**Title of the Project:** Role of vascular risk factors in ageing phenotypes

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**Summary**

**Background**

There is increasing evidence that cognitive and motor decline are influenced by vascular risk factors such as hypertension, diabetes etc. seen to explain up to 50% of the population attributable fraction for dementia in a recent study. There is also evidence that sex steroid hormones may play an important role in age-related phenotypes, including cardiovascular traits and dementia. However, many of the studies to date have been conducted on older populations, often those aged ≥65 years, with the following implications: (i) these studies are necessarily on samples that are selected by competing risks of death, which may bias association estimates; (ii) age related pathophysiological processes in the outcomes of interest (cognitive, mental, physical function) are already under way, leading to the impossibility of ruling out reverse causation; (iii) phenotypes are more difficult to characterize at older ages due to multiple comorbidities.

By focusing on middle age adults (≥45 years) who will be followed over time, CONSTANCES will allow major progress to be made on understanding the evolution of age related changes in functional outcomes (cognitive, mental, physical) and the relative importance of various risk factors, with the view that it will also help gain insight into end stage outcomes (dementia, frailty, disability).

**Objectives**

We will examine vascular risk factors and disease and sex steroid hormones, and their consequences on subsequent cognitive, mental and physical decline and on the risk of dementia and disability. We will pay particular attention to the shape of the associations (linearity, risk trajectories, critical periods) and we will build risk scores allowing to include multiple risk factors in a single model.

**Methods**

Data and measures

Outcomes:

- Repeated measures of: cognitive tests; objective physical measures; mental function.
- Dementia (methods used to ascertain dementia cases are described in another project).
- Disability (defined based on ADLs, IADLs, and mobility).

Exposures:

- Cardiovascular risk factors and diseases (hypertension, dyslipidemia, diabetes and glycemic control; stroke and coronary artery disease, venous thromboembolic events; drugs); cardiovascular risk scores will be built using these variables.
- Endogenous levels of sex steroid hormones (estradiol, testosterone ...) as well as reproductive history (age at menarche, parity, age at menopause ...) and exogenous hormones use (hormonal contraceptives, postmenopausal hormone therapy ...) for women (in association with the group “Santé des femmes”).
- Confounders: health-related behaviors (smoking, alcohol, physical activity, nutrition); socioeconomic factors. We will also examine the main effects of health behaviors, in order to assess the extent to which these potentially modifiable risk factors affect ageing.
In the initial phase of the project we will undertake cross-sectional analyses (N=10 000 subjects ≥45 years old) using the baseline data both for exposures and outcomes (cognitive, motor, and mental function). However, the key thrust of this proposal is on longitudinal data and analyses will develop as repeated measures (exposures, functional outcomes, and incident disease) accumulate:

- Longitudinal analyses of functional decline will rely on at least two waves of data collection (i.e., 10 years).
- Analyses of dementia and disability will be possible after 5 years and the identification of incident cases during this period.

Note: this project is part of the research consortium ‘PRESAGE – PREparing Successful AGEing’