# Caffeine: a cup of care? An exploration of the relation between caffeine consumption and behavioral symptoms in persons with dementia

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## A CUP OF CARE?

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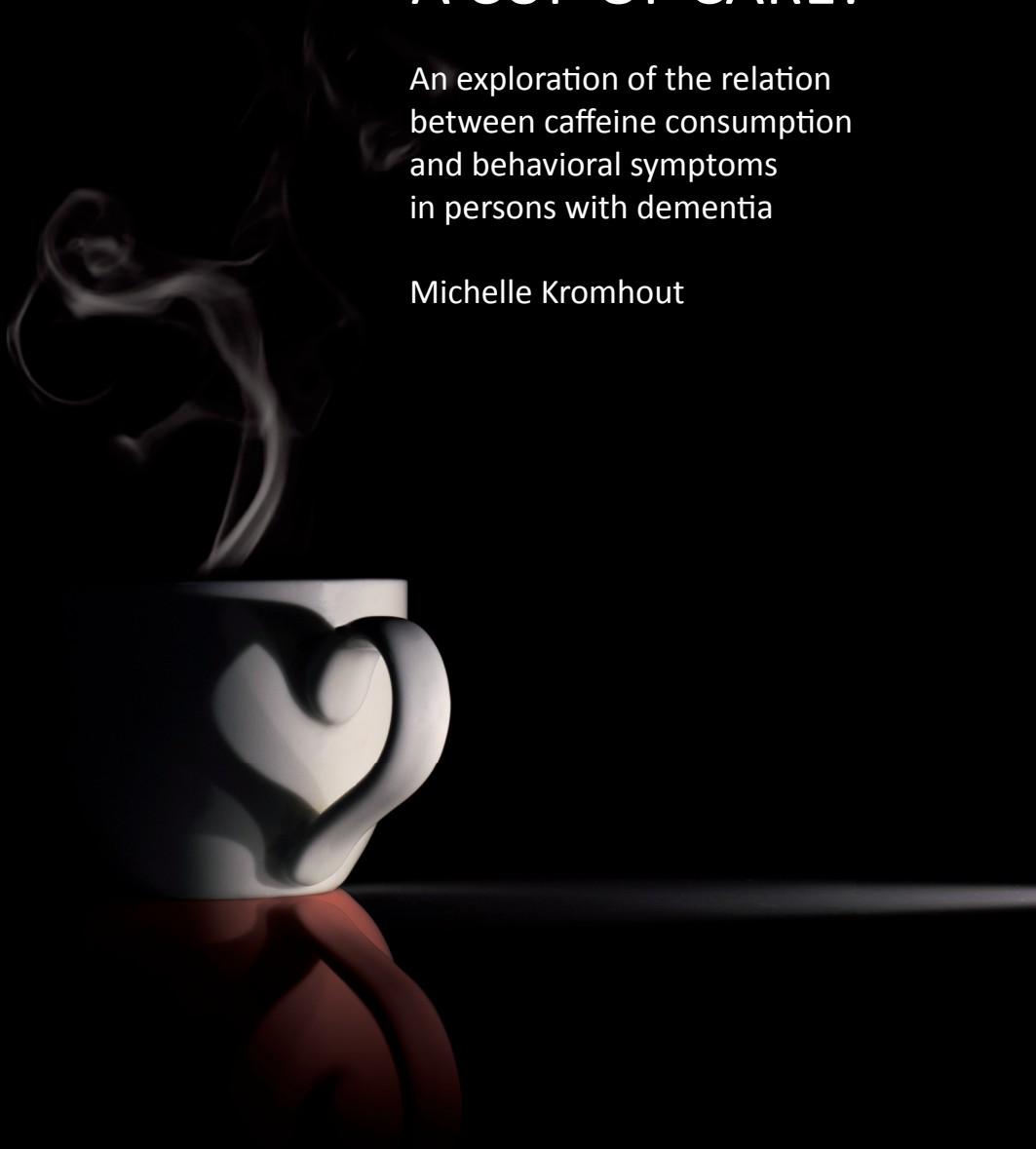
Michelle Kromhout



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None of the studies presented in this thesis received financial support. Financial support for the printing of this thesis was partly provided by Tolokku.

ISBN: 978-94-6361-529-7
Cover: Design by Optima Grafische Communicatie, Rotterdam, The Netherlands. Photo by Teerapong Tanpanit.
Lay-out and Printing: Optima Grafische Communicatie, Rotterdam, The Netherlands

# Caffeine: a cup of care?

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**Proefschrift**

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op dinsdag 18 mei 2021
klokke 15.00 uur

door

Michelle Angelique Wegewijs

geboren 20 augustus 1983
te Helmond

| | |
|---|---|
| **Promotoren:** | Prof. dr. W.P. Achterberg |
| | Prof. dr. M.E. Numans |
| **Copromotor:** | Dr. N. Rius-Ottenheim |
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**To all the persons with**
**dementia for teaching me**
**what is truly important in life**

**Let thy food be thy medicine and medicine be thy food**

– attributed to Hippocrates of Cos (c. 460 BC – c. 370 BC)
but not said nor written by him

**It's far more important to know what person the disease has than what disease the person has**

– Hippocrates of Cos (c. 460 BC – c. 370 BC)

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# GENERAL INTRODUCTION

The word "dementia" derives from the Latin stem 'demens' and literally means 'without mind.' Dementia syndrome is an umbrella term covering over 100 diseases in which cognitive function deteriorates to a greater extent than seen in normal aging. Attention, planning, learning, memory, language, visual perception, spatial skills, social skills or other cognitive functions can all be affected.(1) Alzheimer's disease is the most common cause of dementia, accounting for 60-70% of cases, but other common types of dementia include vascular dementia, Lewy body dementia and frontotemporal dementia. At present, around 50 million people worldwide have dementia and over the next 30 years this number is likely to triple.(2)

**A simple question**

Around ten years ago, when I was working as a physician at a nursing home, the multidisciplinary team was discussing a new resident in the dementia special care unit. She was showing agitated behavior in the evening and at night, but had never displayed this kind of behavior at home. Her behavior was analyzed in the multidisciplinary team meeting, including her (unmet) needs and possible physical or other contributing factors. The team then discussed treatment goals and options. Interestingly, the nurse mentioned an above average coffee consumption and asked whether the coffee could influence behavior. A simple question and one that couldn't be answered at that time, but this question has stayed with me ever since.

Dementia affects everyone differently and has a significant physical, psychological, and social impact. Several factors influence the quality of life of patients with dementia.(3, 4) Factors reflecting relationships, social engagement and functional ability are associated with an increase in quality of life(4), while poorer physical health (e.g. pain), mental health (including behavioral symptoms)(3, 4) and poorer caregiver well-being(4) are associated with a lower quality of life. The global economic costs of dementia are estimated to be around $1 trillion, including the cost of informal care(5), so dementia has a profound effect not only on the patient but also on caregivers and society as a whole. Enabling people with dementia and their caregivers to "live well" and maintain a good quality of life should be the main focus of policy and practice (e.g. the Dutch 'Waardigheid en Trots'(6) and the UK's 'Living well with dementia'(7)).

## BEHAVIORAL SYMPTOMS IN PATIENTS WITH DEMENTIA

Behavior is referred to as 'an observable response to a concrete set of circumstances'. Patients with dementia display non-cognitive symptoms, e.g. aggression, agitation, anxiety, apathy, which are together referred to as behavioral symptoms. These symptoms are also often labeled as behavioral problems, behavioral disturbances, challenging behavior, behavioral and psychological symptoms of dementia (BPSD) or neuropsychiatric symptoms.

The etiology of behavior in patients with dementia is complex and improvements to the traditional medical model regarding the presentation of dementia has been suggested by Kitwood(8):

$$D = NI + H + B + P + SP$$

Kitwood proposed that the symptoms of dementia (D) can be understood as an interplay between neurological impairment (NI), psychosocial factors (health (H), individual psychology (P), biography (B)), and the environment (social context/psychology (SP). This proposal represented a rejection of the standard medical approach to dementia which focused on treating neurological impairments (D = NI). The enhanced model resulted in the Person-centered-care philosophy, which is the underlying philosophy of the 2018 Alzheimer's Association Dementia Care Practice Recommendations.(9) The application of this care philosophy benefits the person with dementia, for example in terms of improved quality of life, fewer behavioral symptoms, lower use of psychotropic medication and the maintenance of self-esteem, in addition to helping staff by improving working conditions.(9)

Almost all patients with dementia will show behavioral symptoms at some point during the disease(10) which decreases quality of life of the patient with dementia(3, 4) and place a high burden on informal caregivers. Due to the caregiver burden, behavioral symptoms are often the main reason for nursing home admission in patients with dementia.(11) Behavioral symptoms are also associated with a decline in general health and quality of life, and increased social isolation of the caregiver. A higher caregiver burden often worsens the relationship between the caregiver and the patient with dementia, which in turn may increase the frequency and severity of neuropsychiatric symptoms.(12) Quick and adequate management of behavioral symptoms in patients with dementia is necessary to prevent further harm for the patient, caregiver overload, avoidable nursing home admissions and avertible society costs.

To manage behavioral symptoms, the first step recommended in guidelines is the detailed analysis of the patients' behavior, including contributory physical, psychological, social and environmental factors, (13) after which interventions can be formulated. Many different pharmacological treatments have been intensively studied. (14, 15) Although there is some evidence pharmacological agents (mainly cholinesterase inhibitors and atypical antipsychotics) can decrease behavioral symptoms in patients with dementia, the clinical effect is small and there are severe safety risks as study dropout, adverse effects and death.(14, 15) Psychosocial approaches have also been widely studied(16, 17) and approaches like behavioral management techniques or cognitive stimulation are proven reduce behavioral symptoms. But in the management of behavioral symptoms, no standardized solution is currently available. All interventions that target behavioral symptoms must be tailored to the individual(16, 18), a policy that is in line with the key components of person-centered care.(19) In view of these considerations, a stepped care approach is generally suggested as the best approach as it takes the different contribution factors and the individual context of the patient into account. However, even in the stepped care approach nutritional factors are not regularly included as a possible cause or intervention.

The management of behavioral symptoms in patients with dementia is complex and the burden for the patient and caregivers is high, often placing both caregivers and professionals at wits end. It is sadly no surprise that refuge is still regularly sought in pharmacological interventions, despite them being largely ineffective and potentially generating severe adverse effects. Therefore, fur-

ther research into the manageable causes and effective treatments of behavioral symptoms in dementia should be one of the focal points in elderly care.

## CAFFEINE

Numerous anecdotes and mythological stories over the last 5,000 years(20) suggest that caffeine use can influence behavior, especially concerning a stimulatory effect that can relieve fatigue and improve mood. In early history people chewed the leaves or seeds, such as the Mate bush or the cocoa bean, releasing the caffeine. The infusions with boiling water that we now know as 'coffee' or 'tea' developed around 1000 AD(20), when it was discovered that boiling water enhanced the stimulatory effect. This discovery gave rise to our current use of coffee and tea, and drinking coffee and tea today has become more than a simple consumption of a stimulant, it is now a social event and a cultural habit. "Having a cup of coffee" or a "tea break" are today associated with socializing and relaxation.

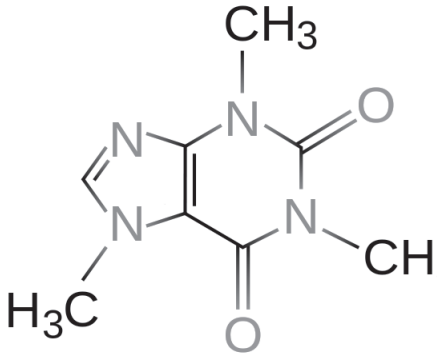


**Figure 1.** Chemical structure of caffeine (adjusted from https://commons.wikimedia.org/wiki/File:Caffeine.svg)

**Figure 2.** Coffee, the most common form of caffeine ingestion (source: Petr Kratochvil)

**The Ethiopian myth of coffee**
In the ancient coffee forests of the Ethiopian plateau, the goat herder Kaldi noticed that his goats became so energetic and agitated, seemingly even dancing, that they could not sleep at night after eating the berries of a certain bush. The goatherd tried the berries himself and reported his discovery to the abbot of the local monastery. From there knowledge of the energizing berries began to spread.

Caffeine is released when ground coffee beans contact hot water, and the longer the contact, the more caffeine is released. In 1819, the German chemist Friedrich Runge isolated pure caffeine from coffee, a discovery that later found application in the soft drinks industry, first by adding caffeine as a bitter seasoning to drinks such as Coca-Cola, Dr Pepper and Pepsi-Cola, and later by

adding caffeine specifically for its stimulatory effect (Xi and Red-Bull). The stimulatory effect of caffeine has also resulted in its use as an additive in certain medicines.

Pharmacologically, caffeine belongs to the alkaloids and is chemically related to nicotine, heroin and cocaine. With oral use, caffeine is absorbed by the body within about 30-60 minutes, and caffeine is then metabolized in the liver to three active metabolites: paraxanthine (approx. 80%), theophylline, and theobromine. In healthy adults, the half-life of caffeine is around 4.5 hours on average, but depends on factors such as age, medication use, liver function and smoking. In elderly people with severe hepatic impairment, the half-life of caffeine can increase to 96 hours (see table 1).

**Table 1.** Pharmacokinetics and pharmacodynamic effects of caffeine

| Pharmacokinetic | Pharmacodynamic effects |
|---|---|
| • Rapidly and completely absorbed from the gastrointestinal tract or oral mucosa | • Non-selective antagonism of A2a and A1 adenosine receptors |
| • $t_{max}$ 15-120 min, $t_{1/2}$ 2-8 hours | • Facilitates dopamine D2 receptor transmission |
| • Metabolization: by CYP1A2 in the liver to paraxanthine, theophylline and theobromine | • Tolerance can develop, attributed to the upregulation of adenosine receptors |
| • Variability in metabolism due to age, genetics (sex, CYP1A2 activity), smoking, medication use | • Tolerance can differ between organs |
| • Excreted in the urine | • Withdrawal symptoms 12-24h after ingestion |

Caffeine is unique in that it is both water and fat soluble.(21) After ingestion caffeine can be found in all body fluids and can cross the blood-brain barrier, leading to a broad range of effects in the human body. General physical effects include but are not limited to: 1) Pain relief, 2) Increase in blood pressure, 3) A dose dependent effect on the heart rate (both bradycardia and tachycardia), 4) Other cardiac effects including arrhythmia, 5) Vasoconstriction that increases the risk of myocardial ischemia, 6) Delayed conception and decreased fertility (high caffeine consumption increases the risk of miscarriage), and 7) Increase in bladder instability.(22)

The effects of caffeine as a stimulant partly derive from the non-selective antagonism of adenosine receptors, especially the adenosine A2a receptors, the A1 receptors(23, 24) and the adenosine A2a receptor-dopamine D2 receptor heteromer.(23) In addition, caffeine also has a (weaker) affinity for benzodiazepine receptor sites and several studies have shown that caffeine can neutralize the effects of benzodiazepines.(24) Chronic consumption of caffeine likely increases the number of adenosine receptors but evidence for receptor regulation of the benzodiazepine receptor sites is conflicting.(24) Caffeine also influences the formation and release of other neurotransmitters such as acetylcholine, epinephrine, norepinephrine, serotonin, dopamine and glutamate.(24, 25)

## CAFFEINE AND BEHAVIOR

As caffeine has been used for several centuries to influence behavior, unsurprisingly the effects of caffeine on behavior in adults have been widely researched. But, for many years the research into caffeine has been troubled by methodological challenges. In the early eighties a review(26) showed several weaknesses reoccurring frequently in caffeine research, namely: the use of weak hypothesis in experimental design, design flaws like excessive high dosages of caffeine, extrapolation of results from caffeine naïve to caffeine tolerant subjects and selective citation of literature. (Although the latter is a challenge for all research, not just caffeine research). A later review showed most studies still used a single high dosage of caffeine instead of the more realistic ingestion of several smaller dosages during the day.(27) Recently, the discussion of methodological challenges in caffeine research focused around confounding due to withdrawal symptoms, the use of caffeine naive participants and the question if these participants are a representative sample of the population and, lastly, the influence of tolerance.(28) It is essential to take these specific methodological challenges in caffeine research into account while interpreting literature, conducting research and choosing the best intervention for a specific patient.

Despite these methodological challenges in researching caffeine, it is now widely accepted that moderate caffeine consumption in healthy adults increases alertness,(27, 29, 30) attention (27, 29, 30) and cognitive function. (29, 30) It also elevates mood (30) and reduces fatigue (27). A high caffeine consumption (usually ≥ 300 mg) increases anxiety,(27, 30) can induce psychotic or manic symptoms (30) and impairs sleep (27). As these effects differ between individuals, people normally adjust their consumption of caffeine based on their personal experience of (non-)beneficial (side)effects.(27, 30)

In children, caffeine consumption has been linked to specific behavioral symptoms, including daytime sleepiness, anger and violent behavior, and an association between caffeine consumption and long-term behavioral symptoms has even been suggested by some.(22)

An exploration of existing literature produced three studies(31-33) on the effect of caffeine on behavioral symptoms in patients with dementia (prior to this thesis). Two of these studies, dating from the seventies(32) and the nineties(31), used evening administration of caffeine to examine the effect of caffeine on sleeping difficulties. The first study wanted to investigate a possible soporific effect of caffeine in patients with dementia, of which there was anecdotal evidence at the time. Twelve patients with Alzheimer's or Pick's disease with sleeping difficulties living in a nursing home were included. The participants were given caffeine beverages 30-45 min before bedtime in 4 different dosages (0-228mg), each dosage for 5 days followed by a 1-day wash-out period. No soporific effect of coffee was observed.(32) The second study was a 'reversed treatment trial'. After noticing a paradoxical effect of sedatives in patients with dementia often leading to a reversal of circadian rhythm according to the authors, they wanted to try the opposite: a stimulant in de evening and a sedative in the morning. For this study 16 patients with multi-infarct dementia and severe sleeping difficulties with a complete reversal of circadian rhythm were given

caffeine at 8pm and a sedative during the day. With this treatment 10 patients showed improvements in their circadian rhythm. The authors concluded that caffeine restores a normal sleep rhythm in patients with dementia.(31)

The third study,(33) a randomized controlled trial, examined the effect of 'coffee therapy' on behavioral symptoms measured with the Neuropsychiatric Inventory (NPI). In groups of 7-8 patients with dementia were welcomed into the room of a coffee shop by a master wearing a gown, an apron and a cap. Fresh coffee was grinded by the patients, after which filter coffee was made, sweetened and served in a china cup with saucer. Every patient was called by their name when receiving the coffee, and again when receiving a cracker. The coffee therapy was concluded with a chat, the reading of a poem or a story and was given twice a week for four weeks. The intervention group showed a significant decrease in NPI. However, the authors mention they administered several factors together (coffee, sugar and the situation of the coffee therapy itself) to create a most pleasant feeling and can determine which was the most effective factor.(33)

Although the effect of caffeine on behavior in adults is widely accepted, the effect of caffeine on behavior in patients with dementia has not been properly investigated. As coffee is regularly consumed, widely available and most nursing homes do not have specific limitations or adjustments in the caffeine consumption of the residents, more insight in the relation between caffeine and behavior in patients with dementia is wanted.

## HYPOTHESES

Based on the known stimulatory effects of caffeine in healthy adults, it seems logical to assume that, in patients with dementia, caffeine increases behavioral symptoms caused by general restlessness, anger and anxiety and increases sleeping difficulties during the night by suppressing fatigue. In healthy adults, insufficient rest at night leads to increased sleepiness during the day, which may in turn lead to increased caffeine use. However, in the absence of this self-compensating mechanism in patients with dementia, sleeping difficulties can lead to greater daytime sleepiness and a reversion of circadian rhythm which in its turn can also increase behavioral symptoms (e.g. irritability).

The opposite can also be hypothesized: certain behavioral symptoms in patients with dementia can be reduced by the use of caffeine. Although the etiology of behavioral symptoms is multifactorial and complex,(13) factors known to induce behavioral symptoms include overstimulation (comparable to patients suffering from autism) and incomprehension of a situation.(34) Caffeine consumption may favorably impact behavioral symptoms by improving concentration and lessening overstimulation due to an increase in alertness. Another possible favorable mechanism is the social aspect of caffeine consumption. Social activities in general can reduce behavioral symptoms in patients with dementia, (34) and a social gathering associated with coffee drinking might positively influence the behavior of patients with dementia.

To summarize, in theory caffeine consumption by patients with dementia could result in both an increase and a decrease in behavioral symptoms. The increase would be most likely seen in anxiety, general restlessness, anger and sleeping difficulties. Behavioral symptoms logical to decrease are those caused by overstimulation and incomprehension, which both can lead to a wide range of behavior. Both hypothesis were considered equally strong, therefore the aim of these studies was to investigate whether there is a relationship between caffeine consumption and behavioral symptoms in patients with dementia, and (if a relationship exists) to determine the direction of any effects.

## DESIGN

In designing the study several of the known methodological challenges in caffeine research as well as known difficulties in behavioral research and research in elderly care were considered:

- Several modern caffeine studies work with caffeine naïve participants or animals, which makes extrapolation to caffeine tolerant patients unreliable. As coffee (and caffeine) is a widely and regularly consumed beverage, caffeine naive patients are the minority and most patients have (some amount of) caffeine tolerance. Therefore, the study population should resemble normal caffeine consumption so reliable extrapolations could be made.
- Frail elderly persons are frequently excluded from studies due to age or comorbidity leading to a severe underrepresentation in scientific research. Just like in any other area of medical research, to advance treatment and care continuously improving and offering new insights are necessary. For this reason the studies have to be pragmatic, excluding as little as patients as possible and conducted as much as possible in normal care situations.
- Caffeine can be seen as a possible cause of behavioral symptoms or an intervention, both asking for different kind of designs. As caffeine is consumed regularly by elderly patients with dementia, it was first seen as a possible cause of behavioral symptoms. If a relation between behavioral symptoms and caffeine consumption is likely, then possible intervention studies could be done.
- Earlies studies used (extremely) high dosages of caffeine. If we want to do justice to the three challenges mentioned above, our conclusions should be based on normal caffeine use (no injections or capsules) and normal caffeine dosages (no add ons).

These considerations lead to a stepwise research design consisting of four different studies. The first step were two different exploratory studies to see if there was some validation in the hypotheses. If these studies showed signs of a relation indicating the need for more thorough research, the following steps would be a systematic literature review and a large multicenter study using more research facilities.

First, an observational pilot study was performed to explore the possibility of a relationship between caffeine and behavioral symptoms in a group of elderly patients with dementia, with a focus on sleep, aggression, depression, anxiety, apathy, irritability and aberrant motor behavior. Over four days, these behavioral symptoms were measured using the Neuropsychiatric Inventory – Nursing Home edition (NPI-NH) questionnaire and a sleep questionnaire, together with careful observation of caffeine consumption in 29 patients with dementia (Chapter 1). Because caffeine shows strong individual variation in effects in healthy adults, a second exploratory study designed to examine the individual effects of caffeine on behavioral symptoms was performed. In two patients with high caffeine use and severe behavioral symptoms, caffeine consumption was regulated over a four-week period by serving either caffeinated or decaffeinated coffee. Behavioral symptoms were then scored using the NPI-NH and the Cohan Mansfield Agitation Inventory (CMAI), with outcomes individualized per patient. (Chapter 2)

The results of the two exploratory studies indicated further research was warranted. Hence, a thorough and systematic literature review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines, with the research question formulated as “Does caffeine or coffee consumption influence neuropsychiatric symptoms, e.g. agitation, aggression, apathy, irritability, in elderly patients with dementia?”. Six (medical) journal databases and gray literature were searched and more than 4000 articles were screened for relevance, resulting in the identification of only seven relevant articles. (Chapter 3)

The final study, a large multicenter cohort study, was conducted with the aim of assessing a possible relationship between caffeine and behavioral symptoms in older nursing home patients with dementia, and if confirmed, to further assess contributory factors including the severity of dementia. The three-year study was embedded in the Elderly Care Physicians training program, and trainees collected data on caffeine consumption, cognition, behavioral symptoms (the NP-NH, the AES-C and MDS depression) and social information. To the best of our knowledge, these efforts resulted in the largest existing dataset on cognition, behavior and caffeine consumption amongst nursing home residents (Design: chapter 4; Results: chapter 5).

Lastly, in the ‘General discussion’ the overall results of the studies will be discussed to answer the simple clinical question “can coffee influence behavior in patients with dementia”.

**Introduction – in short**

As the number of patients suffering from dementia are still growing, most of the patients experience a kind of behavioral symptoms at some time during the disease and these behavioral symptoms lower the quality of life and increase the burden of caregivers, adequate management of these symptoms is warranted. However, the etiology and management of behavioral symptoms is complex, resulting in (mis)use of pharmacological interventions: a cure which is often worse than the disease. In adults, caffeine is known to influence behavior. Four different studies were conducted to see if caffeine is an easy to adjust cause or a pragmatic intervention for behavioral symptoms in patients with dementia.

