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Memory enhancement in Argentinian women during postpartum by the dietary intake of lignans and anthocyanins

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Highlights

Flavonols and flavanones likely are associated with enhanced storage in time of the memory systems

Tyrosols and hydroxybenzoic acids appear to be associated with mild improvements in memory.

Memory enhancement in Argentinian women during postpartum by the dietary intake of lignans and anthocyanins

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Abbreviations

RAVLT; Rey's Auditory Verbal Learning Test

HR; hit rate

MFE; memory failures of everyday

PSS; perceived stress scale

ISI; insomnia severity index

PLS; partial least squares

PPD; postpartum days

MEI; memory efficiency index

HBAs; hydroxybenzoic acids

HCA; hydroxycinnamic acids

ACNs; anthocyanins

CCs; chalcones

DHFs; dihydroflavonols

IFs; isoflavonoids

Σ; sum

α; Cronbach's coefficient

β_{PLS}; PLS regression coefficients

SE; standard error

Mdn; median

A; asymmetry

K; kurtosis

SW; Shapiro-Wilk test for normality

Abstract

Due to their polyphenolic content, vegetable foods have neuroprotective effects which provide health benefits for specific human groups. Thus, they may be a useful dietary component for women who experience mnesic variations during postpartum, and here we examined the hypothesis that polyphenols can differentially enhance memory functioning. In particular, we aimed to associate the dietary intake of polyphenols with different memory systems in Argentinian postpartum women. The daily intakes of polyphenol groups were calculated using a validated food frequency questionnaire and the Phenol-Explorer database. Short-term memory (STM), long-term memory (LTM), learning (L), lexical-semantic memory (LSM), and working memory (WM) were assessed. Partial Least Squares (PLS) regression models were used to analyze the dietary polyphenols (predictors) and memory domains (responses), taking into account demographic, obstetric, and psychological factors. The sample included 71 women, with an average age of 29.59 years (SE = 0.73). Most of these women lived in a couple (91%), were unemployed (63%), and had ≥ 12 years of formal education (72%). STM, LTM, L and LSM correlated with lignans and anthocyanins, with LTM also being correlated with flavanones, flavonols, and tyrosols, and L and LSM also being associated with flavonols. A significant correlation was also found between WM and lignans. In conclusion, a cognitive improvement was demonstrated, mainly associated with the intake of lignans and anthocyanins, in the STM, LTM, WM, L, and LSM systems of postpartum women. This is the first study to our knowledge suggesting a role of polyphenolic effects on memory functioning during postpartum.

Keywords

Memory; Lignans; Anthocyanins; Least-Squares Analysis; Women’s health; Polyphenols.

1. Introduction

It is well known that pregnancy involves changes in maternal physiology, which are necessary to maintain pregnancy, fetal development and childbirth, and also serve to ensure childcare [1]. These changes prepare the woman to face the challenges of motherhood, during which the brain is remodeled [2]. The term "maternal brain" refers to the adaptive-neurophysiological changes that begin with pregnancy and are maintained throughout a woman's life [3]. During postpartum, women experience cognitive changes associated with the maternal brain [3]. Concerning this, some studies have indicated that most women report a cognitive decline, especially in memory, with the most prevalent complaints being forgetfulness and deficits in working memory, visual memory, learning, and verbal memory [4-6].

Hippocampal and cortical remodeling are some of the neuroanatomical changes that follow maternity [6]. The hippocampus, in particular, has an important function in the consolidation of information and its storage, thereby regulating memory and learning [7]. This brain region contains a high content of steroid hormone receptors, and therefore its sensitivity increases during reproductive stages, with the hippocampus responding by modifying its structure and plasticity [7]. This significant remodeling persists for at least two years after childbirth, facilitating the adaptation of women to motherhood and the response to the needs of their children [6]. Synaptic pruning processes at the cortical level lead to a reduction in cortical thickness similar to that of puberty [8]. Both during puberty and pregnancy, the weaker brain connections are eliminated, leaving a more efficient and specialized neural network [6,8]. Research on the permanence of brain changes suggests that some of these changes may be transient and return to pre-pregnancy levels, while others may be more permanent [9].

Cognitive variations are also conditioned by other factors, such as parity, stress and insomnia [9]. For example, there is evidence of a lower performance in memory tasks in primiparous women than in multiparous ones [10,11], with primiparity being related to the high stress and anxiety associated with childbirth and childcare, which results in greater distraction and a lower performance on neuropsychological tests after childbirth. In addition, multiple reproductive experiences are associated with a greater exposure to hormones, which could be modulating the maternal brain [9].

Several nutrients and dietary compounds are neuromodulator agents, which have a positive influence on human health, such as the polyphenols, and are bioactive on the nervous system [12]. These neurotrophic compounds modulate nervous cells and their tissue environment, which can functionally modify neurotransmission [13]. Thus, the consumption of food or drinks rich in polyphenols, the largest group of phytochemicals, improves the acquisition, consolidation, storage and recovery of memory, as well as the learning and psychomotor functions [12,14]. Multiple mechanisms of action have been proposed to explain the psychoactive properties of these compounds, including the maintenance of redox homeostasis, the regulation of neurotransmitters, enzymes and receptors and an anti-inflammatory effect, among others [13]. Therefore, in the current study, we hypothesized that polyphenolic intake is associated with better memory functioning in Argentinian postpartum women, and examined the differential effects among the polyphenol groups.

2. Methods and materials

2.1. Study design and participants

This cross-sectional epidemiological study was performed on 71 lactating women from Córdoba province (Argentina) (Figure 1), who were interviewed face-to-face by health professionals trained in neuropsychology and by dietitians from Primary Care Units of the Public Health System, Maternal Neonatal Hospital "Prof. Dr. Ramón Carrillo" and the Faculty of Medical Sciences. The inclusion criteria were: adult (> 18 years-old), Cordoba inhabitant, postpartum (first six months), and breastfeeding. Exclusion criteria were pregnancy, alcohol and drug abuse, currently-active disease, neuropathology and psychological conditions (e.g. depression).

Women signed an informed consent before being voluntarily included. Data collection took place from April 2017 to April 2019. This research was performed according to the Declaration of Helsinki and current Argentinian legislation. Additionally, the study was approved by the Ethics Committee of the National Hospital of Clinics of the National University of Cordoba, with the following registration codes: RENIS-IS000548, RENIS-IS001262, and RENIS-IS002045 for the national registry, REPIS-145, REPIS-2654, and REPIS-5554 for the provincial registry of Cordoba.

2.2. Demographic characteristics

The following data were collected to determine potential associations and analytical confounding: age (years), educational level (<12 or ≥12 years of instruction), employment (yes or no), marital status (single or in a couple), number of births (primiparous or multiparous), practice of exclusive breastfeeding (yes or no), and days of postpartum [15].

2.3. Dietary assessment

The last 12-month regular dietary intake was recorded using a validated food frequency questionnaire (FFQ), which comprised 127 available food items grouped according to their nutritional profile and origin (e.g.: fruits, vegetables, alcoholic beverages, processed and ultra-processed foods, infusions and other beverages, etc.). This instrument has shown an adequate level of validity and reproducibility for Latin American populations, with a moderate overestimation of 4% and the absence of constant bias [15,16]. Women were asked about the frequency (never or number of times per month/week/day, as appropriate) and the usual portion size of each consumed food (three categories: small, medium, and large), using a validated photographic atlas based on standard portion sizes in Argentina [17].

The questionnaire data were analyzed using the Phenol-Explorer database (Version 3.6) [18], which provides values for 500 different polyphenols in over 400 foods. In the case of regional beverages (e.g. yerba mate), the polyphenols were calculated based on previous studies [19].

