over. These generic ageing studies usually include neurodegeneration as one of the sets of health condition they measure; they

have the advantage of covering a wide range of aspects of people's lives and several of them have frequent follow-ups. The HRS family have a particularly rich set of data on economic, work and social circumstances of people.

The 26 studies with the remit to look at chronic or common conditions do or could measure neurodegenerative conditions. They cover a variety of age ranges from 18 upwards. If not already doing so they have scope to identify onset of symptomatic dementia or cognitive decline. The most obvious shortfall with respect to age is the continuous monitoring of cognitive development through early adulthood. Even if the signs of cognitive decline would be too rare in early adulthood there may be relevant exposures that occur at this time and are not being measured in the ageing studies. Precedents have now been set for asking retrospective information although this is not ideal. Linkage to records, as has been done by the reconstructed cohorts could also be exploited further, perhaps, but would not pick up psychosocial factors. Neither of these approaches would enable tracking of biomarkers.

As some of the biological changes arising with various forms of dementia are not measurable during life, there is value in continuing the follow-ups after death. CFAS, the Cambridge 75s cohort (C75C), the Vantaa study of the 85+ age group and Ageing in Leganes do this with autopsies on donated brains. There are now several brain banks in Europe but these 4 appear to be the only population based studies. The expertise to add brain donation to the cohort studies is clearly there, as long as sensitively done. The last months or year of life can also be informative especially where there is interest in terminal decline and end of life care.

Family studies

Family studies are particularly useful for genetic studies. In our portfolio of cohorts seven clearly enabled multi-generational studies and six more had the potential to do so with scope for some limited links across generations in seven more studies. Internationally perhaps the most well known example is the Framingham series in the USA; although this analysis is focused on Europe, we should not forget that there is a wealth of data elsewhere[13]. Within Europe two studies primarily established to focus on inter-generational health links: are the Scottish Family Health Study (SFHS) and Lifelines. The former recruited people who had a first-degree relative willing to take part; while only 12.3% of the probands approached agreed to take part inevitably bringing some bias into the study, by 2012 they had over 20,000 participants . Studies that start with women giving birth are also good candidates for multi-generational studies; for example the Norwegian Mother and Child cohort (UpCos) and Generation R, although cognitive health is a not being measured as an outcome as yet. The birth cohort studies collect data about mothers of the children and usually fathers also. ALSPAC has taken advantage of the contact with parents children born in the 1990s to create a cohort of parents in their own right and it is planned to study other family members too. Two twin studies are included in our portfolio but there are probably more. Studies that provide some potential for generational linkage include the HUNT studies where the samples of successive studies overlap and the very large biobank studies such as Biobank UK.

Duration and number of data collections.

As seen above, the earliest wholly prospective cohorts started in the 1940s (the National Survey of Health and Development) but some reconstructed cohorts that go back much further (e.g. Boyd Orr Cohort to the 1920s; the, Hertfordshire Birth Cohort dates back to 1911, the first Uppsala birth cohort to 1930). Eighteen of the cohorts on ageing have stopped direct contact with subjects and 13 more have probably stopped. In 12 of these the cohorts would be extinct or nearly extinct (e.g. the Zutphen Elderly Study and the first Hertfordshire cohort). For a further six cohorts it was not clear whether the study was continuing or not. In some cases new cohorts are recruited to enable continued study of the oldest old (e.g. for the H70 or Hertfordshire or CFAS2).

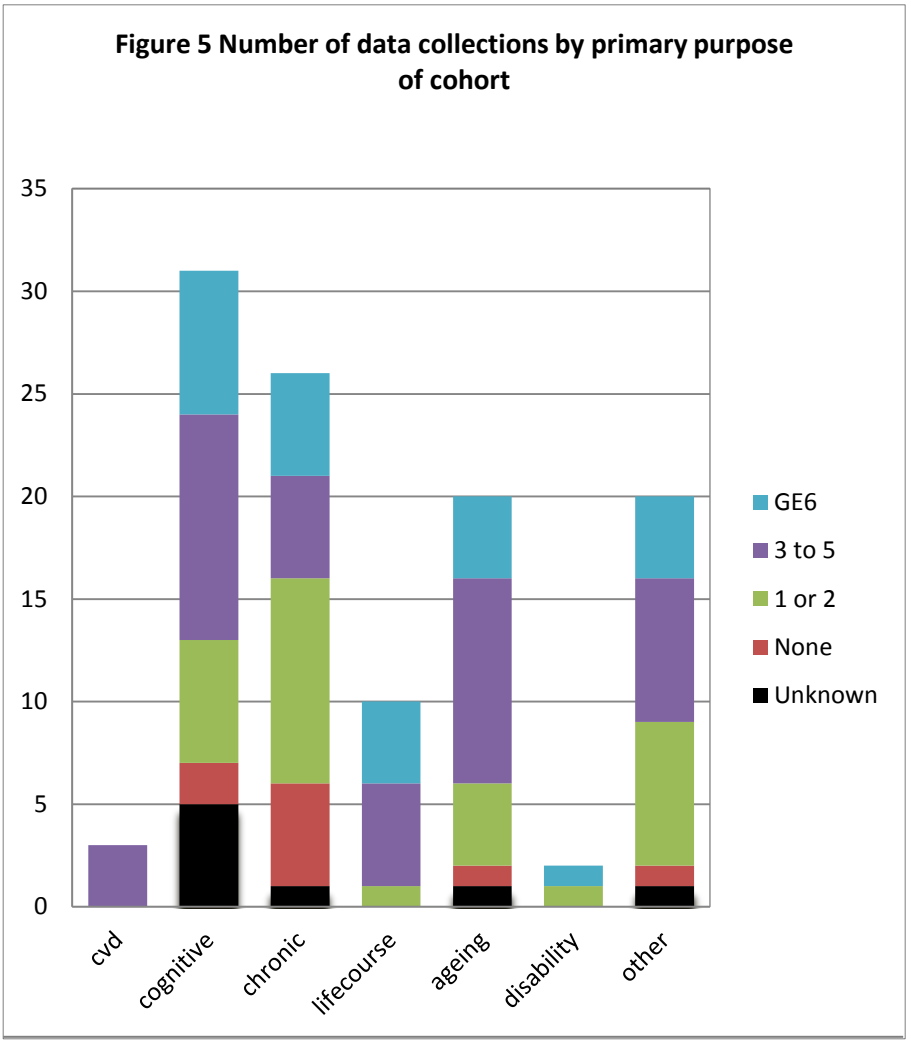
[13] See for example the IALSA network set up by Professor Hofer. https://www.ilifespan.org/ The Honolulu Heart study is another good example of a multi-generational study.

There are studies that have had frequent follow-ups over a 30 year time span or more even if the cohort members were only recruited in middle age or later. The longest is the NSHD. The original H70 cohort had 16 data collections over 30 years or so, the first CFAS had 11 and the first LASA cohort s six. Even the H85 cohort survivors were interviewed at frequent intervals for nearly 20 years.

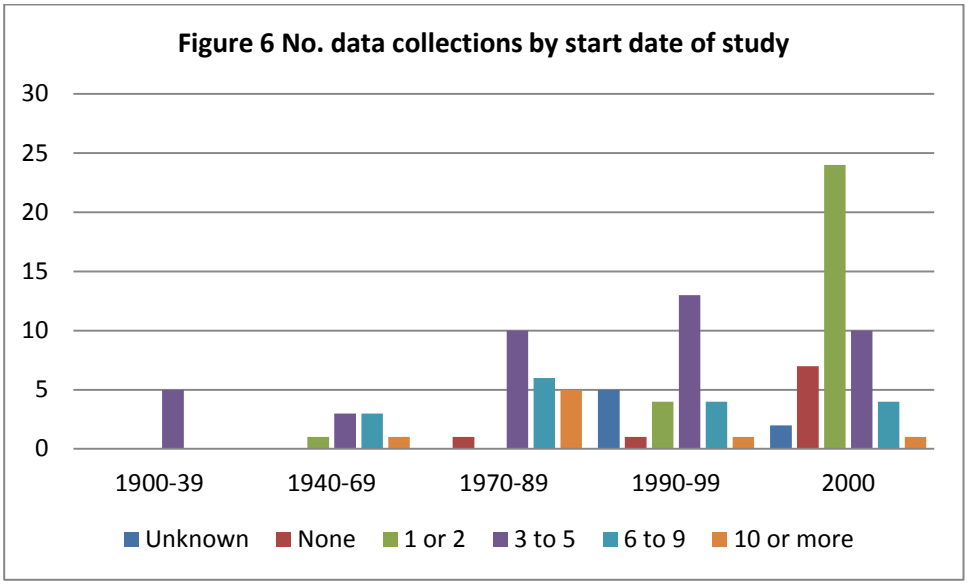
To track through detailed information on neurodegenerative changes using recently developed methods only recent studies will emerge, necessarily. One example is the Cohort for Determinants and Evolution of Alzheimer's Disease and related disorders (MEMENTO) in France which is looking at the prognostic value of several markers on progression of cognitive decline. Another is the Minho Integrative database and the Vallecas project for the early detection of Alzheimer's Disease, CFAS was an earlier European pioneer of this. A Polish study that looks at proteomic markers of degenerative disease as early as 1998 is included in our portfolio but may have been a follow-up of clinic patients rather than a community study.

Figure 5 gives the distribution of cohorts by number of direct data collections – ie. omitting information picked up from record linkages. Fifteen studies have 0 or 1 because either they are in the early stages of follow-up or because they are relying mainly on record linkages. On the other hand 14 studies have 8 or more rounds of data collection enabling tracking of health.

Figure 5 Number of data collections by primary purpose of cohort



Not surprisingly, the number of data collections is correlated with the start period except for the earliest starts which were reconstructed cohorts (Figure 6)



Sex

There are a few single sex studies. The Million Women's study obviously only studies women but its main focus is on hormonal and reproductive influences on health and the information on memory or dementia very limited although this study has established dementia outcomes and other neurodegenerative disorders. The Norwegian Mother and Baby study started with samples of women because its focus is pregnancy and as yet it has little information on cognitive state but children of both sexes are being followed and blood samples collected from fathers. The PPSW Gothenburg study is the only study that is both women only and includes study of dementia in its aims – it focused on women because the prime interest was in menopause. The Caerphilly Study only includes men, mainly because initially it focussed on heart disease and was set up at a time when this was not considered a woman's problem. The Zutphen Elder Study and Uppsala Longitudinal Study are both confined to men, again because heart disease was a first interest. The former cohort started measuring cognitive function when the cohort reached 70 years of age. Women predominate in the Twins UK study, which relied on voluntary registration, whereas men predominate in the GAZEL study, reflecting the sex-balance among employees of the electricity industry in France, the Aragon study similarly.

Ethnicity

Few of the documents used in this exercise mentioned a focus on ethnic variations. Although in Britain it is fairly standard to ask for ethnicity, the numbers may be too small for separate analysis. A superficial search on PubMed for articles[14] turned up ones referring to research predominantly carried out in the USA. The UK Understanding Society has oversampled ethnic minorities; information on the Ageing in Leganes study in Spain and the Generation R study in Rotterdam includes mention of ethnic minority representation. Although individual studies may have insufficient numbers in non-Caucasian white groups, it may be possible to combine across studies.

Geographical – representativeness

Nearly all the studies are limited to one country and the majority of these further localized to specific regions or towns. Some examples of this are the regional studies in Zaragoza province and the Augsburg region of Germany. City-specific studies include, the Rotterdam cohort, LASA, the Cambridge City over 75s cohort, and the Three City Study in France. Thirty-seven studies were wholly urban, only 1 wholly rural, 71 mixed and 2 unspecified. It is not clear the extent to what extent rural-urban differences can be explored in

[14] The title or abstract contains the terms 'ethnic*' and 'cohort' and 'ageing or cognitive'

individual studies but it might be possible to combine studies for an idea of this[15]. Dividing Europe into North, West, East and South, there were only two studies from Eastern Europe (so under-representing the ex-Communist countries) as against 67 from Western Europe, 29 from Northern Europe and 10 from Southern Europe[16]. Small states were missing except for Luxembourg and Iceland.
The advantages of more localized studies are the ability to maintain contact with the participants, to know the context in which people are living, and the relative affordability of carrying out laboratory and clinical tests. Unless populations are stable or there are resources to find and include people who have moved away, losses can be substantial and biased and reporting on the extent to which this has been attempted is not consistent or comprehensive.

Representativeness

The studies included in our portfolio are predominantly community based. These are preferable for life course studies or monitoring of risk factors that may be important many years before onset of symptomatic disease. They also allow study of a wide variety of exposures or potential risk factors whereas studies that purposively select people who have had a specified exposure, e.g. working with a chemical or a history of depression, are then very limited in the conclusions that can be drawn about other factors. On the other hand, community studies may not be sufficiently powerful to assess some rare but potentially strong risk factors, e.g. use of corticosteroids, renal function, or exposure to particular combinations of comorbidities or pollutants and so there is scope for specialist studies. Meta-analyses of community studies might also enable quantification of effects provided there is sufficient homogeneity across the data sets in the measures used and populations covered. The HALCYON collaboration to conduct combined analysis of risk factors across the lifecourse was set up with this as a major aim although there remain methodological challenges in such harmonisation and new methods involving metatechniques may be more practical.
Thirty studies explicitly excluded people who are in long-term care at baseline while 20 explicitly included them, for example CFAS, Neurological Disorders in Salamanca (NEDISA), and the Rotterdam Study. Some studies excluded people who were not able to communicate well or were very ill. For example, the AgeCoDe cohort excludes people with dementia at baseline for this reason but also those who are deaf, blind, expected to die within three months or are in a nursing home. The Augsburg studies explicitly excluded those too ill to take part in medical examinations; the Cohort Minho Integrative Database excluded those with disabling pathologies or disease. Even if, theoretically, people with cognitive deficits could be included, it is likely that most studies had a bias against such inclusion at baseline because of consent issues. The documentation for a few studies (e.g. ELSA, TILDA) noted that contact is maintained where possible when the subject moves into long-term care. However, the logistics of this are not easy because one first has to know that the person is in care and then work through the various gatekeepers to obtain access to the subject.

