


Association Between Osteoarthritis and Social Isolation: Data From the EPOSA Study

Paola Siviero, MSc,*  Nicola Veronese, MD,* Toby Smith, PhD,[†] Brendon Stubbs, PhD,^{‡§} Federica Limongi, PhD,* Sabina Zambon, PhD,[¶] Elaine M. Dennison, PhD,^{||} Mark Edwards, PhD,^{||} Cyrus Cooper, PhD,^{†||} Erik J. Timmermans, PhD,^{**} Natasja M. van Schoor, PhD,^{**} Suzan van der Pas, PhD,^{**} Laura A. Schaap, PhD,^{††} Michael D. Denkiner, PhD,^{‡‡} Richard Peter, PhD,^{§§} Florian Herbolzheimer, PhD,^{¶¶} Ángel Otero, PhD,^{|||} Maria Victoria Castell, PhD,^{|||} Nancy L. Pedersen, PhD,^{***} Dorly J.H. Deeg, PhD,^{**} and Stefania Maggi, PhD,* for the EPOSA Research Group

OBJECTIVE: To determine whether there is an association between osteoarthritis (OA) and incident social isolation using data from the European Project on OsteoArthritis (EPOSA) study.

DESIGN: Prospective, observational study with 12 to 18 months of follow-up.

SETTING: Community dwelling.

PARTICIPANTS: Older people living in six European countries.

MEASUREMENTS: Social isolation was assessed using the Lubben Social Network Scale and the Maastricht Social Participation Profile. Clinical OA of the hip, knee, and hand was assessed according to American College of Rheumatology criteria. Demographic characteristics, including age, sex, multijoint pain, and medical comorbidities, were assessed.

RESULTS: Of the 1967 individuals with complete baseline and follow-up data, 382 (19%) were socially isolated and 1585 were nonsocially isolated at baseline; of these individuals, 222 (13.9%) experienced social isolation during follow-up. Using logistic regression analyses, after adjustment for age, sex, and country, four factors were significantly associated with incident social isolation: clinical OA, cognitive impairment, depression, and worse walking time. Compared to those without OA at any site or with only hand OA, clinical OA of the hip and/or knee, combined or not with hand OA, led to a 1.47 times increased risk of social isolation (95% confidence interval = 1.03-2.09).

CONCLUSION: Clinical OA, present in one or two sites of the hip and knee, or in two or three sites of the hip, knee, and hand, increased the risk of social isolation, adjusting for cognitive impairment and depression and worse walking times. Clinicians should be aware that individuals with OA

From the *National Research Council, Institute of Neuroscience-Aging Branch, Padova, Italy; [†]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom; [‡]Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, United Kingdom; [§]Department of Psychological Medicine, King's College, London, United Kingdom; [¶]Department of Medicina, University of Padova, Padua, Italy; ^{||}MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, United Kingdom; ^{**}Department of Epidemiology and Biostatistics, Amsterdam UMC, Amsterdam Public Health Research Institute, VU University Medical Center, Amsterdam, The Netherlands; ^{††}Department of Health Sciences, Faculty of Science, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; ^{‡‡}AGAPLESION Bethesda Hospital, Geriatric Research Unit/Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany; ^{§§}Institute of the History, Philosophy and Ethics of Medicine, Ulm University, Ulm, Germany; ^{¶¶}Department of Gerontology, Simon Fraser University, Vancouver, British Columbia, Canada; ^{|||}Department of Preventive Medicine and Public Health, Unit of Primary Care and Family Medicine, Faculty of Medicine, Universidad Autonoma de Madrid, Madrid, Spain; and the ^{***}Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

Address correspondence to Paola Siviero, MSc, National Research Council, Institute of Neuroscience-Aging Branch, via Giustiniani 2, 35128 Padova, Italy. E-mail: paola.siviero@in.cnr.it

Siviero and Veronese contributed equally to the manuscript.

Correction added September 26, 2019, after first online publication. Paola Siviero and Nicola Veronese were incorrectly listed with secondary affiliations.

DOI: 10.1111/jgs.16159

may be at greater risk of social isolation. *J Am Geriatr Soc* 68:87-95, 2020.

Key words: epidemiology; EPOSA; osteoarthritis; social isolation

Social isolation has been defined as the consequence of a small social network with few social contacts.¹ It has been reported to be associated with poor physical and mental health.²⁻⁴ Previous literature has suggested there is an association between musculoskeletal pain and social isolation.¹ This has been attributed to comorbid disease²⁻⁶ and physical impairment.⁷

The signs and symptoms commonly associated with osteoarthritis (OA), most notably joint pain and reduced function, may increase the risk of social isolation.^{8,9} People with OA often present with health risk factors that may increase their probability of social isolation. These include anxiety and depression, kinesiophobia, physical inactivity, and reduced self-efficacy, which, depending on their severity, may reduce functional independence.^{1,10,11} However, there has been limited research on the relationship between OA and social isolation.¹ Given that the high prevalence of OA^{12,13} in older people, affecting approximately 30% of persons older than 65 years and especially affecting lower limbs, is associated with poor quality of life and disability, a better understanding of social isolation in this specific population has become urgent. If studies show that age is associated with OA, preventative health and social interventions may be able to reduce the impact of social isolation and to improve quality of life.^{8,9}

Given these considerations and basing its analysis on data from the European Project on OsteoArthritis (EPOSA) study, a large European cohort study with 12 to 18 months of follow-up, the current study aimed to determine whether there is an association between OA and incident social isolation and to identify OA's unique contribution in the presence of other predictors for social isolation.

