The older population is growing rapidly and is already a substantial part of our current patient population. Their part will increase over time and we will see more and more differences in older patients compared to their younger counterparts. Therefore, we devoted this AMSj edition to this particular field of medicine: Geriatric Medicine.

This special geriatrics edition was made in cooperation with Majon Muller and Nathalie van der Velde (Internal medicine department, division of geriatrics VUmc resp. AMC), who enthusiastically contribute to the research field of geriatric medicine. Dr. Muller and dr. Van der Velde both mentioned the elderly being a heterogeneous population and showed us the (clinical) variation in the care of older patients. At the same time, internist-geriatricians oversee the complicated problems of our ageing patients, which is also emphasized in this edition’s trial and error.

We do not only get wrinkles and gray hairs from the outside. M. Al Sharkawy and colleagues describe the association between age carotid intima-media thickness, and its possibilities as a risk factor for cardiovascular diseases in older patients. R. Reuvers and colleagues discuss the relationship between white matter hyperintensities and frailty risk in geriatric patients. J. Tettero reviews the effect of age on the discriminative performance of cerebrospinal fluid biomarkers for patients having mild cognitive impairment and those progressing to dementia.

Talking about cognitive functions, A. Zwagemaker and M. Oosterveld give their expert opinion about older men with low testosterone and age-associated memory impairment, treated with testosterone.

Test your own geriatric knowledge in this edition, radiology image about fractures and the DEXA-scan in older patients, written by J. Opperman and M. Maas, and evaluate a 69-year-old woman’s heart problem in the clinical image, written by A. Leemeijer and J. ten Kulve.

As AMSj is also growing older, we thank Rebecca Holman for her contribution to the previous editions and we give a warm welcome to Rik Zoomer and Lothar Kuijper, our new AMSj statisticians. Besides, we would like to welcome Warsha Krishnasing, Saskia Veldkamp and Jan Willem Bruggeman as our new colleagues in the AMSj board, Daphne Schoenmakers as our creative editor and Vera de Jonge as our new student editor-in-chief.

With special thanks to Majon Muller and Nathalie van der Velde, we present to you our special geriatrics edition. Enjoy growing into the field of geriatrics by reading this mature edition!

Vera de Jonge, Michiel Schuijt, Gabor Linthorst, Frek Daams
Editors in chief
CEREBRAL WHITE MATTER HYPERINTENSITIES AND FRAILTY RISK IN A GERIATRIC POPULATION

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INTRODUCTION

Frailty is a common geriatric syndrome typically described as a clinically recognizable state of increased vulnerability resulting from ageing-associated decline in reserves and function across multiple physiologic systems.1 It is associated with serious adverse outcomes, such as falls, hospitalization and death.2,3 The prevalence of frailty in community-dwelling elderly, defined as people over the age of 65 years, ranges from 4 to 59%, depending on the definition used, while the weighted prevalence of frailty was found to be 10.7%.4 Up until now, no gold standard for a frail exist. Yet, important contributing factors are reduced physical function, reduced cognitive and behavioral function, malnutrition, disabilities in Activities of Daily Life (ADL) and Instrumental ADL (IADL), urinary and fecal incontinence and social isolation.2,5 The pathophysiology of frailty is largely unknown, but it has been hypothesized that microvascular abnormalities/changes in the brain are contributors to frailty.4

White matter hyperintensities (WMH) are an indicator of cerebral microvascular disease and a common finding on brain magnetic resonance imaging (MRI) or computed tomography (CT) in older people and in patients with stroke and dementia.5-8 More than half of all elderly have some degree of cerebral white matter abnormalities. Common frailty characteristics such as immobility, functional problems, cognitive impairment, depression, malnutrition and urinary incontinence have been shown to be closely associated with WMH.9 Therefore, we hypothesize the amount of WMH to be related to risk of frailty. However, most of the studies on frailty characteristics have been performed in the general population. To our knowledge no studies have been performed relating WMH to frailty risk in geriatric patients. Thus, this study aims to examine the association between WMH and risk of frailty in a large cohort of geriatric outpatients with memory complaints.

METHODS

STUDY DESIGN AND POPULATION

Data for this cross-sectional study were collected from a cohort of 475 patients visiting a geriatric outpatient clinic of the Haga hospital in the Netherlands between October 2005 and March 2010. Reasons for referral included somatic, psychological, social or functional problems. All data were collected as part of the regular outpatient care and retrieved from medical records. Patients underwent a comprehensive geriatric assessment and their medical history, medication use, physical status, functional status, demographics and lifestyle were evaluated. Additionally, laboratory tests were performed. Nutritional status, depressive symptoms and cognitive functioning were assessed with validated questionnaires as described below.11-13 A Magnetic Resonance Imaging (MRI) scan of the brain was performed in 357 patients (75%) with memory complaints on indication by a geriatrician. After excluding 48 patients with missing frailty data, 309 patients were included in this study. Ethical approval was granted for this study (according to the Declaration of Helsinki, revised in 2000), but informed consent was waived as data were collected for clinical purposes.

WHITE MATTER HYPERINTENSITIES

White matter hyperintensities (WMH), indicative of cerebral small vessel disease,9,14 were identified with an MRI scan (1.5 T, Philips, The Netherlands) of the brain. A trained radiologist analyzed these scans. The amount of WMH was quantified using the Fazekas score (FIGURE 1). A Fazekas score of 2 or higher was used as a cutoff for severe WMH.15,16

CONCLUSION

In geriatric outpatients with memory complaints, severe WMH are related to an increased risk of frailty, predominantly in the domain of immobility and impairment in ADL or IADL.

ABSTRACT

OBJECTIVE Cerebral small vessel disease, such as white matter hyperintensities (WMH), has been associated with decline in physical and cognitive function, which are both essential elements of frailty. However, little data is available on the association between WMH and frailty risk. This study aims to examine this association in a large cohort of geriatric outpatients with memory complaints.

METHODS In this cross-sectional study the relation between presence of WMH and frailty risk was studied in 309 patients (mean age 79.5 years, SD 6.9, 69% female) who visited a geriatric outpatient clinic between 2005 and 2010. All patients underwent a comprehensive geriatric assessment. Frailty was defined as presence of 2 or more of the following characteristics: immobility, incontinence, malnutrition, depressive symptoms (Geriatric Depression Score), impaired cognitive function, impaired Activities of Daily Life (ADL), and impaired Instrumental ADL (IADL). Magnetic Resonance Imaging of the brain was performed to assess WMH (Fazekas scale) as a marker of cerebral small vessel disease. OR’s were calculated by means of logistic regression analysis, adjusted for age, sex, and education.

RESULTS The prevalence of frailty was 43.4%. Patients with severe WMH (Fazekas ≥ 2) were at increased risk of being frail; OR (95% CI) was 2.98 (1.66-5.35). Further correction for cardiovascular risk factors did not materially change the effect estimates. With respect to the separate frailty characteristics, presence of WMH was significantly associated with immobility, ADL impairment and IADL impairment, but not with depressive symptoms and cognitive function.

CONCLUSION In geriatric outpatients with memory complaints, severe WMH are related to an increased risk of frailty, predominantly in the domain of immobility and impairment in ADL or IADL.

KEYWORDS: frailty; white matter hyperintensities; functional status; magnetic resonance imaging; geriatric outpatients
more impairments were allocated to frail.

CARDIOVASCULAR RISK FACTORS
Smoking and alcohol use (classified as ‘current’ and ‘former/none’), history of cardiovascular disease and cerebrovascular disease were based on data from the medical interview. Systolic and diastolic blood pressure were measured in standing and supine position with an analog sphygmomanometer and values were noted in increments of 5mmHg. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90mmHg, use of antihypertensive medication, or being diagnosed with hypertension [17]. Hypercholesterolemia was defined as a total serum cholesterol level ≥ 5.5mmol/l, use of cholesterol lowering medication, or being diagnosed with hypercholesterolemia.14 Diabetes was defined as a non-fasting glucose level ≥ 11.1mmol/l, use of anti-diabetic medication, or being diagnosed with diabetes.19 A body mass index (BMI) > 25kg/m² was considered overweight.20

OTHER FACTORS
Level of education was classified as ‘lower’, ‘middle’, or ‘higher’. ‘Lower’ was defined as having received no or only primary education, ‘middle’ as having received vocational education and ‘higher’ as having received scientific education.

