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Clinical osteoarthritis of the hip and knee and fall risk: The role of low physical functioning and pain medication

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ABSTRACT

Objective: Several studies have found an increased fall risk in persons with osteoarthritis (OA). However, most prospective studies did not use a clinical definition of OA. In addition, it is not clear which factors explain this risk. Our objectives were: (1) to confirm the prospective association between clinical OA of the hip and knee and falls; (2) to examine the modifying effect of sex; and (3) to examine whether low physical performance, low physical activity and use of pain medication are mediating these relationships.

Methods: Baseline and 1-year follow-up data from the European Project on OSteoArthritis (EPOSA) were used involving pre-harmonized data from five European population-based cohort studies (ages 65–85, n = 2535). Clinical OA was defined according to American College of Rheumatology (ACR) criteria. Falls were assessed using self-report.

Results: Over the follow-up period, 27.7% of the participants fell once or more (defined as faller), and 9.8% fell twice or more (recurrent faller). After adjustment for confounding, clinical knee OA was associated with the risk of becoming a recurrent faller (relative risk=1.55; 95% confidence interval: 1.10–2.18), but not with the risk of becoming a faller. No associations between clinical hip OA and (recurrent) falls were observed after adjustment for confounding. Use of opioids and analgesics mediated the associations between clinical OA and (recurrent) falls, while physical performance and physical activity did not.

Conclusion: Individuals with clinical knee OA were at increased risk for recurrent falls. This relationship was mediated by pain medication, particularly opioids. The fall risk needs to be considered when discussing the risk benefit ratio of prescribing these medications.

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Introduction

About one in three persons aged 65 years and older experience a fall in a year, and about 15% fall twice or more [1–3]. Because of physiological changes during aging acting on sensorimotor and cognitive aspects, the incidence of falls increases with age [4,5]. In addition to soft-tissue injuries, falls may lead to more serious injuries, such as fractures and head trauma [6,7]. Falls may also lead to fear of falling, decreased physical function, restriction of physical activities, loss of independence, a higher mortality risk and high health care costs [4,6,8–11]. According to the American College of Rheumatology (ACR), clinical osteoarthritis (OA) is defined by pain in combination with other symptoms, such as stiffness [12]. As a consequence of these symptoms, persons with OA may have impaired physical function and consequently, an increased fall risk.

Several prospective studies have shown an association between OA and falls. Women with radiographic hip OA had a reduced risk for recurrent falls, while women with self-reported, physician-diagnosed OA had an increased risk [13]. In another study, postmenopausal women with self-reported, physician-diagnosed OA had an increased risk for falls [14]. An increasing number of lower-extremity symptomatic OA joints [15], i.e. a combination of patient-reported symptoms and radiographic evidence of OA in the same joint, and early diagnosed clinical hip and knee OA [16] were associated with an increased odds for falling. Finally, radiographic knee OA in combination with symptoms of pain was associated with injurious falls in men, but not in women [17]. Although most of these results pointed in the same direction, different definitions of OA were used and not all studies used a clinical definition. In an earlier study from our group it was shown that clinical OA only partly overlaps with radiographic OA and self-reported OA [18]. As the clinical symptoms, and associated consequences, might induce the increased fall risk, it is important to focus on a clinical definition of OA when studying the association with falls. In addition, a clinical definition might be most relevant for clinical practice. In the above studies, it is not clear whether sex is an effect modifier in the relationship between OA and falls as two studies were performed in women only, two studies found an association in both men and women, and one study found an association in men but not in women.

It is important to study by which mechanism clinical OA leads to falls as this might give clues for prevention. In a previous report of our European Project on OSteoArthritis (EPOSA), associations between clinical OA of the hip and knee and decreased physical performance were observed [19]. Components of physical performance, such as impaired balance and muscle weakness were also identified as risk factors for fall in clinical knee OA in a recent systematic review [20]. In addition, clinical OA of the knee was shown to be associated with lower physical activity levels [21]. Both low physical performance and low physical activity might increase the risk of (recurrent) falls [22–24]. However, up till now the mediating effects of physical performance and physical activity have not been examined. Another potential mediator might be use of pain medication. Pain is one of the key symptoms in the definition of clinical OA as proposed by the ACR [12]. Because of this pain, analgesics are often prescribed to people with clinical OA [25], which may lead to improvement of physical function. On the other hand, use of analgesics, especially opioids [26], has been related to an increased risk of falls, and therefore, the mediating effects of use of analgesics and opioids will be examined.

