

MULTIDIMENSIONAL FRAILTY INCREASES CARDIOVASCULAR RISK IN OLDER PEOPLE:

AN 8-YEAR LONGITUDINAL COHORT STUDY IN THE OSTEOARTHRITIS INITIATIVE

Nicola Veronese^{1,2}, Ai Koyanagi^{3,4}, Lee Smith⁵, Clarissa Musacchio², Lisa Cammalleri², Mario Barbagallo¹, Alberto Pilotto^{2,6}

1 Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, Palermo, Italy;

2 Department Geriatric Care, Orthogeriatrics and Rehabilitation, Frailty Area, E.O. Galliera Hospital, Genova, Italy;

3 Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, 08830 Barcelona, Spain;

4 ICREA, Pg. Lluís Companys 23, 08010 Barcelona, Spain;

5 The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK;

6 Department of Interdisciplinary Medicine, University of Bari, Bari, Italy.

Corresponding author: Dr Nicola Veronese, MD. Geriatric Unit, Dept. of Internal Medicine and Geriatrics, University of Palermo, Palermo, Italy. Viale F. Scaduto 6/c 90144 Palermo, Italy Tel. 0039-91-6552885 Fax: 0039-91-6552952. Email: nicola.veronese@unipa.it

HIGHLIGHTS

- Frailty is associated with higher CVD risk, even if the definition of frailty was made only using physical activity criteria.
- This the first study showing the multidimensional frailty is associated with a higher CVD risk.
- Our study reinforces the importance of CGA in predicting CVD risk in older people.

ABSTRACT

Background: Cardiovascular diseases (CVDs) are the most important cause of mortality and an important cause of disability. Frailty seems to be associated with higher cardiovascular risk, but limited research has been done using a multidimensional approach to frailty. Thus, the present study aimed to investigate whether the multidimensional prognostic index (MPI), based on comprehensive geriatric assessment (CGA), is associated with CVD risk in the Osteoarthritis Initiative (OAI) study.

Methods: Community-dwellers affected by knee OA or at high risk for this condition were followed for 8 years. A standardized CGA including information on functional, nutritional, mood, comorbidities, medications, quality of life and co-habitation status was used to calculate a modified version of the MPI (range 0-1), with higher scores representing greater risk of mortality. CVDs were recorded using self-reported information. Logistic regression analyses, adjusting for potential confounders, were conducted.

Results: The final sample consisted of 4,211 individuals (mean age 60.8 years, females=58.6%). People with incident CVD had a significant higher baseline MPI value than those without CVD (0.44 ± 0.17 vs. 0.39 ± 0.17). People with an MPI between 0.34 and 0.66 (OR=1.31; 95%CI: 1.03-1.67) and over 0.66 (OR=1.91; 95%CI: 1.26-2.89) experienced a higher risk of CVD (vs. MPI score <0.34). A 0.10 points increase in the MPI score at baseline was associated with a 1.16 (95%CI: 1.09-1.24) times higher odds for incident CVD.

Conclusions and implications: Higher MPI values at baseline were associated with an increased risk of CVD, reinforcing the importance of CGA in predicting CVD risk in older people.

Keywords: multidimensional prognostic index; comprehensive geriatric assessment; cardiovascular risk; cardiovascular disease; Osteoarthritis initiative.

INTRODUCTION

Frailty is typical in older people, with an estimated prevalence of 10% in community-dwellers.¹ Cardiovascular diseases (CVDs) have been found to be strongly associated with frailty. Research addressing this topic has suggested a bidirectional relationship between these two conditions.² In this sense, some CVD risk factors such as obesity³ and physical inactivity in healthy midlife⁴ are each associated with frailty. Furthermore, since frailty and CVD share some common pathways, e.g., low-grade inflammation and insulin-resistance⁵, recent epidemiological research proposed that frailty could be considered a potential CVD risk factor.⁶ However, to date, literature regarding frailty as a potential CVD risk factor has defined frailty using a the physical activity criteria, such as those proposed in the seminal paper of Fried et al.⁷ For example, in a systematic review and meta-analysis regarding frailty as a potential CVD risk factor, only three , out of 21 included studies, used a different definition of frailty⁶ than that proposed by Fried et al. ⁷