DATA ANALYSIS
Patient characteristics were calculated for the total population and according to the presence of WMH. Differences across these categories were calculated with ANOVA for continuous variables and chi-square tests for dichotomous variables. Logistic regression analysis allows multiple predictors to be related to a dichotomous outcome, therefore this method was used to assess the association of WMH with risk of being frail. To gain insight into which frailty characteristics were more strongly related to WMH, effect sizes for all separate frailty characteristics were obtained with logistic regression. All analyses were adjusted for age, sex and level of education (model 1) and additionally for alcohol use and smoking (model 2). The remaining cardiovascular risk factors – coronary heart disease, cerebrovascular disease, hypertension, hypercholesterolemia, diabetes mellitus, overweight and orthostatic hypotension – were added to model 2 to form model 3. Statistical analyses were performed using IBM SPSS Statistics version. 21

RESULTS
Of the 309 patients, 134 patients (43.4%) were ‘frail’. The mean (SD) age of the study population was 79.5 years (6.9), 69% of participants were female (TABLE 1). Patients with severe WMH were older and used less alcohol (TABLE 1). Incontinence, immobility and impaired cognitive function were the most prevalent frailty characteristics (TABLE 2).

Presence of severe WMH was associated with an almost 3-fold increased odds of being frail (TABLE 3); OR 2.98 (95% CI 1.66–5.35). This association was independent of age, sex and education level. Additional adjustments for smoking, alcohol (model 2) and other cardiovascular risk factors (model 3) slightly attenuated the effect estimates, but they remained statistically significant (TABLE 3). Figure 1 shows that the relation between WMH and frailty is non-linear: the percentage of patients with severe WMH was the highest for those with 3 or more frailty characteristics.

Presence of severe WMH was significantly associated with the separate frailty characteristics immobility, impaired ADL, and impaired IADL. However, it was not associated with cognitive impairment, depressive symptoms, incontinence, and malnutrition (TABLE 4). All these associations were independent of age, sex, and level of education.

DISCUSSION
In our study, presence of severe WMH was related to an increased risk of being frail in a large geriatric population. Concerning the separate frailty characteristics, the strongest relations were found with immobility and impairments of (I)ADL and not with cognitive impairment and depressive symptoms. These results were independent of important confounders such as age, gender, level of education, and cardiovascular risk factors.

Our results are in line with several cross-sectional studies on the relation between small vessel disease and frailty risk.3,12 In a community-based study in 962 older adults (mean age 62.5 years, SD 8.6) the presence of cerebral microbleeds in the brain stem was associated with an increased frailty risk. However, only 3% of this population was classified as being frail.2 Further, in 87 older patients (> 65years) presence of WMH and retinal vessel abnormalities were associated with a higher frailty index.2 In addition, numerous studies have examined the association of WMH with separate frailty characteristics such as physical function and cognitive function in more vital and younger populations.2,18 These studies and ours suggest that microvascular disease could be an underlying pathophysiological pathway of frailty.

In our study, presence of WMH was strongly associated with the risk of being frail, mainly by its strong association with immobility and functional problems (both IADL and ADL). Earlier research confirms that WMH are associated with impaired balance, gait, mobility and falls in older people.29 The integrity of the neural network within the brain and the long descending motor fibers are crucial in lower extremity control.29 The fact that WMH seems to have a direct effect on mobility and functional problems could indicate that lesions are mostly found in brain areas associated with motor control. Unfortunately, no data was available on the location of the lesions.

|TABLE 3 Characteristics for the total population (N=309) and according WMH-status. Age and range are measured in years. Group differences were analyzed with ANOVA and chi-squared tests. Fazekas scale is: quantification of the amount of white matter hyperintensities
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Fazekas ≥ 2</strong></td>
<td><strong>Fazekas &lt; 2</strong></td>
<td><strong>Total n=309 (100%)</strong></td>
<td></td>
</tr>
<tr>
<td>Age, Mean ± SD*</td>
<td>81.6 ± 6.09</td>
<td>78.8 ± 6.95</td>
<td>79.5 ± 6.85</td>
</tr>
<tr>
<td>Range</td>
<td>25</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Female gender, n (%)*</td>
<td>55 (74.3)</td>
<td>157 (66.8)</td>
<td>212 (68.6)</td>
</tr>
<tr>
<td>Highest completed education, n (%)</td>
<td>Lower</td>
<td>Middle</td>
<td>Higher</td>
</tr>
<tr>
<td>18 (25.4)</td>
<td>35 (49.3)</td>
<td>18 (25.4)</td>
<td>65 (29.4)</td>
</tr>
<tr>
<td>Current alcohol use, n (%)*</td>
<td>25 (34.2)</td>
<td>104 (46.6)</td>
<td>129 (43.6)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>9 (12.2)</td>
<td>27 (11.7)</td>
<td>36 (11.8)</td>
</tr>
<tr>
<td>Coronary heart disease, n (%)</td>
<td>35 (47.3)</td>
<td>102 (43.4)</td>
<td>137 (44.3)</td>
</tr>
<tr>
<td>Cerebrovascular disease, n (%)**</td>
<td>15 (20.3)</td>
<td>26 (11.1)</td>
<td>41 (13.3)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>66 (89.2)</td>
<td>203 (86.4)</td>
<td>269 (87.1)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>54 (73.0)</td>
<td>152 (64.7)</td>
<td>206 (66.7)</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>21 (28.4)</td>
<td>67 (28.5)</td>
<td>88 (28.5)</td>
</tr>
<tr>
<td>Overweight (BMI&gt; 25), n (%)</td>
<td>31 (43.1)</td>
<td>114 (48.5)</td>
<td>145 (47.2)</td>
</tr>
</tbody>
</table>

* Differences in groups are statistically significant with p< 0.05
** Differences in groups are statistically significant with p< 0.01
The lack of an association between WMH and cognitive or depressive symptoms might be caused by methodological issues. Depression and, according to some but not all studies, cognitive impairment are associated with memory complaints. A possible explanation could be that our selection method, referral of patients with memory complaints, has led to a study population that is too homogeneous to detect differences. Additionally, MMSE and GDS are crude measures and it is possible that the sample size was too small to detect differences.

The strength of this study is the availability of extensive data on both brain MRI and frailty-related characteristics in a large cohort of geriatric outpatients with memory complaints. All data were consistently collected by a geriatrician and trained nurses. Multiple validated measures were used, such as MMSE, GDS-15 and MNA. A limitation of this study is the cross-sectional design, which limits conclusions about causality. Furthermore, data were collected as part of a clinical assessment, which resulted in several missing or incomplete data for some of the variables and the unavailability of certain frailty characteristics that are used in existing measures of frailty. This made the use of validated measures of frailty unreliable and lead to the composition and use of a new frailty measure.

In summary, in a geriatric population that suffers from memory complaints WMH are associated with increased frailty, in particular with risk of immobility and impaired daily functioning. Further research is needed to examine the longitudinal relation between microvascular changes in the brain and the development of frailty.

### TABLE 2 Overall prevalence of frailty characteristics in 309 geriatric patients.

<table>
<thead>
<tr>
<th>Frailty characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incontinence</td>
<td>203 (65.7)</td>
</tr>
<tr>
<td>Impaired ADL</td>
<td>88 (28.5)</td>
</tr>
<tr>
<td>Impaired iADL</td>
<td>80 (25.9)</td>
</tr>
<tr>
<td>Immobility</td>
<td>134 (43.4)</td>
</tr>
<tr>
<td>MNA score &lt; 17</td>
<td>40 (12.9)</td>
</tr>
<tr>
<td>MMSE score &lt; 24</td>
<td>126 (40.8)</td>
</tr>
<tr>
<td>GDS score &gt; 6</td>
<td>89 (28.8)</td>
</tr>
</tbody>
</table>

### TABLE 3 The relation between severe white matter hyperintensities (Fazekas ≥ 2) and risk of being frail in 309 geriatric patients.