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# 1

# RELATION BETWEEN CAFFEINE AND BEHAVIORAL SYMPTOMS IN ELDERLY PATIENTS WITH DEMENTIA: AN OBSERVATIONAL STUDY

Published as Kromhout MA, Jongerling J, Achterberg WP. Relation between caffeine and behavioral symptoms in elderly patients with dementia: an observational study. The journal of nutrition, health & aging. 2014;18(4):407-10

## ABSTRACT

*Objectives:*

Caffeine is known to improve concentration and reduce fatigue in healthy adults, but high doses may induce anxiety and agitation. Because the effects of caffeine in elderly people with dementia are unknown, this study explores the relation between caffeine and behavioral symptoms in a group of elderly patients with dementia.

*Design:*

An observational pilot study.

*Setting:*

A dementia special care unit of a Dutch nursing home.

*Participants:*

A total of 29 elderly patients with dementia.

*Measurements:*

Behavioral symptoms were measured with the NPI-NH, and sleep and caffeine consumption were measured using questionnaires.

*Results:*

A significant relation was found between the total amount of caffeine consumed during the day and apathy [Kendall's tau (KT) -0.287 p=0.03], and the number of times that participants got up at night (KT 0.462; p <0.01). The amount of caffeine consumed after 6 p.m. was also significantly related to the number of times participants got up at night (KT 0.436; p <0.01). Multilevel analysis showed caffeine to be negatively correlated with aberrant motor behavior [b=-0.47 (0.22), Wald (461)=-2.12, p=0.03] and apathy [b=-0.88 (0.45), Wald (461)= -1.96, p=0.05], and showed a significant relation between caffeine consumption after 6 p.m. and the number of times participants got up at night [b=0.48 (0.22), Wald (461)= 2.20, p=0.03].

*Conclusion:*

This study established an association between caffeine consumption and behavioral symptoms in elderly patients with moderately severe dementia. Therefore, adjusting caffeine consumption could be part of an interdisciplinary approach to behavioral symptoms, particularly when aberrant motor behavior, apathy or sleeping difficulties are involved. These results indicate that further research on the effects of caffeine on behavioral symptoms in dementia is warranted.

## INTRODUCTION

Caffeine is a known stimulant and can interfere with several neurotransmissions including acetylcholine, epinephrine, norepinephrine, serotonin, dopamine and glutamate.(1) Animal and clinical studies suggest that caffeine can reduce cognitive decline in Alzheimer's disease.(2, 3) Based on caffeine's interference with neurotransmissions, an effect on behavior can be expected.

The effect of caffeine on the behavior of healthy adults is well studied, but with inconsistent results. One extensive review concluded that caffeine increases concentration and reduces fatigue in healthy adults even with normal use, but used in very large amounts or by sensitive individuals can also lead to increased anxiety and impaired sleep.(4) Anxiety or sleeping difficulties in people with dementia are referred to as behavioral and psychological symptoms of dementia, which also include agitation, depression, aggression, etc.

Behavioral symptoms are common in dementia. Over 80% of patients suffering from dementia exhibit at least one clinically relevant symptom during the course of the disease, especially agitation and apathy.(5) Medication, although frequently used, has only a moderate effect in patients with behavioral symptoms.(6) The use of psychosocial or person-centered interventions are known to positively affect behavior.(7) However, the effect of caffeine on behavioral symptoms is unknown in elderly patients with dementia. Based on the research on the behavioral effects of caffeine in healthy adults, two hypotheses can be formulated on the effect of caffeine on behavioral symptoms in dementia: 1) caffeine might increase behavioral symptoms in dementia; behavioral symptoms such as agitation, aggression and sleeping problems might be a direct result of caffeine consumption due to its stimulating effects on the central nervous system, and 2) caffeine might decrease behavioral symptoms in dementia, i.e. sensory overstimulation, fatigue and decreased alertness can result in agitation or other behavioral symptoms in dementia. Thus, due to its stimulating effects, caffeine might reduce fatigue and increase alertness resulting in a decrease in behavioral symptoms.

Therefore, this study explores the relation between caffeine and behavioral symptoms in elderly patients with dementia, with a focus on sleep, aggression, depression, anxiety, apathy, irritability and aberrant motor behavior (AMB).

## METHODS

### Procedure

The caffeine consumption and behavior of 29 residents living in the psychogeriatric unit of a nursing home were registered over a 96-h period by nursing staff, using several questionnaires. Baseline characteristics and the Reisberg Global Deterioration Scale (GDS) (8) were provided by the elderly-care physician and the medical records.

## Participants

All 31 residents living in the psychogeriatric unit were eligible for the study with the exception of those with active psychiatric (co)morbidity (n=0), or an expected impending death (n=1), or when informed proxy consent was not obtained (n=1); this left 29 available participants for the present study.

## Consumption of caffeine

A questionnaire was used to record the number of cups of coffee, tea and cola eight times a day (breakfast, 10 a.m., lunch time, 2 p.m., 4 p.m., dinner time, 7 p.m. and 21 p.m.). In accordance with conventional practice in the Netherlands, participants were free to choose their beverages. The consumption of these beverages was not limited, stimulated or otherwise regulated by the nursing staff. During the study all coffee was drip (filter) brewed in a standardized way and served in a standardized cup of 150 ml, with a caffeine content of approximately 85 mg per cup.(9)

## Behavioral problems

Behavioral symptoms were scored using an adaptation of the Neuro Psychiatric Inventory-Nursing Home edition (NPI-NH).(10, 11) The NPI-NH is a reliable and valid observation scale which registers the presence, severity and frequency of behavioral symptoms, and the burden for caregivers.(12) Because the present study focused on specific types of behavior the items addressing delusions, hallucinations, euphoria, disinhibition and appetite were excluded, and only the items agitation/aggression, depression/dysphoria, anxiety, apathy/indifference, irritability/lability and AMB were scored at the end of every 8-h nursing shift, by the on-duty nurse.

Sleep problems were defined as night-time behaviors such as wandering around, but also as the inability to sleep, i.e. lying awake in bed. Instead of the NPI item 'nighttime behaviors' we used a specially developed night-time questionnaire which recorded whether a participant got up at night (including frequency and reason) and whether the participant lay awake in bed or was asleep. The participants were closely observed during 4 consecutive nights. All nursing and nutrition staff were trained in the use of the questionnaires administered in this study.

## Statistical analysis

Initially, associations between the total caffeine consumption (during 96 h) and the presence/absence of a specific behavioral symptom (during 96 h) were calculated (SPSS 15.0) using non-parametric Kendall's tau correlation coefficient (KT), due to the small sample size, longitudinal dependency and not normally distributed data.

Because of the nested structure of the data, with (repeated) observations nested within individuals, the data were also analyzed using multilevel analysis. In this analysis data was were perceived as made up of two levels. The first level consisted of the repeated measurements of caffeine consumption (the independent variable), AMB, aggression, depression, anxiety, apathy and irritability (dependent variables). On this level each individual´s scores on a dependent

variable were related to their scores on the independent variable using linear regression equations. The second level consisted of the individuals participating in the study. On this level inter-individual differences in the model parameters of the first level (i.e., the regression coefficients) were modeled. In the current study no predictors for inter-individual differences were included; this means that the parameter values were modeled as normally distributed across individuals. For every dependent variable a separate multilevel analysis was done, and for every dependent variable two models were constructed. The first model analyzed the relation between caffeine and behavioral symptoms during the same time frame, i.e. caffeine consumed in the morning and any behavioral symptoms observed during the morning. However, because the effect of caffeine can last several hours, the relation between caffeine consumption and behavioral symptoms in the subsequent time frame was analyzed in the second model. All variables were entered into the multilevel analysis. Effects that were not significant in this analysis were step-wise removed to arrive at the final models.

## RESULTS

### Participants

The participants had a mean age of 84 (SD 6.6) years and suffered from moderate to severe dementia (Table 1). Over 50% was diagnosed with Alzheimer's disease. Although 12 of the participants used psychotropic drugs on the study days, none of the dosages was adjusted in the 4 weeks prior to or during the study.

### Coffee consumption

During 96 h the participants consumed on average 15 (SD 5.6) units of caffeine. On the first morning the participants consumed a mean of 1.4 (SD 0.9) units of caffeine, followed by 1.8 (0.9), 1.6 (1.5) and 1.4 (1.0) units of caffeine on the subsequent mornings. In the evenings an average of 1.8 (0.8), 1.1 (0.7), 0.8 (0.5) and 1.6 (0.9) units of caffeine were consumed, respectively.

### Behavioral problems

Of the 29 participants, 6 showed no behavioral problems of any kind during the entire observation period. The majority (n=18) showed a behavioral symptom to a maximum of once a day, whereas 5 had behavioral symptoms at least once a day. Irritability was the most frequent (n=20), followed by AMB (n=12). Aggression was observed in 9 participants, 5 of whom displayed aggression more than once during the observation period.

There was a significant negative correlation between the total amount of caffeine consumed and apathy (KT -0.287; p=0.03). Other forms of behavioral symptoms had no significant correlation with daily caffeine consumption (Table 2).

**Table 1:** Baseline characteristics of the study population (n=29).

| | |
|---|---|
| Sex (n) | |
| Female | 21 |
| Male | 8 |
| Age in years: mean (range) | 84 (69-96) |
| Dementia (n) | |
| Alzheimer's disease | 16 |
| Vascular dementia (VD) | 4 |
| Alzheimer' disease/VD | 1 |
| Korsakoff's syndrome | 1 |
| Not otherwise specified | 7 |
| Reisberg Global Deterioration Scale (n) | |
| 5 = Moderate | 8 |
| 6 = Moderately severe | 14 |
| 7 = Severe | 7 |
| Renal function: mean ml/min (range) | 59 (26-90) |
| Caffeine consumption: mean units/day (range) | 3.8 (0.8-6.3) |
| Medical history (n) | |
| Depression | 8 |
| Anxiety disorder | 1 |
| Delirium | 2 |
| Psychotropic medication ATC (n) | |
| Antidepressant | 5 |
| Antipsychotics | 3 |
| Benzodiazepine | 4 |

**Table 2:** Relation between behavior and total caffeine consumption per day (Kendall's tau correlation coefficient).

| | Total caffeine consumption per day |
|---|---|
| Apathy | -0.287 p=0.03* |
| Depression | 0.187 p=0.11 |
| Anxiety | -0.135 p=0.39 |
| Aggression | -0.179 p=0.11 |
| Irritability | 0.000 p=0.50 |
| Aberrant motor behavior | 0.850 p=0.29 |
| Sleep: waking up at night | 0.043 p=0.38 |
| Sleep: getting up at night | 0.462 p<0.01* |

* statistically significant

In the first multilevel analysis, the relation between caffeine consumption and behavior was analyzed in the same time frame. A significant negative correlation was found between total daily caffeine consumption and AMB [b=-0.47(0.22), Wald (461)= -2.12, p=0.03] and apathy [b=-0.88 (0.45), Wald (461)= -1.96, p=0.05].

The second multilevel analysis showed no significant correlation between apathy, AMB, aggression, depression, anxiety or irritability and caffeine consumed in the previous time frame. (Table 3).

**Table 3:** Multilevel analysis of the relation between behavioral symptoms and caffeine consumption

| | Model 1 (same time frame) | Model 2 (subsequent time frame) |
|---|---|---|
| Apathy | b=-0.88 (0.45), Wald (461)= -1.96, p=0.05* | b=-0.49 (0.69), Wald (432)= -0.72, p=0.47 |
| Depression | b=-0.31 (0.29), Wald (461)= 1.01, p=0.28 | b=0.34 (0.36), Wald (432)= 0.94, p=0.35 |
| Anxiety | b=0.48 (0.48), Wald (461)= 1.00, p=0.32 | b=1.53 (0.91), Wald (432)= 1.68, p=0.09 |
| Aggression | b=0.22 (0.27), Wald (461)= 0.84, p=0.40 | b=-0.15 (0.24), Wald (432)= -0.60, p=0.55 |
| Irritability | b=-0.22 (0.15), Wald (461)= -1.40, p=0.16 | b=0.19 (0.18), Wald (432)= 1.07, p=0.29 |
| Aberrant motor behavior | b=-0.47 (0.22), Wald (461)= -2.12, p=0.03* | b=0.49 (0.32), Wald (432)= 1.54, p=0.12 |

* statistically significant

### Quality and quantity of sleep

The nurses walked three rounds each of the 4 nights, totaling 12 observations per participant with a total of 348 observations. Only 3 participants slept continuously during all 4 nights. Of the remaining participants, 3 slept during the nurses' rounds but got up between the rounds, and 23 often lay awake in bed and/or walked around. Of the study participants, 14 (48%) did not get up during the night; the remaining 15 were seen a total of 108 times out of bed by the nurses during the observation period. The most common reason for getting out of bed was to use the bathroom (97 of 108) and, occasionally, just to stretch the legs (3 of 108) and/or due to a general feeling of restlessness (8 of 108). No behavioral symptoms, such as aggression or agitation, were observed during the night.

There was a significant correlation between caffeine consumption during the day and the number of times that participants got up at night (KT 0.462; $p < 0.01$) (Table 2). The amount of caffeine consumed in the evening was also significantly correlated with the number of times participants got up at night (KT 0.436; $p < 0.01$).

In the multilevel analysis, the total amount of caffeine consumed each day showed no significant relation with any form of sleeping problems. However, the amount of caffeine consumed in the evening (after 6 p.m.) was significantly related to the number of times that participants got out of bed [b=0.48 (0.22), Wald (461)= 2.20, p=0.03] (Table 3).

## DISCUSSION

In this sample of elderly patients with dementia living in a special care unit a negative correlation between caffeine consumption and apathy and AMB was found. Caffeine consumption after

6 p.m. was correlated with getting out of bed at night. No significant correlations were found between caffeine and aggression, depression, irritability or anxiety.

This pragmatic, observational study is the first study to explore the effects of caffeine on sleep and behavior in patients with dementia but has some limitations which need to be discussed. First, caffeine was ingested orally and consumption was recorded, but serum caffeine levels were not measured. Also, individual differences in caffeine metabolism are likely and could have influenced the results. Second, the observational period was short (96 h). However, because the effect of caffeine usually lasts only a few hours it is likely that any effect of caffeine on behavior would be observed during the 96-h observation period. Third, the sample size was small. Despite these limitations, correlations were found between caffeine consumption and behavioral symptoms, representing a medium to large effect size which can, therefore, be considered relevant.

In the present study, caffeine consumption was negatively correlated with AMB and apathy. AMB encompasses a wide range of repetitive, often purposeless behaviors like wandering, pacing or plucking and is frequently used interchangeably with agitation.(13) Apathy is almost the opposite, a loss of motivation leading to diminished activity and attention. Apathy is a frequently occurring neuropsychiatric symptom of dementia, with a reported prevalence of around 30%.(5) The negative correlation between apathy and caffeine might be a result of apathy itself, with the participants being too apathetic to consume coffee, but might also imply that caffeine consumption can be used as a therapeutic measure. A possible mechanism for this inverse correlation between caffeine and both apathy and AMB is through the acetylcholinesterase pathway. The acetylcholinesterase inhibitor rivastigmine is known to reduce both apathy and AMB in nursing home residents with moderate to severe Alzheimer's disease.(14) Caffeine is also a non-competitive inhibitor of acetylcholinesterase.(1) Using caffeine as a therapeutic measure in both apathy and AMB might, therefore, be an interesting therapeutic option.

Changes in sleep behavior are common in dementia(15) and sleep disorders tend to be more severe in patients with dementia compared to those found in the elderly without dementia.(16, 17) Sleeping abnormalities are associated with an increase in cognitive decline, caregiver burden and behavioral symptoms in patients with dementia.(16) Therefore, it is important to identify and adequately treat all factors contributing to sleeping difficulties. In the present study, no relation between caffeine use and lying awake in bed was found, which is consistent with a previous study.(18) However, caffeine use after 6 p.m. was significantly correlated with the number of times participants got out of bed at night, mostly to use the bathroom. The sleeping difficulties observed in this study cannot be explained by the stimulating effects of caffeine (increased alertness and decrease fatigue), but could simply be due to the diuretic effects of caffeine. Therefore, reducing caffeine consumption after 6 p.m. in patients who get out of bed frequently during the night, especially combined with frequent noctural micturation, could be a simple intervention to improve sleep in elderly patients with dementia.

In conclusion, in these residents, caffeine consumption is negatively correlated with apathy and AMB and positively correlated with getting out of bed at night. Regulation of caffeine consump-

tion might be an easy, inexpensive and effective way to influence behavioral symptoms in elderly with dementia, especially when AMB, apathy or sleeping difficulties are involved; further study seems to be warranted.

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# 2

# REDUCING BEHAVIORAL SYMPTOMS IN OLDER PATIENTS WITH DEMENTIA BY REGULATING CAFFEINE CONSUMPTION: TWO SINGLE-SUBJECT TRIALS

Published (without abstract) as Kromhout, M.A., Numans, M.E., Achterberg, W.P., 2017. Reducing behavioral symptoms in older patients with dementia by regulating caffeine consumption: Two single-subject trials.
European Geriatric Medicine 8, 496-498

## ABSTRACT

### *Background*

Caffeine is a stimulant with strong individualized effects in adults. In elderly patients with dementia there is a group relation between caffeine and apathy, aberrant motor behavior and sleeping difficulties. A single-subject trial was designed to examine the individual effects of caffeine on behavioral symptoms in older adults with dementia.

### *Method*

Two blinded crossover single-subject trials were conducted in a dementia special care unit. During a 4-week period, caffeine consumption was partly regulated by using caffeinated (C) and decaffeinated (D) coffee pads, in a predetermined order (C-D-D-C). Behavioral symptoms were measured with the NPI-NH and CMAI, and caffeine consumption was measured using questionnaires.

### *Results*

In participant A the specific behavioral symptoms decreased in the 'decaf weeks' and increased slightly when caffeinated coffee was reintroduced (NPI-NH item agitation/aggression scores on weeks 1-4: 12, 3, 1 and 4, respectively). The same pattern emerged in the total CMAI score, the CMAI physically aggressive cluster scores, the CMAI non-aggressive behavior cluster scores, the total NPI-NH score and the NPI-NH psychomotor behavior cluster score. In contrast, in participant B no relation was found between caffeine consumption and behavioral symptoms.

### *Conclusion*

Behavioral symptoms in elderly patients with dementia are complex and require detailed analysis. In some patients, behavioral symptoms can be reduced by a relatively simple regulation of caffeine consumption. A personalized treatment approach is necessary, especially if relatively simple interventions can improve the burden for patients and caregivers.

## INTRODUCTION

Behavioral and psychological symptoms are common in older patients with dementia and place a considerable burden on formal and informal caregivers.(1, 2) The etiology of behavioral symptoms is complex and probably multifactorial. Although many interventions have been well investigated, tailoring these results for the individual patient remains a challenge. Therefore, an individualized approach is necessary.(3)

Caffeine is a commonly consumed stimulant and normal use is known to increase alertness and reduce fatigue. (4) If used in high amounts, caffeine can increase or induce anxiety, restlessness, insomnia and psychomotor agitation.(4, 5) However, the stimulating effects of caffeine show a large individual variation and most people tend to control the caffeine consumption themselves to avoid adverse effects. (4, 5)

The effect of caffeine on behavioral symptoms in older patients with dementia is not extensively investigated. A small pilot study in older patients with dementia showed that caffeine consumption was associated with apathy, aberrant motor behavior and sleeping difficulties.(6) However, individual variation in the effects of caffeine on behavior impedes translating these results to clinical practice. Therefore, to further examine and quantify the individual effects of caffeine on behavioral symptoms, two single-subject trials were performed with two older adults with dementia.

## METHODS

In elderly care, a randomized trial presents substantial methodological barriers, e.g. likely loss to follow-up and the risk of bias by multimorbidity. (7) The single-subject trial is also a randomized blinded study, but conducted with one single patient. It is seen as the ultimate proof for the individual patient,(8) especially if the intervention has shown variation in efficacy between patients,(7) as is the case when considering the effects of caffeine.

In an earlier study , the caffeine consumption and behavior of 29 residents of a dementia special care unit was registered.(6) Of these residents, eligibility for the present single-subject trial included both a high intake of caffeine and severe behavioral symptoms. Four residents met these criteria. Those with active psychiatric (co-)morbidity(n=1) and those in whom informed proxy consent was not achievable(n=1) were excluded. This left two residents. As both were legally incapable to give consent, informed proxy consent was obtained. The local ethics committee was also informed. Withdrawal was possible at any time at the request of the legal representative or staff as they saw fit, without any consequences.

The caffeine consumption was regulated during a 4-week period by serving caffeinated (C) or decaffeinated (D) coffee in a predetermined order per week (i.e. C-D-D-C) to allow for a washout period. The residents and staff were unaware of the predetermined order, and also blinded for

the intervention using unrecognizable coffee pods in unmarked tins. A questionnaire was used to record the number of cups of coffee and of tea consumed during the day. The consumption of these beverages was neither limited nor stimulated by the staff.

Behavioral symptoms were scored using the Neuro Psychiatric Inventory-Nursing Home edition (NPI-NH) (9, 10) and the Cohen Mansfield Agitation Inventory (CMAI).(11, 12) The NPI-NH assesses 12 neuropsychiatric symptoms. The frequency and severity are rated and are multiplied to create a symptom score (range 1-12). The total score is the sum of all 12 symptoms (range 12-144). The NPI identifies three clusters of symptoms: psychosis, psychomotor behavior, and affect. (13) The CMAI assesses 29 agitated behaviors in patients with dementia. All items are scored on a 7-point scale (range 29-203). The CMAI focuses on three clusters of symptoms: physically aggressive, physically nonaggressive and verbally agitated behavior.(14) Both rating scales are validated for use in Dutch nursing homes (14) and, in the present study, were scored weekly by a nurse.

## RESULTS

### Participant A

The first participant is an 85-year-old woman, diagnosed with Alzheimer's disease. In the nursing home she continuously paces through the unit. There is a general restlessness and, occasionally, sadness but no other signs of depression are apparent. If she does not feel in control, she becomes angry and hits the nurses or residents. A detailed multidisciplinary analysis was conducted following national guidelines. (15) As no physical cause was found, environmental and psychological interventions were set in place. Additionally, in the presence of physical aggression endangering herself or others, a small dose of lorazepam was given. A single-subject trial was initiated to examine whether this patient's high level of caffeine consumption influenced her general restlessness, agitation and aggression.

During the 4-week observation period, 3212 mg of caffeine was consumed: 67% from coffee. During the 'decaf weeks' (weeks 2 and 3), 19% of the total amount of caffeine was consumed. There was no medication or comorbidity present which could interfere with caffeine metabolism. The reduction in caffeine consumption coincided with a reduction of NPI-NH item agitation/aggression (scores for weeks 1 to 4 were: 12, 3, 1 and 4, respectively) (Table 1). After the reintroduction of caffeine, there was a slight increase in these behavioral symptoms. The same pattern was seen in the total CMAI score, the CMAI item general restlessness, the CMAI physically aggressive and non-aggressive cluster scores, the total NPI-NH score and the NPI-NH psychomotor behavior cluster score. The decrease of the total NPI-NH score was almost entirely attributable to the items agitation/aggression, irritability and aberrant motor behavior. The changes seen in the total CMAI score were due to several items, including general restlessness and aggressive behavior (Table 1).

