Chocolate Consumption is Associated with a Lower Risk of Cognitive Decline

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Abstract. Cocoa-related products like chocolate have taken an important place in our food habits and culture. In this work, we aim to examine the relationship between chocolate consumption and cognitive decline in an elderly cognitively healthy population. In the present longitudinal prospective study, a cohort of 531 participants aged 65 and over with normal Mini-Mental State Examination (MMSE; median 28) was selected. The median follow-up was 48 months. Dietary habits were evaluated at baseline. The MMSE was used to assess global cognitive function at baseline and at follow-up. 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 were adjusted for age, education, smoking, alcohol drinking, body mass index, hypertension, and diabetes. Chocolate intake was associated with a lower risk of cognitive decline (RR = 0.59, 95%CI 0.38–0.92). This protective effect was observed only among subjects with an average daily consumption of caffeine lower than 75 mg (69% of the participants; RR = 0.50, 95%CI 0.31–0.82). To our knowledge, this is the first prospective cohort study to show an inverse association between regular long-term chocolate consumption and cognitive decline in humans.

Keywords: Adenosine A2A receptors, Alzheimer’s disease, chocolate, cognition, prevention, theobromine

INTRODUCTION

Chocolate consumption is generally considered a pleasant widespread habit. Despite the drawbacks related to the high caloric intake associated with this practice, several potential benefits on different main systems in the human physiology have been investigated, namely in the cardiovascular, immunological, and neurological systems [1]. Many of the advantages of chocolate consumption have been attributed to the properties of some of its components, such as the polyphenolic structures named flavonoids (particularly procyanidins and flavanols) [2] and also the methylxanthine compounds present in chocolate, namely caffeine and theobromine [3]. In the past few years, the existence of enhancing cognitive effects and improvement in mood related to chocolate or chocolate components has been emphasized [4].

It is important to acknowledge that most studies evaluated the cognitive effects of chocolate, cocoa supplements, or cocoa flavonoids given as acute [5–8] and sub-acute [8–11] administration. On the other hand, several epidemiological studies looked at the potential benefits of antioxidants in general or flavonoid-rich foods on cognitive decline or the risk for dementia [12–16]. However, the potential effects of long-term consumption of chocolate on improving cognitive performance, or preventing cognitive decline, remain largely unexplored.

The present study is aimed to assess the association between long-term chocolate consumption and
cognitive decline, extending a previous analysis of the association between caffeine consumption and cognitive decline [17]. The hypothesis that chocolate could decrease the incidence of cognitive decline by at least 2 points in the score of a widely used cognitive test, the Mini-Mental State Examination (MMSE), was specifically tested in subjects aged 65 and over participating in a cohort study.

METHODS

Study population

This study was based on the evaluation of a cohort of adults living in Porto, as previously described [17]. Briefly, a total of 2,485 participants were recruited between 1999 and 2003, by random digit dialing having households as the sampling unit; when a household was selected, all residents were identified by age and gender, and one resident (aged 18 or more years) was randomly selected as the respondent, without replacement if there was a refusal. The participation rate was 70%. A visit to the Department of Clinical Epidemiology, Predictive Medicine and Public Health of Porto Medical School (former Department of Hygiene and Epidemiology of Porto Medical School) was scheduled by telephone according to the participant’s convenience. A personal interview, using a structured questionnaire comprising data on socio-demographic, clinical, and lifestyle exposures, and a physical examination was performed by trained interviewers. From the whole cohort, 648 participants were aged 65 and over and 531 were selected for the present study, after exclusion of 62 cognitively impaired at baseline (the criteria used to define cognitive impairment is defined below), 32 for whom there was no baseline MMSE, and 23 for whom there was no information on chocolate or caffeine intake.

Follow-up evaluation

The follow-up evaluation of the cohort took place between 2 to 9 years after the recruitment moment. A visit to the Porto Medical School was scheduled, for questionnaire evaluation and physical examination of the participants.

Cognitive testing

The MMSE [18, 19] was used to assess global cognitive function at baseline and at follow-up. The MMSE, which includes questions on orientation, registration, attention and calculation, recall, language, and visual construction, was originally designed for clinical practice, but is now extensively used in epidemiological studies. Although it does not assess executive function, a major feature of cognitive decline [18], the MMSE is a reliable and valid test for cognitive impairment, has high test-retest reliability, and is a good indicator of clinically significant cognitive decline [20]. The cut-off values adjusted for education levels were used as proposed in other studies [21, 22]; in the present investigation, the normative cut-off values of MMSE adjusted for education for the Portuguese population were used [19]. Subjects that had a MMSE score below cutoff at baseline were considered to be cognitively impaired and therefore excluded. Participants had to score above 15 if they were illiterate, above 22 if they had ≤ 11 years of education, and above 27 if they had > 11 years of education.