<table>
<thead>
<tr>
<th>Frailty characteristics (Fazekas ≥ 2)</th>
<th>Risk of being frail (OR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td></td>
<td>2.98 (1.66-5.35)**</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
</tr>
<tr>
<td></td>
<td>2.74 (1.49-5.03)**</td>
</tr>
<tr>
<td></td>
<td>Model 3</td>
</tr>
<tr>
<td></td>
<td>2.40 (1.25-4.58)**</td>
</tr>
</tbody>
</table>

### TABLE 4 The relation between cardiovascular risk factors and risk of the separate frailty characteristics in 309 geriatric patients.

<table>
<thead>
<tr>
<th>Frailty characteristics</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incontinence</td>
<td>1.49 (0.81-2.73)*</td>
</tr>
<tr>
<td>Impaired ADL</td>
<td>2.26 (1.26-4.06)*</td>
</tr>
<tr>
<td>Impaired iADL</td>
<td>2.56 (1.41-4.65)*</td>
</tr>
<tr>
<td>Immobility</td>
<td>1.93 (1.08-3.44)**</td>
</tr>
<tr>
<td>MNA score &lt; 17</td>
<td>1.60 (0.75-3.40)</td>
</tr>
<tr>
<td>MMSE score &lt; 24</td>
<td>1.23 (0.69-2.18)</td>
</tr>
<tr>
<td>GDS score &gt; 6</td>
<td>1.10 (0.60-2.02)</td>
</tr>
</tbody>
</table>

The relation between cardiovascular risk factors and risk of the separate frailty characteristics in 309 geriatric patients. Additionally, MMSE and GDS are crude measures and it is possible that the sample size was too small to detect differences.

### REFERENCES

Looking back, I made a detour in my career to become an internist-geriatrician. I have always liked working with elderly. For example, during high school I already had a summer job in an elderly home. Nonetheless my interest in working with the elderly patients came much later. After high school, I initially started studying in the field of Human Movement Sciences. I enjoyed classes in neurology and the musculoskeletal system. I found that I did not only want to know about these subjects, but also treat patients. Therefore, I switched to studying medicine, after my master’s degree in Human Movement Sciences.

I noticed that especially elderly people are not optimally treated. I see the older patient as a complicated puzzle. Other specialists are far more organ-based. This last approach is perfect for young patients with a single problem but does not suffice for older frail patients with multiple problems. In geriatrics, we look at the whole patient and are interested in the interrelation between diseases, medication and functional problems such as physical functioning and cognitive functioning. In deciding what the most suitable treatment is for the patients we use a patient-targeted approach by taking into account patient’s wishes, life expectancy and quality of life. Geriatrics is not protocol based which makes the treatment of patients very interesting.

When I speak with patients about the consequences of their treatment options it often involves ethical dilemmas patients need to deal with. Do they wish treatment for cancer knowing that the side effects could make them sicker and that their quality of life during their remaining life-expectancy will dramatically decrease? Should we start a lipid lowering drug in a 90-year-old patient? Should we stop the anti-coagulants in older patients with a very high risk of falling? These types of decisions require more than a 10-minute talk that doctors usually have. As an internist-geriatrician I have approximately 30-45 minutes consult time per patient, which makes it possible to really engage these patients.

The older population is very heterogeneous, ranging from extremely frail patients to very fit patients. This clinical variation within the population was a motivation for going into research. Most current medical guidelines are founded on research that has been performed in younger adults. In most studies, older patients are underrepresented and it is therefore unknown whether the current evidence of treatments can be translated to the treatment of frail older patients. I often ask myself whether or not I should treat this older patient according to the current guidelines or whether I should use an alternative treatment. Finding tailor-made treatments for older patients is what I like to do. My area of expertise is in the connection between the heart and the brain. Treatment for hypertension in frail older patients requires a different approach. A low blood pressure, for example, might cause less cerebral perfusion, causing neurologic problems. The fun thing about doing research is that once you start working on a problem, you always end up raising more questions you are able to answer.

I hope that my research contributes to the understanding of the interaction and relation between the fields of cardiac and neurovascular system. My ambition is to start an outpatient heart-brain clinic. A lot of people with cardiovascular comorbidities have brain damage with cognitive problems or mood disorders. I would like to contribute to the understanding of this problem and to find appropriate treatments.

My advice for young doctors is to take time and show interest in your older patients, as almost every future doctor will treat a lot of older patients. Ask your older patients what they expect from their remaining years and what they like and love in their life.

“I see the older patient as a complicated puzzle.”

### Curriclum Vitae

- **1991**: Human Movement Sciences, Radboud University (MSc)
- **1994**: Medicine, Radboud university (MD)
- **1999**: AGNIO neurology
- **2000**: PhD student, UMC, Utrecht (PhD)
- **2003**: AIOS Clinical Geriatrics
- **2008**: AIOS internist-geriatrician
- **2009**: Internist-Geriatrician, VUmc
- **2011**: Post doc National Institute on Aging, National Institutes of Health
- **2014**: Internist-geriatrician LUMC

Current position (since 2016): Associate Professor Internal/Geriatric Medicine VUmc
My first job was at the department of clinical geriatrics at Slotervaart hospital. Your first job is always exciting. It is a lot to take in, an exhilarating experience. During my final internship at the clinical geriatrics department I learned that this was the domain I wanted to pursue. I felt that geriatrics reflected what I thought the essence of being a doctor. In geriatrics the patient is observed holistically, opposed to addressing a single organ system. We look from the somatic, psychiatric as well as the functional and social perspective. Therefore, I find clinical geriatrics an inspiring and challenging specialization. It is concerned with all sides of medicine and is centered around quality of life.

After a short while I applied for my specialization. Back in that day it was a national application program. I got a call from Erasmus MC if I was interested in a dual program, combining my training with a PhD program. I had always been interested in doing research. I have had a keen interest in understanding how the human body functions and how to improve health care. After completing this program, I completed training to becoming an internist as well. Then I became staff-member at the AMC as internist-geriatrician.

Nowadays I am a clinician as well as one of the principal investigators of the geriatrics department, focusing on falls and fracture prevention. Clinical questions are key in my research. I believe these questions are solved by combining clinical and translational research. For example, I study how certain genetic profiles predict medication-related falls. Thus, giving way for a better personalized fall prevention advice in the clinic, that can be tested in a randomized clinical trial. Though I find fundamental research interesting, I believe that in the end research must have clinical relevance.

Research within the field of clinical geriatrics is complex due to the heterogeneity of the population. Therefore, for example, a randomized controlled trial may not always be the best way to get useful results. Step-wedged RCT’s or really big cohorts can be more effective. In a step-wedged RCT, the patients are sequentially treated over a period of time and they are observed both as part of the control and of the intervention group. Geriatric patients are a good group to work with as overall they are motivated to contribute to research, are enthusiastic about extra care they receive and that they are relatively compliant.

**“Geriatrics reflects the essence of being a doctor.”**

My research comes from my intrinsic motivation. I find it rewarding to help answer the pending clinical questions. I also enjoy supervising PhD students, which is inspiring and rewarding. Without this, research can be a hassle. There are many obstacles, thus endurance is a key attribute in research. Research is a time-consuming process, which for clinicians means that it continues after work hours. It involves ups and downs, but receiving a research grant or getting an article published is also highly rewarding.

I would advise students to get involved in research early on in order to see for themselves whether they actually enjoy doing research. There are a lot of enthusiastic scientists that can use your help. There is also a difference between different research groups, so if you joined one and it did not match, you can always switch to another group. Also, a (research) internship in another country such as the United States can be really big cohorts can be more effective. In a step-wedged RCT, the patients are sequentially treated over a period of time and they are observed both as part of the control and of the intervention group. Geriatric patients are a good group to work with as overall they are motivated to contribute to research, are enthusiastic about extra care they receive and that they are relatively compliant.