The samples for thirty-six of the studies were selected such that individuals should have a known chance of selection, i.e. random sampling was used. Several of these involved intermediate stages of selection, e.g. general practices or towns, and a further six had random samples within the intermediate unit of selection but those units were purposefully chosen so that overall the sample was not random. In 31 cases everyone in the sampled population was eligible and in 5 cases the sample was a mix of random and non-random components. At least six used specialised lists which might not be representative of the general

[15] Attempted to find out whether rural/urban been analysed by searching whether title or abstract contained 'rural' PubMed search of title/abstract including 'cohort AND (cogniti* OR dementia OR ageing) AND (rural AND (urban OR town OR city)

[16] Northern Europe comprises Iceland, Norway, Sweden, Finland, Latvia, Lithuania, Estonia, Denmark; Western Europe comprises Austria, Belgium, France, Netherlands, Luxembourg, Switzerland, UK, Eire; Eastern Europe comprises Belarus, Bulgaria, Czech Republic, Hungary, Moldavia, Poland, Romania, Slovak Republic, Slovenia, Croatia; and Southern Europe comprises Albania, Cyprus, Greece, Italy, Macedonia, Malta, Spain, and Portugal.

population. Eight studies had samples derived from other studies so probably lost some representativeness through attrition and 13 were clearly not random. In a few cases the sampling was not specified.
Even the random samples may lose their representativeness through non-response. This is a major problem with many longitudinal cohorts. Unfortunately, one of the biases that is likely to arise is under-representation of onset of dementia [17] and participation with retention of the fitter members of society - SHARE had an average response across countries of 62% at its baseline, which probably reflects feasibility rather than insufficient effort for a general population survey that is not local to a town. Response rates can be defined in many ways but it would be rare for cumulative response not to be a concern. The subject is too complex to discuss further here but is one of the factors that should be taken into account in deciding how to use existing studies.

Proxy information
Given the problems of obtaining informed consent and clear information from people with cognitive limitations, researchers resort to third-party information from so-called proxy informants. Proxy informants who know the subject well and live with them or close by can usually provide information on their behaviours, some aspects of their health, and hospital visits. They may surmise the subject's attitudes or expectations but these are less reliable. Also, clearly, they cannot provide blood or biological samples or do cognitive or physical performance tests for the subject. There are validated instruments for assessing cognitive change through third part questions, for example the Blessed Scale[18] and a quality of life instrument has been developed.[19] Some studies comparing answers from proxies and subjects have been carried out, including one concerning anxiety among people with early dementia[20]– good correlation is reassuring but if this lacks one does not which better reflects the subject's situation. The use of proxies was noted in 13 studies and probably used in more.

Linkage (see later section too)
The advantage of such linkages is that they do not rely on re-contacting individuals; however, not all routine records are well maintained and this needs to be checked for any cohort study.
Scandinavian countries have good linkage procedures allowing addition of information on hospitalizations, prescribed medicines, mortality, income and residence to that collected directly from the person. The Uppsala multi-generation study is the best example of this and relies almost entirely on record linkage. Other cohorts mainly using routine data through linkages include Biohealth Norway, the Netherlands Cohort Study, the English and Scottish Longitudinal Studies (not primary health), and the Swiss National Cohort. There are specific notes about linkages for 78 of the studies in our portfolio. The most common linkage is to death records but other health-related linkages contain information on hospitalisations, prescriptions, family doctor records, and national insurance claims. Some also use national registers for income, records, school attainment, migration, and military conscription. For example, the Rotterdam studies make use of local records where follow-up examinations every 2-3 years are complemented by morbidity and mortality obtained from family doctor records and hospital discharges. The Aberdeen Children of the 1950s study linked back to school records and forward to cancer registries, hospitalisations and mortality with just one postal questionnaire in 2001-3. The GAZEL study has used employers' records of health events and employment.

Measures of cognitive function
The detail of these has been documented where available and it is clear that a variety of measures have been used to capture cognitive decline, as a continuously-distributed phenomenon, and as 'caseness'. The researchers were not always attempting to formulate a clinical diagnosis but extensive tests were carried

[17] Matthews F et al BMC Public Health 2004, 4:12

[18] Erkinjuntti et al International Journal of Geriatric Psychiatry 1988: 3(4): 267-73

[19] http://www.hta.ac.uk/fullmono/mon910.pdf

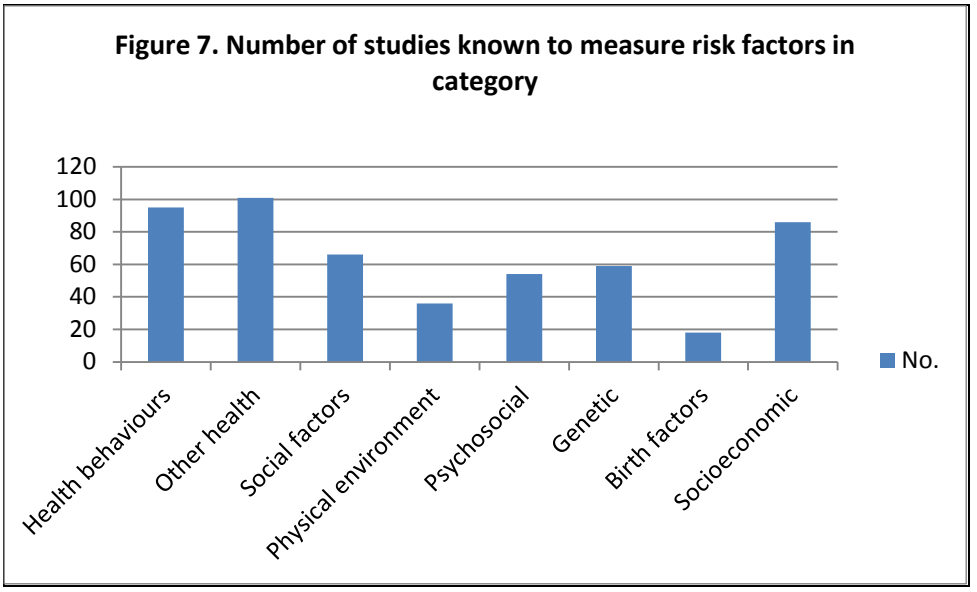
[20] Dawson NT et al. TheGerontologist. Online 2012. doi:10.1093/geront/gns137

out for the specialist studies on cognitive functioning and neuroepidemiology and clinical systems such as DSM-III and NINCDS-ADRDA or -AIREN used for diagnosis. There is a crossover between the less specialist studies and those that are more focused on cognitive measures in that several of the latter have initial screening interviews in which the Mini Mental State Examination or part of the General Mental State are used, and these are also used in the former.
There are studies looking to identify cognitive decline as early as possible in the trajectory. One example is the recently-formed Cohort on Determinants and evolution of Alzheimer's Disease and Related Disorders in France which is looking at the prognostic value of several markers on progression from early signs to clinical dementia or severe cognitive deterioration. There is also a Polish study which started in 1998 but about which I have little information. The Italian Project on Epidemiology of Alzheimer's Disease and the Betula Prospective Study on Aging, Memory and Dementia also study the preclinical phase of dementia. The Cognitive Function and Ageing Studies (CFAS) and German Factors for disease progression in Alzheimer's Disease, the Italian project mentioned above, and the Longitudinal Urban Cohort Ageing Study (LUCAS) are examples of studies monitoring changes in function over time and exploring risk factors for adverse changes. These studies require measures that have a scale rather than, or as well as, a diagnosis threshold so that change can be measured. The CAMCAN project in the UK is focusing on the cognitive abilities that enable us to function in the world and how these can best be retained, including memory, attention, emotion, language, and action.

Risk factors measured
The information collected on risk factors has been grouped into broad categories without distinguishing which of the components were measured on any one study. The groups are noted in Box 2. Categories that were not quantified include reproductive factors, and anthropometric measures. Figure 7 shows the number of studies measuring at least one item within the category.

Box 2. Risk factor Categories

Category of risk factor	Examples of qualifying information
Health behaviours	Tobacco use, alcohol consumption, diet, physical activity
Other health	Self-reported general health, self-reports of diagnosed diseases, medical records of diseases (often cardiovascular); risk factors for cvd e.g. blood pressure, metabolic syndrome.
Social risk factors	Social networks, being alone, marital status, membership of clubs or organisations
Physical environment	Exposure to chemicals, noise, damp;; neighbourhood facilities
Psychosocial factors – sources of potentially negative stress	Traumatic events, imbalance between demand and control at work or home, harassment, negative emotions like loneliness (did not include depression),
Genes	
Birth factors	Mother's health behaviours during pregnancy, gestational age, birthweight, obstetric problems
Socioeconomic	Education, occupation. Less commonly, income, wealth, housing tenure



In total 93 studies specified inclusion of some health behaviours. Three studies had focused on diet and nutrition; there were not such detailed studies on smoking, alcohol consumption, or physical activity. Few studies lacked information on other aspects of health: at least 100 reported some information. The most common aspects of health are self-reported health and diagnosed common chronic diseases. Self-reported difficulties with activities of daily living are also measured in several studies. Social risk factors are also often measured although described fairly vaguely in much of the documentation used. Aspects of social support by family and friends are perhaps an area of importance here (e.g. in a substudy of CFAS, the Newcastle 85+ study)

The term 'environment' can mean many things but the physical environment is rarely mentioned and could perhaps be a factor in progression of dementia that is relatively under-studied. Some form of environmental measures was included in 34 studies but this kind of information was sparse. The West of Scotland Study includes several variables about the neighbourhood but is not strong on cognitive measures. The work environment is covered in some occupational cohorts like the GAZEL cohort in France or another French cohort of agricultural workers for whom pesticides a concern, and in the Panel Survey of Ageing and the Elderly in Sweden. Housing is taken into account in some studies, e.g. the Kungsholmen project in Sweden. The Three City study and the KORA study are measuring air pollution and PAQUID looked at aluminium in water. Although there is some indication of a psychosocial factor in 53 studies, this seemed to be a major factor in few studies and an aspect of cognitive research that is perhaps under-exploited. First, the existing data should be examined but there may be a need for new information; this does not necessarily entail a new cohort as some studies allow additional questions.
Both physical environment and psychosocial factors can take many forms. Apart from birth cohorts and reconstructed cohorts, some studies have asked questions retrospectively about life events or working environment (which could be relevant to both these) but, as mentioned previously, there are many gaps about exposures in earlier life.

Most studies have some measures of differences in incidence across socioeconomic groups, for example by education, income or wealth (e.g. this is a major focus of the National Survey of Health and Development NSHD and ELSA). Eighty-five studies are known to have at least one socioeconomic measure.

Biomarkers
The majority of studies have a selection of biological measures. Some studies include the study of cardiovascular disease among their aims so have details on cardiovascular risk factors such as blood pressure, lipids, inflammatory agents. Examples are the Caerphilly Prospective Cohort Study, the Italian Longitudinal Study of Ageing, the Uppsala Longitudinal Study of ageing men, the Norwegian Mother and Child cohort (MoBa) and the Minho integrative database. Other studies are focusing on the vascular

aspects of dementia, such as Prevention of Dementia by Intensive Vascular Care (PreDIVA), and the Three City Study. The Netherlands Cohort Study has determinants of cancer incidence as a major focus and the Million Women's study a special emphasis on hormonal and reproductive factors affecting women's health while the Prospective Population Study of women in Gothenburg had an initial aim of investigating health factors related to menopause.

Blood samples were taken at least once in 82 studies (and possibly more). Urine and or saliva samples were taken in 19 studies (e.g. the HUNT studies, KORA ELSA, the Cambridge Over 75s cohort)[21] . A few studies had other forms of tissue such as hair or toenail clippings. DNA is known to be extracted either from blood or other tissue in 59 studies. Biobanks were mentioned in 35 studies. The UK and Norwegian biobanks are very large scale (half a million members) and the Netherlands Lifelines Cohort is primarily a genetic study of 165000 participants, comprising 45000 probands and relatives. Many of the studies which have already measured genes are taking the approach that environment – gene interactions may be crucial.

Scanning is increasingly used as technology develops. Twenty-seven studies are known to use MRIs or CTs or PET scans on at least a subsample of their cohort. In nine of these studies it was clear than selected subsamples had the scans; in other cases it is probable that there were refusals among the cohort members so the scans may not be representative.

Health and social care

The details of health and social care information have not been systematically documented although we took note of this information where it was easily available. At minimum 77 studies included some information on health care, ranging from medication taken to contacts with health services. Much of this comes from linkage to hospital or family doctor records. On the other hand only 14 studies clearly mentioned use of social services, including long-term care. Although RCTs are appropriate for drug trials and some aspects of care, there is scope for more exploitation of information from observational cohorts to see how cognitive function varies over time according to the use of services. It may be possible to enhance datasets by more linkages rather than adding too much to the burdens of interviews for members of the cohorts.

Quality of Life

This could become a more standard component of cohorts – there are measures that have been developed to work for those with some cognitive impairment but there is an undoubted difficulty in charting quality of life over time as cognitive capacity diminishes. More methodological work on measurement is needed as to how to track quality of life as cognitive function declines. A paper from 2005[22] found few longitudinal studies looking at how awareness of their condition changes with time for people with dementia. More generally, the subjective reactions of those with cognitive impairment appear to be under-researched.

Strengths and weaknesses

This Annex attempts to summarise information already available in European longitudinal observational studies may be relevant for research into neurodegeneration. It is not completely systematic and is not based on the content of the literature outputs but the descriptions available in overview website or cohort descriptions. It brings together more detail than has previously been available. However, there are still many cohort studies that could be checked out in Europe and it is likely that some major gaps in coverage of European studies have been covered in studies taking place elsewhere, e.g. the USA or Australia. The classifications used in this summary were not those of the researchers carrying out the cohorts and the information has been gleaned from websites, profile papers and other articles. The principal investigators have not been approached directly. The classification may have some errors but also the assignment to categories may be prone to inter-rater variability.

[21] Searched papers on the cohorts for mention of saliva or urine and also PubMed for mention in title or abstract of "saliva AND cohort AND (ageing OR cognitive OR dementia)

[22] Aalton P. et al Awareness in dementia: A review of clinical correlates, Aging & Mental Health, 2005:9:5, 414-422

ANNEX B
Analysis of disease cohort studies

Table 1 (see page 46) describes a number of cohort studies, selected because they differ in terms of their strengths and provide examples of the different types of cohort that the Action Group considered. The recruitment methods vary, ranging from population-based incidence or prevalence cohorts, or clinic-based cohorts.

For a complete summary with web references of all of the cohort studies considered for this report, see Annex D.

The first category of studies in Table 1 gives examples of general population-based studies on older people where there is true population representation. The Rotterdam study is based on a single site, CFAS I is multisite and includes rural representation, and ILSA is an example from a different geographical region, southern Europe.

Second are examples of general population studies where participants who initially are relatively healthy have volunteered to join the cohort. The Three C study is an example of an older population, the EPIC study is inclusive of the full adult population, and UK Biobank and the German National Cohort are selected because both are major studies with considerable potential. UK Biobank has completed recruitment and is available for studies and the German National Cohort will open fully in 2014.