2.4. Cognitive assessment

All the participants underwent a general neuropsychological evaluation that included the study of attention, language, memory and executive functions. This assessment was carried out by mental health professionals trained in neuropsychology.

2.4.1. Rey's Auditory Verbal Learning Test (RAVLT)

This is a well-known tool used to evaluate episodic memory [20]. The adapted version for Argentina was used, which consists of presenting a list of the same15 words over five consecutive trials. The list is read aloud, and then the participant is immediately asked to recall as many words as he/she remembers, with the procedure being repeated 5 consecutive times (Trials 1 to 5). Then, a new list of words (List B) with 15 words is read to the participant, who again must try to immediately recall them. Next, the individual is asked to recall the words from the first list (Trial 6). After a further 30 minutes, the participant must again try to recall the words from the first list (Trial 7), and finally he/she is asked to identify the words from the first list on a sheet with 75 words (list of any random words but containing the 15 words of trial 1)

From this study, the following different scores were obtained from the raw RAVLT scores:

2.4.1.1. Short-term memory: Defined as a mnesic system that stores a limited amount of information for a short period, which is an immediate memory for the stimuli that have just been perceived. The recency index (calculated by dividing the total number of words recalled from the end of the list by the total number of words recalled), middle hit rate and recency hit rate, Trial 1 and List B (Interference Trial) were assessed [21-23].

2.4.1.2. Long-term memory: Defined as the mnesic system that stores a large amount of information for an indefinite time, which is a stable and durable memory and is little vulnerable to interference. The primacy index (calculated by dividing the total number of words recalled from the beginning of the list by the total number of words recalled), primacy hit rate, differed recall (Trial 7) and recognition were calculated [21-23].

2.4.1.3. Learning and global memory: The process by which information is acquired and transformed into a stored mental representation. Learning (Trial 5 - Trial 1), forgetting

(Trial 5- Trial 7), percentage of forgetting (Forgetting/Trial 5), overall hit rate, immediate memory (the sum of scores from 5 first trials), sum 1-6 (immediate memory + Trial 6) and memory efficiency index ([(delayed recall A/15)/(RAVLT Trials 1- 5/75)] + [(delayed recognition hits/15) - (false positive/total number of distractors)]) were obtained [21-23].

2.4.1.4. Working memory: This is a mnesic system that comprises several components (attention, inhibitory control and cognitive flexibility, among others) whose coordinated activity allows the temporary storage and manipulation of information for the execution of a task. The number of total errors (intrusions and perseverations), post-interference (Trial 7), proactive interference (List B/Trial 1) and retroactive interference (Trial 6/Trial 5) were calculated [21-23].

Hit rates (HR) were considered as the proportion of words correctly recognized on List A, and were calculated for each word as follows: word HR = (A + 0.5)/(P + 1), where A is the incidence of evocation of a word in the 5 trials and P is the total possibility of evoking the word. The primacy HR was calculated as the sum of the HR for the first four words divided by 4, the middle HR was determined as the sum of the HR of the seven words in the middle of the list divided by 7, and recency HR was calculated as the sum of the HR of the last four words of the list divided by 4. The overall HR was determined as the average word HR [21].

2.4.2. Verbal Fluency

The lexical-semantic memory is the mnesic system, which stores information through neuronal activity patterns and is interpreted as linguistic symbols of words and abstract concepts. This system was assessed using a semantic (animals) and two phonological (letter P and letter F) verbal fluency tests. Here, participants had to produce in 60 seconds as many words as they could that started with the letters P or F, and also the names of animals (no proper names or families of words were allowed). Semantic tests require lexical retrieval based on the meaning of the words, whereas phonological tests utilize the phonemes or graphemes that make up a word regardless of its meaning [24].

In addition, an excluded letter fluency test (letter A) was used as a working memory measure. Here, the participants had to produce as many words as they could in 60 seconds that did not contain the letter A (proper names and family of words were not allowed). A high fluency level in the excluded letter task implies a greater involvement of executive functions (mainly executive attention and inhibitory control), thereby representing the processing of the working memory [23].

2.4.3. Memory Failures of Everyday Questionnaire

Participants responded to a modified version of the Memory Failures of Everyday (MFE) questionnaire in the Spanish language, to explore the subjective memory complaints and related cognitive processes such as attention, perceptual recognition, and language [25]. This Spanish version of the MFE consisted of 30 items (e.g. “Forgetting a change in your daily routine” and “Getting mixed up and confused about what someone has told you”) and was designed using a 5-point Likert scale (0 to 4, where 0 indicates never and 4 corresponds to always). There is evidence of its reliability (α = 0.930), and in the present investigation, the questionnaire showed an excellent reliability (α = 0.920).

2.5. Additional assessments and measurements

2.5.1. Perceived stress

A Spanish version of the Perceived Stress Scale (PSS-10) was used [26]. This 10 item self-report scale evaluated the level of perceived stress over the previous month (e.g., “In the last month, how often have you been upset because of something that happened unexpectedly?” and “In the last month, how often have you been able to control irritations in your life?”). These items were rated on a 5-point Likert scale (0 to 4, where 0 indicates never and 4 corresponds to very frequently), with higher scores corresponding to a higher perceived stress, and the scores of items 4, 5, 6, 7, 9, 10, and 13 being reversed. In this study, PSS-10 showed an acceptable reliability (α = 0.701).

2.5.2. Sleep quality

The Insomnia Severity Index (ISI) was used to assess the nature, severity, and impact of insomnia in the last monthly period [27]. The ISI is a 7-item self-report questionnaire that evaluates the following dimensions: severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by sleep difficulties (e.g. “How satisfied/dissatisfied are you with your current sleep pattern?”). Each item was rated on a 5-point Likert scale (0 to 4, where 0 indicates no problem and 4 corresponds to a very severe problem), and the scores were transformed to a scale ranging from 0 to 28. Psychometric properties of the English and Spanish versions have been reported, with ISI being found to be a reliable and valid instrument [13]. In this study, ISI showed an acceptable reliability ($\alpha = 0.741$).

2.6. Statistical analyses

All statistical analyses were performed using the InfoStat software (version 2012, Infostat Group, Argentina). P values below 0.05 were considered to be significant ($p < 0.05$). The statistical analyses performed are summarized in Figure 1. Continuous variables were described using means, standard errors, medians and range, whereas qualitative variables were described using frequencies and percentages. A combination of asymmetry, kurtosis, histogram/P-P plot inspection and Shapiro-Wilk tests of normality was used to confirm a normal distribution of the cognitive parameters [27]. Then, associations were studied using partial least squares regression (PLS). PLS combines the principal component analysis and linear regression analysis to predict a set of dependent variables from a predictor set, giving standardized correlations (β_{PLS} coefficients) which can then be plotted as radiating lines, with their length and separation indicating variable intensity and correlation grade, respectively [28]. The PLS technique assumes the decomposition displayed in Figure 1 [29]. PLS is particularly useful in both experimental and non-experimental research when using a large set of independent variables (predictors), such as dietary, demographic, obstetric and psychological factors [30]. For the present study, different PLS models were developed based on memory systems (short-term memory, long-term memory, learning and global memory, lexical- semantic memory and working memory) and polyphenol families (flavonoids and non- flavonoids). Cognitive variables were considered as response variables, while polyphenolic intake, age, days of postpartum, perceived stress and insomnia were computed as predictors. All models were adjusted by educational level and parity. The variables included in the analysis were selected using the criterion of minimal sufficient adjustment according to a directed acyclic graph [31] (Figure 2).

