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THOMAS, M.J., RATHOD-MISTRY, T., PARRY, E.L., POPE, C., NEOGI, T. and PEAT, George <http://orcid.org/0000-0002-9008-0184>

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Triggers for acute flare in adults with, or at risk of, knee osteoarthritis: a web-based case-crossover study in community-dwelling adults

M.J. Thomas † ‡ *, T. Rathod-Mistry † §, E.L. Parry †, C. Pope †, T. Neogi ||, G. Peat †

† Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Staffordshire, ST5 5BG, UK
‡ Haywood Academic Rheumatology Centre, Midlands Partnership NHS Foundation Trust, Haywood Hospital, Burslem, Staffordshire, ST6 7AG, UK
§ Keele Clinical Trials Unit, David Weatherall Building, Keele University, Staffordshire, ST5 5BG, UK
|| Department of Medicine, Section of Rheumatology, Boston University School of Medicine, 650 Albany Street, Suite X-200, Boston, 02118, MA, USA

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SUMMARY

Objective: To identify proximate causes ('triggers') of flares in adults with, or at risk of, knee osteoarthritis (OA), estimate their course and consequences, and determine higher risk individuals.
Methods: In this 13-week web-based case-crossover study adults aged ≥40 years, with or without a recorded diagnosis of knee OA, and no inflammatory arthropathy who self-reported a knee flare completed a questionnaire capturing information on exposure to 21 putative activity-related, psychosocial and environmental triggers (hazard period, ≤72 h prior). Comparisons were made with identical exposure measurements at four 4-weekly scheduled time points (non-flare control period) using conditional logistic regression. Flare was defined as a sudden onset of worsening signs and symptoms, sustained for ≥24 h. Flare characteristics, course and consequence were analysed descriptively. Associations between flare frequency and baseline characteristics were estimated using Poisson regression.
Results: Of 744 recruited participants (mean age [SD] 62.1 [10.2] years; 61% female), 376 reported 568 flares (hazards) and provided 867 valid control period measurements. Thirteen exposures (eight activity-related, five psychosocial/environmental) were positively associated with flare onset within 24 h (strongest odds ratio estimate, knee buckling: 9.06: 95% confidence interval [CI] 5.86, 13.99; weakest, cold/damp weather: 1.45: 95%CI 1.12, 1.87). Median flare duration was 5 days (IQR 3, 8), less common if older (incident rate ratio [IRR] 0.98: 95%CI 0.97, 0.99), more common if female (IRR 1.85: 95%CI 1.43, 2.39).
Conclusions: Multiple activity-related, psychosocial and environmental exposures are implicated in triggering flares. This evidence can help inform prevention and acute symptom management for patients and clinicians.

Introduction

Osteoarthritis (OA) is a multifactorial syndrome, with heterogeneous long-term trajectories (e.g.,[1]) punctuated by variable episodes of increased pain[2]. Inflammation is common in OA[3] and although the lived experience involves complex biopsychosocial interactions, pain is a cardinal feature[4] and the main reason patients seek healthcare.[5]

Unpredictable pain, or episodic flare, can be distressing and disabling for patients[2], disruptive to active lifestyle behaviours and chronic disease management[6]; often leading to work loss and increased healthcare use. Understanding proximate causes of flares is methodologically challenging but important for patients and clinicians to be able to prevent or minimise their impact.

Building on successful applications in acute-onset disease (e.g., myocardial infarction[7] and 'acute-on-chronic' conditions [e.g., gout[8]]), self-controlled and case-crossover study designs are emerging within the musculoskeletal pain/OA literature (e.g.,[9–13]). These designs are efficient for identifying 'acute-on-chronic' events

* Address correspondence and reprint requests to: Martin J. Thomas, Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Staffordshire, ST5 5BG, UK. Tel.: 44 (0) 1782 734874; fax: 44 (0) 1782 734719.
E-mail addresses: m.thomas@keele.ac.uk (M.J. Thomas), t.rathod@keele.ac.uk (T. Rathod-Mistry), e.parry@keele.ac.uk (E.L. Parry), ppi.primarycare@keele.ac.uk (C. Pope), tneogi@bu.edu (T. Neogi), g.m.peat@keele.ac.uk (G. Peat).

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and recurrent exposures within patients. In OA, modifiable excessive or aberrant load exposures to weight-bearing joints are important drivers of etiopathogenesis[14]. In this study, we postulate that intermittent or transient activity-related exposures, including high joint loading activities, are causes of recurrent flares with important implications for acute symptom management and long-term self-management[15].

