OSTEOARTHRITIS AND MORTALITY: A PROSPECTIVE COHORT STUDY AND SYSTEMATIC REVIEW WITH META-ANALYSIS

Short title: osteoarthritis and mortality

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ABSTRACT

Objectives: Osteoarthritis (OA) is a leading cause of disability, but the relationship with premature mortality remains uncertain. We aimed to investigate the relationship between OA and mortality from any cause and from cardiovascular disease (CVD).

Methods: Electronic literature databases searches were conducted to identify prospective studies comparing mortality in a sample of people with and without OA. Risk of call-cause and CVD-mortality were summarized using adjusted hazard ratios (HRs) for joint-specific (hand, hip and knee) and joint non-specific OA. New data from the Progetto Veneto Anziani (PRO.V.A.) study were also included.

Results: From the PRO.V.A. study (N=2,927), there was no significant increase in CVD mortality risk for participants with any-joint OA (N=1,858) compared to non-OA (all-cause, HR=0.95; 95% CI: 0.77-1.15; CVD, HR=1.12; 95% CI: 0.82-1.54). On meta-analysis, seven studies (OA: 10,018/non-OA: 18,541), with a median 12-year follow-up, reported no increased risk of any-cause mortality in those with OA (HR=1.10; 95% CI: 0.97-1.25). After removing data on hand OA, a significant association between OA and mortality was observed (HR=1.18; 95% CI: 1.08-1.28). There was a significant higher risk of overall mortality for (1) studies conducted in Europe, (2) patients with multi-joint OA; and (3) a radiological diagnosis of OA. OA was associated with significantly higher CVD mortality (HR=1.21; 95% CI: 1.10-1.34).

Conclusions: People with OA are at increased risk of death due to CVD. The relationship with overall mortality is less clear and may be moderated by the presence of hand OA.

Keywords: osteoarthritis; mortality; cardiovascular disease.

Osteoarthritis (OA) is a leading cause of years lived with disability worldwide.[1,2] The leading symptom associated with OA is chronic musculoskeletal pain, which is associated with mobility and function.[3,4] Physical inactivity is independently associated with an increased risk of cardiovascular diseases (CVD) and mortality in the general population.[5] Obesity is also commonly seen within the osteoarthritis population, whilst also being associated with morbidities such as type two diabetes, cancers and CVD. .[6]

CVD are a leading cause of global mortality, with recent estimates demonstrating that CVD account for 17.3 million deaths globally.[7] A recent meta-analysis demonstrated that people with OA are at increased risk of CVDs,[8] which may also be influenced by an elevated chronic inflammatory status in some subgroups with OA.[9] Death due to CVD is potentially preventable through appropriate timely pharmacological and non-pharmacological interventions[10] Therefore, to identify people at higher risk of CVD mortality could be of considerable public health importance.

Within the past decade, a number of observational studies have reported that people with OA are at increased risk of premature mortality compared to the general population.[11–13] However, this evidence is heterogeneous and limited by the lack of adjustment for appropriate confounders.

Given this, the purpose of this study was to: i) analyze data from a prospective cohort study on the risk of CVD mortality in OA compared to a non-osteoarthritis cohort, adjusting for important medical morbidities and other confounders; ii) to systematically review the available literature and perform a meta-analysis to

determine whether people with OA present a differential risk of overall and CVD mortality than those without OA. We hypothesized that people with OA had a significant higher risk of overall and CVD death compared to those without OA.

MATERIALS AND METHODS

Prospective cohort study

Overall cohort

Previously unpublished data from the Progetto Veneto Anziani (PRO.V.A. study) were used to investigate the risk of overall and CVD mortality in people with OA over a mean follow-up of 4.4 years. The Pro.V.A. study is an observational cohort study on the Italian population aged over 65 years. The study population initially included 3,099 older Caucasian adults (1,245 men/1,854 women), who were randomly selected between 1995 and 1997 using a multistage stratified method, in two North Italian towns (Camposampiero and Rovigo). Additional details about the study design has been previously reported.[14]

Participant selection

After excluding 172 participants without information about OA, data from 2,927 participants (men:1,179/ women:1,748) were gathered. Hand, hip and knee OA presence was assessed through medical history and records, previous x-ray reports, and clinical evaluation. This latter evaluation included for the hand the presence of Heberden nodes, stiffness, pain at passive moment; for the knee: deformity, pain at passive movement, reduced passive mobility and crepitus; for the hip: pain at passive movement, rotation and palpation, and reduced external rotation. The diagnosis of OA was finally confirmed by a rheumatologist using a standardized algorithm.[15] Mortality was ascertained through direct reviewing of single death certificate, and the main

cause of death was recorded using the ICD-9. Death for CVD reasons was defined using the ICD-9 codes from 390 to 459.