METHODS

Population and Data Collection

Participants were identified from the EPOSA cohort. This is a population-based study of 2942 adults between the ages of 65 and 85 years, who are residents in six European countries (Germany, Italy, The Netherlands, Spain, Sweden, and the United Kingdom). More details about the EPOSA cohort are described elsewhere.¹²

After obtaining written informed consent, all participants underwent a baseline assessment, including a clinical examination and interview on health status performed at home or in a healthcare center between November 2010 and November 2011. A follow-up interview was performed 12 to 18 months later.

The local research ethics committees approved the study (Germany: Universitat Ulm Ethikkommission [312/08]; Italy:

Comitato Etico Provinciale Treviso [XLIV-RSA/AULSS7]; The Netherlands: Medisch Ethische Toetsingscommissie Vrije Universiteit Amsterdam [2002/141]; Spain: Comité Ético de Investigación Clínica del Hospital Universitario La Paz Madrid [PI-1080]; Sweden: Till forskningsetikskommittén vid Karolinska Institutet Stockholm [00-132]; United Kingdom: Hertfordshire Research Ethics Committee [10/H0311/59]).

Outcome

The current study's primary outcome was the social isolation of the participants at baseline and 12 to 18 months later. Social isolation was assessed using two instruments (Supplementary Table S1): Lubben Social Network Scale (LSNS-6)¹⁴ and the Maastricht Social Participation Profile (MSPP).¹⁵

The LSNS-6 tool measures the number and frequency of social contacts with friends (three items) and family members (three items); each question is scored from zero ("not at all") to five ("nine times or more a month"); the total score ranges from zero (indicating high isolation/few social resources) to 30 (indicating low isolation/many social resources); as proposed by Lubben et al, a cutoff point of less than 12 indicates social isolation.¹⁴

The MSPP measures the participant's actual social participation over the preceding 4 weeks.¹⁵ It is composed of three indexes: consumptive participation (CP), which refers to organized activities (six items); formal social participation (FSP), which refers, for example, to volunteer activities (three items); and informal social participation (ISP), which refers to contacts with family members, friends, and acquaintances. The responses are classified using a Likert-type scale from zero ("not at all") to three ("more than twice a week"). Two types of scores are foreseen for each index: diversity (the number of items on which a respondent scored at least one) and frequency (mean score of the items). There is also a total diversity score that refers to the number of indexes with a score of at least one.¹⁵ Higher scores indicate more diverse or more frequent social participation.

Since the EPOSA study needed to harmonize data from six countries, it used two of the three MSPP subscales, the CP and FSP. As the third subscale (ISP) of the MSPP is similar to the Lubben scale, we used the latter, together with its cutoff value (12). The total diversity score of our analysis¹⁵ was calculated considering the CP and the FSP of the MSPP and the LSNS-6. A participant's diversified social participation index was calculated considering the median value of each of the following: total diversity, CP diversity, CP frequency, FSP diversity, and FSP frequency. Since the MSPP does not define cutoff points, we used medians in our analysis as they are considered the most appropriate statistical method for evaluating continuous variable scores.

Social isolation was defined as LSNS-6 of less than 12¹⁵ or less or equal to the median values of all five scores.

Clinical Diagnosis of OA

The study's primary aim was to estimate the effect of the clinical diagnosis of OA on the outcome variable (Supplementary Table S1).

In accordance with the clinical criteria of the American College of Rheumatology¹⁶ and the European League Against Rheumatism,¹⁷ the clinical diagnosis of OA was determined at baseline on the basis of the participant's medical history and a physical examination. Clinical hand OA was diagnosed using specific sections of the AUstralian CANadian Osteoarthritis

Hand Index (AUSCAN).¹⁸ Clinical hip/knee OA, defined as the presence of OA in at least one or both of these joints, was diagnosed using specific Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) sections examining pain and stiffness.^{8,9} Pain in the hip/knee on at least one side was also evaluated during the physical examination.¹⁸

As far as clinical OA was concerned, the participants were classified as: (1) no OA, (2) only hand OA, (3) hip and/or knee OA, or (4) hip and/or knee OA combined with hand OA.

Baseline Characteristics

The baseline characteristics (Supplementary Table S1) considered included: age, sex, country of residence, education level, marital status, income, comorbidity, medications being taken, joint replacements, clinical examination, health, and lifestyle characteristics.

Education level was categorized as up to elementary education vs higher levels of education. Marital status was categorized as being single or never married, divorced, widowed, living apart vs married or cohabitating, or a registered partnership. A monthly income capable of making ends meet was classified as “only with great difficulty,” “with some difficulty,” “fairly easily,” and “easily.” Comorbidity in our analysis referred to: obesity¹⁹; cognitive impairment²⁰; anxiety and depression²¹; self-reported presence of chronic conditions, such as nonspecific lung disease (ie, asthma, chronic bronchitis, or pulmonary emphysema), cardiovascular disease (ie, cardiac valve disease, coronary heart diseases, arrhythmia, pacemaker, or cardiac arrest), peripheral artery disease, diabetes mellitus, stroke, cancer, and osteoporosis, lasting at least 3 months or which caused the individual to seek a physician’s attention (each dichotomized as present vs absent).

