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Research Article

# Cardiovascular disease is associated with activity limitations in osteoarthritis patients

**Visman IM*[1], Van den Oever IAM[1], de Rooij M[2], Roorda LD[2], Lems WF[1,3], Nurmohamed MT1,3, Dekker J[2,4,5], Van der Leeden M[2,4] & Van der Esch M[2,6]**

[1]Amsterdam Rheumatology and Immunology Center | Reade, Amsterdam, Netherlands

[2]Amsterdam Rehabilitation Research Center | Reade, Amsterdam, Netherlands

[3]Amsterdam Rheumatology and Immunology Center | Reade, VU University Medical Center, Amsterdam, Netherlands

[4]Department of Rehabilitation Medicine/ Amsterdam Public Health Research Institute, VU University Medical Center, Amsterdam, Netherlands

[5]Department of Psychiatry, VU University Medical Center, Amsterdam, Netherlands

[6]University of Applied Sciences, Amsterdam, Netherlands

*Author for correspondence:
i.visman@reade.nl

Background: To investigate the associations between Cardiovascular Disease (CVD) and Cardiovascular (CV) risk factors with activity limitations in patients with knee or hip Osteoarthritis (OA).

Methods and Findings: Consecutive patients were included from the Amsterdam Osteoarthritis cohort. A questionnaire assessed CVD and its risk factors and subsequently were confirmed by medical file review. The WOMAC-physical functioning subscale (PF), stair-climb tests and the Get Up and Go (GUG) were used to assess activity limitations. The associations of CVD and CV risk factors with activity limitations, adjusted for sex, age and disease severity were calculated using regression analyses. CVD was reported by 64 out of 447 patients (14%); 32 out of 148 men (22%) and 32 out of 299 women (11%). CV risk factors were reported in 9% (smoking) to 82 % (overweight) of the patients. CVD and the CV risk factors hypertension, hypercholesterolemia, diabetes mellitus and obesity were associated with a worse performance score on the GUG and stair-climb test. Women with CVD took 51% longer on the Get up and Go test (16.0 *vs.* 10.6 seconds). Both men and women with CVD performed significantly worse on the stair climb descent test (6.8 *vs.* 5.3 for men, and 11.3 *vs.* 7.1 for women).

Conclusions: Patients with knee or hip OA show more activity limitations in association with CVD or CV risk factors. An intervention approach to improve daily functioning in the subgroup of patients with knee or hip osteoarthritis tailored to these patients' CVD and CV risk factors is warranted.

**Keywords:** cardiovascular • osteoarthritis • diabetes mellitus

## Introduction

Osteoarthritis (OA) of the knee or hip is associated with Cardiovascular Diseases (CVDs) such as coronary heart diseases, cerebrovascular diseases, congestive heart failure and peripheral arterial diseases [1]. Patients with OA are also more likely to have the CV risk factors hypertension, hypercholesterolemia, Diabetes Mellitus (DM) and obesity with obesity as one of the most characteristic factors [1-5]. Obesity is a substantial component of the metabolic syndrome and associated with low cardiorespiratory fitness and activity limitations [6,7]. Knee or hip OA itself is also characterized by activity limitations [8,9]. However, reports on the relationship between CVD (and its risk factors) and activity limitations for patients with knee or hip OA are lacking.

Physical activity is recommended to reduce CVD risk factors and their consequences for the limitations of daily activities [10]. However, to improve physical activity, it is necessary to first understand the relationship between CVD and CV risk factors and activity limitations in OA patients. As a consequence, a more targeted intervention can be applied that takes into account both the OA characteristics and the CV risk factors in improving daily functioning.

The aim of this study was to investigate the associations of CVD and CV risk factors with activity limitations among OA patients, achieved by multivariable regression analyses with WOMAC-PF, stair-climb test and GUG as the dependent variables, and CVD as the independent variable, controlled for sex, age and disease severity (Kellgren/Lawrence score 2 or higher), making it possible to assess daily activity limitations for patients with knee or hip osteoarthritis.

## Materials and methods

### Study population

Data from consecutive patients enrolled in the Amsterdam Osteoarthritis (AMS-OA) cohort were used for this study. All patients were diagnosed with knee or hip OA in accordance with the American College of Rheumatology criteria [11,12] and referred to Reade, Centre for Rehabilitation and Rheumatology, Amsterdam, the Netherlands, an outpatient rehabilitation centre. Patients with other disease diagnostics, including inflammatory arthritis (e.g. gout,

Psoriatic Arthritis (PsA), Rheumatoid Arthritis (RA), or Ankylosing Spondylitis (AS)) were excluded. All patients provided written informed consent prior to inclusion according to the Declaration of Helsinki. This study was approved by the ethics committee of the Slotervaart Hospital/Reade (nr. U/2782/0851).