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**THE INFLUENCE OF TESTOSTERONE ON COGNITIVE FUNCTIONS IN OLDER MEN**

A. Zwagemaker, M.J.S. Oosterveld

**BACKGROUND**

Older age comes with cognitive decline, with 40% of adults > 65 years experiencing age-associated memory loss.1 In addition, 20% of men > 60 years have physiologically reduced serum testosterone levels.2 Prior observational studies demonstrated an association between low circulating testosterone and impaired cognitive performance.1,3 Two small trials yielded conflicting results, with one showing memory improvement with testosterone supplementation and one reporting negative findings.4,5 Hence, convincing evidence supporting testosterone intervention in this group is lacking. In this article, we discuss the largest trial to date evaluating the cognitive effects of testosterone treatment in older men.

**REVIEW**

In older men with symptomatic hypogonadism, low baseline testosterone and memory loss, testosterone treatment compared with placebo for one year was not associated with significant improvement in memory and other cognitive functions. This lack of effect was seen despite an increase in serum testosterone to levels within the range for men aged 19-40 years.

Strengths of the current study are its large sample size and well-controlled design. The study had a relatively high follow-up of 89%, with equal loss-to-follow-up in both groups. Adherence to treatment was excellent (> 92%). Data was analyzed based on the intention-to-treat principle, minimizing confounding due to dropout. The trial was adequately powered (power 90%) to detect a clinically relevant 3-point increase in the delayed
INTRODUCTION
Atherosclerosis is the main cause of cardiovascular diseases
Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide.\(^1\) The incidence and prevalence rapidly increases with age.\(^2\) Atherosclerosis is the primary cause of CVD and is associated with the presence of cardiovascular (CV) risk factors such as hypertension, smoking, diabetes mellitus, physical inactivity, adverse cholesterol levels and obesity.\(^3,4\)

CAROTID INTIMA-MEDIA THICKNESS IS A BIOMARKER FOR CARDIOVASCULAR DISEASE RISK
Progression of atherosclerosis is characterized by hardening and thickening of arterial vessel walls. Measurement of the thickness of the intimal and medial layers of the carotid artery wall, which constitute the carotid intima-media thickness (CIMT), is a useful method to evaluate alterations in wall structure. CIMT (mm) is assessed by high modulation (B-mode) ultrasound, which is a non-invasive, widely-available and easily accessible imaging technique frequently used in clinical trials to identify individuals at risk for developing CVD. This technique could be an elegant, quick way to individualize a patient’s CV risk in daily clinical practice of older adults. Thickening of the CIMT is an indicator of subclinical vascular disease and is associated with an increased risk of future CV events.\(^5,6\)

Therefore, CIMT is presents an important biomarker of CVD risk.\(^7\)

REFERENCE

ARTICLE
CAROTID WALL THICKNESS IS POSITIVELY ASSOCIATED WITH AGE
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ABSTRACT
BACKGROUND Current cardiovascular risk scores identify all elderly over the age of 70 as at increased risk, necessitating cardiovascular (CV) treatment in all these individuals. Whether adding additional measurements to identify elderly at low risk is beneficial is yet to be examined. Carotid intima-media thickness (CIMT) measured by carotid ultrasound is a non-invasive and widely-used imaging technique to detect early signs of systemic atherosclerosis.

AIM Examine the association between age and CIMT in healthy individuals in different age groups, free from cardiovascular disease (CVD).

METHODS Mean and maximum CIMT were measured by bright modulation ultrasound in 10 healthy young (aged 18-30 years), 10 middle-aged (40-55 years) and 10 older (≥ 65 years) adults. CIMT was measured over a length of 10 mm at the far wall of the left and right common carotid artery (CCA) by two single-blinded sonographers. Linear regression analyses were performed to assess the association between age and CIMT.

RESULTS Median (interquartile range) CIMT (mm) of the left CCA was 0.38 (0.37 – 0.39) in the young, 0.52 (0.46 – 0.59) in the middle-aged and 0.71 (0.56 – 0.91) in the older age group. Results observed in the right CCA were (only) slightly different and slightly higher results were observed for maximum CIMT. Variability in CIMT increased with age. CIMT differed significantly between the young, middle-aged and older adults (p< 0.001). Mean CIMT (confidence interval, CI) in the left CCA was 0.382 (0.312 – 0.452) mm in the young adults. Mean CIMT in the left CCA increased with 0.176 mm (CI: 0.077 – 0.275 mm, p<0.001) in the middle-aged adults and with 0.328 mm (CI: 0.229 – 0.428 mm, p< 0.001) in the older adults compared to the young adults. After adjustment for gender these results did not differ.

CONCLUSION CIMT increases with age in healthy adults, but is also highly variable in older adults. As a marker for subclinical atherosclerotic disease, CIMT might be useful to discriminate older adults at low risk of CVD, who are presumably unlikely to benefit from preventive drugs. This might lower overtreatment in asymptomatic older adults.

KEYWORDS carotid wall thickness, carotid intima-media thickness, CIMT, subclinical atherosclerosis, carotid ultrasound, cardiovascular risk management, elderly, vascular age

CLINICAL VALUE OF CAROTID INTIMA-MEDIA THICKNESS IN OLDER ADULTS
Current CVD risk assessment for patients without CVD consists of determining the presence of CV risk factors as described above. With these, an individual’s 10-year risk of CVD and/or CV death can be determined using the Framingham risk score chart.\(^8,9\) According to current CV risk management guidelines, every adult over the age of 70 has a high (≥20%) 10-years risk of CVD or CV death independent of other risk factors and regardless of their atherosclerotic burden. Thus, they are eligible for treatment with lipid lowering drugs and/or antihypertensive medication. This could lead to overtreatment, which tends to occur frequently in low risk elderly.\(^8\) Current CV risk guidelines do not take into account great variation in atherosclerotic burden at any chronological age. Individualizing treatment decisions with additional measurement of markers of atherosclerotic or CV disease would therefore be preferable. These additional markers could be useful in determining a patient’s vascular age and thus further discriminate older adults at low or high risk of CVD. One such marker could be CIMT. The primary aim of this study was to examine the association between age and CIMT.

METHODS
STUDY DESIGN
This cross-sectional study examining the association between age and CIMT was performed at the department of Internal Medicine at the VU Medical Centre Amsterdam. The study protocol...
was approved by the Medical Ethical Committee of the VU Medical Centre Amsterdam and performed according to the Helsinki declaration. All participants were informed about the study and gave written consent before participating.

STUDY POPULATION
The study population consisted of 30 healthy, free from CVD, Dutch men and women aged 18-30 years (n=10), 40-55 years (n=10) and 65 years and older (n=10). Participants were allowed to have a maximum of 1 CV risk factor (smoking, diabetes, family history of coronary heart disease (CHD), hypercholesterolemia) or take a maximum of 1 CV drug, e.g. lipid-lowering drugs (statins), anticoagulants, platelet inhibitors or antihypertensive drugs. Participants were recruited from hospital staff and VU university students by e-mail.

CARDIOVASCULAR RISK FACTORS
Prior to the carotid examination each participant filled out a questionnaire regarding their family history of CHD (yes/no), use of the above-mentioned CVD medication (yes/no), alcohol use (number of glasses per month) and smoking habits (yes/no). Family history of CHD was positive if participants had a first-degree relative that died due to CHD before the age of 65. Participants were indicated as having hypercholesterolemia due to CHD before the age of 65. Participants if participants had a first-degree relative that died due to CHD before the age of 65. Participants were indicated as having hypercholesterolemia due to CHD before the age of 65.

RESULTS
PARTICIPANT CHARACTERISTICS
Baseline characteristics are presented in TABLE 1. The median (Interquartile Range (IQR)) age of the young participants was 23.0 (21.0 – 25.3) years. 60% of the young participants were female. Median age of the middle-aged participants was 43.5 (42.0 – 51.5) years. 50% of the middle-aged participants were female. In the older participants, median age was 69.5 (65.0 – 74.0). 40% of these were female. Known CV risk-factors did not differ between groups. No differences were observed in BMI, systolic and diastolic blood pressure, heart rate, use of alcohol and physical activity level. None of the participants were diabetic, two participants were smokers, three participants had hypercholesterolemia, one participant used medication for CVD (statins) and two participants had a positive family history of CVD.