In the ACT-FLARE study (ACuTe FLAREs in knee OA), our primary objective was to identify common, consistent proximate causes ('triggers') of flares in adults with, or at risk of, knee OA. Secondary objectives were to, i) estimate flare time course and consequences, and ii) determine whether participant characteristics can identify individuals at higher risk of flares.

Methods

Study design and sample

Adults aged ≥40 years who were resident in England with knee pain, with or without a recorded knee OA diagnosis, with daily access to the internet, and ability to complete questionnaires in English were invited to take part in a 13-week web-based case-crossover study[15,16]. Exclusions included inflammatory arthropathies (including gout), fibromyalgia, joint replacement in the flaring knee or knee surgery in the last 3 months. Participants were identified via three methods: (1) Fifteen general practice (GP) registers (ten, West Midlands; five, South East). Patients with a relevant Read-coded consultation for knee OA or knee OA-related joint symptoms in the last 2 years were identified and invited via mailed invitation and one reminder. (2) Offline community advertisement. Study posters, flyers and business cards were displayed in GPs, pharmacies, hospitals and public libraries across England, where permission was granted. (3) Online social media advertisement. Using Facebook, adverts were targeted at adults ≥40 years. For methods 2 and 3, advertisements directed people to the study registration page where eligibility against the criteria detailed above was self-declared. Ethical approval was obtained from Yorkshire & The Humber-Leeds East Research Ethics Committee (REC reference number: 18/YH/0075). All participants provided informed electronic-consent.

Data collection

Consenting participants who registered an account for login access to the ACT-FLARE study website were invited to complete a Baseline questionnaire, four Scheduled questionnaires (measurement/ascertainment of exposures during control period) and an Event-Driven questionnaire (hazard period) each time they experienced a flare of their knee pain (Fig. 1).

The Baseline questionnaire gathered information on aspects of knee pain[17–26], healthcare use for knee pain[26], general health/physical activity[27–29], and demographic characteristics.

The Scheduled questionnaires, sent at weeks 1, 5, 9 and 13 after Baseline questionnaire completion, featured a matrix reporting exposure to 21 putative activity-related, psychosocial and environmental triggers[29–33] (see Supplementary Data Q1). Questions were answered for day of completion and the 3 days before this. The response options for nine potential trigger questions relating to physical activities were 'not at all', 'a little' or 'a lot'. For the remaining 12 questions response options were 'no/yes'.

Participants who experienced a flare were invited to complete an Event-Driven questionnaire, designed to capture information about the flare and the same potential trigger exposures as in the Scheduled questionnaires, during the day of the flare and the 3 days prior[15]. The Event-Driven questionnaire also invited participants to answer 'yes/no' to a question asking if the flare was unexpected. They were then invited to complete a Daily questionnaire on pain intensity[30], bothersomeness[24], medication use and participant judgement of flare resolution each day until their flare ended. Resolution was defined a priori as return to pre-flare 'normal' state for two consecutive days[15], however this was relaxed to one confirmation due to the lower than expected proportion (36%) meeting the initial definition.