### Clinical and demographic characteristics

Physical examinations were performed by rehabilitation physicians or rheumatologists and the medical history was taken for each patient. A questionnaire about disease history, clinical and psychosocial factors related to OA, demographics, and medication use was completed by the patients. The Kellgren and Lawrence (K/L) grade was determined according to the Buckland-Wright protocol [13,14] by analysing weight-bearing, anteroposterior radiographs of the knees. The K/L grade was subsequently dichotomized as a score of less than <2 or 2 and higher. Physical examination included blood pressure, body height and weight. BMI was calculated (weight divided by squared height in kg/m$^2$). Co-morbidities were assessed with the Cumulative Illness Rating Scale [15].

### Activity limitations

The Dutch version of the Western Ontario and McMaster University Osteoarthritis Index physical function subscale questionnaire (WOMAC-PF) [16,17], the stair-climb test and the Get Up and Go (GUG) were used to assess activity limitations. The WOMAC-PF uses a 5-point scale answer to assess 17 items, with scores ranging between 0-68and lower scores indicate less activity limitations. The GUG test assesses the patient's ability to rise from a seated position, walk, and maintain balance by measuring the time (in seconds) a person requires to rise from a chair and walk fast as possible for 15.2 m [18,19]. With the stair-climb test, patients were timed separately in seconds as they ascended and descended, as fast as possible, a 12 step staircase with 16 cm high steps [20].

### Cardiovascular disease and CV risk factors

Self-reported CVD included coronary heart diseases, cerebrovascular diseases, congestive heart failure and peripheral arterial disease. Patients reported history of CVD, were confirmed by medical chart review of the cardiologist, vascular specialist, neurologist or general practitioner. This was done by the first two authors, who contacted the general practitioner or specialist to send information that confirmed the CVD diagnosis. ICD-9 codes were used to assign CVD on the basis of standardized criteria. Coronary heart diseases consisted of myocardial infarction, Coronary Artery By-pass surgery (CABG), Percutaneous Coronary Intervention (PCI), or angina pectoris. Stroke, transient ischaemic attack or carotid endarterectomy were included in cerebrovascular diseases. A peripheral arterial reconstruction or a history of peripheral arterial insufficiency were classified as Peripheral Arterial Diseases (PAD). In contrast, pericarditis, rhythm disorders, myocarditis or heart valve insufficiency were documented as other heart diseases but were not categorized as CVD.

Recorded (objectively confirmed) CV risk factors were BMI >25 kg/m$^2$ (i.e., overweight and obesity), hypertension (systolic blood pressure ≥140, diastolic blood pressure ≥90, use of antihypertensive drugs or diagnosis), hypercholesterolemia (use of statins or diagnosis), Diabetes Mellitus (DM) and smoking (current smoker or not).

### Statistical analysis

Variable distributions were tested for normality. Continuous, normally distributed and ordered data are presented as mean with Standard Deviation (SD). Median and Interquartile Range (IQR) were used for non-normally distributed data. Numbers and percentages were used for categorical data.

Unpaired t-tests or, its non-parametric equivalent, the Mann-Whitney U test or (for binary data) the Chi-square test, were used, when appropriate, to determine significant differences between patients with and without CVD. This was done for both the groups as a whole and for women and men separately.

Second, univariable regression analyses were utilized to assess the associations of CVD and CV risk factors (e.g. smoking, hypertension, hypercholesterolemia, BMI, and diabetes) with WOMAC-PF, stair-climb test or GUG test.

Thereafter, multivariable regression analyses were used with CVD as the independent variable, controlled for sex, age and disease severity (indicated as Kellgren/Lawrence score ≥ 2) and WOMAC-PF, stair-climb test and GUG as the dependent variables.

P-values <0.05 were considered statistically significant and SPSS version 24.0 was used for all analyses.

## Results

### Patient characteristics

In total, 447 consecutive patients with OA were

enrolled in this study. Of 64 patients with CVD three patients (5%) were unable to perform the stair climb test. In contrast, only one patient did not perform the get up and go test in the group of patients without CVD (n=383). Table 1 presents, per measurement, the number of included patients and their characteristics.