Statistical analysis

Due to the small number of death attributed to non-CVD, it was not possible to appropriate analyses overall mortality, over CVD mortality from this dataset. Accordingly, the risk of CVD mortality associated with OA was investigated using multivariate Cox's regression analysis adjusted for known clinical factors associated with mortality. These included: age (continuous); gender; body mass index (continuous); educational level ($\leq$ 5 vs. >5 years); alcohol drinking (yes vs. no); monthly income ($\geq$500 vs. <500 €); physical activity level ($\geq$4 vs. <4 h/week); presence at baseline of CVD, fractures, chronic obstructive pulmonary disease, orthostatic hypotension (difference in systolic of 20 mmHg or diastolic of 10 mmHg between orthostatism and clinostatism)[16], hypertension (use of anti-hypertensive medications, mean of systolic blood pressure$\geq$140 or mean diastolic blood pressure$\geq$90 mmHg)[17], diabetes (fasting plasma glucose$\geq$126 mg/dl, glycosilated hemoglobin$\geq$7% or use of anti-diabetic medications)[18], frailty (according with a modified Fried' index)[19], cancer (all yes vs. no); number of medications (continuous); smoking status (current/former vs. never); activities of daily living assessed (ADLs)[20], Mini-Mental State Examination (MMSE)[21], Geriatric Depression Scale[22], Geriatric Nutrition Risk Index scores(GNRI) [23] (all as continuous). For all the scores, with exception of GDS, the higher the score the better the status. In the multivariate analysis, data were missing for 258 (=8.8%) of the participants, mainly for information about orthostatic hypotension (n=142), glycosilated hemoglobin (n=244), and MMSE (n=125).

Risk estimates were computed for any joint and anatomical region affected (hand, hip or knee). All analyses were performed using the SPSS 21.0 for Windows (SPSS Inc., Chicago, IL). Statistical significance was assumed for a two-tailed p-value <0.05.

Systematic Review

This systematic review was conducted following the MOOSE (Meta-analysis of observational studies in epidemiology) guidelines and data reporting was performed in agreement with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[24,25]

Data sources and literature search strategy

We created search strategies for the concepts of "osteoarthritis" and "mortality" using a combination of standardized terms and keywords harvested from indices, thesauri, and on-topic articles (**Supplementary Table 1**). The electronic databases (PubMed, Embase, Scopus, CiNAHL [via Ebsco], ASSIA [via Proquest], and Social Work Abstracts [via Ebsco]), were search from database inception to 17th November 2015. We further conducted a manual search of reference lists of included and other relevant articles. Authors were contacted in case of lacking information. All articles were reviewed for inclusion by two independent reviewers (NV and BS). Any discrepancies were resolved by consensus with a third reviewer (EM).

Study selection

Prospective, observational cohort studies were eligible for inclusion if they: reported data on OA diagnosed with clinical and/or radiological assessment; reported mortality risk estimates (hazard ratios [HRs]) along with their 95% confidence intervals (95%CI); and included a control group without OA. Intervention studies and studies including only participants with joint replacement (e.g. total hip or total knee arthroplasty) were excluded.

Data extraction

Overall and CVD risk estimates (adjusted for the maximum number of confounders available) comparing people with OA against people without OA were gathered. One investigator (NV) extracted data from the included articles and two independent investigators (CL and EC) verified these data. For each paper we extracted also data about authors, publication year, study location, setting, participant characteristics by presence of OA (e.g. age, percentage of women, CVD, body mass index [BMI]), follow-up duration (in years), number and list of covariates used in statistical analyses). Study authors were contacted if necessary.