Medication used over the past 2 weeks referred to analgesic and/or anti-inflammatory drugs; the variable was dichotomized as medication use vs nonuse. The presence of previous joint replacements was assessed by asking participants if they had ever had joint replacement surgery. If the response was affirmative, the participant was questioned about the location and time of and the reason for the joint replacement. Self-rated health assessment²² was classified as “fair,” “bad,” “very bad,” “good,” and “very good”. Health-related quality of life was assessed using the EuroQoL instrument (health status using five dimensions [EQ-5D] and health status using the visual analogue scale [EQ VAS]).²³

The clinical examination assessed grip strength and walking-test time. The mean of two right and left hand measurements by a dynamometer of the maximum *grip strength* was calculated.²⁴ The *walking-test time* was determined during a timed three-meter walk test. The participants’ times were classified according to country-specific quartiles to take account the specific method used in each country.

Physical activity was measured using the validated Longitudinal Aging Study Amsterdam Physical Activity Questionnaire (LAPAQ),²⁴ which assesses the frequency and duration of activities, such as: walking, cycling, gardening, light and heavy household work, and participation in sports over the past 2 weeks. The total time dedicated to physical activity was calculated in minutes/day, and the total amount of energy was expressed as kilocalories/day.

Health characteristics considered physical function, pain, and stiffness in hand, hip, and/or knee. These were assessed

using subscales of the AUSCAN¹⁸ and of WOMAC.^{8,9} Hip/knee pain and stiffness were defined as the maximum value reported across two joints.

All the AUSCAN and WOMAC subscales (responses ranging from zero [none] to four [extreme]) were normalized to a 0 to 100 range: higher scores indicated worse health status.^{8,9}

Statistical Analysis

Only participants with complete data on all the variables were included in the analyses. As the age and sex distribution varied in the cohorts from the different countries participating in the EPOSA study, they calculated a weighting variable for each individual within each country. The weights, which were based on sex and 5-year age categories, according to the 2010 Standard European Population, were applied only in the descriptive and not in the analytic statistics.¹² Categorical variables were reported as proportions, and continuous variables were reported as means and SDs or medians with interquartile ranges (IQRs). Significant differences between the groups of participants were evaluated using Wilcoxon rank-sum test or Chi-Square test.

The predictors of social isolation were assessed using logistic regression models adjusted for sex, age, and country. Each independent variable was tested using a significance level of $P \leq .20$ as the screening criterion.²⁵ The appropriate categories for the categorical variables and the linearity in the logit for continuous variables were then examined, and the scale for the continuous variables in the logit was checked.

A multivariable model containing all the variables identified for inclusion was fitted using a stepwise selection procedure ($P = .15$ to enter, and $P = .10$ to remain) to select them. Those excluded were controlled for confounding effects. The collinearity of the predictor variables was assessed with the variance inflation factor, using a cutoff of two to exclude a variable. All the interactions between the variables in the final model were checked; interaction terms with $P \leq .10$ were retained in the final model. Odds ratios (ORs) were presented with their 95% confidence intervals (CIs).

Statistical analyses were performed with SAS software (SAS Institute Inc), version 9.4. All the tests were two sided, and $P < .05$ was considered statistically significant.

RESULTS

Of the 2942 individuals originally enrolled in the EPOSA, 1967 (67%) presented complete baseline and follow-up data on all the variables used in the analyses.

With respect to the participants with complete follow-up data ($n = 1967$), those whose data were uncomplete ($n = 488$) were significantly older, more likely to be female, single/divorced/widowed or living apart, and predominantly Dutch (Supplementary Table S2).

The median age of the 1967 participants was 73 years (IQR = 70-77 years); 50% were women, and almost 30% had a diagnosis of OA (Table 1). At baseline, 382 (19%) of the participants were categorized as socially isolated and 1585 were categorized as nonsocially isolated. The nonsocially isolated individuals differed from the socially isolated participants in many important ways (data not shown), including being younger, being residents in all countries except Spain, being more educated, and having

Table 1. Baseline characteristics for social isolation at 12 to 18 months of follow-up