## Presence of cardiovascular diseases and CV risk factors

CVDs were reported by 64 out of 447 patients (14%), 32 out of 148 men (22%) and 32 out of 299 women (11%). A number of conditions were present in patients with CVD: coronary

**Table 1. Study group characteristics.**

| | Total population n=447 | men with CVD n=32 | men without CVD n=116 | women with CVD n=32 | women without CVD n=267 |
|---|---|---|---|---|---|
| Age, years (n=447) | 61 ± 9 | 66 ± 8 | 61 ± 10* | 66 ± 9 | 60 ± 9** |
| **Cardiovascular risk factors (n=447)** | | | | | |
| Body mass index, kg/m$^2$ | 30 ± 6 | 30 ± 6 | 29 ± 5 | 34 ± 6 | 30 ± 6** |
| Systolic blood pressure, mm/Hg | 144 ± 21 | 134 ± 19 | 144 ± 18* | 141 ± 14 | 145 ± 25 |
| Diastolic blood pressure, mm/Hg | 85 ± 10 | 79 ± 10 | 86 ± 8** | 82 ± 11 | 85 ± 12 |
| Overweight (body mass index >25), No (%) | 366 (82) | 28 (88) | 94 (81) | 32 (100) | 212 (79)** |
| Diagnosis hypertension, No (%) | 166 (37) | 18 (56) | 36 (31)* | 19 (59) | 93 (35)* |
| Diagnosis hypercholesterolemia, No (%) | 72 (16) | 10 (31) | 14 (12)* | 9 (28) | 39 (15) |
| Diagnosis diabetes mellitus type 1 or 2, No (%) | 50 (10) | 7 (22) | 13 (11) | 6 (19) | 23 (9) |
| Smoking, No (%) | 42 (9) | 1 (3) | 17 (15) | 1 (3) | 23 (9) |
| **Medication use (n=447)** | | | | | |
| NSAIDs, No (%) | 150 (34) | 10 (31) | 29 (25) | 10 (31) | 101 (38) |
| Gastroprotective drugs, No (%) | 96 (22) | 15 (47) | 21 (18)** | 14 (44) | 46 (17)** |
| Antihypertensive drugs, No (%) | 170 (38) | 25 (78) | 37 (32)** | 26 (81) | 82 (31)** |
| Cholesterol lowering drugs, No (%) | 96 (22) | 22 (69) | 19 (16)** | 16 (50) | 42 (16)** |
| Anticoagulant drugs, No (%) | 74 (17) | 20 (63) | 13 (11)** | 27 (84) | 14 (5)** |
| Oral antidiabetic drugs, No (%) | 39 (9) | 4 (13) | 12 (10) | 5 (16) | 18 (7) |
| Insulin, No (%) | 13 (3) | 2 (6) | 7 (6) | 0 | 4 (2) |
| **Disease characteristics** | | | | | |
| Duration of complaints < 1 year, No (%) (n=446) | 59 (13) | 2 (6) | 12 (10) | 5 (16) | 40 (15) |
| Duration of complaints > 5 years, No (%) (n=446) | 231 (52) | 16 (50) | 65 (56) | 15 (47) | 135 (51) |
| Radiographic Kellgren/Lawrence score ≥ 2, No (%) (n=405) | 282 (70) | 22 (73) | 90 (82) | 9 (43) | 161 (66) |
| **Activity limitations** | | | | | |
| Get up and go test, seconds (n=446) | 10.4 (9.1-13.2) | 10.4 (9.6-13.2) | 9.7 (8.4-11.1) | 16.0 (12.0-20.1) | 10.6 (9.1-13.2)** |
| Stair-climb time ascent, seconds (n=444) | 6.5 (5.0-8.5) | 6.6 (5.3-7.5) | 5.4 (4.3-6.7) | 9.9 (7.4-16.4) | 6.8 (5.3-8.7)** |
| Stair-climb time descent, seconds (n=444) | 6.8 (5.2-9.4) | 6.8 (5.3-9.9) | 5.3 (4.3-7.2)* | 11.3 (7.6-23.0) | 7.1 (5.6-9.7)** |
| **WOMAC-questionnaire (n=434)** | | | | | |
| WOMAC physical function (0-68) | 27.3 ± 13.0 | 25.2 ± 12.7 | 23.4 ± 12.8 | 29.8 ± 12.6 | 28.9 ± 12.8 |
| WOMAC stiffness (0-8) | 4.0 ± 1.9 | 3.9 ± 1.5 | 3.4 ± 1.9 | 4.2 ± 1.8 | 4.2 ± 1.9 |
| WOMAC pain (0-20) | 8.4 ± 3.9 | 7.4 ± 3.5 | 7.2 ± 3.7 | 8.9 ± 3.8 | 8.9 ± 3.9 |
| WOMAC total (0-96) | 39.6 ± 17.5 | 36.6 ± 16.1 | 34.0 ± 17.5 | 42.9 ± 16.7 | 41.9 ± 17.2 |