Linear regression was used to calculate the food polyphenolic contribution. The internal consistency of the questionnaires was studied using Cronbach's alpha (α), with acceptable values ranging from 0.70 to 0.95. Finally, post hoc analyses showed that the sample size in this study achieved more than 85% power with an alpha of 0.05, and the minimum detectable coefficient was 0.21.

3. Results

The mean age of the study participants was 29.59 years (SE = 0.73), and 91% were in a couple. The postpartum period mean was 92.40 days (SE = 6.34), and the majority reported to be currently practicing exclusive breastfeeding (52%) and being multiparous (61%). In all, 72% had an educational level ≥ 12 years of formal instruction, and 63% indicated that they were unemployed at the moment.

As shown in Table 1, the mean intake of polyphenols was 2543.15 (135.4) mg/day, with the main contributors of these dietary polyphenols being: hydroxycinnamic acids (820.88 (67.22) mg/day), hydroxybenzoic acids (43.57 (3.69) mg/day) and lignans (39.23 (3.08) mg/day).

The descriptive statistics for cognitive performance are shown in Table 2. All variables showed levels of asymmetry and kurtosis lower than ± 2, suggesting normality. Moreover, normality was corroborated, except for MEI, List B, recognition and the number of errors in RAVLT, when analyzing data with the SW test, P-P plots and histograms (Supplemental materials).

A series of ten PLS-models were specified and tested. Table 3 and Figure 3 show five memory models based on the daily intake of flavonoids. In the first model (short-term memory), anthocyanins correlated positively with two scores: middle HR (β_{PLS} = 0.38, p = 0.0230) and List B (β_{PLS} = 0.44, p = 0.0267). The postpartum days showed a direct association with middle HR (β_{PLS} = 0.33, p = 0.0393). Regarding long-term memory (model 2), primacy effect and primacy HR were significantly associated with postpartum days (β_{PLS} = 0.31, p = 0.0448 and p = 0.0437), anthocyanins (β_{PLS} = 0.39, p = 0.0095 and p = 0.0088) and flavanones (β_{PLS} = 0.21, p = 0.0081 and p = 0.0082). Moreover, delayed recall was correlated with anthocyanins (β_{PLS} = 0.41, p = 0.0250) and flavonols (β_{PLS} = 0.21, p = 0.0400).

In the third model, learning and general memory were tested. In this sense, the PLS regression revealed that flavonols were inversely related to forgetting (β_{PLS} = -0.38, p = 0.0101) and the percentage of forgetting (β_{PLS} = -0.37, p = 0.0130), while anthocyanins correlated positively with the overall HR (β_{PLS} = 0.59, = 0.0143), RAVLT immediate (β_{PLS} = 0.43, p = 0.0222) and the sum of trials 1 to 6 (β_{PLS} = 0.44, p = 0.0413). A direct association was found between subjective memory complaints (MFE) and insomnia (β_{PLS} = 0.28, p = 0.0484). When assessing lexical-semantic memory (model 4), the “Animals” task was associated with age (β_{PLS} = 0.09, p = 0.0312), anthocyanins (β_{PLS} = 0.35, p = 0.0106) and flavonols (β_{PLS} = 0.37, p = 0.0103).

The last model revealed no significant associations among working memory-related scores and flavonoids. In most of the PLS models (Figure 3), primiparous and multiparous women with an educational level ≥ 12 years and multiparous women with education < 12 were distributed similarly in the data set, while primiparous women with educational level < 12 years showed the opposite behavior. However, women were distributed differently according to parity in the lexical-semantic memory model.

Table 4 and Figure 4 display the five models regarding memory and non-flavonoid intake. The first one (short-term memory) showed associations for middle HR with postpartum days (β_{PLS} = 0.28, p = 0.0393) and lignans (β_{PLS} = 0.46, p = 0.0342). The following model concerned long-term memory, and demonstrated that the primacy effect and primacy HR were associated with postpartum days (β_{PLS} = 0.29, p = 0.0448 and p = 0.0437), lignans (β_{PLS} = 0.41, p = 0.0030; β_{PLS} = 0.40, p = 0.0028, respectively) and tyrosols (β_{PLS} = 0.21, p = 0.0059; β_{PLS} = 0.20, p = 0.0060, respectively). Also, the consumption of lignans was related with delayed recall (β_{PLS} = 0.31, p = 0.0430). Similarly, lignans in the learning and global memory model were associated with overall HR (β_{PLS} = 0.48, p = 0.0414), RAVLT immediate (β_{PLS} = 0.54, p = 0.0347) and the sum of trials 1 to 6 (β_{PLS} = 0.55, p = 0.0191). Subjective memory complaints were negatively associated with hydroxybenzoic acids (β_{PLS} = -0.53, p = 0.0076), but positively associated with the insomnia severity index (β_{PLS} = 0.21, p = 0.0484). The lexical-semantic memory model revealed direct correlations for lignans and the verbal fluency P letter task (β_{PLS} = 0.61, p = 0.0295), and "Animals" (β_{PLS} = 0.46, p = 0.0009). "Animals" was associated with age (β_{PLS} = 0.03, p = 0.0312) and hydroxybenzoic acids (β_{PLS} = -0.01, p = 0.0219). Finally, when analyzing the working memory model, the daily intake of lignans correlated directly with the excluded "A" letter (β_{PLS} = 0.72, p = 0.0061), post-interference trial (β_{PLS} = 0.46, p = 0.0483) and retroactive interference (β_{PLS} = 0.48, p = 0.0380). As found for the models including flavonoid intakes, primiparous and multiparous women with ≥ 12 years of educational level and multiparous with < 12 years were positively correlated with each other, while primiparous women with educational level < 12 years behaved differently (Figure 4).

4. Discussion

This study investigated whether the daily intake of polyphenols in postpartum lactating women from Córdoba, Argentina, was associated with their cognitive performance. Regarding non-flavonoids, associations were found between the lignan consumption and all the mnesic domains (short-term memory, long-term memory, learning, lexical-semantic memory and working memory). To a lesser extent, tyrosols and hydroxybenzoic acids showed correlations with long-term memory and learning, respectively. On the other hand, when analyzing flavonoids, women with a high anthocyanin intake obtained higher scores in most of the mnesic domains, except working memory. Flavanones and flavanols were positively associated with long-term memory, learning, and lexical-semantic memory. Thus, our hypothesis, that polyphenolic intake is associated with better memory, was demonstrated. Moreover, it was shown that the score in tests related to short and long-term memory increased with the puerperium period.

Different studies have reported the positive effects of lignans on cognitive functions. In this sense, an investigation carried out on healthy women aged 42 to 52 years in the United States showed that the consumption of these compounds had beneficial effects on verbal memory [32]. In addition, an improvement in the functioning of the prefrontal cortex was reported in a study that evaluated the consumption of lignans [33].

Investigations in animal models have also demonstrated the neurological effect of lignans, which cross the blood-brain barrier, bioaccumulate in the hypothalamus, and modulate memory through an improvement of the cholinergic nervous system [33-35]. As well as these biological effects, some investigations have suggested the antiestrogenic and oxidative effects of lignans as possible mechanisms [36].

The interaction of flavonoids with the nervous system has also been well-documented [12]. These compounds can cross the blood-brain barrier and exert a neuroprotective effect on the cerebral architecture, thereby increasing blood flow and strengthening signaling pathways in areas related to learning and memory. Our findings are consistent with different studies suggesting that anthocyanins improve learning [37,38], short and long term memory [38-39], lexical-semantic memory [39], and working memory [40], with our results revealing associations between the intake of anthocyanins and most of these domains, except working memory.