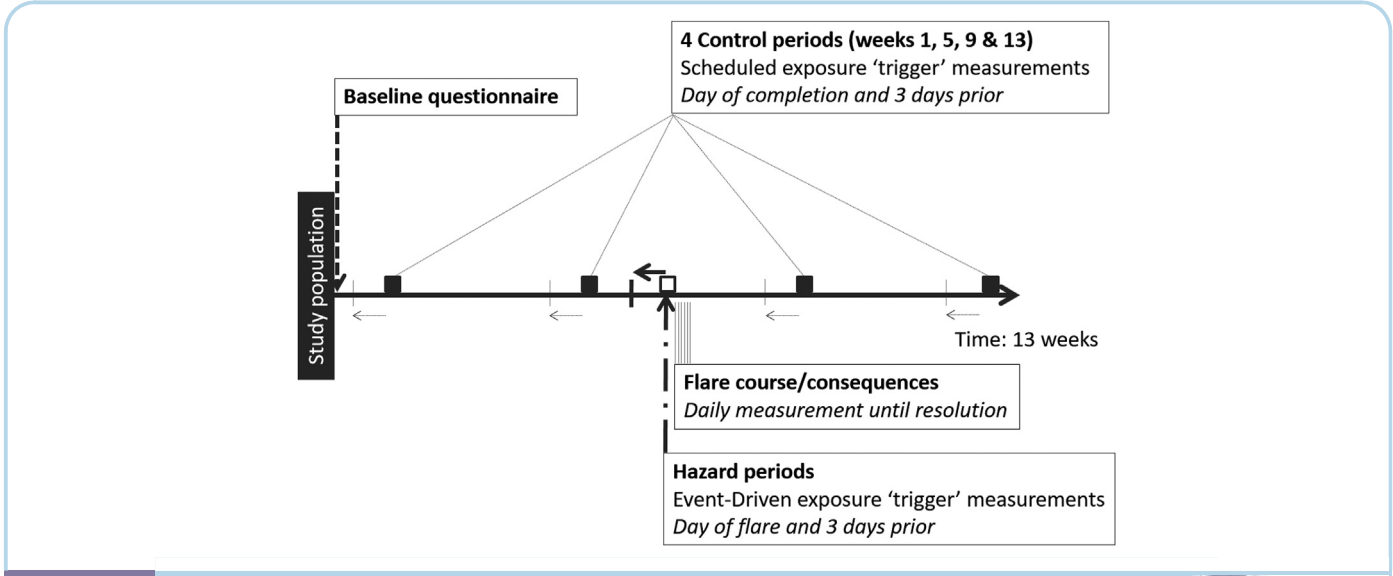

Fig. 1 Schematic representation of the 13-week ACT-FLARE case-crossover study design.

Patient involvement

A Patient Advisory Group confirmed OA flares to be a research priority, provided advice and suggestion across all aspects of preliminary feasibility and pilot work, and inputted to procedures and processes for this full-scale study from inception to dissemination[15,16]. Engagement was via workshops and remote correspondence. A patient with lived experience of OA flares was a co-applicant on the initial research proposal and participated in regular Project Management team meetings across the project lifecycle.

Outcome definition

Self-reported flare of symptomatic knee OA was defined as "an event in the natural course of the condition characterized by a change in the participant's baseline pain that is beyond normal day-to-day variation, sustained for at least 24 h, and is sudden or quick in onset. It may impact on the ability to perform everyday activities and result in an increase in analgesic intake"[15,p9]. This self-determined definition was derived from our pilot study[16], previous literature review[34], discussions with patients and members of the public, and findings from previous survey and daily diary studies[35]. Written explanation and short videos about flares, developed with patients and presented by our patient co-investigator (CP) and clinician-researcher (MJT), were available to view on the ACT-FLARE website for all enrolled and prospective participants for the study duration.

Questionnaire validity

To ensure exposure information was not influenced by a previous flare, questionnaires were only valid for analysis if there was ≥4 days between completion of all hazard and control period questionnaires, and between each flare ending and completion of control period questionnaires.

Statistical analysis

Describing the sample

Our sample size calculation ensured adequate numbers of self-reported flares to sufficiently power the primary analysis identifying potential triggers of knee OA flare[15]. The target sample was 434 participants experiencing a flare. Where available, we compared sociodemographic characteristics of participants of responders and non-responders, and response rates by recruitment method. Summary descriptive statistics were derived for participant demographics and self-reported knee characteristics, as well as features of flares, symptoms, and consequences during flares. Baseline data were collected for left and right knee. For descriptive knee characteristics, the worst knee was selected and reported based on highest 'average pain' score on a 0–10 numerical rating scale (NRS). If scores were equal, the knee with the highest 'worst pain in the last week' followed by the highest 'current pain', followed by random selection were selected. If left, or right knee score was missing, the available knee score was included.

Primary analysis: proximate trigger exposure measurement

With each participant acting as their own control in the analysis, reported trigger exposures in the hazard periods were compared to those reported in the control periods, using conditional logistic regression with m:n matching, so each participant could potentially contribute multiple hazard and control periods[36]. All available controls were utilised and may have occurred before and/or after the hazard period. Odds ratios (OR) with 95% confidence intervals (CI) were derived. Time trends in exposure were examined by comparing exposure frequency across the Scheduled questionnaires at weeks 1, 5, 9 and 13, and before and after the flare. A sensitivity analysis of the primary analysis was restricted to flares that had control periods occurring before and after the hazard period. To explore the exposure induction period, trigger exposure status was compared for day of completion/flare and the 3 days earlier. The proportion of flares deemed unexpected was reported. Sensitivity analyses were conducted by restricting analysis to first flare per participant (to examine carryover effects for multiple flares), flares reported within 3 days of flare onset (to reduce the potential impact of delayed recall), flares reported after baseline (i.e., excluding people who reported to be experiencing a flare at study entry, which could influence how initial questions were answered), spontaneous self-directed flares reported without prompt (i.e., not at Scheduled questionnaire time points[15]), and participants recruited from GP registers (for whom study eligibility was objectively confirmed).