Outcomes

The primary outcome was: - overall mortality in OA compared to non-OA participants. Secondary outcomes included: overall mortality based on anatomical site of OA (i.e. hand, hip and knee) and CVD mortality.

Assessment of study quality

The Newcastle-Ottawa Scale (NOS)[26] was used to evaluate study quality. The NOS assigns a maximum of nine points to studies of highest quality according to three

quality parameters: selection (four points), comparability (two points), and outcome (three points). Each included study was assessed by three reviewers. If discrepancies arose in appraisal, these were addressed by a joint re-evaluation of the article (MS, SM and TS).

Data synthesis and statistical analysis

To compensate for potential between-study heterogeneity, we calculated a pooled HR using DerSimonian-Laird random-effect model.[27] Statistical heterogeneity across studies was assessed using the Cochrane I^2 metric and chi-square statistics.[28] Since the diagnostic criteria for OA involve clinical and radiological parameters[29–31] and evidence has suggested that radiological findings may poorly correlate to clinical presentation[32], in absence of universally agreed recommendations we initially (primary analyses) pooled HRs of overall mortality as provided by the studies regardless of method of diagnosis.. Joint specific estimates for overall mortality and CVD specific death were computed. Within-study pooled estimates were also calculated as necessary (e.g. only joint-specific HRs provided).

Given significant statistical heterogeneity ($I^2 \geq 50\%$) [33], we conducted meta-regression analyses investigating the following moderators: continent (Europe vs. others), type of diagnosis of OA (clinical vs. radiological vs. combined); follow-up duration, NOS score, number of adjustments (all by median value); death ascertainment (using death certificates or other tools), and number of sites affected.

Publication bias was assessed by visually inspecting funnel plots and using the Begg-Mazumdar Kendall tau[34] and the Egger bias test.[35] To account for potential

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publication bias, we used a 'trim-and-fill' method, based on the assumption that the effect sizes of all the studies are normally distributed around the center of a funnel plot. In the event of asymmetries, this procedure adjusts for the potential effect of unpublished (imputed) studies.[36] All analyses were performed using Comprehensive Meta-Analysis 3.

RESULTS

Prospective cohort study

Baseline characteristics

In the PRO.V.A. study, participants with OA (N=1,858; 63.5%) were significantly older, with a greater proportion of women compared to those without OA (n=1,069) (**Table 1**). Subjects with OA had also a significantly higher presence of potential risk factors for early mortality, including lower GNRI, preserved number of ADLs, and higher presence of depressive symptoms, frailty, osteoporotic fractures, orthostatic hypotension and hypertension, diabetes and CVD, compared to the non-OA group (**Table 1**).

Follow-up and CVD mortality

Over the 4.4 years of follow-up, 745 participants (men:380/women:365) died. Using Cox's regression analysis and taking participants with no OA for reference, no significant increased risk of death in people with OA emerged (HR=0.95 [95% CI:0.77-1.15], p=0.58) (**Table 2**). On the multivariate analysis (**Supplementary Table 2**), the significant predictors of death were diabetes (HR=1.50 [95% CI: 1.20-1.88], p<0.001), CVD (HR=1.50 [95% CI: 1.23-1.82], p<0.001), COPD (HR=1.34 [95% CI: 1.04-1.72], p=0.03), cancer (HR=1.37 [95% CI: 1.03-1.81], p=0.03) and frailty (HR=2.12 [95% CI: 1.52-2.97], p<0.001). Higher MMSE and GNRI were protective for mortality (HR=0.96 [95% CI: 0.94-0.98], p<0.001 and HR=0.96 [95% CI: 0.95-0.97], p<0.001, respectively). A similar lack of association was also found when individually analyzing OA by anatomical site (hand, hip or knee) or when lower limbs OA was analyzed (HR=0.97 [95% CI: 0.82-1.14], p=0.48). Finally, OA did not

significantly increase the risk of CVD death (total number of events, n=373; HR= 1.12 [95% CI: 0.83-1.55], p=0.53). Other causes of death could not be investigated (respiratory, n=128; cancer, n=58; others=186).