It has been shown that other polyphenolic compounds can improve cognitive performance [12]. For example, tyrosols have been associated with beneficial effects on learning and memory [41]. These compounds are present in foods of the Mediterranean diet, and this partially explains the neuroprotective effects of this dietary pattern [42]. In our study, a direct association was found between these compounds and the primacy effect, as women who reported higher intakes could efficiently recall the initial words of the RAVLT lists. This is known as the serial position effect, and has been used for the study of long-term (primacy) and short-term memory (recency) [43]. Similarly, a previous study demonstrated that the consumption of olive oil (an important source of tyrosols) increased scores in long-term memory and verbal fluency tasks [44]. Tyrosols are rapidly metabolized and their bioavailability is low compared to other polyphenols [45]. However, pre-clinical studies found that their neuroprotective effects can be explained by an improvement in cerebral circulation [46,47] and long-term potentiation [48].

Consistent with previous research, our study found specific associations between flavanones and flavonols with long-term memory. For example, the consumption of flavanone-rich orange juice and chocolate (sources of flavonols) have been shown to improve memory in randomized trials with healthy subjects [49-51]. Similar to other flavonoids, flavonols modulate important cerebral processes such as synaptic plasticity, neuroplasticity phenomena, neuronal signaling pathways, and vascular regulation [52].

The multivariate analysis allowed us to establish the degree of associations with other variables, and we observed a positive correlation with the postpartum period and short and long-term memory. Cognitive status tends to recover as puerperium progresses, due to the adaptive process involved in motherhood [6]. In addition, a direct relationship has been observed between insomnia and subjective memory complaints. Related to this, maternal insomnia affects about 60% of women after childbirth and produces psychological distress, which can lead to cognitive complaints.

The mean polyphenol intake in this study (2543 mg/d) was higher than that reported in the Polish (1989 mg/d) [53], Danish (1626 mg/d) [54], Japanese (1326 mg/d) [55] and Spanish (1171 mg/d) [56] populations, with these differences possible depending on the specific food preferences of each country. Our study identified *yerba mate* infusions as the main contributor to polyphenol intake, which are non-alcoholic beverages characteristic of Argentina with large amounts of these compounds. The average consumption of yerba mate in our study was 1011.54 ml/d, an amount higher than that reported in national studies. *Yerba mate* plays a socializing role, and its ethnobotanical use relies on its galactagogic properties [57], which explain the higher intake in lactating women in comparison to the rest of the Argentine population. The average polyphenols provided by this traditional beverage in the present study was 616.19 mg/d, representing around 25% of the total polyphenol intake. Thus, these results suggest that the amount of *yerba mate* consumed was the main factor contributing to the intake differences reported in other populations [58]. The cultural differences affecting the consumption of traditional non-alcoholic beverages have been proposed as factors that explain variations in polyphenol consumption between countries [54,58].

To the best of our knowledge, this is the first study which reports associations between diet and cognitive status in postpartum women. Furthermore, most of the available studies evaluated these associations in pathological scenarios. Also, previous investigations of polyphenols and the nutrition of healthy women have usually focused on perimenopause, and to a lesser extent on pregnancy and adolescence. Thus, a better understanding of how diet influences the cognition of lactating puerperal women is of great interest and impact. During this vital stage, there are structural and functional modifications in the nervous system, mediated by psychoneuroimmunoendocrinological changes [9]. As a result, non-pathological variations in the cognitive state arise and are usually expressed by women as complaints, concerns, doubts and fears [9]. Although there is a growing interest in the holistic approach to the health of puerperal women, medical attention continues to focus on the care of the newborn and the genital system of the mother [9]. By identifying foods and nutrients with a neuromodulator potential, health recommendations can be made for the management of cognitive variations in women.

Finally, some limitations must be addressed. First, it should be noted that the main limitation of this study is the small sample size. However, the recommended statistical power was achieved (> 80). Second, the transverse nature of this study limits the possibility of making inferences about causality between variables [59]. It should be noted that as a multivariate methodology was used here to avoid confounding factors, the current results contribute to the available evidence and pose new questions for future research using longitudinal designs. Although the study addresses numerous memory measures, future studies should include other cognitive processes such as attention, executive functions and visuospatial skills. Finally, the FFQ utilized might be a potential limitation.

Although this methodology has been widely used in the field of nutritional epidemiology, it is known that the FFQ can produce some difficulties when estimating the intake of polyphenols that depend on various factors, such as harvest season, food processing and cooking, assessment biases and measurement errors [54,60]. However, this instrument has shown adequate validity indicators and can consider seasonal variations and cooking methods [15,16]. Furthermore, Phenol-Explorer uses the most detailed and extensive worldwide database with a confirmed validity for quantifying polyphenolic compounds [18,54]. Future research could possibly benefit by using other methodological approaches, such as direct quantification of compounds in food and polyphenolic metabolite dosing.

To our knowledge this is the first study to investigate maternal polyphenolic consumption and cognitive functioning. In conclusion, our results suggest that polyphenol-rich foods may counteract puerperal-related mnesic variations. Anthocyanins and lignans in particular revealed positive associations with all memory systems. Future research should now include the study of dietary pattern effects and other cognitive functions (e.g. attention and executive functions).

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Figure captions

Figure 1. Sampling procedure and statistical analysis flowchart.

Figure 2. Directed acyclic graph of the relationship among polyphenol intake, memory functioning, and demographic, obstetric, and psychological factors in postpartum Argentinian women. Black squares indicate the independent (Polyphenol intake) and dependent variables (Memory functioning); grey squares indicate minimal sufficient adjustment variables; white squares indicate other covariables; the bold arrow indicates the relationship between the independent and dependent variables; thin arrows indicate other causal relationships.

Figure 3. Relationship between memory and dietary intake of flavonoids in postpartum Argentinian women. Diagrams of partial least squares regression (PLS) (n = 71). ACN, anthocyanins; CC, chalcones; DHF, dihydroflavonols; IF, isoflavonoids; EL, educational level; Pp, primiparous; Mp, multiparous; R, recency; RHR, recency hit rate; MHR, middle hit rate; T1, Trial 1; LB, List B; PSS, perceived stress scale; ISI, insomnia severity index; PPD, postpartum days; P, primacy; PHR, primacy hit rate; Rcg, recognition; DR, delayed recall; MFE, memory failures of everyday; MEI, memory efficiency index; F, forgetting; %F, percentage of forgetting; L, Learning; ΣT1-6, sum trials 1 to 6; IR, immediate recall; VF-P, verbal fluency letter P; VF-F, verbal fluency letter F; VF-Animals, verbal fluency Animals; Pro-I, proactive interference; Retro-I, retroactive interference; T6, trial 6; VF-ELA, verbal fluency excluded letter A.

Figure 4. Relationship between memory and dietary intake of non-flavonoids in postpartum Argentinian women. Data are diagrams of partial least squares regression

(PLS) (n = 71). HCA, hydroxycinnamic acids; HBA, hydroxybenzoic acids; Sbn, stilbenes; Tyr, tyrosols; Lgn, lignans; EL, educational level; Pp, primiparous; Mp, multiparous; R, recency; RHR, recency hit rate; MHR, middle hit rate; T1, Trial 1; LB, List B; PSS, perceived stress; ISI, insomnia severity index; PPD, postpartum days; P, primacy; PHR, primacy hit rate; Rcg, recognition; DR, delayed recall; MFE, memory failures of everyday; MEI, memory efficiency index; F, forettings; %F, percentage of forgettings; L, Learning; ΣT1-6, sum trials 1 to 6; IR, immediate recall; VF-P, verbal fluency letter P; VF-F, verbal fluency letter F; VF-Animals, verbal fluency Animals; Pro-I, proactive interference; Retro-I, retroactive interference; T6, trial 6; VF-ELA, verbal fluency excluded letter A.