Results are presented as mean, standard deviation (SD), median and Interquartile Range (IQR) or number and percentage (%)
*p<0.05, **p<0.01=Significant differences between men with and without CVD and women with and without CVD.
List of abbreviations: CRP=C-reactive protein, CVD=Cardiovascular disease, ESR= erythrocyte sedimentation rate, NSAIDs=Non-steroidal anti-inflammatory drugs, OA=Osteoarthritis, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

heart disease (n=36, 8%), cerebrovascular accident (n=21, 5%), congestive heart failure (n=8, 2%), and peripheral arterial disease (n=4, 1%). Patients with confirmed CVD were significantly older. Patients with CVD had more diagnosis of hypertension, exhibited more anti-hypertensive drugs use and showed on average a significantly lower blood pressure (both mean systolic and mean diastolic) than non-CVD patients. These findings were more pronounced in men (Table 1). CVD patients had more diagnoses of hypercholesterolemia (30% *vs.* . 14%), overweight BMI (>25) (94% *vs.* . 80%), and DM (20% *vs.* . 10%). Patients with CVD used more gastro-protective drugs (45% *vs.* 18%), more statins (59% *vs.* 16%) and more anticoagulants (73% *vs.* 7%). Furthermore, a KL≥2 grade was observed in 61% of the CVD patients and in 71% of the non CVD patients.

### Associations between activity limitations and cardiovascular disease (and cardiovascular risk factors)

CVD was positively associated with a longer stair-climb test time and a longer GUG-test time. The CV-risk factors hypercholesterolemia, hypertension, and DM were positively associated with activity limitations (as measured by the WOMAC-PF, stair climb test and GUG test). Smoking (despite being a known CV-risk factor) showed no association with activity limitations (data not shown). The presence of CVD was not significantly associated with a more severe Kellgren/Lawrence score overall, although for women a trend was seen (p=0.055) towards less severe OA.

Table 2, shows the results of the various multivariable regression analyses with CVD. CVD was positively associated with a longer stair-climb test time (B=1.18, p<0.01 (ascending) and B=1.22, p<0.01(descending)) and a longer GUG test time (B=1.23, p<0.01), even after controlling for sex, age and Kellgren/Lawrence score.

## Discussion

The focus of this study with knee or hip OA patients was the association of CVD (and CV risk factors) and activity limitations. CVD was diagnosed in 14 % of patients. As expected, more men than women had CVD. CVD and most CV risk factors were associated with both self-reported and performance-based tested activity limitations. This may be due to lower aerobic fitness capacity for the patients with CVD, as a consequence of both CVD and its risk factors.

For patients with OA the cornerstone of treatment is exercise [21]. The results of this study imply that taking into account the presence of CVD in patients with OA is important, because patients with both OA and CVD perform less well on physical tasks. As a result, patients may be at risk of being under treated [1,22]. This cannot only be explained by worse cardiorespiratory fitness, but obesity or muscle weakness can also be more prevalent and can be associated with both OA and CVD. Moreover, patients with both CVD and knee or hip OA are often less suitable candidates for orthopaedic surgery, because the mortality and morbidity risk of CVD patients is considerably higher than in non-CVD patients with OA [23]. In addition, physicians may be more reluctant to prescribe pain medication, such as NSAIDs and glucocorticoids to patients with knee or hip OA and CVD. These medications are somewhat contra-indicated in patients with CVD, as these patients have an increased risk of hypertension, diabetes mellitus or kidney failure [24]. However, if these OA patients are

