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DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Qualification en Gériatrie

Supplémentation calcique et fonctions cognitives chez la personne âgée non démente: résultats de la cohorte MEMENTO

Calcium supplementation and cognitive function in older adults without dementia: results from the MEMENTO cohort

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Sous la direction de Monsieur le Professeur ANNWEILER Cédric

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Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs. Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

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J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque ».

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Liste des abréviations

95%CI	95% Confidence Interval
CDR	Clinical Dementia Rating
DMS48	Delayed Matching to Sample 48
FAB	Frontal Assessment Battery
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
NPI	Neuropsychiatric Inventory
TMT A	Trail Making Test – part A
TMT B	Trail Making Test – part B

Plan

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Calcium supplementation and cognitive function in older adults without dementia: results of the MEMENTO cohort

ABSTRACT

Introduction. Calcium is a known cardiovascular risk factor, of which homeostasis may play a role in the development of cognitive disorders in older adults. The use of calcium supplements has therefore been questioned, although they are still widely prescribed for the prevention of osteoporosis. The aim of this study was to determine whether the use of calcium supplements in non-demented older adults was associated with cognitive and behavioral disorders.

Materials and methods. The MEMENTO cohort involved 2323 patients aged 60 years and over with a subjective cognitive complaint or a recent diagnosis of mild cognitive impairment from 26 French memory consultations between April 2011 and June 2014. At enrolment, sociodemographic data, medical history and medication were collected, together with standardized clinical, biological and neuropsychological tests (global cognitive performance: MMSE; episodic memory: DMS48; executive functions: FAB, TMT A and B, Digit Span, Go/No Go). Behavioral disorders were assessed using the Neuropsychiatric Inventory (NPI) frequency and gravity scores. From these 2323 patients, we excluded the ones with no available data on serum calcium concentration and those who didn't have complete data at the time of inclusion, which corresponds to a total of 1497 participants. Age, sex, BMI, education level, marital status, functional autonomy, history of hypertension, anxiety/depression, physical performance and vitamin D supplementation were considered as potential confounders.

Results. Of the 1497 participants included in the analysis (mean, 73 years ; 61.1% women), 202 were receiving calcium supplements (n=13.5%). The use of calcium supplements was associated with longer completion times for TMT A and TMT B (respectively, β=5.03[95%CI:2.43-8.10] p=0.0014, and β=10.46[95%CI:1.14-19.77] p=0.0279), independently of potential confounding factors. No significant association was found for the other cognitive tests. The use of calcium supplements was also associated with an increase in

the frequency (β=0.75 [95%CI:0.06-1.44] p=0.0322) and severity (β=0.68[95%CI:0.16-1.19] p=0.0099) of behavioral disorders.

Conclusion. Receiving calcium supplements was associated with poorer information processing speed and mental shifting, and with more frequent and severe behavioral disorders.

INTRODUCTION

Calcium is an essential mineral in the body that has many roles, particularly in bone formation and cells signalling. Calcium deficiency is a risk factor for osteoporosis, so a daily intake of 1g to 1.5g of calcium is recommended. When dietary calcium intake is insufficient, calcium supplements are often prescribed, primarily for the elderly who are the population at maximum risk of osteoporosis.

But the use of calcium supplements has been questioned these past few years, with several studies suggesting an association between calcium supplementation and vascular events, especially cerebral ones (1,2). Given that vascular risk factors are known to promote cognitive disorders (3,4), it has become relevant to inquire about the effects of calcium supplementation on cognitive function.

First calcium has a direct toxic effect on the brain because, as it passes through the blood-brain barrier, an increase in extra-cellular calcium leads to an intra-neuronal influx of calcium via calcium channels, leading to calcium overload and neuronal death (5). Moreover, a swedish study published in 2016 in Neurology (6) showed that, in older women with cerebrovascular disease, calcium supplementation increased the risk of developing dementia after a 5-years follow up. Other studies have also shown an association between serum calcium levels, calcium supplementation and the onset and worsening of cognitive disorders in people aged over 75 years (7,8). Conversely, other studies found no link between combined calcium and vitamin D supplements and cognitive impairment in older women (9).

Thus, the objective of this study is to determinate whether the use of calcium supplements is associated with memory and/or executive function disorders in non-demented adults aged 60 years and over. The primary hypothesis proposes that calcium, as a vascular risk factor, contributes to cognitive decline in executive functions, rather than memory capacity.

MATERIALS AND METHODS

1. Study design

The MEMENTO cohort (10) is a large French cohort of participants consulting in memory clinics for either isolated cognitive complaints or recently diagnosed mild cognitive impairment (MCI). A total of 2323 patients from 26 French memory clinics were included in the study between April 2011 and June 2014, and consented to be followed over a 5-years period. In our study, we used baseline data from the participants recruited in this cohort.

2. Participants

In this study we used data from the participants recruited in the MEMENTO cohort. A participant was eligible for inclusion if they were aged 60 years or older, had at least mild cognitive impairment in one or more cognitive domains, or had subjective cognitive complaints without an objective cognitive deficit. In addition, participants had to have a Clinical Dementia Rating (CDR) ≤0.5 and not be demented. They also had to have visual and auditory acuity adequate for neuropsychological testing, to have health insurance and to give their written informed consent.