Baseline characteristics	Total (n = 1967)	12-18 mo Follow-up (n = 1585)		P value
		Isolated (n = 222)	Not isolated (n = 1363)	
Age, mean ± SD (median [IQR]), y	73.7 ± 5.3 (73 [70-77])	74.0 ± 5.0 (73.5 [70-78])	73.3 ± 4.8 (73 [70-76])	.058
Female sex, %	49.6	49.7	54.1	.234
Country, %				
Germany	13.3	9.8	15.2	<.001
Italy	15.5	20.3	15.3	
The Netherlands	17.5	20.5	17.6	
Spain	19.7	25.9	14.8	
Sweden	20.4	14.9	22.2	
United Kingdom	13.6	8.7	14.9	
Up to elementary education, %	41.7	47.0	36.8	
Marital status (single/divorced/ widowed/living apart), %	32.4	32.6	31.7	.804
Income, %				
With great difficulty	2.7	2.4	2.5	.001
With some difficulty	13.9	18.5	10.9	
Fairly easily	50.4	53.7	50.3	
Easily	33.1	25.4	36.4	
Obesity (BMI ≥30 kg/m ²), %	24.7	26.1	23.8	.479
Cognitive impairment (MMSE score ≤23), %	6.1	9.7	4.2	.001
Anxiety (HADS ≥8), %	17.8	19.1	16.1	.292
Depression (HADS ≥8), %	9.6	12.0	6.0	.001
Chronic lung disease, %	12.5	11.4	11.5	.97
Cardiovascular disease, %	23.6	22.1	23.1	.744
Peripheral artery disease, %	9.8	10.0	9.3	.728
Diabetes mellitus, %	11.6	12.7	10.9	.453
Stroke, %	4.5	5.8	3.7	.143
Cancer, %	13.9	10.6	14.9	.101
Osteoporosis, %	14.7	16.4	14.4	.448
Analgesic/anti-inflammatory medication, %	24.8	27.6	22.8	.128
Clinical osteoarthritis, %				
No	70.5	63.9	72.2	.007
Hand	8.4	6.9	8.8	
Hip and/or knee	13.6	20.3	12.5	
Hand and (hip and/or knee)	7.6	9.0	6.5	
Joint replacements, %	10.9	12.8	11.0	.452
Self-rated health (fair/bad/very bad), %	33.5	41.0	28.9	<.001
EQ-5D (time trade-off), mean ± SD	0.8 ± 0.2	0.82 ± 0.20	0.84 ± 0.18	.12
(median [IQR]) ^a	(0.8 [0.7-1.0])	(0.8 [0.7-1.0])	(0.85 [0.73-1.0])	
EQ VAS (health state today), mean ± SD	75.9 ± 17.7	73.6 ± 18.5	77.1 ± 17.3	.006
(median [IQR]) ^b	(80 [70-90])	(75 [65-90])	(80 [70-90])	
Grip strength, mean ± SD	28.0 ± 10.1	26.5 ± 9.4	28.5 ± 10.3	.054
(median [IQR]), kg ^c	(26.5 [20-35])	(25.5 [20.0-32.5])	(27.0 [20.5-36.5])	
Walking time, % ^d				
≤Q1	27.4	15.5	31.3	<.001
Q1-Q2	26.2	30.5	25.6	
Q2-Q3	23.6	27.3	22.8	
>Q3	22.8	26.8	20.3	
Total physical activity time (LAPAQ), mean ± SD	201.8 ± 130.8	201.1 ± 137.9	207.3 ± 126.8	.11
(median [IQR]), min/d	(180.0 [110.7-262.5])	(169.3 [105.1-258.9])	(184.3 [120.0-267.9])	
Total physical activity amount (LAPAQ), mean ± SD	870.8 ± 644.4	824.0 ± 635.2	907.3 ± 635.4	.01
(median [IQR]), kcal/d	(717.2 [451.8-1101.1])	(6501.4 [440.0-1026.1])	(754.5 [489.6-1148.9])	

Table 1 (Contd.)

Baseline characteristics	Total (n = 1967)	12-18 mo Follow-up (n = 1585)		P value
		Isolated (n = 222)	Not isolated (n = 1363)	
WOMAC hip/knee physical function score, mean ± SD	7.4 ± 12.4	9.3 ± 13.6	6.6 ± 11.9	.001
(median [IQR]) ^b	(1 [0-10])	(3 [0-13])	(0 [0-8])	
WOMAC hip/knee pain score, mean ± SD	9.6 ± 14.1	10.8 ± 13.4	8.8 ± 13.7	.006
(median [IQR]) ^b	(0 [0-15])	(5 [0-20])	(0 [0-10])	
WOMAC hip/knee stiffness score, mean ± SD	11.9 ± 18.1	14.3 ± 19.0	11.9 ± 17.5	.04
(median [IQR]) ^b	(0 [0-25])	(0 [0-25])	(0 [0-25])	
AUSCAN hand physical function score, mean ± SD	7.7 ± 13.9	8.8 ± 14.5	7.2 ± 13.5	.025
(median [IQR]) ^b	(0 [0-8])	(0 [0-11])	(0 [0-8])	
AUSCAN hand pain score, mean ± SD	7.2 ± 14.9	6.8 ± 14.2	6.9 ± 14.6	.76
(median [IQR]) ^b	(0 [0-5])	(0 [0-5])	(0 [0-5])	
AUSCAN hand stiffness score, mean ± SD	9.4 ± 17.9	10.8 ± 18.3	9.4 ± 18.0	.453
(median [IQR]) ^b	(0 [0-0])	(0 [0-25])	(0 [0-25])	

Note: Weighted data, except numbers of participants, age, and sex.

Abbreviations: AUSCAN, AUStralian CANadian Osteoarthritis Hand Index; BMI, body mass index; EQ-5D, health status using five dimensions; EQ VAS, health status using the visual analogue scale; HADS, Hospital Anxiety and Depression Scales; IQR, interquartile range; LAPAQ, Longitudinal Aging Study Amsterdam Physical Activity Questionnaire; MMSE, Mini-Mental State Examination; Q, quartile; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

^aPossible scores range from -0.594 to 1, with lower values indicating worse health status.