In particular, no study so far has explored the potential association between frailty, defined using a multidimensional approach, and CVD risk. According to the multidimensional model, the identification of frailty could be approximated by a comprehensive geriatric assessment (CGA), in particular, if a tool may convey information on several domains.⁸ The Multidimensional Prognostic Index (MPI)⁹ is a product of the CGA that leads to a multidimensional definition of frailty. MPI is a well-calibrated tool with a relevant discrimination and accuracy for short/long-term mortality, both in hospital¹⁰ and in primary care settings.¹¹ Among all indexes available in geriatric medicine for clinical-decision making, the MPI is the only index obtained from a CGA exploring comprehensively several domains, including health, functional, cognitive, and nutritional parameters, as well as social aspects, using standardized and extensively validated rating scales.¹² A large body of literature has shown that MPI is significantly and strongly associated with several negative outcomes in older

people, such as mortality and (re)hospitalization^{9,10,13-19}, but also other conditions, such as poor quality of life²⁰ and depression.²¹

However, to the best of our knowledge, no study has explored the relationship between MPI values and risk of CVD. Given this background, the present study aimed to investigate the association between MPI scores (at baseline) and risk of CVD in a large cohort of North American adults followed over 8 years, participating in the Osteoarthritis Initiative (OAI).

MATERIALS AND METHODS

Data source and subjects

Data from the Osteoarthritis Initiative (OAI) database were used for this research. The participants were included across four clinical sites in the United States of America (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. Inclusion criteria were: (1) had knee osteoarthritis (OA) with knee pain for a 30-day period in the past 12 months or (2) were at high risk of developing knee OA (e.g. overweight/obese (body mass index, BMI $\geq 25\text{kg/m}^2$), family history of knee OA).²² For the aims of this research, the data were collected at baseline and during the follow-up evaluations, with the last follow-up after 8 years. All participants provided written informed consent. The OAI study was given full ethics approval by the institutional review board of the OAI Coordinating Center, at the University of California in San Francisco.

Calculation of the MPI

The MPI was calculated as established in a previous study in the OAI.²³ Six domains were assessed by using standardized CGA scales: 1) physical functioning was assessed through the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index²⁴; 2) physical activity was measured through the Physical Activity Scale for the Elderly scale (PASE)²⁵; 3) nutritional aspects were evaluated using Body Mass Index (BMI); 4) comorbidity was assessed by the Charlson Comorbidity Index score²⁶; 5) the number of medications used; and 6) cohabitation status was reported, categorized as living alone (yes vs. no); 7) the assessment of depressive symptoms by using the Center for Epidemiologic Studies Depression Scale (CES-D)²⁷, and 8) quality of life assessed through a specific subscale of the Knee injury Osteoarthritis Outcome Score (KOOS).²⁸

This modified MPI, obtained as a weighted sum of each domain, ranged from 0.0 (low risk) to 1.0 (highest risk). Moreover, MPI was categorized into three different risk groups of CVD [low risk 0-0.33 (MPI group 1), moderate risk 0.34-0.66 (MPI group 2) and severe risk >0.66 (MPI group 3)], similar to the original division of this score.²⁹

Outcome: cardiovascular disease incidence

The main outcome of interest was the onset of CVD during the follow-up period of eight years. The presence of CVD was recorded through self-reported information. We defined the development of CVD as the presence of heart attack, heart failure, unclog or bypass arteries in legs, and stroke, cerebrovascular accident, or transient ischemic attack. The presence of CVD in the OAI was recorded, other than baseline, after 24, 48 and 96 months.³⁰

Covariates

Other than age and sex, we identified several potential confounders in the possible relationship between MPI and incident CVD. These included: (1) smoking habits, categorized as previous/current vs. never; (2) ethnicity, categorized as whites vs. others; (3) educational level, categorized as degree vs. others; (4) yearly income, divided as < vs. \geq 50,000 \$ or missing data; (5) presence of hypertension defined as systolic blood pressure values over 140 and/or diastolic over 90 mmHg³¹, as this was not included in the Charlson comorbidity index; and (6) the use of non-steroidal anti-inflammatory drugs (NSAIDs) that are associated with higher CVD risk.³² The presence of diabetes was reported descriptively since this condition was already included in the Charlson comorbidity index.

Statistical analyses

After removing those with CVD at the baseline, data on continuous variables were normally distributed according to the Kolmogorov-Smirnov test. Data were presented as means and standard deviation values (SD) for quantitative measures and absolute numbers (and percentages) for the discrete variables, by MPI categories (≤ 0.33 ; 0.34-0.66; > 0.66). Levene's test was used to test the homoscedasticity of variances and, if its assumption was violated, Welch's ANOVA was used. P values for trends were calculated using the Jonckheere-Terpstra test for continuous variables and the Mantel-Haenszel Chi-square test for categorical ones.