Exclusion criteria were as follows: being under guardianship, residence in skilled nursing facility, pregnant or breastfeeding women, Alzheimer disease known as being caused by gene mutation, history of intracranial surgery, neurological disease such as treated epilepsy or Parkinson's disease, brain tumour, subdural haematoma, progressive supranuclear palsy, history of head trauma followed by persistent neurological deficits, stroke diagnosed in the last 3 month preceding enrolment visit or stroke followed by persistent neurological deficits, schizophrenia history and illiteracy.

In the study presented below, we excluded patients who had no available data on serum calcium concentration, as well as those who didn't have complete data at the time of inclusion, which corresponds to a total of 1497 participants (figure 1).

3. Study examination

Baseline data collection included socio-demographic characteristics, personal and familial medical history, neurological and physical examination (including anthropometric measurements and three measures of blood pressure), neuropsychiatric symptoms presence and severity using the Neuropsychiatric Inventory (NPI), current medication intake (including calcium supplementation) and a full neuropsychological test. All data were recorded via secured online electronic data capture.

4. Outcome

The primary outcome measures were the results at global cognitive performance test (Mini-Mental State Examination (MMSE) /30), episodic memory test (Delayed Matching to Sample 48 (DMS48) /48) and executive functions tests (Frontal Assessment Battery (FAB) score /18, Trail Making Test (TMT) A and B in seconds, Digit span standard score /20 and Go/No Go score /3).

The secondary outcome measures were the Neuropsychiatric Inventory (NPI) frequency and gravity scores. The NPI being a questionnaire that assesses behavioral and psychological changes in patients diagnose with cognitive impairment. Multiple symptoms are evaluated such as delirium, hallucinations, agitation/aggressivity, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, sleep and appetite disorders. Highest scores are associated with more severe and frequent behavioral disorders.

5. Covariates

The following covariates were included as potential cofounders in the statistical models: serum calcium concentration (mmol/L), serum creatininemia concentration (µmol/L), age (years), gender, education level (≤ Primary school as reference), marital status, Body Mass Index (Kg/m^2), disability (Instrumental Activities of Daily Living score below 4 out of 4), high blood pressure (systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg), anxiety and/or depression (asked to the participants at enrolment visit), low or intermediate physical performances (Short Physical Performance Battery score below 10 out of 12), and the use of vitamin D supplements at the enrolment visit.

6. Statistical analysis

Firstly, qualitative variables were compared using a Chi-square test or a Fisher exact test, and quantitative variables were compared using a nonparametric Mann-Whitney U test.

Secondly, we applied multiple linear regression to determine the association between different cognitive scores and the use of calcium supplement (independent variable), and to determine the association between behavioral disorders and the use of calcium supplement adjusted for potential confounders.

7. Ethics

All participants in the study provided written informed consent for research. The MEMENTO study protocol has been approved by the local ethics committee ("Comité de Protection des Personnes Sud-Ouest et Outre Mer III"; approval number 2010-A01394-35), and the study was conducted in accordance with the guidelines of the Declaration of Helsinki.

RESULTS

A total of 202 cases using calcium supplements (mean±SD, 74.7±6.6 years; 89,6% women) and 1295 controls without calcium supplementation (mean±SD, 72.7±6.6 years; 56.6% women) were included in the study.

As illustrating in table 1, there was no between-group differences regarding calcium serum concentration (mean±SD, 2.37±0.10mmol/L in both groups, p=0.634), disability (14.4% in cases group versus 17.6% in controls, p=0.2546) and Mild Cognitive Impairment (MCI) (78% in cases versus 75.5% in controls, p=0.6821). In cognitive performances, controls had better results that cases at TMT A time (respectively, 49.3±20.5 seconds versus 57.3±27.0 seconds, p<0.0001), FAB score (16.2±1.9 versus 15.9±1.9, p=0396) and TMT B time (113.1±64.8 seconds versus 134.0±73.5 seconds, p<0.0001). In contrast, there were no between-group differences for MMSE score (27.8±2.0 versus 28.0±1.9 in controls, p=0.4001), DMS48 score (43.8±5.1 versus 44.4±4.1 in controls, p=0.7046), digit span (9.7±2.8 versus 10.1±3.1 in controls, p=0.2830) and Go/No Go score (2.4±0.8 in both groups, p=0.6807).

The multiple linear regression models measuring the association between different cognitive scores and the use of calcium supplements (table 2) shows that the use of calcium supplements was associated with a longer time of realisation of TMT A and B (respectively, β=5.03[95% Confidence Interval (95%CI):2.43-8.10] p=0.0014 and β=10.46[95%CI:1.14-19.77] p=0.0279). Whereas no association was found for the others cognitive tests, including FAB score.

Results of the multiple linear regression model measuring the cross-sectional association of behavioral disorders with the use of calcium supplements (adjusted for potential confounders) were reported in table 3. We found that the use of calcium supplements was positively associated with NPI frequency score (β=0.75[95%CI:0.06-1.44] p=0.0322) and NPI gravity score (β=0.68[95%CI:0.16-1.19] p=0.0099).

DISCUSSION AND CONCLUSION

The main finding of the study was that non-demented patients using calcium supplements had lower performance at TMT A and B score, irrespective of all studied potential confounders. In contrast, there were no significant differences in other cognitive tests that we studied. We also found that behavioral disorders were more frequent and severe in patients using calcium supplements.

It is consistent with the 2016 Swedish study (6) that discovered an increased risk of developing dementia, specifically vascular or mixed dementia, in older women with cerebrovascular disease using calcium supplements. However, the DSM-III criteria were used to diagnose dementia and no further analysis were conducted to determine which cognitive subdomains were primarily affected. To our knowledge, no previous study has evaluated which cognitive domains are more significantly impacted by calcium supplementation.

