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# A multivariate disease progression model for identifying subtypes in CADASIL

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## Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenic form of cerebral small artery disease caused by mutations in the NOTCH3 gene. The multifaceted clinical presentation of this disorder can be assessed using various measures that allow us to describe patients' cognitive efficiency, memory performance, disability, neurological deficits, daily activities, and quality of life[1]. We implemented the multivariate version of a bayesian mixed-effects model (Leaspy), which includes a time reparametrisation to analyse the evolution of the disease. We were also able to identify different subgroups of individual evolution using a GMM classification algorithm on the individual parameters and to evaluate the influence of baseline covariates such as gender, education level, hypertension, and location of the mutation.

## Data & Method

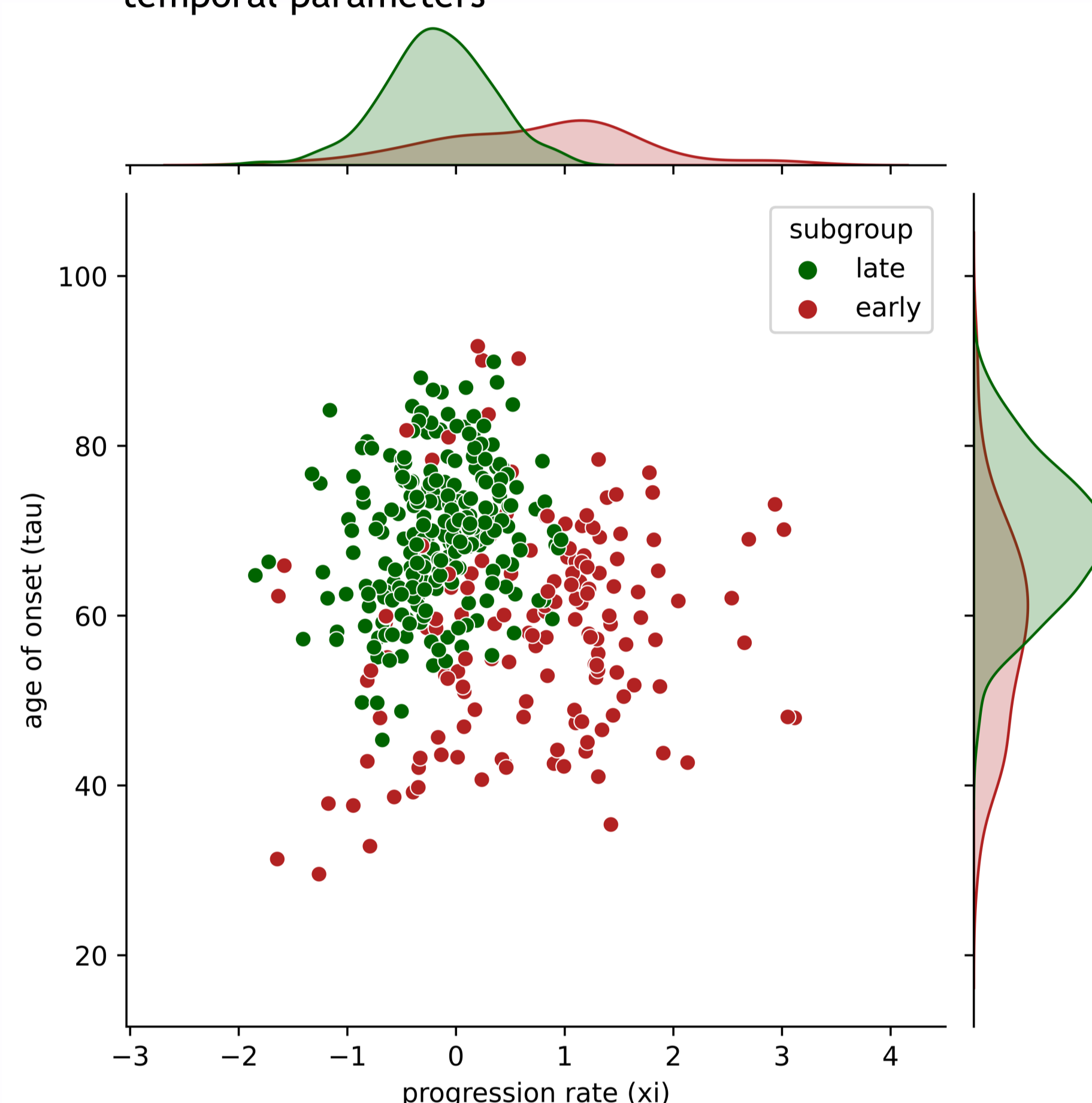
We analysed data obtained from **395 patients** recruited at the French National Referral Centre CERVCO over a median number of **4 visits** per individual (IQR:3-7) (total visits: **2007**), with follow-up ranging from 6 months to 19 years with a median interval of **6.5 years** (IQR:3.5-11).

They were 45% men, 72% with a high school education or less and 21% with hypertension with a median inclusion age of 53 years (IQR:45-61). 66% had the mutation in the EGFr domains considered as high risk 1-6,8,11 and 26[2].