To summarize, the first objective of our study was to confirm whether a clinical diagnosis of hip and knee OA, according to the ACR criteria, is related to an increased fall risk. The second objective was to examine whether sex is an effect modifier in this relationship. The third objective was to examine the potentially mediating effects of physical functioning, physical activity, and use of analgesics and opioids. The study was performed using data of the EPOSA study, a prospective, population-based cohort study in community-dwelling older men and women from different European countries.

Materials and methods

Design and participants

Baseline and follow-up data were used from the EPOSA study, which is a European study focusing on the personal and societal burden of OA, and its determinants, in older persons. A detailed description of the study design and data collection of the EPOSA study has been published previously [27]. In summary, random samples were taken from five existing population-based cohorts from Germany (GER), the Netherlands (NL), Spain (ES), Sweden (SWE), and the United Kingdom (UK). In Italy (IT), a new sample was drawn. Out of 4040 persons who were invited, a total of 2942 participants participated (response rate 72.8%, for more details [27]). The age-range was between 65 and 85 years in most countries except for the UK, which had an age-range of 71–79 years. There were no further inclusion or exclusion criteria.

For the current sub-study, German participants were excluded from the analyses as no data on fall rate were available (n = 407) leaving 2535 participants for the analyses. Data collection started from November 2010 to March 2011 in all countries. All participants were interviewed at baseline and after 12–18 months of follow-up by a trained researcher at home or in a clinical center, using a standardized questionnaire and a clinical exam. An English version of the questionnaire was developed during a workshop with all EPOSA partners at the start of the project. The questionnaire was translated (and retranslated) into different languages. In addition, a rheumatologist (M.H. Edwards, UK) visited all sites, together with one of the researchers (S. van der Pas, NL). The rheumatologist gave trainings to prospective interviewers to ensure that the clinical exam of the OA measurement was performed in a standardized way in all countries. He also made a videotape showing how the clinical exam should be performed. The researcher trained the questionnaire and other clinical measurements. For all five countries, the study design and procedures were approved by the Medical Ethics committees of each site (NL: Medisch Ethische Toetsingscommissie Vrije Universiteit Amsterdam [2002/141]; ES: Comité Ético de Investigación Clínica del Hospital Universitario La Paz Madrid [PI-1080]; SWE: Till forskningsetikkommittén vid Karolinska Instituted Stockholm [00–132]; UK: Hertfordshire Research Ethics Committee [10/H0311/59]; Italy: Comitato Etico Provinciale Treviso[XLIV-RSA/AULSS7]), and research was performed in compliance with the Helsinki Declaration. All participants provided written informed consent.

Independent variables

Independent variables include: clinical hip OA and clinical knee OA. Diagnoses of clinical hip OA and knee OA were based on both self-report and physical examination using algorithms based on the ACR clinical classification criteria [12]. Clinical hip OA was defined as: pain in the hip as evaluated by the Western Ontario and McMaster Universities OA Index (WOMAC) pain subscale score (score of 3 or higher out of 20), plus all of: pain associated with hip internal rotation in at least one side; morning stiffness lasting <60 min evaluated by the WOMAC stiffness subscale (score from 'mild' to 'extreme'); and over 50 years of age [28,29]. Clinical knee OA was defined as: pain in the knee as evaluated by the WOMAC pain subscale score (score of 3 or higher out of 20), plus any 3 of: morning stiffness lasting <30 min evaluated by the WOMAC stiffness subscale (score from 'mild' to 'extreme'); crepitus on active motion in at least one side; bony tenderness in at least one side; bony enlargement in at least one side, no palpable warmth of synovium in both knees; and over 50 years of age. For more details, see design paper [27].

