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Potential surrogate outcomes in individuals at high risk for incident knee osteoarthritis

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SUMMARY

Objective: To study potential surrogate outcomes for osteoarthritis (OA) incidence by evaluating the association of short-term changes in clinical and imaging biomarkers with long-term clinical knee OA incidence.

Design: Middle-aged women with overweight/obesity, but free of knee symptoms were recruited through their general practitioners. At baseline, after 2.5 years, and after 6.5 years, questionnaires, physical examination, radiographs, and Magnetic resonance imaging (MRI) scans were obtained. The percentage of knees with a minimal clinically important difference for knee pain severity, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain/stiffness/function, and joint space narrowing, and of those with progression/regression of medial knee alignment, chronic knee pain, radiographic osteophytes, and cartilage defects, bone marrow lesions, osteophytes, and effusion/synovitis on MRI were determined. For each of these potential surrogate outcomes with ≥10% improvement or progression in the population over 2.5 years, the association with incident clinical knee OA, defined using the combined ACR-criteria, after 6.5 years was determined.

Results: Most pre-defined potential surrogate outcomes showed ≥10% change in the population over 2.5 years, but only worsening of TF cartilage defects, worsening of TF osteophytes on MRI, and an increase in pain severity were significantly associated with greater clinical knee OA incidence after 6.5 years. These potential surrogate outcomes had high specificity and negative predictive value (89–91%) and low sensitivity and positive predictive value (20–28%)

Conclusions: Worsening of TF cartilage defects and TF osteophytes on MRI, and increased pain severity could be seen as surrogate outcomes for long-term OA incidence. However, higher positive predictive values seem warranted for the applicability of these factors in future preventive trials.

Introduction

The worldwide prevalence of osteoarthritis (OA) and the associated social and healthcare costs are very high[1–3]. Without a drastic change in the way we handle OA, the number of OA patients and the burden of OA will become unmanageable in the near future. Experts in the field of OA have suggested that a shift in research focus towards primary prevention is needed[4,5].

A key challenge for studies in OA prevention is its slowly developing nature. Using traditional outcomes of OA incidence, e.g., Kellgren & Lawrence (KL) grade ≥2 for radiographic knee OA[6] or the ACR-criteria for clinical knee OA[7], annual incidence rates within high-risk subjects, e.g., overweight/obese individuals or those sustained a serious knee injury, are only ±2–5%[8–12]. Therefore, although advocated as a plausible strategy for OA prevention, clinical trials evaluating the incidence of knee OA in these high-risk groups require large samples and a very long follow-up[5,13]. Surrogate outcomes for the incidence of knee OA can boost the research on preventive treatments[14].

A surrogate outcome can lead to a "reduction in sample size and trial duration when a […] distant disease is replaced by a more frequent or proximal endpoint"[15]. This could potentially "reduce

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costs and enhances feasibility" of clinical trials[15–17]. To illustrate the potential, for the evaluation of treatment effects of certain medications in other chronic diseases, surrogate outcomes have successfully substituted traditional primary outcomes that have a direct and serious impact on patients (e.g., cardiovascular events or mortality)[18]. For instance, in 436 registered RCTs on diabetes drugs, most trials (82%) used surrogate or laboratory markers as primary outcome rather than 'patient-important' outcomes, such as death or quality of life measures[18].

Potential surrogate outcomes can be validated using a stepwise approach[16], which is also advocated by the European Medicines Agency (EMA)[19]. Biological plausibility of the relation between the surrogate outcome and the true outcome is the lowest form of evidence (level 3). Evidence is considered level 2 if "consistent associations between the surrogate and final outcome" from observational studies exists. Results from multiple RCTs that show that the changes in the surrogate outcome are associated with commensurate changes in the true outcome are seen as level 1 evidence[16].