In our study, the TMT test is in two parts: TMT A which consists in connecting 25 numbers in a consecutive order, and TMT B which consists in connecting alternately numbers and letters in order. Both parts of the test evaluate speed of information processing and visual scanning abilities, while TMT B part additionally evaluates executive functions such as shifting, working memory and mental shifting (11, 12). We know that mental shifting is needed to adapt thinking and attention in response to environmental stimuli in order to behave appropriately.

Indeed, previous studies found that TMT test induced prefrontal cortex activation (11), which we know controls executive functions and behavioral management. On an anatomical level executive functions are linked to 3 subcortical frontal circuits: the anterior cingulate and the orbitofrontal circuits, responsible for inhibition and behavior, and the dorsolateral circuit responsible for mental shifting and information updating (13, 14). Any lesion on these circuits, whether vascular of degenerative, will result in executive functions impairment. It turns out that calcium is a vascular risk factor leading to vessels calcifications, and that this risk appears

to be higher with calcium supplements than dietary intake of calcium (15). This might be explained by highest increase in calcium serum levels with calcium supplements that dietary one (16). However, in our study serum calcium concentration wasn't significantly impacted by calcium supplements (table 1). This could be explained by the fact that we measured total uncorrected calcium and not ionized calcium, which is known to be its active form. Moreover, serum calcium levels depend on many other variables such as parathyroid hormone levels, magnesium levels and vitamin D levels, which to a certain degree are also associated with cognitive function (17,18). Unfortunately, we didn't adjust our results for these three parameters.

Furthermore, it is worth noting that no significant results were found in the other cognitive function, including global cognitive performances (MMSE) and visual episodic memory (DSM48) which are more likely impacted in neurodegenerative disorders such as Alzheimer's disease. However, lower scores in these areas might have been expected with calcium supplements, considering the impact of calcium homeostasis on the pathophysiology of Alzheimer's disease (19, 20).

Several limitations in our study should be considered. Firstly, the cohort recruitment was done in memory clinics of university hospital centres among patients with cognitive complaint or MCI diagnosis, which might not be representative of all older adults. Moreover, the median age at baseline was 73 years which is quite young for a geriatric population. Secondly, we did not know for how long calcium supplements were taken at the time of inclusion, which might impact our results. Moreover, the observational design of the study prevents determining if calcium supplements precipitate cognitive disorders, compared to an interventional longitudinal study. It would be interesting to investigate the long-term effects of calcium supplements in a longitudinal study, or by comparing the results with those at the end of the 5-year MEMENTO follow-up.

In conclusion, we found reduced performance in mental shifting and information processing speed and more frequent and severe behavioral disorders among older adults with cognitive complaint or MCI using calcium supplements. We found no other association of the use of calcium supplements neither with the cognitive performance as a whole nor with other studied domain-specific cognitive domains. These findings may reveal greater risks of vascular and neurodegenerative diseases with calcium supplementation. Further longitudinal studies are needed to confirm these associations and to determine the long-term effects of calcium supplementation on neurocognitive health and function.

BIBLIOGRAPHIE

1. Bolland, M. J., A. Grey, A. Avenell, G. D. Gamble, et I. R. Reid. « Calcium Supplements with or without Vitamin D and Risk of Cardiovascular Events: Reanalysis of the Women's Health Initiative Limited Access Dataset and Meta-Analysis ». *BMJ* 342, nº apr19 1 (19 avril 2011): d2040-d2040. https://doi.org/10.1136/bmj.d2040

2. Larsson, Susanna C., Jarmo Virtamo, et Alicja Wolk. « Potassium, Calcium, and Magnesium Intakes and Risk of Stroke in Women ». *American Journal of Epidemiology* 174, nº 1 (1 juillet 2011): 35-43. https://doi.org/10.1093/aje/kwr051

3. Skoog, Ingmar, et Deborah Gustafson. « Hypertension, Hypertension-Clustering Factors and Alzheimer's Disease ». *Neurological Research* 25, nº 6 (septembre 2003): 675-80. https://doi.org/10.1179/016164103101201986

4. Kloppenborg, Raoul P., Esther van den Berg, L. Jaap Kappelle, et Geert Jan Biessels. « Diabetes and Other Vascular Risk Factors for Dementia: Which Factor Matters Most? A Systematic Review ». *European Journal of Pharmacology* 585, nº 1 (6 mai 2008): 97-108. https://doi.org/10.1016/j.ejphar.2008.02.049

5. Berliocchi, Laura, Daniele Bano, et Pierluigi Nicotera. « Ca2+ Signals and Death Programmes in Neurons ». *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 360, nº 1464 (29 décembre 2005): 2255-58. https://doi.org/10.1098/rstb.2005.1765

6. Kern, Jürgen, Silke Kern, Kaj Blennow, Henrik Zetterberg, Margda Waern, Xinxin Guo, Anne Börjesson-Hanson, Ingmar Skoog, et Svante Östling. « Calcium Supplementation and Risk of Dementia in Women with Cerebrovascular Disease ». *Neurology* 87, nº 16 (18 octobre 2016): 1674-80. https://doi.org/10.1212/WNL.0000000000003111.