Secondary analysis 1: estimating time course and consequences

Analysis was restricted to participants who reported Event-Driven flare questionnaires and indicated via Daily questionnaires their flare had ended. Unresolved flares were excluded from the analysis as the distribution of flare duration was more skewed (median [interquartile range] 19 [5, 87] days) than resolved flares (6 [3, 11] days). Flare characteristics, and daily course and consequences (pain, bothersomeness, medication use in last 24 h) were analysed descriptively. The Kaplan–Meier curve for time to flare resolution was derived. Effects of covariates on time to flare resolution were assessed using accelerated failure-time model, with generalised gamma survival distribution yielding unadjusted time ratios and 95%CI.

Secondary analysis 2: frequency of acute flares

Analysis was restricted to participants who completed at least two Scheduled questionnaires: the prespecified minimum amount of engagement with study follow-up required for inclusion. Poisson regression with robust standard errors examined the effect of selected baseline participant or knee symptom characteristics on the number of reported flares over the 13-week follow-up period. Unadjusted incidence rate ratios (IRR) and 95%CI were calculated.

All analyses were conducted using STATA V.15.0 (Stata Corporation, Texas, USA).

Results

Study population

Between July 2018 and February 2019, emails were sent to 1454 potentially eligible participants, of whom 744 responded, were eligible and consented to participate (recruitment source: GP registers [515], online advertisement [129], offline advertisement [57], unknown [43]). Participants reporting flares were more likely female (Table I) (Supplementary Figs. S1–2, Tables S1–5). The key descriptive characteristics of the 744 respondents are provided in Table II (Supplementary Tables S6–8).

Proximate triggers of acute flares

During the study period, 714 flares were reported by 493 participants. For the primary analysis, 376 participants provided ≥1 control period and ≥1 hazard period (mean age [SD] 61.8 [10.1] years; 68% female and mean body mass index [SD] 29.5 [5.9] kg/m^2), resulting in 568 flares (hazards) and 867 controls for analysis (Table III). The distribution of baseline characteristics was generally similar between

Characteristics of participants	Completed baseline ($N = 744$)	Completed ≥1 scheduled questionnaire ($N = 591$)	Completed ≥1 flare questionnaire ($N = 493$)
Female	451 (61)	361 (61)	323 (66)
Age (years); mean (SD)	62.1 (10.2)	62.4 (10.1)	61.8 (10.3)
<55	185 (25)	141 (24)	129 (26)
55–64	247 (34)	195 (34)	168 (35)
65+	299 (41)	247 (42)	190 (39)
Males, age; mean (SD)	63.7 (10.4)	64.5 (10.1)	63.7 (10.7)
<55	59 (20)	41 (18)	36 (21)
55–64	90 (31)	70 (31)	49 (29)
65+	140 (48)	116 (51)	83 (49)
Females, age; mean (SD)	61.0 (10.0)	61.1 (9.9)	60.8 (10.0)
<55	126 (29)	100 (28)	93 (29)
55–64	157 (36)	125 (35)	119 (37)
65+	159 (36)	131 (37)	107 (34)
IMD			
Most deprived	99 (13)	74 (13)	73 (15)
2nd most deprived	137 (18)	103 (17)	94 (19)
Mid-deprived	174 (23)	141 (24)	113 (23)
2nd least deprived	191 (26)	149 (25)	123 (25)
Least deprived	142 (19)	124 (21)	90 (18)

Figures are numbers (%) unless otherwise stated. SD, Standard Deviation; IMD, Index of Multiple Deprivation.

Table I Gender, age and deprivation scores between responders at each data collection point

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the 376 eligible and 368 ineligible participants in this analysis, although eligible participants had a higher prevalence of females. Target sample size was exceeded. Thirteen exposures (six physical activities) were positively associated with flare onset within 24 h. The overall strongest positive association was with knee buckling (OR 9.06: 95%CI 5.86, 13.99). The strongest positive physical activity association was with squatting or kneeling (OR ['a lot' vs 'not at all'], 3.30: 95%CI 1.95, 5.59). Three exposures were inversely associated with flares: sitting for long periods without a break (OR 0.67: 95%CI 0.46, 0.98), reducing or missing planned medication (OR 0.34: 95%CI 0.18, 0.63) and cough, cold or minor infection (OR 0.72: 95%CI 0.52, 0.99). The frequency of most physical activity exposures suggested a graded relationship with risk of flare (a lot > a little > not at all). Going up/down stairs, driving, stressful events at work, home, and friend/family related stress were not statistically significantly associated with flares. Flares were reported as unexpected by 70% of participants. Exposure-outcome associations were strongest for exposures occurring within 24 h; exposures up to 3 days prior had lower, if any, significant associations with risk of flare (Supplementary Table S9).

