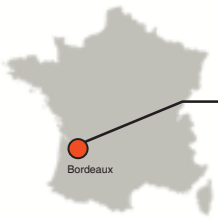
MEMENTO:

deterMinants and Evolution of AlzheiMer's disEase aNd relaTed disOrders



Geneviève Chêne, MD, PhD
Professor of Biostatistics and Public Health, Bordeaux School of Public Health (ISPED)
genevieve.chene@isped.u-bordeaux2.fr

Carole Dufouil, PhD
Director of research at Inserm, Bordeaux School of Public Health (ISPED)
carole.dufouil@isped.u-bordeaux2.fr

OVERVIEW

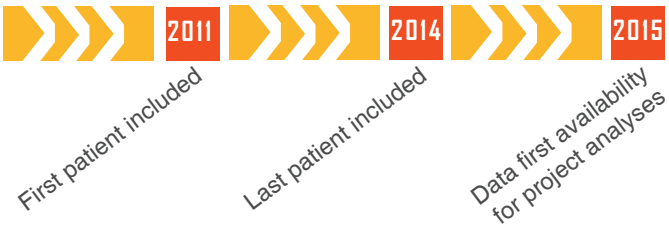
AT A GLANCE

> **Neurology, Aging & Neurodegenerative diseases**
> Patients with either isolated **cognitive complaints** or **mild cognitive impairment**
> Coordinated by **Geneviève Chêne** and **Carole Dufouil**
> **Bordeaux University Hospital Sponsorship**
> Funded by Fondation Plan Alzheimer, French clinical research projects funding program (PHRC) and industrial partnerships
> **Key words**: Alzheimer's disease, biomarkers, natural history, early diagnosis, longitudinal, imaging

KEY FACTS & FIGURES

> Status: **enrollment ended in 2014**
> **Multicenter cohort** in 28 memory clinics in France
> **2 323 non demented participants** enrolled
> At least **5 years follow-up**
> **Centralized biobank** at Pasteur Institute (Lille) comprising serum, plasma, DNA, RNA, & CSF samples
> Process for linkage with SNIIRAM database initiated

The objective of MEMENTO is to better **understand the natural history of Alzheimer's disease and related disorders** (AD) by characterizing, through the **analysis of risk factors** and **multiple biomarkers alone or in combination,** the **determinants of transitions** from early signs and symptoms of AD (cognitive complaints, mild cognitive impairment) to clinical dementia.



Positioning

> MEMENTO is a large **observational study** enrolling patients at an early stage before dementia and with a **highly comprehensive and standardized workup** (clinical, biological, imaging, socio-economics)
> **A unique platform for research:** no similar cohort at an international level
> Collaboration with **the Framingham cohort**
> **Partnerships with pharmaceutical companies** already ongoing

LEADERSHIP

Geneviève Chêne, Biostatistics and Public Health Professor, ISPED, Bordeaux

- Teaches clinical epidemiology at the Bordeaux school of Public health, including e-learning since 2001
- Head of EUCLID, a F-CRIN services platform for clinical trials
- Coordination of large scale studies, including EU-funded collaborations
- Member of the «Comité des sages» for the National Strategy for health, 2013
- Deputy Chair of the evaluating committee of National Program for clinical research (PHRC), 2013
- Director of Public Health AVIESAN Institute
- Major Collaborations with MRC, UCL, Bristol & Boston University
- Top 1% ISI researchers
- More than 360 publications, H-Index=54
- External reviewer for NIH, MRC, UCL

Carole Dufouil, Neuroepidemiology, Director of research Inserm, ISPED, Bordeaux

- Co-PI of the 3C-Dijon study (large population based study on dementia)
- PI of the neuroimaging ancillary study of the MAPT trial (national multi-domain prevention trial of cognitive decline)
- Coordinator of an international collaboration on optimizing methods in longitudinal analyses of dementia database (Melodem)
- Collaborations with the Framingham study (Boston university), the Institute of Public Health (Cambridge, UK) and the department of epidemiology (UC, San Francisco)
- Top 1% ISI researchers
- More than 150 publications, H-index=42
- External reviewer for NIH, MRC, UCSF, Boston University, ERC