Table 1: Daily intakes of polyphenol classes and demographic characteristics of postpartum women from Argentina

	Mean	SE	Range	Mdn
Polyphenol intake (mg/day)				
Anthocyanins	17.10	2.65	0.00-92.33	9.74
Chalcones	3.18	0.47	0.00-19.37	2.74
Dihydroflavonols	1.81	0.37	0.00-16.32	0.38
Flavanols	93.70	10.73	0.55-368.18	70.67
Flavanones	50.60	5.72	0.66-195.48	32.71
Flavones	3.44	0.66	0.07-36.74	1.80
Flavonols	68.08	4.87	6.85-187.70	64.16
Hydrocoumarins	0.00	0.00	0.00-0.08	0.00
Hydroxibenzaldehyde	0.24	0.05	0.00-2.13	0.05
Hydroxibenzoic	43.57	3.69	1.62-147.41	36.92
Hydroxicinnamic	820.88	67.22	73.77-2558.84	739.55
Hydroxiphenilpropenes	0.00	0.00	0.00-0.01	0.00
Hydroxybenzoketones	0.00	0.00	0.00-0.00	0.00
Hydroxyphenylacetic	0.76	0.12	0.00-4.33	0.34
Hydroxyphenylpropanoic	0.21	0.04	0.00-1.32	0.00
Isoflavonoids	3.83	1.20	0.00-54.88	0.06
Lignanos	39.23	3.08	3.61-118.68	31.94
Stilbenes	1.49	0.30	0.00-13.12	0.32
Tyrosols	6.40	0.80	0.00-23.83	4.17
Other polyphenols	0.41	0.07	0.00-3.25	0.15
Total flavonoid intake	241.74	16.56	15.70-577.40	199.59
Total polyphenol intake	2612.09	150.04	519.64-7299.65	2423.67
Demographic characteristics				
Age (years)	29.59	0.73	19-41	30
Postpartum (days)	92.40	6.34	4-190	91
	N	*%*		
Educational level				
< 12 years of instruction	20	28		
≥12 years of instruction	51	72		
Work				
Yes	26	37		
No	45	63		
Marital status				
Single	6	9		
In couple	65	91		
Number of births				
Primiparous	28	39		
Multiparous	43	61		
Exclusive breastfeeding				
Yes	37	52		
No	34	48		

SE, Standard Errors; Mdn, Medians.

Table 2. Memory performance, insomnia and perceived stress of postpartum women from Argentina

	Mean	SE	Mdn	A	K	SW
Short-term memory						
RAVLT Trial 1	5.72	0.25	5.00	0.58	0.23	0.0917
Recency	0.68	0.02	0.70	-0.49	-0.28	0.2045
Middle HR	0.54	0.02	0.54	-0.16	-0.35	0.4759
Recency HR	0.64	0.02	0.67	-0.40	-0.48	0.2093
List B	5.29	0.29	5.00	1.01	0.99	0.0312
Long-term memory						
Primacy	0.65	0.02	0.65	-0.23	-0.74	0.4303
Primacy HR	0.62	0.02	0.63	-0.19	-0.76	0.4351
Delayed recall	10.19	0.35	10.00	-0.31	-0.56	0.6868
Recognition	12.91	0.30	14.00	-1.58	2.21	0.0000
Learning and global memory						
Learning	5.89	0.24	6.00	-0.29	-0.36	0.4054
Forgetting	1.33	0.23	1.00	0.02	0.03	0.9999
% de forgetting	0.13	0.02	0.09	0.37	-0.27	0.7334
Overall HR	0.59	0.01	0.61	-0.07	-0.47	0.9130
MEI	1.97	0.04	2.02	-0.69	0.93	0.0072
RAVLT immediate	45.72	1.33	47.00	-0.10	-0.43	0.5260
ΣT1-6	56.31	1.67	57.00	0.04	-0.46	0.9196
Memory complaints (MFE)	29.10	2.39	26.00	1.22	1.21	0.2773
Lexical-semantic memory						
PVF “P” letter	14.04	0.54	13.00	0.47	-0.61	0.0703
PVF “F” letter	9.71	0.45	9.00	0.59	0.35	0.1881
SVF “Animals”	17.41	0.69	16.00	-0.13	0.24	0.6041
Working memory						
PVF Excluded “A” letter	7.62	0.48	8.00	0.16	-0.03	0.6763
Post-interference assay	10.15	0.33	10.00	-0.21	-0.56	0.9934
Number of RAVLT errors	7.79	0.60	7.00	0.74	0.20	0.0100
Proactive interference	0.94	0.05	0.93	0.33	-0.60	0.3081
Retroactive interference	0.87	0.02	0.89	-0.25	-0.19	0.7897
Perceived stress and insomnia						
Perceived stress (PSS)	17.94	0.67	17.00	0.39	-0.27	0.3664
Insomnia (ISI)	9.79	0.60	9.00	0.43	-0.07	0.5720

SE, Standard Errors; Mdn, Medians; A, values of asymmetry; K, values of kurtosis; SW, p-values in Shapiro-Wilk test for normality; RAVLT, Rey's Auditory Verbal Learning Test; HR, Hit Rate; MEI, Memory Efficiency Index; PVF, Phonemic Verbal Fluency Test; SVF, Semantic Verbal Fluency Test; ΣT1-6, Sum of trials 1 to 6; MFE, Memory Failures of Everyday Questionnaire; PSS, Perceived Stress Scale; ISI, Insomnia Severity Index.

Table 3. Correlations among flavonoid intakes, memory systems and health characteristics of postpartum women from Argentina

	Age	PPD	ISI	PSS	ACNs	CCs	DHFs	Flavanols	Flavanones	Flavones	Flavonols	IFs
Short-term memory												
RAVL Trial I	-0.01	0.04	-0.04	0.02	0.46	-0.08	-0.27	-0.28	-0.13	0.05	0.26	-0.17
Recency	0.00	0.12	-0.08	0.10	0.40	-0.08	-0.26	-0.13	0.08	0.04	-0.04	-0.20
Middle HR	0.07	**0.33***	0.15	-0.04	**0.38***	0.14	-0.13	-0.04	-0.03	0.13	0.07	-0.26
Recency HR	-0.04	0.13	-0.07	0.07	0.42	-0.09	-0.27	-0.16	0.04	0.03	0.01	-0.21
List B	0.09	0.06	-0.03	0.11	**0.44***	0.15	-0.16	-0.08	-0.04	-0.12	-0.08	-0.03
Long-term memory												
Primacy	0.12	**0.31****	0.00	0.12	**0.39****	-0.05	-0.10	0.03	**0.21****	0.15	-0.05	0.04
Primacy HR	0.10	**0.31****	0.00	0.13	**0.39****	-0.06	-0.10	0.06	**0.21****	0.15	-0.05	0.04
Delayed recall	-0.01	0.10	0.01	-0.02	**0.41***	0.11	-0.21	-0.18	0.10	0.06	**0.27***	-0.03
Recognition	-0.23	-0.05	-0.06	0.02	0.19	0.05	-0.05	-0.01	0.07	-0.06	0.15	0.05
Learning and memory												
Learning	0.01	0.22	0.00	0.06	-0.07	0.11	0.22	0.37	0.22	0.15	-0.35	0.06
Forgetting	-0.11	-0.05	-0.20	0.09	-0.13	-0.16	0.19	0.14	-0.13	0.08	**-0.38***	-0.17
% of forgetting	-0.11	-0.07	-0.20	0.10	-0.19	-0.16	0.16	0.16	-0.13	0.03	**-0.37***	-0.15
Overall HR	0.03	0.29	0.10	0.00	**0.59***	0.10	-0.34	-0.11	0.02	0.15	0.08	-