Systematic Review

Search results

In total, 2,139 non-duplicated articles were identified. After excluding 2,124 articles based on title/abstract review, 15 articles were fully retrieved and six were included[37–42] along with data from the PRO.V.A study (**Supplementary Figure 1**). For one conference abstract[38], additional data were gathered from the Authors.

Study and Population Characteristics

As reported in **Table 3**, the seven meta-analyzed studies followed 28,559 participants (OA: 10,018/non-OA: 18,541) for a median duration of 12 (IQR: 6.5 to 18) years. Participants were all community-dwellers, mainly European (N=4; 57%). The assessment of OA was heterogeneous across studies with two [37,38] and five (PRO.V.A) and [39–42] reporting a radiological and a combined (clinical + radiological) assessment, respectively. Different methods of death ascertainment were also observed, but six out of seven were of high reliability and quality [37–41]. Finally, among the studies included, four provided data also for CVD mortality (PRO.V.A) and [37,38,41].

Quality Assessment

The median NOS score was seven (IQR: 6-8). The most common source of bias was the ascertainment of exposure (particularly missing data on radiological or standardized criteria for the assessment of OA; **Supplementary Table 3**). On the other, only one study has not considered pertinent linkage to high-quality records.[42]

Hazard ratios for overall mortality

For the calculation of pooled overall mortality estimate we used joint-specific HRs for three studies.[40–42] Compared to those without OA, participants with OA had no significantly different risk for overall mortality (HR=1.10; 95% CI: 0.97 to 1.25; p=0.12; I^2=67%; **Figure 1**), also after adjusting for a median of 13 (IQR: 9 to 14) confounders (**Supplementary Table 4**). After excluding studies providing risks for site specific OA, the pooled risk of death from all causes was found to be significant with low heterogeneity (HR=1.18; 95% CI: 1.08 to 1.28; p<0.001; I^2=47%).

Sub-group analyses demonstrated that the presence of OA in hand, hip and knee was not associated with an increased risk of mortality (**Figure 1**). Funnel plot inspection indicated that publication bias was unlikely, as confirmed by Begg's (p=0.90) and Egger's tests (p=0.89).

Hazard ratios for cause-specific (CVD) mortality

In four studies (PRO.V.A) and [37,38,41], OA was significantly associated with CVD death without heterogeneity or publication bias (HR=1.21; 95% CI: 1.10 to 1.34; p<0.001; I^2=0%). Cause-specific mortality for single joints could not be computed due to the limited number of studies.

Meta-regression analysis

Since the overall mortality analyses showed evidence of heterogeneity (I^2=67%), a meta-regression analysis was undertaken (**Table 4**). In a great part of the strata heterogeneity remained high. However, in some studies there was a significantly higher risk of overall mortality and a moderate-to-substantial reduction of between-

study heterogeneity: European studies; death ascertainment using death certificates; multiple joints affected; radiological diagnosis of OA.

Since the pooled HR for hand OA on overall mortality appeared to be marginally protective (p=0.07), a sensitivity analysis was conducted to remove the effect of three datasets (PRO.V.A [40,41]). This analysis demonstrated that for hand OA, pooled HR for mortality was 1.18 (95% CI: 1.07 to 1.30; p=0.001; I^2=48%) [(PRO.V.A) and [33-35,37,38]]

DISCUSSION

To the best of our knowledge, this is the first meta-analysis investigating the association between OA and mortality. The seven meta-analyzed studies (including 10,018 participants with and 18,541 people without OA) demonstrated that the presence of OA was not associated with mortality, although this appeared to substantially depend on between-study heterogeneity. When analyzing studies conducted in Europe, we observed a significantly higher risk of mortality and lower heterogeneity. A significant confounding factor to mortality seems to be the inclusion of the studies reporting data on hand OA. Finally, when considering cause-specific mortality, it appears that people with OA are at increased risk of CVD mortality.