^bPossible scores range from 0 to 100, with 0 indicating worst health status.

^cLower values indicate worse performance.

^dBy country quartiles, class of Q1 or less indicates best performance, and class greater than Q3 indicates worst performance.

higher income. The nonsocially isolated people also presented a significantly lower prevalence of cognitive impairment, anxiety, depression, chronic lung disease, and stroke. They were less likely to use analgesic/anti-inflammatory medications. They reported a lower rate of clinical OA, but only when all the sites (hand, hip, and/or knee) were considered; they had a better health status, and they were more likely to partake in physical activity. They were quicker on the walking test, were stronger, and had less physical function impairment and a lower perception of pain.

According to logistic regression analyses, when clinical OA was adjusted for age, sex, and country, it was associated with social isolation only when it was present in all three sites. But this association was not confirmed in the multivariable model in which low education, low income, depression, joint replacement (protective), and a pattern of fair/bad/very bad self-rated health and anxiety were found to be associated with social isolation (data not shown).

Baseline Demographic and Clinical Characteristics of Incident Cases of Social Isolation

Of the 1585 nonsocially isolated individuals at baseline, 222 (13%) incident cases of social isolation were found 12 to 18 months after baseline (Table 1). The participants who had become socially isolated were less educated and predominantly Spanish, Dutch, and Italian. They reported that their income easily or fairly easily covered their needs. They presented higher percentages of cognitive impairment,

depression, and clinical OA of the hip and/or knee and of the hand and hip and/or knee. They presented worse self-rated health status (self-rated health and EQ VAS) and lower levels of physical activity. They had slower walking times, higher levels of physical functioning impairments, worst stiffness in the hip/knee and hand, and a higher perception of pain in the hip/knee.

Predictors of Incident Social Isolation

According to logistic regression analyses, adjusted for age, sex, and country, clinical OA was associated with incident social isolation. As only the hip and/or knee level was significantly associated to social isolation (data not shown), at the next step, “no OA” or “only hand OA” was compared to “hip and/or knee OA” and “hand OA and hip and/or knee OA.” The other 11 univariable predictors of social isolation that were identified were: income, cognitive impairment, depression, cancer, self-rated health, EQ-5D, EQ VAS, walking time, physical function, pain (dichotomized in correspondence with the third quartile as <15 vs ≥15), and stiffness of the WOMAC hip/knee (Table 2).

Four variables proved significant in the multivariable analysis (Table 2): clinical OA, cognitive impairment, depression, and walking time. The distribution of these variables at baseline among those who will develop social isolation vs those who will remain socially active is presented in Figure 1. When we controlled for confounding factors, no mediators were found. The resulting model uncovered only one significant interaction: depression and sex.

Table 2. Univariable and multivariable models for social isolation 12 to 18 months after baseline

Variable	Univariable-adjusted model					Multivariable-adjusted model				
	β	SE	P value	OR	95% CI	β	SE	P value	OR	95% CI
Clinical osteoarthritis			.004					.032		
No/only hand				1.00					1.00	
Hip and/or knee or hand and (hip and/or knee)	0.487	0.169		1.63	1.17-2.27	0.384	0.179	.032	1.47	1.03-2.09
Income			.160							
With great difficulty				1.00						
With some difficulty	0.654	0.514	.203		0.70-5.27					
Fairly easily	0.333	0.494	.501		0.53-3.67					
Easily	0.110	0.511	.829		0.41-3.04					
Cognitive impairment (MMSE score ≤ 23)	0.673	0.275	.015	1.96	1.14-3.36	0.640	0.282	.022	1.90	1.09-3.29
Depression (HADS ≥ 8) ^a	0.592	0.242	.014	1.81	1.13-2.90	-0.434	0.435	.332	0.66	0.28-1.54
Male sex								.001	2.78	1.50-5.15
Female sex										
Cancer	-0.390	0.235	.097	0.68	0.43-1.07					
Self-rated health (fair/bad/very bad)	0.298	0.164	.068	1.35	0.98-1.86					
EQ-5D (time trade-off) ^b	-0.639	0.373	.087	0.53	0.25-1.10					
EQ VAS (health state today) ^a	-0.007	0.004	.076	0.99	0.99-1.00			.003		
Walking time ^c			.0008							
$\leq Q1$				1.00					1.00	
Q1-Q2	0.742	0.224	.001	2.10	1.36-3.26	0.748	0.225	<.001	2.11	1.36-3.28
Q2-Q3	0.807	0.229	<.001	2.24	1.43-3.51	0.750	0.231	.001	2.12	1.35-3.33
>Q3	0.870	0.238	<.001	2.39	1.50-3.81	0.724	0.244	.003	2.06	1.28-3.33
WOMAC hip/knee physical function score ^d	0.010	0.005	.069	1.01	1.00-1.02					
WOMAC hip/knee pain score (≥ 15) ^d	0.436	0.160	.006	1.55	1.13-2.12					
WOMAC hip/knee stiffness score ^d	0.006	0.004	.139	1.01	1.00-1.01					

Note: Models adjusted for age, sex, and country.

