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Wu L, Sun D, He Y. Coffee intake and the incident risk of cognitive disorders: A dose–response meta-analysis of nine prospective cohort studies. Clin Nutr. 2017;36(3):730–6.

What We Know, Think We Know, or Are Starting to Know

Global consumption of coffee is astounding, with up to 166-million 60kg bags estimated to be consumed in 2019/2020 [(1)]. By default, this makes caffeine the most widely consumed psychoactive drug worldwide. This means that in substantial population numbers, coffee - and the bioactive compounds in it - are consumed habitually at levels that are physiologically relevant, i.e., known to exert effects on a range of systems, from blood pressure to the brain [(2)].

Coffee, however, isn't simply caffeine, given that coffee itself is rich in polyphenols, with the main bioactive compounds in coffee [other than caffeine, which is a xanthine] including chlorogenic acids, cholinergic compounds, hydroxycinnamates, and quinic acids [(2)]. However, it is important to note that while caffeine has psychoactive effects, xanthines are not polyphenols, and caffeine itself is not as high in coffee as chlorogenic acids, which together with the other compounds mentioned above, are polyphenolic compounds [(2)]. Regular coffee consumers could consume over 1g/d of chlorogenic acids, providing a major source of dietary polyphenolic compounds [(2)].

Substantial mechanistic research exists for the cognitive effects of both caffeine and polyphenols [(2-4)]. Down-regulation of inflammation and up-regulation of endogenous antioxidant defences, together with effects on vascular function and specific domains of cognition associated with learning and memory, may all combine to underpin a neuroprotective effect of coffee, caffeine, and chlorogenic acids [(2-4)].

Thus, what of coffee and the brain in long-term studies? In the Italian Longitudinal Study on Aging, consumption of 1-2 cups of coffee per day was associated with a significant reduction in risk for mild-cognitive impairment in healthy older adults [(5)]. Interestingly, the effect was seen only in persons with habitual constant coffee consumption.

The present study analysed prospective cohort studies of coffee consumption and cognitive outcomes.

The Study

The investigators conducted a meta-analysis of coffee intake and risk of cognitive disorders, i.e., cognitive impairment, cognitive decline, dementia, and Alzheimer's Disease. To be included, a study had to:

- Have a prospective design
- Report the relationship between coffee and cognitive disorders
- Report the association using relative risks, hazard ratios, or odds ratios, and corresponding 95% confidence intervals

Coffee intake was classified according to three categories: <1 cup per day; 1-2 cups per day; >3 cups per day. A dose-response analysis was also conducted. The quality of the studies was assessed using the Newcastle-Ottawa Scale*.

*Geek Box: The Newcastle-Ottawa Scale

The Newcastle-Ottawa Scale (NOS) is a grading tool to assess the quality of non-randomised trials included in a meta-analysis. Observational studies of exposures may have small relative risks, but a large population attributable fraction (PAF): the PAF is the reduction in risk of disease across the whole population from changing an exposure. This potential population benefit means that it is important to have tools which can assess the quality of observational studies, to arrive at conclusions which may result in shifting the burden of disease in the population. The NOS uses three domains to assess the quality of cohort studies: selection of the cohorts (4 'stars' maximum), comparability of the cohorts (2 'stars' maximum) and assessment of outcome (3 'stars' maximum). 9 stars is therefore the maximum available score for a given study. Selection considers the representativeness of the exposed and non-exposed groups, the ascertainment of the exposure (for example, dietary assessment method), and clear demonstration that the entire group was free of the outcome (i.e., disease) at the start of the study. Comparability assesses the design and analysis of the cohorts, specifically what variables the study controlled/adjusted for. Outcome considers the assessment of the outcome (i.e., medical records), the follow-up duration, and the numbers included in the follow-up. The NOS is a straightforward, convenient tool to assess the quality of prospective cohort studies included in a meta-analysis.

Results: 9 prospective cohort studies were included, with a total sample size of 34,282 participants. Average age at baseline in all studies was 60yrs or over. Follow-up ranged from 1.3 to 28yrs, with less than 10yrs follow-up in 5/9 studies.