**Table 1:** Results of the trial: participant A

| | Week 1 (C) [a] | Week 2 (D) [a] | Week 3 (D) [a] | Week 4 (C) [a] |
|---|---|---|---|---|
| Caffeine (total mg)[b] | 1420 | 303 | 309 | 1180 |
| CMAI (total) | 60 | 51 | 44 | 51 |
| *CMAI item scores*[c] | | | | |
| Pacing | 6 | 6 | 5 | 6 |
| Inappropriate robing/disrobing | 5 | 5 | 5 | 5 |
| Cursing or verbal aggression | 5 | 3 | 1 | 3 |
| Hitting | 4 | 2 | 1 | 1 |
| Grabbing | 4 | 2 | 1 | 1 |
| Pushing | 1 | 1 | 1 | 2 |
| Get to different place | 3 | 1 | 4 | 1 |
| Hoarding things | 6 | 5 | 5 | 6 |
| General restlessness | 6 | 6 | 1 | 6 |
| *CMAI cluster scores* | | | | |
| Physically aggressive behavior | 18 | 12 | 8 | 11 |
| Physically non-aggressive behavior | 28 | 25 | 22 | 26 |
| Verbally agitated behavior | 4 | 4 | 4 | 4 |
| NPI-NH (total) | 49 | 25 | 1 | 8 |
| *NPI-NH item scores*[d] | | | | |
| Agitation/aggression | 12 | 3 | 1 | 4 |
| Depressed mood | 9 | 0 | 0 | 0 |
| Irritability | 12 | 8 | 0 | 0 |
| Aberrant motor behavior | 12 | 12 | 0 | 4 |
| Might time behavior | 4 | 2 | 0 | 0 |
| *NPI-NH cluster scores* | | | | |
| Psychosis | 0 | 0 | 0 | 0 |
| Psychomotor behavior | 24 | 11 | 1 | 4 |
| Affect | 9 | 0 | 0 | 0 |

[a] C: caffeinated coffee; D: decaffeinated coffee

[b] cup of tea 30 mg; cup of coffee 70 mg; cup of decaffeinated coffee 3 mg

[c] all other CMAI items (spitting, constant request for attention, repetitious sentences/ questions, kicking, throwing things, making strange noises, screaming, biting, scratching, intentional falling, complaining, negativism, eating inappropriate substances, hurting oneself or others, handling things inappropriately, hiding things, tearing things, performing repetitious mannerisms, verbal sexual advances and physical sexual advances) had a continuous score of 1 during the study

[d] all other NPI-NH items (delusions, hallucinations, anxiety, euphoria, apathy, disinhibition and eating change) had a continuous score of 0 during the study

CMAI: Cohen Mansfield Agitation Inventory

NPI-NH: Neuro Psychiatric Inventory-Nursing Home edition

### Participant B

Participant B, a 91-year-old woman, was diagnosed 6 years earlier with mixed type dementia. After admission, she kept to herself. If someone entered her room she became angry and aggressive, often pushing people out of the room. Her family perceived her behavior as being 'her nature'. Following the national guidelines,(15) an extensive multidisciplinary evaluation of her behavior was made, resulting in environmental and psychological interventions. No psychotropic medication was prescribed. A single-subject trial was initiated to investigate whether her high level of caffeine consumption influenced her anger and aggression. However, during the 4-week observation period no relationship was found between total caffeine consumption.

## DISCUSSION

Two single-subject trials were performed to explore whether specific behavioral symptoms could be reduced by regulating caffeine consumption in older patients with dementia with high caffeine intake and behavioral symptoms.

In participant A, the behavioral symptoms decreased in the 'decaf weeks' and increased slightly when regular coffee was reintroduced. In participant B, no relationship was found between caffeine consumption and behavioral symptoms.

This is the first report of single-subject trials to investigate the effects of caffeine on the management of behavioral symptoms in older patients with dementia. To evaluate the clinical value of the results, the limitations and strengths of the study need to be addressed. In these trials, the CMAI ratings pertain only to the week prior to the administration of the CMAI, instead of the usual 2-week period. However, because of the frequent nature of the behavioral symptoms, it is unlikely that our results were adversely affected. On the other hand, this study has several strengths. First, both the NPI-NH and the CMAI were scored by a single caregiver who knew the participant well; this is known to increase the validity of the ratings.(13) Second, although this was a real-life situation, no other interventions took place during the trial period (e.g. pharmacotherapy), which serves to increase the internal validity.

In general, the single-subject trial is uniquely suited for individualized research: it is a fast and flexible method to evaluate treatment effects, especially in complex situations. Moreover, the double-blinded crossover design creates a perfectly matched control. However, it is less suited for generalization to all patients with dementia and behavioral symptoms. This makes the single-subject trial the ideal design to determine individual effects of caffeine on specific behavioral symptoms.

Caffeine can have a positive or negative effect, depending on the amount consumed and the individual sensitivity. The single-subject trials presented here reveal the differences between the individuals.

Several reviews have shown that individuals generally regulate their caffeine consumption to maximize the beneficial effects and decrease negative effects.(4, 5) However, patients who are dependent on others, such as patients with dementia, are unable to regulate this and are, therefore, more likely to experience negative effects.

In conclusion, behavioral symptoms seem to be influenced by caffeine consumption in some older patients with dementia. In accordance with the effects of caffeine in adults, there seems to be a strong individual effect and tolerance to caffeine in older patients. These two single-subject trials support the need for detailed analysis of behavioral symptoms in dementia and also show the need for individually-based management of behavioral symptoms.

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# 3

# CAFFEINE AND NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH DEMENTIA: A SYSTEMATIC REVIEW

Published as: Kromhout MA, Rius Ottenheim N, Giltay E, Numans ME, Achterberg WP. Caffeine and neuropsychiatric symptoms in patients with dementia: A systematic review. Exp Gerontol. 2019;122:85-91.

## ABSTRACT

*Background*:

The consumption of caffeine has well known effects on the behavior and sleep of healthy adults. Behavioral symptoms and sleeping difficulties are common in patients with dementia which may be affected by caffeine consumption. This systematic review examines the association between caffeine intake and neuropsychiatric symptoms in patients with dementia.

*Methods*:

In January 2019 an extensive search was conducted in Medline (PubMed), Embase, Emcare, Cochrane, PsychInfo, Web of Science and gray literature. Studies were included when they: i) investigated patients diagnosed with dementia, ii) reported neuropsychiatric symptoms, iii) used caffeine or coffee consumption as an intervention, and iv) reported associations between caffeine or coffee consumption and neuropsychiatric symptoms. Studies were excluded when they also included participants *without* a diagnosis of dementia, or presented a review or expert opinion. Two reviewers independently rated the studies and reached consensus on the appraisal.

*Results*:

Of the seven studies eligible for this review, four reported on sleeping difficulties and five on behavioral symptoms. There was no consistent effect of caffeine administration on neuropsychiatric symptoms: e.g., both high caffeine consumption and eliminating caffeine were associated with less apathy, the total Neuropsychiatric Inventory (Nursing Home) decreased after both coffee therapy and after eliminating caffeine, and both caffeine consumption and eliminating caffeine improved sleep.

*Conclusion*:

These findings suggest that caffeine can either induce or reduce neuropsychiatric symptoms in individual patients with dementia. Therefore, in these patients, caffeine consumption requires a prudent individualized approach and further research on the effects of caffeine on individual neuropsychiatric symptoms in required.

## INTRODUCTION

In 2018 around 50 million people worldwide were reported to have dementia, with considerable impact on the patients and their caregivers.(1) Neuropsychiatric symptoms (e.g. aggression, agitation, anxiety, depression) are common in patients with dementia(2, 3) and lower the quality of life of both patients (4) and their caregivers.(5) Moreover, the etiology of these symptoms is complex and thought to be multifactorial, requiring detailed analysis of the contributory factors, followed by stepwise, tailored interventions.

In some guidelines on problematic behavior in dementia, caffeine is mentioned as a possible contributing factor in agitated behavior during the night (6) and, in healthy adults, is known to have physical effects on the body (e.g. increased diuresis) and influence behavior. For example, normal caffeine consumption in healthy adults increases alertness,(7-10) attention(7, 8, 10) and cognitive function,(7, 8) and elevates mood(8, 11) and reduces fatigue.(10) In higher dosages (usually ≥ 300 mg) caffeine may increase anxiety,(8, 10, 12) and induce psychotic or manic symptoms.(8) Caffeine intake prolongs sleep latency,(10, 12, 13) reduces sleep duration,(10, 12, 13) sleep efficiency(13) and fatigue(8), and also reduces subjective quality of sleep.(13) In adults, the effects of caffeine on sleep are dose and time dependent.(10, 13) The effect of caffeine on sleep and behavior in *older* persons is less well investigated. However, both older people and individuals with mental health problems may be more sensitive to caffeine compared to younger adults.(13) This places older people with dementia at potentially higher risk for an adverse influence of caffeine on behavior and sleep.

In view of the clear effects of caffeine on behavior and sleep in adults and the prevalence of neuropsychiatric symptoms in older patients with dementia, we hypothesized that there would be a correlation between caffeine intake and neuropsychiatric symptoms in patients with dementia. Therefore, this review examines the association between caffeine and neuropsychiatric symptoms in older patients with dementia.

## METHODS

### Search strategy

This systematic review was designed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.(14, 15) Details of the protocol were registered at PROSPERO and can be assessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018094098.

In January 2019 the following databases were searched: Medline (PubMed), Embase, Emcare, Cochrane, PsychInfo and Web of Science. At the same time, a second search was conducted in the gray literature: GLIN, Greylit, AACN Research & Data center, WHO, OpenGray, HSO and Clinicaltrials.gov. Moreover, all references of eligible articles were scrutinized for potential ad-

ditional studies. The search strategy was designed by the authors in collaboration with a medical information specialist.

### Selection

Two reviewers (MK and NRO) independently conducted the search and assessed the relevance of each article. The reviewers compared the articles and reached consensus on the final eligibility of each article. Another independent reviewer was available if consensus was not reached; however, involvement of a third reviewer was not required.

Studies were included when they: i) included patients diagnosed with dementia, ii) reported neuropsychiatric symptoms, preferably using a valid scale or index: e.g. the Neuropsychiatric Inventory (NPI) (16) or the Cohen-Mansfield Agitation Inventory (17), iii) included caffeine or coffee consumption as an intervention, and iv) reported associations between caffeine or coffee consumption and neuropsychiatric symptoms.

Studies were excluded when they also included participants *without* a diagnosis of dementia, or presented a review or expert opinion.

### Data extraction

One reviewer (MK) extracted the following data: study characteristics (authors, year of publication, country, study design, inclusion/exclusion criteria), patient characteristics (number, mean age, sex, type of dementia), caffeine, neuropsychiatric symptoms (scale/index used, results), associations between caffeine and neuropsychiatric symptoms, adjustments made for confounding/risk of bias, and funding. The data extraction was checked by a second reviewer (NRO).

### Appraisal

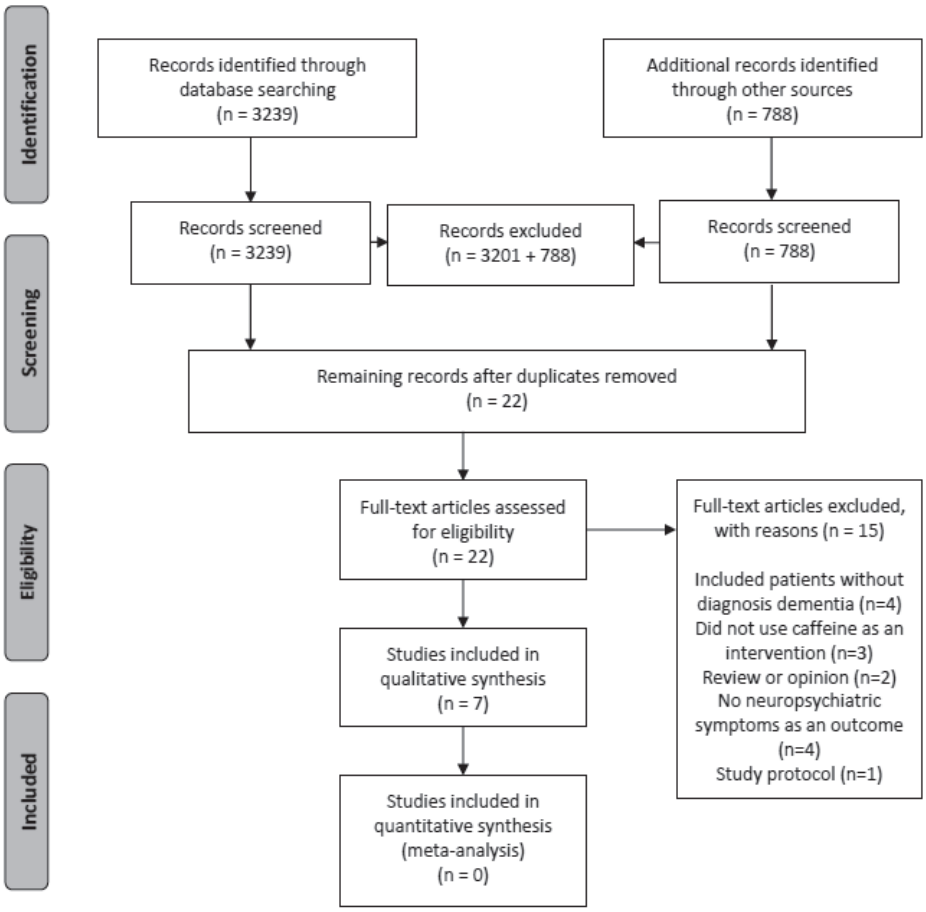
Since this review included mixed method studies, the Mixed Methods Appraisal Tool (MMAT) was used during the appraisal stage. The MMAT has been designed to assess the methodological quality of studies included in a systematic mixed studies review. The MMAT consists of two screening questions and five sections of specific questions regarding study type, e.g. qualitative, quantitative randomized controlled trial (RCT), quantitative non-RCT, quantitative descriptive, and mixed methods. For a mixed methods study three sections were used, i.e. the qualitative section to appraise the qualitative component, the appropriate section for the quantitative component, and the mixed methods section. For all types of studies, an overall quality score was calculated to indicate methodological quality.(18) Two reviewers (MK and NRO) independently assessed the studies and reached consensus on the scoring metrics. However, since one of the reviewers (MK) co-authored two of the included studies, in the assessment of these latter studies MK was replaced by the third reviewer (EJG).

## RESULTS

### Search results

The primary search resulted in 3,239 potentially relevant articles; after screening for eligibility, only 7 studies remained. The secondary search yielded 788 potentially relevant articles, of which none met the inclusion criteria (Fig. 1).

**Figure 1:** flowchart




### Study characteristics

The seven included studies differed in almost all aspects, including: i) study type (from a case report(19) to a RCT(20)), ii) publication date (ranging from 1976 (21) to 2018 (22)), and iii) methodology (qualitative and quantitative). However, all studies included patients with some type of dementia.

One study excluded patients with certain types of dementia.(21) In five studies caffeine was regulated,(20-24) one study observed caffeine consumption(25) and one used self-reported consumption.(19) Three studies measured behavioral problems,(19, 20, 24) two studies reported on sleeping difficulties(21, 23) and two studies reported on both.(22, 25) Characteristics of the included studies are presented in Tables 1 and 2.

## Appraisal

The one quantitative RCT, and the one mixed method and five quantitative non-RCTs were scored using the MMAT criteria. The mixed method study(21) scored lowest (0%), mainly due to the qualitative part of the study in which none of the MMAT criteria were met. The oldest quantitative non-RCT(23) lost points (MMAT score 25%) due to unclear selection, inappropriate measurements, and the absence of control persons. Three studies scored 50% on the MMAT.(19, 22, 24) The qualitative case report did not analyze the data and did not consider the influence of the researchers.(19) In the two single-subject trials (both reported in (24)), the participants were carefully selected and the article did not report complete outcome data. The most recent qualitative non-RCT also had incomplete outcome data and did not correct for possible confounders.(22) The other two studies met all the criteria for the appropriate study method.(20, 25) (Tables 1 and 2)

## Caffeine or coffee consumption

In all studies, the investigated hypothesis was whether caffeine was a determinant for the reported neuropsychiatric symptoms. However, the way the caffeine was ingested ranged from injections,(23) caffeinated beverages,(20-22, 24, 25) medication,(19) to oral ingestion (not further specified).(23) The following were used as (de)caffeinated beverages: instant coffee, filter coffee, pour-over coffee, coffee from pads, black tea and cola.

The amount of caffeine in coffee varies according to the method used to make the coffee, e.g. filter coffee contains more caffeine than espresso due to the longer extraction time. Two studies mentioned the exact caffeine dosage,(21, 23) two made estimates based on the method of coffee making,(24, 25) and one study made an estimation based on self-reported medication use.(19) Since two trials did not mention caffeine dosage during the intervention (20, 22), an estimation was made (if possible) based on the information in the article. In the seven studies, caffeine consumption ranged from 0-300 mg/day, and was reported to be 1300 mg/day in the case report (Table 3).

## Neuropsychiatric symptoms

Two trials,(20, 22) the two single-subject trials,(24) an observational study,(25) and the case report(19) assessed the relationship between caffeine and various behavioral symptoms. The included studies reported both positive and negative effects of caffeine on behavioral symptoms.

**Table 1:** Characteristics of the studies with sleep as outcome

| Article | Study characteristics | | | | Patient characteristics | | | |
|---|---|---|---|---|---|---|---|---|
| | Design | Inclusion criteria | Exclusion criteria | Setting | N | Age (yrs) | Sex (% F) | Type of dementia |
| Ginsburg et al. 1976 USA[1] | Qualitative and quantitative double-blind trial | Medication resistant sleeping difficulties | Dementia by trauma, infection, metabolic or vascular diseases, intoxication, neoplasms or NPH | Nursing home | 12 | - | - | Alzheimer or Pick's disease |
| Domzal. 1990 Poland | Reversed treatment non-rando-mized trial | - | - | Hospital | 16 | 51-81 | 44 | Multi-infarct dementia |
| Kromhout et al. 2014 Netherlands | Obser-vational study | All residents of a dementia special care unit | Psychiatric morbidity; terminal phase; no informed proxy consent | Nursing home | 29 | 84 (69-96) | 72 | 55% Alzheimer<br>14% VD<br>3% Mixed<br>3% Korsakoff<br>24% NOS |
| de Pooter-Stijnman et al. 2018 Netherlands | Pre-post intervention trial | Diagnoses of dementia, at least 1 cup of coffee/day | No informed consent, life expectancy < 1 month or living < 4 weeks in the unit at start of the study | Nursing home | 21 | 87 (70-98) | 81 | 24% Alzheimer<br>19% VD<br>14% Mixed<br>5% FTD<br>38% NOS |

NPS: neuropsychiatric symptoms; MMAT: Mixed Methods Appraisal Tool; NPH: Normal pressure hydrocephalus;; CMAI: Cohen-Mansfield Agitation Inventory; AMB: aberrant motor behavior; F: female; VD: vascular dementia; FTD: frontotemporal dementia; NOS: dementia not otherwise specified

[1] Authors do not explicitly state the country of study, but both are affiliated with the University of Rochester, New York, USA.

[2] All non-significant results are also reported in the article.

[3] More results reported in the article. None of the articles mention funding.

| Caffeine | NPS -sleep<br>Outcome and scale/ index used | Results | Conclusion | Adjustments made for confounding and bias | MMAT score |
|---|---|---|---|---|---|
| 4 x 5 days separated by 1-day washout: 1. A hot liquid (0 mg)<br>2. Coffee (48mg)<br>3. Coffee (138mg)<br>4. Coffee (228mg)<br>30-45 min before bedtime | Sleep induction time; quality of sleep; total length of sleep; time wake during the night and a global sleep rating | N=3: increased sleep on 138 mg caffeine. No significant difference was found between the placebo and the 3 dose levels of caffeine. | No soporific effect of coffee in patients with dementia. | No hypnotics or tranquilizing medication the month before and during the trial | 0% |
| Caffeine at 8 p.m.: 0.1-0.2 caffeine oral or per injection.<br>Sedatives during the day. | Circadian rhythm sleep disorders | N=6: no change<br>N=10: average 4 h improvement in sleep rhythm<br>N=3: died | Caffeine restores the normal sleep rhythm. | - | 25% |
| Consumption of coffee, tea and cola was recorded 8 times/day during 4 days. Average use: 15 units of caffeine (SD 5.6) per person during 4 days. | Sleep: if a patient got up at night and lay awake in bed or was asleep. | Total caffeine and getting up at night (KT 0.462 p<0.01). Evening caffeine and getting up at night (KT 0.436, p<0.01; ML b=0.48 (0.22), Wald (461) = 2.20, p=0.03).[2] | Caffeine consumption is positively correlated with getting up at night. | All nursing and nutrition staff were trained in the use of the questionnaires. Multilevel analysis was used to correct for the nested structure of the data. | 100% |
| 3x2 weeks: 1. Baseline (pre-intervention). 2. Wash-out period (gradually reducing caffeine intake to intervention situation.) 3. Post-intervention (caffeinated coffee from 6 a.m. to 12 a.m. and decaffeinated coffee from 12 a.m.) | Sleep questionnaire: quietly sleeping, restlessly sleeping, quietly awake or restlessly awake. A total sleep score (good vs. poor sleep) | Quietly sleeping (pre 83%. post 87% p=0.032)<br>The total sleep score improved significantly post-intervention compared to pre-intervention (p=0.015).[3] | Eliminating caffeine in the afternoon and evening improves sleep. | Several possible confounders were noted, but not statistically corrected | 50% |

**Table 2:** Characteristics of studies with behavior as outcome.

| Article | Study characteristics | | | | Patient characteristics | | | |
|---|---|---|---|---|---|---|---|---|
| | Design | Inclusion criteria | Exclusion criteria | Setting | N | Age (yrs) | Sex (% F) | Type of dementia |
| Matsuda et al. 2012 Japan | Random-ized trial | - | - | Geriatric hospital | 29 | 81 ± 8 | 66 | Dementia (DSM-IV criteria) |
| Kromhout et al. 2014 Netherlands | Obser-vational study | All residents of a special care unit for dementia | Psychiatric morbidity; terminal phase; no informed proxy consent | Nursing home | 29 | 84 (69-96) | 72 | 55% Alzheimer 14% VD 3% Mixed 3% Korsakoff 24% NOS |
| Golden et al. 2015 USA | Case report | - | - | ER and ICU | 1 | 61 | 0 | Dementia |
| Kromhout et al. 2017 Netherlands | Two double-blinded single-subject trials | Patients with a high intake of caffeine and severe NPS | Psychiatric morbidity; no informed proxy consent | Nursing home | 2 | 85 -91 | 100 | 50% Alzheimer 50% Mixed |
| de Pooter-Stijnman et al. 2018 Netherlands | Pre-post intervention trial | Diagnoses of dementia, at least 1 cup coffee a day | No informed consent, life expectancy < 1 month or living < 4 weeks in the unit at start of the study | Nursing home | 21 | 87 (70–98) | 81 | 24% Alzheimer 19% VD 14% Mixed 5% FTD 38% NOS |

NPS: neuropsychiatric symptoms; MMAT: Mixed Methods Appraisal Tool; NPH: Normal pressure hydrocephalus; NPI(-NH): neuropsychiatric inventory (nursing home edition); CMAI: Cohen-Mansfield Agitation Inventory; AMB: ambulant motor behavior; F: female; ER: emergency room; ICU: intensive care unit; VD: vascular dementia; FTD: fronto-temporal dementia; NOS: dementia not otherwise specified

[1] All non-significant results are also reported in the article.

[2] More results reported in the article.