CAROTID INTIMA-MEDIA THICKNESS
Differences in median (IQR) mean and maximum CIMT of the left and right CCA are presented in TABLE 2 and differed significantly between the young, middle-aged and older age group (p<0.001). Median mean CIMT (mm) of the left CCA was 0.38 (0.37 – 0.39) in the young, 0.52 (0.46 – 0.59) in the middle-aged and 0.71 (0.56 – 0.91) in the older age group. Median maximum CIMT (mm) of the left CCA was 0.44 (0.43 – 0.45) mm in the young, 0.61 (0.56 – 0.69) mm in the middle-aged and 0.84 (0.68 – 1.06) mm in the older age group. Results observed in the right CCA were slightly different. As apparent in FIGURE 1, variability in CIMT values increased with age.

ASSOCIATION BETWEEN AGE AND CIMT
Mean CIMT (confidence interval, CI) in the left CCA was 0.382 (0.312 – 0.452) mm in the young adults. Mean CIMT in the left CCA increased with 0.176 mm (CI: 0.077 – 0.275, p=0.001) in the middle-aged adults and with 0.328 mm (CI: 0.229 – 0.428, p<0.001) compared to the young adults. After adjustment for gender, a well-known CV risk factor, these results did not differ (TABLE 3).

DISCUSSION
The results of the present study show CIMT to increase with age in healthy adults. This positive association is independent of CV risk factors. These results are in agreement with previous studies12 and in line with the pathophysiology behind atherosclerosis. It is well known that the development of atherosclerosis starts around early adulthood and progresses with age. Since CIMT is a marker for subclinical atherosclerosis, it is likely that CIMT increases with age.

In our study, slightly different results for CIMT in the left and right carotid arteries were found. In previous studies a significant difference between the two sides has been reported, with a thicker carotid intima-media thickness on the left side.13,14 It has been suggested that this can be explained by a different vascular anatomy of the left and right sides. The left CCA originates directly from the aortic arch which may result in different shear stresses between the two sides.15

ULTRASOUND EXAMINATIONS
Measurements of CIMT were performed by carotid ultrasound using the Samsung RS80A (Samsung Medison, Seoul, Korea) scanner with a 12 MHz linear array transducer. Participants were examined in the supine position on an examination table with their head slightly tilted to the opposite direction of the transducer.

IMAGE ACQUISITION
Longitudinal B-mode scans of the left and right CCA were acquired using a postero-lateral position of the transducer. The CCA was examined 1 cm proximal to the carotid artery bifurcation. Near and far wall of the artery were visualized simultaneously. Gain settings were adjusted to optimally visualize the artery walls to measure CIMT. If images were not horizontal, ‘heel-toe’ motion of the transducer was performed to realign images.3 All scans were performed by two single-blinded sonographers, who both scanned each segment twice. Three-to-five beat cine-loop videos were captured and stored for later offline assessment of CIMT.

READING PROCEDURE
CIMT was measured over a length of 10 mm at the far wall of the CCA in a single, automatically selected frame. Analysis of the images was performed by the two operators previously mentioned. Semi-automated edge-detection software (Arterial Analysis™, Version 3.001; Samsung Medison, Seoul, Korea) was applied on the images to obtain mean and maximum CIMT (mm) values. CIMT was defined as the distance between the lumen-intima and media-adventitia interface.3

STATISTICAL ANALYSIS
Baseline characteristics in the three age groups were assessed. Depending on the distribution of the variable, Kruskal-Wallis and Chi-square tests were used to calculate median values and frequencies respectively. Differences between groups in mean and maximum CIMT (mm) of the left and right CCA were initially analyzed by Kruskal Wallis tests to assess a potential relation between groups. Subsequently, linear regression analyses were performed to evaluate the association between age and CIMT. Gender was included as covariate in the adjusted model. A two-tailed p ≤ 0.05 was considered statistically significant. Data analysis was conducted using IBM SPSS Statistics 22.0.
Furthermore, we observed larger variability in CIMT values with increasing age, which may indicate that inter-individual variability in atherosclerotic burden increases in older adults. Therefore, it is likely CIMT could aid in discriminating between older adults at low risk and at high risk for CVD. However, further research is needed to confirm this.

Multiple studies have examined the association between age and CIMT. However, in most studies CIMT was examined in patients with major CV risk factors or clinical CVD. Few studies examined the association between age and CIMT in adults free from CVD. This study has the strength of exclusively including participants with very low CV risk. This way, solely the effect of age on CIMT can be observed and potential bias of CV risk factors is eliminated.

Our study was limited by the small number of participants in each age group. Therefore, outliers might have influenced our results. However, the large observed effect size indicates that the small study population did not significantly influence our conclusions. We only scanned the CCA and did not include CIMT measurements in the carotid bifurcation. Atherosclerosis initially develops in bifurcations and measuring CIMT in the carotid bifurcation may therefore be worthwhile. However, the carotid bifurcation is generally difficult to visualize, which could lead to poor-quality images. Therefore, it might be hard to accurately measure the corresponding CIMT. In our study, good-quality images of the CCA were obtained in every participant.

Furthermore, it is generally difficult to visualize, which could lead to poor-quality images. Therefore, it might be hard to accurately measure the corresponding CIMT. In our study, good-quality images of the CCA were obtained in every participant.
Measured values of CIMT were therefore valid and reliable.

According to traditional CV risk stratification scores, every older adult ≥ 70 years has the same high CV risk solely based on their age and should be treated with preventive drugs, independent of other CV risk factors and regardless of their atherosclerotic burden. This might lead to overtreatment, which especially tends to occur in low risk elderly. This may be harmful, especially in those who are frail. In our study, variability in CIMT values increased with age, indicating large inter-individual variability in atherosclerotic burden in older adults. Based on CIMT values, older adults might therefore be categorized into more vascular fit and more vascular frail. We believe that CIMT, combined with information on traditional CV risk factors, could aid to identify older adults at low risk of CVD. This may be useful in deciding which patients without traditional CV risk factors, are unlikely to benefit from using preventive medication such as lipid-lowering or antihypertensive drugs. Further research is needed to assess whether using CIMT to discriminate older adults at low risk leads to positive outcomes in elderly who might be prevented from statin therapy.

In conclusion, CIMT measured by non-invasive ultrasound increases with age. This is in line with traditional risk classification scores in which age is the most dominant driver of CV risk. As a marker for subclinical atherosclerotic disease, CIMT could provide information on a patient’s vascular age. In older adults without other traditional CV risk factors, CIMT could be useful in discriminating between those who are and those who are unlikely to develop CVD. This way, older adults who are presumably unlikely to benefit from preventive treatment can be identified. This might lower overtreatment in these older adults. Prospective studies are needed to determine if CVD risk management incorporated with CIMT measurements improves long-term CVD outcomes in elderly.

REFERENCES

A 69-YEAR-OLD WOMAN WITH CHEST PAIN AND SYNCOPE
A. Leemeijer, J. ten Kulve

CASE
A 69-year-old woman, with a medical history of myocardial infarction and hypertension, visits the doctor with the following symptoms: fatigue, confusion, chest pain and syncope. These symptoms occur a few times a week. Ambulatory ECG monitoring for two weeks was indicated. During her symptoms the ECG shows the following:

QUESTION
Which diagnosis should be considered?

a. Atrial fibrillation
b. Third-degree atrioventricular (AV) block
c. Sick sinus syndrome
d. Bradycardia

ANSWER ON P. 36
Geriatric medicine has always fascinated me. I wanted to gain more experience with complex cases of the growing population of the elderly with comorbidities and polypharmacy. Therefore, I decided to pursue my last medical internship at the geriatric medicine department. Evaluating my first patient I realized how easy it is for a (soon to be) doctor to think a patient current medication would not need any alternations. After all, all drugs are all prescribed for a reason. As you would figure, I was naïve too. When I discussed the first patient with my supervisor I was confronted with the question: “What is the indication to continue this drug?” To be honest, I had no idea. I knew what the indications were of certain drugs, but I did not look into the indications for which this specific drug was prescribed to this patient. It seemed quite straightforward to me: this patient had pregabalin, marketed under the brand name Lyrica, so she was probably suffering from neuropathic pain.