The objective of the current study was to study potential surrogate outcomes for OA incidence by evaluating the association of short-term changes (2.5 years) in several clinical and imaging biomarkers with long-term (6.5 years) clinical knee OA incidence, among high-risk middle-aged women with overweight and obesity, free of knee OA at baseline. Given their sex, age and body weight status, this population should be regarded as a high-risk population for future knee OA incidence and with that form an excellent target population for future preventive trials.

Methods

Data of the PRevention of knee Osteoarthritis in Overweight Females (PROOF) study were used[11]. In PROOF, 407 women (eligibility criteria: aged 50–60 years, body mass index (BMI) ≥27 kg/m^2, and free of knee symptoms)[7] were recruited (between 2006 and 2009) through 50 general practices in the greater Rotterdam region and followed for 6.5 years. Originally, PROOF was an intervention study evaluating the preventive effects of a lifestyle intervention and glucosamine sulfate on OA incidence after 2.5 and 6.5 years, but due to the absence of any intervention effects the data is considered as a cohort[8,11]. All participants gave written informed consent prior to any measurements and the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The PROOF study was approved by the Medical Ethical Committee of Erasmus MC University Medical Center.

At baseline, 2.5 years, and 6.5 years, questionnaires, physical examination, standardized semi-flexed posterior-anterior (PA) radiographs, and multi-sequential MRI scans were obtained. The questionnaires included questions on demographics (i.e., age, menopausal status, history of knee injury), knee symptoms (i.e., presence of chronic pain, defined as 'pain on most days of the last month', pain severity on a 0–10 numeric rating scale, WOMAC scores for subscales of pain, functional limitations, and stiffness on a 0–100 scale, and the presence of knee joint stiffness <30 min). From the radiographs, osteophytes on the medial and lateral femur and tibia were scores on a 0–3 scale, minimal joint space width was measured in mm, and the medial knee alignment was measured in degrees and stratified into varus, neutral and valgus aligned knees[11]. MRIs at baseline and 2.5 years MRIs were evaluated for the presence and severity of osteophytes, cartilage defects, and bone marrow lesions (for the patellofemoral (PF) and tibiofemoral (TF) compartments separately), meniscal pathologies, meniscal extrusion, and effusion/synovitis according to the MRI Osteoarthritis Knee Score (MOAKS)[20].

Potential surrogate outcomes

For the present study, validated patient-reported clinical outcomes (e.g., WOMAC and visual analogue scale (VAS) pain scores), structural outcomes on radiography [e.g., joint space narrowing (JSN) and osteophytes], and structural items on MRI (e.g., cartilage defects and meniscal pathologies) were selected for evaluation. Published measures of the Minimal Clinically Important Difference (MCID) were used to determine the number of knees/subjects with changes over 2.5 years, based on knee pain severity (≥1 point change[21]), WOMAC pain (≥8.3 points change[22]), WOMAC stiffness (≥8.0 points change[22]), WOMAC function (≥10.1 points change[22]), and medial and lateral JSN (≥30% change[23]). For changes in medial knee alignment, no MCID was available. Hence, we used one unit (1°) to define its change; ≥1° more varus in varus/neutral aligned knees or more valgus in valgus/neutral aligned knees was defined as 'worsening', while ≥1° less varus in varus aligned knees or less valgus in valgus aligned knees was defined as 'improvement'. Incident chronic knee pain was defined as no chronic knee pain at baseline and presence of chronic knee pain at 2.5 years, improvement was defined as chronic knee pain at baseline and no chronic knee pain at 2.5 years, and when chronic knee pain status was identical for baseline and at 2.5 years, knees were labeled as 'no change'. For osteophytes scored on radiographs, progression ≥1 grade in ≥1 anatomical location was used to determine the 2.5 years progression (excluding progression from 0 to 1 to match the incidence or progression of definite osteophytes). For MOAKS features, published definitions by Runhaar *et al.*[24] were used to define progression per compartment (TF/PF), given the known clinical importance of the PF compartment in OA incidence[25]. Additionally, any change ≥1 grade in either 'effusion/synovitis' or 'Hoffa synovitis' was defined as a change in effusion/synovitis[26].