SCIENTIFIC NETWORK & MANAGEMENT

SCIENTIFIC NETWORK

Current collaborations

> **EMIF-AD** (IMI call 2011) : pooled cohort studies on presymptomatic AD and prodromal AD across Europe for discovery of new biomarkers for AD

> **Framingham cohort:** determinants of dementia and associated disorders with a special focus on vascular risk factors, temporal trends in dementia, cross validation of neuroimaging biomarkers between Memento and Framingham

> **MELODEM** (Methods in longitudinal dementia research)

Future collaborations

> **Mayo Clinic Study of Aging,** Rochester, Minnesota, USA : To replicate in a different setting (population based study) and different country findings from Memento

> **Center Brain Health,** New-York, USA : To set up ancillary studies to test the added value of novel biomarkers

> Involved in two **IMI-H2020** applications

SCIENTIFIC MANAGEMENT

Through its external scientific committee, MEMENTO involves experts in:

> **Basic science:** Mony de Leon (New York University School of Medicine and Scientist, US)

> **Social sciences:** Lisa Berkman (Harvard, US)

> **Neurology:** Ronald Petersen (Rochester, US)

> **Biostatistics:** David Clayton (MRC, UK)

> **Neuroimaging** and **biomarkers of AD:** Philip Scheltens (Vrije Universiteit Amsterdam, Netherlands)

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

Main objective

> **Identification and validation of biomarkers or combination of biomarkers** that best predict the occurrence of dementia

Secondary objectives

> Provide **an extensive characterization of the natural history** of well phenotyped patients **with potential early signs of Alzheimer's disease**

> Investigate the **impact of vascular burden on cognitive health**

> Document the **socio-economic burden of Alzheimer's disease** and related disorders for patients, caregivers and society

> Provide for **a national integrated research platform** with standardized clinical, biological and imaging assessments

INNOVATIVE SCIENTIFIC FEATURES

The **largest naturalistic cohort on brain health**, with a rigorous prospective design

Extensive follow-up (at least 5 years)

Standardized procedures, multiple biomarkers (imaging, blood CSF) assessed with **standardized acquisitions and analyses**

METHODOLOGY QUALITY

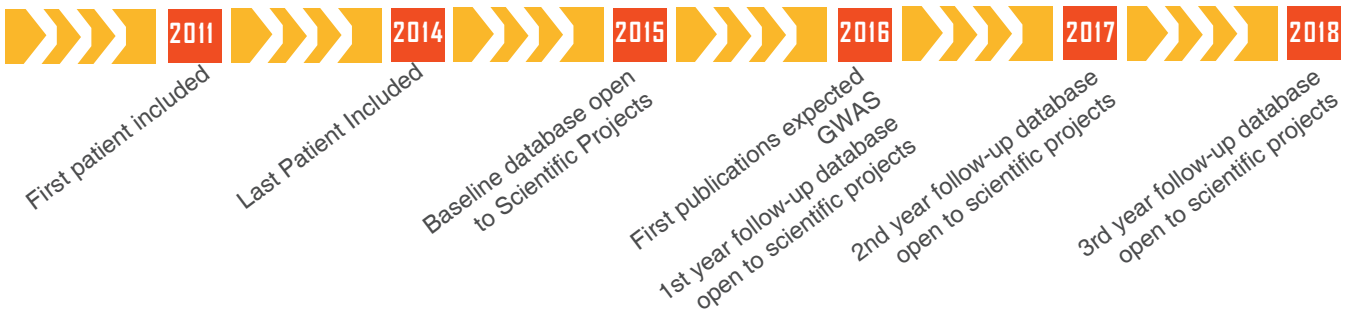
Harmonization and Standardization of assessments

E-CRF and robust **data-monitoring**

Certification of imaging centers, centralized imaging analysis through Neurospin **CATI** (Saclay)

Centralized biobank and neuroimaging (CATI, Neurospin)

DESIGN, METHODOLOGY & TIMELINE



Recruitment objectives:	2 323 consecutive individuals recruited
Sites:	28 Memory Research Centers in France
Inclusion criteria:	Adults; either a recently evaluated (< 6 months) cognitive performance worse than one standard deviation to the mean in one or more domains or an isolated cognitive complaint (patient aged ≥ 60 years); Non-demented; Clinical Dementia Rating Scale (CDR) ≤0.5
Exclusion criteria:	Guardianship; Meeting brain MRI exclusion criteria or refusing MRI; Illiteracy

