Summary and Conclusions

Dementia is the most common form of neurodegenerative condition and is increasingly frequent as world population ages. It is a leading cause of death and is responsible for considerable morbidity, expressed in the high levels of functional dependence and need for burdensome interventions characteristic of late stages of dementia. This has profound social and economical consequences which justify a multidisciplinary approach regarding research and social interventions, aiming to minimize the impact of dementia.

The fact that there are at present no disease-modifying treatments justifies an investment in the identification of modifiable risk factors that may be contemplated in prevention strategies. The association between exposure to environmental exposures and dementia has received considerable attention. Among these, dietary habits are increasingly investigated, as occurs for most chronic illnesses. Caffeine is a widely available substance, being present in coffee, tea, soft drinks, chocolate and dietary supplements and consistent epidemiological evidence suggests that exposure to this substance is protective for Parkinson´s disease. Caffeine has the potential to induce changes in adenosine-dependent modulating mechanisms, which have been described to influence synaptic plasticity; in addition, it participates in non-adenosine dependent mechanisms that may modulate synaptic and molecular events involved in cognition. This makes caffeine a potentially interesting target for research on preventive strategies to neurodegenerative conditions, namely dementia.

Two investigations were conducted, with the following specific objectives:

- To quantify the association between caffeine intake and cognitive decline in a cohort of Portuguese urban elderly subjects (manuscript 1).
- To review systematically and summarize the published studies addressing the effect of caffeine in cognitive decline and dementia, and to discuss the methodological heterogeneity of the available evidence (manuscript 2).

Manuscript 1: Caffeine intake is associated with a lower risk of cognitive decline: a cohort study from Portugal

A cohort of 648 subjects aged ≥65 years was recruited between 1999-2003. Follow-up evaluation (2005-2008) was carried out on 58.2% of the eligible participants and 10.9% were deceased. Caffeine exposure in the year preceding baseline evaluation was assessed with a validated food frequency questionnaire. Cognitive evaluation consisted of baseline and follow-up Mini-Mental State Examination (MMSE). Cognitive decline was defined by a decrease ≥2 points in the MMSE score between evaluations. Relative risk (RR) and 95% confidence interval (95%CI) estimates adjusted for age, education, smoking, alcohol drinking, body mass index, hypertension and diabetes were computed using Poisson regression.

The present study confirms a protective effect of caffeine intake on cognitive decline, in women. Results in this group were concordant across different criteria to define levels of exposure to caffeine and when using two different endpoints: the decrease in two or more points in the MMSE ([3rd third vs 1st third]: RR=0.49, 95%CI 0.24-0.97; [≥75 mg/day vs <75 mg/day]: RR=0.47, 95%CI 0.22-0.93) and the presence of a MMSE score below the cut-off for cognitive impairment ([3rd third vs 1st third]: RR=0.10, 95%CI 0.01-0.81; [≥75 mg/day vs <75 mg/day]: RR=0.19, 95%CI 0.02-1.48). Among men, the findings were similar when considering the decrease in the MMSE score of two or more points ([3rd third vs 1st third]: RR=0.65, 95%CI 0.27-1.54), but the reduced precision of the RR estimates, due to the small number of cognitive impairment events, precluded more robust conclusions.

Manuscript 2: Caffeine intake and dementia: systematic review and meta-analysis

We reviewed studies quantifying the relation between caffeine intake and cognitive decline or dementia published up to September 2009. Published reports were identified through Medline, LILACS, Scopus, Web of Science and reference lists searches. Three independent reviewers selected the studies and extracted the data on to standardized forms. Nine cohort and two case-control studies were included.

Quantitative data synthesis of the most precise estimates from each study was accomplished through random effects meta-analysis. Heterogeneity was quantified using the I^2 statistic.

The outcomes of the studies considered for meta-analysis were Alzheimer's disease in four, dementia or cognitive impairment in two and cognitive decline in three studies.

The summary relative risk (RR) for the association between caffeine intake and different measures of cognitive impairment/decline was 0.84 (95%CI 0.72-0.99; I^2=42.6%). When considering only the cohort studies the summary RR was 0.93 (95%CI: 0.83-1.04, I^2=0.0%), and 0.77 (95%CI: 0.63-0.95, I^2=34.7%) if the most influential study was excluded.

Conclusions:

- Regarding the association between caffeine intake and cognitive decline in a cohort of Portuguese urban elderly subjects, the results do not rule out a negative association between caffeine intake and cognitive decline in men, and confirm the protective effect of caffeine in women. However, the large associations observed may be partially explained by potentially important confounding factors not accounted in the analysis.

- The systematic review and meta-analysis of studies on the association between caffeine intake and dementia/cognitive decline found a trend towards a protective effect of caffeine, but the large methodological heterogeneity across a still limited number of epidemiological studies is probably the most remarkable observation of this investigation. Further prospective studies conducted on more valid and homogeneous methodological basis are needed before robust and definite conclusions can be drawn.