Dependent variables

Falls were assessed at follow-up using 2 questions: (1) Did you fall in the past year? (2) If yes, how often did you fall in the past year?. Two dichotomous outcomes were defined: fallers (1 or more falls) versus no fallers (0 falls); recurrent fallers (2 or more falls) versus no recurrent fallers (0–1 falls); and one trichotomous outcome: 2 or more falls, 1 fall, 0 falls.

Potential effect modifier

Sex was examined as a potential effect modifier.

Potential confounders

Potential confounders were selected based on earlier studies on OA and fall risk and on studies examining risk factors for falls in the general population or in persons with OA: age [13,15,17,30], sex (if no effect modifier) [15,17], country, level of education [17,31], body mass index (BMI) [15,17,31], smoking [17], alcohol use [31], and number of chronic diseases [17,20]. All confounders were assessed at baseline. Information on age and sex were derived from the existing cohort data. Educational level was assessed by the highest level of education completed. Because of country differences in the distribution of educational level [32], educational level was dichotomized into elementary school (not) completed versus vocational education/general secondary education or higher. BMI was calculated as measured weight in kilograms divided by measured height in meters squared. Smoking (never, former, current) and current alcohol use (no/yes) were assessed by self-report. Number of chronic diseases was assessed by self-report of the presence of chronic non-specific lung disease, cardiovascular diseases, peripheral artery diseases, stroke, diabetes, cancer, and osteoporosis. The number of chronic diseases was categorized into 0, 1, 2 or more chronic diseases.

Potential mediators

Potential mediators were physical performance, physical activity, analgesics use and opioids use. Physical performance was assessed using three tests of walking speed, repeated chair stands and standing balance based on the methods described by Guralnik et al. [19,33]. Total score ranges from 0 to 12 with 12 indicating good performance. Physical activity was assessed using the validated LASA Physical Activity Questionnaire (LAPAQ) [34] and reported in minutes/day. Current use of analgesics (yes/no) and current use of opioids (yes/no) were assessed by self-report. Participants were asked to show which medications, prescribed by a doctor, they had used during the past two weeks. The Anatomical Therapeutic Chemical (ATC) Classification was used to define use of analgesics (NO2) and opioids (NO2A, NO2BE51). Nonsteroidal anti-inflammatory drugs (NSAIDs, M01) were not included as the effect estimate of NSAIDs on falls was small and non-significant in a recent meta-analysis (pooled OR=1.09; 95% CI: 0.96–1.23) [26].

Statistical analyses

First, baseline tables were created in which fallers (1 or more falls) were compared with no fallers (0 falls); and recurrent fallers (2 or more falls) were compared with no recurrent fallers (0–1 falls). Mean differences were tested using Student's t-tests for normally distributed variables; differences in frequencies were tested using Pearson Chi-square Tests. Second, the prevalence of clinical hip and knee OA and the prevalence of (recurrent) falls were calculated for the total population. In the descriptive analyses, sample weights were used to adjust for differences in age and sex distribution across country samples [27].

Before proceeding with the multivariable analyses, multiple imputation of missing values was performed using the Multivariate Imputation by Chained Equations (MICE) procedure using all variables included in the models [35]. Based on the percentage of participants with missing data on at least one variable (25%), we created 25 different imputed data sets [36]. Based on evaluation of the missing data patterns and reasons for non-response, it was assumed that the data fulfilled the missing at random (MAR) assumption. Rubin's rules were applied for pooling estimates across the imputed datasets [37].

Cox Proportional Hazards Model with equal survival time for all subjects was used to examine the association between clinical OA of the hip and knee, respectively, and the risk of becoming a faller or recurrent faller. By using equal survival time for all subjects, Cox Proportional Hazards Model generates a relative risk instead of an odds ratio. As the prevalence of falls is relatively high, an odds ratio would be an overestimation of the true effect. As a first step, it was tested whether sex was an effect modifier in a model including age, sex and country ($P<0.10$). In case of an interaction effect, the analyses were stratified on sex. As a second step, potential confounders were added. In the first model, the analyses were adjusted for age, sex (if no interaction effect was present) and level of education. In the second model, the analyses were adjusted for body mass index, smoking, alcohol use, and number of chronic diseases. To check validity of the multiple imputation procedure, we also performed the above analyses as complete case analyses. As a sensitivity analysis, the associations between clinical OA of the hip and knee, respectively, and number of falls (0, 1, 2 or more falls, 0 falls=reference group) were analyzed using multinomial regression analyses.