7. Schram, Miranda T., Stella Trompet, Adriaan M. Kamper, Anton J. M. de Craen, Albert Hofman, Sjoerd M. Euser, Monique M. B. Breteler, et Rudi G. J. Westendorp. « Serum Calcium and Cognitive Function in Old Age ». *Journal of the American Geriatrics Society*

55, nº 11 (novembre 2007): 1786-92. https://doi.org/10.1111/j.1532-5415.2007.01418.x.

8. Ma, Ling-Zhi, Zi-Xuan Wang, Zuo-Teng Wang, Xiao-He Hou, Xue-Ning Shen, Ya-Nan Ou, Qiang Dong, Lan Tan, et Jin-Tai Yu. « Serum Calcium Predicts Cognitive Decline and Clinical Progression of Alzheimer's Disease ». *Neurotoxicity Research* 39, nº 3 (juin 2021): 609-17. https://doi.org/10.1007/s12640-020-00312-y.

9. Rossom, Rebecca C., Mark A. Espeland, Joann E. Manson, Maurice W. Dysken, Karen C. Johnson, Dorothy S. Lane, Erin S. LeBlanc, Frank A. Lederle, Kamal H. Masaki, et Karen L. Margolis. « Calcium and Vitamin D Supplementation and Cognitive Impairment in the Women's Health Initiative ». *Journal of the American Geriatrics Society* 60, nº 12 (décembre 2012): 2197-2205. https://doi.org/10.1111/jgs.12032.

10. Dufouil, Carole, Bruno Dubois, Bruno Vellas, Florence Pasquier, Frédéric Blanc, Jacques Hugon, Olivier Hanon, et al. « Cognitive and Imaging Markers in Non-Demented Subjects Attending a Memory Clinic: Study Design and Baseline Findings of the MEMENTO Cohort ». *Alzheimer's Research & Therapy* 9, nº 1 (29 août 2017): 67. https://doi.org/10.1186/s13195-017-0288-0.

11. Lancia, Stefania, Jongkwan Choi, Jiyeong Baek, Silvia Mammarella, Denise Bianco, Valentina Quaresima, et Marco Ferrari. « Trail Making Test Induces Prefrontal Cortex Activation as Revealed by a Cw Wearable-Wireless FNIRS/DOT Imager ». *Advances in Experimental Medicine and*

Biology 1072 (2018): 139-44. https://doi.org/10.1007/978-3-319-91287-5_22.

12. Amieva, H., S. Lafont, S. Auriacombe, C. Rainville, J. M. Orgogozo, J. F. Dartigues, et C. Fabrigoule. « Analysis of Error Types in the Trial Making Test Evidences an Inhibitory Deficit in Dementia of the Alzheimer Type ». *Journal of Clinical and Experimental Neuropsychology* 20, nº 2 (avril 1998): 280-85. https://doi.org/10.1076/jcen.20.2.280.1161.

13. Cummings, J. L. « Frontal-Subcortical Circuits and Human Behavior ». *Archives of Neurology* 50, nº 8 (août 1993): 873-80. https://doi.org/10.1001/archneur.1993.00540080076020.

14. Krueger, Casey E., Victor Laluz, Howard J. Rosen, John M. Neuhaus, Bruce L. Miller, et Joel H. Kramer. « Double Dissociation in the Anatomy of Socioemotional Disinhibition and Executive Functioning in Dementia ». *Neuropsychology* 25, nº 2 (mars 2011): 249-59. https://doi.org/10.1037/a0021681.

15. Bolland, Mark J., Alison Avenell, John A. Baron, Andrew Grey, Graeme S. MacLennan, Greg D. Gamble, et Ian R. Reid. « Effect of Calcium Supplements on Risk of Myocardial Infarction and Cardiovascular Events: Meta-Analysis ». *BMJ (Clinical Research Ed.)* 341 (29 juillet 2010): c3691. https://doi.org/10.1136/bmj.c3691.

16. Green, J. Hilary, Chris Booth, et Richard Bunning. « Postprandial Metabolic Responses to Milk Enriched with Milk Calcium Are Different from Responses to Milk Enriched with Calcium Carbonate ». *Asia Pacific Journal of Clinical Nutrition* 12, nº 1 (2003): 109-19.

17. Annweiler, Cedric, David J. Llewellyn, et Olivier Beauchet. « Low Serum Vitamin D Concentrations in Alzheimer's Disease: A Systematic Review and Meta-Analysis ». *Journal of Alzheimer's Disease: JAD* 33, nº 3 (2013): 659-74. https://doi.org/10.3233/JAD-2012-121432.

18. Peeri, Noah C., Kathleen M. Egan, Weiwen Chai, et Meng-Hua Tao. « Association of Magnesium Intake and Vitamin D Status with Cognitive Function in Older Adults: An Analysis of US National Health and Nutrition Examination Survey (NHANES) 2011 to 2014 ». *European Journal of Nutrition* 60, nº 1 (février 2021): 465-74. https://doi.org/10.1007/s00394-020-02267-4.

19. Vliet, P. van, A. M. Oleksik, S. P. Mooijaart, A. J. M. de Craen, et R. G. J. Westendorp. « APOE Genotype Modulates the Effect of Serum Calcium Levels on Cognitive Function

in Old Age ». *Neurology* 72, nº 9 (3 mars 2009): 821-28. https://doi.org/10.1212/01.wnl.0000343852.10018.24.