Logistic binary regression analysis was performed, taking the MPI at the baseline (in categories or as increase in 0.10 points) as the exposure variable and incident CVDs as the outcome variable, reporting the data as odds ratios (ORs) with their 95 % confidence intervals (CIs), adjusted for age, sex, ethnicity, education, smoking status, monthly income, use of NSAIDs, and presence of hypertension.

All the analyses were performed using the SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and statistical significance was assumed for a p-value < 0.05 .

RESULTS

Sample selection

The OAI dataset included, at the baseline evaluation, a total of 4,796 individuals. After removing 313 people with a diagnosis of CVD already at the baseline, 172 without data during follow-up regarding CVD and 100 for which no sufficient data regarding MPI at the baseline were available, 4,211 participants were finally included.

Baseline characteristics

The participants included were mainly women (58.6%), with a mean age of 60.8 years (\pm SD 9.1 years; range: 45-79 years). The mean MPI at baseline was $0.40 \pm$ SD 0.17 (range: 0.0 – 1.0).

Table 1 illustrates the sample characteristics by MPI values. Participants in the highest MPI category (MPI group 3) (n=282) were significantly more likely to be female, older, non-white, smokers and less educated than those in the lowest category (MPI group 1) (n=1,565). People in MPI 3 group used more frequently NSAIDs and were more frequently affected by hypertension and diabetes than their counterparts.

During the 8 years of follow-up, 411 participants (=9.8%) experience a CVD for a global incidence of 13 events per 1,000-year (95%CI: 12-14). People with incident CVD had a significant higher MPI baseline value than those without CVD ($0.44 \pm$ SD 0.17 vs. $0.39 \pm$ SD 0.17, $p < 0.0001$). **Table 2** shows the logistic regression analysis taking MPI at baseline as the exposure and incident CVD during the 8 years of follow-up as the outcome. People in MPI 3 group had an incidence of CVD more than doubled than those in MPI 1 group (10 events in MPI 1 group and 24 events in MPI 3 group per 1,000-year). After adjusting for 8 potential confounders, people in MPI 2 group (OR=1.31; 95%CI:

1.03-1.67; $p=0.03$) and MPI 3 group (OR=1.91; 95%CI: 1.26-2.89; $p=0.009$) experienced a higher risk of CVD (vs. MPI group 1). A 0.10 points-point increase in MPI score corresponded to an increase in CVD risk by 16% (OR=1.16; 95%CI: 1.09-1.24; $p<0.001$) (**Table 2**).

DISCUSSION

In this longitudinal study, during eight years of follow-up, we found that MPI at baseline predicts the onset of CVD in community-dwellers affected by OA or at high risk for this condition. The incidence of CVD was more than doubled in people with higher MPI values and these findings remained substantially unaltered after analytical adjustment for eight potential confounders.

In the present study, people having higher MPI values at baseline had a significantly higher presence of several potential CVD risk factors than people with lower values, such as lower educational level and higher presence of smoking, hypertension, and higher use of NSAIDs. All of them are traditional and well-known risk factors for CVD. However, also after adjusting for these potential confounders, the association between MPI and incident CVDs remained significant. Several explanations may underlie our finding. First, it has been reported that frail people might have relevant sub-clinical vascular and cardiac alterations.^{33,34} Moreover, frail people report several cellular (such as deoxyribonucleic acid damage and shorter telomere length)^{35,36} and bio-humoral alterations (e.g. higher oxidative stress and inflammatory levels)^{37,38} that can increase CVD risk.⁶ Finally, frail people seem to have a pro-thrombotic profile³⁹, higher oxidative stress levels³⁷ and some endocrine dysregulations⁴⁰ which are important CVD risk factors. In this sense, MPI seems to be associated to several of these alterations such as higher inflammatory and thrombotic levels indicating a bio-humoral signature of frailty as demonstrated in other studies.⁴¹

The present findings are of importance since this is the first report showing that multidimensional frailty may be associated with CVD and since CGA is an essential step in CVD management. For example, MPI is a strong predictor of mortality in older people affected by acute myocardial infarction⁴² or heart failure.⁴³ In particular, a sensitive measure of the multidimensional impairment,

such as MPI, might be useful for clinicians in older people at higher risk of CVD for tailored interventions, e.g., reduction of unnecessary medications or for increasing physical activity levels people affected by high MPI values.