It is known that participants with OA frequently exhibit a number of medical morbidities which increase their risk for death.[8,39,43] In the PRO.V.A. study, people with OA reported a higher presence of frailty, cardiovascular and metabolic diseases than those without. The role of these potential confounders in explaining the relationship between OA and mortality seems to be relevant[44], consistent with the findings of a recent large scale prospective study[37] reinforcing the importance of CVD risk in influencing mortality of people with OA. In the PRO.V.A. study we have tried to better identify the specific risk factors for mortality in participants with OA, in order to propose appropriate and specific interventions. Independent predictors of early death significantly different between those with OA and those without were diabetes, CVD, frailty and poorer nutrition index. Hierarchically, frailty seems to be the most important and, since frailty is reversible if appropriately treated[45], our findings suggest that people with OA should be more active to reduce the risk of

premature death. Thus, the association between OA and overall mortality appears to be more related to confounders than for OA itself. This is likely supported in our meta-analysis by strata analysis as the number of adjustments appeared to partially explain between-study heterogeneity. Strata analyses suggested not only that ethnicity could be a potential risk modifier, but also that evidence of an association may depend on study methodology. Particularly, our study highlights the need of providing evidence-based or at least consensus-based criteria for homogenous case ascertainment.

The secondary analyses explored whether the anatomical site of OA was associated with earlier mortality. Hip or knee OA did not predict early death, while for hand OA there was a trend towards a significant reduction in mortality. Since lower limbs OA are associated with high rate of disability and other risk factors for mortality[46], more research is needed to better understand the role of lower limbs OA in predicting mortality. Regarding hand OA, one study[40] suggests that not only radiographic, but also symptomatic hand OA is protective for mortality, although both these conditions are associated with a higher incidence of CVD.[40] A possible reason is that hand OA was associated with a reduced cancer-related mortality.[40] The reasons of this association are not known and further research is obviously needed.

Our data from the meta-analysis suggests that people with OA are at increased risk of premature mortality due to CVD also after accounting for potential confounders. People with OA are known to have high levels of CVD[8,47], an increased inflammatory profile[9] and low levels of physical activity[48], all of which may predispose people with OA to premature mortality due to CVD. Moreover, they use a higher proportion of

analgesic medications with an unfavorable CVD profile.[49] Given that exercise has been reported as being equally effective in managing some types of CVD as pharmacological interventions[50], interventions targeting physical activity, frailty and inappropriate medication should be a priority among people with OA at higher risk of mortality. An indirect confirmation of this hypothesis was given by a recent study showing that patients with knee OA who underwent joint replacement had a lower risk of future CVD events, potentially due to an increased post-operative physical activity levels and decreased use of analgesics compared to pre-operatively. [51]

Whilst our primary data and meta-analyses are novel, the findings of our work should be interpreted within its limitations. First, there was some evidence of statistical heterogeneity. However, we attempted to address the issue of between study heterogeneity, as advised by the MOOSE guidelines[24], suggesting some factors could moderate the association between OA and mortality. Second, it was not possible to stratify our meta-analysis results according to gender, although is known that women are at higher risk of OA and its complications.[52] Third, no study included considered nor the duration of OA at inclusion, nor its progression (clinically or radiologically) neither the incidence of new cases within the follow-up period. It is therefore unclear whether OA disease progression influenced the outcomes. Furthermore, there was no record as what treatments were prescribed and adhered to in the OA cohort, which clearly might influence mortality. Therefore it is unclear whether disease medication (or symptom modification) impacted on mortality. Fourth, there was some discrepancy in the prevalence of OA across the PRO.V.A. study and the meta-analysis. Reasons for this difference may include: ii) the higher mean age of the PRO.V.A. cohort; and ii) the potential higher prevalence of OA in Italy than other

countries.[6] Fifth, we did not assess the association of OA with specific cause mortality other than CVD mortality. This was because there remains limited evidence on other cause mortality for people with OA. Consequently such analyses would have been underpowered and potentially meaningless. However, this should be considered in the future once more studies are published in this area. Finally, the analyses pertaining to site-specific OA are preliminary and should be interpreted with cautious. These are based on a limited number of studies for each outcome, and appeared to be contrasting (lower limbs OA seems to increase and hand OA seems to decrease the risk of death). Further analyses should be undertaken to re-explore the potential importance of joint location with mortality as more studies are published in this area

The strengths of this paper are that it is the first meta-analysis to: i) assess for the association between OA and mortality; and ii) has specifically explored for factors to explain for the heterogeneity in individual study results. This therefore provides important knowledge to increase the awareness of CVD in this population. This is important since CVD is potentially preventable through appropriate timely interventions.[10] to impact on the health of people with osteoarthritis. Secondly, since the cohorts included in these analyses were large, the collective pooled analyses provided lower risk of committing a type two statistical error which would have occurred if these studies were interpreted individually. Finally, in the adjusted analyses, a number and wide variety of different confounders were included in the analysis to be able to answer our research question with these potentially factors accounted for.