												0.22
MEI	0.03	0.00	-0.03	0.05	0.11	0.16	-0.06	-0.15	0.17	-0.09	0.12	0.07
Immediate RAVLT	0.03	0.30	0.06	-0.01	**0.43***	0.07	-0.17	-0.17	0.04	0.19	0.14	-0.15
ΣT1-6	0.02	0.28	0.03	0.00	**0.44***	0.07	-0.21	-0.21	0.03	0.18	0.17	-0.13
MFE	-0.13	0.26	**0.28***	0.20	0.01	-0.09	0.07	0.04	0.16	-0.04	-0.26	-0.34
Lexical-semantic memory												
VF P letter	-0.13	0.02	0.14	-0.32	0.26	-0.10	-0.38	-0.13	0.04	0.18	0.33	-0.13
VF F letter	-0.10	0.08	0.28	-0.12	0.45	0.02	-0.30	-0.05	-0.17	0.04	0.17	-0.14
VF Animals	**0.09***	0.15	-0.01	-0.20	**0.35***	-0.12	-0.10	-0.10	-0.11	0.24	**0.37***	-0.14
Working memory												
VF excluded A letter	0.16	-0.09	0.11	-0.10	0.26	0.14	-0.44	-0.13	0.27	-0.18	0.08	-0.13
RAVLT errors	0.07	0.16	-0.05	-0.25	0.04	0.00	0.07	0.09	-0.15	0.36	-0.27	0.10
RAVLT Post-interference	-0.12	0.23	-0.11	-0.03	0.38	-0.04	-0.35	-0.18	-0.02	0.13	0.34	-0.04
Proactive interference	0.30	0.05	0.04	0.18	0.01	0.32	0.16	0.11	0.14	-0.26	-0.49	0.18
Retroactive interference	-0.04	0.09	-0.15	-0.07	0.15	-0.01	-0.31	-0.30	0.03	0.01	0.43	0.13

Values are beta-PLS coefficients. * $p < 0.05$; ** $p < 0.01$. RAVLT, Rey's Auditory Verbal Learning Test; HR, Hit Rate; MEI, Memory Efficiency Index; ΣT1-6, sum of trials 1 to 6; VF, Verbal Fluency Test; MFE, Memory Failures of Everyday Questionnaire; PPD, postpartum days; PSS, Perceived Stress Scale; ISI, Insomnia Severity Index; ACNs, Anthocynins; CCs, Chalcones; DHFs, Dihydroflavonoids; IFs, Isoflavonols.

Table 4. Correlations among non-flavonoid intakes, memory systems and health characteristics of postpartum women from Argentina

	Age	PPD	ISI	PSS	HBAs	HCAs	Lignans	Stilbenes	Tyrosols
Short-term memory									
RAVLT Trial 1	0.00	0.01	0.10	-0.05	-0.07	-0.14	0.34	-0.01	0.05
Recency	0.00	0.07	-0.03	0.04	-0.15	-0.14	0.25	0.00	-0.01
Middle HR	0.02	**0.28***	0.14	-0.11	-0.22	-0.20	**0.46***	0.15	0.09
Recency HR	-0.02	0.08	-0.01	0.00	-0.14	-0.11	0.24	-0.01	0.00
List B	0.06	0.09	0.00	0.01	-0.14	-0.18	0.16	0.15	0.10
Long-term memory									
Primacy	0.00	**0.29***	0.10	0.05	-0.04	-0.13	**0.41****	0.07	**0.21****
Primacy HR	-0.02	**0.29***	0.10	0.06	-0.02	-0.19	**0.40***	0.08	**0.20***
Delayed recall	0.00	0.19	0.06	-0.02	-0.03	-0.06	**0.31***	0.04	0.02
Recognition	-0.26	0.04	-0.01	0.06	-0.05	-0.29	0.35	0.15	-0.11
Learning and memory									
Learning	-0.01	0.15	-0.16	0.12	0.05	0.01	-0.19	0.22	0.01
Forgetting	-0.11	-0.20	-0.28	0.03	-0.20	-0.02	-0.16	0.12	0.02
% of forgetting	-0.12	-0.21	-0.27	0.04	-0.18	-0.03	-0.15	0.06	-0.02
Overall HR	-0.01	0.22	0.13	-0.14	-0.24	-0.11	**0.48***	0.00	0.14
MEI	0.02	0.12	-0.01	0.12	0.08	-0.11	0.10	0.06	-0.10
Immediate RAVLT	-0.04	0.26	0.09	-0.07	-0.24	-0.19	**0.54***	0.08	0.07
ΣT1-6	-0.05	0.26	0.08	-0.05	-0.21	-0.19	**0.55***	0.06	0.04
MFE	-0.21	0.15	**0.21***	0.04	**-0.53****	-0.19	0.50	0.15	-0.18
Lexical-semantic memory									
VF P letter	-0.18	-0.06	0.24	-0.48	-0.27	0.13	**0.61***	-0.34	0.10
VF F letter	-0.12	0.01	0.37	-0.31	-0.09	0.07	0.25	-0.12	0.25
VF Animals	**0.08***	0.09	0.13	-0.23	**-0.01***	-0.08	**0.46*****	0.06	0.09
Working memory									
VF excluded A letter	-0.02	-0.05	0.19	-0.38	-0.33	-0.01	**0.72****	-0.37	0.12
RAVLT errors	0.01	0.03	-0.10	-0.21	0.04	0.00	-0.16	0.03	0.21
RAVLT Post-	-	0.24	0.00	-0.01	-0.08	-0.12	**0.46***	-0.10	-0.10

interference	0.11								
Proactive interference	0.17	0.15	-0.06	0.11	-0.13	-0.19	-0.13	0.23	0.10
Retroactive interference	-0.09	0.18	0.00	-0.08	-0.08	0.00	**0.48***	-0.27	-0.11

Values are beta-PLS coefficients. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. RAVLT, Rey's Auditory Verbal Learning Test; HR, Hit Rate; MEI, Memory Efficiency Index; ΣT1-6, sum of trials 1 to 6; VF, Verbal Fluency Test; MFE, Memory Failures of Everyday Questionnaire; PPD, postpartum days; PSS, Perceived Stress Scale; ISI, Insomnia Severity Index; HBA, hydroxybenzoic acids; HCA, hydroxycinnamic acids.

Highlights

- Polyphenol intake in postpartum women is higher than in other populations.
- Anthocyanin and lignan are positively associated with memory performance.
- Flavonols and flavanones enhance the memory systems to extend storage in time.
- Tyrosols and hydroxybenzoic acids cause mild improvements in memory.