We used the logistic multivariate version of the disease progression model(Leaspy) to analyse the progression of these outcomes. As with any mixed effect model we obtained the individual parameters (random effects) representing the **time shift** ( $\tau$ ), **acceleration rate** ( $\xi$ ) and inter-marker space shifts. A negative value indicates that a given score for a given patient will begin to deteriorate at an earlier age than for the average population. However, there are some common patterns within a population, and it is unlikely that all rearrangements exist. Thus, we employ the use of another parameter called **sources** ( $s$ ) which determines the degrees of freedom for the sequence of events. The number of sources is always smaller than the number of omegas making the estimation process less complex. To interpret the results, the omegas can then be found by an independent component analysis of the sources.

## Results

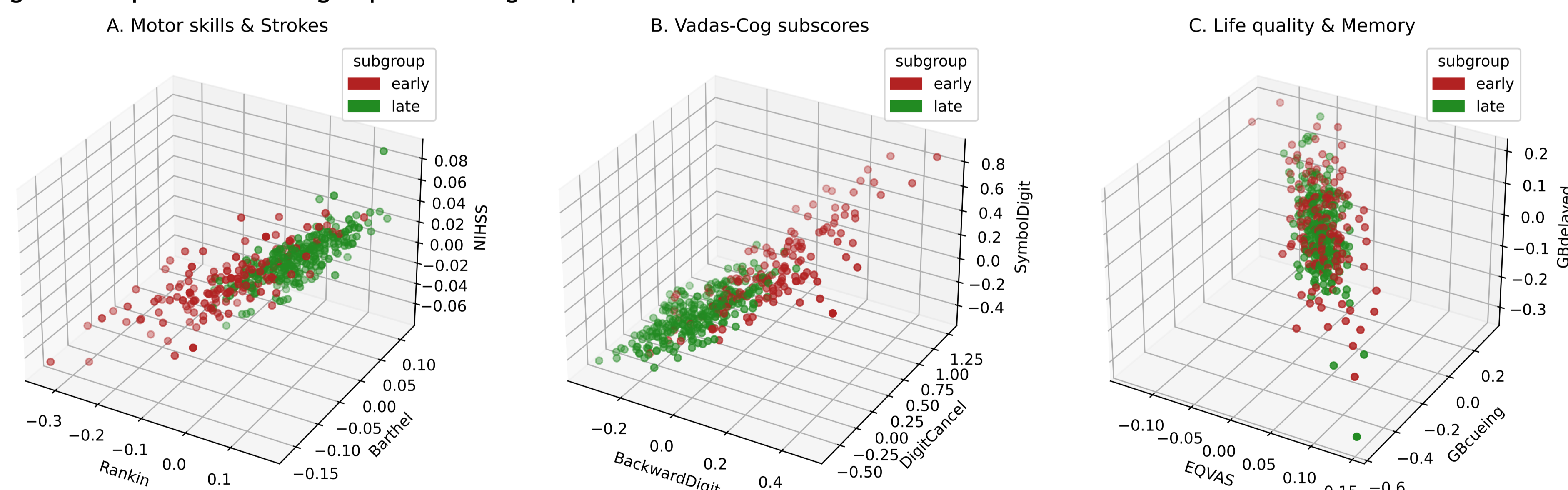
Figure 1. Repartition of subgroups according to temporal parameters



We implemented a Gaussian Mixture Model classification for the individual Leaspy parameters describing the spatiotemporal variability( $\tau, \xi$  and  $s$ ). The first subgroup, labelled **early**, included 37% of the patients with a **median tau of 59.02** (Q1-Q3: 48.89-66.32) and a **median xi of 0.84** (0.07-1.31) grouping the patients with an early disease onset and a fast rate of progression. The remaining 63% of the patients belonged to the second subgroup, termed **late**, with a **median tau of 69.24** (63.36-75.11) and a **median xi of -0.18** (-0.48-0.14), indicating a later disease onset and a slower progression rate. The differences are highlighted with a scatterplot and the subgroup specific distributions of the temporal parameters in Figure 1.

The differences in the space shift distributions between the two groups revealed that the **early** subgroup of patients showed **motor symptoms and neurological deficits earlier**, and the **late** subgroup a group who showed **cognitive symptoms earlier**. Memory performance and life quality was similar for the two subgroups. The repartitioning of the subgroups according to a selection of space shifts is shown in Figure 2. Once the subgroups were formed, we tested the effect of various covariates with a multivariate logistic regression and we concluded that that the early subgroup was associated with **male gender** (OR: 2.86), **lower education** (OR: 2.66), **hypertension** (OR: 1.82) and the **EGFr domains 1-6** of the mutation (OR: 1.84).

Figure 2. Repartition of subgroups according to space shifts



## Conclusion

- Profiling, which considered all aspects of **individual spatiotemporal evolution**, revealed two CADASIL subtypes. Patients with an early onset and a fast progression also develop symptoms of motor disability and strokes earlier, whereas patients with late onset and slower progression develop cognitive symptoms first.
- These subtypes are influenced by gender, education, hypertension, and the location of the mutation.

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