20. Fedrizzi, Laura, et Ernesto Carafoli. « Ca2+ Dysfunction in Neurodegenerative Disorders: Alzheimer's Disease ». *BioFactors (Oxford, England)* 37, nº 3 (2011): 189-96. https://doi.org/10.1002/biof.157.

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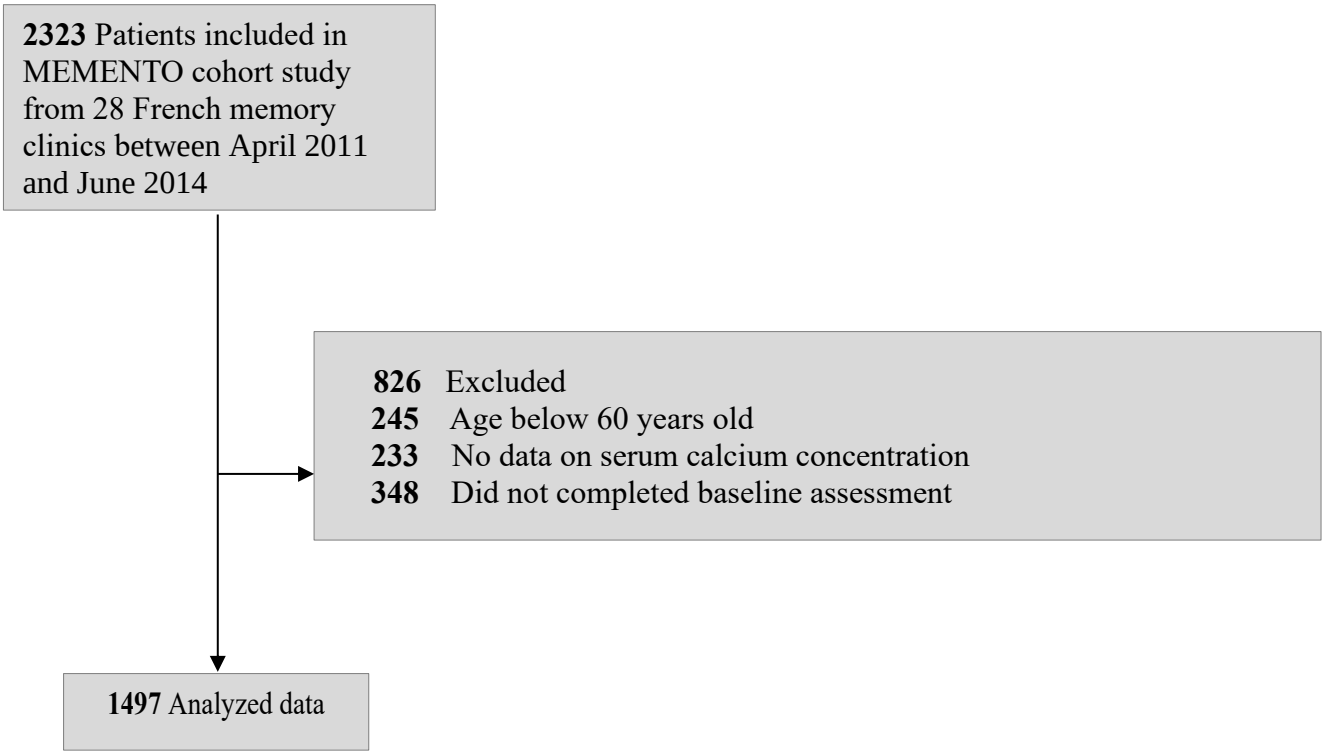

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Table I. Baseline characteristics according to the use of calcium supplements (n=1497).

	Total cohort (n=1497)	Use of calcium supplements		P-value*
		No (n=1295)	Yes (n=202)	
Serum calcium concentration (mmol/L)	2.37±0.10	2.37±0.10	2.37±0.10	0.6340
Serum creatinemia concentration (µmol/L)	73.0±17.9	73.6±18.2	69.2±14.9	**0.0024**
Demographical measures:				
Age (years)	73.0±6.7	72.7±6.6	74.7±6.6	**<0.0001**
Women	914(61.1)	733(56.6)	181(89.6)	**<0.0001**
Education level (≤ Primary school as ref.)				**0.0003**
Vocational training certificate	335(22.4)	280(21.6)	55(27.2)	
Baccalaureat degree	325(21.7)	275(21.2)	50(24.5)	
≥ Superior	626(41.8)	569(43.9)	57(28.2)	
Single status	552(36.9)	446(34.4)	106(52.5)	**<0.0001**
Clinical measures :				
BMI	25.6±4.2	25.8±4.2	24.2±3.9	**<0.0001**
Disability †	257(17.2)	228(17.6)	29(14.4)	0.2546
MCI (*n=484)* ‡	367(75.8)	321(75.5)	46(78.0)	0.6821
Hypertension $	745(49.8)	647(50.0)	98(48.5)	0.7021
Anxiety and/or depression	792(52.9)	683(52.7)	109(54.0)	0.7468
Low or intermediate physical performance ¶	365(24.4)	306(23.6)	59(29.2)	0.0859
Use of vitamin D supplements	308 (20.6)	240(18.5)	68(33.7)	**<0.0001**
Cognitive performance				
MMSE score (/30)	28.0±1.9	28.0±1.9	27.8±2.0	0.4001
TMT A time (sec) *(n=1491)*	50.4±21.7	49.3±20.5	57.3±27.0	**<0.0001**
Deferred DMS48 score (/48) *(n=1479)*	44.3±4.3	44.4±4.1	43.8±5.1	0.7046
FAB score (/18) *(n=1491)*	16.1±1.9	16.2±1.9	15.9±1.9	**0.0396**
TMT B time (sec) *(n=1458)*	115.9±66.4	113.1±64.8	134.0±73.5	**<0.0001**
Digit span – standard score (/20) *(n=1478)*	10.1±3.1	10.1±3.1	9.7±2.8	0.2830
Go/No Go score (/3) *(n=1487)* |	2.4±0.8	2.4±0.8	2.4±0.8	0.6807