Next, potentially mediating effects of physical performance, physical activity, analgesics use and opioids use were examined by decomposing the total effect of clinical OA on (recurrent) falls into a direct and indirect effect. The direct effect is the effect of clinical OA on (recurrent) falls after adjustment for the mediator. The indirect effect was estimated as the multiplication of the effect of clinical OA on the mediator and the effect of the mediator on (recurrent) falls after adjustment for clinical OA [38]. The indirect effect quantifies the effect of OA on recurrent (falls) that is channeled through the potential mediator. In case the indirect effect is statistically significant ($p<0.05$), the total effect is considered to be mediated by the potential mediator. Mediation analyses were performed irrespective of the presence of a significant total effect, as the absence of a significant total effect does not necessarily imply the absence of a direct and indirect effect [39]. When performing mediation analyses it is highly important to carefully choose the adequate time lags between the measurements of the exposure, mediator and outcome, as poorly chosen time lags can be a poor representation of the mediated effects [40]. In our study, we made the assumption that the clinical diagnosis was made prior to the measurement of the mediators and that the outcome was measured after the mediators. In the analyses, the determinant and mediator (a-path) were chosen at baseline, as we know that clinical OA of the hip and knee are characterized by pain and stiffness, which might directly influence physical performance and physical activity. In addition, because pain is a key feature, pain medication is often prescribed immediately after the diagnosis. Falls were assessed during 12 to 18 months of follow-up. Thus, by design, the outcome (falls) takes place after the mediator (b-path). Multivariable regression analyses were performed for continuous outcomes, and Cox Proportional Hazards Model with equal survival time for all subjects for dichotomous outcomes [41,42]. All mediation analyses were adjusted for the complete set of confounding variables. Since the indirect effect usually has a skewed distribution, Monte Carlo 95% confidence intervals using 20,000 replications were estimated for the indirect effect [43]. All analyses were performed in IBM SPSS Statistics version 22, except for the 95% confidence interval around the indirect effect, which was calculated using R statistical software version 3.1.1.

Results

In Table 1, baseline characteristics are presented for fallers (1 or more falls) versus non-fallers (0 falls), and for recurrent fallers (2 or more falls) versus non-recurrent fallers (0–1 falls). Both fallers and recurrent fallers were significantly older, more often female, more often never smokers, had more often 2 or more chronic diseases, lower physical performance scores and were more often users of analgesics and opioids as compared with no (recurrent) fallers. In addition, recurrent fallers were less often alcohol users as compared with no recurrent fallers.

In the total sample, 6.7% had clinical hip OA and 22.1% had clinical knee OA according to the ACR criteria. During follow-up, 27.7% reported a fall (classified as faller) and 9.8% reported two or more falls (classified as recurrent faller).

In Table 2, the associations between clinical hip OA and clinical knee OA, respectively, with falls and recurrent falls are presented. Sex was not an effect modifier of these associations (p-value for interaction ≥ 0.49). Although most associations pointed in the same direction, only the association between clinical knee OA and recurrent falls was statistically significant after adjustment for confounding (RR=1.55; 95% CI: 1.10–2.18 in the fully adjusted model). Similar results were observed in the complete case analyses (data not shown), and when analyzing the outcome number of falls in three categories (0, 1, 2 or more falls) using multinomial regression analyses. A statistically significant association was observed only between clinical knee OA and the risk of 2 or more falls versus 0 falls (OR=1.49; 95% CI: 1.10–2.38), but not for 1 fall versus 0 falls. No significant associations were observed for clinical hip OA in the multinomial regression analyses (data not shown).

In Table 3, it can be seen that use of opioids mediated the associations between hip OA and recurrent falls, and between knee OA and recurrent falls. In addition, use of analgesics mediated the associations between knee OA and (recurrent) falls. Clinical hip and knee OA were significantly related to lower physical performance, but physical performance was not significantly related to (recurrent) falls. Clinical knee OA was significantly related to lower physical activity, but physical activity was not significantly related to (recurrent) falls. The indirect effects through physical performance and physical activity were not statistically significant, indicating that the effect of clinical OA on (recurrent) falls was not mediated by physical performance and physical activity.