The third category is of younger cohorts where risk is tracked into later life, such as CAIDE and FINGER and the 1946 birth cohort which was more-or-less population based at commencement. To these are added EPIC, where a cohort initially set up for other purposes has already been examined for AD and PD outcomes and the Rhineland study which will offer deep phenotyping and currently is in the set-up phase.

Fourth are cohorts that feature the oldest old. Listed are the Swedish National Study on Aging and Care, which includes an older category, the Cambridge city over-75s study which has been extended from its original remit to look at depression and physical disability, as well as health active life, and Vantaa 85+, which has a focus on vascular comorbidity. The CFAS studies also include an oldest old category which allows intergenerational comparison between the studies which are based on the same design.

In the Brains for Dementia Research is distinct in that volunteers over 65 are recruited to a programme of brain donation.

Finally there are:

- new generation dementia studies: the Swedish National Study and CFAS II
- cohorts specifically recruited in the prodromal or early disease phase such as Memento which is based on nationwide memory clinics, ADNeuroMed Europe, which invites volunteers who have MCI or an early clinical diagnosis of AD, the TREND study which includes prodromal PD and ICICLE and ParkWest that track incident PD and

recruit from specific geographical areas

- prevention studies: the effects of lifestyle intervention are studied in FINGER where participants carry an at-risk phenotype for AD that was defined in the CAIDE study.

Table 1 : Examples of different cohort types considered by the JPND Action Group. Additional cohorts are located in Annex D.

Title of the cohort	Web link	Additional inclusion criteria	Country	City/Centre	Cohort type	Aim	Data collection start date	Size of the cohort	Age at inclusion (mean, range)	Clinical measures	Biomarkers	Cognitive assessment	MRI/ neuroimaging	Genetic DNA analysis possible	Consent for autopsy	Blood sample
General Population																
IPREA Italian Project on Epidemiology of Alzheimer's disease	www.iss.it	None specified	Italy	12 municipalities	True general population	To study the preclinical phase of dementia, including AD, in Italy. The IPREA consists of a cross-sectional phase, to study the prevalence of, and factors associated with the preclinical phase of dementia, and a longitudinal phase, to evaluate the incidence and transition to dementia, also assessing the predictive value of biological markers and neuropsychological tests.	2003	5000	65-84	yes	yes	yes	yes	yes	unknown	yes
ILSA Italian longitudinal study on ageing	www.iss.it	All participants were Italian.	Italy	Rome	True general population	To investigate frequency, risk and protective factors of major age-associated conditions, and to study physical and functional changes among an Italian elderly cohort. The chronic diseases investigated were cardiovascular diseases (hypertension, myocardial infarction, angina pectoris, cardiac arrhythmia, congestive heart failure), diabetes, peripheral artery disease, stroke, dementia, parkinsonism, and distal symmetric neuropathy.	1992	5000	65-84	yes	no	yes	no	no	unknown	no

Title of the cohort	Web link	Additional inclusion criteria	Country	City/Centre	Cohort type	Aim	Data collection start date	Size of the cohort	Age at inclusion (mean, range)	Clinical measures	Biomarkers	Cognitive assessment	MRI/ neuroimaging	Genetic DNA analysis possible	Consent for autopsy	Blood sample
Rotterdam study' - ERGO (Erasmus Rotterdam Gzondheid Onderzoek)	http://www.ergo-onderzoek.nl/wp/	Living in the Ommoord area	NL	Rotterdam	True general population	To investigate causes and determinants of chronic (incl. neurologic) disease in the elderly. Emphasis on molecular and genetic analyses. For neuro-epidemiological research, focuses on frequency, etiology & early recognition of the most frequent neurological diseases in the elderly.	1990	15000	55+	yes	MRI	yes	yes	yes	unknown	yes
CFAS I	http://www.cfas.ac.uk	Resident of Cambridge, Oxford, Gwynned, Nottingham, Liverpool, or Newcastle	UK	Cambridge	True general population	The initial aim was to investigate dementia and cognitive decline in a representative sample of more than 18,000 people aged over 65 years. The range of information collected has also allowed the study to investigate depression and physical disability in the older population and also look at healthy active life expectancy. CFAS II started in 2008, and builds on the design and infrastructure of CFAS It will provide data on generational and geographical differences including people in institutions.	late 1980 s	18000	65+	yes	yes	yes	no	yes	yes	yes

Title of the cohort	Web link	Additional inclusion criteria	Country	City/Centre	Cohort type	Aim	Data collection start date	Size of the cohort	Age at inclusion (mean, range)	Clinical measures	Biomarkers	Cognitive assessment	MRI/ neuroimaging	Genetic DNA analysis possible	Consent for autopsy	Blood sample
3C Study Three-City study	http://www.three-city-study.com/	Resident of Bordeaux, Dijon, or Montpellier	France	Bordeaux	Volunteer general population	To study the risk of dementia attributable to vascular factors. The main outcomes are dementia (Alzheimer's disease and other types of dementia), vascular diseases (coronary heart disease and stroke), and mortality. Specific objectives: To assess the associations of vascular diseases (CHD and stroke) with dementia and cognitive impairment; To quantify the associations between cerebral white matter hyperintensities and dementia; To quantify the associations of dementia with factors that increase or decrease the risk of vascular diseases; To quantify the associations of cerebral measures (white matter hyperintensities and atrophy) with factors that increase or decrease the risk of vascular diseases	1999	9294	65+	yes	yes	yes	yes	yes	unknown	yes
EPIC Norfolk	http://www.srl.cam.ac.uk/epic/	Resident in Norfolk, UK	England	Norfolk – East Anglia	Volunteer general population	Prevention, diagnosis and treatment of cancer, heart diseases, stroke, diabetes, depression, dementia. Data collected on diet, lifestyle and health through questionnaires and health checks.	1993	500000	45-74	yes	yes	yes	no	yes	no	yes

Title of the cohort	Web link	Additional inclusion criteria	Country	City/Centre	Cohort type	Aim	Data collection start date	Size of the cohort	Age at inclusion (mean, range)	Clinical measures	Biomarkers	Cognitive assessment	MRI/ neuroimaging	Genetic DNA analysis possible	Consent for autopsy	Blood sample
German National	http://www.nationale-kohorte.de/index_en.html	Resident in Germany	Germany	Across Germany	Volunteer general population	Large-scale, nationwide, long-term population study with the aim of •explaining the causes of widespread diseases such as cardiovascular disease, cancer, diabetes, dementia, and infectious diseases, •identifying risk factors, •highlighting effective forms of prevention, and •identifying options for the early detection of diseases.	To start in 2013	200000	20-69	yes	yes	yes	MRI of sub-set	yes	no	yes
UK Biobank	http://www.ukbiobank.ac.uk/about-biobank-uk/	Resident in UK	England, Scotland and Wales	Oxford	Volunteer general population	Prevention, diagnosis and treatment of cancer, heart diseases, stroke, diabetes, depression and forms of dementia	2006	502713	40-69	yes	yes	yes	yes (pilot study on subset of 8000 in 2013/ 14; expan-sion to 100k)	Geno-typing entire cohort in 2014/ 2015	no	yes
Younger cohorts																
NSHD National Survey of Health and Development (1946 cohort)	http://www.nshd.mrc.ac.uk/	Born March 3-9, 1946	England, Scotland and Wales	London	Population	To study ageing	1946	16695	0	no	no	yes	no	yes	no	yes
CAIDE (Cardiovascular Risk Factors, Aging and Dementia)	http://www.uef.fi/caide/home	None	Finland	Kuopio	Population	Investigate the connection between social, lifestyle, and cardiovascular risk factors and cognition, dementia, and structural changes in the brain.	1997	2000	71 (first seen at 50)	no	yes	yes	yes	yes	unknown	yes

Title of the cohort	Web link	Additional inclusion criteria	Country	City/Centre	Cohort type	Aim	Data collection start date	Size of the cohort	Age at inclusion (mean, range)	Clinical measures	Biomarkers	Cognitive assessment	MRI/ neuroimaging	Genetic DNA analysis possible	Consent for autopsy	Blood sample
EPIC Norfolk	http://www.srl.cam.ac.uk/epic/	None specified	England	Norfolk – East Anglia	Population	To investigate the relationship between dietary intake and cancer.	1993	10000	45-74	yes	yes	yes	no	yes	unknown	yes
FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Dementia)	www.thl.fi/finger	Elevated Dementia Risk Score (Kivipelto et al, Lancet Neurology 2006) and cognitive performance slightly lower than expected for age	Finland	Study centre is in Stockholm	MCI & high dementia risk score	To study the effect of the multi-domain lifestyle intervention on cognitive impairment and incidence of dementia/AD to understand dementia prevention	2009	1200	60-77	yes	yes	yes	yes	yes	unknown	yes
The Rhineland Study	http://www.dzne.de/en/research/research-areas/population-studies.html	None specified	Germany	Bonn	Population	Preclinical multimodal biomarker profiles of neurodegenerative	2013	30000	30+	yes	yes	yes	yes	yes	unknown	yes
Oldest Old																
SNAC-K The Swedish National study on Aging and Care in Kungsholmen	http://www.snac-k.se/	Resident of central Stockholm	Sweden	Kungsholmen	Population	To trace the changes in health status and detect factors leading to negative health and functional outcomes in the elderly. First, health from a broad perspective, including medical/physical, psychological, and social health. Second, a life course perspective to identify the determinants of good or bad health in the elderly.	1987	1500	75+	yes	no	yes	no	no	unknown	no

Title of the cohort	Web link	Additional inclusion criteria	Country	City/Centre	Cohort type	Aim	Data collection start date	Size of the cohort	Age at inclusion (mean, range)	Clinical measures	Biomarkers	Cognitive assessment	MRI/ neuroimaging	Genetic DNA analysis possible	Consent for autopsy	Blood sample
Cambridge city over-75s Cohort Study (CC75C)	http://www.cc75c.group.cam.ac.uk/	75+	UK	Cambridge	Population	The initial aim was to investigate dementia and cognitive decline in a representative sample of more than 18,000 people aged over 65 years. The range of information collected has also allowed the study to investigate depression and physical disability in the older population and also look at healthy active life expectancy.	1985	2600	75+	yes	yes	yes	yes	yes	yes	yes
Vantaa 85+	http://www.hi.helsinki.fi/english/research/groups/pathology/vantaa85study.html	85+	Finland	Vantaa	Population	The Vantaa 85+ study is a prospective population-based study, which was established in 1991. All people aged 85 years or over living in the city of Vantaa in April 1, 1991 were included in the study (N= 601). The current main focus is 1) to investigate the impact of cerebral amyloid angiopathy and other neuropathologies on clinical dementia, and 2) to investigate the genetic background of these neuropathologies by using a genome-wide analysis, as part of an international ECLIPSE (Epidemiological ClinicoPathological Studies in Europe) study.	1991	553	85+	yes	yes	yes	yes	yes	yes	yes

Title of the cohort	Web link	Additional inclusion criteria	Country	City/Centre	Cohort type	Aim	Data collection start date	Size of the cohort	Age at inclusion (mean, range)	Clinical measures	Biomarkers	Cognitive assessment	MRI/ neuroimaging	Genetic DNA analysis possible	Consent for autopsy	Blood sample
Brain donation cohort																
Brains for Dementia Research	http://brainsfordementiaresearch.co.uk/	Willing to donate brain	UK	England and Wales	Volunteers	Pathology	2008	1400	65+	no	yes	yes	no	yes	yes	40%
New generation dementia studies																
SNAC-K The Swedish National study on Aging and Care in Kungsholmen	http://www.snac-k.se/	Resident of central Stockholm	Sweden	Kungs-holmen	Population	To study ageing	2001	3500	60+	yes	no	yes	no	no	unknown	no
CFAS II	http://www.cfas.ac.uk	Residents of Cambridge, Newcastle, Nottingham, Gwynedd and Neath, West Glamorgan.	UK	UK	True general population.	CFAS II started in 2008, and builds on the design and infrastructure of CFAS I. It will provide data on generational and geographical differences including people in institutions. This study will provide the opportunity to investigate the implications of changes in morbidity and frailty on health itself, as well as the use of services and expenditure in health and social care.	2007	7800	65-84 and 85+	no	no	yes	no	yes	yes	yes

Title of the cohort	Web link	Additional inclusion criteria	Country	City/Centre	Cohort type	Aim	Data collection start date	Size of the cohort	Age at inclusion (mean, range)	Clinical measures	Biomarkers	Cognitive assessment	MRI/ neuroimaging	Genetic DNA analysis possible	Consent for autopsy	Blood sample
Specifically recruited prodromal/ early disorder																
Memento (Determinants and evolution of Alzheimer's Disease and related disorders)	http://www.chu-bordeaux.fr/chub/media/les-infos-a-la-une-2011/maladie-d-alzheimer-au-chu-de-bordeaux/la-cohorte-memento-le-centre-hospitalier-universitaire-de-bordeaux-promoteur-de-la-cohorte-nationale-alzheimer/	Performing below mean minus one standard deviation in tests for one or more cognitive domains.	France	Bordeaux, Lille, Marseille, Paris Sud and Toulouse	MCI	The principal objective is to study the evolution of early symptoms (complaints or cognitive deficits, behavioural problems) as well as the prognostic value of different markers (biological, genetic, neuropsychological, psychopathological, vascular, sociodemographic and neuro-imagery) in the progression of the illness from the first signs of clinical dementia through deterioration to severe cognitive disability and on to death.	Jul-05	2300	18	yes	yes	yes	MRI PET	yes	unknown	yes

Title of the cohort	Web link	Additional inclusion criteria	Country	City/Centre	Cohort type	Aim	Data collection start date	Size of the cohort	Age at inclusion (mean, range)	Clinical measures	Biomarkers	Cognitive assessment	MRI/ neuroimaging	Genetic DNA analysis possible	Consent for autopsy	Blood sample
ADNeuroMed Europe	http://www.innomed-addneuromed.com/index.cfm?PID=19	Individuals with probable AD, normal elderly controls and those at risk of AD	Cross European	Clinical trials in six European centres. Data co-ordination centres in Stockholm, Montreal and other sites	Clinic-based	Alzheimer's Disease biomarkers suitable for diagnosis, prediction and monitoring disease progression for use in clinical trials and in clinical practice	2006	750	Not specified	yes	yes	yes	yes	yes	unknown	yes
TREND (Tübinger evaluation of Risk factors for Early detection of NeuroDegeneration)	http://www.trend-studie.de/english/	RBD, Hyposmia, or depression	Germany	Tübingen	High risk cohort (RBD, Hyposmia, or Depression)	Prodromal PD (and AD) longitudinal	2009	1200	50-80	yes	yes	yes	yes	yes	yes	yes
ICICLE-PD (Study to Investigate the genetiCs of In situ Carcinoma of the ductaL subtypE)	http://www.ncl.ac.uk/caru/research/project/2909	Patients with newly diagnosed PD and age-matched controls.	UK	Newcastle, Cambridge	Clinic-based longitudinal	High risk. To identify patients the factors that predict PD evolution.	2009	160	not specified	yes	yes	yes	yes	yes	yes	yes

Title of the cohort	Web link	Additional inclusion criteria	Country	City/Centre	Cohort type	Aim	Data collection start date	Size of the cohort	Age at inclusion (mean, range)	Clinical measures	Biomarkers	Cognitive assessment	MRI/ neuroimaging	Genetic DNA analysis possible	Consent for autopsy	Blood sample
ParkWest study (Patients with incident Parkinson's Disease from Western and Southern Norway)	http://www.parkvest.no/?page_id=16	Incident PD	Norway	Four centres	Population	Tracking PD	2004	196	All	yes	yes	yes	yes	yes	yes	yes
Prevention																
FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Dementia)	www.thl.fi/finger	Based on CAIDE phenotype of Elevated Dementia Risk Score (Kivipelto et al, Lancet Neurology 2006) and cognitive performance slightly lower than expected for age	Finland	Study centre is in Stockholm	MCI & high dementia risk score	To study the effect of the multi-domain lifestyle intervention on cognitive impairment and incidence of dementia/AD to understand dementia prevention	Sep-09	1200	60-77	yes	yes	yes	yes	yes	unknown	yes

ANNEX C

Analysis of imaging studies in cohorts relevant to research on ND disease

Table 2 on the following page summarises information gathered by the Action Group on cohort studies that include imaging, to present an overview of the types of study and the imaging information that is available.

