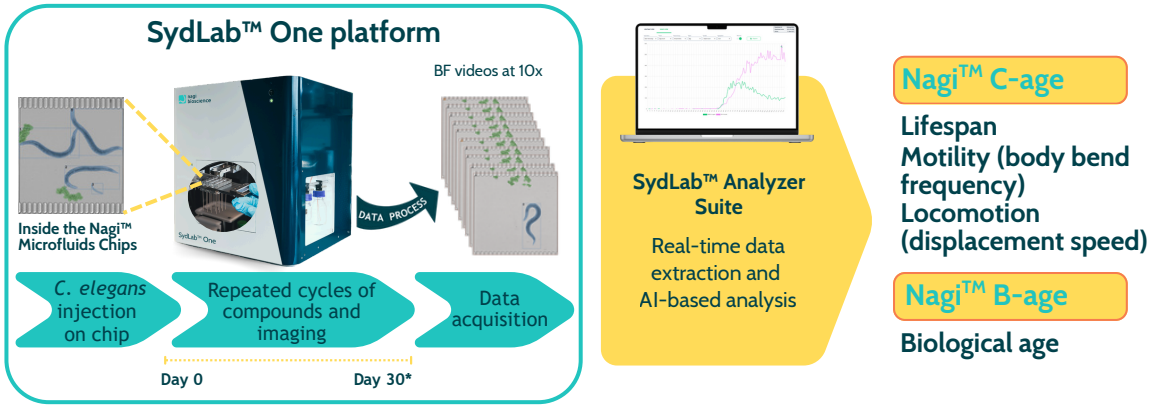
Investigating caloric restriction (CR) effects on Alzheimer's Disease (AD) progression: A *C. elegans* model study with SydLab™ One

Alzheimer's disease (AD), the most common form of dementia, is an age-related disease strongly associated with mitochondrial dysfunction and metabolic imbalance, both of which accelerate cellular and neuronal decline. Mitochondrial dysfunction, such as mitochondrial hypermetabolism, has been identified as a critical event in the onset and progression of AD (1). In parallel, caloric restriction (CR) stands out as one of the most robust approaches, consistently demonstrating beneficial effects on healthspan and lifespan across species. Its benefits are closely correlated with preserved mitochondrial integrity, highlighting the central role of mitochondrial function in aging and neurodegenerative processes (2). As mitochondrial function represents a key feature of aging and Alzheimer's disease, Prof. Palikara's research team, specialized in the molecular mechanisms of aging with particular emphasis on mitochondrial homeostasis, used *C. elegans* Alzheimer's disease models to investigate how CR influences disease progression and to gain deeper insights into its mechanistic action.

Using the **SydLab™ One platform**, the research team was able to perform precise, automated, and longitudinal monitoring of lifespan and behavioral phenotypes. In parallel, **Nagi™ B-Age** was applied to quantify biological age. This integrated toolkit provided a comprehensive picture of how CR influences both lifespan and biological aging in Alzheimer's disease nematode models.

Dual approach: SydLab™ One platform + Nagi™ B-Age



Results

C. elegans serves as a well-established nematode model for Alzheimer's disease, with transgenic strains typically expressing key pathological proteins, including amyloid-beta (Aβ) peptides and tau proteins. In this case study, wild-type nematodes (N2) were tested in parallel with nematodes expressing Tau40 and $A\beta_{1-42}$ under CR and a standard diet (ad libitum). **The results indicated that CR improves lifespan and healthspan in both the wild-type (wt) and tau-expressing populations, whereas the Aβ-expressing population shows a minimal or delayed response.**

CR extends the lifespan of *C. elegans* wild-type and tau40-expressing populations

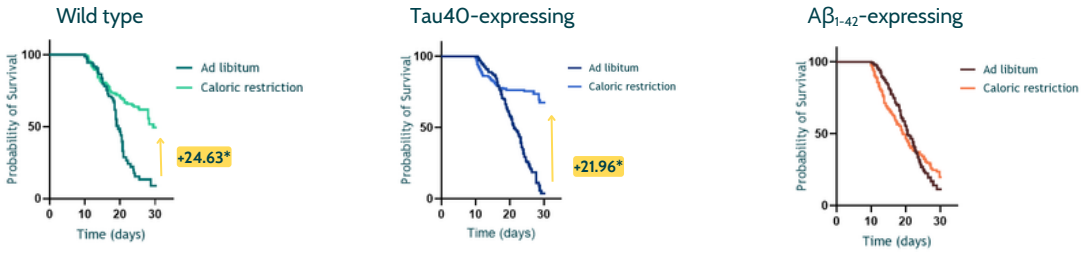


Figure 1. Survival curves of different *C. elegans* populations across their entire lifespan. Survival analyses were performed using the Kaplan-Meier method, and statistical significance between survival curves was calculated using the log-rank test. * Values show the difference between CR and standard diet in percentage p<0.05