None of the articles mention funding.

| Caffeine | NPS -behavior<br>Outcome and scale/index used | Results | Conclusion | Adjustments made for confounding and bias | MMAT score |
|---|---|---|---|---|---|
| Coffee therapy (n=14) vs control therapy (n=15), 2/week for a month. | NPI | Intervention: NPI baseline 23 ±12, end 15 ±11 (*p<0.05)*.<br>Control: NPI baseline 22 ±13, vs 20 ±12. | Coffee therapy might be one of the non-medical treatments for NPS. | Outcome was measured blinded to treatment status. | 100% |
| Consumption of coffee, tea and cola was recorded 8 times/day for 4 days. Average use: 15 units of caffeine (SD 5.6) pp in 4 days. | NPI-NH items agitation, depression, anxiety, apathy, irritability and AMB. | Total caffeine and apathy (KT -0.287 p=0.03; ML b=-0.88 (0.45) Wald (461) = -1.96, p=0.05); AMB (ML b= -0.47 (0.22) Wald (461)= -2.12, p=0.03).[1] | Caffeine consumption is negatively correlated with apathy and AMB. | All nursing and nutrition staff were trained in the use of the questionnaires. Multilevel analysis was used to correct for the nested structure of the data. | 100% |
| BC Powder (845mg aspirin/ 65mg caffeine)<br>5-20 packets a day | - | - | Overuse of aspirin/ caffeine induced psychosis in this patient with dementia. | - | 50% |
| 4 weeks of regulated caffeine consumption using unrecognizable caffeinated or decaffeinated coffee pods. | NPI-NH and CMAI.<br>Patient A: general restlessness, agitation and aggression.<br>Patient B: anger and aggression. | A: NPS decreased in the decaffeinated weeks and increased slightly on reintroduction of regular coffee (NPI-NH agitation week 1 to 4 12, 3, 1, 4; CMAI general restlessness 6, 6, 1, 6.)[2]<br>B: no relationship. | NPS is influenced by caffeine in some patients with dementia. | Patients and staff were unaware of the predetermined order and blinded for the intervention.<br>Patients were their own controls. | 50% |
| 3x2wks: 1. Pre-intervention. 2. Wash-out period (gradually reducing caffeine to intervention situation.) 3. Post-intervention (caffeinated coffee from 6 a.m. to 12 a.m. decaffeinated coffee from 12 a.m.) | NPI-NH items agitation, apathy, irritability and AMB | Apathy (pre 35% 1-2 post 10% 1 p=0.020). NPI-NH items agitation, irritability and AMB did not differ between pre -and post-intervention.[2] | Eliminating caffeine in the afternoon and evening decreases apathy. | Several possible confounders were noted, but not statistically corrected | 50% |

**Table 3:** Caffeine consumption and results per study

| Study | (Estimated) caffeine consumption (per day) | Result |
|---|---|---|
| Ginsburg | 0mg – 48mg – 138mg – 228mg | In 3 patients increased sleep on 138mg |
| Domzal | 0,1 – 0,2 caffeine (oral or per injection) | 10 patients improved their duration of sleep |
| Matsuda | ½ cup filter coffee 2/week<br>Estimate: 85mg/2/7*2 = 12mg | NPI score on baseline 23, at the end 15 |
| Kromhout 2014 | Average use 15 units of caffeine pp in 4 days: 85mg*15/4 = 319mg | Negative correlation with apathy and AMB<br>Positive correlation with getting up at night |
| Golden | 5-20 packets a 65mg = 325 – 1300mg | Psychoses |
| Kromhout 2017 | 203mg – 43mg – 44mg – 169mg | Relation between specific NPS and caffeine consumption |
| Pooter | Baseline: mean 300mg (range 150-375)<br>Intervention: no caffeine after 12 a.m. | Eliminating caffeine in the afternoon and evening decreases apathy and improves sleep. |

The trial from Japan used the NPI to measure the difference in neuropsychiatric symptoms between coffee therapy and control therapy in a group of 29 patients with dementia.(20) Coffee therapy was described as a 30-min social activity in which fresh coffee was ground, brewed and served. Compared to the control group, the coffee therapy group had a significant drop in the total NPI score.(20) In one of the single-subject trials, a decrease in total Neuropsychiatric Inventory Nursing Home edition (NPI-NH) was seen during the decaffeinated period.(24) The other studies did not report the total NPI-NH score, but reported on specific NPI-NH items. In the observational study, a higher use of caffeine was associated with a lower score on the NPI-NH item 'apathy' and a higher score on 'aberrant motor behavior'.(25) Interestingly, the most recent study showed a decrease in 'apathy' after eliminating caffeine after 12 a.m. and no relation with 'aberrant motor behavior'.(22) One of the single-subject trials showed no effect of caffeine on behavior, whereas the other showed a negative effect of caffeine on several NPI-NH items (e.g. agitation/aggression) and on the NPI-NH psychomotor behavior cluster score.(24) The case report identified caffeine abuse, in combination with aspirin, as being the main cause of psychoses.(19)

Four studies reported on sleeping difficulties (Table 2). Caffeine was found to increase the number of times patients with dementia got out of bed (25) and eliminating caffeine increased the number of times patients with dementia were quietly sleeping and also improved the total sleep score,(22); these effects are similar to those reported in healthy adults. However, in contrast to the effects in healthy adults, in patients with dementia no relationship was found with sleep induction time,(21) quality of sleep,(21) time awake during the night(21, 25) and global sleep rating.(21) In two trials caffeine was administered in the evening, i.e. at 8 p.m. (23) or 30-45 min before bedtime(21). In both these studies some of the participants showed an improvement in sleep: 3 of 12 showed increased sleep on 138 mg of caffeine and 10 of 16 showed improvement in the circadian rhythm.

## DISCUSSION

Although caffeine is widely used and its effects have been extensively studied in healthy adults, our comprehensive search yielded only seven small studies assessing the relation between caffeine consumption and neuropsychiatric symptoms in patients with dementia. Thus, the evidence is limited and most studies had methodological issues. Despite our thorough analysis of these studies, no consistent conclusions could be drawn regarding caffeine consumption and neuropsychiatric symptoms in patients with dementia. However, in each trial, the behavior of some participants seemed to be (strongly) influenced by caffeine consumption but in unpredictable ways, thereby emphasizing the need for an individualized approach.

The absence of a consistent effect might be due to the relatively normal dosage of caffeine used in the studies. In healthy adults, a chronic caffeine consumption of up to 400 mg a day is generally regarded as safe;(26, 27) in the case of caffeine abuse the daily dosage exceeded this level and resulted in psychosis.(19) Individuals who are sensitive to caffeine, pregnant women, and people with mental or psychiatric disorders and disabilities (e.g. individuals with dementia) might be more susceptible(28) and experience adverse effects at a much lower dosage. In the studies in the present review, this might be why some of the participants showed a change in behavior that was attributed to caffeine.

A second reason for the absence of a consistent effect might be the differences in study populations. Although all studies included patients with dementia, some of the studies included only patients with dementia and behavioral symptoms(Golden et al., 2015; Ginsburg and Weintraub, 1976; Kromhout et al., 2017). However, there was no consistent effect of caffeine on behavior in the studies that included only patients with dementia and behavioral symptoms, nor in the studies that included patients with dementia with and without behavioral symptoms. This suggests other factors contribute to the effect of caffeine on behavioral symptoms.

Another reason for the absence of a consistent effect might be the way that neuropsychiatric symptoms are reported. In the present review, with the exception of the case report, all studies used a version of the NPI to assess neuropsychiatric symptoms. The NPI consists of 12 neuropsychiatric symptoms (hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior, sleep and night-time behavior change, and appetite/eating change) of which the severity and frequency are rated and multiplied to create a symptom score.(16) The NPI implies that neuropsychiatric symptoms tap from one underlying latent variable construct, thus representing a single underlying disorder, where the level of severity is measured as a sum score. The questions in the NPI-NH have the same content as the questions of the NPI but have been rephrased for the nursing home population. (16, 29) Caffeine is known to have heterogeneous effects, potentially increasing several neuropsychiatric symptoms (e.g. agitation, anxiety, sleep disorders) and decreasing others (e.g. depression or apathy), both measured with the NPI(-NH). Therefore, a net neutral result could be based on the total NPI(-NH) score, whereas important insights might be derived by analyzing the

effects on neuropsychiatric symptoms in individual patients. This implies that larger studies are required on the effects of caffeine on individual neuropsychiatric symptoms.

In healthy adults, the negative effects of caffeine on sleep are thought to be caused by antagonizing the adenosine (A1 and A2) receptors in the brain.(13) Similar to the effects in healthy adults, caffeine was found to negatively impact sleep in some patients with dementia.(22, 25) However, surprisingly, in some patients the use of caffeine seemed to improve circadian rhythm(23) and sleep.(21) This positive effect of caffeine on sleep was also found in a 71-year-old man with a sleeping problem unresponsive to sedatives, who slept soundly after a cup of strong coffee before bedtime.(30) The author suggested that sleeping problems could have been caused by confusion. The consumed coffee could diminish the confusion by increasing attention and therefore have a positive effect on sleep. In the present review, no data were available on the amount of confusion of older patients with dementia who responded positively to caffeine,(21, 23); however, due to their illness, confusion might have played a role.

Another possible mechanism is the neurobiological changes in adenosine receptors, as A1 receptor density reduces and the A2 receptor expression increases during the progression of Alzheimer dementia.(31) The A1 receptor inhibits a cascade of effects which promote 'wakefulness', while the A2 receptor stimulates several mechanisms which induce 'sleepiness'.(32) By antagonizing both A1 and A2 receptors, caffeine impairs sleep. However, due to the different changes in receptor expression during disease progression, this effect might differ between healthy adults, patients with a mild dementia, and patients with severe Alzheimer dementia. In the treatment of dementia, the same paradox has been suggested, i.e. as in early dementia, an adenosine agonist might improve cognitive function and, as the disease progresses, adenosine antagonists have a more positive effect.(33) Therefore, caffeine may have a positive effect on sleep in patients with severe dementia, unless the diuretic effect of caffeine awakens them.

In adults, the effects of caffeine on behavior differ between individuals and can be influenced by genetics, expectations, frequency of use and tolerance developed. Generally, if there are effects, the individual regulates their caffeine consumption to minimize the adverse effects (12) or maximize the positive effects.(10) However, patients with dementia (especially institutionalized patients) cannot always modulate their caffeine consumption for their own benefit. Therefore, caretakers need to know the prior caffeine use/preferences of their patients and, in the case of behavioral symptoms, actively assess whether these might be attributable to caffeine use. However, this may not be easy and involves considering that something as common as caffeine (often used on a daily basis) can have both a positive or negative impact on complex behavior and neuropsychiatric symptoms in patients with dementia.

## CONCLUSION

This systematic review found no consistent effect of caffeine administration on neuropsychiatric symptoms in patients with dementia. Further research on the effects of caffeine on individual neuropsychiatric symptoms in patients with dementia is therefore warranted. However, there were indications that caffeine can both induce and reduce neuropsychiatric symptoms and sleeping difficulties in individual patients with dementia. Since ingestion of caffeine is an easily adaptable intervention, it is recommended to include caffeine consumption in the individualized approach of neuropsychiatric symptoms in patients with dementia.

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# 4

# CAFFEINE CONSUMPTION AND BEHAVIORAL SYMPTOMS IN NURSING HOME RESIDENTS: A STUDY PROTOCOL AND EVIDENCE-BASED MEDICINE TRAINING PROGRAM

Shortened version published as Kromhout MA, van Eijk M, Pieper MJC, Chel VGM, Achterberg WP, Numans ME. BeCaf study: caffeine and behaviour in nursing homes, a study protocol and EBM training program. Neth J Med. 2018;76(3):138-40.

## ABSTRACT

*Background:*

Since nursing home populations are diverse and often underrepresented in medical research, physicians in these homes need to assess the applicability of the limited research for the individual patient. Research rarely focuses on simple everyday interventions, such as caffeine, despite that in healthy adults caffeine is known to influence behavior. Although behavioral symptoms in patients with dementia are frequent in nursing homes, the effects of caffeine on the behavior of older patients with dementia is not well researched. Therefore, this study aims to i) assess the relation between caffeine and behavioral symptoms in older patients, and ii) create an educational innovation of evidence-based medicine (EBM) training for elderly care physicians (ECPs). The study protocol is presented here.

*Methods:*

This study is a prospective multicenter cohort study and embedded in the Dutch ECP training program. Trainees collect data from their own patients, based on medical records and interviews with nursing staff. Patient characteristics, nutritional data (including caffeine), functional status (e.g. functional comorbidity index), cognition (e.g. global deterioration scale), behavioral symptoms (e.g. Neuropsychiatric Inventory, Apathy Evaluation Scale and Minimum Data Set Depression Rating Scale) and social information are collected at baseline and at 2-months post-baseline. None of the instruments used places any burden on the patients. All data entered in the dataset are anonymized. Univariate analysis is used to assess the relation between caffeine and behavior, and multivariate analysis will correct for potential confounding factors. A subgroup analysis will assess the relation between caffeine and behavioral symptoms in patients with dementia. Trainees can formulate their own research questions and apply appropriate statistical techniques to answer their questions. During the entire study, all trainees are supervised by senior researchers and a professor.

*Discussion:*

This is the first large-scale study to assess the relation between caffeine and behavioral symptoms in older patients in nursing homes, with the aim to identify a potential simple intervention to deal with a complex problem. This study is part of an educational innovation of EBM training for ECPs which integrates EBM training, research and clinical practice.

## BACKGROUND

The vast majority of older people in the Netherlands live at home, with or without home care. If the demand for care exceeds the potential of home care, admission to a nursing home might be required. In the Netherlands, because the demand for care is the main reason for nursing home admission, this results in a heterogeneous population. Also, in Dutch nursing homes a differentiation is made based on the type of care, e.g. most older people with moderate to severe dementia are admitted to a specialized psychogeriatric ward, whereas physically disabled older people are generally admitted to a somatic ward. However, this differentiation is not absolute, as cognitive disorders are also commonly seen in patients on somatic wards. Moreover, besides the main diagnosis, since most patients have multiple comorbidities this tends to make nursing home populations even more diverse.

Dutch nursing homes not only employ nursing staff but also have their own medical, paramedical and psychosocial staff. The nursing home population requires a readily available medical generalist for all types of medical questions, as well as a specialist in the specific needs of the geriatric patient (1, 2), e.g. geriatric diseases, advanced care planning, behavioral symptoms and geriatric rehabilitation. Medical care in Dutch nursing homes is provided by elderly care physicians (ECPs), a medical specialty unique to the medical world.

The 3-year specialist training program for ECPs takes place in three Dutch universities and consists of three training periods in an educational nursing home, three internships, and a theoretical course lasting 100-120 days. Evidence-based medicine (EBM) is taught during the theoretical course. Currently, the EBM training of the ECP training at Leiden University Medical Center comprises: 1) several lectures on the basics of research and critical reading, 2) the writing of three Critically Appraised Topics (CATs) (3, 4) with questions initiated by the trainees themselves, and 3) participation in a group of ECP trainees to analyze an existing dataset and present the results to their peers. Teaching EBM is essential to create lifelong learners who can critically appraise information and assess the applicability of this information for the individual patient.(5) This applies, in particular, to elderly care medicine, due to the underrepresentation in medical research of frail elderly persons and nursing home residents. Although classroom teaching of EBM improves knowledge, clinically integrated teaching not only improves knowledge but also related skills, attitude and behavior.(6) Compared to traditional teaching, a blended learning approach is more effective in improving the attitude towards EBM and results in a higher self-reported use of EBM in clinical practice.(7) The EBM training program is regularly evaluated and updated to maintain a state-of-the-art program. Our latest innovation is the integration of a prospective cohort study assessing the relation between caffeine and behavioral symptoms, and the EBM training program; this is described in the study protocol presented here.

Of all patients admitted to Dutch nursing homes, ≥ 50% are diagnosed with cognitive disorders or dementia. In patients with dementia behavioral symptoms are often the main reason for nursing home admission, often due to the heavy burden placed on the caregivers (8), resulting in a high demand for care. In addition, behavioral symptoms lower the patient's quality of life.(9) Behavioral symptoms are present in ≥ 80% of patients with dementia in a nursing home.(10, 11)

In patients with dementia the etiology of behavioral symptoms is complex and thought to be multifactorial.(12) To manage these symptoms, national guidelines recommend a detailed analysis of the patient, including contributing physical, psychological, social and environmental factors. (12) Moreover, the intervention on behavioral symptoms is complex. Despite that many pharmacological (13, 14) and psychosocial interventions have been studied,(15, 16) no standardized solution is available and all interventions targeting behavioral symptoms must be tailored.(15, 17) A customized, stepwise intervention, including not only analysis of the contributing factors but also the psychological and psychosocial unmet needs, has proven effective in targeting behavioral symptoms in patients with dementia.(18)

The Dutch national guideline on behavioral symptoms in patients with dementia mentions caffeine consumption as a possible contributing factor.(12) However, this conclusion is not based on research on patients with dementia or on patients in nursing homes. To date, the only study available on caffeine and behavioral symptoms in older patients with dementia in nursing homes is a small observational study showing an association with apathy, and an inverse association with aberrant motor behavior and caffeine consumption.(19) On the other hand, the effect of caffeine on behavior in adults has been widely investigated. Reviews show that normal caffeine consumption in healthy adults increases alertness,(20-22) attention (20-22) and cognitive function (20, 21), elevates mood (21) and reduces fatigue (22). In higher dosages (usually ≥ 300 mg) caffeine is known to increase anxiety,(21, 22) induce psychotic or manic symptoms (21) and impair sleep (22). These effects differ between individuals, and people normally adjust their consumption of caffeine based on their own experienced (non-)beneficial side-effects.(21, 22) However, institutionalization and cognitive disorders tend to impair the ability to self-adjust caffeine consumption. Based on research among healthy adults, in older patients with dementia in nursing homes both a positive or a negative influence of caffeine consumption on behavioral symptoms can be expected. However, additional research in larger study populations is needed to gain more insight into the effects of caffeine consumption in older people.

The purpose of this study is two-fold. The primary aim is to assess the relation between caffeine and behavioral symptoms (e.g. apathy and agitation) in older patients in nursing homes and to assess factors contributing to this relation. The second aim is to create an educational innovation of EBM training for ECPs, leading to a new EBM curriculum which stimulates trainees' interest in research and integrates research into clinical practice. The study protocol is presented here.

## METHODS

### Study design

This study is a prospective multicenter cohort study, embedded in the ECP training program during the theoretical course. In the new EBM program several improvements will be made. First, the basics of research and critical reading will be taught using classroom activities (lectures and

part-task practice) and online learning. Second, each trainee will participate in a complete medical study and this study will be embedded in their clinical practice. Writing three CATs remains part of the program. The result is a complete EBM curriculum with research skills introduced in manageable parts, a blended learning approach, and integration of the EBM program in clinical practice.

## Setting and study population

All trainees are asked to collect data from their own patients, thereby making every educational nursing home a possible center of study. As the maximum capacity of the ECP training program at Leiden University is 26 new trainees/year, a maximum of 26 nursing homes can participate in the study per year. The contracted educational nursing homes are situated in the southern/mid-western part of the Netherlands.

As the population in nursing homes is highly diverse, a more homogeneous study population was desired, but without limiting the study population to a specific ward or unit; this would allow every trainee, irrespective of their training period, to participate. Therefore, to create a more homogeneous study population, a 'ward transcending' factor was chosen, i.e. diabetes mellitus type I and II. In European nursing homes, 21.8% of patients in nursing homes are diagnosed with diabetes mellitus.(23) A trainee on a full-time contract is supposed to provide medical care for 50-80 patients. For this study, trainees were asked to include all patients under their care who had a diagnosis of diabetes (type I or II); no other inclusion criteria were applied. All participants and educational nursing homes received adequate oral and written information about the study.

## Ethical approval

The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center. In accordance with Dutch legislation, a full review procedure by the Medical Ethics Committee was not deemed necessary because, in an observational study, no rules of conduct are imposed and no patients are subjected to any (medical) acts. Therefore, no formal written consent was required from the participants.

## Study procedure

As this prospective multicenter cohort study is embedded in the ECP training program, all data will be collected by ECP trainees who participate in the study for three years. In the first year of training, data are collected and research questions formulated, the second and third years are used to analyze/interpret the data and formulate conclusions (preferably in the form of an article). During the entire EBM training program, supervision is provided by senior researchers (MP, ME) and a professor in elderly care medicine (WA) from the Department of Public Health and Primary Care.

Currently, the study comprises a baseline measurement (T0) and a second measurement 2-months post-baseline (T1). In the near future, a third measurement (T2, 4-months post-baseline) will be added to the program.

Trainees identify all patients under their care who have diabetes and assess them using a given set of instruments (see below). After assessment, the data are entered in a secure online platform (NetQ Healthcare) by the trainees. If any data are missing, the senior researcher contacts the trainee to complete the data. The title page, including (amongst other data) the name of the patient, are filed separately at the Department of Public Health and Primary Care. Only anonymized data remain in the dataset. The dataset is stored on a secure location at the same department, managed by the scientific staff. After trainees have formulated a research question, they are only provided with data required to answer their question.

## Assessment instruments

All data used in the present study are part of data collected for routine/usual care in the nursing home. Data are collected by trainees, based on medical records and interviews with the nursing staff. The data are gathered according to the Somatic, Activities of daily living, Social, Psychological and Communication (SASPC) system, a problem-oriented system for multidisciplinary care,(24) which creates a complete overview of the patient. The components of the SASPC system are similar to those of the Comprehensive Geriatric Assessment (CGA): medical v. somatic; psychosocial vs. social and psychological; and functional limitations vs. activities of daily living and communication. Although both the CGA and the SASPC are regularly used in the Netherlands, the SASPC system is more often used in nursing homes.

Only reliable and validated instruments are used to collect the data. None of the instruments burdens or bothers the patient in any way. The instruments used are described below (Table 1).

**Table 1:** The assessment instruments used.

| | Instrument | T0* | T1* | T2* |
|---|---|---|---|---|
| **Somatic** | Patient characteristics | X | X | X |
| | Height, weight and body mass index | X | X | X |
| | Functional comorbidity index | X | X | X |
| | Medication | X | X | X |
| | Nutritional data | X | X | X |
| | Minimum Data Set Resident Assessment Instrument – subscale pain | X | X | X |
| **Functional status/ activities of daily living** | Barthel index | X | X | X |
| | Functional ambulation categories | X | X | X |
| **Social** | Date of admission to nursing home | X | X | X |
| | Marital status | X | X | X |
| **Psychological** | Global deterioration scale | X | X | X |
| | Neuropsychiatric Inventory – Nursing Home edition | X | X | X |
| | Minimum Data Set Depression Rating Scale | X | X | X |
| | Apathy evaluation scale | X | X | X |
| **Communication** | Vision | X | X | X |

* T0: baseline; T1: 2 months post-baseline; T2: 4 months post-baseline (although not currently part of the study, this measurement will soon be added)

*Somatic*

General patient characteristics are registered, including information on advanced care planning and medication, as well as specific diabetes-related information as blood pressure, heart rate, height, weight and (if present in the records) the serum hemoglobin, serum glycated hemoglobin (Hba1C) and kidney function (MDRD/GFR). Nutritional data are gathered on caffeine consumption (recorded six times a day: the observed number of cups of coffee/tea/cola consumed, and the way the coffee was brewed), food consistency, and energy-enriched diets.

The Functional Comorbidity Index (FCI) is a comorbidity index which has physical function as the outcome of interest. The FCI contains 18 diseases and conditions: arthritis, osteoporosis, asthma, COPD, angina, congestive heart failure, prior heart attack, neurological diseases, prior stroke or transient ischemic attack, peripheral vascular disease, diabetes, upper gastrointestinal disease, depression, anxiety, visual impairment, hearing impairment, low back pain and obesity. The total score ranges from 0 (absence of comorbidity) to 18 (highest number of comorbid illnesses).(25)

The presence of pain in the last 7 days is scored using the subscale of the Minimal Data Set Resident Assessment Instrument (MDS RAI).(26) If pain was present, the frequency and intensity were also registered on a 2 and 3-point Likert scale, respectively.

Additionally, the presence of a urinary tract infection in the last 7 days was registered.

*Functional status/activities of daily living*

The modified Barthel index (BI)(27) measures mobility and dependency in activities of daily living (ADL) and records (using 10 items) the ADL of each patient. Total score ranges from 0 (completely dependent) to 20 (complete functional independence). When used for older people, the BI has a high inter-rater reliability for the total score, and a fair to moderate agreement for the individual items.(28)

The dependency of gait is classified using the Functional Ambulation Categories (FAC).(29) The FAC requires observation of gait over various slopes and surfaces, after which a rating ranging from 0 (non-functional ambulation) to 5 (independent) is given. The use of walking aids is allowed.

*Social*

The date of admission to the nursing home and marital status are registered.

*Psychological*

The stage of cognitive decline is assessed using the Reisberg Global Deterioration Scale (GDS).(30) The GDS consists of seven stages ranging from 1 (no cognitive decline) to 7 (very severe cognitive decline/severe dementia).

Behavioral symptoms are measured using the Dutch version of the Neuropsychiatric Inventory-Nursing Home edition (NPI-NH).(31-33) The NPI-NH assesses 12 different types of behavioral symptoms: delusions, hallucinations, agitation, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, nighttime distur-

bances and appetite/eating change. Both severity and frequency are rated on a Likert scale. For each symptom, a score is calculated by multiplying the severity and frequency scores. The total score is calculated by summing the symptom scores. Symptom scores range from 0-12, and the total score ranges from 0-144. The NPI-NH is a valid and reliable tool for Dutch nursing home settings and has a high inter-rater agreement.(33)

Depressive symptoms are measured with the Minimum Data Set Depression Rating Scale (MDS-DRS), an observation-based instrument to screen for depression in nursing home residents. (34) The MDS-DRS consists of seven items which are scored irrespective of the assumed cause: 0 (indicator not exhibited in the last 30 days), 1 (indicator of this type exhibited at least once in last 30 days and up to 5 days a week) or 2 (indicator of this type exhibited daily or almost daily (6-7 days a week)). Total score ranges from 0-14. At a cut-off point score of 3 the MDS-DRS has a 91% sensitivity and 69% specificity compared to the DSM-IV diagnosis of depression.(34)

Apathy is measured using the Dutch Apathy Evaluation Scale-Clinician version (AES-C).(35, 36) It consists of 18 items, all scored on a 4-point Likert scale (not at all characteristic, slightly characteristic, somewhat characteristic, and very characteristic). A higher score represents greater apathy. Total score ranges from 18-72 and a score ≥ 38 is indicative of apathy.(36, 37) The AES-C has a high interrater reliability and can be used to discriminate between apathy and depression. (36)

*Communication*

Because patients with diabetes are at greater risk for eye problems, the last measured visual acuity by an ophthalmologist is obtained from the medical records.