In conclusion, it appears that people with OA are at increased risk of CVD-specific mortality while the association with overall mortality is less clear. Additional prospective research is required to further explore the relationship between OA and mortality.

ACKNOWLEDGMENTS

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Figure 1. Meta-analysis and pooled hazard ratios of mortality in participants with osteoarthritis from prospective cohort studies (*****, for this study the estimate was obtained by pooling within-study risks for symptomatic and radiographic osteoarthritis; ******, for this study the estimate was obtained by meta-analysing within-study risks for different joints after pooling hazard ratios for only symptomatic, only radiographic and painful radiographic osteoarthritis).

	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	Hazard ratio and 95% CI

ALL-CAUSE MORTALITY (any joint OA)

	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Barbour. 2015 (hip)	1.14	1.05	1.24	3.088	0.002
Castano Betancourt. 2013 (hip and/or knee)	1.23	1.11	1.37	3.856	0.000
Cacciatore. 2014 (any joint)	1.28	0.98	1.67	1.815	0.069
Haugen. 2013 (hand) *	0.81	0.66	0.99	-2.037	0.042
Kluzek. 2015 (hand + knee [pooled]) **	1.34	0.67	2.67	0.830	0.407
Liu. 2015 (knee) *	1.47	0.94	2.31	1.680	0.093
PRO.V.A. study (hand and/or hip and/or knee)	0.95	0.78	1.16	-0.501	0.616
Overall (I^2=67% [p=0.006])	1.10	0.97	1.25	1.540	0.124

ALL-CAUSE MORTALITY (hand OA)

	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Haugen. 2013 *	0.81	0.66	0.99	-2.037	0.042
Kluzek. 2015 **	0.97	0.76	1.26	-0.236	0.813
PRO.V.A. study	1.00	0.78	1.29	0.000	1.000
Overall (I^2=2% [p=0.36])	0.91	0.79	1.04	-1.447	0.148

ALL-CAUSE MORTALITY (hip OA)

	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Barbour. 2015	1.14	1.05	1.24	3.088	0.002
PRO.V.A. study	0.96	0.77	1.20	-0.361	0.718
Overall (I^2=51% [p=0.15])	1.08	0.92	1.26	0.639	0.333

ALL-CAUSE MORTALITY (knee OA)

	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Kluzek. 2015 **	1.47	1.08	2.01	2.431	0.015
Liu. 2015 *	1.47	0.94	2.31	1.680	0.093
PRO.V.A. study	0.86	0.66	1.12	-1.118	0.264
Overall (I^2=76% [p=0.017])	1.21	0.82	1.78	1.939	0.348

CV MORTALITY (any joint OA)

	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Kluzek. 2015 (hand + knee [pooled]) **	1.50	0.82	2.74	1.317	0.188
Barbour. 2015	1.24	1.09	1.41	3.276	0.001
Castano Betancourt. 2013 (hip and/or knee)	1.16	0.95	1.42	1.447	0.148
PRO.V.A. study	1.12	0.83	1.55	0.711	0.477
Overall (I^2=0% [p=0.79])	1.21	1.10	1.34	3.747	<0.001

Table 1. Baseline characteristics by diagnosis of osteoarthritis at baseline: the

PRO.V.A. study.