CR enhances motility in wild-type and tau40-expressing *C. elegans* populations

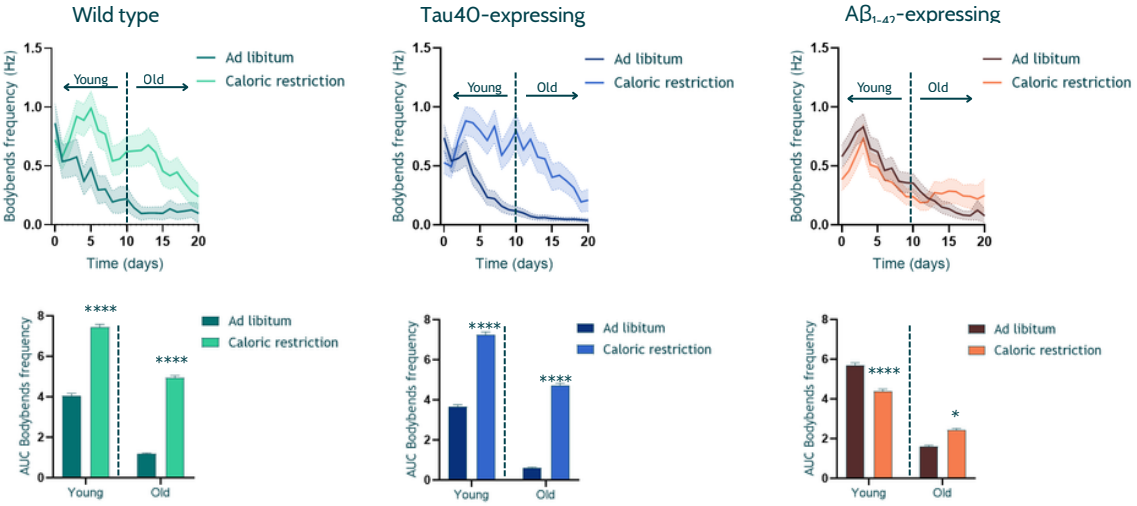


Figure 2. Body bending frequency was measured longitudinally. Statistical analysis was performed using two-way ANOVA to assess overall differences across curves, followed by Bonferroni's multiple comparisons test. * p<0.05 **** p<0.0001.

CR improves locomotion in wild-type and tau40-expressing *C. elegans* populations

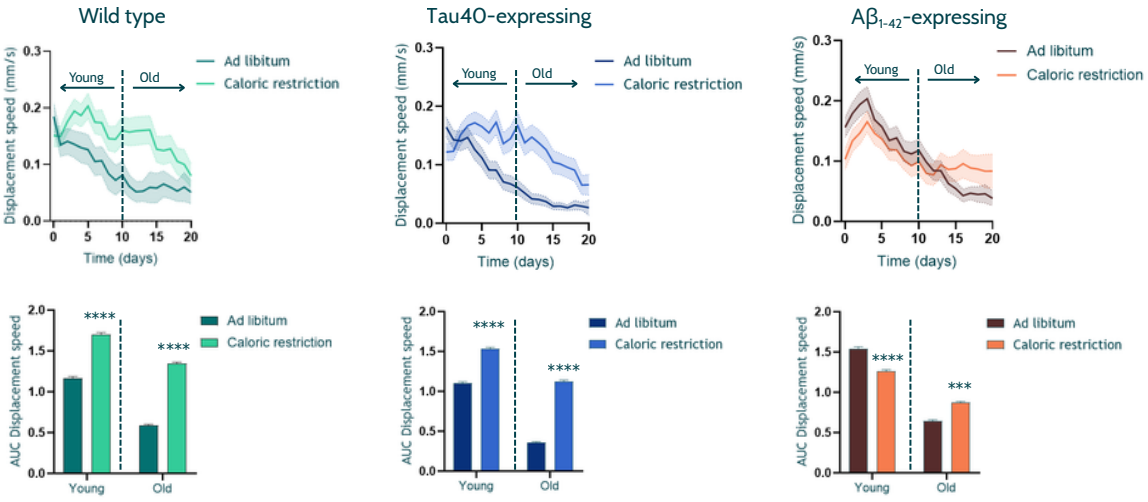


Figure 3. Locomotion was measured longitudinally. Statistical analysis was performed using two-way ANOVA to assess overall differences across curves, followed by Bonferroni's multiple comparisons test. *** p<0.001, **** p<0.0001.