BMI : Body Mass Index (measure of weight in kilograms divided by height in meters squared); MCI : Mild cognitive impairment; MMSE : Mini Mental State Examination; TMT A : Trail Making Test – part A; DMS48 : Delayed Matching to Sample 48; FAB : Frontal Assessment Battery; TMT B : Trail Making Test – part B;

† : Instrumental Activities of Daily Living score below 4 out of 4;

‡ : Taking into account the Global Clinical Dementia Rating (CDR) scales filled in with a caregiver. MCI status was considered if the CDR score was equal to 0.5 out of 3.

$: Systolic blood pressure ≥ 140 mmHg or Diastolic blood pressure ≥ 90 mmHg

¶ : Short Physical Performance Battery score below 10 out of 12.

| : FAB subscore for cognitive inhibition;

*: comparisons based on Chi-square test or the Fisher exact test for qualitative variables, and the Student's t-test or the nonparametric Mann-Whitney U test for quantitative variables, as appropriate;

Table II. Results of multiple linear regression models measuring the association between different cognitive scores (dependent variables) and the use of calcium supplements (independent variable).

	Global cognitive performances (MMSE score) n=1497			**Speed of information processing** (TMTA time) n=1491			**Visual episodic memory** (Deferred DMS48 score) n=1479			**Executive Functions**										
										FAB score n=1491			Shifting (TMTB time) n=1458			Updating (Digit Span standard note) n=1478			Cognitive inhibition (Go/No Go score) n=1487		
	β	IC 95%	p-value	β	IC 95%	p-value	β	IC 95%	p-value	β	IC 95%	p-value	β	IC 95%	p-value	β	IC 95%	p-value	β	IC 95%	p-value
Use of calcium supplements	0.04	[-0.23; 0.31]	0.7786	5.03	[2.43; 8.10]	**0.0014**	-0.39	[-1.02; 0.23]	0.2191	-0.15	[-0.42 ; 0.12]	0.2881	10.46	[1.14; 19.77]	**0.0279**	-0.23	[-0.69; 0.24]	0.3382	0.03	[-0.10; 0.16]	0.6524
Calcium (mmol/L)	-0.29	[-1.15 ; 0.57]	0.5112	12.25	[2.43 ; 22.07]	**0.0145**	-0.75	[-2.75 ; 1.24]	0.4580	0.17	[-0.70 ; 1.04]	0.6984	22.06	[-7.68 ; 51.80]	0.1459	-1.84	[-3.31 ; -0.37]	**0.0143**	0.10	[-0.31 ; 0.52]	0.6302
Creatinémie	0.004	[-0.001;0.010]	0.1341	0.01	[-0.05;0.08]	0.7355	0.00	[-0.01;0.01]	0.7581	0.00	[-0.01;0.01]	0.2466	-0.13	[-0.33;0.07]	0.1928	0.00	[-0.01;0.01]	0.3365	0.00	[-0.01;0.01]	0.5425
Age (years)	-0.02	[-0.04;0.01]	**0.0011**	0.76	[0.59;0.93]	**<0.0001**	-0.11	[-0.14;-0.07]	**<.0001**	-0.05	[-0.07;-0.04]	**<.0001**	2.12	[1.61;2.64]	**<.0001**	0.06	[0.03;0.09]	**<0.0001**	-0.016	[-0.023;0.009]	**<0.0001**
Women	0.20	[-0.03;0.43]	0.0829	0.29	[-2.32;2.90]	0.8289	0.83	[0.30;1.36]	**0.0023**	0.29	[0.05;0.52]	**0.0155**	-3.52	[-11.42;4.40]	0.3836	0.12	[-0.28;0.51]	0.5595	0.03	[-0.08;0.14]	0.5733
Education level (≤ Primary school as ref.)			**<0.0001**			**<0.0001**			**<0.0001**			**<0.0001**			**<0.0001**			**<0.0001**			**0.0012**
Vocational training certificate	0.76	[0.46;1.06]		-9.34	[-12.76;-5.92]		1.07	[0.38;1.77]		0.68	[0.37;0.98]		-36.28	[-46.85;-25.70]		0.91	[0.40;1.43]		0.08	[-0.06;0.22]	
Baccalaureat degree	1.20	[0.89;1.50]		-12.08	[-15.54;-8.62]		1.64	[0.94;2.35]		1.21	[0.90;1.51]		-56.62	[-67.25;-45.99]		1.31	[0.78;1.83]		0.13	[-0.02;0.28]	
≥ Superior	1.51	[1.23;1.78]		-12.96	[-16.15;-9.78]		2.12	[1.48;2.77]		1.35	[1.06;1.63]		-58.62	[-68.45;-48.79]		2.16	[1.68;2.64]		0.24	[0.11;0.38]	
Single status	-0.04	[-0.23;0.16]	0.7215	-0.92	[-3.17;1.32]	0.4198	0.09	[-0.37;0.54]	0.7061	0.00	[-0.20;0.20]	0.9721	4.21	[-2.61;11.03]	0.2262	0.01	[-0.33;0.35]	0.9623	0.01	[-0.08;0.11]	0.8300
BMI	0.02	[0.001;0.04]	**0.0427**	-0.23	[-0.48;0.02]	0.0696	0.03	[-0.02;0.08]	0.2237	0.00	[-0.02;0.02]	0.8920	-0.91	[-1.66;-0.16]	**0.0172**	0.02	[-0.02;0.06]	0.2943	0.00	[-0.01;0.01]	0.5415
Disability †	-0.95	[-1.19;-0.71]	**<0.0001**	6.18	[3.44;8.91]	**<0.0001**	-1.76	[-2.32;-1.21]	**<.0001**	-0.50	[-0.74;-0.26]	**<.0001**	27.52	[19.15;35.89]	**<0.0001**	-0.63	[-1.04;-0.21]	**0.0030**	-0.07	[-0.19;0.04]	0.2175
Hypertension ‡	0.29	[-0.47;-0.11]	**0.0015**	1.15	[-0.92;3.22]	0.2746	-0.27	[-0.69;0.15]	0.2064	-0.29	[-0.47;-0.11]	**0.0020**	4.96	[-1.30;11.23]	0.1204	-0.40	[-0.71;-0.09]	**0.0119**	-0.13	[-0.22;-0.05]	**0.0025**
Anxiety and/or depression	0.06	[-0.12;0.24]	0.5153	1.71	[-0.35;3.78]	0.1034	-0.01	[-0.43;0.41]	0.9778	0.06	[-0.12;0.25]	0.4881	5.18	[-1.05;11.42]	0.1034	-0.13	[-0.44;0.18]	0.3970	-0.01	[-0.10;0.08]	0.8373
Low or intermediate physical performance $	-0.23	[-0.46;-0.01]	**0.0389**	6.42	[3.88;8.96]	**<0.0001**	-1.01	[-1.53;-0.49]	**0.0001**	-0.28	[-0.51;-0.06]	**0.0145**	13.87	[6.18;21.55]	**0.0004**	-0.47	[-0.85;-0.08]	**0.0170**	-0.02	[-0.13;0.08]	0.6800
Use of vitamin D supplements	0.002	[-0.22;0.22]	0.9890	-0.55	[-3.08;1.99]	0.6724	-0.25	[-0.76;0.27]	0.3466	0.26	[0.03;0.48]	**0.0249**	-1.40	[-9.08;6.28]	0.7202	-0.02	[-0.40;0.36]	0.9131	0.08	[-0.02;0.19]	0.1223