Soon I realized you cannot get away with assumptions, as doctors it is our duty to provide medical care and be critical about the care we provide. This patient was not suffering from neuropathic pain anymore and removing pregabalin from her medication list did not result in recurrence of pain. I should have evaluated whether pregabalin was still indicated for this patient. During my internship, I saw many more elderly patients on pregabalin, a drug with side effects such as sedation, sleepiness, dizziness and headaches and can therefore increase the risk of falling. It should be noted, evaluating the effect of starting or discontinuing a drug can be challenging during hospital admission, because it can be time consuming. Also, once the elderly patient is familiar to certain drug, it can be hard for them when you change the routine of taking it. Patients themselves often do not realize that at some point continued drug use at older age can lead to more side-effects. For instance, hydrochlorothiazide, an antidiuretic drug which was once perfectly tolerated, could lead to electrolytic imbalance based on changes in pharmacokinetics in ageing patients.

I think I secretly thought the widely-known phenomenon of polypharmacy in geriatric medicine was just an exaggeration. Later on in my internship, I was not so naïve anymore. I became more critical when it came to polypharmacy and eagerly tried to find the most optimal medication scheme for my patients. This has been a great experience and great lesson, now knowing that polypharmacy is more underestimated than exaggerated. I will preserve my newly-gained critical approach, as it is my duty as a soon to be doctor, health promoter and academic.
**BACKGROUND**

The performance of activities of daily living (ADL) at home is important for the recovery of older individuals after hip fracture. However, 20-90% of these individuals lose ADL function and never fully recover. Although exercise interventions have been proven to improve physical function, especially elderly do not seem to benefit from these interventions. In this prospective, stepped-wedge randomized controlled trial, care as usual (CaU) is compared to 1) occupational therapy (OT) with coaching based on cognitive behavioural treatment (CBT) (OTc); and 2) OT-CBT with sensor monitoring embedded (OTcsm). More specifically, during 12 months, six nursing homes will start with providing CaU, then cross over to provide OTc and finally cross over to provide OTcsm. The timing of crossing over is randomized: two nursing homes will cross over for the first time after two months, two after four months and the last two after six months. OTc will always be provided for 4 months, CaU for two, four and six months respectively, and OTcsm for six, four and two months. The primary outcome measure, perceived daily functioning, is measured 6 months after start of rehabilitation and compared to baseline functioning.¹

**QUESTION**

Why would a stepped-wedge design be chosen over an ordinary randomized controlled trial?

**ANSWER**

Randomized controlled trials (RCTs) are considered to be the most reliable form of scientific evidence. Ideally, each individual participating in the trial is randomized to receive one of the treatments. However, especially in geriatric research in nursing homes, individual randomization is difficult and may introduce bias. Therefore, (wards of) nursing homes are generally randomized to treat all their inhabitants with one of the treatments. This is called cluster randomization. In a stepped-wedge RCT, the new treatment is rolled out sequentially over multiple time points, and usually the crossover from one treatment to the other is in one direction (from care as usual to new). Of note, in both a stepped-wedge RCT and a cluster RCT, participants are usually not blinded for the treatment, as is the case in the paper of Pol et al.¹, and therefore could be at risk of selection bias.

Now that we set the terminology, let’s look at differences between an ordinary (cluster) randomized controlled trial and a stepped-wedge randomized controlled trial. The first advantage of a stepped-wedge design is that it allows for phased introduction of the intervention. This is especially important when an intervention has been proven effective on subject level, but it is still under investigation whether implementation on population level is effective. By the end of the trial all clusters will apply the new treatment. When the clusters are relatively heterogeneous (for example a nursing home in urban environment versus a nursing home in rural environment), the stepped-wedge design will have more statistical power than an ordinary cluster RCT. In one nursing home participants received either care as usual or new treatment (depending on the cross-over time), so each intervention group also has a control group in the same nursing home.

These are the two important differences between a cluster RCT and a stepped-wedge RCT. So, my answer to the question would be: I think for this specific trial, the stepped-wedge design was chosen over a cluster RCT because of the heterogeneity of the clusters. Nursing homes in the Northwest and Midwest part of the Netherlands would participate, covering both rural and urban parts of the Netherlands.

One last remark, on the statistics of stepped-wedge RCTs: in a stepped-wedge design, all clusters are exposed to the new treatment at end of the study so that its effect might be confounded with an underlying time trend. Therefore, the analysis of a stepped-wedge RCT should always consider confounding of time (which is not needed in a cluster RCT).

**REFERENCES**


**FIGURE 1**

Table showing the timing of crossing over in a stepped-wedge design. Each nursing home starts with care as usual, then crosses over to provide OTc for two months, OTcsm for four months, and OTcsm for six months. The timing of crossing over is randomized.

<table>
<thead>
<tr>
<th>Month</th>
<th>NH1</th>
<th>NH2</th>
<th>NH3</th>
<th>NH4</th>
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<td>3-4</td>
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<td>5-6</td>
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<td>9-10</td>
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<td>11-12</td>
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**HIGHLIGHTED RANDOMIZED CONTROLLED TRIAL (RCT):** A clinical trial, in which participants are at random allocated to either receive a new treatment (intervention group) or no/standard treatment (control group). The random allocation minimises selection bias, and any differences between the two groups are due to change. An RCT is considered the gold standard to prove efficacy of a new treatment.

**STATISTICAL TERMINOLOGY**

- **Randomized controlled trial (RCT):** A clinical trial, in which participants are at random allocated to either receive a new treatment (intervention group) or no/standard treatment (control group). The random allocation minimises selection bias, and any differences between the two groups are due to change. An RCT is considered the gold standard to prove efficacy of a new treatment.

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**Read a paper, but question (or do you have a question regarding) the statistical methodology? Let us know via www.AMSj.nl!**
OSTEOPOROSIS SCREENING AFTER A BIKE FALL

J. Opperman & M. Maas

PATIENT DATA
- Age: 62
- Gender: female
- Ethnicity: Caucasian
- Medical history: fallen off her bike, 6 months ago. Suffered a distal radius fracture.
- Initial presentation: since a low energy trauma caused a fracture, the patient is screened for osteoporosis.

CHECKLIST DEXA-SCAN LUMBAR SPINE AND PROXIMAL FEMUR
1. Patient information: age, sex, ethnicity
2. Appropriate positioning:
   a. Centred vertebrae
   b. Femur straight in 20° internal rotation.
3. Analysis of the image
   a. Regions of interest:
      Lumbar spine: correct numbering of vertebral bodies; exclusion of altered vertebrae; inclusion of at least two vertebral bodies
      Proximal femur: greater trochanteric notch as landmark; lesser trochanter not visible
4. Interpretation of T-scores and estimation of fracture risk

RADIOLOGY IMAGE

FIGURE 1 DEXA of the lumbar spine

FIGURE 2 DEXA of the proximal femur

FIGURE 3 Lateral view of lower spine

FIGURE 4 Lateral view of lower spine with VFA
Question 1: What is the diagnosis?
A. Osteopetrosis
B. Osteopenia
C. Osteomalacia
D. Osteoporosis

Hint: in which range are the vertebral T-scores located?

Question 2: What condition may overestimate BMD on DEXA?
A. Scoliosis
B. Hyperparathyroidism
C. Degenerative changes
D. Lumbar laminectomy

Hint: think of what increases or decreases BMD.

Question 3: Which anomaly is visible on the VFA-image?
A. Wedge fracture
B. Biconcave fracture
C. Crush fracture
D. None

Hint: identify and compare the vertebrae.

Question 4: Which treatment is indicated for this case?
A. Life-style interventions
B. Bisphosphonates
C. Supplementation of vitamin D3 and calcium
D. Selective Estrogen Receptor Modulators

Hint: which therapy directly influences bone metabolism?

REFERENCES

ANSWER ON P. 37

PUTTING BEDREST TO REST
T. Kortlever, N. Rol

In the previous century, bedrest was often used as a therapy by itself. The ancient Greeks prescribed it, as did clinicians in the late 19th century until the Second World War. Back then, a myocardial infarction required patients to lie down for four weeks.