There was little evidence of time trends in exposure during the 13-week study period. The trigger exposure prevalence remained constant across the four Scheduled questionnaires, and before and after a flare was reported. Furthermore, restricting the analysis to flares with control periods on either side of the flare had little impact on the odds ratio estimates (data not shown).

Sensitivity analyses restricted to first flare per participant, flares notified within 3 days of onset, flares reported after baseline, without prompt and GP recruited participants only, did not change the overall interpretation (data not shown). Rates of missing data for triggers were low, with ≥95% of hazard and control periods utilised in modelling.

Time course and consequences of acute flares

Based on 314 participants providing 459 flares with known resolution date, the median (interquartile range) flare duration was 5 (3, 8) days (Supplementary Table S10; Fig. 2). The first recorded NRS pain score was ≥2 compared to average pain at baseline in 44% of participants reporting flares on day of onset. Knee changes noticed since flare onset included stiffness (64%), limping (58%), increased difficulty with everyday activities (57%), sleep disturbance (48%) and swelling (33%) (Supplementary Table S11). Levels of pain, bothersomeness and medication usage reduced over flare episodes (Supplementary Fig. S3; Table S12). No associations were found between age, gender or symptom duration and time to flare resolution, however those with longer symptom duration appeared to have slightly slower resolution (Supplementary Table S13).

Frequency of acute flares

Among 476 participants who engaged throughout study follow-up, 242 (51%) reported ≥1 flare. Flares were less common in older ages (IRR 0.98: 95%CI 0.97, 0.99), and more common in females (IRR 1.85: 95%CI 1.43, 2.39), and those with severe frequent knee pain at baseline (IRR 2.06: 95%CI 1.17, 3.63). Associations with prior knee injury/surgery and deprivation were weak or absent (Supplementary Table S14). These 476 participants had better knee pain, physical function and quality of life than the 268 participants who did not engage in the study (Supplementary Table S15 compares baseline characteristics across ineligible and eligible participants for each primary and secondary objective analysis).

Discussion

Our study provides a comprehensive examination of flare triggers, episode duration and characterisation of higher risk individuals within a large community-based sample of people with, or at risk of, knee OA. We found that a wide range of activity-related, psychosocial and environmental factors transiently increase the risk of an acute flare that typically goes on to last 3–8 days, with two-thirds of sufferers experiencing increased stiffness alongside pain. Flares were most likely to manifest within 24 h of exposure and the strongest positive associations were with

Characteristic	Baseline responders ($N = 744$)
Participant characteristic	
Age (years); mean (SD)	62.1 (10.2)
Female	451 (61)
Current employment	
Employed/Self-employed	325 (44)
Retired	318 (43)
Looking after home and/or family	40 (5)
Unable to work (sick/disabled)	31 (4)
Unemployed/Voluntary work	15 (2)
Full, part-time student	2 (<1)
None of the above	6 (1)
BMI (kg/m^2); mean (SD)	29.2 (5.7)
Family history of total/partial knee replacement	112 (15)
Knee characteristic*	
Time since onset of pain	
<1 year ago	119 (16)
1–4 years ago	269 (36)
5–9 years ago	132 (18)
≥10 years ago	202 (27)
Knee pain pattern in the last year	
Single episode	36 (5)
Few episodes	213 (29)
Few episodes and some pain	261 (35)
Severe episodes and up and down pain	178 (24)
Severe pain all the time	42 (6)
Pain experience over last 6 months	
No knee pain	46 (6)
Pain is predictable	211 (28)
Predictable, becoming more unpredictable	324 (44)
Constant	155 (21)
Pain, aching, stiffness in last month	
None	41 (6)
Few days	114 (15)
Some days	166 (22)
Most days	211 (28)
All days	206 (28)
Worse pain last week (0–10 NRS); mean (SD)	5.5 (2.7)
Least pain last week (0–10 NRS); mean (SD)	3.4 (2.9)
Average pain (0–10 NRS); mean (SD)	4.8 (2.4)
Pain right now (0–10 NRS); mean (SD)	3.4 (2.9)
Bothersomeness of knee pain in the last 24 h	
Not at all	128 (17)
Slightly	175 (24)
Moderately	214 (29)
Very much	164 (22)
Extremely	56 (8)
KOOS Physical Function (0–100); mean (SD)†	39.3 (18.3)
KOOS Quality of Life (0–100); mean (SD)‡	43.7 (23.7)
Flare at present	254 (34)
Varus-valgus malalignment	
Very bow legged	7 (1)
Bow legged	77 (10)
Normal	558 (75)
Knock-knee	81 (11)
Very knock-knee	6 (1)
Previous knee injury	399 (54)
Foot rotation	
Very turned out feet	14 (2)
Turned out feet	190 (26)
Straight	467 (63)
Turned in feet	58 (8)
Very turned in feet	4 (1)