Table 2
Associations between clinical OA of the hip or knee and (recurrent) falls.

	RR (95% CI) for one or more falls	RR (95% CI) for recurrent falls
Clinical hip OA		
- Model 1	1.35 (1.00–1.82)*	1.48 (0.93–2.38)
- Model 2	1.34 (0.99–1.81)	1.47 (0.91–2.38)
Clinical knee OA		
- Model 1	1.13 (0.93–1.39)	1.57 (1.13–2.18)*
- Model 2	1.10 (0.90–1.36)	1.55 (1.10–2.18)*

RR=relative risk; 95% CI: 95% confidence interval; OA=osteoarthritis.
* = $p<0.05$
The analyses were performed using Cox Proportional Hazards Model with equal survival time for all subjects. Model 1: Adjusted for age, sex, country and level of education. Model 2: Additionally adjusted for body mass index, smoking, alcohol use, number of chronic diseases.

Discussion

In this study, individuals aged 65–85 years with clinical knee OA had a 1.5 times higher risk to become a recurrent faller in the following year as compared with persons without clinical knee OA. This association was similar for men and women. Use of opioids and use of analgesics were mediators, while physical performance and physical activity were not. No statistically significant associations between clinical hip OA and (recurrent) falls were observed after adjustment for confounding.

Our results are partly in line with earlier prospective studies that observed an association between OA and falls [13–16], but there are

Table 1
Baseline characteristics of fallers versus non-fallers, and recurrent fallers versus non-recurrent fallers (weighted).

	Fallers (n = 555)	Non-fallers (n = 1446)	P-value	Recurrent fallers (n = 195)	Non-recurrent fallers (n = 1801)	P-value	Nr of missings per variable in total population (n = 2535)
Age[a]	74.9 (6.2)	73.9 (5.9)	0.002	76.0 (6.0)	74.0 (6.0)	<0.001	0
Sex (female)[b]	63.6%	54.0%	<0.001	65.6%	55.7%	0.008	0
Educational level[b]	41.4%	42.6%	0.628	44.1%	42.1%	0.589	0
- Elementary school completed or lower	58.6%	57.4%		55.9%	57.9%		
- Vocational education or general secondary education or higher							
Body mass index[a]	27.8 (4.8)	27.6 (4.9)	0.507	28.1 (4.6)	27.6 (4.6)	0.131	65
Smoking[b]	53.8%	47.4%	0.004	57.3%	48.3%	0.013	11
- Never	4.7%	8.3%		3.1%	7.8%		
- Current	41.5%	44.3%		39.6%	43.9%		
- Former							
Alcohol use (yes)[b]	70.0%	73.7%	0.098	64.1%	73.5%	0.005	18
Nr. of chronic diseases[b]	32.5%	38.6%	0.039	27.8%	37.8%	0.020	11
- 0	38.7%	34.5%		39.2%	35.2%		
- 1	28.9%	26.9%		33.0%	26.9%		
- 2 or more							
Physical performance[a, c]	8.1 (2.9)	8.5 (2.5)	0.002	7.6 (3.1)	8.5 (2.6)	<0.001	107
Physical activity (min/day)[d]	151.4 (2.1)	147.2 (2.3)	0.487	148.7 (2.3)	148.2 (2.2)	0.960	49
Analgesics use[b]	22.3%	17.8%	0.020	29.7%	17.9%	<0.001	1
Opioids use[b]	6.5%	3.0%	<0.001	9.2%	3.4%	<0.001	1

OA=osteoarthritis.
[a] Differences in mean were tested using independent Student's t-test.
[b] Differences in frequencies were tested using Pearson Chi-square Test.
[c] Total score ranges from 0–12 with 12 indicating good performance.
[d] LN-transformed data were used in the Student's t-test; in the Table these data were back transformed.

Table 3
Mediation analyses: physical performance, physical activity, analgesics use and opioids use as potential mediators (M) in the association between clinical OA of the hip and knee (Determinant, D) and falls (Outcome, O).