The logistic challenges of the Second World War changed the paradigm. Hospitals full of wounded soldiers had to make room for the most wounded, thus mobilising patients earlier than usual. Clinicians noted that this improved outcomes. Additionally, studies carried out in preparation for space missions demonstrated muscle loss and functional decline in immobile subjects. Since then, detrimental health effects of immobilisation have been reported for almost any organ in the human body. Myocardial damage, postural hypotension, atelectasis, higher rate of pulmonary and urinary tract infections, thrombosis, sarcopenia, reflux disease, constipation, diverticulitis and numerous other effects are associated with prolonged bedrest.

This insight has shaped current practice: the use of physiotherapists and enhanced ambulatory care are examples of measures implemented throughout modern medicine. However, while the importance of mobilisation is undeniable, health institutions are still designed primarily around the bed. Further measures, for example altered ward designs, may be introduced to promote patient mobility and further reduce adverse health effects in an increasingly sedentary, obese and aging society.

REFERENCES
THE EFFECT OF AGE ON THE PREDICTIVE VALUE OF CEREBROSPINAL FLUID BIOMARKERS FOR DIAGNOSING UNDERLYING ALZHEIMER’S DISEASE IN MILD COGNITIVE IMPAIRMENT, A SYSTEMATIC REVIEW

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2 Alzheimer Center, Department of Neurology, VU University Medical Centre, Amsterdam Neuroscience, Amsterdam, the Netherlands

INTRODUCTION
The worldwide prevalence of Alzheimer’s disease (AD) will quadruple by the year of 2050 to 106.2 million patients worldwide.1 Mild cognitive impairment (MCI) is an intermediate stage between normal cognitive function and dementia. MCI can have different underlying causes. It can be caused by AD (called pre-dementia stage of AD), but can also have other (non-neurodegenerative) causes.2 Patients with MCI have an increasing probability of progressing to dementia due to AD. Around 25% of patients diagnosed with MCI will develop dementia due to AD in 5 years.3,4 For both clinicians and patients, it is relevant to know if they have underlying Alzheimer’s disease or not.

Cerebrospinal fluid (CSF) biomarkers can identify the presence or absence of underlying AD cause.5 Amyloid beta 1–42 (AB42) reflects cortical amyloid deposition, total tau (T-tau) and phosphorylated-tau (P-tau) correlate with neuronal degeneration.5,6 These three biomarkers have a high sensitivity and specificity to discriminate between dementia due to AD from controls, as well for the discrimination between stable MCI patients and patients who progressed to dementia due to AD.5,6 However, decrease in AB42, and increase in T-tau and P-tau is also associated with an increasing age. This is why some studies recommend age related cut-offs for different CSF biomarkers to increase the diagnostic value.7 Clinical guidelines such as the International Working Group (IWG) and the National Institute of Aging Alzheimer’s Association (NIA-AA) are unfortunately inconclusive, which might cause clinicians to be reluctant to use CSF biomarkers for prognostic in elderly MCI patients.8,9 The vulnerability of CSF biomarkers to age effects is important for several reasons. First, the diagnostic performance could be different for patients above 75 years of age in comparison with younger patients. Secondly, because the vast majority of patients with Alzheimer’s disease are older than 75 years.10

In this systematic review, the aim was to determine whether the prognostic performance between stable MCI (sMCI) and progressive MCI (pMCI) of CSF biomarkers is influenced by increasing age. To clarify the effect of age, relevant articles were collected by searching on different medical databases and use different inclusion and exclusion criteria. The hypothesis, based on the literature, was that the discriminative performance between stable MCI and progressive MCI, will decrease with increasing age.

METHODS
SEARCH STRATEGY AND SELECTION CRITERIA
A systematic search was conducted to identify relevant studies investigating associations between ‘CSF biomarkers’, ‘Mild Cognitive Impairment’, Age and ‘Diagnostic Performance’. The keywords were used to search on PubMed, Web of Science, Cochrane Library, Karger and Embase. The search was broadened using different Medical Subject Headings (Mesh) terms to broaden the search. The final combined search can be found in the supplementary data. Two relevant PhD thesis manuscripts were added in the literature search.

DATA COLLECTION
A single reviewer made the search string,
examined and identified the articles. A total list of inclusion and exclusion criteria along with the search queries can be found in Table 1.

RESULTS

SELECTION OF STUDIES

A total of 418 study titles and 166 abstracts were screened, 43 papers were assessed for eligibility of which six were included in the review. The number of inclusions and exclusions at each stage can be found in the PRISMA flowchart (Figure 1). Three inclusions were derived through PubMed 14, 15, 17 and two through Embase. 18, 19 The reference lists of the included papers and other articles published by the same author as an already included article were searched for relevant publications, with no result. All patient population/databases of the included articles were checked to filter out duplicates. This process resulted in 5 papers for inclusion in this review.

MAIN CHARACTERISTICS OF INCLUDED STUDIES

Main study characteristics can be found in Table 2. Studies used different age cut-off points. Some used dichotomous age groups and other used more categories. The number of people in each study ranged from 155 to 1583, with a range of mean age between 69 to 74 years (age range min-max 43-89). In total the five studies consisted of 2254 patients.

TABLE 2 Main characteristics of included studies.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>N</th>
<th>Mean age (range)</th>
<th>Age cut-off</th>
<th>Biomarkers</th>
<th>Study design</th>
<th>Effect of age</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caroli, A et al. (2015)</td>
<td>188</td>
<td>71 (58-85)</td>
<td>&lt; 75&lt;br/75+</td>
<td>AB42</td>
<td>Cohort</td>
<td>Yes</td>
<td>Predictive for progression in early-onset</td>
</tr>
<tr>
<td>Hampel, H. et al. (2004)</td>
<td>155</td>
<td>73 (55-87)</td>
<td>No age cut of used</td>
<td>AB42&lt;br/T-tau&lt;br/P-tau</td>
<td>Cohort</td>
<td>No</td>
<td>Discriminative power did not change with age</td>
</tr>
<tr>
<td>Mattson, N. et al. (2012)</td>
<td>1583</td>
<td>71 (43-89)</td>
<td>≤ 64&lt;br&gt;65-74&lt;br&gt;≥ 75</td>
<td>AB42&lt;br/T-tau&lt;br/P-tau</td>
<td>Cross-sectional</td>
<td>Yes</td>
<td>Discrimination accuracy between MCI progression and stable MCI and between AD and controls decreases with age</td>
</tr>
<tr>
<td>Schmand, B. et al. (2012)</td>
<td>175</td>
<td>74 (67-82)</td>
<td>&lt; 75&lt;br&gt;75+</td>
<td>AB42&lt;br/T-tau&lt;br/P-tau</td>
<td>Cohort</td>
<td>Yes</td>
<td>Biomarkers lose potential to predict conversion MCI to AD in older patient group</td>
</tr>
<tr>
<td>Vos, S. et al. (2012)</td>
<td>153</td>
<td>69 (61-78)</td>
<td>&lt; 70&lt;br&gt;70+</td>
<td>AB42&lt;br/T-tau</td>
<td>Cohort</td>
<td>No</td>
<td>Biomarkers changed with age but the progression to AD was not differed in the two groups</td>
</tr>
</tbody>
</table>

DISCUSSION

In this review, the effects of age on the discriminative performance of AB42, increased t-tau and p-tau between stable and progressive MCI patients were investigated. Three out of the five articles found an age-related difference in discriminative power between stable MCI and progressive MCI. Overall, discriminative power of the three-core cerebrospinal fluid biomarkers decreased with age.

The three studies that reported a decrease in discriminative power between MCI and progressive MCI all supported their results with ROC curves. 14, 15, 17 AUC decreased with age for all biomarkers. One study focussed alone on CSF AB42 17, and the other two focussed on all three core biomarkers. All articles have ‘the effect of age on core biomarkers’ as primary outcome and their study focussed on examining the effect of age. Two studies did not find an age related discriminative difference. 17, 18 They both focussed on AB42 and T-tau. Their primary outcome is focussed on identifying the best diagnostic test for predicting AD dementia in subjects with MCI using CSF. The effect of age is a secondary outcome. Hampel et al., used multiple Cox proportional Hazard models to calculate the effect of age and the other study repeated analyses for predictive accuracy using age-adjusted cut-offs (< 70 vs. > 70 years). 17 The studies that found a difference in discrimination used ROC curves. This varied from the studies that found no age-related difference. One could conclude that the articles do not weigh equally because some studies have age as a secondary outcome. The results tend more towards a decrease in diagnostic performance for patients older than 75 years.