Comparing <1 cup per day to 1-2 cups per day resulted in the following:

- Overall cognitive disorders [14 studies]: 18% reduction in risk [RR 0.82, 95% CI 0.71-0.94]
- Dementia [6 studies]: 22% reduction in risk [RR 0.78, 95% CI 0.67-0.91]
- Alzheimers Disease [3 studies]: 28% reduction in risk [RR 0.71, 95% CI 0.54-0.94]

There was no significant association for cognitive impairment or cognitive decline outcomes, respectively. There was also no significant association in relation to any outcome in the analysis comparing <1 cup per day to >3 cups per day. There was no evidence of heterogeneity* between studies in the meta-analysis.

In the dose-response analysis, a "J-shaped curve" was observed, with a statistically significant benefit also observed in the 1-2 cups range.

*Geek Box: Heterogeneity

When you read a meta-analysis, you will inevitably come across the term 'heterogeneity', which reflects statistical tests for heterogeneity between the included studies. Heterogeneity between studies may relate to clinical factors, like participant characteristics or outcomes, methodological differences in study design, or variations in the results. These are all important because it can indicate that the effect of the same nominal exposure is not observed in all circumstances. You

can sometimes observe heterogeneity with your own eyes, if the forest plot of a meta-analysis shows studies either side of the 'null' 1.0 and to varying magnitudes of effect. But statistical tests provide more precision, and the two most common are the Chi-squared (χ^2) test and the I^2 test. The Chi-squared is a simple yes/no hypothesis test to determine whether heterogeneity is present, and assumes all studies are the same: if the resulting p-value is significant (which for this test is often <0.1, not the customary <0.05), this means there is heterogeneity between studies. The I^2 test measures the extent the heterogeneity expressed as a percentage: 0%-40% may not be important, 30-60% may represent moderate heterogeneity, 50%-90% substantial heterogeneity, and 75%-100% considerable heterogeneity. Heterogeneity is neither 'good' nor 'bad', as it may be often be an inevitable result of differing methodology in trial designs. It can allow for important differences to be teased out in subgroup or sensitivity analysis. However, high heterogeneity is an indication that a meta-analysis may not have been appropriate.