Figures are numbers (%) unless otherwise stated.
SD, Standard Deviation; BMI, Body Mass Index; NRS, Numerical Rating Scale; KOOS, knee injury and Osteoarthritis Outcome Score. Percentages may not add to 100 due to missing data (Supplementary Table S6).

* The index knee was selected based on the knee with highest 'average pain' score on a 0–10 numerical rating scale. If scores were equal, then the knee with the highest 'worst pain in the last week' followed by the highest 'current pain', followed by random selection were selected. If left, or right knee score was missing, the available knee score was included.

† Higher scores indicate worse physical function.
‡ Lower scores indicate worse quality of life.

Table II Participant and knee characteristics of sample

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activity-related exposures. Although flares were slightly more common amongst younger participants of working age, females and those with severe frequent knee pain at baseline, the self-selecting nature of the sample and the possibility that females were more likely to engage with the flare notification system should be recognised.

The direction of our observed associations with exposure to one or more physical activities is consistent with previous study[35], as is our positive association with knee buckling[37]. More broadly, our observed associations with a range of physical and psychosocial exposures are consistent with previous study of back pain[9], knee/hip OA[10], knee OA[11,13] and hip OA[12,38]. Contrasting observations on psychological associations with hip OA[39], may be explained by different exposure measurements. Although our positive association with cold/damp weather contrasts previous study[40], our brief self-report exposure measurement is crude by comparison to the objective weather analysis by Ferreira *et al.*[40].

Collectively, our observations provide support for our hypothesis that intermittent activity-related exposures are risk factors for flares. Mechanical exposures, including occupational physical loading[41,42], often associated with incidence and progression, may also contribute to 'acute-on-chronic' flares. These exposures have been proposed to have an etiological role, and also represent potentially modifiable risk factors for the etiopathogenesis[14]. In the absence of traumatic events (injury), the periodic sudden onset of increased pain (acute flare) may represent short-lived consequences of transient mechanical exposures. Whilst the low-level cumulative and repetitive nature of these exposures may be important for the OA etiopathogenesis, they are likely to be frequent day-to-day encounters, often experienced as innocuous events for many people and not always causal antecedents to a flare[43]. Interestingly, 70% of flares reported during the study were reported as unexpected, but the majority (two-thirds) hold the belief that physical/mechanical factors are their most likely triggers. Further research is needed to confirm whether the cumulative frequency of flare episodes drives OA etiopathogenesis[43]. Our observed median 5-day flare duration, is broadly consistent with previous estimates[35,44]. The nature of trigger exposures and the duration of flare episodes are important insights for patient-healthcare professional consultations, particularly as our data suggest flares appear more common among working age adults.

Collaboratively with patients we defined a self-reported flare lasting ≥24 h to represent a sudden change in perceived pain state, irrespective of pain score. Whilst previous studies have imposed an NRS change score of ≥2 from baseline to define a flare[12,13,35,45], we and our patient group preferred a more patient-centred approach. Previous work by Marty *et al.*[46] showed clearly that patient-identified flares agreed well with clinician-defined flares. The similarity of findings with others[11,13,35,37] also provides some valuable replication and suggest that these associations may not be too highly sensitive to this choice of flare definition. Other signs and symptoms, for example, stiffness, swelling and functional impact may be earlier or more important initial symptoms associated with flare onset. Defining flares and their mechanism of action are important research priorities. Knee changes noticed since flare onset by