The findings from this study should be interpreted within its limitations. First, the OAI study includes only people who already have or are at high risk of knee OA. Thus, whether our results can be applied to the general population is not yet demonstrated. Second, CVDs were self-reported by the patients and not validated by a specialist in cardiology. This may lead to an under-representation of these conditions⁴⁴, particularly in the case of chronic stable conditions, such as heart failure or angina pectoris.⁴⁵ Finally, data regarding cause-specific mortality are not available, but this information could modify the strength of the association between MPI and incident CVD.

In conclusion, findings from this study suggest that higher MPI values at baseline might be associated with an increased risk of CVD over eight years of follow-up suggesting the importance of comprehensive geriatric assessment in predicting these conditions that are particularly relevant in older people. Our study suggests that people identified as frail by a geriatrician through a multidimensional assessment should be early screened from a cardiovascular point of view, in order to avoid the consequences of CVD in older people. Other longitudinal studies conducted in the general population are needed to confirm our findings.

REFERENCES

1. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community - dwelling older persons: a systematic review. *Journal of the American Geriatrics Society*. 2012;60(8):1487-1492.
2. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *Journal of the American College of Cardiology*. 2014;63(8):747-762.
3. Stenholm S, Strandberg TE, Pitkälä K, Sainio P, Heliövaara M, Koskinen S. Midlife obesity and risk of frailty in old age during a 22-year follow-up in men and women: the Mini-Finland Follow-up Survey. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*. 2014;69(1):73-78.
4. Savela SL, Koistinen P, Stenholm S, et al. Leisure-time physical activity in midlife is related to old age frailty. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*. 2013;68(11):1433-1438.
5. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *The lancet*. 2013;381(9868):752-762.
6. Veronese N, Cereda E, Stubbs B, et al. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: Results from a meta-analysis and exploratory meta-regression analysis. *Ageing research reviews*. 2017;35:63-73.
7. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2001;56(3):M146-M157.
8. Pilotto A, Custodero C, Maggi S, Polidori MC, Veronese N, Ferrucci L. A multidimensional approach to frailty in older people. *Ageing Research Reviews*. 2020;60:101047.
9. Pilotto A, Ferrucci L, Franceschi M, et al. Development and validation of a multidimensional prognostic index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. *Rejuvenation research*. 2008;11(1):151-161.
10. Sancarolo D, D'Onofrio G, Franceschi M, et al. Validation of a Modified-Multidimensional Prognostic Index (m-MPI) including the Mini Nutritional Assessment Short-Form (MNA-SF) for the prediction of one-year mortality in hospitalized elderly patients. *The journal of nutrition, health & aging*. Mar 2011;15(3):169-173.
11. Angleman SB, Santoni G, Pilotto A, Fratiglioni L, Welmer A-K. Multidimensional Prognostic Index in Association with Future Mortality and Number of Hospital Days in a Population-Based Sample of Older Adults: Results of the EU Funded MPI_AGE Project. *PloS one*. 2015;10(7):e0133789-e0133789.
12. Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK. Prognostic indices for older adults: a systematic review. *Jama*. Jan 11 2012;307(2):182-192.
13. Bureau ML, Liuu E, Christiaens L, et al. Using a multidimensional prognostic index (MPI) based on comprehensive geriatric assessment (CGA) to predict mortality in elderly undergoing transcatheter aortic valve implantation. *International journal of cardiology*. Feb 16 2017;236:381-386.
14. Pilotto A, Addante F, Ferrucci L, et al. The multidimensional prognostic index predicts short- and long-term mortality in hospitalized geriatric patients with pneumonia. *The journals of gerontology. Series A, Biological sciences and medical sciences*. Aug 2009;64(8):880-887.
15. Pilotto A, Sancarolo D, Panza F, et al. Multidimensional Prognostic Index based on a comprehensive geriatric assessment predicts short-term mortality in older patients with heart failure. *Circulation Heart failure*. 2010;3(1):191-199.