Clinical OA (D)	Mediating variable (M)	Outcome (O)	Effect of D on M (a-path)	Effect of M on O (b-path)	Direct effect (c'-path)	p-value (c'-path)	Indirect effect (a x b)	95% CI (ab)
Hip OA	Physical performance	Falls	−1.440*	−0.024	0.255	0.100	0.035	(−0.013; 0.086)
	LN (Physical activity)	Falls	−0.054	−0.014	0.288	0.061	0.001	(−0.009; 0.012)
	Analgesics use	Falls	0.184	0.272*	0.280	0.068	0.050	(−0.049; 0.183)
	Opioids use	Falls	1.111*	0.285	0.256	0.095	0.317	(−0.062; 0.760)
Hip OA	Physical performance	Recurrent falls	−1.440*	−0.053	0.306	0.219	0.076	(−0.004; 0.166)
	LN (Physical activity)	Recurrent falls	−0.054	−0.044	0.379	0.124	0.002	(−0.013; 0.023)
	Analgesics use	Recurrent falls	0.184	0.417*	0.364	0.139	0.077	(−0.075; 0.283)
	Opioids use	Recurrent falls	1.111*	0.585*	0.309	0.211	0.650	(0.088; 1.353)*
Knee OA	Physical performance	Falls	−1.035*	−0.026	0.072	0.498	0.027	(−0.007; 0.064)
	LN (Physical activity)	Falls	−0.096*	−0.013	0.097	0.358	0.001	(−0.011; 0.014)
	Analgesics use	Falls	0.378*	0.269*	0.076	0.470	0.102	(0.016; 0.217)*
	Opioids use	Falls	0.913*	0.308	0.077	0.472	0.281	(−0.033; 0.657)
Knee OA	Physical performance	Recurrent falls	−1.035*	−0.047	0.385	0.029*	0.049	(−0.009; 0.117)
	LN (Physical activity)	Recurrent falls	−0.096*	−0.032	0.431	0.014*	0.003	(−0.016; 0.024)
	Analgesics use	Recurrent falls	0.378*	0.381*	0.398	0.023*	0.144	(0.015; 0.322)*
	Opioids use	Recurrent falls	0.913*	0.539*	0.391	0.026*	0.492	(0.032; 1.073)*

Analyses were performed using multivariable regression analyses for continuous outcomes and Cox proportional hazards model with equal survival time for all subjects for dichotomous outcomes. Presented are the Beta's unless stated otherwise. All analyses were adjusted for age, sex, country, level of education, body mass index, smoking, alcohol use, number of chronic diseases. The b-path was additionally adjusted for clinical OA. The c'-path was additionally adjusted for the potential mediator.

* $p<0.05$.

some differences. Two studies using a clinical definition of lower limb OA, and of clinical knee and hip OA, respectively, observed associations with one or more falls [15,16]. In the first study, recurrent falling was examined in a sensitivity analysis showing similar results as the results on falls [15]; in the second study, a higher cumulative number of falls was observed in people with early diagnosed hip or knee OA [16]. In our study, we only observed an association of clinical knee OA with recurrent falling, and not with falling. Although the estimates for the association with falling pointed in the same direction, they were weaker. It may be that an association with recurrent falls is easier to detect as a single fall may be coincidental, while recurrent falls are more likely to have an internal, disease-related cause. Another difference is that the second study also found an association between clinical hip OA and falls, while we only found a statistically significant association in the model adjusted for age, sex, country and level of education but not in the fully adjusted model. However, also in the fully adjusted model, estimates pointed in the same direction. Because of the relatively low prevalence of hip OA in our representative sample of community-dwelling older people, power may have been too low to detect a statistically significant difference.

Two other studies examined self-reported, physician-diagnosed OA in women, without specification of the site of OA. In these studies, an increased risk for recurrent falling [13] and falling [14] was observed. Interestingly, in the SOF study, women with radiographic hip OA had a reduced risk for recurrent falls [13]. The associations in the SOF study were not explained by factors known to be associated with falls [13]. It is not clear whether the contradicting results between self-reported and radiographic OA in these studies can be explained by the difference in site (non-specified self-reported OA versus radiographic hip OA), or that OA is only related to falls in the presence of clinical symptoms.