Abbreviations: β , regression coefficient; CI, confidence interval; EQ-5D, health status using five dimensions; EQ VAS, health status using the visual analogue scale; HADS, Hospital Anxiety and Depression Scales; MMSE, Mini-Mental State Examination; OR, odds ratio; Q, quartile; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

^aPossible scores range from 0 to 100, with 0 indicating worst health status.

^bPossible scores range from -0.594 to 1, with lower values indicating worse health status.

^cBy country quartiles, reference class of Q1 or less indicates best performance, and class greater than Q3 indicates worst performance.

^dPossible scores range from 0 to 100, with 100 indicating worst health status.

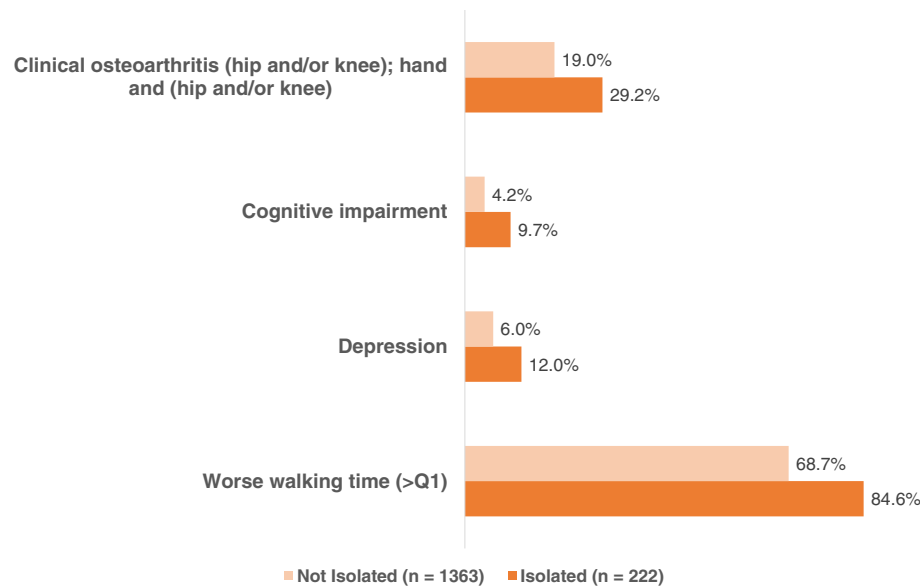


Figure 1. Proportion of isolated and not isolated participants at follow-up by baseline factors. Weighted data. Walking time is classified by country quartiles (Qs); reference class of Q1 or less indicates best performance.

The estimate of the OR for clinical OA of the hip and/or knee combined or not with hand OA was 1.47 (95% CI = 1.03-2.09) times greater than the odds for someone with similar characteristics (with respect to the other covariates in the model) without OA or with only hand clinical OA. The estimate of the OR for cognitive impairment was 1.90 (95% CI = 1.09-3.29). Walking time was associated to social isolation with odds at each level greater than one (quartile [Q] 1-Q2: OR = 2.11; 95% CI = 1.36-3.28; Q2-Q3: OR = 2.12; 95% CI = 1.35-3.33; >Q3: OR = 2.06; 95% CI = 1.28-3.33). The odds of incident social isolation for a person with worse walking times was two times greater than the odds for a person whose walking time was better (\leq Q1).

There was an interaction between depression and sex: each increased the odds of social isolation in the presence of the other. Females who were depressed were found to be almost three times more likely to become socially isolated 12 to 18 months after baseline with respect to their female counterparts without depression (OR = 2.78; 95% CI = 1.50-5.15).

DISCUSSION

This study shows that OA increases the risk of incident social isolation onset. People with hip and/or knee OA combined or not with hand OA at baseline are at increased risk of social isolation in a community cohort. The presence of cognitive impairment and worse walking times in both sexes and depression in the females also increased the risk of becoming socially isolated during the follow-up period.

While it is absolutely known that a complex of deficits, including mobility limitations, predict isolation, we focused on OA, because in our opinion it is interesting that OA remains an independent predictor in the multivariate analyses, even after adjusting for functional limitations and pain. Moreover, as we have previously reported,²⁶ OA has an independent effect also on self-reported physical function impairment, even after adjusting for pain, which can probably be explained by

the “expected pain” that OA may cause during physical activity. Probably, the fear of pain is more important than pain itself as far as OA patients are concerned. This would explain why OA independently predicts isolation.

A large meta-analysis examining 148 studies assessing the association of social isolation and mortality reported that individuals who had more supportive social relationships had a lower mortality risk.²⁷ Similarly, socially isolated older adults tend to have an increased risk of experiencing a decline in mobility.²⁸ Finally, social isolation is associated with an increased risk of cardiovascular disease²⁹ and dementia.³⁰ Since social isolation is a potentially reversible condition, increasing research efforts are attempting to identify as early as possible socially isolated older people.