BMI : Body Mass Index (measure of weight in kilograms divided by height in meters squared);
† : Instrumental Activities of Daily Living score below 4 out of 4;
‡ : Systolic blood pressure ≥ 140 mmHg or Diastolic blood pressure ≥ 90 mmHg;
$: Short Physical Performance Battery score below 10 out of 12.

Table III. Multiple linear regression model showing the cross-sectional association of behavioral disorders (dependent variable) with the use of calcium supplements adjusted for potential confounders.

	Frequency (NPI frequency score) N=888			**Gravity** (NPI gravity score) N=878		
	β	IC 95%	p-value	β	IC 95%	p-value
Use of calcium supplement	0.75	[0.06;1.44]	**0.0322**	0.68	[0.16;1.19]	**0.0099**
Serum calcium concentration (mmol/L)	-1.62	[-3.92;0.68]	0.1667	-1.48	[-3.21;0.26]	0.0946
Serum creatinemia concentration (µmol/L)	-0.01	[-0.02;0.01]	0.5225	-0.00	[-0.01;0.01]	0.8465
Age (years)	-0.04	[-0.08;0.00]	0.0674	-0.03	[-0.065;-0.003]	**0.0293**
Women	-0.33	[-0.93;0.27]	0.2794	-0.19	[-0.64;0.27]	0.4193
Education level (≤ Primary school as ref.)			0.0600			0.4501
Vocational training certificate	-0.46	[-1.23;0.30]		-0.22	[-0.80;0.35]	
Baccalaureat degree	-0.99	[-1.78;-0.20]		-0.48	[-1.06;0.11]	
≥ Superior	-0.83	[-1.56;-0.11]		-0.32	[-0.86;0.23]	
Single status	-0.40	[-0.95;0.15]	0.1577	-0.01	[-0.42;0.40]	0.9599
BMI	0.00	[-0.05;0.06]	0.8727	0.03	[-0.01;0.08]	0.1351
Disability †	1.89	[1.26;2.51]	**<0.0001**	1.18	[0.72;1.64]	**<0.0001**
Hypertension ‡	-0.21	[-0.69;0.28]	0.4009	-0.13	[-0.49;0.23]	0.4696
Anxiety and/or depression	1.83	[1.36;2.31]	**<0.0001**	1.22	[0.86;1.57]	**<0.0001**
Low or intermediate physical performance $	0.89	[0.29;1.50]	**0.0039**	0.44	[-0.01;0.89]	0.0541
Use of vitamin D supplements	0.19	[-0.40;0.77]	0.5322	0.04	[-0.40;0.47]	0.8713

BMI : Body Mass Index (measure of weight in kilograms divided by height in meters squared);
† : Instrumental Activities of Daily Living score below 4 out of 4;
‡ : Systolic blood pressure ≥ 140 mmHg or Diastolic blood pressure ≥ 90 mmHg;
$: Short Physical Performance Battery score below 10 out of 12.