A decline of at least 2 points in the score of the MMSE from baseline to the follow-up visit was considered meaningful from a clinical point of view [23].

Chocolate and caffeine dietary intake

Dietary habits in the 12 months preceding the baseline interview were evaluated using a semi-quantitative food frequency questionnaire (FFQ) comprising 82 food and beverage items or groups. It was designed according to Willett et al. [24], and was adapted by inclusion of a variety of typical Portuguese food items and validated as previously described. For each FFQ item, subjects were asked the average frequency of consumption and the portion size usually consumed (based on a photograph manual with small, medium, and large portion sizes). This information was used to estimate the average daily intake of each item by multiplying the usual frequency of intake per day by the average portion size of the corresponding item.

The food items/groups of the FFQ used to address chocolate overall consumption were chocolate bars, chocolate snacks, and cocoa powder. Although the FFQ used in the present study required the assessment of the consumption of chocolate bars, chocolate snacks, and cocoa powder, only the overall consumption of chocolate was recorded, with no discrimination whether it was milk of dark. Food Processor Plus®, version 5.0, was used to obtain estimates of caffeine dietary intake. The food items/groups of the FFQ from which caffeine could
be obtained were: Coffee, tea, ice-tea, coke, and chocolate. A common limitation in dietary studies is the error in the estimates of nutrients. If the types of certain foods are not specified (i.e., dark chocolate versus milk chocolate), it is possible to over or underestimate true associations with outcomes [25]. In the case of chocolate, there is a wide variety on theobromine concentration among different types of chocolate and the theobromine/caffeine ratio has also been observed to be highly variable, from 1.9 to 10.6 [26]. Because of this limitation, we decided to focus on chocolate intake, data we could access directly from the FFQ.

Socio-demographic, clinical, and other behavioral factors

The assessment of socio-demographic, clinical, and other behavioral factors was previously described in detail [17] and is briefly described in footnotes of Table 1.

Statistical analysis

Data analysis was conducted in 309 subjects who at baseline were aged 65 or more and had a MMSE not compatible with cognitive impairment, and who were re-evaluated. Comparison of the baseline characteristics between subjects that were followed, died, or were lost to follow up was done using the Chi-Square or the Kruskal-Wallis tests, as appropriate, to compare all groups.

The association between chocolate intake and the development of cognitive impairment was quantified through crude and age-, education-, body mass index-, diabetes-, hypertension-, smoking- and alcohol drinking-adjusted relative risks (RR) and respective 95% confidence intervals (95%CI) using Poisson regression. Data were analyzed using STATA®, version 11.

Decline in cognitive performance was defined as a decrease of at least two points on the MMSE from the baseline assessment to follow up and impairment in cognitive performance was defined based on normative cut-off values of MMSE adjusted for education for the Portuguese population [19].

Ethics

This study was approved by a local Ethics Committee, and all participants gave written informed consent.

RESULTS

Among the 531 participants that were eligible, 309 (58.2%) completed the follow-up evaluation (median follow-up: 48 months), 58 (10.9%) died before follow-up could be accomplished and there were 164 (30.9%) losses to follow-up. Participants

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Socio-demographic, clinical, and behavioral characteristics of the cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 309)</td>
<td>(n = 58)</td>
</tr>
<tr>
<td>Sex (% women)</td>
<td>58.6</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>70 (67–74)</td>
</tr>
<tr>
<td>Age (% ≥75 years)</td>
<td>20.71</td>
</tr>
<tr>
<td>Education (years)*</td>
<td>4 (4–8)</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>6.5</td>
</tr>
<tr>
<td>&lt;12 years</td>
<td>79.2</td>
</tr>
<tr>
<td>≥12 years</td>
<td>14.2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>27.8 (25.0–29.9)</td>
</tr>
<tr>
<td>Body mass index (%)</td>
<td></td>
</tr>
<tr>
<td>≤25.0 kg/m²</td>
<td>24.59</td>
</tr>
<tr>
<td>25.0–29.9 kg/m²</td>
<td>50.49</td>
</tr>
<tr>
<td>≥30.0 kg/m²</td>
<td>24.92</td>
</tr>
<tr>
<td>Smoking (% ever smokers)</td>
<td>34.0</td>
</tr>
<tr>
<td>Alcohol drinking (% ever drinkers)</td>
<td>86.1</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>79.7</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>12.0</td>
</tr>
<tr>
<td>MMSE*</td>
<td>28 (27–29)</td>
</tr>
<tr>
<td>Caffeine intake (mg/day)*</td>
<td>32.8 (10.6–78.8)</td>
</tr>
<tr>
<td>Chocolate intake (% consumers)</td>
<td>40.1</td>
</tr>
</tbody>
</table>