Table 2: Analysis to show the imaging measures used in cohort studies relevant to ND research

Study	Sample/N subj with MRI	Serial MRI	Scanner Manufacture and Model	Field Strength	Structural 3D MPRAGE					Diffusion	Rest fMRI	T2*w	T2-w	MT-MRI	Spectroscopy	FLAIR	Other Imaging
					ADNI compatible	*Sequence*	*Voxel size (e.g., 1x1x1 mm^3)*	*TR/TI/TE/*	*Parallel imaging & method*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	Performed	
The Cognitive Funcctions and Ageing Studies (CFAS) (PI Brayne) (Fernando MS et al., 2004)	Elderly (N=33)	No	Siemens	1.0T	No	MPRAGE	nr	6838ms/600ms/60ms	nr	No	No	No	Yes	No	No	No	PD
The Rotterdam Scan Study (PI: Ikram MA) (Ikram MA et al., 2011)	Population	No	General Electric (from 2005)	1.5T	No	T1 –w3D	nr	13.8ms/400ms/2.8ms/nr/nr	nr	Yes	No	Yes	No	No	No	Yes	PD
Parkinson's disease and dementia: a longitudinal study (DEMPARK) (PI: Dodle R) (Balzer-Geldsetzer M et al., 2011)	PD, PD-MCI	Yes	Several	3.0T	No	MPRAGE, IR-SPGR	nr	nr	nr	Yes	Yes	Yes	Yes	No	No	No	PD

Study	Sample/N subj with MRI	Serial MRI	Scanner Manufacture and Model	Field Strength	Structural 3D MPRAGE					Diffusion	Rest fMRI	T2*w	T2-w	MT-MRI	Spectroscopy	FLAIR	Other Imaging
					ADNI compatible	*Sequence*	*Voxel size (e.g., 1x1x1 mm^3)*	*TR/TI/TE/*	*Parallel imaging & method*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	Performed	
The EUROSCA Natural History Study (PI: Klockgether T) (Schulz JB et al., 2010)	Spinocerebellar ataxia (SCA) Ctrl=31 SCA=82	No	Philips, Siemens Sonata Vision, GE	1.5T	No	FFE, MPRAGE, SPGR	1x1x1 mm	**TR:** FFE=6-15, MPRAGE= 1200-1500; SPGR=2200 -3000/**TI**: FFE,MPRAGE,SPGR=450-700/**TE:** FFE,MPRAGE,SPGR=2-7	nr	No	No	No	No	No	No	No	
Cam-CAN study (PI: Tyler LK) http://www.cam-can.org/	Healthy Adults	nr	Siemens Trio	3.0T	No	MPRAGE	nr	nr	nr	Yes	No	No	Yes	No	No	No	PD
Lothian Birth Cohorts of 1921 (PI : Deary I) (Shenkin et al., 2005)	105 volunteers in1921, in 1936 not specified	No	GE Signa LX	1.5 T	No	IR-SPGR	nr	7.3ms/400 ms/3.1ms/	nr	Yes	No	No	Yes	Yes	No	Yes	

Study	Sample/N subj with MRI	Serial MRI	Scanner Manufacture and Model	Field Strength	Structural 3D MPRAGE					Diffusion	Rest fMRI	T2*w	T2-w	MT-MRI	Spectroscopy	FLAIR	Other Imaging
					ADNI compatible	*Sequence*	*Voxel size (e.g., 1x1x1 mm^3)*	*TR/TI/TE/*	*Parallel imaging & method*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	Performed	
Lothian Birth Cohorts of 1936 (PI : Deary I) (Wardkaw et al., 2011)		Yes	GE Signa Horizon HDx	1.5T	No	IR-Prep FSPGR	1x1x1.3 mm/160	10ms/500 ms/4ms	nr	Yes	No	Yes	Yes	Yes	No	Yes	T1-mapping
Pomerania (SHIP) (PI: H. Völzke) (Hegenscheid K et al., 2009)	194 healthy volunteers	No	Siemens Avanto	1.5T	No	MPRAGE	1x1x1 mm	19000ms/nr/34ms	nr	No	No	No	Yes	No	No	Yes	Angiography
3 city study http://www.three-city-study.com/study-schedules.php (Godin O et al., 2008)	1292 participants aged less than 80 years	Yes	Siemens	1.5T	No	3D IR-SPGR	1.0 x0.98x0 .98 mm	97ms/66ms /4ms/	nr	No	No	No	Yes	No	No	No	PD
ADDNEUORMED (PI: Simon Lovestone)(Simmons A et al., 2009) (Spulberg G et al., 2012)	MRI in 130AD, 131 MCI, 117 healthy controls	No	GE, Siemens, Picker	1.5T	Yes	MPRAGE	1.1x1.1x 1.2 mm	nr	nr	No	No	No	Yes	No	Yes	No	PD

Study	Sample/N subj with MRI	Serial MRI	Scanner Manufacture and Model	Field Strength	Structural 3D MPRAGE					Diffusion	Rest fMRI	T2*w	T2-w	MT-MRI	Spectroscopy	FLAIR	Other Imaging
					ADNI compatible	*Sequence*	*Voxel size (e.g., 1x1x1 mm^3)*	*TR/TI/TE/*	*Parallel imaging & method*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	Performed	
Maastricht Aging study (PI: Jolles J) https://mhens.unimaas.nl/div1/maas/ (Tisserand DJ et al., 2004)	nr	Yes	Philips	1.5T	No	MPRAGE	0.94x0.94x0.94 mm	35ms/nr/7 ms	nr	No	No	No	No	No	No	No	
Italian Project on the Epidemiology of Alzheimer's Disease (IPREA) (PI: Scafato E)	420 subjects	No	Siemens Symphony	1.0T	No	MPRAGE	nr	11.4ms/nr/ 4.4ms	nr	No	No	No	Yes	No	No	Yes	PD
The Norwegian ParkWest study (PI JP Larsen; Tysnes O-B) (Apostolova L et al., 2012)	MRI in 182 PD and 108 Healthy controls	No	Phillips Intera, Siemens Symphony	1.5 T/1.0 T	No	MPRAGE	nr	**Phillips Intera TR/TE:** 10.0/4.6 ms; **Phillips Intera TR/TE**: 20.0/4.6ms ,;Siemens Symphony TR/TE: 2130.0/3.9 ms; **1.0 T Philips Intera system**: TR/TE: 25/6.9ms	nr	No	No	No	Yes	No	No	Yes	

Study	Sample/N subj with MRI	Serial MRI	Scanner Manufacture and Model	Field Strength	Structural 3D MPRAGE					Diffusion	Rest fMRI	T2*w	T2-w	MT-MRI	Spectroscopy	FLAIR	Other Imaging
					ADNI compatible	*Sequence*	*Voxel size (e.g., 1x1x1 mm^3)*	*TR/TI/TE/*	*Parallel imaging & method*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	Performed	
PPMI study (http://www.ppmi-info.org/) (PI:K Marek)	241 subjects	Yes	Siemens Trio, Verio	3T	No	MPRAGE	1x1x1mm	2300ms/900ms/2.98ms	GRAPPA	Yes	Yes	No	Yes	No	No	No	PD/SPECT/amyloidPET
MEMENTO (PI Chêne G)	AD	nr	nr	nr	No	MPRAGE	nr	nr	nr	Yes,	Yes	Yes	Yes	No	nr	Yes	
DESCRIPA Study (PI: F.R.J. Verhey) (va de Pol LA et al., 2009)		No	Several	1.0 or 1.5 T	No	MPRAGE	nr	nr	nr	No	No	No	nr	No	No	Yes	
The Vallecas Project - Early detection of Alzheimer's Disease (PI: Dobato-Ayuso JL)	AD and dementia 3T MRI Elaboration of a protocol for image acquisition, analysis and validation of the different acquisition techniques in post-processing laboratory	Yes	GEHC 3T HDXt	3T	No	3D-SPGR	nr	nr/600ms/ Min Full	ASSET, acceleration factor 1	Yes	Yes	Yes	Yes	No	No	Yes	

Study	Sample/N subj with MRI	Serial MRI	Scanner Manufacture and Model	Field Strength	Structural 3D MPRAGE					Diffusion	Rest fMRI	T2*w	T2-w	MT-MRI	Spectroscopy	FLAIR	Other Imaging
					ADNI compatible	*Sequence*	*Voxel size (e.g., 1x1x1 mm^3)*	*TR/TI/TE/*	*Parallel imaging & method*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	Performed	
Cohort - Factors for disease progression in Alzheimer's disease (PI Inga Zerr)		nr	nr	nr	No	MPRAGE	nr	30ms/nr/4, 6ms	nr	Yes	No	Yes	Yes	No	No	Yes	T2-PD TSE
Cohort - Human prion diseases: molecular characteristics (PI Inga Zerr)		nr	nr	nr	No	MPRAGE	nr	30ms/nr/4, 6ms	nr	Yes	No	Yes	Yes	No	No	Yes	T2-PD TSE
AMI cohort (PI: Michèle ALLARD)(Peres K et al., 2012 or NCT00951197)	Elderly Farmer N=318	Yes	Philips Achieva	3T	No	MPRAGE	1x1x1mm	8.2ms/nr/3.5ms	nr	Yes	No	No	No	Yes	No	Yes	
Minho Integrative Neuroscience Database (MIND) database (PI: Sousa N.) (PauloAC et al., 2011)	472 individuals older than 55 years	nr	Siemens Magnetom Avanto	1.5T	No	MPRAGE	1x1x1 mm	2730ms/1000ms/3.48 ms	nr	Yes	Yes	No	Yes	No	No	No	

Study	Sample/N subj with MRI	Serial MRI	Scanner Manufacture and Model	Field Strength	Structural 3D MPRAGE					Diffusion	Rest fMRI	T2*w	T2-w	MT-MRI	Spectroscopy	FLAIR	Other Imaging
					ADNI compatible	*Sequence*	*Voxel size (e.g., 1x1x1 mm^3)*	*TR/TI/TE/*	*Parallel imaging & method*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	Performed	
Prospective study of individuals at risk for spinocerebellar ataxia type 1, type 2, type 3 and type 6 (RISCA) (PI: Klockgether T) (Jacobu H et al., 2012, Abstract)	277 unaffected (non-ataxic) adult at risk individuals	nr	Philips,Siemens Sonata+ Symphony, Siemens Vision,GE	1.5T	No	MPRAGE, SPGR	1x1x1 mm, 160 slices	Philips and Siemens Sonata:TR=15,TE=5; Siemens Vision:TR=11.6, TE=4.9; GE:TR=2500,TI=500, TE=Minimum	nr	No	No	No	Yes	No	No	No	
LANDSCAPE (Langzeitbeobachtung dementieller Symptome und cognitiver Parameter sowie Anwendbarkeit neuer prognostischer Marker bei der Parkinson-Erkrankung) (PI:Dodel R)	nr	Yes	Siemens.Magnetom Trio, Trio Tim, Allegra,Verio/ Philips:Achieva	3T	No	MPRAGE	192 axial slices/1x1x1 mm	2500ms/1100s/4,37ms/	nr	Yes	Yes	Yes	No	No	No	Yes	
High-field MRI for parkinsonian disorders and **Morphometric correlates and predictors of impaired gait and balance in parkinson´s disease (PI: Keppi S)**	92 PD and 30 CTRLS	Yes	Siemens Magnetom Verio syngo MR B17	3T	No	MPRAGE	1.1×0.9×1.2 mm	1800ms/900ms/2,18ms	nr	Yes	Yes	No	No	No	No	No	SWI, T2-PD

Study	Sample/N subj with MRI	Serial MRI	Scanner Manufacture and Model	Field Strength	Structural 3D MPRAGE					Diffusion	Rest fMRI	T2*w	T2-w	MT-MRI	Spectroscopy	FLAIR	Other Imaging
					ADNI compatible	*Sequence*	*Voxel size (e.g., 1x1x1 mm^3)*	*TR/TI/TE/*	*Parallel imaging & method*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	Performed	
Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation – Parkinson's Disease (ICICLE-PD) (PI: Burn D)	300 PD and 100 CTRLS	Yes	Philips Intera Achieva, Siemens Tim Trio	3T	No	MPRAGE	nr	9.6 ms/nr/ 4.6ms	nr	Yes	Yes	No	No	No	No	Yes	FDG-PET
Cognitive Imaging and Genetic Predictor of Behavioural Disturbances in Parkinson's Disease (PI: Antonini A)	nr	nr	Philips Achieva	1.5T	No	MPRAGE	0.868x0. 868 mm	8.3ms/981. 1ms/4.1	nr	Yes	Yes	Yes	Yes	No	No	Yes	FLAIR 3D/9. DWI_H R
Oxford Parkinson's Disease Centre Cohort (PI: Wade-Martin R)	40 PD patients, 20 controls and 10-at-risk subjects	No	Siemens Trio	3T	No	MPRAGE	1x1x1 mm	2040ms/90 0ms/4.7ms	nr	Yes	Yes	Yes	Yes	No	No	No	
Disrupted neural networks in Parkinson's disease (PI: Berendse H)	nr	Yes	GE Signa	3T	No	T1 FSPGR	nr	min(7,8)/mi n full/	nr	Yes	Yes	No	No	No	No	Yes	T2-PD, SWI
FINGER-study (Finnish Geriatric Intervention Study to Prevent Cognitive Decline) (Kivipelto M)	150 subjects	Yes	Siemens Avanto	1.5T	No	MPRAGE	nr	2400ms/nr /3.5ms	nr	Yes	No	No	Yes	No	No	Yes	PD
Heinz Nixdorf Recall Studie (Jöckel K-H) (Ladd SC et al., 2007)	160 Coronary Heart Disease	No	Siemens Sonata	1.5T	No	MPRAGE	nr	40ms/nr/7, 2ms	nr	Yes	No	No	Yes	No	No	Yes	