Potential trigger	Control periods $N = 867$ N (%)	Hazard periods $N = 568$ N (%)	OR (95% CI)
Physical activities			
Walking outside without a rest			
Not at all	213 (25)	113 (20)	1
A little	476 (55)	292 (52)	1.34 (0.97, 1.86)
A lot	172 (20)	154 (28)	2.41 (1.63, 3.57)
Standing for long periods without a rest			
Not at all	362 (42)	201 (36)	1
A little	408 (47)	237 (43)	1.14 (0.86, 1.52)
A lot	91 (11)	119 (21)	3.29 (2.22, 4.87)
Sitting for long periods without a break			
Not at all	199 (23)	158 (28)	1
A little	451 (52)	259 (46)	0.65 (0.48, 0.89)
A lot	213 (25)	141 (25)	0.67 (0.46, 0.98)
Moderate-to-vigorous physical activity			
Not at all	414 (48)	272 (49)	1
A little	336 (39)	187 (33)	0.90 (0.67, 1.20)
A lot	108 (13)	100 (18)	1.64 (1.12, 2.39)
Going up and down stairs			
Not at all	133 (16)	85 (15)	1
A little	521 (61)	337 (61)	1.14 (0.73, 1.79)
A lot	206 (24)	134 (24)	1.35 (0.82, 2.23)
Driving			
Not at all	365 (43)	238 (43)	1
A little	404 (48)	257 (47)	0.96 (0.71, 1.30)
A lot	80 (9)	58 (10)	1.03 (0.63, 1.70)
Squatting or kneeling			
Not at all	559 (65)	347 (63)	1
A little	260 (30)	144 (26)	1.09 (0.79, 1.51)
A lot	40 (5)	63 (11)	3.30 (1.95, 5.59)
Lifting or moving heavy objects			
Not at all	637 (75)	401 (72)	1
A little	200 (23)	124 (22)	1.00 (0.74, 1.34)
A lot	18 (2)	31 (6)	3.28 (1.62, 6.65)
Going up and down ladders			
Not at all	798 (94)	501 (90)	1
A little	34 (4)	34 (6)	2.10 (1.20, 3.66)
A lot	18 (2)	21 (4)	2.92 (1.35, 6.33)
Slips, trips, sprains, and strains			
Slip, trip or fall			
No	843 (98)	536 (96)	1
Yes	16 (2)	23 (4)	2.33 (1.11, 4.86)
Episode of buckling or giving way			
No	788 (93)	377 (68)	1
Yes	64 (8)	178 (32)	9.06 (5.86, 13.99)
Health and healthcare use			
Reduce or miss medication			
No	792 (93)	535 (96)	1
Yes	60 (7)	20 (4)	0.34 (0.18, 0.63)
Take extra pain medication in anticipation of increased activity/busier			
No	800 (94)	439 (79)	1
Yes	52 (6)	120 (21)	5.37 (3.48, 8.28)
Cough, cold or other minor infection			
No	668 (78)	448 (80)	1
Yes	187 (22)	113 (20)	0.72 (0.52, 0.99)
Stress and other things			
Work-related stress			
No	790 (93)	506 (91)	1
Yes	59 (7)	49 (9)	1.16 (0.72, 1.88)
Home-related stress			
No	767 (89)	484 (86)	1
Yes	92 (11)	77 (14)	1.32 (0.90, 1.93)
Friend/family-related stress			
No	779 (91)	498 (89)	1
Yes	80 (9)	63 (11)	1.11 (0.73, 1.68)
Low mood/depression			
No	728 (85)	404 (72)	1
Yes	132 (15)	158 (28)	2.30 (1.67, 3.16)
Feeling angry, irritable or hostile			
No	760 (89)	453 (80)	1
Yes	98 (11)	112 (20)	2.04 (1.43, 2.90)
Poor night's sleep			
No	515 (60)	216 (39)	1

(*continued on next page*)

Table III (*continued*)

Potential trigger	Control periods $N = 867$ N (%)	Hazard periods $N = 568$ N (%)	OR (95% CI)
Yes	345 (40)	342 (61)	3.04 (2.29, 4.02)
Generally cold and damp weather			
No	373 (43)	203 (36)	1
Yes	486 (57)	358 (64)	1.45 (1.12, 1.87)

OR, odds ratio; CI, confidence interval.
Participants may have reported multiple hazard and control periods thus *N* will exceed the total number of participants.

Table III Associations between potential trigger exposures and flare onset within 24 h (***n*** = 376 participants)

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participants in our study are consistent with important patient-centred flare domains previously identified by international consensus[47]. In our sample, the proportion of participants, willing in principle, to provide a magnetic resonance imaging scan or knee joint aspiration during a future flare was 92% and 77%, respectively in 376 responders.