16. Sancarolo D, Pilotto A, Panza F, et al. A Multidimensional Prognostic Index (MPI) based on a comprehensive geriatric assessment predicts short- and long-term all-cause mortality in older hospitalized patients with transient ischemic attack. *Journal of neurology*. Apr 2012;259(4):670-678.
17. Volpato S, Bazzano S, Fontana A, Ferrucci L, Pilotto A. Multidimensional Prognostic Index predicts mortality and length of stay during hospitalization in the older patients: a multicenter prospective study. *The journals of gerontology. Series A, Biological sciences and medical sciences*. 2015;70(3):325-331.
18. Pilotto A, Veronese N, Daragjati J, et al. Using the Multidimensional Prognostic Index to Predict Clinical Outcomes of Hospitalized Older Persons: a Prospective, Multicentre, International Study. *The journals of gerontology. Series A, Biological sciences and medical sciences*. Oct 17 2018.
19. Lai S, Amabile MI, Mazzaferro S, et al. Association between Multidimensional Prognostic Index and Hospitalization and Mortality among Older Adults with Chronic Kidney Disease on Conservative or on Replacement Therapy. *Journal of Clinical Medicine*. 2020;9(12):3965.
20. Rarek MP, Meyer AM, Pickert L, et al. The prognostic signature of health-related quality of life in older patients admitted to the emergency department: a 6-month follow-up study. *Aging Clinical and Experimental Research*. 2020:1-9.
21. Veronese N, Koyanagi A, Smith L, et al. Relationship between multidimensional prognostic index (MPI) and incident depressive symptoms in older people: Findings from the Irish longitudinal study on ageing. *International Journal of Geriatric Psychiatry*. 2020.
22. Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. *Medical Hypotheses*. // 2006;67(2):362-370.
23. Veronese N, Siri G, Cella A, et al. The Multidimensional Prognostic Index predicts falls in older people: an 8-year longitudinal cohort study of the Osteoarthritis Initiative. *Journal of the American Medical Directors Association*. 2020;21(5):669-674.
24. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. 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. *The Journal of rheumatology*. 1988;15(12):1833-1840.
25. Washburn RA, McAuley E, Katula J, Mihalko SL, Boileau RA. The physical activity scale for the elderly (PASE): evidence for validity. *Journal of clinical epidemiology*. 1999;52(7):643-651.
26. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? *Medical care*. 1996;34(1):73-84.
27. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychology and aging*. 1997;12(2):277-287.
28. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self-administered outcome measure. *Journal of Orthopaedic & Sports Physical Therapy*. 1998;28(2):88-96.
29. Pilotto A, Ferrucci L, Franceschi M, et al. Development and validation of a multidimensional prognostic index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. *Rejuvenation research*. 2008;11(1):151-161.
30. Veronese N, Stubbs B, Solmi M, Smith TO, Reginster JY, Maggi S. Osteoarthritis increases the risk of cardiovascular disease: Data from the osteoarthritis initiative. *The journal of nutrition, health & aging*. 2017/06/15 2017.

31. Veronese N, Stubbs B, Solmi M, et al. Knee Osteoarthritis and Risk of Hypertension: A longitudinal cohort study. *Rejuvenation research*. Jun 24 2017.
32. Marsico F, Paolillo S, Filardi PP. NSAIDs and cardiovascular risk. *Journal of cardiovascular medicine*. 2017;18:e40-e43.
33. Gharacholou SM, Tashiro T, Cha SS, Scott CG, Takahashi PY, Pellikka PA. Echocardiographic indices associated with frailty in adults ≥ 65 years. *The American journal of cardiology*. 2015;116(10):1591-1595.
34. Katayama PL, Dias DPM, Silva LEV, Virtuoso-Junior JS, Marocolo M. Cardiac autonomic modulation in non-frail, pre-frail and frail elderly women: a pilot study. *Aging clinical and experimental research*. 2015;27(5):621-629.
35. Ashar FN, Moes A, Moore AZ, et al. Association of mitochondrial DNA levels with frailty and all-cause mortality. *Journal of molecular medicine*. 2015;93(2):177-186.
36. Zaslavsky O, Cochrane BB, Thompson HJ, Woods NF, Herting JR, LaCroix A. Frailty: a review of the first decade of research. *Biological research for nursing*. 2013;15(4):422-432.
37. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing research reviews*. 2016;31:1-8.
38. Uchmanowicz I. Oxidative Stress, Frailty and Cardiovascular Diseases: Current Evidence. *Frailty and Cardiovascular Diseases*: Springer; 2020:65-77.
39. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the US Preventive Services Task Force. *Annals of internal medicine*. 2009;151(7):483-495.
40. Veronese N. Frailty as Cardiovascular Risk Factor (and Vice Versa). *Frailty and Cardiovascular Diseases*: Springer; 2020:51-54.
41. Fontana L, Addante F, Copetti M, et al. Identification of a metabolic signature for multidimensional impairment and mortality risk in hospitalized older patients. *Aging cell*. 2013;12(3):459-466.
42. Cammalleri V, Bonanni M, Buetti FM, et al. Multidimensional Prognostic Index (MPI) in elderly patients with acute myocardial infarction. *Aging Clinical and Experimental Research*. 2020:1-9.
43. Pilotto A, Addante F, Franceschi M, et al. Multidimensional Prognostic Index based on a comprehensive geriatric assessment predicts short-term mortality in older patients with heart failure. *Circulation: Heart Failure*. 2010;3(1):14-20.
44. Wu S-C, Li C, Ke D. The agreement between self-reporting and clinical diagnosis for selected medical conditions among the elderly in Taiwan. *Public health*. 2000;114(2):137-142.
45. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *Journal of clinical epidemiology*. 2004;57(10):1096-1103.