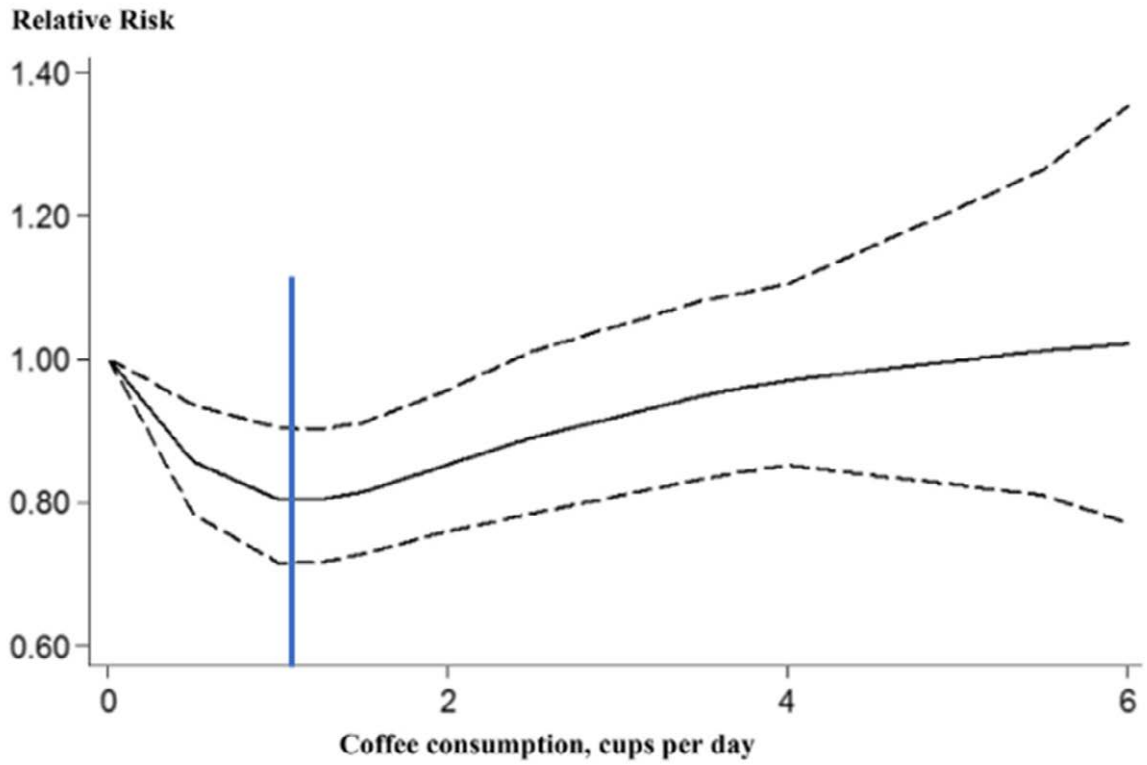


***Figure** from paper demonstrating the 'J-shaped curve' relationship coffee cups per day and cognitive disorders. I've inserted the blue vertical line to demonstrate the 'sweet spot' in the curve, also known as a biphasic dose-response [more under **Interesting Finding**, below], where the benefits of an exposure are greater than no exposure at all, but which benefits are not evident at highest exposures.*

Critical Breakdown

Pros: The inclusion criteria was clearly defined, confined to prospective cohort studies only and with clear assessment of outcome. Both a comparative analysis of high vs. low coffee consumption, and a dose-response analysis, were conducted. Sensitivity

analysis was also conducted to determine if factors like race, gender, duration of follow-up, number of participants in a study, and method of dietary assessment, influenced the results.

Cons: A majority of the weight was derived from a select number of studies. It may have been useful to include studies reporting cognitive assessments as outcomes, as a distinct subgroup analysis. With the limited number of studies, it is possible that the meta-analysis and dose-response analysis lacked sufficient power to detect associations beyond 1-2 cups of coffee per day, which reflected the significance finding in the small number of studies reporting positive associations.

Key Characteristic

The fact is that not many prospective cohort studies meet the inclusion criteria for a direct assessment of coffee intake and cognitive outcomes. In this regard, it is important to note that in the overall analysis of 14 studies, and the subgroup analysis of dementia and Alzheimers Disease [AD], the majority of the statistical weight was derived from 3 studies, and only two of these studies reported statistically significant findings. Thus, although this study was a meta-analysis, in fact the results reflect two studies in particular: the Ohsaki Cohort Study [6] from Japan, and the Canadian Study of Health and Aging [7]. Of these, the Canadian study reported only on "daily consumption", with no quantification of a dose. The Ohsaki study found a significant reduction in risk at 1-2 cups per day, however the finding for >3 cups was borderline significant [HR 0.82, 95% CI 0.65-1.02] with the trend toward reduction in risk. Taking these studies in the context of the present meta-analysis, it may be that the meta-analysis lacked sufficient power from the included studies to detect any true associations beyond 1-2 cups per day.

Interesting Finding

The 'J-shaped curve' is a common phenomenon in biological sciences, and the finding of this type of curve in the dose-response analysis of coffee is interesting given the level of phytochemical compounds in coffee. The fancy term for a J-shaped curve is a 'biphasic dose-response', which is a characteristic of a phenomena known as 'hormesis'. Hormesis describes a qualitatively different physiological response of an organism to an exposure relative to the concentration dose of the exposure, i.e., beneficial stimulatory effects are exerted at low concentrations, but negative adverse effects at higher concentrations [8]. The lower dose exposure stimulates low levels of stress, inducing inducing beneficial adaptations in an organism or cell as a compensatory response [8]. Polyphenols are treated as xenobiotics by the body, i.e., foreign compounds that the body responds to through metabolising them similar to drugs [9]. This is hypothesised to be one reason why antioxidant supplements - taking the compound in high doses - may have adverse effects [9]. Nonetheless, the consistent observation of a J-shaped curve, i.e., biphasic dose-response for coffee, implies that coffee - and the bioactive compounds it provides - may act in a similar way.

