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

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

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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

REFERENCES

1. Hoek JF, Ribbe MW, Hertogh CM, van der Vleuten CP. The role of the specialist physician in nursing homes: the Netherlands' experience. Int J Geriatr Psychiatry. 2003;18(3):244-9.
2. Koopmans RT, Lavrijsen JC, Hoek JF, Went PB, Schols JM. Dutch elderly care physician: a new generation of nursing home physician specialists. J Am Geriatr Soc. 2010;58(9):1807-9.
3. Sauve S, Lee H, Meade M, Lang J, Farkouh M, Cook D, et al. The critically appraised topic: a practical approach to learning critical appraisal. Ann R Coll Phys Surg Canada. 1995;28:3.
4. Mackway-Jones K, Carley SD, Morton RJ, Donnan S. The best evidence topic report: a modified CAT for summarising the available evidence in emergency medicine. J Accid Emerg Med. 1998;15(4):222-6.
5. Bordley DR, Fagan M, Theige D. Evidence-based medicine: a powerful educational tool for clerkship education. Am J Med. 1997;102(5):427-32.
6. Coomarasamy A, Khan KS. What is the evidence that postgraduate teaching in evidence based medicine changes anything? A systematic review. BMJ. 2004;329(7473):1017.
7. Ilic D, Nordin RB, Glasziou P, Tilson JK, Villanueva E. A randomised controlled trial of a blended learning education intervention for teaching evidence-based medicine. BMC Med Educ. 2015;15:39.
8. Borsje P, Hems MA, Lucassen PL, Bor H, Koopmans RT, Pot AM. Psychological distress in informal caregivers of patients with dementia in primary care: course and determinants. Fam Pract. 2016;33(4):374-81.
9. van de Ven-Vakhteeva J, Bor H, Wetzels RB, Koopmans RT, Zuidema SU. The impact of antipsychotics and neuropsychiatric symptoms on the quality of life of people with dementia living in nursing homes. Int J Geriatr Psychiatry. 2013;28(5):530-8.
10. Zuidema SU, Derksen E, Verhey FR, Koopmans RT. Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia. Int J Geriatr Psychiatry. 2007;22(7):632-8.
11. Zuidema SU, van der Meer MM, Pennings GA, Koopmans RT. [Prevalence of behavioural problems in a group of demented nursing home patients]. Tijdschr Gerontol Geriatr. 2006;37(1):19-24.
12. Verenso. Richtlijn Probleemgedrag met herziene medicatieparagraaf 2008 2008 [Available from: http://www.verenso.nl/assets/Uploads/Downloads/Richtlijnen/VER00316Probleemgedragherzien02.pdf.
13. Seitz DP, Gill SS, Herrmann N, Brisbin S, Rapoport MJ, Rines J, et al. Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: a systematic review. Int Psychogeriatr. 2013;25(2):185-203.
14. Wang J, Yu JT, Wang HF, Meng XF, Wang C, Tan CC, et al. Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2015;86(1):101-9.
15. Van Mierlo LD, Van der Roest HG, Meiland FJ, Droes RM. Personalized dementia care: proven effectiveness of psychosocial interventions in subgroups. Ageing Res Rev. 2010;9(2):163-83.
16. Vernooij-Dassen M, Vasse E, Zuidema S, Cohen-Mansfield J, Moyle W. Psychosocial interventions for dementia patients in long-term care. Int Psychogeriatr. 2010;22(7):1121-8.
17. van der Putten MJ, Wetzels RB, Bor H, Zuidema SU, Koopmans RT. Antipsychotic drug prescription rates among Dutch nursing homes: the influence of patient characteristics and the dementia special care unit. Aging Ment Health. 2014;18(7):828-32.
18. Pieper MJ, Francke AL, van der Steen JT, Scherder EJ, Twisk JW, Kovach CR, et al. Effects of a Stepwise Multidisciplinary Intervention for Challenging Behavior in Advanced Dementia: A Cluster Randomized Controlled Trial. J Am Geriatr Soc. 2016;64(2):261-9.