Study	Sample/N subj with MRI	Serial MRI	Scanner Manufacture and Model	Field Strength	Structural 3D MPRAGE					Diffusion	Rest fMRI	T2*w	T2-w	MT-MRI	Spectroscopy	FLAIR	Other Imaging
					ADNI compatible	*Sequence*	*Voxel size (e.g., 1x1x1 mm^3)*	*TR/TI/TE/*	*Parallel imaging & method*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	Performed	
Aberdeen Birth Cohort of 1921 –and Aberdeen Birth Cohort of 1936 (PI: Whalley LJ) (Murray AD et al., 2012**)**	100 subjects from Aberdeen Birth Cohort of 1921 and 223 subjects from Aberdeen Birth Cohort of 1936	Yes	General Electric	1.0T and 1.5T	No	nr	nr	nr	nr	No	Yes	No	Yes	No	No	Yes	
Parelsnoer-Neurodegenerative disease Cohort (PIs: Verhey F and de Flier WM)	800 patients	nr	nr	1.5 and 3T	No	MPRAGE	nr	TR and TE according to local protocol	nr	Yes	Yes	Yes	Yes	No	No	Yes	
Amsterdam Dementia Cohort (PIs: Scheltens P and de Flier WM	3000 patinets	nr	nr	1.5 and 3T	No	MPRAGE	nr	TR and TE according to local protocol	nr	Yes	Yes	Yes	Yes	No	No	Yes	

Study	Sample/N subj with MRI	Serial MRI	Scanner Manufacture and Model	Field Strength	Structural 3D MPRAGE					Diffusion	Rest fMRI	T2*w	T2-w	MT-MRI	Spectroscopy	FLAIR	Other Imaging
					ADNI compatible	*Sequence*	*Voxel size (e.g., 1x1x1 mm^3)*	*TR/TI/TE/*	*Parallel imaging & method*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	*Performed*	Performed	
Israel Diabetes and Cognitive Decline Study (IDCD; PI, Michal Beeri)	1200/35	nr	GE Scanner SIGNA ,CRM 55cm Bore, most updated version 16 Vo2 SP1	3T	nr	3D BRAVO FSPGR	nr	nr	nr	Yes	Yes	Yes	Yes	No	No	Yes	
Israel Registry for Alzheimer's Prevention (IRAP; Michal Beeri)	330/60	Nr	GE Scanner SIGNA ,CRM 55cm Bore, most updated version 16 Vo2 SP1	3T	nr	3D BRAVO FSPGR	nr	nr	nr	Yes	Yes	Yes	Yes	No	No	Yes	

ANNEX D

Cohort reference list

Table 3 on the following page provides references to the 171 European cohorts that were used or discussed in the report.

Table 3: European cohorts discussed in the report of the JPND action group.

Title of Cohort	Country	Aim	Website
20-07 The West of Scotland Twenty 07 Study	UK	The Twenty-07 Study was set up in 1986 in order to investigate the reasons for differences in health by socio-economic circumstances, gender, area of residence, age, ethnic group, and family type. After 20 years , can examine the effect of people's circumstances on their health across 60 years of the life span; compare the experiences of different generations of people at the same points in history; explore the health of people of the same age at different points in time.	http://www.sphsu.mrc.ac.uk/research-programmes/ss/sineq/20-07.html
3C Study Three-City study	France	To study the risk of dementia attributable to vascular factors in persons aged 65 and over; The main outcomes are dementia (Alzheimer's disease and other types of dementia), vascular diseases (coronary heart disease and stroke), and mortality. Specific objectives: To assess the associations of vascular diseases (CHD and stroke) with dementia and cognitive impairment; To quantify the associations between cerebral white matter hyperintensities and dementia; To quantify the associations of dementia with factors that increase or decrease the risk of vascular diseases; To quantify the associations of cerebral measures (white matter hyperintensities and atrophy) with factors that increase or decrease the risk of vascular diseases.	http://www.three-city-study.com/
Aberdeen Birth Cohorts of 1921 and 1936	UK	The Aberdeen Birth Cohort study 1936 was established to follow-up a cohort of individuals who took the Scottish Mental Survey test on 4th June 1947. The study allows researchers to track the effects of ageing, and to compare intelligence in childhood and later life, looking at how the brain ages and the factors that affect this. Also under study are the Aberdeen Birth Cohort 1921 who sat the test of mental ability on 1st June 1932.	http://www.abdn.ac.uk/aberdeen-birth-cohort/
Aberdeen Children of the Nineteen Fifties	UK	The 'Children of the 1950s' cohort study is designed to investigate influences in early life – biological and social circumstances – on health in later life.	http://www.abdn.ac.uk/childrenofthe1950s/
ADNeuroMed	Europe	Alzheimer's Disease biomarkers suitable for diagnosis, prediction and monitoring disease progression for use in clinical trials and in clinical practice.	http://www.innomed-addneuromed.com/index.cfm?PID=19
AgeCoDe Cohort	Germany	To determine the incidence and rate of progression of degenerative dementia in the elderly (>85). To determine risk factors and predictors of dementia in the elderly.	http://www.knd-demenzen.de/die-verbuende/verbund-epidemiologie/projektbeschreibung.html

Title of Cohort	Country	Aim	Website
Ageing in Leganes (Envejecer en Leganes)	Spain	Initially designed to assess social support, health and function of Spanish home-dwelling elderly people but at a follow up included dementia and cognitive impairment.	No website available at present.
AGES Age, Gene, Environment Susceptibility	Iceland	To study all body systems to study healthy aging.	http://www.hjartarannsokn.is/index.aspx?GroupId=406
ALPHA: Ageing in Liverpool Project-Health Aspects. (Part of CFAS)	UK	To estimate the age- and sex-specific incidence of dementia by subtype in those aged 65 and over living in the community. To elucidate the natural history and course of dementia and explore the relationship between clinical, psychological, brain imaging and neuropathological measures.	http://www.cfas.ac.uk/pages/bldata/index.html
ALSPAC - other family members	UK	To understand how health, well-being and disease are passed through families.	http://www.bristol.ac.uk/alspac/researchers/resources-available/coco90s/
ALSPAC Children of the 90s	UK	Originally to understand the modifiable influences on childhood health and development, it expanded to provide a trans-generational prospective observational study investigating influences on health and development across the life course. It considers multiple genetic, epigenetic, biological, psychological, social and other environmental exposures in relation to a similarly diverse range of health, social and developmental outcomes.	http://www.bris.ac.uk/alspac/
ALSPAC mothers. The Avon Longitudinal Study of Parents and Children	UK	To determine ways in which genotype and environmental characteristics influence health and development in both children and parents.	http://www.bris.ac.uk/alspac
AMI Cohort - Integrated multidisciplinary approach	France	To analyse occurrence of Alzheimer disease in a rural aged population and compare it with the urban population. The main goal is to know if a routine pesticide use is a risk factor for Alzheimer disease.	http://www.isped.u-bordeaux2.fr/FR_HTM_equipe_activites_details.aspx?CLE_EQU=3
AMSTEL Amsterdam Study of the Elderly	Netherlands	Investigate incidence, prevalence and determinants of common mental disorders and their prognosis among older persons.	No website available at present.

Title of Cohort	Country	Aim	Website
Amsterdam Dementia Cohort	Netherlands	3 main research lines: (1) develop new markers (blood, CSF, imaging) for early diagnosis, (2) understand (endo)phenotypical heterogeneity, (3) understand the interaction between neurodegenerative disease and vascular disease.	www.neurosciencecampus-amsterdam.nl
ANCOG The Antwerp Cognition Study	Belgium	To analyse the prevalence and incidence of dementia in an aged population of community-dwelling elderly, living in socio-economically differing districts of Antwerp, Belgium, taking into account possible differences in gender and education level.	No website available at present.
Aragon Workers Health Study	Spain	To evaluate the trajectories of traditional and emergent CVD risk factors and their association with the prevalence and progression of subclinical atherosclerosis in a population of middle-aged men and women in Spain.	http://www.iacs.aragon.es/awgc/inicio.inicio.do
Austrian Stroke Prevention Study	Austria	To monitor the progression of CNS white matter lesions in community-dwelling volunteers aged 50-75 years without neuropsychiatric disease.	No website available at present.
BASEI and BASEII Berlin Ageing Studies	Germany	Base1 provided and examination of aging- and death-related changes in very old age. BaseII aims to identify and characterize the factors associated with "healthy" versus "unhealthy" aging. Both are multi-disciplinary studies.	http://www.base-berlin.mpg.de/Home.html
BCS70 1970 British Cohort Study	UK	Initially designed to examine the social & biological characteristics of mothers in relation to neonatal morbidity & to compare with 1958 cohort. Then broadened like BCS58.	http://www.cls.ioe.ac.uk/page.aspx?&sitesectionid=795&sitesectiontitle=Welcome+to+the+1970+British+Cohort+Study+(BCS70)
Belgian Ageing Studies Project (BAS)	Belgium	Collected information from 64,000 participants aged 60 and over, living at home. Aimed to measure the quality of life of older people in Belgian municipalities, and conducted follow up studies to examine trends across municipalities, and to determine the impact of policy measures.	http://www.belgianageingstudies.be/
Biohealth Norway	Norway	To improve prevention and treatment of disease by increased knowledge of the molecular nature of disease, based on discoveries of new genes and interaction between genes and environmental factors.	http://www.fhi.no/eway/default.aspx?pid=240&trg=List_6673&Main_6664=6894:0:25,7685:1:0:0:::0:0&MainContent_6894=6671:0:25,7764:1:0:0:::0:0&List_6673=6674:0:25,7776:1:0:0:::0:0

Title of Cohort	Country	Aim	Website
Born in Bradford	UK	To explore the determinants of childhood and adult disease in an ethnically diverse population with high levels of ill-health. Offers the potential to: • assess the determinants of childhood and adult disease • assess the impact of migration • explore the influences of pregnancy and childbirth on subsequent health • generate and test hypotheses that have the potential to improve health for some of the most disadvantaged within our society.	http://www.borninbradford.nhs.uk/
Boyd Orr Cohort	UK	To investigate the long-term impact of environmental factors in early life on adult chronic disease and function.	http://www.bris.ac.uk/social-community-medicine/projects/boyd-orr/
Brains for Dementia Research	UK	Brains for Dementia Research is an initiative funded jointly by the Alzheimer's Society and the Alzheimer's Research UK to address the shortage of brain tissue from individuals that have been assessed regularly during life that is so essential for research into dementia.	http://brainsfordementiaresearch.co.uk/
BRHS British Regional Heart Study	UK	The British Regional Heart Study (BRHS) is a prospective study in middle-aged men drawn from general practices in 24 British towns, set up to determine the factors responsible for the considerable variation in coronary heart disease, hypertension and stroke in Great Britain. It also seeks to determine the causes of these conditions in order to provide a rational basis for recommendations towards their prevention.	http://www.ucl.ac.uk/pcph/research-groups-themes/brhs-pub/study-design
BWHHS British Women's Heart and Health Study	UK	The Study aims to provide information about existing patterns of treatment of heart disease among women aged 60-79 at baseline, and further the understanding of risk factors and disease prevention	http://www.lshtm.ac.uk/eph/ncde/research/bwhhs/
CAIDE - Cardiovascular risk factors in ageing and dementia	Sweden	To investigate cardiovascular and life style risk factors for dementia / Alzheimer's disease.	http://www.uef.fi/caide/home
CAM_CAN	UK	A main aim of the CamCAN project is to identify the cognitive and neural basis of both risk factors for cognitive decline and intervention potentials based on abilities that are preserved by neural flexibility. The current CamCAN cohort provides the basis for examining longitudinal trends in both healthy ageing and the precursors to cognitive decline. Findings will help specify normal age-related deficits and how normal ageing differs from pathological aging in conditions such as Alzheimer's Disease.	http://www.cam-can.org/

Title of Cohort	Country	Aim	Website
CaPS Caerphilly Prospective Cohort Study	UK	To examine the importance of lipids, haemostatic factors, and hormones such as testosterone, cortisol and insulin in the development of ischaemic heart disease, cognitive function and other age-related phenotypes.	http://www.bris.ac.uk/social-community-medicine/projects/caerphilly/about/
CFAS Cognitive function and ageing studies	UK	The initial aim was to investigate dementia and cognitive decline in a representative sample of more than 18,000 people aged over 65 years. The range of information collected has also allowed the study to investigate depression and physical disability in the older population and also look at healthy active life expectancy. CFAS II started in 2008, and builds on the design and infrastructure of CFAS I. It will provide data on generational and geographical differences including people in institutions. This study will provide the opportunity to investigate the implications of changes in morbidity and frailty on health itself, as well as the use of services and expenditure in health and social care.	http://www.cfas.ac.uk
CFAS Wales Cohort - Maintaining function and well-being in later life	UK	To identify biopsychosocial influences on the development of cognitive impairment and the maintenance of well-being in later life in Wales. The study complements CFAS I e.g. aims to look at generational changes by comparing CFASI and CFASII and exploring the impact of policy changes that have taken place in Wales.	http://cfaswales.bangor.ac.uk/
COAST China Cognition and Aging Study	China	No information available at present.	No website available at present.
Cognitive Complaints Cohort - Longitudinal Neuropsychological Assessment	Portugal	To predict the stability or evolution to dementia of subjects with cognitive complaints based on a comprehensive neuropsychological evaluation	http://www.imm.fm.ul.pt/web/imm/neurologicalclinicalresearch
Cohort - 95+	Sweden	To study dementia, other mental disorders (depression, psychotic disorders, and anxiety disorders), suicidal behaviour, and cognitive function in the very old in longitudinally followed 95 year-olds.	www.epinep.gu.se
Cohort - ALS	Finland	Genetic analysis of Finnish ALS	http://www.biomedicum.com/index.php?page=279&lang=2