### Statistical analysis

The relation between caffeine and behavioral symptoms will be assessed using several techniques. Descriptive analysis is used for patient characteristics, behavior characteristics, disease characteristics and caffeine consumption; univariate analysis to identify the relation between caffeine and behavioral symptoms; and multivariate analysis is used to correct for potential confounding factors, such as age, gender and stage of cognitive decline. To assess the relation between caffeine and behavioral symptoms in patients with dementia, subgroups according to the Reisberg GDS will be created and analyzed.

The trainees will use statistical techniques appropriate to their research questions. All data are analyzed using the Statistical Package for Social Science version 23.0.

## DISCUSSION

This study assesses the relation between caffeine and behavioral symptoms among older patients in nursing homes. If caffeine proves to be related to (several types of) behavioral symptoms, a

relatively simple intervention (such as adjusting caffeine consumption) might prove beneficial and improve the patient's quality of life. This study also serves to innovate the EBM training program in ECP training.

Few studies have examined the effects of caffeine among older patients. To our knowledge, this study (embedded in the ECP training program) will comprise the largest group of older patients with data on their behavior, cognition and caffeine consumption. To ensure that all trainees can participate, all patients with diabetes are included. However, as all trainees are engaged in data collection this might affect reliability; therefore, only validated instruments are used which (mostly) have a high level of interrater agreement.

Behavioral symptoms are not limited to dementia, but can be present in patients with all types of cognitive and/or psychiatric disorders. Due to the inclusion of all patients with diabetes, the complete spectrum of cognitive disorders (ranging from mild to severe) will be represented in this study. The consumption of both caffeinated and decaffeinated coffee is associated with a dose-responsive decreased risk of type 2 diabetes.(38, 39) Therefore, in theory, high coffee consumers might be underrepresented in the present study. However, the underlying mechanism of the inverse association between coffee and diabetes is not yet fully understood (38-40); moreover, this inverse association is reported to be present only in patients aged ≤ 60 years.(41)

Based on caffeine research in healthy adults, (20-22) both an increase and decrease in behavioral symptoms in patients with dementia can be expected. A small observational study on a group of older patients with dementia, reported that an increase in caffeine consumption is associated with a decrease in apathy, and an increase in aberrant motor behavior and sleeping difficulties (19); this confirms both the positive and negative effects of caffeine. Due to this dual effect, the overall group total of behavioral symptoms might result in a neutral score, falsely suggesting that caffeine has no relation with behavioral symptoms. Therefore, detailed analysis of not only the group total, but also the individual items, is appropriate.

Although EBM is considered essential in practicing medicine, obstacles in teaching EBM include: insufficient interest and/or limited time of trainees and faculty, lack of trainee research skills, absence of a research curriculum, and inadequate funding.(42) As this study is embedded in the EBM training program, the above obstacles related to teaching EBM have been tackled. Integration with clinical practice is beneficial for the trainees (6, 43) and might also improve the knowledge and attitude of current ECPs.(44)

In conclusion, this is the first large study to focus on caffeine and behavioral symptoms in older patients in nursing homes. Embodiment of this study in the ECP training program serves to update the medical research training program and facilitates a continuous link between education and research.

## ABBREVIATIONS

ADL: Activities of daily living
AES-C: Apathy Evaluation Scale-Clinician version
BI: Barthel Index
COPD: Chronic Obstructive Pulmonary Disease
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition
EBM: Evidence-Based Medicine
ECP: Elderly Care Physician
FAC: Functional Ambulation Categories
FCI: Functional Comorbidities Index
GDS: Global Deterioration Scale
MDRD/GFR: Modification of Diet in Renal Disease formula for Glomerular Filtration Rate
MDS-DRS: Minimum Data Set – Depression Rating Scale
MDS RAI: Minimum Data Set Resident Assessment Instrument
NPI-NH: Neuropsychiatric Inventory – Nursing Home edition
SASPC: Somatic, Activities of daily living, Social, Psychological and Communication

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# 5

# CAFFEINE CONSUMPTION AND BEHAVIORAL SYMPTOMS IN NURSING HOME RESIDENTS: A CROSS-SECTIONAL ANALYSIS

Published as Kromhout MA, Rius Ottenheim N, Putter H, Numans ME, Achterberg WP. Caffeine consumption and behavioral symptoms in nursing home residents: a cross-sectional analysis. The journal of nutrition, health & aging. 2021; 25(1):100-107

## ABSTRACT

*Objective:*

Although behavioral changes are common in nursing home residents with dementia and caffeine is known to influence behavior in healthy adults, the effects of caffeine on the behavior of persons with dementia has received little attention. In this study we assessed the relationship of caffeine and behavioral symptoms in older persons with dementia.

*Design:*

A multicenter sub-cohort study embedded in the Elderly Care Physicians (ECP) training program.

*Setting:*

Dutch nursing homes associated with the ECP training program.

*Participants:*

A total of 206 individuals with both diabetes and dementia resident in Dutch nursing homes.

*Measurements:*

Trainee ECPs collected data on caffeine consumption, cognition and behavioral symptoms using the NPI-NH, MDS-DRS and AES-C. Data on factors known to influence behavior in persons with dementia (e.g. marital status, kidney function, urinary tract infection and medication) were also collected.

*Results:*

Of the 206 participants, 70% showed behavioral symptoms. An increase in caffeine consumption was associated with a decrease in the presence of behavioral symptoms in the NPI-NH cluster affect and NPI-NH item agitation. Caffeine consumption groups also differed on the presence of disinhibition and depression. In addition, the severity of dementia influenced agitation, anxiety and the clusters affect and psychomotor.

*Conclusion:*

In a large group of older persons with dementia resident in nursing homes, a low daily consumption of caffeine was associated with greater behavioral symptoms.

## INTRODUCTION

By our definition, behavior is an 'observable response to a particular situation'. The mechanisms underlying behavior are mostly unconscious, complex and are probably shaped by a range of factors. The consumption of coffee and other caffeinated beverages is known to influence behavior. In healthy adults, reviews show that normal caffeine consumption increases alertness and attention(1-3), elevates mood(2), and reduces fatigue.(3) At higher dosages (usually ≥ 300 mg) caffeine is known to increase anxiety,(2, 3) induce psychotic or manic symptoms(2), and impair sleep.(3) Effects differ between individuals and people usually adjust their caffeine consumption to minimize adverse effects.

In persons with dementia, behavioral symptoms that may include aggression, agitation, or anxiety are seen in almost all cases at some point during the disease. These symptoms are also referred to as behavioral problems, behavioral and psychological symptoms of dementia' (BPSD) or neuropsychiatric symptoms. Behavioral symptoms accompanying dementia have a negative impact on a person's quality of life(4), place a heavy burden on caregivers,(5) result in a high demand for care, and are therefore often the reason for nursing home admission.(6) Over half of all persons admitted to Dutch nursing homes are diagnosed with cognitive disorders or dementia, and behavioral symptoms are present in more than 80% of persons with dementia resident in nursing homes.(7, 8)

A review of the limited evidence currently available on caffeine consumption in persons with dementia found inconsistent data regarding the effects of caffeine administration on neuropsychiatric symptoms: high caffeine consumption was associated with less apathy in one study; in another study coffee therapy decreased the Neuropsychiatric Inventory (NPI) total score and eliminating caffeine lowered the total NPI; in a third study caffeine consumption improved sleep in some persons and eliminating caffeine improved sleep in others.(9) Current data are therefore ambiguous and inconclusive, as caffeine was reported to both induce and reduce neuropsychiatric symptoms and sleeping difficulties in individual persons with dementia. Based on caffeine research in healthy adults (1-3) and a review in persons with dementia (9), both an increase and decrease in behavioral symptoms in persons with dementia can be expected. Specifically, we hypothesized that caffeine consumption may increase anxiety and aberrant motor behavior in persons with dementia, while decreasing apathy. Therefore, in this study we explore 1) the relation between caffeine consumption and behavioral symptoms in persons with dementia, and 2) the influence of dementia severity on any possible relationship.

## METHODS

This multicenter cohort study was embedded in the Dutch Elderly Care Physician (ECP) training program, and was conducted according to a study protocol published in detail earlier.(10) Briefly,

during the ECP training program, trainees spend three periods at an educational nursing home and gain experience on several types of wards (e.g. a dementia special care unit or rehabilitation unit). To allow every trainee to participate, the study population could not be limited to individuals living in a specific type of ward, which means a diagnosis of dementia could not be an inclusion criterion as this would have excluded some trainees. To create a homogenous study population that would allow inclusion of all trainees, a ward transcending inclusion measure was chosen that was not associated with behavioral symptoms in persons with dementia.(10) After careful deliberation, diabetes was chosen and ECP trainees were asked to include, during their first year of training, all persons under their care who had a diagnosis of diabetes (type I or II); no other inclusion or exclusion criteria were applied. Persons were included over three consecutive years, resulting in three cohorts. Data was collected based on medical records and interviews with nursing staff. None of the instruments used placed any burden on study subjects, and the study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Centre. In accordance with Dutch legislation, a waiver was given for a full review procedure by the Medical Ethics Committee because no rules of conduct were imposed and no participants were subjected to any (medical) intervention.

### Data collection

Patient characteristics (age, gender) and known factors influencing behavior in persons with dementia (e.g. marital status, kidney function, presence of a urinary tract infection and medication) were collected from the medical records.

In interviews with nursing staff, the presence of pain, the modified Barthel Index (BI), the stage of cognitive decline, caffeine consumption and behavioral symptoms were measured. The presence of pain in the last 7 days was scored using the subscale of the Minimal Data Set Resident Assessment Instrument (MDS RAI).(11)

The modified BI(12) measures mobility and dependency in activities of daily living (ADL) and records (using 10 items) the ADL of each patient. Total scores ranges from 0 (completely dependent) to 20 (complete functional independence). When used in older people, the BI has a high inter-rater reliability for the total score, and a fair to moderate agreement for the individual items.(13)

The stage of cognitive function was assessed using the Reisberg Global Deterioration Scale (GDS), which consists of seven stages ranging from 1 (no cognitive decline) to 7 (very severe cognitive decline/severe dementia). (14)

To measure caffeine consumption the number of cups of coffee, tea and cola consumed was observed and recorded six times a day. The amount of caffeine in coffee differs depending on how coffee is brewed: the longer the coffee grounds are in contact with water, the more caffeine is released. Therefore, the manner of coffee preparation was also noted, and based on the brewing method, ingested caffeine was estimated in milligrams (mg) as in previous studies (15, 16) and subjects divided into three groups based on low, normal or high caffeine consumption.

Behavioral symptoms were measured using the Neuropsychiatric Inventory-Nursing Home edition (NPI-NH)(17-19), depression was measured with the Minimum Data Set Depression Rating Scale (MDS-DRS)(20) and apathy with the Dutch Apathy Evaluation Scale-Clinician version (AES-C).(21, 22)

The NPI-NH assesses the severity and frequency of 12 different types of behavioral symptoms: delusions, hallucinations, agitation, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, nighttime disturbances and appetite/eating change. For each symptom, an item score can be calculated by multiplying the severity and frequency scores. The total score is the sum of all the symptom scores. Symptom scores range from 0-12, and the total score ranges from 0-144. The NPI-NH items can also be combined in clinically meaningful clusters: cluster psychosis (delusions and hallucinations), cluster psychomotor (agitation, disinhibition and irritability) and affect (depression and euphoria).(17) The NPI-NH is a valid and reliable tool in Dutch nursing home settings and shows high inter-rater agreement.(17) Individual NPI-NH items with a score of $\geq 4$ are considered clinically relevant.(7, 23)

The MDS-DRS is an observation-based screening instrument for depression in nursing home residents.(20) It consists of seven items that are scored 0-1-2, irrespective of the assumed cause, and total scores range from 0-14. At a cut-off score of 3, the MDS-DRS has a 91% sensitivity and 69% specificity compared to the DSM-IV diagnosis of depression.(20)

Apathy was measured using the 18 item AES-C.(21, 22) Total scores range from 18-72 and a score ≥ 38 is indicative of apathy.(21, 22) The AES-C has a high inter-rater reliability and can be used to discriminate between apathy and depression.(21)

## Statistical analysis

The three cohorts were merged, checked for duplicate cases and a subgroup created containing only persons with dementia. Patient characteristics, behavioral characteristics, disease characteristics and caffeine consumption were then defined using descriptive analysis. Differences in caffeine consumption between persons with and without clinically significant behavioral symptoms were analyzed for total NPI-NH score, the MDS-DRS and the AES-C. The NPI-NH clusters and individual NPI-NH items were also analyzed if a behavioral symptom was present in at least 15% of participants. A chi-squared test was used to analyze categorical outcomes and the Cochran-Armitage test was used to analyze trends. A Pearson correlation coefficient was computed to assess the relationship between daily ingested caffeine (in mg) and the NPI-NH total score. Finally, multiple logistic regression, with robust standard error estimation adjusting for clustered design (General Estimated Equations (GEE)), was used to correct for potential confounding factors. Per outcome two models were considered: 1. Based on the variables age, gender and stage of cognitive decline; 2. The variables age, gender and stage of cognitive decline together with of any of the following variables that were significantly related to the specific outcome (the use of psychotropic medication, marital status, Barthel Index total score, the presence of pain, cohort and kidney function). A p value less than 0.05 was considered statistically significant. Statistical analyses were performed using the IBM Statistical Package for Social Sciences (SPSS) version 23, with additional analysis in R+.

## RESULTS

The dementia subgroup consisted of 206 persons with a Reisberg GDS of ≥ 4 and a mean age of 82 years. Over half were female (59%) and three quarters were resident in a dementia special care unit. The average consumption of caffeine was within the normal range at 237mg a day, as high consumption is defined as over 300mg a day. The majority (70%) of participants had clinically relevant behavioral symptoms (defined as one or more NPI-NH item with a score of ≥ 4). Patient characteristics are presented in table 1.

**Table 1.** Patient characteristics for all persons with dementia, and for persons with dementia with and without clinically relevant behavioral symptoms

| | All | Behavioral symptoms | |
|---|---|---|---|
| | | With | Without |
| *Somatic* | | | |
| Age (mean ± SD) | 82 years ± 9 | 82 years ± 8 | 81 years ± 10 |
| Gender | (n=206) | (n=139) | (n=59) |
| Female | 59% | 61% | 56% |
| Male | 41% | 39% | 44% |
| Medication: number of prescriptions (mean ± SD) | 7 ± 3 | 7 ± 3 | 8 ± 3 |
| Psychotropic medication | (n=199-202) | (n=132-135) | (n=58-59) |
| Antidepressant | 20% | 25% | 14% |
| Antipsychotics | 16% | 19% | 9% |
| Benzodiazepine | 19% | 24% | 14% |
| Antiepileptic | 9% | 8% | 14% |
| Kidney function (MDRD/GFR (mean ± SD)) | 62ml/min ± 23 | 61ml/min ± 21 | 63ml/min ± 23 |
| Pain in the last 7 days | (n=206) | (n=139) | (n=59) |
| Yes | 30% | 34% | 24% |
| No | 70% | 66% | 76% |
| Caffeine consumption (median (range)) | 237mg/day (0-680) | 230mg/day (0-595) | 285mg/day (12-680) |
| *Functional status/activities of daily living* | | | |
| Barthel Index (median (range)) | 8 (1-20) | 8 (1-20) | 11 (1-20) |
| *Social* | | | |
| Department | (n=206) | (n=139) | (n=59) |
| Dementia special care unit | 76% | 78% | 75% |
| Somatic department | 24% | 22% | 25% |
| Marital status | (n=206) | (n=139) | (n=59) |
| Married | 27% | 28% | 27% |
| Widowed | 54% | 55% | 53% |
| Divorced | 5% | 4% | 10% |
| Single | 13% | 14% | 10% |
| *Psychological* | | | |
| Reisberg GDS | (n=206) | (n=139) | (n=59) |
| 4 | 17% | 14% | 27% |
| 5 | 35% | 30% | 46% |
| 6 | 33% | 37% | 22% |
| 7 | 16% | 19% | 5% |

A small negative correlation was seen between the total NPI-NH score and the daily consumption of caffeine (r = -0.179, n = 142, p = 0.033*). No associations between caffeine consumption and apathy, as measured with the NPI-NH and the AES-C, were found.

An increase in caffeine consumption was associated with a decrease in the presence of clinically relevant behavioral symptoms in the NPI-NH cluster affect and the NPI-NH item agitation. A difference was also noted between caffeine consumption groups for the presence of disinhibition (measured with the NPI-NH) and depression (according to the MDS Depression Rating Scale), but without evidence of a trend. Other NPI-NH items, the NPI-NH clusters and the AES-C did not differ between caffeine consumption groups. (See table 2).

**Table 2.** Behavioral symptoms and caffeine consumption

| Behavioral symptoms | N | Caffeine consumption (%) | | | Statistics | |
|---|---|---|---|---|---|---|
| | | Low | Normal | High | $\chi^2$ (2) | Trend test (*p*) |
| *NPI-NH* | | | | | | |
| Cluster psychosis | 146 | | | | 0.72, *p* = 0.697** | 0.444 |
| With | | 10 | 10 | 15 | Fishers exact *p* = 0.765 | |
| Without | | 90 | 90 | 86 | | |
| Cluster psychomotor | 146 | | | | 2.65, *p* = 0.266 | 0.245 |
| With | | 59 | 43 | 47 | | |
| Without | | 41 | 58 | 53 | | |
| Cluster affect | 145 | | | | 7.45, *p* = 0.024* | 0.008* |
| With | | 40 | 33 | 16 | | |
| Without | | 60 | 68 | 84 | | |
| Delusions | 147 | | | | 0.29, *p* = 0.864** | 0.593 |
| With | | 8 | 10 | 11 | Fishers exact *p* = 0.938 | |
| Without | | 92 | 90 | 89 | | |
| Hallucinations | 146 | | | | 0.60, *p* = 0.741** | 0.449 |
| With | | 4 | 5 | 47 | Fishers exact *p* = 0.899 | |
| Without | | 96 | 95 | 93 | | |
| Agitation | 146 | | | | 8.28, *p* = 0.016* | 0.006* |
| With | | 47 | 28 | 22 | | |
| Without | | 53 | 73 | 78 | | |
| Depression/dysphoria | 145 | | | | 1.07, *p* = 0.586 | 0.312 |
| With | | 20 | 15 | 13 | | |
| Without | | 80 | 85 | 87 | | |
| Anxiety | 146 | | | | 5.21, *p* = 0.074 | 0.054 |
| With | | 24 | 25 | 9 | | |
| Without | | 77 | 75 | 91 | | |
| Euphoria/elation | 147 | | | | 1.71, *p* = 0.425** | 0.319 |
| With | | 8 | 2 | 4 | Fishers exact *p* = 0.555 | |
| Without | | 92 | 98 | 96 | | |
| Apathy/indifference | 145 | | | | 0.98, *p* = 0.611 | 0.340 |
| With | | 32 | 30 | 24 | | |
| Without | | 68 | 70 | 76 | | |
| Disinhibition | 146 | | | | 7.73, *p* = 0.021* | 0.233 |
| With | | 28 | 5 | 18 | | |
| Without | | 73 | 95 | 82 | | |
| Irritability/lability | 146 | | | | 0.99, *p* = 0.609 | 0.375 |
| With | | 35 | 28 | 27 | | |
| Without | | 65 | 73 | 73 | | |

**Table 2.** Behavioral symptoms and caffeine consumption (continued)

| Behavioral symptoms | N | Caffeine consumption (%) | | | Statistics | |
|---|---|---|---|---|---|---|
| | | Low | Normal | High | $\chi^2$ (2) | Trend test (*p*) |
| Aberrant motor behavior | 146 | | | | 0.50, *p* = 0.779 | 0.665 |
| With | | 18 | 20 | 15 | | |
| Without | | 82 | 80 | 86 | | |
| Nighttime disturbances | 147 | | | | 0.55, *p* = 0.758 | 0.458 |
| With | | 10 | 12 | 15 | | |
| Without | | 90 | 88 | 86 | | |
| Appetite | 147 | | | | 1.99, *p* = 0.370** | 0.652 |
| With | | 14 | 5 | 11 | Fishers exact p = 0.404 | |
| Without | | 86 | 95 | 89 | | |
| *Other* | | | | | | |
| MDS-DRS | 145 | | | | 6.44, *p* = 0.040* | 0.308 |
| With | | 39 | 15 | 29 | | |
| Without | | 61 | 85 | 71 | | |
| AES-C | 147 | | | | 3.77, *p* = 0.152 | 0.064 |
| With | | 52 | 66 | 70 | | |
| Without | | 48 | 34 | 30 | | |

NPI-NH: Neuropsychiatric Inventory – nursing home edition, MDS-DRS: minimal data set – depression rating scale, AES-C: Apathy evaluation scale – clinicians edition

* significant

** statistical assumptions were not met for chi-square due to low number of persons with the symptoms, therefore the results of a two-sided Fisher's Exact test in R+ is also given

We found no association between caffeine consumption and the total NPI-NH score when adjusted for the 'in nursing home' clustered design ($p$ = 0.572). However, there were percentage differences for the NPI-NH clusters psychomotor and affect, the NPI-NH items agitation, disinhibition and anxiety, and the MDS-DRS with respect to caffeine consumption (adjusted for model variables and for the clustered design). Persons with dementia and diabetes consuming high amounts of caffeine were less likely to have symptoms in the NPI-NH affect cluster and the NPI-NH item agitation compared to those consuming low amounts of caffeine. The group consuming low amounts of caffeine was less likely to show agitation than the group consuming normal amounts of caffeine. Persons consuming normal amounts of caffeine had fewer symptoms on the NPI-NH psychomotor cluster, and the NPI-NH items disinhibition and depression (measured with both the NPI-NH and the MDS), compared to those consuming low amounts of caffeine (see table 3 for model 1 and table 4 for model 2).

The presence (%) of behavioral problems differed with the severity of dementia. In both the adjusted models, persons with moderately severe and severe dementia had a higher percentage of psychomotor behavior and agitation (p values 0.005, 0.043, 0.001 and 0.001, respectively). In the second model (in which the variables age, gender and stage of cognitive decline were entered, with addition of any variables significantly related to a specific outcome) behavioral symptoms in the NPI cluster affect and the NPI item anxiety were highest in persons with mild dementia (p values 0.046 and <0.000, respectively).