Patients' characteristics	OA (n=1,858)	No OA (n=1,069)	p value*
Age (years), Mean±SD	77.5±7.9	74.6±7.6	<0.001[†]
Female gender, %	66.4	48.2	<0.001[‡]
General and anthropometric characteristics			
Alcohol drinking, %	65.1	72.8	<0.001
Current/former smokers, %	33.3	47.3	0.60
Educational level > 5 years, %	13.0	17.4	0.002
Physical activity≥4 h/week, %	19.0	22.8	<0.001
Monthly income (≥500 €), %	36.1	44.7	<0.001
GNRI (score), Mean±SD	105.6±5.7	106.5±5.6	0.048
ADL (score), Mean±SD	4.6±1.8	5.4±1.4	<0.001
BMI (kg/m^2), Mean±SD	28.0±4.8	26.8±4.2	<0.001
GDS (score), Mean±SD	9.5±6.0	8.1±5.0	<0.001
MMSE (score), Mean±SD	22.3±7.0	23.8±6.2	0.51
Medical conditions			
Frailty, %	12.6	4.9	<0.001
Fractures, %	11.6	5.9	<0.001
Diabetes, %	17.7	14.7	0.03
Hypertension, %	76.3	70.8	0.001
Orthostatic hypotension, %	34.1	28.8	0.004
CVD, %	25.5	20.4	0.002
COPD, %	10.0	9.1	0.44
Cancer, %	7.9	7.4	0.67
Number of drugs, Mean±SD	3.1±2.2	2.4±2.1	<0.001

*Unless otherwise specified, p values are adjusted for age and gender using a general

linear model or logistic regression, as appropriate.

[†]Not adjusted for age.

[‡]Not adjusted for gender.

Abbreviations: ADL: activities of daily living; BMI: body mass index; COPD:

chronic obstructive pulmonary disease; CVD: cardiovascular diseases; GDS: Geriatric

Depression Scale; GNRI: Geriatric Nutrition Risk Index; MMSE: Mini Mental State Examination; OA: osteoarthritis; SD, standard deviation.

Table 2: Association of osteoarthritis (OA) with the onset of all-cause mortality in the PRO.V.A. study cohort.

	Events (N)	*Participants* (N)	*Unadjusted HR (95%CI)*	*p– value*	*Fully- adjusted* * *HR (95%CI)*	*p– value*
No OA	241	1,068	reference		reference	
Presence of OA	504	1,857	1.16 (0.96-1.40)	0.12	0.95 (0.77-1.15)	0.58
Hand OA	180	695	1.13 (0.89-1.43)	0.33	1.00 (0.78-1.29)	0.99
Hip OA	231	966	1.07 (0.87-1.33)	0.52	0.96 (0.77-1.20)	0.69
Knee OA	140	549	1.05 (0.81-1.35)	0.74	0.86 (0.66-1.12)	0.25

Data are presented as hazard ratios and 95% confidence intervals [HR (95%CI)].

*The **fully-adjusted model** includes: age (continuous); gender; body mass index (continuous); educational level ($\leq$ 5 vs. >5 years); alcohol drinking (yes vs. no); monthly income ($\geq$500 vs. <500 €); physical activity level ($\geq$4 vs. <4 h/week); presence at baseline of cardiovascular diseases, fractures, chronic obstructive pulmonary disease, orthostatic hypotension, hypertension, diabetes, frailty, cancer (all yes vs. no); number of medications (continuous); smoking status (current/former vs. never); Activities of Daily Living, Mini-Mental State, Geriatric Depression Scale, Geriatric Nutrition Risk Index scores (all as continuous).

Table 3. Characteristics of the studies according to the presence of osteoarthritis or not.

First author, year	Continent (Country)	Setting	Diagnosis criteria for OA	OA	N	Mean age (SD)	Females (N)	CVD (N)	Mean BMI (SD)	Death ascertainment	Follow-up (years)	Adjustments (N)	NOS score
Barbour, 2015	North America (USA)	Community	Radiological	Yes	635	72.7 (5.3)	635	53	26.7 (4.6)	Phone calls + death certificates	16	7	8
				No	7254	71.2 (5.0)	7254	464	26.5 (4.6)				
Castano Betancourt, 2013	Europe (The Netherlands)	Community	Radiological	Yes	4733	≥ 55	2721	--	--	GP records	5	11	7
				No	6261	≥ 55	--	--	--				
Cacciatore, 2014	Europe (Italy)	Community	Clinical + Radiological	Yes	698	74.8 (6.5)	559	--	27.0 (5.1)	Death certificates	12	13	6
				No	590	72.7 (6.9)	175	--	25.8 (4.5)				
Haugen, 2015	North America (USA)	Community	Clinical + Radiological	Yes	1162	66.3 (7.6)	422	55	27.9 (4.6)	Linkage to different registries	20	14	9
				No	622	57.6 (6.4)	303	37	27.4 (4.5)				
Kluzek,	Europe (UK)	Community	Clinical +	Yes	689	57.5 (6.0)	709	31	--	Death certificates	23	13	9

