Background:

With the progress in research on treatment of dementia, there is increasing interest in identifying the disease at its most early stage in order to minimize its impact and even prevent symptom appearance. There is, in fact, converging evidence supporting that the pathological process may start years before any symptomatic complaint.

The Framingham cohort showed that, 22 years before a diagnosis of dementia, people had a decrease performance in neuropsychological testing suggesting the existence of a preclinical stage (Merril, 2000). Few studies however have looked at serial measurements of cognitive decline preceding the diagnosis of dementia (Small, Howieson, Jacobs, Kawas). The PAQUID group has done a prospective population-based study over a 9-year period showing a progressive cognitive decline in MMSE and visual memory before the diagnosis of Alzheimer’s disease (Amieva et al. 2005). Similar changes in performance on complex instrumental activities of the daily living have also been noted prior to the diagnosis of dementia. Restriction in 2 of these 4 activities (telephone use, transportation, medication and finance management) increased the risk of dementia 10 years later and difficulty at baseline with finances was a predictor of dementia in
Pérès’ study. (Pérès, 2008) This suggests, as opposed to our current conception, that impairment in ADL may actually be an early marker of the disease rather than an exclusion criterion for MCI and a diagnostic criterion for dementia.

To this time, no study has presented the trajectory of decline in cognition and functional status prior to a diagnosis of dementia or mild cognitive impairment (MCI) on a follow-up as long as 20-years and on such a large cohort of oldest-old women. The SOF database offers us this great opportunity.

We hypothesize that patients who develop dementia will show a lower baseline MMSE, Trail B performance and functional status and that their decline will be steeper than cognitively intact and MCI patients. With these findings in mind, we might eventually be able to identify high-risk patients and offer more aggressive preventive measures. This will also reinforce the knowledge that the pathological process responsible for dementia starts years before the clinical diagnosis and that there is a need to find preventive treatments.

**Research Aims:**

1) To describe the trajectories of cognitive change (mMMSE, Trails B) over 20 years prior to diagnosis of dementia or MCI among oldest old women.

2) To describe the trajectories of functional change (activities of daily living) over 20 years prior to diagnosis of dementia or MCI among oldest old women.

**Hypothesis:**

1) We believe that patients who develop dementia will show a lower baseline MMSE and Trail B and that their decline will be steeper than cognitively intact and MCI patients.

2) We believe that patients who develop dementia will show a lower functional status at baseline and a more rapid deterioration preceding the diagnosis of dementia than cognitively intact and MCI patients.
Predictor:
Diagnoses of normal cognition, mild cognitive impairment (MCI) and dementia at Year 20
- v9prmcog v92ndcog

Outcomes:
Modified Mini-Mental Examination (mMMSE) over 20 years
- vXsht3ms over 20 years
Trail Making Test Part B (Trails B) over 20 years
- vXtrlbts over 20 years
Functional Status over 20 years
- Activities of daily living: vXfxst61, vXfxst62, vXfxst51, vXfxst52 over 20 years
- Walking: vXwlk1, vXwlk2 over 20 years
- Climbing stairs: vXclb1, vXclb2 over 20 years
- Preparing meals: vXck1, vXck2 over 20 years
- Heavy housework: vXhh1, vXhh2 over 20 years
- Shopping: vXsh1, vXsh2 over 20 years
- Descending stairs: vXstp1, vXstp2 over 20 years
- Household chores: vXch1, vXch2
- Dressing: vXdr1, vXdr2
- Getting out of bed: vXbed1, vXbed2
- Drinking: vXcup1, vXcup2
- Washing: vXwsh1, vXwsh2
- Picking up clothes from floor: vXbnd1, vXvnd2
- Turning faucets: vXfau1, vXfau2
- In and out of car: vXcar1, vXcar2

Confounders:
- Age (vXage over 20 years)
- Education (v1educ)
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- Depressive symptoms (vXgds15 over 20 years)
- Smoking (v1smoke, v2smok, v4smok, v5smok, v6smok, aasmoke, v8smoke)
- Hypertension (v1hyten, v3ehyten, v4ehyten, v6shyper, aaehyten, v8ehyten, v9ehyten)
- Diabetes (v1ediab, v3ediab, v4ediab, v5sdiab, v6sdiab, aaediab, v8ediab)
- BMI (vX bmi over 20 years)
- Stroke (vXestrk over 20 years)
- Heart attack (vXeheart over 20 years)
- Blocks Walked (vXblkcal over 20 years)
- ApoE4

**Analytic Plan:**

Either analysis of variance (ANOVA) or chi-squared ($\chi^2$), as appropriate, will be used to examine associations between cognitive status at year 20 (normal, MCI, or dementia) and participant characteristics at baseline (Table 1).

We will use random effect regression to examine the relationship between cognitive status at year 20 and changes in cognition (mMMSE, Trails B) over the examinations. Each model will be adjusted for factors that are significantly associated ($p<0.05$) with cognitive status at year 20 from descriptive analyses.

**Abstract?**

Yes - TBA.

**Analyses?**

Will be done by our center

**References:**

**Mock Tables:**

Table 1. Characteristics of oldest old women with no cognitive impairment, mild cognitive impairment (MCI), and dementia.

<table>
<thead>
<tr>
<th>Late-Life Characteristic</th>
<th>Normal (n=xxx)</th>
<th>MCI (n=xxx)</th>
<th>Dementia (n=xxx)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (SD)</td>
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<tr>
<td>Years of education, mean (SD)</td>
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<tr>
<td>Medical History</td>
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<tr>
<td>Diabetes, %</td>
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<tr>
<td>Hypertension, %</td>
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<tr>
<td>Stroke, %</td>
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<tr>
<td>Myocardial Infarction, %</td>
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<tr>
<td>Depression (Geriatric Depression Scale ≥6), %</td>
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<tr>
<td>Ever smoker, %</td>
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<tr>
<td>Body mass index, mean (SD), kg/m²</td>
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<td>APOE4</td>
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Table 2. Modified Mini-Mental Examination (mMMSE) scores over 20 years prior to diagnosis among oldest old women.

Table 3: Trail Making Test Part B (Trails B) scores over 20 years prior to diagnosis among oldest old women.
Similar to example in Table 2