19. Kromhout MA, Jongerling J, Achterberg WP. Relation between caffeine and behavioral symptoms in elderly patients with dementia: an observational study. J Nutr Health Aging. 2014;18(4):407-10.
20. Einother SJ, Giesbrecht T. Caffeine as an attention enhancer: reviewing existing assumptions. Psychopharmacology (Berl). 2013;225(2):251-74.
21. Lara DR. Caffeine, mental health, and psychiatric disorders. J Alzheimers Dis. 2010;20 Suppl 1:S239-S48.
22. Smith A. Effects of caffeine on human behavior. Food Chem Toxicol. 2002;40(9):1243-55.
23. Szczerbinska K, Topinkova E, Brzyski P, van der Roest HG, Richter T, Finne-Soveri H, et al. The Characteristics of Diabetic Residents in European Nursing Homes: Results from the SHELTER Study. J Am Med Dir Assoc. 2015;16(4):334-40.
24. Hertogh CM, Deerenberg-Kessler W, Ribbe MW. The problem-oriented multidisciplinary approach in Dutch nursing home care. Clin Rehad. 1996;10:8.
25. Groll DL, To T, Bombardier C, Wright JG. The development of a comorbidity index with physical function as the outcome. J Clin Epidemiol. 2005;58(6):595-602.
26. Fries BE, Simon SE, Morris JN, Flodstrom C, Bookstein FL. Pain in U.S. nursing homes: validating a pain scale for the minimum data set. Gerontologist. 2001;41(2):173-9.
27. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. Int Disabil Stud. 1988;10(2):61-3.
28. Sainsbury A, Seebass G, Bansal A, Young JB. Reliability of the Barthel Index when used with older people. Age Ageing. 2005;34(3):228-32.
29. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther. 1984;64(1):35-40.
30. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry. 1982;139(9):1136-9.
31. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology. 1997;48(5 Suppl 6):S10-6.
32. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308-14.
33. Zuidema SU, Buursema AL, Gerritsen MG, Oosterwal KC, Smits MM, Koopmans RT, et al. Assessing neuropsychiatric symptoms in nursing home patients with dementia: reliability and Reliable Change Index of the Neuropsychiatric Inventory and the Cohen-Mansfield Agitation Inventory. Int J Geriatr Psychiatry. 2011;26(2):127-34.
34. Burrows AB, Morris JN, Simon SE, Hirdes JP, Phillips C. Development of a minimum data set-based depression rating scale for use in nursing homes. Age Ageing. 2000;29(2):165-72.
35. Lampe IK, Kahn RS, Heeren TJ. Apathy, anhedonia, and psychomotor retardation in elderly psychiatric patients and healthy elderly individuals. J Geriatr Psychiatry Neurol. 2001;14(1):11-6.
36. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res. 1991;38(2):143-62.
37. Clarke DE, Van Reekum R, Patel J, Simard M, Gomez E, Streiner DL. An appraisal of the psychometric properties of the Clinician version of the Apathy Evaluation Scale (AES-C). Int J Methods Psychiatr Res. 2007;16(2):97-110.
38. Ding M, Bhupathiraju SN, Chen M, van Dam RM, Hu FB. Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. Diabetes Care. 2014;37(2):569-86.

39. Jiang X, Zhang D, Jiang W. Coffee and caffeine intake and incidence of type 2 diabetes mellitus: a meta-analysis of prospective studies. Eur J Nutr. 2014;53(1):25-38.
40. Higdon JV, Frei B. Coffee and health: a review of recent human research. Crit Rev Food Sci Nutr. 2006;46(2):101-23.
41. Greenberg JA, Axen KV, Schnoll R, Boozer CN. Coffee, tea and diabetes: the role of weight loss and caffeine. Int J Obes (Lond). 2005;29(9):1121-9.
42. Rothberg MB. Overcoming the obstacles to research during residency: what does it take? JAMA. 2012;308(21):2191-2.
43. Del Mar C, Glasziou P, Mayer D. Teaching evidence based medicine. BMJ. 2004;329(7473):989-90.
44. Vrdoljak D, Petric D, Diminic Lisica I, Kranjcevic K, Dosen Jankovic S, Delija I, et al. Knowledge and attitudes towards evidence-based medicine of mentors in general practice can be influenced by using medical students as academic detailers. Eur J Gen Pract. 2015;21(3):170-5.