*Results are presented as median (percentile 25-percentile 75).
who died during the follow-up period were more likely to be older, hypertensive, to have a lower BMI, and worse MMSE score. No statistically significant differences between the groups were found regarding education, smoking, alcohol, diabetes, and caffeine or chocolate consumption (Table 1).

About one third of the participants suffered decline in the MMSE during the follow-up, defined as ΔMMSE≤-2 between baseline and follow-up. Chocolate intake was independently associated with an about 40% lower risk of cognitive decline (Table 2). Analyzing different levels of chocolate consumption, the lower risk of cognitive decline was statistically significant for lesser levels of chocolate intake, that is, for participants with an average weekly consumption of chocolate lower than one standard portion, corresponding to three pieces of chocolate bar, one chocolate snack, or one tablespoon of cocoa powder (Table 2). To see whether the lower risk of cognitive decline in moderate chocolate consumers was modified by caffeine intake, a stratified analysis according to the levels of caffeine dietary intake was performed. The protective effect of chocolate consumption was observed only among participants with an average daily consumption of caffeine lower than 75 mg, the average caffeine content in one espresso (Fig. 1). Since the duration of follow-up was relatively heterogeneous, we conducted a sensitivity analysis including only the participants with duration of follow-up within the interquartile range of its distribution, which corresponds to approximately half the sample, confirming that chocolate intake was independently associated with a lower risk of cognitive decline. A stratified analysis by sex was also performed, and no differences were observed between women and men regarding the association of chocolate intake with a lower risk of cognitive decline.

During the follow-up few participants showed decline in the MMSE score to values below the cutoffs for cognitive impairment, and chocolate intake was not significantly associated with a decreased risk of cognitive impairment (Table 2). Similarly to the observed for cognitive decline, we found that the overall caffeine intake modified the association between chocolate consumption and cognitive impairment, and chocolate had a protective effect only among participants with the lowest levels of overall exposure to caffeine, though this was not statistically significant (Fig. 1).

**DISCUSSION**

The present results suggest that regular long-term consumption of chocolate has a protective effect on cognitive decline in elderly patients, as defined by the decrease in two or more points in the MMSE. To the best of our knowledge, this is the first prospective

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**Table 2**

Association between chocolate consumption and cognitive decline (ΔMMSE≤-2) or development of cognitive impairment

<table>
<thead>
<tr>
<th>Chocolate consumer</th>
<th>Follow-up</th>
<th>Δ MMSE≤-2</th>
<th>Cognitive impairment*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PM</td>
<td>No. subjects with outcome</td>
<td>Crude</td>
</tr>
<tr>
<td>Yes</td>
<td>7128</td>
<td>31</td>
<td>0.57 (0.37–0.87)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chocolate intake</th>
<th>Follow-up</th>
<th>Δ MMSE≤-2</th>
<th>Cognitive impairment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 portion^1 / week</td>
<td>4668</td>
<td>21</td>
<td>0.59 (0.37–0.97)</td>
</tr>
<tr>
<td>≥1 portion^1 / week</td>
<td>2460</td>
<td>10</td>
<td>0.54 (0.28–1.04)</td>
</tr>
</tbody>
</table>