Title of Cohort	Country	Aim	Website
Cohort - Diagnosis and treatment of dementia patients	Poland	Research on clinical, genetic and proteomic markers of neurodegenerative disorders in early stage of the disease	http://www.imdik.pan.pl/en/research-groups/departments/121-department-of-neurodegenerative-disorders
Cohort - Factors for disease progression in Alzheimer's disease	Germany	To determine the rate of progression into AD.	http://www.knd-demenzen.de/die-verbuende/verbund-rpad/projektbeschreibung.html
Cohort - H70	Sweden	To study dementia and other mental disorders (depression, psychotic disorders, anxiety disorders) in longitudinally followed elderly populations from different birth cohorts. Original aims were : i) to contribute to the knowledge of normal ageing processes and of normal conditions within the age group; ii) to make a survey of the social and medical conditions of the population ; iii) to obtain basic data for planning the care of the elder; iv)to offer the subjects a thorough medical examination.	http://www.neurophys.gu.se/english/departments/psychiatry_and_neurochemistry/Neuropsychiatric_Epidemiology/
Cohort - Human prion diseases: molecular characteristics	Germany	To analyse molecular determinants of the disease.	http://www.cjd-goettingen.de/Projekte-e.html
Cohort - The Kungsholmen project	Sweden	The aim is to detect occurrence and determinants of dementia and Alzheimer Disease. Took lifetime perspective so can consider critical periods: birth; childhood (0-19); adult (20-59); transitional (60-74); old age (75+). Often take overall dementia as outcome in belief that detection of any risk factor can be used to decrease or delay dementia and that in the very old many mechanisms play a simultaneous role in causing dementia syndrome. Interest in 1ry, 2ry(shorter duration) & 3ry (red. complication) prevention.	http://www.kungsholmenproject.se/
Cohort -H85	Sweden	To study dementia and other mental disorders (depression, psychotic disorders, anxiety disorders) in longitudinally followed elderly populations from different birth cohorts.	www.epinep.gu.se
CONOR Cohort of Norway	Norway	To create a unique database with health data and biological samples of about 200 000 individuals. The purpose of CONOR is investigating the aetiology of rare diseases by testing environmental, inheritable, cultural & social factors. Suitable for gene-environment interactions. CONOR brings together 10 Norwegian studies.	http://www.fhi.no/eway/default.aspx?pid=240&trg=Main_6664&Main_6664=6898:0:25,7785:1:0:0:::0:0

Title of Cohort	Country	Aim	Website
CONSTANCES Cohorte de consultants des centres d'examens de sante	France	To provide a platform wide open to the research community and public health, to contribute to the development of epidemiological research and to provide information referred to public health. Themes include conditions of work, social determinants of health, women's health, ageing.	http://www.constances.fr/fr/
DEMPARK cohort	Germany	To investigate the development of and risk factors of dementia in patients with Parkinson's disease and Lewy body dementia. early diagnostic biomarkers and predictors for dementia in PD.	http://www.therapieforschung-neurologie.eu/html/de/forschung/versorgungsforschung_laufende_studien_dempark.html
DESCRIPA I	11 countries	To develop screening guidelines and clinical criteria for AD in people who do not have dementia.	http://www.descripa.eu/
DISCAPARAGON Aged 50 and over, residents in Zaragoza province	Spain	To explore the distribution of disability and its major determinants and provide a bases for the development of disability-related services.	No website available at present.
Doetinchem Cohort Study	Netherlands	To provide insight into health changes and its determinants during ageing.	http://www.rivm.nl/Onderwerpen/Onderwerpen/D/Doetinchem_Cohort_Studie
e-catalyst & The Caerphilly Health and Social Needs study	UK	To inform & support collaborative multi-agency working to reduce inequalities in health. To achieve detailed spatial understanding of relations between social, environmental & economic deprivation & health in Caerphilly county borough; inform the development of local community strategies for health improvement & reduction of health inequalities.	http://medicine.cf.ac.uk/primary-care-public-health/research/healthy-places/current-projects/caerphilly-health-social-needs-study/
EHDN - European Huntingdon's Disease Network/ European Huntington's Disease Registry	European Wide	Provides the infrastructure for European-wide large scale clinical trials on Huntingdon's disease.	http://www.euro-hd.net/html/network

Title of Cohort	Country	Aim	Website
ELSA English Longitudinal Study of Ageing	UK	The primary objective is to collect longitudinal multidisciplinary data from a representative sample of the English population aged 50 and older. The study includes objective and subjective data relating to health and disability, biological markers of disease, economic circumstance, social participation, networks and well-being.	www.ifs.org.uk/elsa
ENCALS - European Network for the Cure of ALS	European Wide	To develop a European ALS trial network and database/biobank.	http://www.encals.eu/
Erasmus Rucphen Study	Netherlands	A family-based cohort study embedded in the Genetic Research in Isolated Populations (GRIP) programme. The aim was to identify genetic risk factors in the development of complex disorders.	http://www.gefos.org/?q=content/erasmus-rucphen-family-study-2
ERGO-onderzoek Cohort - Rotterdam study	Netherlands	To investigate causes and determinants of chronic (incl. neurologic) disease in the elderly. Emphasis on molecular and genetic analyses. Focuses on frequency, etiology & early recognition of most frequent neurologic diseases in the elderly.	http://www.ergo-onderzoek.nl/wp/
EURALS - European ALS Consortium	Europe	A consortium of population based registries and clinic-based cohorts. Aims to identify risk factors for ALS and to understand ALS heterogeneity.	No website available at present.
EurHEALTHAgeing project	Europe	The aim is to identify OMICs (genomics, metabolomics and proteomics) and other markers that can predict healthy or unhealthy ageing at early life stages when lifestyle and therapy might be more effective.	www.eurhealth.org
European Health Examination Survey	Luxembourg	To study public health determinants.	http://www.ehes.info/
European Male Ageing Study	8 countries	Aims: i) to document geographical variations in ageing-related involution decline in endocrine function in European men ii) to explain variability in rate of secular decline in endocrine functions on basis of sociodemographic lifestyle, comorbid, ethnic racial or genetic factors iii) to predict physical and psychological health status of individuals based on variation in ageing-related endocrine decline and changes in body composition.	http://www.emas.man.ac.uk/main.asp

Title of Cohort	Country	Aim	Website
European Prospective Investigation into Cancer and Nutrition (EPIC)	10 countries	To investigate the relationships between diet, nutritional status, lifestyle and environmental factors and the incidence of cancer and other chronic diseases in 10 European countries.	http://epic.iarc.fr/
EUROSCA-NHS European Spinocerebellar Ataxia Natural History Study	Germany	The key goal is to determine and compare the rate of disease progression in SCA1, SCA2, SCA3 and SCA6. Secondary aims include determination of the order and occurrence of non-ataxia symptoms, assessment of health-related quality of life, and identification of predictors of disease progression and survival.	http://www.ataxia-study-group.net/html/studies/eurosca
FINE. Finland, Italy, the Netherlands, Elderly	Finland, Italy, Netherlands	The Seven Countries Study was designed to study risk factors for cardiovascular disease. The expanded FINE study added cognitive measures, self-reported health, depression and functioning	No website available at present.
FINGER study (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Dementia)	Finland	To study the effect of the multi-domain lifestyle intervention on cognitive impairment and incidence of dementia/AD to understand dementia prevention	www.thl.fi/finger
Finnish Twin Cohort Study	Finland	A cohort of 12,966 monozygotic and dizygotic twin pairs (25,932 individuals) where both twins are still alive and willing to take part in studies. Twins were ascertained from the general population register across three stages in 1974 (older like-sexed pairs born before 1958), 1987 (born 1968-1987), and 1995 (opposite-sex pairs 1938-1957). Individuals have been studied in a longitudinal manner through follow up studies, with DNA collection routine since the mid-90s.	www.twinstudy.helsinki.fi
FTLD - Frontotemporale Lobardegeneration	Germany	To develop and evaluate parameters which will help clinicians to diagnose FTLD at an early stage and follow its progression, with the overall aim of eventually developing effective objective targets for therapeutic strategies.	http://www.ftld.de

Title of Cohort	Country	Aim	Website
GAP (Gipuzkoa Alzheimer Project)	Spain	To investigate the impact of physical exercise and diet on AD.	No website available at present.
GAZEL	France	A sample of employers in the electricity and gas industries to provide an open epidemiological laboratory to facilitate epidemiological research on various diseases and multiple health-related factors.	www.gaze l.inserm.fr/
Generation R study	Netherlands	To identify early environmental and genetic causes and causal pathways leading to normal and abnormal growth, development and health during fetal life, childhood and adulthood. Six areas of research: maternal health; growth; physical development; behavioural & cognitive development; respiratory health & allergies; disease in childhood; health & healthcare for children & parents.	http://www.generationr.nl/
Generation Scotland Family Health Study	Scotland	A large, intensively phenotyped study of individuals and their first degree relatives with which to study the genetic basis of common complex diseases and response to treatments.	http://www.generationscotland.org/index.php?option=com_content&view=article&id=14&Itemid=14
GenFi - The Genetic Frontotemporal Dementia Initiative	UK	Investigating brain imaging changes, performances in cognitive tests and blood and spinal fluid markers in a cohort with abnormalities in genes associated with frontotemporal dementia. Cohort is a mixture of affected and at risk individuals.	http://www.ucl.ac.uk/drc/research/current-studies/genfi
German National Cohort	Germany	To develop a large prospective cohort to be used as a common, national resource for studies on the risk factors and etiologic mechanisms of major disease in the German population. Four general objectives: Identification of etiological pathways from life-style and environmental risk factors to major chronic diseases and functional impairments; Studies of the geographic and socio-economic disparities in health status and disease risks in Germany and possible causes and explanations; Development of risk prediction models for identifying individuals at increased risk of developing major chronic diseases, so as to allow personalized prevention strategies; Evaluation of markers for early detection of disease and pre-disease phenotypes, so as to develop effective tools for disease prevention.	http://www.nationale-kohorte.de/index_en.html
GOAL Good ageing in Lahti Region	Finland	Community diagnoses to be used as tools in municipal health policy-making Needs' assessment to guide community-based health promotion interventions. Evaluation of the interventions.	http://www.palmenia.helsinki.fi/ikihyva/InEnglish.html

Title of Cohort	Country	Aim	Website
Gospel Oak	UK	Study based in one neighbourhood of London which looked at prevalence and incidence of dementia and depression and various risk factors for these.	No website available at present. Project closed.
GS=SFHS Scottish Family Health Study	UK	Family based population genetic study	http://generationscotland.org
H2000 Cohort Health 2000	Finland	Provide an up-to-date comprehensive picture of health and functional ability in the working-aged and aged population by studying the prevalence and determinants of most important health problems and associated need for care, rehabilitation and help.	http://www.terveys2000.fi/background_001.html
HALCyon - Healthy Aging Across the Life Course	UK	Programme bringing together nine UK cohort studies (Lothian 1921, Herts 1920-39, Boyd Orr 1923-37, Aberdeen 1936, NSHD 1946, NCDS 1946, ELSA, and Caerphilly) to understand healthy ageing. Investigates physical and cognitive capability, psychological and social wellbeing, and the underlying biology of ageing (cortisol, telomere lengths, and genetics).	http://www.halcyon.ac.uk
Health Survey for England (HSE)	UK	To monitor the health of the public in England; Especially to monitor progress to health targets set by Government.	http://www.ucl.ac.uk/hssrg/studies/hse
Healthy Ageing in Europe (HALE)	11 countries	To discover biological determinants of healthy ageing - European cohorts of 7 countries study, socio-demographic and lifestyle determinants from FINE and SENECA. Special interest in nutrition.	No website available at present. Project closed.
Heinz-Nixdorf Recall Study	Germany	A population-based prospective cohort study for risk prediction for major cardiovascular events above and beyond traditional cardiovascular risk factors.	http://www.uk-essen.de/recall-studie/?L=1
Hellenic Longitudinal Investigation of Aging and Diet (HELIAD)	Greece	A prospective population study focusing on cognition dementia and other aspects of geriatric comorbidity and function including nutrition and lifestyle factors.	Website in preparation

Title of Cohort	Country	Aim	Website
Hertfordshire Ageing Study (HAS) and other cohorts	UK	To discover as much as possible about how a person's inbuilt makeup (genome), and the environment they experienced during early life (in the womb and first few years of childhood), affect their health and ageing in later life.	http://www.mrc.soton.ac.uk/herts/index.asp
HUNT studies The Nord-Trøndelag health study	Norway	The Nord-Trøndelag health study (HUNT) is one of the largest health studies ever performed - there are three studies so far each of which also has a component concerning offspring. It is a unique database of personal and family medical histories. The database has information about approximately 120,000 people that integrates family data and individual data and can be linked to national health registries.	http://www.ntnu.edu/hunt
ICICLE-PD (Study to Investigate the genetics of In situ Carcinoma of the ductal subtype)	UK	A PD sub-study of the ICICLE study. The study aims to accurately characterise two independent cohorts of incident parkinsonism in Newcastle-Gateshead and Cambridgeshire. A key objective is to identify patients who develop PDD and the factors that predict its evolution. From this information, the aim is to establish a simplified panel of tests that can be used to predict PDD.	http://www.ncl.ac.uk/caru/research/project/2909
IDCD (The Israel Diabetes and Cognitive Decline Study)	Israel	A large scale longitudinal study of 1200 initially non-demented diabetic elderly who are examined for cognition, genetics, inflammation, and life style.	http://neuroscience-web.tau.ac.il/en/?post_type=portfolio&p=1185
ILSA Italian longitudinal study on ageing	Italy	To investigate frequency, risk and protective factors of major age-associated conditions, and to study physical and functional changes among an Italian elderly cohort. The chronic diseases investigated were cardiovascular diseases (hypertension, myocardial infarction, angina pectoris, cardiac arrhythmia, congestive heart failure), diabetes, peripheral artery disease, stroke, dementia, parkinsonism, and distal symmetric neuropathy.	www.iss.it
ILSE Inter-disciplinary longitudinal study of adult development	Germany	To provide a resource for prospective analyses linking successive Censuses or Censuses and vital events.	http://www.psychologie.uni-heidelberg.de/ae/apa/research/ilse.html