Table 1. Descriptive statistics of patients' characteristics according to their baseline MPI value.

		MPI 1 (0.00-0.33) (n=1,565)	MPI 2 (0.34-0.66) (n=2,382)	MPI 3 (0.67-1.00) (n=282)	p-values for trend
Sex, n(%)	F	809 (51.7)	1492 (62.6)	194 (73.5)	<0.0001
	M	756 (48.3)	890 (37.4)	70 (26.5)	
Age, mean(sd)		60 (9)	61 (10)	62 (9)	<0.0001
Whites, n(%)		1383 (88.4)	1866 (78.4)	162 (61.4)	<0.0001
College or higher education, n(%)		601 (38.4)	674 (28.3)	39 (14.8)	<0.0001
Smoking status, n(%)		639 (41.0)	1154 (48.7)	143 (58.4)	<0.0001
Use of NSAIDs, n(%)		114 (7.3)	297 (12.5)	49 (18.6)	<0.0001
Presence of hypertension, n(%)		265 (16.9)	526 (22.1)	69 (36.1)	<0.0001
Presence of diabetes, n(%)		36 (2.3)	193 (8.3)	57 (22.5)	<0.0001
Living alone, n(%)		1417 (90.5)	1768 (74.2)	101 (38.3)	<0.0001
CES-D, mean(sd)		2.5 (3.0)	7.7 (6.5)	17.4 (9.0)	<0.0001
WOMAC-mean, mean(sd)		5.4 (10.3)	13.2 (15.1)	27.5 (21.7)	<0.0001
PASE, mean(sd)		197 (85)	148 (74)	106 (53)	<0.0001
Comorbidity, mean(sd)		0.1 (0.4)	0.3 (0.7)	1.1 (1.3)	<0.0001
Number of Drugs mean(sd)		2.7 (1.7)	3.7 (2.4)	5.8 (3.4)	<0.0001
KOOS – QoL, mean(sd)		78 (19)	64 (21)	47 (21)	<0.0001
BMI, mean(sd)		26.8 (3.9)	29.2 (4.8)	31.8 (5.4)	<0.0001

Notes: p-values for trends were calculated using the Jonckheere-Terpstra test for continuous variables and the Mantel-Haenszel Chi-square test for categorical ones.

Abbreviations: BMI, body mass index, CES-D, Center for Epidemiologic Studies-Depression; KOOS, Knee Injury and Osteoarthritis Outcome Score; MPI, Multidimensional Prognostic Index; PASE, Physical Activity Scale for Elderly; QoL, quality of life; SD, standard deviation; WOMAC, Western Ontario and Mc Master University

Table 2. Association between MPI and incident cardiovascular diseases during 8 years of follow-up.

		CVD (incidence rate, per 1,000-year)	Unadjusted OR (95%CI)	OR¹ (95%CI)
MPI (per 0.10 increase)		13 (12-14)	1.19 (1.12-1.26) (p<0.0001)	1.16 (1.09-1.24) (p<0.0001)
MPI	MPI 1 (0.00-0.33)	10 (8-12)	1 [reference]	1 [reference]
	MPI 2 (0.34-0.66)	15 (13-15)	1.47 (1.17-1.85) (p=0.001)	1.31 (1.03-1.67) (p=0.03)
	MPI 3 (0.67-1.00)	24 (17-32)	2.32 (1.58-3.41) p<0.0001	1.91 (1.26-2.89) (p=0.009)

¹ Odds ratios are adjusted for: age, sex, ethnicity, education, smoking status, monthly income, use of non-steroidal anti-inflammatory drugs, and presence of hypertension

Abbreviations: MPI, Multidimensional Prognostic Index; OR, odds ratio; CI, confidence intervals; CVD, cardiovascular disease