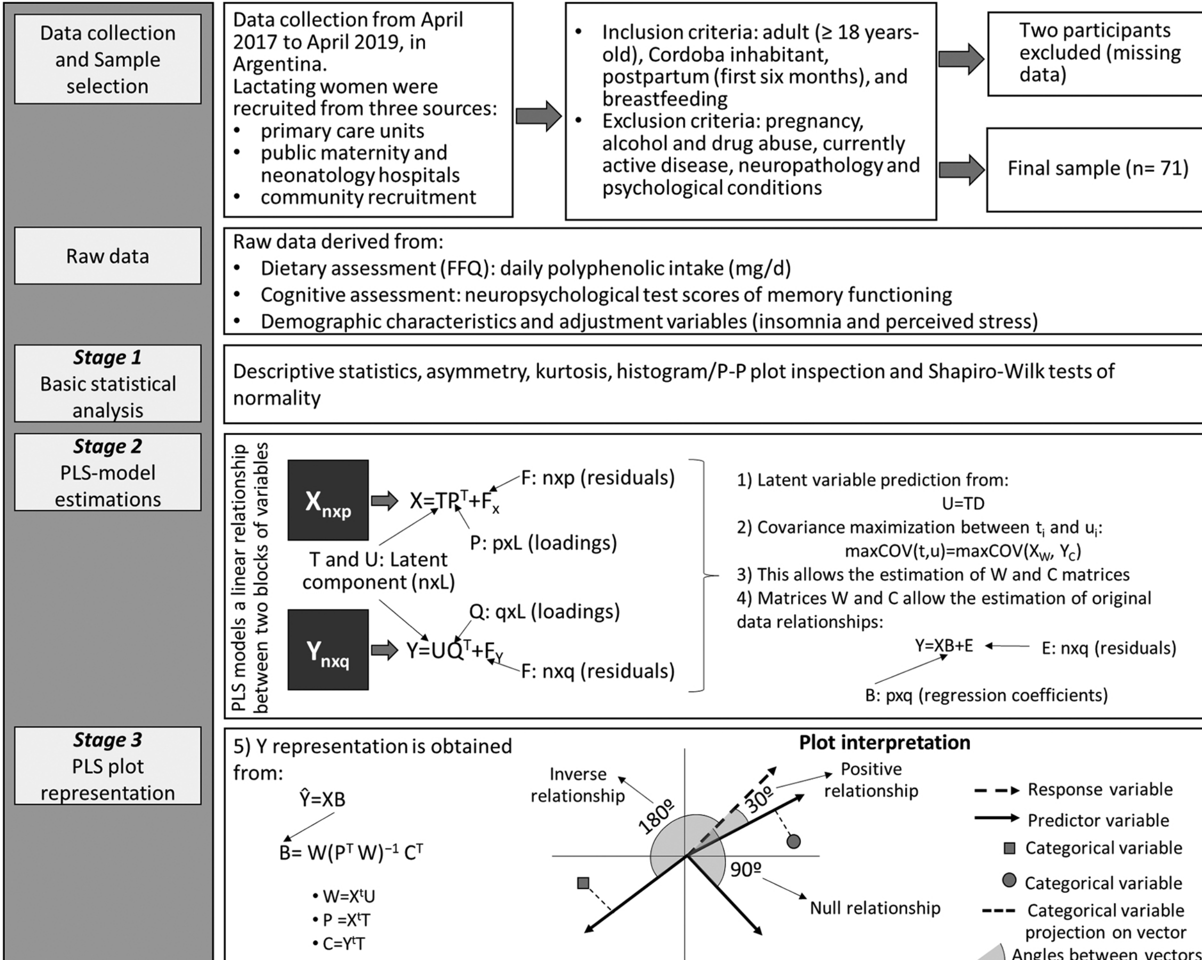

Data collection and Sample selection
Data collection from April 2017 to April 2019, in Argentina.
Lactating women were recruited from three sources:
• primary care units
• public maternity and neonatology hospitals
• community recruitment
• Inclusion criteria: adult (≥ 18 years-old), Cordoba inhabitant, postpartum (first six months), and breastfeeding
• Exclusion criteria: pregnancy, alcohol and drug abuse, currently active disease, neuropathology and psychological conditions
Two participants excluded (missing data)
Final sample (n= 71)
Raw data
Raw data derived from:
• Dietary assessment (FFQ): daily polyphenolic intake (mg/d)
• Cognitive assessment: neuropsychological test scores of memory functioning
• Demographic characteristics and adjustment variables (insomnia and perceived stress)
Stage 1
Basic statistical analysis
Descriptive statistics, asymmetry, kurtosis, histogram/P-P plot inspection and Shapiro-Wilk tests of normality
Stage 2
PLS-model estimations
PLS models a linear relationship between two blocks of variables
X_{nxp}
$X=TP^T+F_x$
F: nxp (residuals)
P: pxL (loadings)
T and U: Latent component (nxL)
Q: qxL (loadings)
Y_{nxq}
$Y=UQ^T+F_Y$
F: nxq (residuals)
1) Latent variable prediction from:
U=TD
2) Covariance maximization between t_i and u_i:
$maxCOV(t,u)=maxCOV(X_W, Y_C)$
3) This allows the estimation of W and C matrices
4) Matrices W and C allow the estimation of original data relationships:
Y=XB+E
E: nxq (residuals)
B: pxq (regression coefficients)
Stage 3
PLS plot representation
5) Y representation is obtained from:
$\hat{Y}=XB$
$B= W(P^T W)^{-1} C^T$
• $W=X^tU$
• $P =X^tT$
• $C=Y^tT$
Plot interpretation
Inverse relationship
180º
30º
Positive relationship
90º
Null relationship
Response variable
Predictor variable
Categorical variable
Categorical variable
Categorical variable projection on vector
Angles between vectors