INCLUSION COLLECTION
Clinical data:
Cognitive testing, cognitive complaints, psychopathology, social & human sciences, vascular risk factors and history
Imaging collection:
Brain MRI (including DTI and rs-fMRI), 18F-FDG PET, Amyloid PET
Biobank:
Cerebrospinal fluid (CSF) and blood samplings

FOLLOW-UP: AT LEAST YEARLY
At least every year: Cognitive testing, cognitive complaints, psychopathology, social & human sciences; vascular damages
Every 2 years:
- Brain MRI (including DTI and rs-fMRI), 18F-FDG PET, Amyloid PET
- CSF and blood samplings

DATABASE & BIOBANK CONTENTS

DATABASE

Clinical data

The database is comprehensive, with a clinical assessment of patients every 12 months, for at least 5 years

> **Clinical** assessment, **memory** tests, **neurological** and **psychiatric** assessment, **socioeconomic** data (burden of disease), **quality of life, social sciences** (social and family environment, caregiver's assessment) etc…

> **Linkage** of the database with other databases as **SNIIRAM is on going**

Imaging collection

Imaging is performed at inclusion and every 24 months -

> Cerebral MRI

>> 3D-T12D, T2 FLAIR, 2D-T2* (GRE) + phase, 2D-T2 TSE/FSE 1 echo, Resting state (BOLD EPI), diffusion (DTI – DWI EPI)

>> Visual assessment recorded in e-CRF

>> Quality assessment of each sequence with automated test procedures and report

>> Automated analyses: brain tissues and hippocampus volumes, global and ROI-based cortical thickness, gyrification index, fold opening

> FDG PET

>> Harmonization using phantoms

>> Optimization of reconstruction parameters

>> Automatic quantitative analysis

BIOBANK

Originality

> Collection according to **standardized procedures (SOPs) for the treatment, storage and transfer of the sampled biospecimens**

> A duplication of all the biospecimens has been organized through the constitution of a **Mirror Biobank** hosted at the ICM (Institut du Cerveau et de la Moelle Epinière, Paris) to ensure **the biological samples safety**

> Repeated measures are performed to ensure the biospecimens **quality**

Scientific objective

> **Developing novel blood-based biomarkers** for Alzheimer's disease

Samples

> **Blood** (mandatory and includes serum, plasma, DNA, RNA) and CSF (optional)

Biobank Key Facts

> Sampling **at baseline, 2 and 4 year follow-up**

>> **Baseline samples** obtained **for 2 283 participants**

>> 2- and 4-year follow-up samples ongoing

> For blood sampling at each wave: **28 aliquots** stored

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- **Centralized storage** in a **principal and a mirror biobanks**
  - > Principal storage at the Genomic Analysis Lab, (LAG, Pasteur Institute, Lille)
  - > Mirror storage at ICM (Brain & Spine Institute, Paris)
- LAG is responsible for organizing transport from local biobanks to centralized biobank as part of its assignments in contract
- Biological samples are identified using a **bar code system**

SPECIFICATIONS

- The first sampling has been performed in **July 2011**
- Sampling frequency: **every 2 years**
- **Responsible** for the biobank: **Bordeaux University Hospital**
- The **database associated to each sample** includes information on:
  - > Collection, transport & storage conditions
  - > Date of birth
  - > Gender of participant
- Biobank is being constituting according to standardized protocol for sampling, **Standard Operating Procedure** for ensuring the homogenization in terms of treatment and storage quality and **high standards with quality checking procedures**
- **Biological samples are** available for collaborations through a research project application, according to the modalities specified in the MEMENTO data **access charter**