Title of Cohort	Country	Aim	Website
IPREA Italian Project on Epidemiology of Alzheimer's disease	Italy	To study the preclinical phase of dementia, including AD, in Italy. The IPREA consists of a cross-sectional phase, to study the prevalence of, and factors associated with the preclinical phase of dementia, and a longitudinal phase, to evaluate the incidence and transition to dementia, also assessing the predictive value of biological markers and neuropsychological tests.	www.iss.it
IRAP (Israel Registry for Alzheimer's Prevention)	Israel	A large scale longitudinal study of 330 offspring of Alzheimer's disease patients who are examined for cognition, genetics, inflammation, life style, structural and functional MRI, and LPs for Abeta 40-42, total tau and P tau.	http://neuroscience-web.tau.ac.il/en/?post_type=portfolio&p=1185
KNDD-LANDSCAPE	Germany	To investigate the development of and risk factors of dementia in patients with Parkinson's disease and Lewy body dementia.	http://www.therapieforschung-neurologie.eu
KORA-Age and KORA-Age II . Cohort - Cooperative Health Research in the Augsburg Region	Germany	The focus of the KORA Studies is the survey of the development and course of chronic diseases, and in particular of myocardial infarction and diabetes mellitus. Risk factors are being analysed with regard to individual health behaviour (as e.g. smoking, diet, or exercise), to the environment (e.g. air pollution, environmental noise) and to genetics. For the purpose of health services research issues as to utilization and costs of health care are looked into.	http://www.helmholtz-muenchen.de/en/kora-en/kora-homepage/index.html
LASA Longitudinal Ageing study Amsterdam; collection cohorts	Netherlands	To study the determinants, trajectories and consequences of physical, cognitive, emotional and social functioning in relation to ageing. Which predictors of change can be recognized in these components of functioning? How are changes in the four components of functioning interrelated? What are the consequences of changes in functioning in terms of contributions to society, the necessity of adjustment, and the need for care?	http://www.lasa-vu.nl
LeARN In vivo molecular diagnostics in Alzheimer's. WP4	Netherlands	To validate and assess the clinical and economic added value of existing and new diagnostic tests for Alzheimer's disease. Work package 4 (WP4) aims to make an earlier and more reliable diagnosis of AD during life and to create the conditions for an effective evaluation of novel medication therapies of AD patients.	www.alzheimercentrumlimburg.nl
Life Study. 2014 birth cohort	UK	To answer a set of specific research questions based around the following broad themes: Social inequality and the parental life course; Parental employment and the economic security of families; Maternal and paternal health and wellbeing; Child health, development and educational trajectories; Childhood neuropsychiatric, developmental and neurological disorders; Growth in infancy, childhood obesity, nutrition and physical activity; Environment and health.	http://www.lifestudy.ac.uk

Title of Cohort	Country	Aim	Website
LifeLines Cohort Study	Netherlands	To unravel the interaction between genetic and environmental factors in the development of multifactorial diseases, their concurrent development in individuals and their complications as a complex trait.	http://www.lifelines.nl
Lolipop (London Life Sciences Population) Study	UK	To record baseline characteristics for Indian Asian men and women who are currently free from clinically manifest cardiovascular disease.	http://www.clininf.eu/projects/lolipop-study.html
Longitudinal Study of Young People in England (LSYPE)	England	The Longitudinal Study of Young People in England (LSYPE) follows the lives of around 16,000 people born in 1989-90. The study began in 2004, when the cohort members were aged 13-14, and has collected information about their education and employment, economic circumstances, family life, physical and emotional heath and wellbeing, social participation and attitudes.	http://www.cls.ioe.ac.uk/page.aspx?&sitesectionid=1246&sitesectiontitle=Welcome+to+the+Longitudinal+Study+of+Young+People+in+England+
Lothian Birth Cohorts (1921 and 1936)	UK	To advance research into how ageing affects cognition, and how mental ability in youth affects health and longevity. The studies described here were initially set up to study determinants of non-pathological cognitive ageing; i.e. the ageing of cognitive functions largely in the normal range, and not principally dementia or other pathological cognitive disorders.	http://www.lothianbirthcohort.ed.ac.uk/
LS Longitudinal study	UK	The LS was planned in the late 1960s at a time of considerable concern about the adequacy of mortality data collected from death registrations, and about the lack of data on fertility patterns. It links administrative data on births, marriages, deaths and migration to Census information. For example, it enables analyses of fertility and mortality (including cause of death) by socioeconomic status, and analysis of family formation.	http://www.ucl.ac.uk/celsius
LUCAS Longitudinal Urban Cohort Ageing Study	Germany	To describe and document certain aspects of the ageing process, e.g. the transitions from robust to frail or disabled health status. To find determinants of healthy ageing based both on self-reported health information and preclinical and clinical markers obtained through medical examinations and comprehensive geriatric assessments (CGA) in subsets of the cohort selected according to self-reported functional status. To measure the long-term effects of a health promotion intervention that showed favourable results at 1-year follow up.	http://www.albertinen.de/krankenhaeuser/geriatrische_klinik/leistungsspektrum/lucas/teilprojekt1_

Title of Cohort	Country	Aim	Website
Luxembourg Cohort	Luxembourg	No fixed aims given at time of preparing this spreadsheet but aims to be a broad vehicle for study of health and wellbeing in Luxembourg.	www.crp-sante.lu
MAAS Maastricht Aging Study	Netherlands	To study the determinants of adult cognitive development - to explore the characteristics of people who age successfully, the age-related cognitive changes seen in usual aging, and finally, the determinants of pathological aging, such as dementia.	https://mhens.unimaas.nl/div1/maas/
MCS Millennium Cohort Study	UK	A multi-disciplinary research project following the lives of around 19,000 children born in the UK in 2000-01 with additional data on siblings and parents. MCS's field of enquiry covers such diverse topics as parenting; childcare; school choice; child behaviour and cognitive development; child and parental health; parents' employment and education; income and poverty; housing, neighbourhood and residential mobility; and social capital and ethnicity.	http://www.cls.ioe.ac.uk/page.aspx?&sitesectionid=851&sitesectiontitle=Welcome+to+the+Millennium+Cohort+Study
Melton Mowbray	UK	To understand the nature of healthy ageing in a community population. A series of cross sectional studies carried out in 1981, 1985 and 1988 have been linked to the on-going health assessments of older people carried out in general practice.	No website available at present.
MEMENTO Cohort - DeterMinants and Evolution of Alzheimer's disease and related disorders	France	The principal objective is to study the evolution of early symptoms (complaints or cognitive deficits, behavioural problems) as well as the prognostic value of different markers (biological, genetic, neuropsychological, psychopathological, vascular, sociodemographic and neuro-imagery) in the progression of the illness from the first signs of clinical dementia through deterioration to severe cognitive disability and on to death.	http://www.chu-bordeaux.fr/chub/media/les-infos-a-la-une-2011/maladie-d-alzheimer-au-chu-de-bordeaux/la-cohorte-memento-le-centre-hospitalier-universitaire-de-bordeaux-promoteur-de-la-cohorte-nationale-alzheimer/
Memo_Vie	Luxembourg	To provide national prevalence of subjects suffering from MCI and from AD as well as to identify the "environmental" conditions and biological factors in association with the occurrence of MCI and their evolution to AD.	www.crp-sante.lu

Title of Cohort	Country	Aim	Website
Men in Gothenburg "50-year olds in Gothenburg" samples - 5 cohorts. From 2003 include women.	Sweden	To investigate coronary risk factors and the development of coronary disease in a group of Swedish urban men in the same age: 50 years	http://snd.gu.se/en/
Metropolit	Denmark	To study the association between social and biological risk factors and health in a life course perspective.	http://publichealth.ku.dk/about/departments/social/research/cohorts/metropolit/
Midspan family studies (3 cohort studies: Main and Tiree, Renfrew and Paisley, Collaborative Study all started 1964-76. The Family Study started 1993 comprising offspring of Renfrew and Paisley)	UK	Main and Tiree an occupational cohort to measure cardiorespiratory health in the population at a time when TB was in decline. The other two were general population but also seem to focus on cardiorespiratory. With the Family Study the availability for study of large numbers of adult offspring, provide major continuing opportunities to study inter-generational trends and the familial aggregation of risk and disease.	http://www.gla.ac.uk/researchinstitutes/healthwellbeing/research/publichealth/midspan/thestudies/thefamilystudy/
Million woman study	UK	To study hormonal, reproductive and other factors affecting women's health from middle age onwards.	http://www.millionwomenstudy.org/
MIND Cohort - Minho Integrative Database on Ageing	Portugal	To identify predictors of healthy cognitive ageing, including socio-demographic factors. Registers to act as central repository of info on socio-cultural, cognitive, genetic, biochemical, neurostructural & functional domains.	http://www.icvs.uminho.pt/neurosciences/Mind%20%20Ageing/index_mindageing.html

Title of Cohort	Country	Aim	Website
MoBa Norwegian Mother and Child Cohort Study	Norway	To assess cognition, brain neuroimaging and neuroendocrine function as well as risk factors for cardiovascular and kidney disorders; serum, blood cells and urine are being kept for a biobank.	http://www.fhi.no/eway/default.aspx?pid=240&trg=Main_6664&Main_6664=6894:0:25,7372:1:0:0:::0:0
NCDS 1958 National Child Development Study	UK	Originally designed to address concerns re perinatal mortality, the study broadened out first to look at transitions from school through early adulthood then as a biomedical survey to examine how developmental, lifestyle and environmental factors influence current ill health, and physiological and psychological function in early middle age.	http://www.cls.ioe.ac.uk/page.aspx?&sitesectionid=724&sitesectiontitle=National+Child+Deve..
NCLS Netherlands Cohort Study	Netherlands	To study determinants of cancer incidence; it can in principle also be used for mortality follow-up for other diseases like neurodegenerative diseases on a country-wide scale, or on ageing. Incidence follow-up of certain other diseases like neurodegenerative diseases on a regional scale is a possibility.	http://epi.grants.cancer.gov/Consortia/members/nlcs.html
NEDICES Neurological Disorders of Central Spain	Spain	To conduct a prospective study of an elderly cohort (65 years old and above) with state of health, lifestyle (including cardiovascular risk factors –RF-) data. Its neurological aims were to analyse the epidemiological aspects (prevalence, incidence and RF) of several chronic neurological disorders: dementia and its subtypes (including Alzheimer disease), and mild cognitive impairment (MCI), Parkinson disease and Parkinsonisms, stroke and transient cerebral ischaemia, and senile tremor. During the time the study was being carried out (1995-2005) a number of sub-studies were designed, including some that sought to investigate these and other neurological diseases (headaches, epilepsy) and later on the analysis of the mortality rate of the cohort and its determining factors.	http://www.ciberned.es/en/estudio-nedices.html
NEDISA Neurological Disorders in Salamanca	Spain	To analyse the prevalence rates of neurological diseases in the elderly, including stroke, dementia, mild cognitive impairment, essential tremor (ET), Parkinson's disease (PD) and restless legs syndrome.	No website available at present.
Newcastle 85+ study	UK	Main aims: 1) To assess in detail the spectrum of health in the oldest old. 2) To examine the associations of health trajectories and outcomes with biological, clinical and social factors as the cohort ages. 3) To identify factors which contribute to the maintenance of health and independence. 4) To advance understanding of the biological nature of human ageing.	http://www.ncl.ac.uk/iah/research/areas/biogerontology/85plus/
NFBC66, NFBC86 N. Finland birth cohorts	Finland	To explore the genetic and environmental evolution of long-term morbidity, intermediate disease markers, symptom variation and social wellbeing throughout the life-course, from the foetal period, through childhood, adolescence, and adulthood as a means of identifying high risk groups and biological markers amenable to early intervention and prevention.	http://kelo.oulu.fi/NFBC/

Title of Cohort	Country	Aim	Website
NICOLA Northern Ireland Cohort for Longitudinal Study of Ageing	UK	To obtain information in relation to the experiences of ageing together with a range of other dimensions of lifestyle, health and socioeconomic circumstances.	No website available at present.
NILS Northern Ireland longitudinal study and NIMS	UK	The NILS is a large-scale record linkage study of approximately 500,000 people (a representative c. 28% sample of the Northern Ireland population) that has been created by linking statistical and administrative data sources within Northern Ireland. The NIMS is an additional major record linkage study that links the 2001 Census returns for the whole of the enumerated population (approximately 1.6 million individuals) to subsequently registered mortality data. The NILS and the NIMS are innovative research resources which allow for the exploration of health and socio-demographic characteristics and, as such, can be used to provide an insight into the status of the Northern Ireland population.	http://www.qub.ac.uk/research-centres/NILSResearchSupportUnit/
NLSAA Nottingham Longitudinal Study of Activity and Ageing	UK	Three core objectives: (i) to quantify customary physical activity (CPA) and physical capabilities within a representative sample of elderly people living at home; (ii) to quantify physical and psychological wellbeing within a representative sample of elderly people living at home; and (iii) to examine, cross-sectionally and longitudinally, inter-relationships between CPA, health and psychological wellbeing.	No website available at present.
Northern Ireland Study of Health and Stress	UK	To establish the prevalence and correlates of mental health using DSM and ICD criteria.	No website available at present.
Northern Swedish cohort (Lulea)	Sweden	To assess the health consequences of youth unemployment.	http://www.medfak.umu.se/english/research/research-projects/lulea_cohort_project/
NSHD National Survey of Health and Development (1946 cohort)	UK	During their childhood, the main aim of the NSHD was to investigate how the environment at home and at school affected physical and mental development and educational attainment. During adulthood, the main aim was to investigate how childhood health and development and lifetime social circumstances affected their adult health and function and how these change with age. Now, as participants reach retirement, the research team is developing the NSHD into a life course study of ageing.	http://www.nshd.mrc.ac.uk/