Figure 1

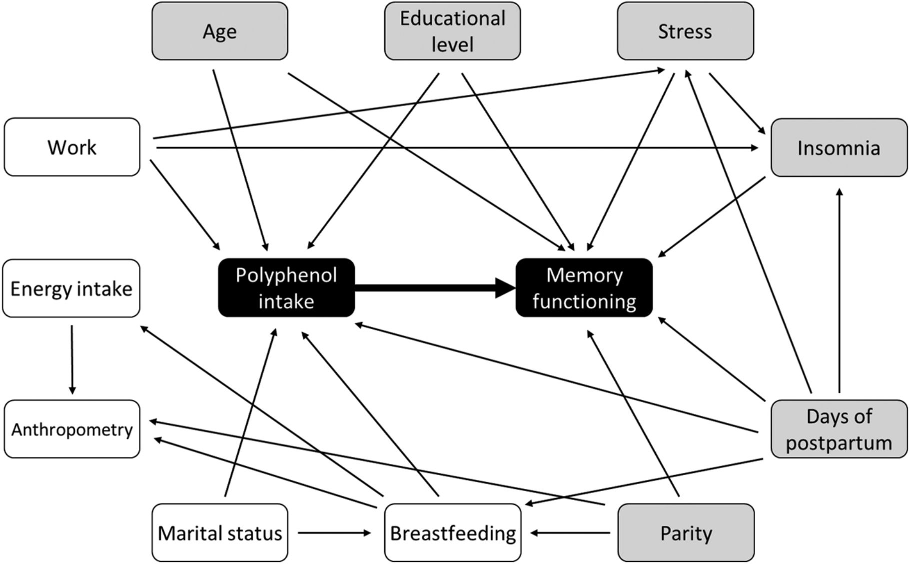
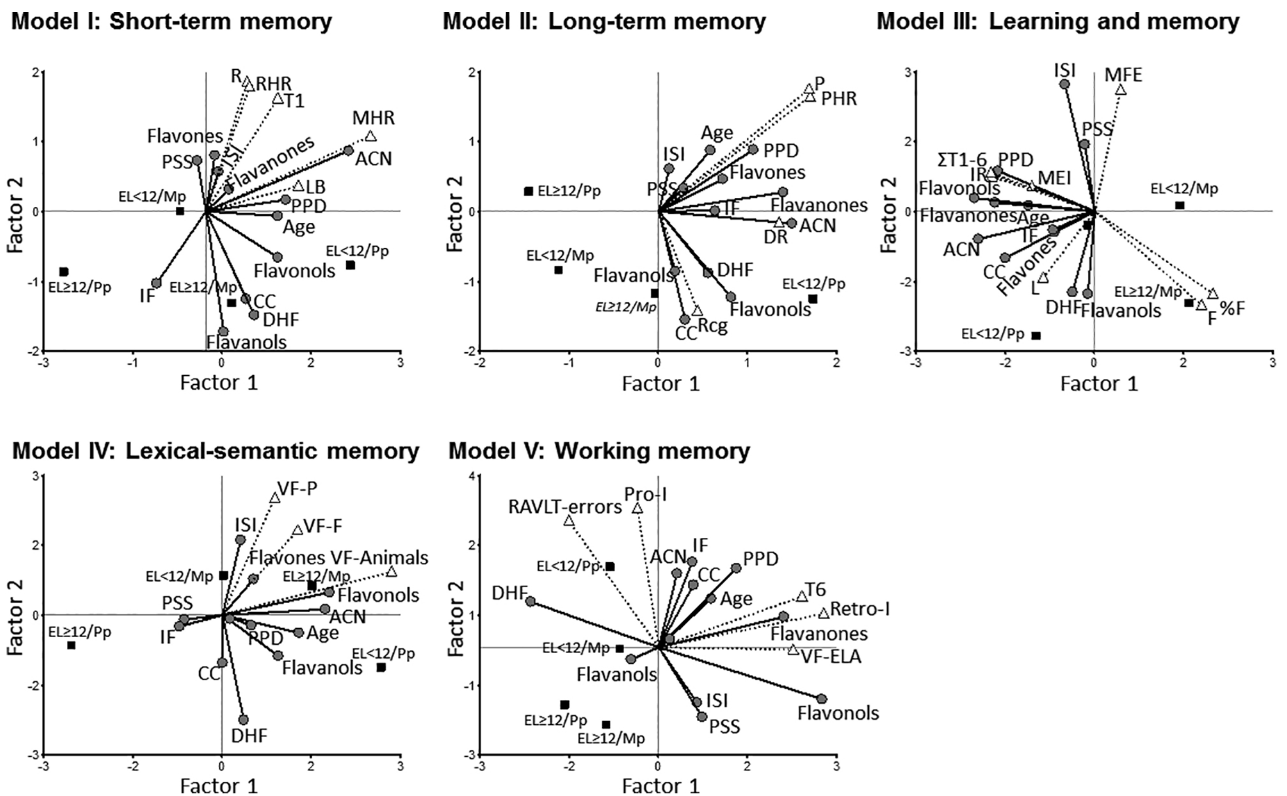
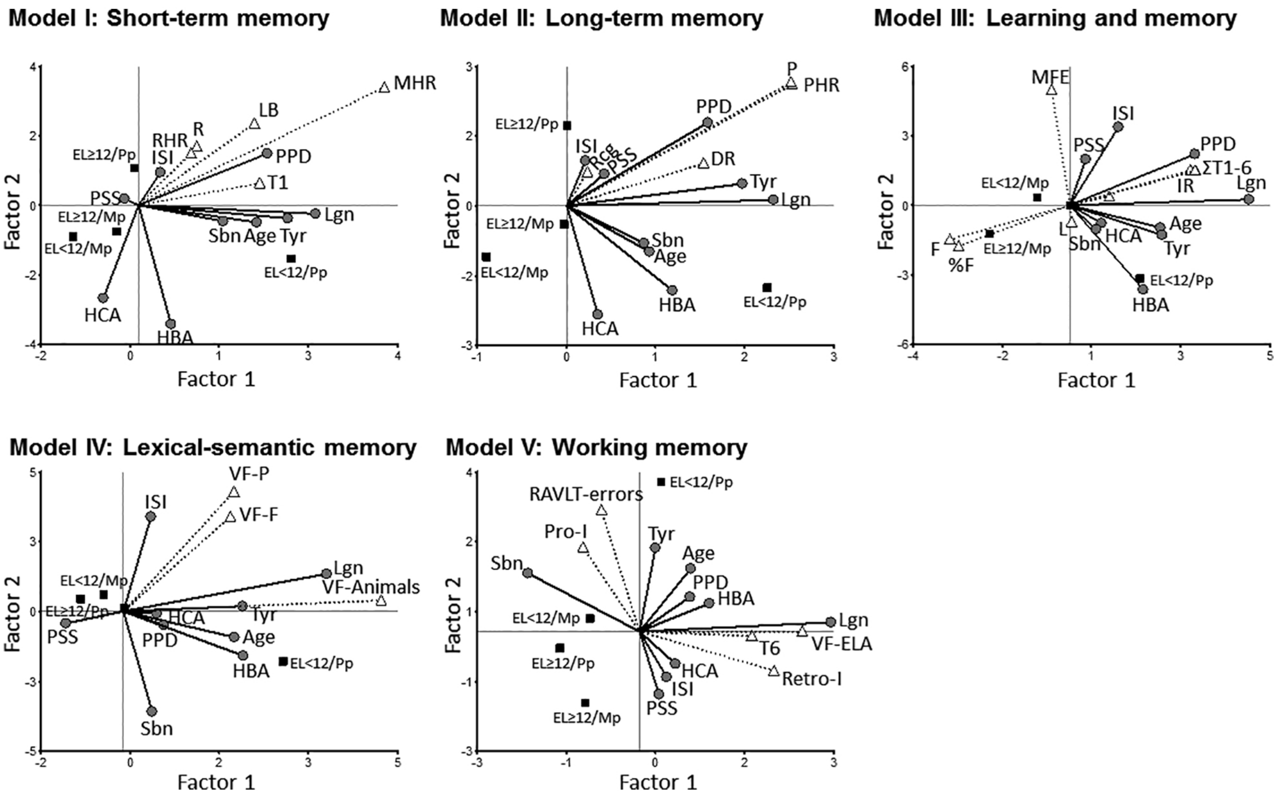

Age
Educational level
Stress
Work
Insomnia
Energy intake
Polyphenol intake
Memory functioning
Anthropometry
Days of postpartum
Marital status
Breastfeeding
Parity

Figure 2



Model I: Short-term memory
Model II: Long-term memory
Model III: Learning and memory
Model IV: Lexical-semantic memory
Model V: Working memory
Factor 1
Factor 2
R
RHR
T1
MHR
Flavones
ISI
Flavanones
PSS
ACN
LB
PPD
EL<12/Mp
Age
EL<12/Pp
Flavonols
EL≥12/Pp
IF
EL≥12/Mp
CC
DHF
Flavanols
P
PHR
DR
Rcg
ΣT1-6
IR
MEI
MFE
L
%F
F
VF-P
VF-F
VF-Animals
RAVLT-errors
Pro-I
T6
Retro-I
VF-ELA

Figure 3



Model I: Short-term memory
MHR
LB
R
RHR
ISI
PPD
T1
EL≥12/Pp
PSS
EL≥12/Mp
EL<12/Mp
Lgn
Sbn
Age
Tyr
EL<12/Pp
HCA
HBA
Factor 2
Factor 1
Model II: Long-term memory
P
PHR
PPD
EL≥12/Pp
ISI
Rcg
PSS
DR
Tyr
Lgn
EL≥12/Mp
EL<12/Mp
Sbn
Age
HBA
EL<12/Pp
HCA
Factor 2
Factor 1
Model III: Learning and memory
MFE
ISI
PSS
PPD
ΣT1-6
IR
Lgn
EL<12/Mp
Age
L
HCA
Tyr
Sbn
F
%F
EL≥12/Mp
EL<12/Pp
HBA
Factor 2
Factor 1
Model IV: Lexical-semantic memory
VF-P
ISI
VF-F
Lgn
VF-Animals
EL<12/Mp
EL≥12/Pp
HCA
Tyr
PSS
PPD
Age
HBA
EL<12/Pp
Sbn
Factor 2
Factor 1
Model V: Working memory
EL<12/Pp
RAVLT-errors
Tyr
Pro-I
Age
Sbn
PPD
HBA
EL<12/Mp
Lgn
T6
VF-ELA
EL≥12/Pp
HCA
Retro-I
ISI
PSS
EL≥12/Mp
Factor 2
Factor 1

Figure 4