Long-term OA incidence

Knee OA incidence after 6.5 years was defined by using the combined ACR-criteria[7]; presence of chronic knee pain, ≥1 definite osteophyte on radiography (grade ≥2), and one or more of the following: age >50 years, stiffness <30 min, or crepitus.

Statistical analysis

All knees free of clinical knee OA according to the combined ACR-criteria at baseline, with all potential surrogate outcomes at 2.5 years and the long-term OA incidence measures available were selected for the analyses. Baseline characteristics were determined and compared between included and excluded knees.

First, for each of the potential surrogate outcomes, the proportion of knees/subjects showing improvement, no change, and progression over 2.5 years was determined, using MCID measures described above. Those potential surrogate outcomes with ≥10% improvement or with ≥10% progression in the study sample over 2.5 years were selected to assess the association of the change in the potential surrogate outcome (improvement or progression) with clinical knee OA incidence after 6.5 years. Three-level surrogate outcomes were restructured into two-level outcomes if one level of the outcome (improvement or progression) did not reach the 10% threshold, by merging the specific level with the 'no change' level. For potential surrogate outcomes measured on a knee-level (i.e., knee pain severity, medial and lateral JSN, medial knee alignment, osteophytes on radiography, and all MOAKS features), the association of the change in the potential surrogate

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outcome with clinical OA incidence in a knee (yes/no) was determined using Generalized Estimating Equations to account for repeated measures within persons. For potential surrogate outcomes measured on a subject-level (i.e., all WOMAC scores), a simple logistic regression was used where clinical OA incidence was recoded into yes/no within a person (i.e., incident clinical OA in ≥1 knee vs no incident clinical OA). As we aimed to identify surrogate outcomes that predict long-term OA incidence, rather than those causally linked to long-term OA incidence, confounding is of little importance and presented odds ratios are unadjusted[17].

Next, for all potential surrogate outcomes showing a significant association with incident clinical knee OA, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. All analyses were performed using IBM SPSS version 25, and a *P*-value <0.05 for statistical significance.

As sensitivity analyses, potential imaging surrogate outcome markers in the tibiofemoral compartment were analyzed separately for medial and lateral involvement.

Results

In total, 236 individuals and 464 knees were free of clinical knee OA at baseline, had required follow-up measures available, and thus were selected for the analyses. Baseline characteristics for the analytic and the excluded populations were presented in Table I. After 2.5 years, 7.2% of knees developed clinical knee OA, after 6.5 years this was 11.3%.

Table II presents the 2.5-years changes in the potential surrogate outcomes. Medial knee alignment angle, WOMAC pain, and WOMAC stiffness showed worsening and improvement in ≥10% of subjects/knees over 2.5 years. PF and TF BMLs, PF and TF cartilage defects, TF osteophytes, meniscus pathologies, meniscus extrusion, pain severity, and WOMAC function only showed worsening in ≥10% of knees over 2.5 years, while JSN was the only factor showing improvement in ≥10% of knees over 2.5 years.

Table III presents the long-term (6.5 years) incidence of clinical knee OA for subjects/knees with short-term worsening or improvement in the selected potential surrogate outcomes, and the corresponding odds ratios. Short-term worsening of TF cartilage defects and of TF osteophytes, and an increase in pain severity were significantly associated with greater clinical knee OA incidence after 6.5 years.

In Table IV, sensitivity, specificity, PPV, and NPV are presented for the worsening of TF cartilage defects, TF osteophytes, and increased pain severity against long-term clinical knee OA incidence. Overall, results showed the potential surrogate outcomes had high specificity and NPV (89–91%) and low sensitivity and PPV (20–28%) against knee OA incidence.