**Table 3.** Model 1. Log regression analyses with robust SE estimation adjusting for in nursing home clustered design (General Estimated Equations).

| Behavioral symptom | n | GEE | | | Adjusted % of behavioral problems by caffeine consumption (%(CI)) | | |
|---|---|---|---|---|---|---|---|
| | | Normal vs low (OR (CI)) | High vs low (OR (CI)) | *p* ** | Low | Normal | High |
| *NPI-NH* | | | | | | | |
| Cluster Psychomotor | 146 | 0.5 (0.2-1.0)* | 0.6 (0.3-1.0) | 0.040* | 62 (48-73) | 42 (28-57) | 48 (36-59) |
| Cluster Affect | 146 | 0.7 (0.3-1.5) | 0.3 (0.1-0.7)* | 0.025* | 42 (31-55) | 33 (17-55) | 18 (9-32) |
| Agitation | 146 | 0.3 (0.1-0.9)* | 0.3 (0.2-0.5)* | 0.000* | 49 (38-60) | 25 (13-42) | 23 (17-32) |
| Depression | 145 | 0.6 (0.2-1.8) | 0.6 (0.2-2.1) | 0.630 | 22 (12-37) | 15 (6-32) | 14 (6-31) |
| Anxiety | 146 | 1.1 (0.6-2.2) | 0.3 (0.1-1.2) | 0.028* | 23 (14-35) | 25 (15-39) | 10 (4-23) |
| Apathy | 145 | 0.9 (0.4-1.8) | 0.7 (0.3-1.8) | 0.773 | 27 (15-43) | 24 (13-40) | 21 (11-36) |
| Disinhibition | 146 | 0.1 (0.0-0.6)* | 0.6 (0.2-2.2) | 0.001* | 25 (13-43) | 4 (2-11) | 17 (8-35) |
| Lability | 146 | 0.6 (0.3-1.4) | 0.7 (0.4-1.2) | 0.313 | 34 (26-43) | 25 (13-43) | 25 (17-36) |
| *Other* | | | | | | | |
| AES-C | 147 | 1.6 (0.7-3.9) | 2.2 (0.8-6.4) | 0.327 | 56 (38-73) | 68 (48-83) | 74 (56-86) |
| MDS | 145 | 0.3 (0.1-0.7)* | 0.7 (0.4-1.3) | 0.015* | 35 (23-50) | 14 (8-23) | 28 (18-40) |

NPI-NH: Neuropsychiatric Inventory – nursing home edition, MDS-DRS: minimal data set – depression rating scale, AES-C: Apathy evaluation scale – clinicians edition

Variables entered in the model: caffeine consumption, Reisberg GDS, gender and age

* statistically significant (p value < 0,05)

** p value for difference in percentage of behavioral problems with respect to caffeine consumption group, adjusted for the variables entered in the model

**Table 4:** Model 2. Log regression analyses with robust SE estimation adjusting for in nursing home clustered design (General Estimated Equations).

| Behavioral symptom | n | GEE | | | Adjusted % of behavioral problems by caffeine consumption (%(CI)) | | |
|---|---|---|---|---|---|---|---|
| | | Normal vs. low (OR (CI)) | High vs. low (OR (CI)) | *p* ** | Low | Normal | High |
| *NPI-NH* | | | | | | | |
| Cluster Psychomotor [a,b,c,d,e,f] | 140 | 0.4 (0.2-0.9)* | 0.6 (0.4-1.1) | 0.049* | 59 (38-76) | 36 (17-61) | 47 (27-67) |
| Cluster Affect [a,b,c,d,e] | 139 | 0.5 (0.3-1.2) | 0.2 (0.1-0.5)* | 0.002* | 47 (34-60) | 32 (16-54) | 17 (9-30) |
| Agitation [a,b,c,d,e] | 140 | 0.3 (0.1-0.9)* | 0.3 (0.2-0.5)* | 0.000* | 50 (37-62) | 24 (11-44) | 24 (17-32) |
| Depression [a,b,c,d,e,f] | 139 | 0.3 (0.1-0.8)* | 0.4 (0.1-1.8) | 0.056 | 22 (9-45) | 9 (3-21) | 10 (4-26) |
| Anxiety [a,b,c,d,e,g] | 134 | 1.5 (0.6-4.0) | 0.3 (0.1-1.6) | 0.089 | 18 (10-31) | 26 (13-44) | 7 (2-24) |
| Apathy [a,b,c,d,g] | 139 | 0.9 (0.4-1.9) | 0.8 (0.3-2.5) | 0.933 | 23 (11-42) | 21 (10-39) | 21 (10-37) |
| Lability [a,b,c,d,h] | 146 | 0.7 (0.3-1.7) | 0.8 (0.4-1.4) | 0.633 | 34 (25-45) | 27 (13-46) | 29 (19-40) |
| *Other* | | | | | | | |
| AES-C [a,b,c,d,g,I,j] | 141 | 1.7 (0.6-4.6) | 1.8 (0.4-8.0) | 0.567 | 48 (29-69) | 62 (44-76) | 63 (32-86) |
| MDS [a,b,c,d,e] | 140 | 0.3 (0.1-0.7)* | 0.6 (0.3-1.3) | 0.017* | 36 (21-54) | 13 (7-22) | 27 (17-39) |

NPI-NH: Neuropsychiatric Inventory – nursing home edition, MDS-DRS: minimal data set – depression rating scale, AES-C: Apathy evaluation scale – clinicians edition

The variables entered in the model are indicated with a superscript letter behind the behavioral symptom: [a] Caffeine consumption, [b] Reisberg GDS, [c] gender, [d] age, [e] the use of psychotropic medication, [f] marital status, [g] Barthel Index total score, [h] the presence of pain, [i] cohort, [j] kidney function

* statistically significant (p value < 0.05)

** p value for difference in percentage of behavioral problems with respect to caffeine consumption group, adjusted for the variables entered in the model

## DISCUSSION

In this cross-sectional study of nursing home residents with dementia, we found a number of associations between caffeine consumption and behavioral symptoms, including consistent differences between caffeine consumption groups for behavioral symptoms in the NPI-NH cluster affect, the NPI-NH items agitation, disinhibition and depression, and depression as measured with the MDS-DRS. Persons consuming low amounts of caffeine were most likely to have behavioral symptoms. Furthermore, some behavioral symptoms differed between persons with mild, moderate, moderately severe and severe dementia.

Few studies to date have considered the role of caffeine consumption in behavioral symptoms in persons with dementia, and most previous studies have methodological flaws that preclude consistent conclusions.(9) The results of the present study in accordance with some studies but contradict others. In the present group of older persons with diabetes and dementia, a higher total NPI-NH score initially correlated with lower caffeine consumption, but this association disappeared when adjusted for the clustered design and potential confounders. A Japanese study reported a significant drop in the total NPI score in a group that received coffee therapy compared to a control group.(24) In a single subject trial of a patient with a high caffeine use and high total NPI score, a decrease was seen during the decaffeinated period.(16) However, neither study corrected for potential confounders.

Regarding caffeine consumption and apathy in persons with dementia, both negative(15) and positive associations have been reported, with elimination of caffeine reportedly leading to a decrease in apathy.(25) The present study found no association between caffeine consumption and apathy, as measured by the NPI-NH and the AES-C. In both of the earlier studies apathy was the least frequent behavioral symptom and the studies were conducted in dementia special care units. In the present study persons with dementia were included both from somatic departments and from dementia special care units, and apathy was one of the most frequently noted behavioral symptoms. In our experience, persons with dementia assigned to somatic departments are more likely to have vascular dementia than other forms of dementia. Apathy is known to be more common in persons with vascular dementia than in patients with Alzheimer's disease, possibly as a direct result of damaged subcortical circuits, (26) and may therefore explain the above mentioned differences and lack of association in the present study.

Perhaps the most interesting finding in this study was that high caffeine consumption was consistently associated with lower agitation. This is in contrast to earlier studies, which found no relation between caffeine consumption and agitation in persons with dementia.(15, 25) In addition, two single subject trials including individuals consuming very high amounts of caffeine found either no effect or a negative effect of caffeine on agitation.(16)

As the present study was cross-sectional, causality could not be determined and the identified association might be due to agitated persons spending less time consuming coffee (or other beverages) rather than caffeine itself reducing agitation in other persons with dementia. Agitation

is known to increase as dementia progresses,(27) and in our sample agitation was more common in persons with (moderately) severe dementia. Therefore, lower caffeine consumption could also be due to other dementia-related factors. Nevertheless, a dose-dependent effect of caffeine on aggression in animal models follows an inverted-U shaped curve, with lower aggression at very low and very high doses of caffeine.(28) This finding suggests that the relationship between agitation and caffeine consumption may be more complex than simple positive or negative individual associations.

The group with normal caffeine consumption had fewer depressive symptoms compared to the group consuming low amounts of caffeine. Studies of depression and caffeine consumption are scarce, but two reviews (2002 and 2018) both suggested that moderate to intermediate consumption of caffeine is beneficial for depression in healthy adults.(3, 29) The same pattern is visible in our study, as the group with high caffeine consumption had a higher level of depression than the normal caffeine consumption group. Caffeine is a known receptor antagonist of the A1 and A2a adenosine receptors,(29) which are involved in cognition, motivation and emotions (amongst other effects). However, at high doses caffeine may no longer behave as an adenosine receptor antagonist,(30) potentially explaining the U-shaped association between depression and caffeine consumption.

To the best of our knowledge, this investigation is the largest study of behavior, cognition, and caffeine consumption in older persons conducted to date. The cross-sectional design and embedding in the Dutch Elderly Care Physician training program made it possible to study such a large group. However, this design has two limitations that should be mentioned. Firstly, data were collected by ECP trainees in an educational setting rather than by professional researchers in a study setting. Nonetheless, data collection was supervised by a senior researcher and there is no reason to suppose that an ECP trainee would collect incorrect data. Secondly, the choice for a 'ward transcending' inclusion criterion (diabetes) allowed all trainees to participate irrespective of department, but resulted in inclusion limited to persons with diabetes. As there is no evidence of a relationship between caffeine consumption and diabetes in persons over 65 years of age, and no known relationship between diabetes and behavioral symptoms, the results of this study are likely to be valid for nursing home residents with dementia without diabetes.

In conclusion, a low daily consumption of caffeine was associated with behavioral symptoms in a large group of nursing home residents with dementia and diabetes. To determine causality, intervention studies are warranted. Due to the highly individualized effects of caffeine on behavior, a study with individualized outcome measurements is preferred before firm recommendations can be made for specific groups. However, as caffeine consumption is an easily adaptable intervention, it can be considered as a potentially beneficial component in an individualized approach to neuropsychiatric symptoms in persons with dementia.

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# G

# GENERAL DISCUSSION

The work presented in this thesis aims to expand knowledge on the relationship between caffeine consumption and behavior in persons with dementia. As stated in the general introduction, we hypothesized that caffeine consumption and behavior likely interact in persons with dementia and that both an increase and a decrease in behavioral symptoms would be possible. The known stimulatory effects of caffeine suggest the possibility of an increase in behavioral symptoms by suppressing fatigue and inducing restlessness in persons with dementia. However, caffeine consumption might also reduce behavioral symptoms in persons with dementia by improving concentration, lessening overstimulation or due to the social aspect of caffeine consumption.

The studies in this thesis support the hypothesis outlined above, as both positive and negative relationships were found in the course of our studies:

- In our observational pilot study (chapter 1), a negative correlation was found between caffeine consumption and apathy and aberrant motor behavior (AMB), whereas a positive correlation was found between late evening consumption of caffeine and getting up in older persons with moderate to severe dementia resident in a dementia special care unit.(1)
- In two single subject trials (chapter 2), reduction of caffeine consumption decreased several behavioral symptoms, including agitation/ aggression, irritability, AMB and general restlessness, in one 85-year-old woman with Alzheimer's disease but did not influence the aggressive behavior of another person diagnosed with mixed type dementia.(2)
- In a thorough systematic review of literature (chapter 3) we found indications that caffeine can both induce and reduce behavioral symptoms in persons with dementia. However, no consistent effect of caffeine consumption on behavioral symptoms could be demonstrated.(3)
- In our large cross-sectional study (chapter 5), behavioral symptoms (e.g. agitation, disinhibition and depression) were most common in persons with a low caffeine consumption.

To answer the question 'can coffee use influence the behavior of persons with dementia', we will first take a closer look at the most recent pathophysiological insights concerning the main target receptors of caffeine in the brain and what is currently known about the role these receptors play in the changing brain of a person with dementia. Insights into caffeine, adenosine receptors (AR) and dementia changed during the course of our research and our findings contribute to these changes. We will then explore the possible influences of caffeine consumption and behavioral symptoms in persons with dementia. To fully appreciate our results, several methodological considerations will also be discussed, after which we round up with the clinical implications of our findings and suggestions for further research.

## CAFFEINE AND ADENOSINE RECEPTORS IN THE BRAIN

Caffeine has several targets in the brain, of which the most commonly discussed is the nonselective antagonism of adenosine receptors. Caffeine also known to interfere with dopamine, serotonin,

norepinephrine, epinephrine, acetylcholine and glutamate neurotransmission in the brain,(4, 5) to induce direct release of intracellular calcium, to inhibit cyclic nucleotide phosphodiesterase and to block GABA receptors.(4, 6) However, the doses required to achieve the latter effects (on calcium, cyclic nucleotide phosphodiesterase and GABA) are beyond toxic levels in humans.(6) Caffeine also has a weak affinity for benzodiazepine receptor binding sites and can counteract or alter the effect of benzodiazepines on human behavior,(7) although it has been suggested that the level of caffeine needed to antagonize the benzodiazepine receptors is likely toxic in humans and the modifying effect of caffeine on benzodiazepines might therefore actually be mediated via the adenosine receptors.(7) Taken together, these data suggest that antagonism of adenosine receptors in the brain is likely to be the primary mechanism of action of caffeine.(6)

Adenosine has several regulatory functions, but the most important are thought to be maintenance of energy homeostasis in the body and neuromodulation in the brain.(8, 9) Within the brain, adenosine is known to affect the release of neurotransmitters, neuronal excitability, synaptic plasticity and neuroinflammation.(9, 10) Four distinct adenosine receptors have been identified to date, adenosine (A)1, A2a, A2b and A3, each of which shows different expression patterns in brain regions and synaptic sites and each has different effects.(8, 9) The A1 and A3 receptors both have inhibitory effects, while both forms of the A2 receptor are stimulatory.(9) Only the A1, A2a and A3 receptors are present in the brain. The A1 receptors are mostly present in the cortex, hippocampus and cerebellum,(9) and presynaptically-distributed A1 receptors inhibit the release of glutamate, dopamine, serotonin and acetylcholine,(8) whereas postsynaptically-distributed A1 receptors inhibit neuronal signaling and reduce excitability.(8) The A2a receptors are mainly concentrated in the striatum and are only weakly present in the cortex and hippocampus.(9) The A3 receptors have a moderate presence in the hippocampus and cerebellum and are less prominent elsewhere in the brain.(9)

The exact function of the ARs is still unknown, but the various roles of the AR subtypes are currently being unraveled using so-called knockout mice (KO; living mice in which a part of the DNA is artificially switched off).(9) (See table 1). However, in humans the ARs appear to have both overlapping and unique roles. A recent review of the role of ARs in mood and anxiety disorders(8) concluded that agonism of the A2a receptors increases depression-like symptoms, while agonism of the A1 receptors has antidepressant effects. In anxiety, agonism of A1 receptors had anxiolytic (reducing) effects, whereas antagonism of A1 receptors or non-specific antagonism of ARs induces anxiety-related behaviors.(8) The distribution of ARs in the brain, differences in synaptic sites and multiple subtypes of ARs together provide many different pathways through which brain functions can be influenced by AR antagonism. This complexity makes characterization of the specific functions of ARs more difficult.(9)

As discussed above, caffeine is a known non-selective AR antagonist that impacts several AR subtypes, showing effects that differ depending on acute or chronic use(11) and low or high doses.(12) The effects of caffeine are primarily meditated through the A1 and A2a receptors, and major differences and even conflicting effects on ARs are seen following either acute or

**Table 1.** Changes in behavior shown in AR knock-out (KO) mice(9)

| Behavior | A1 KO mice | A2a KO mice | A3 KO mice |
|---|---|---|---|
| Mood | | Reverse behavioral despair/antidepressive | More behavioral despair |
| Anxiety | More anxiety-like behavior | (Inconsistent) | Some anxiety, but attributed to hyperactivity |
| Aggression | Increased aggression | Increased aggression | |
| Psychomotor activity | (Nihil) | Reduced and increased psychomotor activity | |

chronic intake of caffeine.(11) Chronic consumption of caffeine has various neuroprotective effects which are characterized by upregulation of the A1 receptors but stable expression of the A2a receptors,(11) resulting in a shift in the balance of ARs.(11) Our study participants(1, 2, 13) were probably chronic coffee consumers, but the influence on behavior of the expected shift in AR balance is still too poorly understood to allow clear prediction of expected outcomes. However, we know that the number of ARs in the brain normalizes between one and five days after cessation of caffeine consumption.(6) This rapid normalization suggests that the participants in the single subject trials(2) probably had a normalized AR balance within a week of the shift to decaffeinated coffee. Their behavior over the following two weeks during which alternately decaffeinated or caffeinated coffee was consumed might represent behavior uncolored by the effects of chronic caffeine intake. These single subject trials could therefore, inadvertently, provide additional insight into the potential roles of ARs in behavior. In one subject, no relation between caffeine consumption and behavior could be detected. However, in the other subject an increase in behavioral symptoms consisting mainly of aggression and aberrant motor behavior was seen as caffeine was reintroduced during the second week. Interestingly, the item scores for these behavioral symptoms following the decaffeinated washout period were lower compared to the baseline (caffeinated) score prior to washout, suggesting that antagonism of the A1 receptor might be the main driver of behavior in this person with dementia. However, as this observation was confined to a single individual, firm conclusions cannot be drawn regarding the impact of the ARs on behavior and further research will be necessary to explore these intriguing preliminary insights.

In addition to the differences that occur following acute or chronic use, caffeine may also have biphasic effects, with differences in effect apparent between low and high doses.(12) In chapter 5, this biphasic effect was observed for the NPI item disinhibition and depressive symptoms as measured with the MDS-DRS. The exact mechanism underlying this biphasic effect is as yet unknown, but several mechanisms have been proposed(12):

1. Differences may be due to individual variation, some of which appear to have a genetic origin.(12)
2. The effects of low dose caffeine are mediated through mechanisms that are distinct from those of high dose caffeine. The inhibition of phosphodiesterase (PDE) has been suggested as a possible mechanism controlling some of the effects of caffeine.(12)

3. The biphasic effect might be due to the involvement of A3 receptors. In both A1 receptor knockout mice, A2a receptor knockout mice and control mice high dose caffeine influences behavior in a similar manner. However, A3 receptor knock-out mice showed a different response to caffeine than control mice at a dose that failed to produce a difference in A1 and A2a knock-out mice. The authors conclude that the A3 receptors may be responsible for the effects of caffeine following high dosages.(9)

Although antagonism of ARs in the brain is thought to be the primary mechanism of action of caffeine, nevertheless the involvement of different subtypes of ARs, the effect of AR upregulation with chronic caffeine use, the influence of the ARs at different brain sites and the dose response effects of caffeine all remain unresolved. A clear description of the mechanisms through which caffeine influences behavior, even in healthy persons, is therefore still lacking.

## ADENOSINE RECEPTORS AND THE CHANGING BRAIN IN PERSONS WITH DEMENTIA

Dementia is a neurodegenerative disorder and the expression of the adenosine receptors is known to change with disease progression. In persons with Alzheimer dementia, the A2a receptors are increased in the hippocampus and cerebral cortex,(10, 14) A1 receptor density is reduced by 40-60% in the hippocampus and striatum, (10, 14) and both A1 and A2a receptor levels in the frontal cortex are increased in either the early or advanced stages of Alzheimer's.(15) It has been suggested that A1 receptors may play a role in the pathogenesis of Alzheimer dementia, and that modulating the A2a receptors might have neuroprotective effects during progression.(14) While the impact of changes in the expression of ARs on behavior during the progression of dementia is presently unknown, the fact of changes suggests that the influence of caffeine is also likely to change.

## CAFFEINE AND BEHAVIOR IN PERSONS WITH DEMENTIA

Taking into account the results of the studies presented in this thesis, the known functions of ARs and the changes that occur during the progression of dementia, the relationship between caffeine consumption and behavior in persons with dementia is either immensely complex or very straightforward. Previous studies have reported associations between behavioral symptoms and caffeine consumption in persons with dementia, but the direction and size of effects varied to such an extent that if we were to pool results, the net effect would be close to zero. The straightforward explanation is that all study results are coincidental or biased, and there is no consistent association between caffeine use and behavior.

A more complex and nuanced explanation is that the relationship between caffeine and behavioral symptoms is multifactorial, and factors influencing associations most likely include personal differences, dosage, chronic use, progression of neurodegenerative diseases and other multimorbidities. We discuss these factors in more detail below.

The effects of caffeine differ, even among healthy adults, and these differences are known to affected by many factors, for example the polymorphisms in cytochrome P450 CYP1A2, which metabolizes caffeine, and adenosine A2a receptor, which is the target of caffeine in the brain and is thought to be responsible for most of the behavioral effects.(16) There is also no evidence to suggest that individual sensitivities to caffeine disappear in the event of dementia. Consequently, and similarly to healthy adults, some individuals with dementia will be unaffected by caffeine while others will have sleeping difficulties after just a single cup of coffee in the afternoon. This pattern was also seen in the single subject trials.(2) Healthy adults tend to adjust their personal caffeine consumption to minimize the adverse effects or maximize the benefits, but persons with dementia are unlikely to be able to self-adjust caffeine consumption and may therefore be more prone to suffer adverse effects.

As discussed, the effect of caffeine on behavior is generally attributed to antagonism of adenosine receptors, but when consumed in high doses caffeine may no longer act as an adenosine antagonist(12), whereas low doses might not reach the threshold for effect. Depending on specific circumstances, the dose-dependent effects of caffeine might follow both a straight line and a U (or inverted U)-shaped curve, as described in chapter 5.

Different effects on behavior are seen upon chronic versus acute consumption of caffeine,(17-19) an outcome most likely due to upregulation of the A1 receptors shifting the balance of ARs.(11) In addition to the upregulation or ARs due to chronic consumption, dementia is a neurodegenerative disease that also may influence adenosine receptors in the brain, leading to effects of caffeine that may differ amongst healthy persons, persons with mild dementia and persons with severe dementia.(3)

To summarize, current evidence suggests that the individual, the disease (dementia), the intervention (caffeine) and behavior may all be interdependent, resulting in a very complex relationship between caffeine and behavioral symptoms in persons with dementia.

## KITWOOD'S EQUATION

The complexity of the relationship between caffeine and behavioral symptoms in dementia can also be explored using Kitwood's equation. Kitwood stated that the symptoms of dementia can be understood as an interaction between neurological impairment (NI), physical health (H), psychological factors (P), personal biography (B) and the social context [social psychology] (SP):(20)

$$D = NI + H + B + P + SP$$

NI ↓ = A recent systematic review concluded that consumption of coffee, tea and caffeine or higher plasma caffeine levels may protect against the onset of dementia, but the evidence was too limited to draw conclusions regarding an effect on the progression of dementia. (21) Although an exact mechanism has yet to be identified, it has been suggested that caffeine might directly reduce amyloid beta production in the brain(22) and thus have a direct influence on neurological impairment in persons with dementia.

H ↕ = Caffeine has widespread pathophysiological effects on the body, both positive and negative. On the positive side, due to adenosine antagonism and a vasoconstricting effect, caffeine is known to reduce pain, especially when taken in addition with regular analgesics. (23) In our cross-sectional study (chapter 5), pain was tested as a possible confounder and was found to influence the association between caffeine and the NPI-item lability. Caffeine is also known to induce cardiac arrythmias, especially in persons with preexisting cardiac comorbidity. The physical health of a person with dementia can be influenced by caffeine but depending on the comorbidity, caffeine might improve or worsen physical health.

P ↕ = Mood and anxiety are among the psychological factors that can impact the behavior of a person with dementia. In some adults, consumption of high doses of caffeine can lead to increased anxiety,(18) but a similar relationship has not been found in studies of persons with dementia(3) (as presented in chapter 3 of this thesis). In our latest study (presented in chapter 5 of this thesis) the group with high caffeine consumption had less anxiety compared to the group with low caffeine consumption, when corrected for the clustered design. In humans, both high and low caffeine consumption seems to be associated with anxiety. Caffeine is a non-selective adenosine antagonist, and the adenosinergic system has a role in both the etiology and treatment of depression and anxiety.(8) Studies in rodents have helped unravel specific roles of the adenosine receptors in anxiety, as knockout of the A1 and A2a adenosine receptors increases anxiety-like behavior in mice(8), while overexpression of the A2a receptor in mice resulted in a decrease in exploratory behavior (also indicative of an increase in one aspect of anxiety).(24) Just as A2a knockout and A2a overexpression both result in behavioral changes indicative of increase anxiety in mice, human consumption of caffeine results in a similar pattern of anxiety-related changes.

In chapter 5, we also found that depressive symptoms were lower in the group with normal caffeine consumption compared to the group with low caffeine consumption, an outcome consistent

with findings in healthy adults.(18) (25) Although the exact mechanisms are not (yet) known, it is clear that caffeine can have a direct influence on depressive symptoms and anxiety in persons with dementia.

SP ↑ =

The effects of caffeine are not limited to the physical and psychological, the consumption of caffeine-containing beverages also has a strong social aspect, as the social consumption of coffee is the customary way to ingest caffeine. Having a cup of coffee together with others, sitting quietly, chatting or reading a paper are all regular social rituals. According to the Unmet Needs Model by Cohen-Mansfield, unmet needs for social contacts or social activities can lead to behavioral symptoms in persons with dementia.(26) Both the Dutch(27) and the UK Alzheimer foundations(28) advise caregivers to take social activities into account when faced with behavioral symptoms. Although having a cup of coffee together is not specifically mentioned, it can act as a calming social ritual as suggested in one study.(29)

$D = NI + \mathbf{H} + B + \mathbf{P} + \mathbf{SP}$

Example 1. Less neurological impairment and pain, improved mood and a strong social effect of caffeine consumption leading to less behavioral symptoms.

$\mathbf{D} = NI + H + B + P + SP$

Example 2. Sleeping difficulties due to caffeine consumption, resulting in agitated behavior during the day.

$D = NI + H + B + P + SP$

Example 3. No changes in health or other factors in the equation due to genetic factors.

Accordingly, and depending on genetic variation, age, gender, sensitivity to caffeine, severity of dementia and any comorbidity, the equation of dementia might be influenced in specific ways by the consumption of caffeine (see examples).

## METHODOLOGICAL CONSIDERATIONS

Although the studies presented in this thesis are very different in design, size and level of evidence, they all share certain strengths.

Firstly, these studies were the first of their kind to study the effects of caffeine on behavior in persons with dementia. During the progression of the studies that make up this thesis, a stepwise design was used that started with a small pilot study and a single subject trial to test whether the hypothesis was sufficiently robust to justify the later, larger studies. The combination of both small and large studies provided important insights into the complexity and treatment possibilities of caffeine in the behavioral symptoms of dementia.