This study was the first analysis to assess an association between OA and social isolation based on prospective data. Several explanations for the association could be proposed. First, people with OA are more disabled and show poorer physical performance, which are both independent risk factors for social isolation.³¹ Moreover, worse walking times in the patients studied were found to be a significant predictor of social isolation. Second, OA has also been associated with depression.³¹ In the current study, depression was, in fact, another significant predictor of social isolation.³²

The findings suggest that people with OA are at increased risk of social isolation. Given the important negative health outcomes associated with social isolation, interventions should be developed and tested to address this unmet healthcare need. These should include forms of physical activity, social engagement, and community participation as well as some type of psychological assistance.³³ According to a systematic review on interventions to reduce social isolation, educational and social activities targeting specific groups can lower social isolation in older people.³⁴ Referring older adults with OA to social activity/senior centers in their area offering these types of activities may be useful, especially when these interventions are specifically designed for older people with OA presenting physical impairments limiting social participation.

The study presents some limitations. First, the presence of comorbidity was evaluated on the basis of self-reported information and was not ascertained clinically. Self-reported information regarding comorbidities has nevertheless a good accuracy compared to gold standard methods of diagnosis.³⁵ Second, although a 12- to 18-month follow-up time may be considered insufficient to determine incident cases of social isolation, a large number of participants did become socially isolated during that time period. Third, variables linked to life events, such as the death of a family member or friend or being admitted to the hospital, which may be important predictors of isolation, were not considered by the designers of the EPOSA study. Finally, the high number of participants whose data were incomplete might have caused a selection bias. Nevertheless, the high number of participants living in six different European nations who were studied can be considered the study's strength. Moreover, standardized international guidelines were used for the clinical diagnosis of OA in all participants.¹²

CONCLUSION

In conclusion, data from the EPOSA study suggest that OA is associated with incident social isolation, adjusting for cognitive impairment, depression, and worse walking times. Future research is warranted.

ACKNOWLEDGMENTS

The corresponding author, Siviero, affirms that she has listed everyone who contributed significantly to the work and has obtained written consent from all contributors who are not authors and are named in this section. Appreciation is expressed to Linda Inverso Moretti for assistance in editing the manuscript.

Financial Disclosure: The study was supported by a noncommercial private funder. The Indicators for Monitoring COPD [Chronic Obstructive Pulmonary Disease] and Asthma-Activity and Function in the Elderly in Ulm study was supported by the European Union (No. 2005121) and the Ministry of Science, Baden-Württemberg. The Italian cohort study is part of the National Research Council Project on Aging. The Longitudinal Aging Study Amsterdam is financially supported by The Netherlands Ministry of Health Welfare and Sports, Directorate of Long-Term Care. The Peñagrande study was partially supported by the National Fund for Health Research (Fondo de Investigaciones en Salud) of Spain (project Nos. FIS PI 05/1898, FIS RETICEF RD06/0013/1013, and FIS PS09/02143). The Swedish Twin Registry is supported in part by the Swedish Ministry of Higher Education. The Hertfordshire Cohort Study is funded by the Medical Research Council of Great Britain, Arthritis Research UK, the British Heart Foundation, and the International Osteoporosis Foundation. Smith and Cooper are supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre. The views expressed are those of these author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

Conflicts of Interest: The authors have no conflicts.

Author Contributions: Siviero has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Smith, Stubbs, Zambon, Dennison, Edwards, Cooper, van Schoor, van der Pas, Schaap, Denkinge, Peter, Otero, Castell, Pedersen, Deeg, and Maggi.

Acquisition of data: Siviero, Limongi, Zambon, Cooper, Dennison, Edwards, Timmermans, van der Pas, Schaap, van Schoor, Denkinge, Peter, Herbolsheimer, Otero, Castell, Pedersen, Deeg, and Maggi.

Analysis and interpretation of data: Siviero, Veronese, Smith, Stubbs, Limongi, Dennison, Edwards, Cooper, Timmermans, van Schoor, van der Pas, Schaap, Denkinge, Peter, Herbolsheimer, Castell, Pedersen, Deeg, and Maggi.

Preparation of manuscript: All the authors contributed to the drafting and critical revision of the manuscript, and all the authors have approved the final manuscript.

Sponsor's Role: The sponsor had no role in the study design; the collection, analysis, and interpretation of the data; the writing of the report; and the decision to submit the article for publication.