Sensitivity analyses indicated predominant involvement of the medial TF compartment. Only short-term worsening of medial TF osteophytes on MRI showed a significant association to long-term OA incidence, with comparable accuracy to the overall TF compartment (see Appendix tables).

Discussion

The current study showed that among overweight and obese, middle-aged women at high-risk for knee OA incidence, worsening of TF cartilage defects, worsening of TF osteophytes on MRI, and increased pain severity meet the requirements for surrogate outcomes, as their short-term change was significantly associated to long-term clinical knee OA incidence. However, based on the strength of the associations and the corresponding sensitivity, specificity, PPV, and NPV values, the relevance of these factors as surrogate outcomes for future intervention studies can be questioned.

The presented significant ORs indicated 'small' to 'moderate' associations[27] between the potential surrogate outcomes and the incidence of clinical knee OA after 6.5 years. To put it differently one could look at the predictive ability; for the entire population, the

	Analytic cohort (Mean ± sd*)	Excluded (Mean ± sd*)
N (individuals)	236	171
Age	55.7 ± 3.1 years	55.7 ± 3.3 years
BMI	31.8 ± 3.7 kg/m^2	33.1 ± 4.8**
WOMAC Pain (0–100)	5.5 ± 9.1	8.3 ± 13.6**
WOMAC Stiffness (0–100)	10.4 ± 15.0	20.3 ± 1.5**
WOMAC Function (0–100)	4.8 ± 7.5	8.7 ± 14.1**
N (knees)	464	346
Radiographic OA severity		
- KL grade 0	53%	48%
- KL grade 1	44%	42%
- KL grade 2	4%	11%**
Joint space width, medial	4.7 ± 0.7 mm	4.7 ± 0.9 mm
Joint space width, lateral	6.1 ± 1.0 mm	6.1 ± 1.0 mm
Medial knee alignment angle	182 ± 2.2°	182 ± 2.6°
Osteophytes on radiography	8%	4%**
Chronic pain	12%	2%**
Pain severity (0–10)	0.4 ± 1.3	0.6 ± 1.5**

BMI, KL, sd: standard deviation.
** significant difference ($P < 0.05$) between groups.
* unless indicated otherwise.

Table I

Osteoarthritis and Cartilage

Baseline characteristics for the analytic cohort and excluded individuals

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Potential surrogate outcome	Worsening (%; mean ± sd*)	Improvement (%; mean ± sd*)	No change (%; mean ± sd*)
Radiography markers			
JSN (change ≥30%)	3%	**13%**	85%
Medial knee alignment (change ≥1°†)	**37%**	**42%**	21%
Osteophytes (change ≥1 grade)	3%	0%	97%
MRI markers			
BML‡			
PF	**24%**	9%	63%
TF	**13%**	9%	73%
Cartilage defects‡			
PF	**23%**	2%	70%
TF	**12%**	1%	83%
Osteophytes‡			
PF	7%	1%	88%
TF	**12%**	0%	83%
Meniscal pathologies‡	**25%**	2%	68%
Meniscal extrusion†	**18%**	2%	74%
Effusion/synovitis (change ≥1 grade)	9%	3%	84%
Clinical markers			
Chronic pain (incident at 2.5 years)	9%	1%	90%
Pain severity (change ≥1 point)	**11%;**	7%;	79%;
	4.6 ± 2.2	−3.2 ± 1.5	0.0 ± 0.0
WOAMC pain§ (change ≥8.3)	**20%**;	**11%;**	69%;
	28.2 ± 16.0	−15.8 ± 10.7	−0.5 ± 2.8
WOMAC stiffness§ (change ≥8.0)	**22%**;	**19%;**	59%;
	31.1 ± 18.9	−19.2 ± 7.9	0.0 ± 0.0
WOMAC function§ (change ≥10.1)	**14%**;	4%;	81%;
	29.2 ± 16.7	−17.8 ± 6.3	−0.3 ± 3.8

* For continuous measures.
† Worsening: ≥1° more varus in varus/neutral aligned knees or more valgus in valgus/neutral aligned knees, improvement: ≥1° less varus in varus aligned knees or less valgus in valgus aligned knees.
‡ As defined by Runhaar *et al.* (OA&C 2014).
§ Determined on a subject-level. Bold figures represent change in ≥10% of the population.