Secondly, these pragmatic studies were all conducted with frail older persons representing the reality of the nursing home resident, in contrast to most medical research that unfortunately excludes older persons with dementia or persons with multimorbidity, resulting in limited evidence concerning this rapidly expanding group. In the pragmatic observational (chapter 1) and cross-sectional multicenter (chapters 4 and 5) studies the caffeine consumption was not altered or regulated. The results of these studies are based on normal caffeine consumption, instead of

the extremely high caffeine dosages regularly seen in caffeine research.(18, 30) Thus the influence of withdrawal is expected to be next to nothing. The conclusions from these studies can therefore be reliable extrapolated and offer directly applicable insights on caffeine consumption and behavioral symptoms in patients with dementia.

Thirdly, a common bias in food research is the recall bias. An example is smoking or alcohol consumption: participants (unconsciously) want to put themselves in a better light by underestimating the number of cigarettes or liters of beer they consume. But the other way around is also prevalent, for example the overestimation of the amount of vegetables one consumes in a day. The recall bias is also seen in caffeine research.(31) However, in the three studies to chance of a recall bias is small as the amount of caffeine consumed was observed and noted during the same shift, not recalled later.

Lastly, most studies research high-tech, theoretical interventions aimed at tomorrows' patients. Our studies of caffeine are unique in the sense that this is an intervention for todays' patients and current patients with dementia will benefit from the results.

However, to fully understand the results the following weaknesses have to be taken into account.

Firstly, persons with dementia were treated as a single study population, even though dementia is an umbrella term covering over 100 different diseases. Much is still poorly understood regarding the impact of disease on the brain in persons with dementia (a 'black box brain'). As caffeine influences brain neurotransmitters, it is possible that effects of caffeine differ depending on a specific disease or its stage. In a larger study, subgroup analysis based on major causes of dementia could be conducted to test whether this hypothesis is valid.

Secondly, a wide variety of behavioral symptoms were included in these initial pilot studies, including scores for several total scales. As caffeine may both induce and reduce behavioral symptoms, symptom-specific follow-up research would be advisable, preferably tailored to the individual.

Thirdly, in chapter 5 we described the dose-dependent effects of caffeine might follow both a straight line and a U (or inverted U)-shaped curve. Although our results do not stand alone and the response threshold and receptor regulation can be an explanation for the observed effects, severe design errors like a differential misclassification error can also lead to a reversal of results. However, in the studies in this thesis the measurements of the caffeine consumption and the scoring of behavioral symptoms was done by different persons and at the moment of scoring the participant was not yet assigned to a specific group. Therefore, the chance a structural severe differential misclassification influenced the results of both of these studies is small. However, there is a risk of non-differential misclassifications like incorrectly quantifying the amount of caffeine consumed (e.g. by over- or underestimating the amount of coffee in a cup or the amount of caffeine in the coffee). During the studies these measurements were standardized were possible and the amount of caffeine was calculated based on the way the coffee was brewed. When the brewed method was unknown or there was no average caffeine level know for the brew method,

the caffeine consumed could not be estimated. It is therefore possible the amount of caffeine is over- or underestimated, however, the best guess possible was made.

Fourthly, there are factors that are both associated with caffeine consumption and with behavioral symptoms in patients with dementia. In the multi-center cross-sectional study corrections were made for all know confounders. Due to the possible widespread influence of caffeine as shown in the paragraph 'Kitwood's equation' there is a potential of residual confounding. A lot of possible confounders were included in the study (see chapter 4 for the complete list of measurements). Several psychosocial and other lifestyle factors were not included in the study. All of the participants lived in nursing homes and had, at least at the moment of study, a similar general lifestyle. However, it is possible different nursing homes have different styles and thereby influencing both caffeine consumption and behavior. Although we did not correct for lifestyle as a single confounder, a correction for the nursing home (the clustered design) was made. However, residual confounding cannot be ruled out completely.

Finally, parts of this study were embedded in the Elderly Care Training Program. This program made it possible to collect data on cognition, caffeine consumption and behavior in a larger number of elderly nursing home residents (as described in chapter 4(13) and 5), but also required us to limit inclusion to persons with diabetes and thereby limit the range of possible inclusion. As far as we now there is no relation between diabetes and caffeine consumption or diabetes and behavior in elderly patients, so the selection of participants was unrelated to their behavior and their caffeine consumption. The results of the study are most likely also valid for patients with dementia without diabetes. However, this design has one important potential weakness: is the risk that trainees are more prone to make mistakes in data collection than trained researchers. However, as the trainees were supervised by senior researchers and subsample cross-checking was conducted to identify potential mistakes, we believe that any risk was minimal. Therefore, we stand by the results of this study and consider them reliable.

Despite these possible limitations, the studies described in this thesis provide unique insights into the relationship between caffeine and behavioral symptoms in persons with dementia, and have clinical implications that could benefit today's patients (discussed below).

## CLINICAL IMPLICATIONS

As mentioned above, if one assumes that any association will necessarily be unidirectional and consistently linear, one might draw the conclusion that there is no relation between caffeine and behavioral symptoms in persons with dementia and, therefore, no clinical implications. However, this thesis provides data to support the argument that there is a relationship between caffeine and behavioral symptoms in persons with dementia, and this relationship differs per person, is dose-dependent, and changes with age and the presence of dementia.

However, even if we accept the relationship between caffeine and behavioral symptoms in persons with dementia as proven, there will still be some individuals in whom the consumption of caffeine has no effect on behavioral symptoms. Conversely, some individuals with dementia will show a (strong) response following consumption of caffeine. As caffeine consumption is an easy-to-manage intervention against the background of hard-to-manage behavioral symptoms that place a major burden on caregivers and reduce the quality of life of the person with dementia, it is advisable to take caffeine consumption into account when planning a stepwise, individualized approach to behavioral symptoms. While caffeine isn't one of the 'usual suspects' in behavioral symptoms, there is enough evidence to argue that it should at least be included in the line-up.

A stepwise, personalized approach to behavioral symptoms in persons with dementia should include a detailed analysis of the individual and their surroundings. In the diagnostic approach, we look for probable or possible contributory factors in a multidisciplinary journey into known behavioral symptoms such as pain, psychosis, infections, or over-stimulation, while also considering the unknown, unmet needs of a person who is incapable of communicating needs in any other way. The evidence is clear: caffeine is not just another ingredient in a drink. It should be included in the vocabulary of the professional as a possible influencing factor, similarly to over- and under-stimulation, toothache, constipation and miscommunication. If an analysis shows new agitation that started directly after admittance to a dementia special care unit and no other probable explanations are identified, a detailed analysis of the differences between home and nursing home might show a switch from decaffeinated to caffeinated coffee, suggesting that a switch to decaffeinated coffee is worth a try. Analysis might also show a significant decrease in coffee consumption on admission, in which case an increase in coffee consumption is also worth a try. It might also show that at home the person with dementia always went for a small walk in the garden after a coffee break. In terms of caffeine, analysis of behavioral symptoms involves not just asking 'do you prefer your coffee black, or with milk or sugar?' but taking into account all the nuances of coffee, such as 'do you prefer filter or espresso, black, with milk or sugar, at what time would you like the coffee, with a newspaper or a conversation, etc.'

## FURTHER RESEARCH

In medical research, the ultimate proof of an intervention is a randomized controlled trial that is designed to prevent factors other than the intervention from influencing outcome by standardizing participants, measurements and the intervention itself.(32) This evidence-based method has been called into question, as it's based on standardized situations which simplify reality and ignores the multifactorial nature of daily practice. To put the evidence into practice, nuances of the evidence are needed. Therefore, the Dutch Council for Public Health and Society recommends that evidence-based medicine should be extended to embrace the context of the person.(32) If we hold to standard evidence-based practice, confirmation of the relationship between caffeine

and behavior remains unlikely due to the complexity of this relationship. However, when the context of the person is taken into account, a complex relationship between caffeine and behavioral symptoms suddenly becomes probable. We would therefore argue that the results concerning the effect of caffeine on behavior in persons with dementia warrant further research.

In our opinion both experimental and fundamental research into this subject is needed. At the moment, changes occurring in the brain of persons with dementia are poorly understood, but more research in this area could lead to potential new interventions for future patients with behavioral symptoms and dementia, perhaps also including more detailed insights into the effects of caffeine on the brain or even clues for additional interventions. However, persons with dementia who have behavioral symptoms today will clearly not benefit from these studies. These people require interventions now. The research detailed in this thesis shows that caffeine could be one such intervention but a clearer picture is needed. As changes to the brain and the sensitivity to caffeine of persons with dementia are both individual, a traditional randomized controlled trial will not suffice to provide clarity. The ideal design should include the context of the person, and cover both individual and group effects. An approach including the context of the patient could involve either a large series of single subject trials or a randomized controlled trial with goal attainment scaling. As stated in chapter 3, the single-subject trial is a randomized blinded study with one single patient. Usually it has a crossover design in which an intervention and a placebo both are tried multiple times to determine which is more beneficial.(33) It is seen as the ultimate proof for the individual patient(34, 35), especially if the intervention has shown individual variation in efficacy (35) like caffeine. Although a single single subject trial is the ultimate proof for a single patient, several single subject trials can be combined to estimate a population effect(33) and identify distinguishing features between those who benefit and those who do not benefit from the intervention.(35) Another practical element in this approach is that the single subject trials might differ slightly in design as long as the design is robust and the results are valid.(35) This means the design can be matched to the specific circumstances of the patient with dementia, the caffeine consumption and the behavioral symptoms involved, e.g. a longer washout period in patients with hepatic impairment or an extra crossover period. In an randomized controlled trial with goal attainment scaling, the design is standardized but for each participant a personal outcome (goal) is defined.(36) However, every goal is scored in a standardized way: a 5-point Likert scale ranging from '-2: much less than expected' to '+2: much more than expected'). In both methods, the large series of single subject trials and the more traditional randomized controlled trial with goal attainment scaling, the outcomes are defined for a specific participant. In addition, in the single subject trials the design could also be slightly altered to fit a specific participant better. As both are some kind of randomized controlled trial, their ideal designs have several similarities but some remark differences. In the table the headlines of these two possible designs for further research are illustrated.

These study designs need to be worked out in more detail and several caffeine related challenges have to be specified. First, the way of measurement of caffeine has to be defined. To

**Table 2.** Overview of two different study designs for further research into the effect of caffeine consumption on specific behavioral symptoms in patients with dementia

| Study type | Series of single subject trials | RCT with goal attainment scaling |
|---|---|---|
| **Participants** | Patients with dementia who consume caffeine, and have behavioral symptoms in which caffeine is expected to have a positive or negative influence | Patients with dementia who consume caffeine, and have behavioral symptoms which are thought to be negatively influenced by caffeine consumption |
| **Estimated number of participants needed** | 60 | 120 |
| **Randomisation** | ABBAAB | Participants are randomized in two groups: intervention and control |
| **Study period** | 6 periods of a week each (length of periods adjustable to the participant) | Two-week baseline and two-week intervention period, followed by a two week return to normal |
| **Intervention/ 'A'** | Caffeinated coffee and tea, in standardized cups and brew method | Decaffeinated coffee and tea, in standardized cups and brew method |
| **Control/ 'B'** | Decaffeinated coffee and tea, in standardized cups and brew method | No adjustment in caffeine consumption |
| **Outcome measurements** | For each participant an individual target behavioral symptom is defined, including the scale or index used to score and the preferred outcome | Goals attainment scaling: a personal goal per participant and the standardized scoring system.<br>In addition, the NPI-NH for every participant once during every study period. |
| **Blinding** | Caffeine consumption and behavioral symptoms scored by different professionals.<br>Study period blinded for the participant and professionals. | Caffeine consumption and behavioral symptoms scored by different professionals.<br>Study group blinded for the participant and professionals. |

determine the relation between caffeine consumption and behavior in patients with dementia, a continuous measurement of caffeine levels in combination with a continuous observation of behavior would yield the most precise results. The continuous measurement of caffeine levels bypasses the individual caffeine metabolism, but it does not surpass the individual ARs layout in the brain. So, we would know how much caffeine was in de blood during behavioral symptoms, but not how the brain is affected by the caffeine, so the added effect is limited. A single measurement of plasma caffeine levels might be arrangeable in nursing homes, but the added value is even less due to the same reason. If the purpose of the study is to measure the clinical effect, then the observation of ingested caffeine is sufficient, cheap and practical. However, the second specification has to be the way the caffeine is ingested. Caffeine can be administered in different ways: by injections, capsules or cups of coffee (with or without added caffeine). If caffeine is given by injection or capsule, the dosage of caffeine is exact. The amount of caffeine in coffee differs between the coffee bean used, the way the coffee is made and several other factors. Depending on the study goal, the preferred way of administering the caffeine can differ. An intervention trial into the positive effects of caffeine would probably have more use for a standardized dosage

which can be easily administered like a capsule. A trial into the etiology of behavioral symptoms and the role of caffeine would benefit more by including to normal caffeine consumption, like cups of coffee. To make an estimated guess of the caffeine consumed, the cup size and the brew method have to be included in the design. The other effects of caffeine in the body also have to be taken into account: adding more caffeine can have physical effects confounding the results, which makes a continuation of normal caffeine use more appealing for research in the frail population.

If the methodological challenges into caffeine research, behavioral research and research in frail elderly patients with dementia are taken into account, there are several reliable and valid study designs possible for further research. However, to make the designs feasible in complex situations like elderly care a certain amount of pragmatism is needed for researchers.

## CONCLUSION

This thesis suggests caffeine has a place in a detailed analysis of behavioral symptoms in persons with dementia. However, advice on the treatment of behavioral symptoms cannot be given for a group of persons with dementia. As always, this depends on the multidisciplinary analysis of contributing factors.

**A simple question: a complex answer**
Coffee can influence behavior in persons with dementia, but most likely not in all persons, not in all situations and not all of the time; but it can have an influence. Therefore, it is recommended to consider caffeine as a possible moderator in the clinical assessment of behavioral symptoms in persons with dementia.

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# S

# SUMMARY

The word “dementia” derives from the Latin stem ‘demens’ and literally means ‘without mind.’ The medical term dementia covers over 100 diseases in which cognitive function deteriorates to a greater extent than seen in normal aging. Attention, planning, learning, memory, language, visual perception, spatial skills, social skills or other cognitive functions can all be affected. Patients with dementia can also display non-cognitive symptoms, e.g. aggression, agitation, anxiety, apathy, which are together referred to as behavioral symptoms. The etiology of behavior in patients with dementia is complex. Almost all patients with dementia will show behavioral symptoms at some point during the disease which decrease quality of life of the patient with dementia and place a high burden on informal caregivers. A higher caregiver burden often worsens the relationship between the caregiver and the patient with dementia, which in turn may increase the frequency and severity of behavioral symptoms. Quick and adequate management of behavioral symptoms in patients with dementia is necessary to prevent further harm for the patient, caregiver overload, avoidable nursing home admissions and avertible society costs.

To manage behavioral symptoms, the first step recommended in guidelines is the detailed analysis of the patients’ behavior, including contributory physical, psychological, social and environmental factors, after which interventions can be formulated. Although there is some evidence pharmacological agents can decrease behavioral symptoms in patients with dementia, the clinical effect is small and there is a high risk of severe adverse effects and even death. Psychosocial approaches have also been widely studied. Approaches like behavioral management techniques or cognitive stimulation are proven reduce behavioral symptoms. But in the management of behavioral symptoms, no standardized solution is currently available. All interventions that target behavioral symptoms must be tailored to the individual. However, even in the individualized approach nutritional factors are not regularly included as a possible cause or intervention.

Caffeine has been used for several centuries to influence behavior and the effects of caffeine on behavior in adults have been widely researched. It is now widely accepted that moderate caffeine consumption in healthy adults increases alertness, attention and cognitive function. It also elevates mood and reduces fatigue. A high caffeine consumption increases anxiety, can induce psychotic or manic symptoms and impairs sleep. As these effects differ between individuals, people normally adjust their consumption of caffeine based on their personal experience of (non-)beneficial (side) effects. Although the effect of caffeine on behavior in adults is widely accepted, the effect of caffeine on behavior in patients with dementia has not been properly investigated. As coffee is regularly consumed, widely available and most nursing homes do not have specific limitations or adjustments in the caffeine consumption of the residents, more insight in the relation between caffeine and behavior in patients with dementia is wanted.

Based on the known stimulatory effects of caffeine in healthy adults, it seems logical to assume that caffeine increases behavioral symptoms caused by general restlessness, anger and anxiety and increases sleeping difficulties during the night by suppressing fatigue in patients with dementia. The sleeping difficulties can lead to greater daytime sleepiness and a reversion of circadian

rhythm in patients with dementia which in its turn can also increase behavioral symptoms (e.g. irritability).

However, the opposite can also be hypothesized: caffeine consumption may favorably impact behavioral symptoms by improving concentration and lessening overstimulation due to an increase in alertness. Another possible favorable mechanism is the social aspect of caffeine consumption as social activities in general can reduce behavioral symptoms.

Both hypotheses were considered equally strong, therefore **the aim of this thesis** was to investigate whether there is a relationship between caffeine consumption and behavioral symptoms in patients with dementia, and (if a relationship exists) to determine the direction of any effects.

This thesis consists of four studies conducted in a stepwise design. First, two different studies were done to explore the hypotheses. If these studies showed signs of validation of the hypotheses, the second step would include more thorough research: a systematic literature review and a large multicenter cohort study. **Chapter 1** describes the observational pilot study which was performed to explore the possibility of a relationship between caffeine and behavioral symptoms in a group of elderly patients with dementia, with a focus on sleep, aggression, depression, anxiety, apathy, irritability and aberrant motor behavior. Over four days, these behavioral symptoms were measured using the Neuropsychiatric Inventory – Nursing Home edition (NPI-NH) and a sleep questionnaire, together with careful observation of caffeine consumption. In this sample of 29 elderly persons with dementia living in a special care unit a negative correlation between caffeine consumption and apathy and aberrant motor behavior (AMB) was found and positively correlated with getting out of bed at night. No significant correlations were found between caffeine and aggression, depression, irritability or anxiety. This exploratory study showed an association between caffeine consumption and some behavioral symptoms in a group of persons with moderately severe dementia.

**Chapter 2** describes the second exploratory study. Because caffeine shows strong individual variation in effects on behavior in healthy adults, the second study was designed to examine the individual effects. In two persons with dementia, a high caffeine use and severe behavioral symptoms, caffeine consumption was regulated over a four-week period in a blinded crossover trial. The participants were served caffeinated or decaffeinated coffee in a predetermined order (C-D-D-C). Behavioral symptoms were then scored using the NPI-NH and the Cohan Mansfield Agitation Inventory (CMAI), with outcomes individualized per patient. Participant A was an 85-year-old woman with Alzheimer's disease and participant B was a 91-year-old women with mixed type dementia. Participant A had a decrease in her specific behavioral symptoms in the decaf weeks and a small increase on reintroduction of caffeine. In participant B no relation between caffeine and behavioral symptoms was found. This second study confirmed the association between caffeine and behavioral symptoms, but also showed the individual variation in effects.

The results of the two exploratory studies necessitated further research. **Chapter 3** describes the thorough and systematic literature review which was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines. The study proto-

col is registered at PROSPERO. The research question was formulated as “Does caffeine or coffee consumption influence neuropsychiatric symptoms, e.g. agitation, aggression, apathy, irritability, in elderly patients with dementia?”. Six (medical) journal databases (Medline (PubMed), Embase, Emcare, Cochrane, PsychInfo and Web of Science) and gray literature (GLIN, Greylit, AACN Research & Data center, WHO, OpenGray, HSO and Clinicaltrials.gov) were searched and more than 4000 articles were screened for relevance by two reviewers. After screening for eligibility, only seven articles remained. The seven studies differed in almost all facets: study type (from a case report to a RCT), publication date (ranging from 1976 tot 2018), methodology (qualitative and quantitative), the way of administering caffeine (beverages to injections) and measuring behavior. Most of the studies had methodological issues and despite a thorough analysis, no consistent conclusions could be drawn regarding caffeine consumption and behavioral symptoms. However, in each trial, the behavior of some participants seemed to be influenced by caffeine consumption both in a positive and in a negative way.

As fourth and final study, a large multicenter cohort study was conducted with the aim of assessing the possible relationship between caffeine and behavioral symptoms in a large group of nursing home residents with dementia. The three-year study was embedded in the Elderly Care Physicians training program, and trainees collected data on caffeine consumption, cognition, behavioral symptoms and social status. The study design is described in detail in **chapter 4.** To the best of our knowledge, these efforts resulted in the largest existing dataset on cognition, behavior and caffeine consumption amongst nursing home residents. In **chapter 5** we discuss the results of a subgroup analysis of the persons with dementia. Just over 200 persons were included, of which 70% showed behavioral symptoms. People consuming low amounts of caffeine were most likely to have behavioral symptoms. Furthermore, some behavioral symptoms differed between persons with mild, moderate, moderately severe and severe dementia.

The **general discussion** starts with a closer look at the main target receptors of caffeine and the changing brain of a person with dementia. Subsequently, conclusions on the exploration of the relation between caffeine consumption and behavioral symptoms in persons with dementia are discussed in detail, including the clinical implications and considerations for further research.

In short, if one assumes that any association will have to be unidirectional and consistently linear, one might draw the conclusion that there is no relation between caffeine and behavioral symptoms in persons with dementia. However, this thesis provides data to support the argument that there is a complex relationship between caffeine and behavioral symptoms in persons with dementia, and this relationship differs per person, is dose-dependent, and changes with age and the presence of dementia. As caffeine consumption is an easy-to-manage intervention against the background of hard-to-manage behavioral symptoms that place a major burden on caregivers and reduce the quality of life of the person with dementia, it is advisable to include caffeine consumption in the vocabulary of the professional as a possible influencing factor.

**Brief summary**

As the number of patients suffering from dementia is still growing, most of the patients display behavioral symptoms at some time during the disease and these behavioral symptoms lower the quality of life and increase the burden of caregivers, adequate management of these symptoms is warranted. However, the etiology and management of behavioral symptoms is complex, resulting in (mis)use of pharmacological interventions: a cure which is often worse than the disease. In healthy adults, caffeine is known to influence behavior. Four different studies were conducted to see if caffeine is an easy to adjust cause or a pragmatic intervention for behavioral symptoms in patients with dementia. The first study found caffeine consumption to be correlated with less apathy, lower aberrant motor behavior and getting up at night. The second study found a reduction in caffeine consumption led to a decrease in behavioral symptoms (aggression, irritability, general restlessness and aberrant motor behavior) in one participant, but no difference in the other participant. A review of literature found few studies on the subject and some with severe methodological flaws, therefore no consistent conclusion on the relation between caffeine consumption and behavioral symptoms could be drawn. The last study showed behavioral symptoms (like agitation, disinhibition and depression) were most common in persons with low caffeine consumption. Based on these studies, we conclude caffeine can influence behavior in persons with dementia, but most likely not in all persons, not in all situations and not all of the time; but it can have an influence. In clinical practice it is advisable to consider caffeine as a possible moderator in the clinical assessment of behavioral symptoms in persons with dementia.

# S

# SAMENVATTING

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# DUTCH SUMMARY

Het woord ‘dementie’ is afgeleid van de Latijnse stam ‘demens’ en betekent letterlijk ‘zonder geest’. Het syndroom dementie kan veroorzaakt worden door meer dan 100 ziekten waarbij de cognitieve functie sterker verslechtert dan verwacht kan worden op basis van normale veroudering. Alle cognitieve functies zoals aandacht, planning, leren, geheugen, taal, visuele waarneming, ruimtelijke vaardigheden of sociale vaardigheden kunnen door dementie worden beïnvloed. Patiënten met dementie kunnen ook niet-cognitieve symptomen vertonen, zoals probleemgedrag in de vorm van agressie, agitatie, angst, apathie. De etiologie van gedrag bij patiënten met dementie is complex. Bijna alle patiënten met dementie zullen op enig moment tijdens de ziekte probleemgedrag vertonen dat de kwaliteit van leven van de patiënt verminderen en een zware belasting vormen voor de mantelzorgers. Een hogere belasting van de mantelzorger verslechtert vaak de relatie tussen de mantelzorger en de patiënt met dementie, wat op zijn beurt de frequentie en ernst van het probleemgedrag kan verhogen. Snel en adequaat beheer van gedragssymptomen bij patiënten met dementie is noodzakelijk om verdere schade voor de patiënt, overbelasting van de mantelzorger, vermijdbare verpleeghuisopnames en vermijdbare maatschappelijke kosten te voorkomen.