REFERENCES

- Ethgen O, Vanparijs P, Delhalle S, Rosant S, Bruyère O, Reginster JY. Social support and health-related quality of life in hip and knee osteoarthritis. *Qual Life Res.* 2004;13:321-330.
- Veronese N, Cereda E, Maggi S, et al. Osteoarthritis and mortality: a prospective cohort study and systematic review with meta-analysis. *Semin Arthritis Rheum.* 2016;46:160-167.
- Veronese N, Punzi L, Sieber C, et al. Sarcopenic osteoarthritis: a new entity in geriatric medicine? *Eur Geriatr Med.* 2018;9:141-148.
- Veronese N, Smith T, Reginster JY, et al. Osteoarthritis increases the risk of cardiovascular disease: data from the osteoarthritis initiative. *Osteoporos Int.* 2017;28:S58-S59.
- Veronese N, Stubbs B, Solmi M, et al. Association between lower limb osteoarthritis and incidence of depressive symptoms: data from the osteoarthritis initiative. *Age Ageing.* 2017;46:470-476.
- Veronese N, Stubbs B, Solmi M, et al. Knee osteoarthritis and risk of hypertension: a longitudinal cohort study. *Rejuvenation Res.* 2018;21:15-21.
- McAlindon T, Cooper C, Kirwan J, et al. Determinants of disability in osteoarthritis of the knee. *Ann Rheum Dis.* 1993;52:258-262.
- 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.* 1988;15:1833-1840.
- Roorda L, Jones C, Waltz M, et al. Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. *Ann Rheum Dis.* 2004;63:36-42.
- Herbolsheimer F, Schaap LA, Edwards MH, et al. Physical activity patterns among older adults with and without knee osteoarthritis in six European countries. *Arthritis Care Res.* 2016;68:228-236.
- Timmermans EJ, de Koning EJ, van Schoor NM, et al. Within-person pain variability and physical activity in older adults with osteoarthritis from six European countries. *BMC Musculoskelet Disord.* 2019;20:12.
- Van Der Pas S, Castell MV, Cooper C, et al. European project on osteoarthritis: design of a six-cohort study on the personal and societal burden of osteoarthritis in an older European population. *BMC Musculoskelet Disord.* 2013;14:138.
- Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet.* 2019;393:1745-1759.
- Lubben J, Blozik E, Gillmann G, et al. Performance of an abbreviated version of the Lubben Social Network Scale among three European community-dwelling older adult populations. *Gerontologist.* 2006;46:503-513.
- Mars GM, Kempen GI, Post MW, et al. The Maastricht social participation profile: development and clinimetric properties in older adults with a chronic physical illness. *Qual Life Res.* 2009;18:1207-1218.
- Altman RD. Classification of disease: osteoarthritis. *Seminars in Arthritis and Rheumatism.* Canada, Vancouver: Elsevier; 1991;20(6):40-47.

17. Zhang W, Doherty M, Leeb B, et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. *Ann Rheum Dis.* 2009;68:8-17.
18. Bellamy N, Campbell J, Haraoui B, et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. *Osteoarthr Cartil.* 2002;10:863-869.
19. World Health Organization Obesity: preventing and managing the global epidemic. report of a WHO consultation. *World Health Organ Tech Rep Ser.* Vol 894:i-xii; 2000:1-253.
20. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc.* 1992;40:922-935.
21. Zigmond A, Snaith R. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67:361-370.
22. van Sonsbeek J. The self-rating of health: methodological effects of the rating of health in health interview surveys. *Maandbericht Gezondheid.* 1991;10:15-23.
23. Brooks R, Rabin R, De Charro F. The Measurement and Valuation of Health Status Using EQ-5D: A European Perspective: Evidence From the EuroQol BIOMED Research Programme. The Netherlands: Springer Science & Business Media; 2013.
24. Roberts HC, Denison HJ, Martin HJ, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing.* 2011;40:423-429.
25. Hosmer DW Jr, Lemeshow S, Sturdivant RX. *Applied Logistic Regression.* New Jersey, Hoboken: John Wiley & Sons; 2013.
26. Zambon S, Siviero P, Denkinger M, et al. Role of osteoarthritis, comorbidity, and pain in determining functional limitations in older populations: European project on osteoarthritis. *Arthritis Care Res.* 2016;68(6):801-810.
27. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. *PLoS Med.* 2010;7:e1000316.
28. Luo Y, Hawkey LC, Waite LJ, Cacioppo JT. Loneliness, health, and mortality in old age: a national longitudinal study. *Soc Sci Med.* 2012;74:907-914.
29. Valtorta NK, Kanaan M, Gilbody S, Ronzi S, Hanratty B. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. *Heart.* 2016;102:1009-1016.
30. Rafnsson SB, Orrell M, d'Orsi E, Hogervorst E, Steptoe A. Loneliness, social integration, and incident dementia over 6 years: prospective findings from the English Longitudinal Study of Ageing. *J Gerontol B Psychol Sci Soc Sci.* 2017. <https://doi.org/10.1093/geronb/gbx087>. [Epub ahead of print].
31. Iredell H, Grenade L, Nedwetzky A, et al. Reducing social isolation amongst older people: implications for health professionals. *Geriatrics.* 2004;22:13.
32. Santini ZI, Fiori KL, Feeney J, Tyrovolas S, Haro JM, Koyanagi A. Social relationships, loneliness, and mental health among older men and women in Ireland: a prospective community-based study. *J Affect Disord.* 2016; 204:59-69.
33. Routasalo PE, Tilvis RS, Kautiainen H, Pitkala KH. Effects of psychosocial group rehabilitation on social functioning, loneliness and well-being of lonely, older people: randomized controlled trial. *J Adv Nurs.* 2009;65:297-305.
34. Cattan M, White M, Bond J, et al. Preventing social isolation and loneliness among older people: a systematic review of health promotion interventions. *Ageing Soc.* 2005;25:41-67.
35. Galenkamp H, Huisman M, Braam AW, Schellevis FG, Deeg DJH. Disease prevalence based on older people's self-reports increased, but patient-general practitioner agreement remained stable, 1992-2009. *J Clin Epidemiol.* 2014; 67:773-780.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1: Construction of variables.

Supplementary Table S2: Characteristics of excluded participants at baseline and 12 to 18 months later.