**Table 2. Uni and multivariable linear regression analyses of Cardiovascular Disease (CVD) on activity limitations in knee/hip OA patients, adjusted for sex, age and KL grade.**

| | WOMAC-PF | | Get up and go test | | Stair-climb test ascend | | Stair-climb test descend | |
|---|---|---|---|---|---|---|---|---|
| | B (95%CI) | *p* | B (95% CI) | *p* | B (95% CI) | *P* | B (95% CI) | *P* |
| Cardiovascular disease | 0.27 (-3.23-3.78) | 0.88 | 1.23 (1.12- 1.34) | <0.01 | 1.18 (1.03-1.35) | 0.01 | 1.22 (1.05-1.41) | 0.01 |
| Model I | | | 1.27 (1.16- 1.39) | <0.01 | 1.28 (1.13-1.46) | <0.01 | 1.34 (1.15-1.55) | <0.01 |
| Model II | | | 1.23 (1.12- 1.34) | <0.01 | 1.22 (1.07-1.39) | <0.01 | 1.24 (1.09-1.41) | <0.01 |
| Model III | | | 1.23 (1.12- 1.35) | <0.01 | 1.24 (1.09-1.41) | <0.01 | 1.28 (1.11-1.48) | <0.01 |

Results are shown as unstandardized regression coefficients B and 95% Confidence Intervals (CI).
WOMAC-PF=Western Ontario and McMaster University questionnaire physical function score (0-68), Get up and go and stair-climb tests in seconds.
Model I: Adjusted for sex; Model II: Adjusted for sex and age; Model III: Adjusted for sex, age and Kellgren/Lawrence score (≥2).

insufficiently treated with respect to their pain and activity limitations, it will be more difficult to improve physical activity and thus will remain at a higher CV risk. Physical inactivity is a known risk factor for CVD and the patients in our study with CVD experienced more activity limitations. The experience of more limitations in daily life can lead to more inactivity, creating a vicious circle process. This process may again facilitate the chance of CVD.

Some limitations as well as strong points in this study merit attention. A limitation of this study is that causal conclusions cannot be drawn due to the cross-sectional design of the study. Secondly, willingness to participate in the study of the patients with knee or hip OA included in the study might have influenced the results. Patients who were unable to complete the physical assessments were excluded in the AMS-OA cohort (as this was an exclusion criterion). This might result in an underrepresentation of patients with more severe activity limitations, weakening the strength of the associations found. In addition, a number of women with CVD were in too much pain or too weak to complete the physical fitness tests at all. This may lead to an underestimation of the association of CVD and its risk factors with activity limitations.

The relatively low number of patients with CVD might have been another reason for underestimation of the results. The patients with knee or hip OA in our sample were referred primarily due to their pain and activity limitations as a result of knee or hip OA and not due to the presence of CVD: many patients had high BMI, diabetes mellitus or heart disease. As a consequence, our findings reflect a representative clinical sample of patients with knee or hip OA in secondary care. Larger studies, however, with a focus on CVD and other comorbidities and their association with activity limitations are needed. The gathering of reliable data on comorbidities and clinically relevant limitations in daily activities is a strong point of our study. All CV events in our study were verified by general practitioners or specialists, as opposed to relying solely on self-reported CVD in questionnaires and this led to a more accurate identification of patients with CVD.

## Conclusion

Knee or hip OA patients show more observed activity limitations in the presence of CVD and CV risk factors. A patient tailored intervention approach for OA patients with CVD and CV risk factors is supported by these findings. This will help patients with OA and CVD to reach the same effects on daily functioning as knee and/or hip osteoarthritis patients without CVD and CV risk factors. Therefore, longitudinal intervention studies to examine the effects of specific exercise programs and cardiovascular risk management in OA patients are warranted, as are studies that include more females with CVD and CV risk factors to detect more subtle effects in women.

## Key messages

- Patients with a history of CVD and knee or hip osteoarthritis (OA) have more activity limitations and do not perform as well in the stair-climb test and get up and go test compared to OA patients without a history of CVD.
- Our findings support the need for more longitudinal studies in patients with knee or hip osteoarthritis to examine the effects of exercise and cardiovascular risk management on daily functioning, CVD and CV risk factors.