A lot of research is conducted into discriminative power of core CSF biomarkers, but only a few studies stratified for age. To the best of our knowledge, no systematic review was ever conducted into the effect of age on diagnostic performance of the core biomarkers. A thorough investigation was performed to include the limited amount of studies that do stratify for age. This search was performed on different

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research written in English</td>
<td>Research used the same patients/data-base as another (already included) article</td>
</tr>
<tr>
<td>Patients diagnosed with Alzheimer’s disease or mild cognitive impairment</td>
<td>Patients who have not been diagnosed with Alzheimer’s disease but with a different form of dementia</td>
</tr>
<tr>
<td>Patients included in the studies are older than 55 years of age</td>
<td>Article published before 1996-1996</td>
</tr>
<tr>
<td>Usage of one of three following CSF biomarkers: amyloid beta 1-42 (AB42), total tau (T-tau) or phosphorylated tau (P-tau)</td>
<td></td>
</tr>
<tr>
<td>Mention the diagnostic performance of core CSF biomarkers or use a synonym for ‘diagnostic performance’ (for example: ‘prognostic value’, ‘prognostic assessment’, ‘diagnostic accuracy’, ‘sensitivity and specificity’)</td>
<td></td>
</tr>
<tr>
<td>Discriminating outcome between younger and older patients</td>
<td></td>
</tr>
<tr>
<td>Only human studies</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 1 Inclusion and exclusion criteria
online databases. All included studies used a large sample size, this strengthens the conclusions drawn. There are several limitations to this review. All titles, abstracts, and full-text articles were reviewed by a single reviewer. The lack of two independent data extractors could form an inclusion bias.

Furthermore, most research is conducted in relatively young patients, even while most demented patients are older than 75 years. The age gap between patients in clinical studies and the general population may result in a bias. The conclusions drawn from research could be invalid for 75+ patients. This limitation is also present in this review. The mean age of the included articles is around 70 years (range 65-74), but the oldest included patient is ‘only’ 89 years old. No research is done above the age of 89 and results may differ for patients above 90 years. Finally, almost all studies used different cut-offs for when biomarkers were pathologic. This is still a bottleneck for both the International Working Group (IWG) and the National Institute of Aging Alzheimer’s Association (NIA-AA). Although many studies have shown a high diagnostic accuracy, the variations between clinics is high.24,25 The use of different cut-offs may lead to different diagnoses.

The lack of a universal test in combination with between-laboratory variations prevents the authorities from setting a specific cut-off that works for all clinics. Additionally, there is still no consensus as to which specific combination of CSF core biomarkers has the greatest utility in AD diagnosis.26

In summary, CSF biomarkers can discriminate between healthy controls and Alzheimer’s disease and stable and progressive MCI. The core biomarkers can play a vital role in finding the right patients, even before cognitive decline is noticeable. Till this day, the loss of predictive potential with increasing age is not considered when core CSF biomarkers are examined in clinics in Europe. The absence of an age-related cut-off leads to a lower sensitivity and specificity. This may cause a profound effect, especially while most patients with AD are above the age of 75. CSF biomarkers change during life span and AD-like biomarker profile are more frequently seen in cognitive healthy elderly above the age of 75 years. This review found a trend that the discriminative power decreases with an increasing age, both between stable MCI and progressive MCI. Age must be considered when assessing CSF biomarkers in a clinic to counter the effect, or even better, use age-specific cut-offs for the core CSF biomarkers.

REFERENCES

In addition, the bidirectional orientation of this table can be used to look up cumulative cancer risks between two older ages, e.g., an 70-year old male has an 25.2% risk to be diagnosed with any cancer before his 80th birthday. One can see that the cumulative cancer risks increase most rapidly in the seventh and eighth decade of life. Knowing that with an aging population, the absolute increase in population demographics is highest in the age group of 65 to 85 years, it is not surprising to see the incidence of cancer rising so rapidly.

REFERENCES
2. Integrale Kankerregistratie Nederland (IKNl), www.cijfersoverkanker.nl, accessed on 12 July 2017

ANSWERS
A. Leemeijer, J. ten Kulve

a. Atrial fibrillation

This is not the correct answer. Atrial Fibrillation is characterized by an increased rate of P-tops and as seen on the ECG. Not every P-top is followed by a QRS-complex. In the ECG of our patient, every P-top is followed by a QRS-complex.

b. Atrioventricular (AV) block

This is not the correct answer. An AV block is also referred as a complete heart block, since there is no conduction through the AV node. The illustrative ECG starts with a P-top followed by a QRS-complex. Hereafter it shows a total AV block: several P-tops in a regular rate, but without a QRS-complex following.

c. Sick sinus syndrome

This is the correct answer. A sick sinus syndrome (SSS), also known as the bradycardia-tachycardia syndrome, is characterized by a sinus node dysfunction. SSS consists a group of signs or symptoms that indicate the sinus node is not functioning properly. A person with SSS may have a heart rhythm that is too slow, too fast or alternates between the fast and slow rhythm. ECG: The rhythm is both tachycardic and bradycardic with a pause during alternation. Besides, every P-top is followed by a QRS-complex!
Symptoms: Patients present with fatigue, syncope, pain on the chest, palpitations, slower pulse, confusion, disturbed sleep and dyspnoea. Risk factors for a SSS are older age, history of a myocardial infarction, medication for hypertension and heart surgery. Therapy: Risk factors are treated and, since the pacemaker cells in the sinus node are ineffective, a pacemaker is recommended to maintain a proper heart rhythm.

d. Bradycardia

This is not the correct answer. Bradycardia is a normal sinus rate, but with a frequency less than 60 bpm. In bradycardia, the rhythm is not altered by faster heart rhythms.
compression in DEXA-scanning. A vertebral fracture is defined as a decreased vertebral height of ≥40% on VFA (see fig. 4). VFA can aid in identifying patients with non-deviant BMD measures who would otherwise not qualify for osteoporotic treatment. To prevent future fractures in postmenopausal women or other high-risk patients, bisphosphonates (alendronate or risendronate) are the treatment of first choice.\(^4\)

Acknowledgements to Z. Cheung, resident nuclear medicine.

The diagnosis is based on the lowest T-scores of the lumbar spine (L1-L4) and femoral neck. In case of degenerative changes of the lumbar spine or bilateral total hip replacement, the distal radius may be used. In this case, T-scores are -3.6 and -2.5 for the lower spine and left femoral neck, respectively. Therefore the diagnosis osteoporosis can be confirmed. Note that also the lesser trochanter is visible which may overestimate the actual BMD.\(^2\)

Additionally, DEXA-scanning is indicated in patients older than 60 years with increased fracture risk. This risk is expressed as a score ≥4 points on the Fracture Risk Assessment Tool (FRAX\(^\text{®}\), see QR). This tool includes factors such as age, gender, previous fractures, smoking and steroid use.

Of all osteoporotic fractures, vertebral fractures in particular are often misdiagnosed as the clinical presentation can be aspecific or do not give clinical symptoms at all. Meanwhile, vertebral fractures are predictive for future fractures – independent of the BMD \(^{1}\).\(^3\) VFA is a special software which calculates the degree of vertebral

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**EXPLANATION OF THE IMAGES**

Dual-energy x-ray absorptiometry (DEXA) is a quantitative imaging technique used to measure bone mineral density (BMD) in the diagnosis and treatment of osteopenia and osteoporosis. The WHO classification of decreased BMD is defined by T-scores, being the standard deviation (SD) by which the BMD differs from that of a young adult reference population. A T-score of ≥ -1 is considered as normal, a score ≤ -1.0 as osteopenic and a score of ≤ -2.5 as osteoporotic (at any skeletal site). This definition is applicable to postmenopausal women and men above their 50’s. With each SD decrease of BMD, the fracture risk is doubled.\(^1\)

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**COLOPHON**

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