Improved healthspan of wild-type and tau40-expressing *C. elegans* populations

To further explore the impact of CR on AD, Prof. Palikara's research team leveraged the novel Nagi™ B-Age, the phenotypic clock that allowed them to quantify the biological age of *C. elegans.*

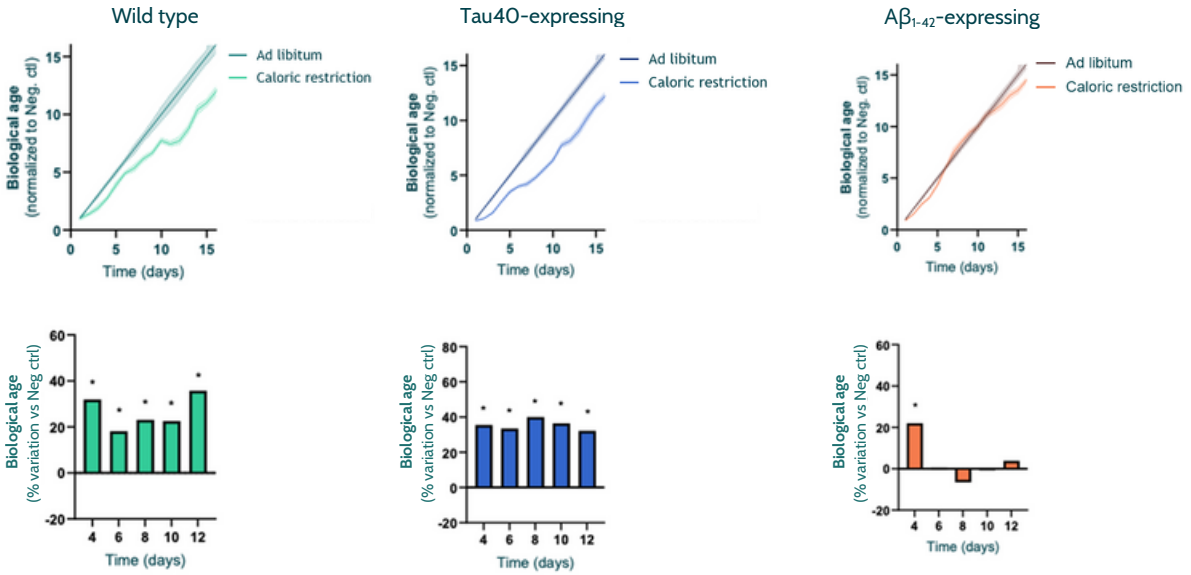


Figure 4: Evaluation of CR on the healthspan of different *C. elegans* populations using Nagi™ B-Age. Biological age was predicted for wild-type, tau40-expressing, and $A\beta_{1-42}$-expressing strains from day 0 to day 15. Statistical significance was assessed with two-way ANOVA followed by Bonferroni's multiple comparisons test. * p<0.05.

Based on all findings provided by **SydLab™ One** and **Nagi™ B-Age:**

- CR induces mitophagy in both neuronal and muscle cells of the wild-type *C. elegans* population. In this population, as well as in the tau-expressing *C.elegans* population, CR improves lifespan, reduces biological age, and enhances motility. These protective effects are consistent across multiple parameters, underscoring the role of CR in delaying age-related decline.
- In contrast, the Aβ-expressing *C.elegans* population shows only minimal or delayed responses to CR. This pathology-specific effect suggests that amyloid-driven mitochondrial dysfunction triggers metabolic stress and blunts the benefits of CR.

Collectively, Prof. Palikara's research group highlighted the need for additional or combined interventions to address metabolic defects in Alzheimer's disease models.

Having a clearer understanding of the mechanistic differences between the two AD disease models, Prof. Palikaras's team is now investigating compounds with the potential to reveal new therapeutic strategies for improving healthspan and delaying neurodegeneration.

Ready to transform your aging pipeline?

1. (Naia L. *et al.*, *Nature*. 2023). https://www.nature.com/articles/s41380-023-02289-4
2. (Green C. *et al.*, *Nature Reviews Molecular Cell Biology)* https://www.nature.com/articles/s41580-021-00411-4
3. (Teo E. *et al.*, *eLife*. 2019*)* https://elifesciences.org/articles/50069