Strengths of this self-controlled observational study are that all fixed or slow-varying person-level confounding is eliminated by design and the web-based data collection facilitates real-time data capture. Our findings should be interpreted in the context of several methodological limitations. First, for participants recruited via community-advertising (31%), eligibility criteria were defined by participant self-report. However, by restricting the primary analysis to those recruited via GP registers with objective support for their knee OA status, the overall interpretation remained the same. Second, although many of the selected potential triggers were based on previous literature, our brief items for categorising exposure levels have not been validated against longer-form self-report or objective measurements (where these are available). However, our approach was intended to enable direct comparison across related exposures and facilitate the examination of induction time, by reducing participant burden when invited to recall responses to repeated questions over 3-day periods. In keeping with the focus on within-person change in case-crossover studies, our underlying assumption was that change in exposure level ('unusual for me') rather than attaining an absolute level of exposure ('objectively high exposure') was likely to be most important. Future studies using more detailed self-report or objective measurement would be able to test this assumption although due to respondent burden they would most likely be restricted to a single or smaller set of exposures than the current study. Third, while confounding between exposures is still possible, correlations between exposures was low (≤0.4), therefore independence was assumed and the potential to combine related exposures (e.g., Rasch analysis) was not supported. Fourth, the study design remains vulnerable to differential recall bias between retrospective data ascertainment at Scheduled and Event-Driven (flare) questionnaires. If flares were reported more than 1 day after onset, recall time between hazard periods and control periods may be different. Direct matching of exposure recall time between hazard and control periods illustrated variations in direction and magnitude of some estimates, suggesting there may be some random differential misclassification, although the sample was smaller (data not shown). Fifth, our flare resolution definition was relaxed from confirmation on two consecutive days, to one confirmation, as only 36% fulfilled the a priori definition. Also 128 participants did not complete daily questionnaires and the majority had at least one missing day. Flares for which we did not receive confirmation of their resolution were excluded from our analysis estimating the duration of flares. Excluded flares include those that had not resolved by the end of the study period (censored) and those that had resolved but where participants had not provided confirmation of this (unobserved resolution). We cannot know the exact effect of this on biasing our estimate of flare duration, but censoring would tend to result in systematic under-estimation of flare duration. Our estimate of median flare duration should therefore be treated as conservative. If some flares ended before they were reported the flare duration may be overestimated. Finally, participant ethnicity was not captured.

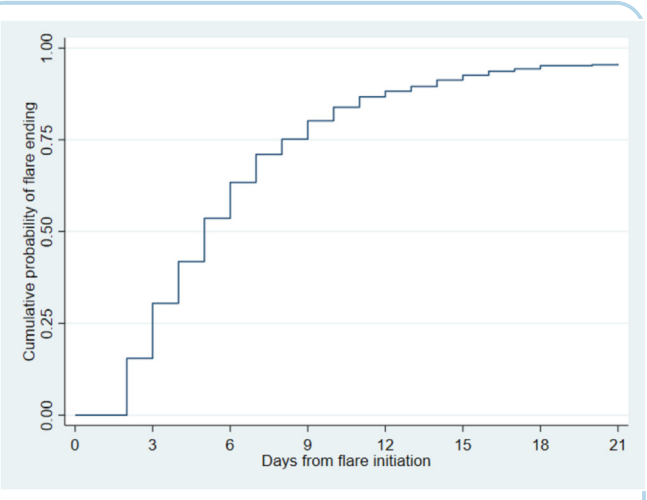

Fig. 2 Probability of flare ending over time: median time to flare resolution is 5 days.

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In summary, this study provides evidence for multiple activity-related, psychosocial and environmental proximate exposures that can trigger acute flares in adults with, or at risk of, knee OA within 24 h. Episodes usually last about 5 days, possibly affecting working age adults and females more frequently. These findings support the view that exposures associated with incidence and progression are also potential risk factors for acute flares. This evidence can help patients and clinicians work together to better predict, prevent and manage knee OA flares.

Author contributions

MJT and GP conceived and designed the study. TR-M completed the analysis in conjunction with MJT and GP. ELP contributed to the design and content of the study questionnaires. CP acted as patient and public involvement and engagement representative. TN contributed to the protocol development and provided senior

methodological/statistical expertise. MJT drafted the manuscript and all authors contributed to the manuscript. All authors approved the final version.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Supplementary data

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