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### Competing and conflicting interests

The authors declare that they have no conflict of interests

## References

1. Hall AJ, Stubbs B, Mamas MA *et al.* Association between osteoarthritis and cardiovascular disease: Systematic review and meta-analysis. Eur *J. Prev. Cardiol.* 23(9), 938–946 (2016).
2. Berenbaum F, Griffin TM, Liu-Bryan R. Review: Metabolic regulation of inflammation in osteoarthritis. *Arthritis. Rheumatol.* 69(1), 9–21 (2017).
3. Ong KL, Wu BJ, Cheung BM *et al.* Arthritis: Its prevalence, risk factors, and association with cardiovascular diseases in the United States, 1999 to 2008. *Ann. Epidemiol.* 23(2), 80–86 (2013).
4. Hoeven TA, Leening MJ, Bindels PJ *et al.* Disability and not osteoarthritis predicts cardiovascular disease: A prospective population-based cohort study. *Ann. Rheum. Dis.* 74, 752–756 (2015).
5. Philbin EF, Ries MD, Groff GD *et al.* Osteoarthritis

as a determinant of an adverse coronary heart disease risk profile. *J. Cardiovasc. Risk.* 3(6), 529–533 (1996).

6. Meyers DA, Goldberg AP, Bleecker ML *et al.* Relationship of obesity and physical fitness to cardiopulmonary and metabolic function in healthy older men. *J. Gerontol.* 46(2), M57–M65 (1991).
7. Hulens M, Vansant G, Claessens AL *et al.* Predictors of 6-minute walk test results in lean, obese and morbidly obese women. *Scand. J. Med. Sci. Sports.* 13(2), 98–105 (2003).
8. Pisters MF, Veenhof C, van Dijk GM *et al.* Avoidance of activity and limitations in activities in patients with osteoarthritis of the hip or knee: A 5-year follow-up study on the mediating role of reduced muscle strength. *Osteoarthritis. Cartilage.* 22(2), 171–177 (2014).
9. Holla JF, van der Leeden M, Peter WF *et al.* Proprioception, laxity, muscle strength and activity limitations in early symptomatic knee osteoarthritis: results from the CHECK cohort. *J. Rehabil. Med.* 44(10), 862–868 (2012).
10. Lear SA, Hu W, Rangarajan S *et al.* The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet.* 390(10113), 2643–2654 (2017).
11. Altman R, Asch E, Bloch D *et al.* Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis. Rheum.* 29(8),1039–1049 (1986).
12. Altman R, Alarcon G, Appelrouth D *et al.* The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis. Rheum.* 34(5), 505–514 (1991).
13. Buckland-Wright JC, Bird CF, Ritter-Hrncirik CA *et al.* X-ray technologists' reproducibility from automated measurements of the medial tibiofemoral joint space width in knee osteoarthritis for a multicenter, multinational clinical trial. *J. Rheumatol.* 30(2), 329–338 (2003).
14. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann. Rheum. Dis.* 16(4), 494–502 (1957).
15. Parmelee PA, Thuras PD, Katz IR *et al.* Validation of the cumulative illness rating scale in a geriatric residential population. *J. Am. Geriatr. Soc.* 43(2), 130–137 (1995).
16. Bellamy N, Buchanan WW, Goldsmith CH *et al.* Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J. Rheumatol.* 15(12), 1833–1840 (1988).
17. Roorda LD, Jones CA, Waltz M *et al.* Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. *Ann. Rheum. Dis.* 63(1), 36–42 (2004).
18. Hurley MV, Scott DL, Rees J *et al.* Sensorimotor changes and functional performance in patients with knee osteoarthritis. *Ann. Rheum. Dis.* 56(11), 641–648 (1997).
19. Piva SR, Fitzgerald GK, Irrgang JJ *et al.* Get up and go test in patients with knee osteoarthritis. *Arch. Phys. Med. Rehabil.* 85(2), 284–289 (2004).
20. Rejeski WJ, Ettinger WH, Schumaker S *et al.* Assessing performance-related disability in patients with knee osteoarthritis. *Osteoarthritis. Cartilage.* 3(3), 157–167 (1995).
21. Fransen M, McConnell S, Harmer AR *et al.* Exercise for osteoarthritis of the knee: A Cochrane systematic review. *Br. J. Sports. Med.* 49(24), 1554–1557 (2015).
22. de Rooij M, van der Leeden M, Cheung J *et al.* Efficacy of tailored exercise therapy on physical functioning in patients with knee osteoarthritis and comorbidity: A randomized controlled trial. *Arthritis. Care. Res (Hoboken).* 69(6), 807–816 (2016).
23. Ashton CM, Petersen NJ, Wray NP *et al.* The incidence of perioperative myocardial infarction in men undergoing non cardiac surgery. *Ann. Intern. Med.* 118(7), 504–510 (1993).
24. Schmidt M. Cardiovascular risks associated with non-aspirin non-steroidal anti-inflammatory drug use. *Dan. Med. J.* 62, piiB4987 (2015).