Title of Cohort	Country	Aim	Website
OCTO-Twin Origins of variance in the Old-Old: Octogenarian Twins	Sweden	Twin Registry established 1950s to study smoking and alcohol with regards to cancer and CVD. For OCTO twin primary interest in importance of genetic and environmental factors contributing to continued well-being, health and functional capacity in this unique material. Interest in early identification of high-risk for dementia.	http://ki.se/ki/jsp/polopoly.jsp?l=en&d=13903&a=30151
PAQUID Cohort Seniors	France	To study brain and functional ageing after age 65 years, distinguish the normal and pathological conditions, and identify people at high risk of physical or mental deterioration in which preventive action could be possible.	http://www.isped.u-bordeaux2.fr/FR_HTM_equipe_activites_details.aspx?CLE_EQU=3
Parelsnoer - neurodegenerative diseases	Netherlands	To establish a nation-wide database with biobank for patients with (prodromal forms of) dementia	www.parelsnoer.org
Parkinson's Incidence in the North East (PINE)	UK	To establish the incidence of Parkinson's disease in the North East of Scotland.	http://www.abdn.ac.uk/iahs/research/chronic-disease/neurology-253.php
ParkWest study (Patients with incident Parkinson's Disease from Western and Southern Norway)	Norway	A prospective longitudinal cohort study to track patients with incident Parkinson's Disease.	http://www.parkvest.no/?page_id=16
Patterns of multimorbidity in primary health care (multicare1)	Germany	To identify prognostic variables for the course of multimorbidity, and to describe the severity and the somatic and psychosocial long-term consequences of multimorbidity patterns as well as health care utilisation. Includes identification of clusters of combinations of diseases / disorders (multi-morbidity patterns) in the elderly general practice population and determination of their frequency and severity in relation to each other.	http://www.uke.de/institute/allgemeinmedizin/index_46738.php
Penagrande	Spain	To study factors associated with the onset of frailty in the elderly and the possibilities for early detection & prevention.	http://www.idipaz.es/

Title of Cohort	Country	Aim	Website
PopGen biobank	Germany	To develop a better understanding of the causes of common diseases. Asthma, heart attack, cancer, chronic inflammatory bowel disease and many neurological diseases such as Parkinson's disease or the so-called mental illnesses affect more and more people.	http://www.popgen.de/
PPSW Prospective Population Study of Women in Gothenburg	Sweden	To study dementia, other mental disorders (depression, psychotic disorders, anxiety disorders), suicidal behaviour and cognitive function in women followed from 1968-2011. Initial purpose to investigate anaemia and health factors related to menopause, but later included examination of determinants among middle age women that have importance for the development of cardiovascular disease, diabetes, cancer, dementia and other mental illness in high age.	http://snd.gu.se/en/catalogue/study/604
ProSenior	Poland	2 sub-studies: Upper Silesia - how housing compatible with functional status; Warsaw - impact of physical training on physical ability.	No website available at present.
PSAE Panel Survey of Ageing and the Elderly 2010	Sweden	To provide an overall broad picture of living conditions, general health, and economic conditions among older Swedes.	No website available at present.
Reykjavik Heart Study	Iceland	To identify risk factors for cardiovascular disease.	http://www.hjartarannsokn.is/index.aspx?GroupId=406
RISCA Prospective study of individuals at risk for spinocerebellar ataxia type 1, type 2, type 3 and type 6	Germany	To enrol and study a cohort of asymptomatic gene carriers for spinocerebellar ataxia(SCA1, SC2, SCA3, SCA6) .	http://www.ataxia-study-group.net/html/studies/risca/
SATSA Swedish Adoption/Twin Study of Aging - also HARMONY	Sweden	To study the importance of genetic and environmental factors that may underlie differing aging outcomes. To study patterns of change within and across domains and how these predict health and diseases of aging.	http://ki.se/ki/jsp/polopoly.jsp?d=13903&a=30148&l=en

Title of Cohort	Country	Aim	Website
Scottish Health Survey	UK	To achieve a representative sample of the Scottish Household Population; it does not focus on any single disease or condition but is designed to make a major contribution to the monitoring of health in Scotland.	http://www.scotland.gov.uk/Topics/Statistics/Browse/Health/scottish-health-survey
Scottish longitudinal study	UK	To provide a high quality longitudinal research dataset that can be used to provide an insight into the health and social status of the Scottish population and how it changes over time.	http://www.lscs.ac.uk/sls/
SENECA Survey in Europe on Nutrition and the Elderly: a Concerned Action	Europe	To see whether diet and lifestyle influence health of older people in 8 European countries.	No website available at present.
SHARE Survey of Health, Ageing and Retirement in Europe	Europe	The Survey of Health, Ageing and Retirement in Europe (SHARE) is a multidisciplinary and cross-national panel database of micro data on health, socio-economic status and social and family networks of more than 45,000 individuals aged 50 or over.	www.share-project.org/
SHIP Study of Health in Pomerania: two cohorts.	Germany	To assess the prevalence and incidence of common risk factors, subclinical disorders and clinical diseases and investigate associations among risk factors, subclinical disorders and clinical diseases. 2nd cohort enhances to also analyse secular trend of subclinical and overt diseases (comparing two cohorts) and assess the prevalence of sub-clinical findings defined by highly innovative non-invasive methods.	http://www.medizin.uni-greifswald.de/cm/fv/english/ship_en.html
SNAC-K The Swedish National study on Aging and Care in Kungsholmen	Sweden	To trace the changes in health status and detect factors leading to negative health and functional outcomes in the elderly. First, health from a broad perspective, including medical/physical, psychological, and social health. Second, a life course perspective to identify the determinants of good or bad health in the elderly.	http://www.snac-k.se/
Speedwell	UK	Sister study to Caerphilly. To examine risk factors (known and newly discovered) for ischaemic heart disease.	No website available at present.

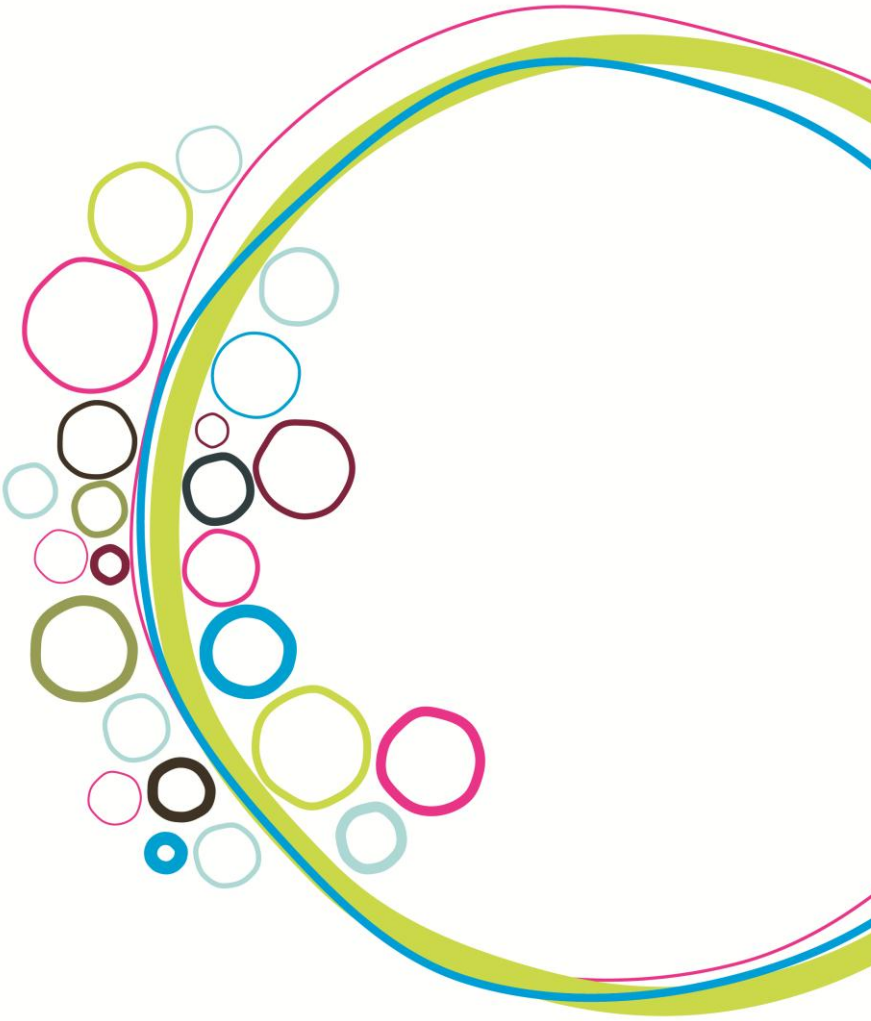
Title of Cohort	Country	Aim	Website
Stockholm Birth cohort. Two parts: Project Metropolitain (1953-83) and Stockholm Birth Cohort (1980-2007)	Sweden	To provide resource for research in psychology, public health science and sociology.	http://www.stockholmbirthcohort.su.se/
Swedish panel of living conditions	Sweden	To study welfare of populations.	http://www.sofi.su.se/english/2.17851/research/three-research-departments/lnu-level-of-living/the-swedish-level-of-living-survey-lnu-1.65112.
SWEOLD Swedish Panel Study of Living Conditions of the Oldest Old	Sweden	To describe and analyse the living conditions of elderly people in Sweden.	http://www.sweold.se/start.htm
Swiss National Cohort	Switzerland	A long-term, 1990 census based, multipurpose cohort and research platform including currently mortality follow-up and other disease outcomes to be linked to this population in the future.	http://www.swissnationalcohort.ch/index.php?id=2985
SWS Southampton Women's study	UK	To learn more about the dietary and lifestyle factors that influence the health of women and their children.	http://www.mrc.soton.ac.uk/sws/index.asp
TEMPO	France	To understand the health needs of young adults in France. Initially looking at psychological difficulties linked to alcohol, cannabis and illicit drugs. To understand the roles of family and professional life; to understand health inequalities better.	http://www.tempo.inserm.fr/objectifs.html

Title of Cohort	Country	Aim	Website
The Aberdeen Children of the 1950s study	UK	To provide a population-based resource for the study of biological and social influences on health across the life-course and between generations.	http://www.abdn.ac.uk/childrenofthe1950s/
The Betula Prospective Study on Aging, Memory, and Dementia	Sweden	Focus on cognitive and genetic risk factors. To measure how memory functions change during adult life and old age, to identify risk factors for dementia and to identify early preclinical signs of dementia.	http://www.betula.su.se/en/
The Cambridge city over 75s cohort study	UK	Initially designed to measure prevalence and incidence of dementia in Cambridge The long-term follow-up study covers a variety of aspects of cognition, falls and functional ability and use of services.	http://www.cc75c.group.cam.ac.uk/
The Maastricht Study	Netherlands	A study on 5000 patients with Type 2 Diabetes and 5000 healthy control participants including biomarkers and functional and cognitive assessments, with five year follow up planned.	http://www.demaastrichtstudie.nl/englishpages/themaastrichtstudy/
The National FINRISK Study	Finland	A large population survey of 15.000 people to identify risk factors of chronic, non-communicable disease, including Alzheimer's disease and other dementias. Repeated every 5 years.	http://www.thl.fi
The Rhineland study	Germany	To research into the epidemiology of neurodegenerative diseases with detailed examinations and assessments.	http://www.dzne.de/en/research/research-areas/population-studies.html
TILDA The Irish Longitudinal Study on Ageing	Eire	To improve the understanding of how health, economic and social circumstances contribute to (successful) ageing.	www.tcd.ie/tilda

Title of Cohort	Country	Aim	Website
TRACK HD/TRACK-ON HD	4 countries	To look for early signs of brain degeneration, compensatory brain mechanisms, changes in behaviour and physical movement, and blood biomarkers in the early stages of Huntingdon's disease. Study involves no experimental treatment.	http://hdresearch.ucl.ac.uk/current-studies/trackon-hd/
TREND (Tübinger evaluation of Risk factors for Early detection of NeuroDegeneration)	Germany	To identify, characterize and validate risk and prodromal markers for Parkinson's and Alzheimer's disease.	http://www.trend-studie.de/english/
Twins UK	UK	To study the genetic and environmental aetiology of age related complex traits and diseases. The Healthy Ageing Twin Study (HATS) to enable assessment of longitudinal changes in ageing traits and their genetic and environmental components. HATS uses measurements of twins taken over ten years ago and compares them to repeat measurements taken recently. This longitudinal study allows to assess changes with time (in this case, in different organs such as lungs and bone) and to disentangle the genetic and environmental factors influencing these changes.	http://www.twinsuk.ac.uk/
UK Biobank	UK	To create a major medical research resource that can support research with the intention of improving the prevention, diagnosis and treatment of serious illnesses.	http://www.ukbiobank.ac.uk/
UK Women's cohort	UK	To explore the effect of diet on cancer.	http://www.leeds.ac.uk/medicine/ceb/NutEp/ukwcs/method.html
ULSAM Uppsala Longitudinal Study of Adult Men	Sweden	To increase knowledge about the following disorders in an ageing population: cardiovascular and dementia disorders, diabetes, osteoporosis, nutrition and muscle function, and successful ageing.	http://www2.pubcare.uu.se/ULSAM/
Understanding Society	UK	Captures important information every year about the social and economic circumstances and attitudes of people living in 40,000 UK households.	http://www.understandingsociety.ac.uk

Title of Cohort	Country	Aim	Website
UpCos Uppsala birth cohort multi-generational	Sweden	To investigate life course and intergenerational determinants of social inequalities in health. (i) To address the extent to which and the mechanisms whereby social advantage and disadvantage are transmitted from one generation to the next;(ii) to explore how early social and biological factors, especially those related to cardiovascular risk, are transmitted from the parent generation to offspring generation; (iii) to try to integrate the understanding of broader social mechanisms with the understanding of disease specific aetiology to answer the question of how, and to what extent, health inequalities are reproduced into each new generation.	http://www.chess.su.se/ubcosmg/
Utilisation and costs of health and nursing services for elderly patients with multimorbidity in the German Statutory Health Insurance System – an observational cohort study	Germany	To analyse medical and nursing services utilized by elderly patients with multimorbidity, estimation of costs of services of statutory medical and nursing care for elderly patients with multimorbidity	No website available at present.
Vitality 90+	Finland	A multidisciplinary project focusing on longevity and the oldest-old. The sub-projects address the biological basis of aging, predictors of health, functioning and longevity, old age as an individual experience, and the need for and use of care and services.	http://www.gerec.fi/en/research/health-functioning-and-longevity/vitality-90
VP-EDAD The Vallecas Project - Early detection of Alzheimer's Disease	Spain	To obtain an algorithm of probability (based on historical, clinical, neuroimaging, and biological data) for calculation of the dementia/AD risk in a 5-year horizon.	www.fundacioncien.es
Whitehall II Stress & Health	UK	To investigate biological, behavioural, and psychosocial factors underlying social inequalities in health and disease. Specific project has aims of looking at health behaviours as risk factors for cognitive ageing, at the impact of cognitive decline on health behaviours, and at mechanisms by which the previous two might operate.	http://www.ucl.ac.uk/whitehallII

Title of Cohort	Country	Aim	Website
ZARADEMP Zaragoza dementia / depression project cohort	Spain	To examine incidence of dementia & risk factors.	No website available at present.
Zutphen Elderly Study	Netherlands	To obtain insight into changes in and risk factors for physical, social, and psychological functioning, including cognitive decline and depression, among elderly men.	No website available at present.



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