The associations between clinical OA and (recurrent) falls were mediated by pain medication in our study, while physical performance and physical activity were not mediators. In an earlier study performed in persons with or at risk for knee OA, opioid use was related to an increased risk for recurrent falls [44], which is in line with our study. In that study, also persons using antidepressants had an increased risk for recurrent falls. Differences with our study were that all participants had symptomatic knee OA or were at risk for knee OA, the study sample was younger (45–79 years), and that medication use was analyzed as a determinant and not as a mediator.

Besides pain medication, several other factors may contribute to the increased risk for recurrent falls in persons with clinical knee OA. In a review, the role of neuromuscular changes on dynamic postural control were discussed [45]. The authors conclude that greater neuromuscular deficits are seen in musculoskeletal conditions such as OA as compared with normal aging. Neuromuscular changes in OA affecting dynamic postural control include joint pain, reduced proprioception, muscle weakness and diminished muscle power [45]. More advanced mobility measures than our physical performance tests may show a mediating effect of neuromuscular changes in the relationship between clinical OA and falls, and may be worthwhile to study in future research.

In our study, 6.5% of participants used opioids and 22.3% used analgesics (including opioids). The mediating effects of opioids alone were larger than those of analgesics. In a recent randomized controlled trial, patients with moderate to severe back pain or hip or knee OA pain, the use of opioid vs non-opioid medication therapy did not result in significantly better pain-related function over 12 months. The authors conclude that their results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain [46]. In addition, a recent meta-analysis concluded that oral opioids were associated with an increased risk of adverse events of the gastrointestinal, dermatologic and central nervous system [47]. They recommend to follow the treatment algorithm of the taskforce of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), which recommends that opioids should only be used as a step 3 treatment in case of severely symptomatic OA, and preferably for short periods of time [47,48], which we fully agree with. It should be noted that when patients are already using opioids, one should be very careful in stopping this medication, as pain itself might also increase the fall risk (e.g. [49]) and stopping opioids might have other undesirable consequences. Based on our results and the above trial, one might consider lowering the dose and/or replacing opioid by non-opioid medication therapy while closely monitoring pain levels. In addition, one might discuss alternative therapies for relieving pain together with the patient, such as physiotherapy and weight loss. For example, in a Cochrane review it was concluded that land-based therapeutic exercise in knee OA provides short term benefit in terms of reduced pain (high quality evidence) [50]. Finally, other fall prevention strategies that have proven to be successful in persons at risk for falls, such as multifactorial interventions and exercise [51] should be studied in, and adapted for persons with OA.

Strengths of this study are the clinical definition of hip and knee OA according to the ACR criteria; the prospective design of the EPOSA study; the ability to study different mediators; and the large representative sample from five different European countries. It should be noted that although our clinical definition of hip and knee OA was based on the ACR clinical classification criteria, some misclassification might have occurred. Another weakness may be the retrospective self-report of falls as compared to using prospective diaries. Previous research has shown that sensitivity lies between 80 and 89% and specificity between 91 and 95% for the recall of falls in the previous year [52], indicating that some misclassification might have occurred. This may especially be true for persons having cognitive deficits. In addition, it was not possible to adjust for pain as it was highly correlated with our definition of clinical OA. Therefore, we cannot exclude that pain itself is a mediator in the relationship between clinical OA and falls. Finally, because of the low prevalence of hip OA, we might have had too low power to detect an association here.

In conclusion, this study highlights the risk of recurrent falls in patients with clinical knee OA. This relationship was mediated by the use of pain medication, particularly opioids. This needs to be considered when discussing the risk benefit ratio of prescribing these medications. In addition, other mechanisms leading to an increased fall risk in persons with clinical knee OA, such as neuromuscular changes and pain, should be studied in future research.

Declarations of Competing Interest

Professor Cooper reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB. Professor Dennison reports payment for lecture by Pfizer and UCB. Dr. Edwards reports travel/accommodation/meeting expenses paid by Eli Lilly, Pfizer, UCB, Chugai and Abbvie. All other authors: none.

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