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CLAVEIROLE Agathe

Supplémentation calcique et fonctions cognitives chez la personne âgée non démente: résultats de la cohorte MEMENTO

RÉSUMÉ

Introduction. Le calcium est un facteur de risque cardio-vasculaire connu, dont l'homéostasie pourrait jouer un rôle dans la survenue des troubles cognitifs chez les personnes âgées. L'utilisation des suppléments calciques a dès lors été remise en cause, ceux-ci étant encore largement prescrits dans le cadre de la prévention ostéoporotique. L'objectif de cette étude est de déterminer si la prise de suppléments calciques chez les personnes âgées non démentes est associée aux troubles cognitifs et du comportement.

Matériel et Méthodes. La cohorte MEMENTO regroupe 2323 patients âgés de 60 ans et plus présentant une plainte cognitive subjective ou un diagnostic récent de troubles neurocognitifs mineurs, issus de 26 centres de consultation mémoire français entre avril 2011 et juin 2014. Etaient recueillis à l'inclusion les données socio-démographiques, antécédents médicaux, traitements médicamenteux, et étaient réalisés un examen clinique et biologique standardisés ainsi qu'une batterie de tests neuropsychologiques (performance cognitive globale : MMSE ; mémoire épisodique : DSM48 ; fonctions exécutives : BREF, TMT A et B, empan, Go/No Go). Les troubles du comportement étaient évalués par l'inventaire neuropsychiatrique (NPI) en fréquence et en sévérité. Des 2323 patients de la cohorte, nous avons exclus ceux dont les données sur les concentrations sériques de calcium n'étaient pas disponibles ainsi que ceux n'ayant pas complété l'ensemble des données à l'inclusion, correspondant à un total de 1497 participants. L'âge, le sexe, l'IMC, le niveau d'éducation, le statut marital, l'autonomie, l'hypertension artérielle, l'anxiété/dépression, les performances physiques et la supplémentation en vitamine D ont été utilisés comme potentiels facteurs de confusion.

Résultats. Sur les 1497 patients inclus dans l'étude (moyenne, 73 ans ; 61.1% de femmes), 202 utilisaient des suppléments calciques (n=13.5%). L'utilisation de suppléments calciques était associée à un temps de réalisation plus long des TMT A et B (respectivement, β=5.03[95%CI:2.43-8.10] p=0.0014 et β=10.46[95%CI:1.14-19.77] p=0.0279), indépendamment des potentiels facteurs confondants. Aucune association significative n'a été trouvée pour les autres tests cognitifs. L'utilisation de suppléments calciques était également associée à une augmentation des troubles du comportement en fréquence (β=0.75[95%CI:0.06-1.44] p=0.0322) et en sévérité (β=0.68[95%CI:0.16-1.19] p=0.0099).

Conclusion. La prise de suppléments calciques était associée à une vitesse de traitement de l'information et une flexibilité mentale plus faibles, et à de plus nombreux et sévères troubles du comportements.

Mots-clés: calcium, neurocognition, comportement, sujet âgé, gériatrie

Calcium supplementation and cognitive function in older adults without dementia: results from the MEMENTO cohort

ABSTRACT

Introduction. Calcium is a known cardiovascular risk factor, of which homeostasis may play a role in the development of cognitive disorders in older adults. The use of calcium supplements has therefore been questioned, although they are still widely prescribed for the prevention of osteoporosis. The aim of this study was to determine whether the use of calcium supplements in non-demented older adults was associated with cognitive and behavioral disorders.

Materials and methods. The MEMENTO cohort involved 2323 patients aged 60 years and over with a subjective cognitive complaint or a recent diagnosis of mild cognitive impairment from 26 French memory consultations between April 2011 and June 2014. At enrolment, sociodemographic data, medical history and medication were collected, together with standardized clinical, biological and neuropsychological tests (global cognitive performance: MMSE; episodic memory: DMS48; executive functions: FAB, TMT A and B, Digit span, Go/No Go). Behavioral disorders were assessed using the Neuropsychiatric Inventory (NPI) frequency and gravity scores. From the 2323 patients, we excluded the ones with no available data on serum calcium concentration and those who didn't have complete data at the time of inclusion, which correspond to a total of 1497 participants. Age, sex, BMI, education level, marital status, functional autonomy, history of hypertension, anxiety/depression, physical performance, and vitamin D supplementation were considered as potential confounders.

Results. Of the 1497 participants included in the analysis (mean, 73 years; 61.1% women), 202 were receiving calcium supplements (n=13.5%). The use of calcium supplements was associated with longer completion times for TMT A and B (respectively, β=5.03[95%CI:2.43-8.10] p=0.0014 and β=10.46[95%CI:1.14-19.77] p=0.0279), independently of potential confounding factors. No significant association was found for the other cognitive tests. The use of calcium supplements was also associated with an increase in the frequency (β=0.75[95%CI:0.06-1.44] p=0.0322) and severity (β=0.68[95%CI:0.16-1.19] p=0.0099) of behavioral disorders.

Conclusion. Receiving calcium supplements was associated with poorer information processing speed and mental shifting, and with more frequent and severe behavioral disorders.

Keywords: calcium, neurocognition, behavior, older adults, geriatrics

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