Study	Region	Setting	OA definition	OA	N	Age (SD)			BMI (SD)	Mortality ascertainment			
2015			Radiological	No	940	55.0 (5.7)	940	35	--				
Liu, 2015	Asia (China)	Community	Clinical + Radiological	Yes	244	62.0 (10.2)	163	--	23.7 (3.7)	Interview with relatives	8	7	8
				No	1806	56.0 (7.7)	877	--	--				
PRO.V.A. study	Europe (Italy)	Community	Clinical + Radiological	Yes	1857	77.5 (7.9)	1233	473	28.0 (4.8)	Death certificates	4	21	7
				No	1068	74.6 (7.6)	515	218	26.8 (4.2)				

Abbreviations: BMI: body mass index; CVD: cardiovascular disease; GP: general practitioner; NOS score: Newcastle Ottawa scale score; OA: osteoarthritis; SD: standard deviation.

Table 4. Adjusted all-cause mortality risk for strata of different moderators

Moderator	Strata	Analysis details	Adjusted HRs
Continent	Europe	*Pooled estimate*, HR (95%CI) P-value for HR *Heterogeneity, I² (P-value)* *Number of studies*	1.18 (1.08-1.28) <0.001 47% (0.13) 4
	Other	*Pooled estimate*, HR (95%CI) P-value for HR *Heterogeneity, I² (P-value)* *Number of studies* P-value *	1.06 (0.80-1.25) 0.68 82% (0.004) 3 0.82
Study quality†	NOS score ≤7	*Pooled estimate*, HR (95%CI) P-value for HR *Heterogeneity, I² (P-value)* *Number of studies*	1.14 (0.96-1.36) 0.13 64% (0.06) 3
	NOS score >7	*Pooled estimate*, HR (95%CI) P-value for HR *Heterogeneity, I² (P-value)* *Number of studies* P-value*	1.09 (0.84-1.39) 0.53 74% (0.01) 4 0.74
Number of adjustments †	<13	*Pooled estimate*, HR (95%CI) P-value for HR *Heterogeneity, I² (P-value)* *Number of studies*	1.18 (1.10-1.27) <0.0001 8% (0.34) 3
	≥13	*Pooled estimate*, HR (95%CI) P-value for HR *Heterogeneity, I² (P-value)* *Number of studies* P-value *	1.00 (0.81-1.26) 0.95 63% (0.05) 4 0.18
Follow-up duration †	<15	*Pooled estimate*, HR (95%CI) P-value for HR *Heterogeneity, I² (P-value)* *Number of studies*	1.17 (1.00-1.38) 0.05 53% (0.09) 4
	≥15	*Pooled estimate*, HR (95%CI) P-value for HR *Heterogeneity, I² (P-value)* *Number of studies* P-value*	1.02 (0.76-1.36) 0.91 79% (0.008) 3 0.39
Diagnosis of death	Death certificates	*Pooled estimate*, HR (95%CI) P-value for HR *Heterogeneity, I² (P-value)* *Number of studies*	1.18 (1.08-1.28) <0.001 47% (0.13) 4
	Others	*Pooled estimate*, HR (95%CI) P-value for HR *Heterogeneity, I² (P-value)* *Number of studies* P-value *	1.06 (0.80-1.25) 0.68 82% (0.004) 3 0.82
Diagnosis of osteoarthritis	Radiological + clinical	*Pooled estimate*, HR (95%CI) P-value for HR *Heterogeneity, I² (P-value)*	1.07 (0.85-1.34) 0.57 65% (0.02)

Bolded HR values: p<0.05

Abbreviations: HR: hazard ratio; NOS: Newcastle-Ottawa Scale

[*] The P-value for the t-test between the two statistical analysis strata according to meta-regression procedure.

[†] Stratification was performed by median NOS score, median follow-up time and median number of adjustments as appropriate.