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biological specimens	Origin	Quantity available	No. of aliquot	No. of subjects who have been sampled (expected/sampled)	Storage conditions
At Baseline: start in July 2011					
Serum	Blood	0.25 mL	12	2 323/2 283	-80°C
Plasma EDTA	Blood	0.25 mL	8	2 323/2 283	-80°C
Total blood heparin	Blood	1 mL	2	2 323/2 283	-80°C
Plasma heparin	Blood	500 µg	4	2 323/2 283	-80°C
Blood EDTA without plasma	Blood	0.25 mL	1	2 323/2 283	-80°C
Blood heparin without plasma	Blood	3 mL	1	2 323/2 283	-80°C
Tempus	Blood	3 mL	2	2 323/2 283	-80°C
CSF	CSF	O.25 µL	16	400 sampled (sampling on going)	-80°C
During the follow-up sampling frequency: every 2 years					
Same collection as baseline					

BIOBANK SAMPLE ACCESS MODALITIES

- A charter **specifying biobank access modalities is available since 2013** and describes the MEMENTO general principles and path to follow for data and biospecimen access, ancillary project and publication submission
- **The biobank is opened to a large scientific community (academic and industrial), without any restriction regarding the nature of the biospecimens and in accordance with the charter terms**
- Industrials wishing to access to the MEMENTO biobank have to submit a research project to the Steering and the Scientific Committees for review
- **Transfer of biological samples** to public or to private/industrial teams is possible **upon granted access and after following specific rules of the charter**
- Biological samples may be shareable with a foreign company under conditions depending on the purpose, the analysis,….

BIOLOGICAL SAMPLE ANALYSES

- The collected samples are **used for the validation of disease diagnosis**
- The biological sample **analysis-derived data are accessible** to the scientific community, **according to the charter rules**
- Industrial research team proposing a project are **invited to identify the laboratory able to perform sample analyses** and find **the specific funding** for biological measurements

COST

- A **financial estimation** of the MEMENTO biological samples is **not yet available but is underway**

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

Translational research

> **Identification and validation of new biomarkers** or combination of biomarkers **for the early diagnosis** of Alzheimer's disease and associated disorders

> **Identification of prognosis factors** for transition from isolated cognitive complaints to mild cognitive impairment to dementia

> **Validation of surrogate markers** of Alzheimer's disease for future clinical trials

> **Validation of preclinical and pre-dementia stages** of Alzheimer's disease

Clinical development

> **Definition phenotypes of patients at high risk** of clinical dementia that should be the target of future clinical trials

> **Structuration of clinical research** in the field of Alzheimer's disease

> **Platform** for clinical research

Outcomes research

> **Better characterization** of etiologies of dementia

> **Pharmaco-economic studies** cost/benefit of new biomarkers for Alzheimer's disease and associated disorders

> **Provide data to health authorities** on the added value of biomarkers for care and treatment of patients

> **Assess the impact of early diagnosis** of Alzheimer's disease and associated disorders on the patient and its family

BIBLIOGRAPHY

Translational research

> Chêne G, **Translational epidemiology: are we ready for a population perspective in our research?** Harvard School of Public Health, Department of Society, Human Development and Health Seminar Series, Boston, USA, 09/2012.

> Dufouil C and Brayne C. **The Continuing Challenge of Turning Promising Observational Evidence About Risk for Dementia to Evidence Supporting Prevention.** JAMA Intern Med. Feb 3 2014.

Methodological development

> Weuve J et al., **Guidelines for reporting methodological challenges and evaluating potential bias in dementia research.** MELODEM Initiative. Alzheimers Dement. 2015 Sep;11(9):1098-109. doi: 10.1016/j.jalz.2015.06.1885. Review.

Outcomes research

> Satizabal CL et al., **Dementia Incidence over the Last Three Decades in the Framingham Study.** New England Journal of Medicine (in press)

> Vivot A et al., **Association of Alzheimer's related genotypes with cognitive decline in multiple domains: results from the Three-City Dijon study.** Mol Psychiatry. 2015 Oct;20(10):1173-8.

> Chêne G et al., **Gender and incidence of dementia in the Framingham Heart Study from mid-adult life.** Alzheimers Dement. 2014 Jan 10.

> Glymour MM et al., **Brain MRI markers and dropout in a longitudinal study of cognitive aging: the Three-City Dijon Study.** Neurology 2012 Sep 25;79(13):1340-8.

> Godin O et al., **Antihypertensive treatment and change in blood pressure are associated with the progression of white matter lesion volumes: the Three-City (3C)-Dijon Magnetic Resonance Imaging Study.** Circulation 2011;123(3):266-73.