Volgens de richtlijnen is de eerste stap in het behandelen van probleemgedrag een gedetailleerde analyse van het gedrag, inclusief de mogelijk bijdragende fysieke, psychologische, sociale en omgevingsfactoren, waarna interventies kunnen worden geformuleerd. Hoewel er enig bewijs is dat farmacologische middelen gedragssymptomen bij patiënten met dementie kunnen verminderen, is het klinische effect klein en zijn er grote risico’s op bijwerkingen en zelfs overlijden. Psychosociale interventies zijn ook uitgebreid bestudeerd. Het is bewezen dat benaderingen zoals gedragsmanagementtechnieken of cognitieve gedragstherapie de symptomen verminderen. Echter, voor het behandelen van probleemgedrag is er geen gestandaardiseerde oplossing beschikbaar. Alle interventies gericht op gedrag moeten op het individu worden afgestemd. Maar zelfs in deze geïndividualiseerde benadering worden voedingsfactoren niet regelmatig als mogelijke oorzaak of ingreep meegenomen.

Cafeïne wordt al enkele eeuwen gebruikt om gedrag te beïnvloeden en de effecten van cafeïne op het gedrag bij volwassenen zijn uitgebreid onderzocht. Het is algemeen aanvaard dat matige cafeïneconsumptie bij gezonde volwassenen de alertheid, aandacht en cognitieve functie verhoogt. Ook verbetert het de stemming en vermindert vermoeidheid. Een hoge cafeïneconsumptie verhoogt angst, kan psychotische of manische symptomen veroorzaken en verslechtert slaap. Omdat deze effecten van persoon tot persoon verschillen, passen mensen hun cafeïneconsumptie normaal gesproken aan op basis van hun persoonlijke ervaring met (on)gunstige (bijwerkingen) effecten. Hoewel het effect van cafeïne op het gedrag van volwassenen algemeen wordt aanvaard, is het effect van cafeïne op het gedrag van patiënten met dementie niet goed onderzocht. Omdat koffie regelmatig wordt gedronken, overal verkrijgbaar is en de meeste verpleeghuizen geen specifieke beperkingen of aanpassingen hebben in het cafeïnegebruik van de bewoners, is meer inzicht in de relatie tussen cafeïne en gedrag bij mensen met dementie gewenst.

Op basis van de bekende stimulerende effecten van cafeïne bij gezonde volwassenen, lijkt het logisch om aan te nemen dat cafeïne bij mensen met dementie gedragssymptomen kan veroorzaken door algemene rusteloosheid, woede en angst te verhogen en slaapproblemen geeft door vermoeidheid te onderdrukken. De slaapproblemen bij mensen met dementie kunnen weer leiden tot meer slaperigheid overdag en een omkering van het dag en nacht ritme, wat op zijn beurt ook gedragssymptomen kan verergeren (bijv. Prikkelbaarheid).

Maar, het tegenovergestelde kan echter ook worden beredeneerd: cafeïneconsumptie kan gedragssymptomen gunstig beïnvloeden door de concentratie te verbeteren en over stimulatie te verminderen als gevolg van een verhoogde alertheid. Een ander mogelijk gunstig mechanisme is het sociale aspect van cafeïneconsumptie. In het algemeen kunnen sociale activiteiten gedragssymptomen bij patiënten met dementie verminderen.

Beide hypothesen werden als even sterk beschouwd, daarom was **het doel van dit proefschrift** om te onderzoeken of er een verband bestaat tussen cafeïneconsumptie en gedragssymptomen bij mensen met dementie, en (als er een verband bestaat) om de richting van het effect te bepalen.

Dit proefschrift bestaat uit vier onderzoeken die stapsgewijs zijn uitgevoerd. Als eerste zijn twee verschillende onderzoeken gedaan om de hypothesen te verkennen. Als uit deze onderzoeken enige validatie van de hypothesen zou komen, dan zou de tweede stap volgen: een systematische literatuurstudie en een grote multicenter cohortstudie. **Hoofdstuk 1** beschrijft de observationele pilotstudie die als eerste is uitgevoerd om de mogelijkheid van een verband te onderzoeken tussen cafeïne en probleemgedrag bij een groep oudere patiënten met dementie. Tijdens deze studie lag de nadruk op slaap, agressie, depressie, angst, apathie, prikkelbaarheid en doelloos repetitief gedrag (DRG). Gedurende vier dagen werden deze gedragssymptomen gemeten met behulp van de Neuropsychiatric Inventory - Nursing Home edition (NPI-NH) en een slaapvragenlijst, samen met een zorgvuldige observatie van het cafeïnegebruik. In deze groep van 29 ouderen met dementie die op een psychogeriatrische afdeling wonen, werd een negatieve correlatie gevonden tussen cafeïneconsumptie en apathie en DRG en een positieve correlatie met het ‘s nachts uit bed komen. Er werden geen significante correlaties gevonden tussen cafeïne en agressie, depressie, prikkelbaarheid of angst. Deze verkennende studie toonde een verband aan tussen cafeïneconsumptie en enkele vormen van probleemgedrag bij een groep mensen met matig ernstige dementie.

**Hoofdstuk 2** beschrijft de tweede verkennende studie. Omdat cafeïne een sterke individuele variatie vertoont in effecten op gedrag bij gezonde volwassenen, was de tweede studie bedoeld om deze individuele effecten te onderzoeken. Bij twee personen met dementie, een hoog cafeinegebruik en ernstig probleemgedrag, is het cafeïnegebruik gereguleerd over een periode van vier weken in een geblindeerde cross-over studie. De deelnemers kregen cafeïne houdende of cafeïnevrije koffie geserveerd in een vooraf bepaalde volgorde (C-D-D-C). Gedragssymptomen werden vervolgens gescoord met behulp van de NPI-NH en de Cohan Mansfield Agitation Inventory (CMAI), met geïndividualiseerde uitkomsten per patiënt. Deelnemer A was een 85-jarige vrouw met de ziekte van Alzheimer en deelnemer B was een 91-jarige vrouw met gemengde

dementie. Deelnemer A had een afname van haar specifieke gedragssymptomen in de cafeïneweken en een kleine toename bij herintroductie van cafeïne. Bij deelnemer B werd echter geen verband gevonden tussen cafeïne en het gedrag. Deze tweede studie bevestigde een verband tussen cafeïne en probleemgedrag, maar toonde ook de individuele variatie in effecten.

De resultaten van de twee verkennende onderzoeken waren aanleiding tot groter vervolgonderzoek. **Hoofdstuk 3** beschrijft het systematische literatuuronderzoek dat is uitgevoerd volgens de Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) richtlijnen. Het studieprotocol is geregistreerd bij PROSPERO. Met de onderzoeksvraag "Heeft cafeïne of koffieconsumptie invloed op neuropsychiatrische symptomen, bijv. agitatie, agressie, apathie, prikkelbaarheid, bij oudere patiënten met dementie?" is er gezocht in zes (medische) tijdschriftdatabases (Medline (PubMed), Embase, Emcare, Cochrane, PsychInfo en Web of Science) en grijze literatuur (GLIN, Greylit, AACN Research & Data center, WHO, OpenGray, HSO en Clinicaltrials.gov). Meer dan 4000 artikelen werden door twee recensenten op relevantie gescreend. Na screening op geschiktheid bleven slechts zeven artikelen over. De zeven onderzoeken verschilden op vrijwel alle facetten: studietype (van casusrapportage tot RCT), publicatiedatum (variërend van 1976 tot 2018), methodologie (kwalitatief en kwantitatief), de wijze van toediening van cafeïne (dranken tot injecties) en het meten van het gedrag. De meeste onderzoeken hadden methodologische problemen en ondanks een grondige analyse konden er geen consistente conclusies worden getrokken over cafeïneconsumptie en probleemgedrag. Maar, bij elk onderzoek bleek het gedrag van sommige deelnemers echter zowel in positieve als in negatieve zin te worden beïnvloed door cafeïneconsumptie.

Als vierde is een grote multicenter cohortstudie uitgevoerd met als doel de mogelijke relatie tussen cafeïne en probleemgedrag te beoordelen bij een grote groep verpleeghuisbewoners met dementie. Dit driejarige onderzoek is ingebed in de opleiding tot specialist ouderengeneeskunde en de artsen in opleiding verzamelden gegevens over cafeïneconsumptie, cognitie, gedrag en sociale status. De onderzoeksopzet wordt gedetailleerd beschreven in **hoofdstuk 4**. Voor zover wij weten, heeft dit geresulteerd in de grootste bestaande dataset over cognitie, gedrag en cafeïneconsumptie onder verpleeghuisbewoners. In **hoofdstuk 5** bespreken we de resultaten van een subgroep analyse van de mensen met dementie. Iets meer dan 200 personen werden geïncludeerd, van wie 70% gedragssymptomen vertoonde. Mensen die weinig cafeïne consumeerden, hadden de meeste kans op gedragssymptomen. Bovendien verschilden sommige gedragssymptomen tussen personen met milde, matige, matig ernstige en ernstige dementie.

De **algemene discussie** begint met een verdieping in de belangrijkste receptoren waarop cafeïne aangrijpt en het veranderende brein van een persoon met dementie. Daarna worden conclusies over de relatie tussen cafeïneconsumptie en gedragssymptomen bij mensen met dementie in detail besproken, inclusief de gevolgen voor de praktijken overwegingen voor verder onderzoek. Samengevat, als men aanneemt dat een associatie uni directioneel en consistent lineair moet zijn, zou men tot de conclusie kunnen komen dat er geen verband bestaat tussen cafeïne en gedragssymptomen bij mensen met dementie. Dit proefschrift levert echter het argument dat er

een complexe relatie bestaat tussen cafeïne en gedragssymptomen bij mensen met dementie, en dat deze relatie verschilt per persoon, dosisafhankelijk is en verandert met de leeftijd en het beloop van dementie. Aangezien cafeïneconsumptie een gemakkelijk te beïnvloeden interventie is, gedragssymptomen in het algemeen moeilijk te behandelen zijn en een grote belasting vormen voor zorgverleners en de kwaliteit van leven van de persoon met dementie verminderen, is het raadzaam om cafeïneconsumptie op te nemen in het vocabulaire van de professional als mogelijke gedrag beïnvloedende factor.

# DANKWOORD

Isaac Newton schreef aan Robert Hooke in 1675 “if I have seen further it is by standing on the shoulders of giants.” Bij mijn promotietraject heb ik van vele schouders gebruik mogen maken. Hoewel mijn naam op het proefschrift staat zijn er velen zonder wiens kennis, steun en aanmoediging dit proefschrift niet geschreven was. Dank aan iedereen op wiens schouders ik heb mogen staan, op wiens schouders ik heb mogen leunen en aan hen die me geholpen hebben de schouders op te halen.

Dank aan mijn promotieteam. Prof.dr.W.P.Achterberg, eerste-promotor: Beste Wilco, als collega SO stimuleerde je de nieuwsgierigheid in een jonge SO. Uit die nieuwsgierigheid is (jaren later) dit proefschrift is ontstaan. Dank voor het vertrouwen, de kansen die je hebt gecreëerd, je wijsheid en begeleiding. Ik kan me geen prettigere eerste-promotor voorstellen.
Prof.dr.M.E.Numans, promotor: Beste Mattijs, dank voor onze gesprekken en je perspectief, zowel op dit onderzoek als op de rest van mijn werkzaamheden.
Dr.N.Rius-Ottenheim, co-promotor: Beste Nathaly, bij jou kon ik terecht voor antwoorden op praktische vragen, voor nuanceringen en overwegingen. Dank voor waardevolle feedback, ik keek er iedere keer weer naar uit.

Zonder de aan de onderzoeken deelnemende mensen met dementie en hun vertegenwoordigers, de verzorgenden van Zorgspectrum en de aios specialisme ouderengeneeskunde in Leiden, waren deze onderzoeken niet mogelijk geweest. Dank voor jullie betrokkenheid en inzet. Ik hoop dat de conclusies bijdragen aan een betere kwaliteit van leven en goede koffie.

Tijdens het promotietraject heb ik veel vragen gesteld, zowel inhoudelijk als procedureel. Dank aan de collega docenten en onderzoekers, Joran Jongerling, Linda Breeman en anderen voor het beantwoorden van mijn vragen en het stellen van nog meer vragen. En dank aan José Tielerman-Shamier, die mogelijkheden zag in agenda’s waar alleen maar overlap zichtbaar was.

Maxim Veen, Joost Leopold, Wilco Admiraal en andere barista’s hebben me geleerd dat er zoveel meer in koffie zit en er zoveel (smaak)nuance mogelijk is, als je weet welke factoren je kan beïnvloeden. Dank voor de verdieping in iets alledaags.

Onder het genot van vele goede koppen koffie hebben Maaike de Jong, Stefan van Osch, Bastiaan Smit, Jantine van den Bosch, Erik van Tulder en Linda Breeman geluisterd, gerelativeerd en genuanceerd. Jullie schouders heb ik nodig gehad en gewaardeerd.

Dank aan mijn ouders en grootouders, jullie zijn reuzen.

Pepijn, dank voor het samen delen van onze schouders.

# C

# CURRICULUM VITAE

Michelle Angelique Wegewijs was born on August 20th, 1983 in Helmond, the Netherlands. She graduated cum laude at Dr. Knippenberg College in 2001. After completing her Ms in Medicine at the University of Utrecht in 2007, Michelle specialized as an elderly care physician (ECP) at Gerion in Amsterdam and continued to specialize by additional training on people with dementia and behavioral symptoms.

> Good health is more than an absence of disease. Good healthcare does not focus exclusively on treating the disease but involves the whole person and contributes to the (highest attainable) quality of life, with or without disease.

As an ECP she used a holistic, multidisciplinary approach: taking both the context and person into account to realize a best possible quality of life together with the person and team. Besides her employment as an ECP she followed a second career path, first as project and program manager at SOON, later as deputy head of the ECP training program at the Leiden University Medical Center. This second path was also characterized by the holistic approach.

In 2018, she combined these two career paths into one and started as a business consultant in elderly care to realize the (organizational) conditions necessary for a good quality of care. Instead of treating behavioral symptoms with a multidisciplinary team, she now helps to solve all kinds of problems and creatively builds solutions to unblock bottlenecks. Just like the treatment of behavioral symptoms, she does not jump to a solution, but first takes a careful look and analyzes at what is really going on after which the best possible solution is chosen together.

Besides solving problems and finding solutions, Michelle enjoys walking, cycling, hiking, reading, cooking, baking, creating all kinds of things and changing things for the better.

She is married to Pepijn.

# P

# PORTFOLIO

## Mandatory PhD courses

| | |
|---|---|
| 2018 | Basic course on regulations and organization of clinical trials (eBrok), NFU |
| 2017 | PhD Introductory Meeting |
| 2016 | Basic Methods and Reasoning in Biostatistics (exempted because of the e-learning Practical Biomedical Statistics (Chapter 1-10), AMC) |

## Selection of professional qualifications and courses

| | |
|---|---|
| 2020 | Writing with flair, Udemy |
| 2020 | Writing a bestselling novel (writing mastery), Udemy |
| 2017 | Drawing for meetings, presentations and trainings, Udemy |
| 2017 | Writing with Impact: writing that persuades' Clare Lynch, Cambridge University |
| 2017-2018 | Upcycling of Leadership, Double Healix LEAD |
| 2017 | Governance - Population Health Management, LUMC |
| 2017 | MBA in one day, Ben Tiggelaar |
| 2017 | Designing e-learning for Health, University of Nottingham (Futurelearn) |
| 2017 | SCAE Brewing Foundation, Koffieschool |
| 2016 | SCAE Barista Skills Foundation, Koffieschool |
| 2013 | Test design: constructing and using test matrixes, Uitgevers Academie |
| 2013 | General Instructors Course, SBOH en Plato |
| 2012-2013 | Designing multiple choice questions, Uitgevers Academie |
| 2008-2009 | Interprofessional course in geriatric psychiatry, Altrecht |
| 2007 | Passivities of daily living in persons with dementia (Pdl), Zorgspectrum |
| 2007 | Introduction to work- and organizational psychology, Open Universiteit |
| 2006 | Organization and Management, Open Universiteit |

## Teaching experience

| | |
|---|---|
| 2018-2020 | Supervising medical students and ECPs in the writing of a CAT, LUMC |
| 2017-2018 | Teacher at the management training' Policy and management' for GPs, LUMC |
| 2017 | College on elderly care at BsC Medicine, LUMC |
| 2016-present | Guest teacher, Master of Advanced Nurse Practition, Hogeschool Utrecht |
| 2014-present | Several classes on behavioral symptoms, dementia and leadership for the ECP training program, LUMC |
| 2014-2018 | Various educational activities as deputy head of the ECP training program, e.g. teaching, educational development, quality of education, educational innovation and interdisciplinary collaboration, LUMC |

## Research history

| | |
|---|---|
| 2014-present | The relation between caffeine and behavioral symptoms in persons with dementia, under supervision of prof.dr.W.P.Achterberg and prof.dr.M.E.Numans, LUMC |
| 2007-2014 | Several CATs (unpublished) |
| 2007 | Sexological dysfunction in women with pelvic floor problems, under supervision of dr. C.H. van der Vaart |
| 2006-2007 | Baseline study for the project "accessible night and weekend help for mental health care clients", commissioned by Platform GGz Utrecht, Primair Huisartsenposten and Altrecht, under the supervision of Dr. ME Van Baar and prof.dr. A.J.P. Schrijvers |
| 2006 | Review into hypothermia as an adverse effect of antipsychotic drug use, under supervision of dr. R.J. van Marum |

## Employment history

| | |
|---|---|
| 2019-present | Managing consultant, P5COM |
| 2018-present | Consultant, trainer and project manager, Tolokku |
| 2017-2018 | Project manager/ coordinator of the management training 'Leadership & organization' for elderly care physicians (ECP), LUMC |
| 2017-2019 | Advisor to the board, Double Healix Educational Media |
| 2014-2018 | Deputy and substitute head of the ECP training program, responsible for educational innovation and quality, national and local educational development, LUMC |
| 2013-2016 | Projectmanager 'multiple choice testing', Samenwerkende Opleidingen Ouderengeneeskunde Nederland (SOON) |
| 2012-2016 | Elderly care physician, Zorgspectrum |
| 2011-2014 | Program manager STAR(t)class, SOON |
| 2011-2012 | Elderly care physician, Gerimedica Aveant |
| 2011 | Interim (temporarily extra support after a fire) Elderly care physician, Zorgspectrum |
| 2010-2011 | Elderly care physician, Stichting de Rijnhoven |
| 2007-2010 | Trainee eldery care physician, SBOH |
| 1999-2004 | Various side jobs, including on-call care worker in a nursing home |

## Professional service

| | |
|---|---|
| 2021-present | Vice president of guideline commission 'sleep disturbances in elderly persons', SKILZ |
| 2018-present | Editor in chief of Socares (journal and e-learning for professionals in elderly care) |

| | |
|---|---|
| 2016-2019 | Commission member 'toekomstbestendige competenties', Verenso project 'SO 2020' |
| 2012-2016 | Member of the expert team on behavioral symptoms, Zorgspectrum |
| 2010-2017 | Member of guideline commission "dying in nursing homes", with representatives of the police, justice department and elderly care |

**Education**

| | |
|---|---|
| 2017 | Grand for realization of an innovative educational improvement by using VR360 in classes on behavioral symptoms in persons with dementia, Centre-4Innovation. |
| 2016 | Basic education qualification (BKO), LUMC. |
| 2014-2016 | Psychogeriatrics management training (kaderopleiding Psychogeriatrie), Gerion. |
| 2012 | Nutritionist, Civas. |
| 2010-2013 | Natural nutritionist, Kraaybeekerhof Academy. |
| 2007-2010 | Eldely care physician, Gerion. |
| 2001-2007 | Bsc and Ms in Medicine, Utrecht University. Elective courses: Organization and Management (policy staff UMC Utrecht); nursing home medicine; rehabilitation (Military Rehabilitation Centre); medicine in developing countries. |
| 1995-2001 | Cum laude High School A-level, Dr. Knippenberg College. |

**Publications in peer reviewed journals in this thesis**

| | |
|---|---|
| 2020 | "Caffeine consumption and behavioral symptoms in nursing home residents: a cross-sectional analysis"Kromhout MA, Rius Ottenheim N, Putter H, Numans ME, Achterberg WP. The Journal of Nutrition, Health and Aging. |
| 2019 | "Caffeine and neuropsychiatric symptoms in patients with dementia: A systematic review" M.A.Kromhut, N.Rius Ottenheim, E.Giltay, M.E.Numans, W.P.Achterberg. Experimental Gerontology 122 (2019) 85–91 |
| 2018 | "Caffeine consumption and behavioral symptoms in nursing home residents: a study protocol and evidence-based medicine training program" Michelle A. Kromhout, Monica van Eijk, Marjoleine J.C. Pieper, Victor G.M. Chel, prof. Wilco P. Achterberg, prof. Mattijs E. Numans. April 2018, NJM. |
| 2017 | "Reducing behavioral symptoms in elderly patients with dementia by regulating caffeine consumption: two single-subject trials" M.Kromhout, prof. M.Numans, prof. W.Achterberg. EGM, published online: July 28, 2017. |
| 2014 | "Relation between caffeine and behavioral symptoms in elderly patients with dementia: an observational study" M.Kromhout, J.Jongerling, W.Achterberg Journal of Nutrition Health and Aging 2014 Apr;18(4):407-10. |

## Selection of other publications

| | |
|---|---|
| 2017 | "Te hoog? Ervaren werkbelasting bij eerste jaars aios ouderengeneeskunde" Michelle Kromhout and Saskia van Eck-Memelink. Tijdschrift voor Ouderengeneeskunde |
| 2017 | "Probleemgedrag bij dementie", M.A. Kromhout, F.J.Bruijel. TPO de Praktijk |
| 2017 | "Letter to the editor: amyloidosis: a case report and review of literature" M.A.Wegewijs, P.C. de Bruin, E.J. ter Borg. Journal of Clinical Rheumatology. |
| 2016 | "De specialist ouderengeneeskunde van de toekomst – kunnen we in vliegende vaart mee?" C. de Ruiter, R. Leeuwis, M.Kromhout, Tijdschrift voor Ouderengeneeskunde |
| 2016 | Contributed to an article in the Volkskrant 12 October 2016 "Er is vrijwel geen geld voor onderzoek naar alledaagse kwalen" about research into everyday ailments and their treatments, such as coffee for sleeping problems in people with dementia |
| 2010 | "Cafeïne en probleemgedrag bij dementie" M.Kromhout, J.Jongerling, W.Achterberg Tijdschrift voor ouderengeneeskunde 35;5:209 |
| 2007 | "Antipsychotic drug use and hypothermia. Reported cases in literature and WHO database." M.A.Wegewijs, E.Beers, A.J.M.Loonen, R.J. van Marum. Br J Clin Pharmacol 62;6: 736-7. |
| 2007 | Hypothermia following antipsychotic drug use." R.J. van Marum, M.A.Wegewijs, A.J.M. Loonen, E.Beers. Eur J Clin Pharmacol. June; 63(6): 627–631 |

## Selection of relevant oral and poster presentations

| | |
|---|---|
| 2019 | Presentation on behavioral symptoms in persons with dementia and the law 'Als het niet anders kan', at V&VN POH/PVK congress |
| 2017-2018 | Workshop "de verschillende gezichten van dementie", at V&VN congress |
| 2017 | Presentation "Elderly care specialist training – does it refer to dignity?" at LUMC international congress "Dignity in old age" |
| 2016 | Presentation "Probleemgedrag – geen probleem voor de praktijkverpleegkundige" V&VN congress |
| 2016 | Workshop (with Corinne de Ruiter, Verenso) "De specialist ouderengeneeskunde van de toekomst" at Verenso congress Dementia & Domotica |
| 2015 | Presentation "Hoe leiden we de SO van de toekomst op?" at My-Doc congress Artsen in control |
| 2014 | Presentation (with F.J.Bruijel, psychologist) "Mevrouw hangt in de gordijnen - rollen en keuzes van de praktijkverpleegkundige bij probleemgedrag" at V&VN congress |
| 2014 | Presentation "Samenwerking tussen specialisten ouderengeneeskunde en huisartsen" at Zorgspectrum congress 'een dementievriendelijke gemeente' |

| | |
|---|---|
| 2014 | Presentation “Kopje koffie mevrouw Jansen – de relatie tussen cafeïne en gedrag bij mensen met dementie” at Boerhaave Vorderingen in het specialisme ouderengeneeskunde |
| 2010 | Presentation “cafeïne en probleemgedrag bij dementie” at Verenso Congress |
| 2010 | Posterpresentation at IPA congress “The effect of caffeine on behavioral problems in elderly patients with dementia” |
| 2008 | Panelmember at congress ‘Bewegingsvrijheid voor mensen met dementie’ vereniging voor psychogeriatrie in samenwerking met stichting IDé |
| 2006 | Posterpresentation “Antipsychotic drug use and hypothermia” at the research meeting of the Nederlandse Vereniging voor Klinische Farmacologie en Biofarmacie |