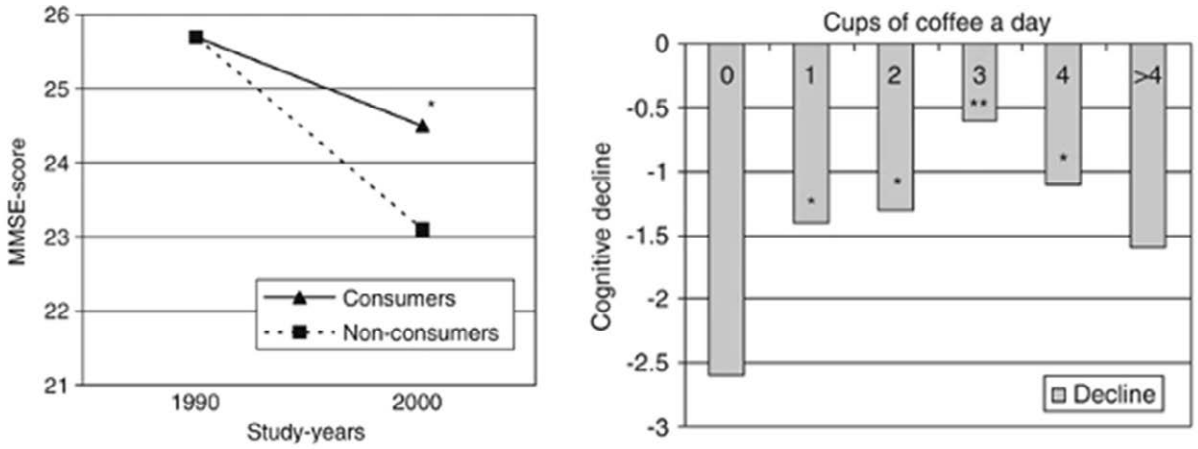
Relevance

Coffee contributes significantly to polyphenol and caffeine intake in the population, and while we tend to think of polyphenol intake in terms of fruits and vegetables, the contribution of beverages - coffee, tea, and wine - is substantial [2,4]. There is biological

plausibility for why coffee, through its bioactive compounds, may have positive effects on cognitive function [2,4].

The present meta-analysis, like any such study, is a reflection of its included studies, and in this case it is a handful of studies from which the results are derived. Nevertheless, from those handful of studies emerges a consistent picture: in the Italian Longitudinal Study on Aging 1-2 cups of coffee per day was effect, while in the Ohsaki Cohort Study 1-2 cups was significant, while >3 cups trended to significance.

The present study should also be contextualised having regard to the Finland, Italy and The Netherlands Elderly [FINE] Study [10], which was likely excluded because it reported outcomes as Mini-Mental State Examination [MMSE] scores, rather than relative risks. Nonetheless, the FINE Study demonstrated a significant protection against cognitive decline assessed by MMSE scores over a 10yr period, with a J-shaped curve indicating 3 cups per day as the most significant dose-response.



Graph from the FINE Study (10) demonstrating the decline in MMSE scores in coffee drinkers ***(left graph)*** *relative to non-drinkers, and* ***(right graph)*** *the dose-response evident, with the most significant protection against cognitive decline observed with 3 cups per day.*

Thus, the biphasic dose-response between coffee intake and cognitive outcomes - either 'hard' endpoints like dementia or 'soft' endpoints like cognitive scores - is consistent across a number of studies [5-7,10]. And, intervention studies are starting to emerge supporting beneficial effects of coffee, and chlorogenic acids, on cognitive domains [11,12].

Application to Practice

We' ll start with the caveat that coffee intake should be monitored, reduced, and/or eliminated in the context of sleep issues, hypertension, and pregnancy. Specific considerations aside, habitual coffee consumption in the range of 1-3 cups per day may have benefits for brain health over the long-term.

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