RR, relative risk; 95% CI, 95% confidence interval; PM, person months; MMSE, Mini-Mental State Examination; Δ, MMSE at follow-up - MMSE at baseline. ^The normative cut-off values of MMSE adjusted to the education for the Portuguese population were used. Subjects were classified as cognitively impaired at follow-up when having a MMSE score below 16 if they were illiterate, 28 if they had < 11 years of education, 28 if they had > 11 years of education. ^adjusted for age (continuous), education (continuous), body mass index (BMI) (continuous), diabetes, hypertension, smoking (never/ever), and alcohol drinking (never/ever). Hypertension, diabetes, IMC, tobacco and alcohol consumption were assessed as previously described [17]. Arterial hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or current antihypertensive drug therapy [46]. Participants on anti-diabetic therapy and/or with fasting plasma glucose concentrations ≥ 126 mg/dL and/or diagnosed with diabetes by a health professional were considered to have diabetes mellitus [47]. BMI was calculated as weight (kg) divided by squared height (m^2), and further divided into the following categories [48]: Obese (≥30 kg/m^2), overweight (25.0–29.9 kg/m^2), normal and underweight (<24.9 kg/m^2). Regarding smoking habits and the consumption of alcoholic beverages, subjects were categorized in never- and ever-smokers and never- and ever-drinkers. ^one standard portion corresponds to three pieces of chocolate bar, one chocolate snack, or one tablespoon of cocoa powder.
Fig. 1. Effect of caffeine consumption on the association between chocolate consumption and cognitive decline or development of cognitive impairment. *Cognitive impairment was considered as decline in the MMSE score to values below the cutoffs for cognitive impairment; 75 mg was used as cut-off for caffeine consumption, corresponding to the average caffeine content in one espresso.

cohort study that specifically addresses the long-term effects of chocolate consumption on cognitive decline in humans.

Effects of cocoa-related products on animal cognitive function were previously described. One study investigated the short-term effect of a cocoa polyphenolic extract, Acticoa powder, on free radicals produced by leucocytes after heat exposure and the protective effects on subsequent cognitive impairments. The authors concluded that 14-days oral administration of Acticoa powder could protect heat-exposed rats from cognitive impairment, and suggested that the improved cognitive outcomes may have been consequence of preservation of brain function as a result of reduced inflammatory aggression, or enhanced cerebral plasticity [27]. Another study addressed the effects of long-term (12 months) oral supplementation of the same polyphenolic extract, Acticoa powder, on cognitive functions in aged rats, showing improved cognitive performance in terms of spatial memory and short- and long- term learning. In this light, the authors suggested that Acticoa powder could be beneficial in retarding age-related brain impairments, including cognitive deficits in normal ageing and perhaps neurodegenerative disorders [28].

Regarding human studies, the effects of chocolate/cocoa administration on cognition were systematically reviewed by Scholey et al. in 2013. The authors found that 3 out of the 8 studies that met the criteria for inclusion revealed evidence for cognitive enhancement following cocoa flavanols and methylxanthine intake [29]. All studies examined the cognitive effects of potentially psychoactive fractions of chocolate: 5 studies focused on cocoa flavanol fractions of cocoa [5–7, 9, 10] and 3 (from two articles) on combinations of the methylxanthines, caffeine, and theobromine [30, 31]. This review concluded that there are measurable neurocognitive effects with acute administration of cocoa flavanols, caffeine, and theobromine, in isolation and in combination, and suggested that some effects of chocolate and chocolate components could be due to attenuation of negative mood. Furthermore, the review pointed out that the dosing periods of the enrolled studies varied from 5 days to 6 weeks, and it was hypothesized that the lack of positive outcomes was related to possible methodological limitations [29]. Three other randomized controlled trials were published after this systematic review. One study recruited patients with mild cognitive impairment set to consume cocoa drinks once daily for 8 weeks providing the first evidence that regular cocoa flavanol consumption could positively enhance cognitive function in cognitively impaired adults [32]. Another study found that daily cocoa consumption for 8 weeks can improve specific aspects of cognitive performance in a group of cognitively intact older adults [11]. The third study, conducted to investigate the effects of both acute
and sub-acute (four-weeks) Theobroma cacao seed extract on mood and mental fatigue, cognitive performance and cardiovascular functioning in young, healthy adults, could find no benefit for the supplementation with this cocoa extract [8].

It is possible that regular ingestion of chocolate/cocoa might have long-term cognitive protection or enhancement effects that are not revealed in short-term studies. Notwithstanding the methodological limitations due to difficulties in controlling confounding and minimizing potential bias due to losses of follow-up, observational epidemiological studies may address consequences of long-term exposure to chocolate/cocoa. Despite not being focused solely on chocolate but also on the consumption of tea and wine, a cross-sectional study involving 2031 subjects (aged 70–74 years) by Nurk et al. in 2009, based on the food habits reported in the previous year, concluded that habitual chocolate consumers performed better in all cognitive tests applied and that the risk for poor test performance had been significantly reduced by chocolate consumption [16].

The present study confirmed in longitudinal cohort design that regular long-term consumption of chocolate has a protective effect on cognitive decline in elderly patients. Certainly this effect might be due to several components of cocoa/chocolate. The methylxanthines present in chocolate, caffeine and theobromine, are nonspecific antagonists of adenosine receptors at concentrations attained with common dietary intake [3]. Whereas caffeine is the most abundant methylxanthine in coffee, theobromine has been found to be the main xanthine in all types of chocolate [3, 33]. The combination of caffeine and theobromine in the proportions found in cacao and chocolate has been shown to display psycho-stimulant effects [30, 34]. Caffeine has been more widely explored, showing a protective effect against cognitive impairment and cognitive decline [35] and a possible preventive effect on the development of Alzheimer’s disease (AD) [36]. On the other hand, the effects of theobromine have been less studied than those of caffeine, and the potential neurobiological effects of theobromine are still poorly understood [33, 37], partially due to the prevalent idea that it is a weak central nervous system stimulant [38, 39], and has only been showed to produce very minor subjective effects compared to caffeine [40]. In fact, while theobromine displays a longer half-life compared to caffeine (7.2 h against 4.1 h) [41], theobromine seems to be 2- to 3-fold less active than caffeine as an antagonist of the adenosine A1 receptors in rat brain and at least 10-fold less active than caffeine as an antagonist of A2A receptors [42]. However, theobromine may have other actions, independent on adenosine receptors blockade, as gene inducer or repressor [37]. Interestingly, contrary to what is observed for humans, theobromine appears to be toxic in some mammals [33]. The reasons for this different profile of toxicity are not well established but this might suggest that in humans the pharmacodynamic properties of theobromine may be different from other mammals [37]. It should be kept in mind that methylxanthines are metabolized in humans by demethylation by the enzyme superfamily cytochrome P450, especially its member CYP1A2 which is responsible for more than 95% of the primary metabolism of caffeine [43]. Whereas the trimethylxanthine caffeine is metabolized to different compounds, including theobromine, theobromine does not metabolize into other dimethylxanthines (i.e., theophylline or paraxanthine), nor does it “upgrade” to the trimethylxanthine caffeine. Because of this, the consumption of cocoa-related products exposes humans both to theobromine from the demethylation of caffeine, in addition to the direct ingestion of theobromine contained in these products [33]. Remarkably, a recent study showed a significant positive correlation between the concentrations of theobromine in the cerebrospinal fluid (CSF) and in the plasma with the AD CSF biomarker Aβ42, suggesting that theobromine is associated with a healthier CSF biomarker profile and eventually may have a protective effect against the development of AD [44]. The observation that the protective effect of chocolate consumption on cognitive decline was observed only among subjects with low daily consumption of caffeine may suggest that caffeine is not the relevant component involved in this protective effect. It is interesting that the protective effects of caffeine on cognitive decline may be more consistent in women [23, 35], but we did not observe any gender differences regarding the association of chocolate intake with a lower risk of cognitive decline. Alternatively, the potential protective effect could be due to the caffeine present in chocolate, and this effect would just be masked in the population consuming higher amounts of caffeine from other sources. In any case, the importance of the methylxanthines in general for the beneficial long-term protective effects of the regular consumption of coffee or chocolate appears reinforced. This does not exclude that other components of chocolate/cocoa, such as the flavonoids, due to their antioxidant properties, could
also be relevant for the beneficial long-term effects of chocolate on cognitive decline.

Some limitations of this study must be pointed out. The protective effect of chocolate consumption on cognitive decline was driven by subjects with an average weekly consumption of chocolate lower than one standard portion. It is possible that the lack of statistical significance for greater intakes was due to the relatively small number of participants, and a larger study would clarify the dose-effect relationship. Another issue is the insufficient detail of the food questionnaire regarding the characterization of the chocolate type, namely discriminating whether it was milk of dark chocolate, as well as limited published data regarding different types of chocolate/cocoa foods and beverages, which limits a more precise quantification of its components. Finally, chocolate consumption may be related with healthy and social lifestyles that contribute to the protective effects, or some medical conditions may be overrepresented and negatively affect cognitive functions [45], and therefore residual confounding may have affected our estimates, despite several potentially important confounding factors were taken into account.

In conclusion, regular long-term consumption of chocolate has protective effects on cognitive decline in elderly patients. The specific components of chocolate and the biological mechanisms involved should be investigated in further studies. The possibility of taking advantage of simple lifestyle and dietary interventions to attenuate cognitive decline in the elderly is of great interest.

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Authors’ disclosures available online (http://j-alz.com/manuscript-disclosures/16-0142r1).

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