Table II

Osteoarthritis and Cartilage

Short-term (2.5 years) changes in potential surrogate outcomes

incidence of clinical knee OA after 6.5 years was 11% (pre-test probability), but for knees with worsening of TF cartilage defects, worsening of TF osteophytes on MRI, and increased pain severity, the incidence of clinical knee OA after 6.5 years (post-test probability) was 20%, 24% and 28%, respectively. These figures highlight two important observations: (1) among middle-aged women with overweight/obesity, most knees fulfilling these surrogate outcomes will not develop knee OA, and (2) the overall incidence of clinical knee OA after 6.5 years is fairly low, even in this high-risk population.

One could argue that a good surrogate outcome should have a high PPV for the incidence of the long-term condition under investigation[17]. In the current population, middle-aged overweight and obese women at high risk for knee OA incidence, this would equal an incidence of the surrogate outcome of ≤11% after 2.5 years. Such incidence would still require a large sample size to demonstrate significant and clinically relevant reductions in an intervention study, limiting the feasibility of such a preventive study. To overcome this serious challenge in OA prevention research, establishing valid outcomes for early-stage knee OA, which are anticipated to have higher short-term incidence numbers among high-risk populations, is urgently warranted[5,13,28,29].

For the feasibility of a prevention study that aims to reduce the incidence of knee OA, a surrogate outcome with a relatively high short-term incidence would be preferred. In the population described here, any such surrogate outcome will have a short-term incidence larger than the long-term incidence of clinical knee OA, and hence would show high NPV and sensitivity, but low PPV and specificity. To establish significant and clinically relevant reductions in such a surrogate outcome will require a smaller sample size than for a surrogate outcome with high PPV. However, in the hypothetical situation of an effective intervention, the significant reduction in the surrogate outcome will then only translate in a small reduction in the long-term incidence of clinical knee OA, due to the low PPV. Of note, what reductions in long-term OA incidence or what short-term changes in a (potential) surrogate outcome qualify as 'clinically relevant' in a preventive setting, is still to be agreed upon by the OA community.

Previously, using the same data set, we showed that short-term changes in cartilage thickness and short-term changes in cartilage surface integrity were not associated with long-term clinical knee OA incidence[32]. Therefore, these markers did not meet the criteria for a surrogate outcome for long-term clinical knee OA. Interestingly, weight loss was associated to the short-term change in cartilage surface integrity and its change was significantly associated to long-term radiographic knee OA incidence[32]. However, given the clinical importance of OA illness over OA disease[5], the current study focused on incident clinical knee OA. Potentially,

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Potential surrogate outcome	Incident OA for worsening	Incident OA for improvement	Incident OA for no change	Odds ratio for worsening*	Odds ratio for improvement*
Radiography markers					
JSN medial and/or lateral (change ≥30%)	1/12 (8%)	5/60 (8%)	47/392 (12%)	–	0.8 (95% CI 0.3–2.0)
Medial knee alignment (change ≥1°)†	20/171 (12%)	19/194 (10%)	14/99 (14%)	0.7 (95% CI 0.4–1.3)	0.6 (95% CI 0.3–1.2)
MRI markers					
BML, PF‡	12/109 (11%)	7/42 (17%)	31/290 (11%)	1.0 (95% CI 0.5–2.1)	–
BML, TF‡	13/61 (20%)	6/43 (14%)	32/345 (9%)	2.0 (95% CI 0.9–4.2)	–
Cartilage defects, PF‡	12/105 (11%)	2/9 (22%)	35/325 (11%)	1.2 (95% CI 0.6–2.3)	–
Cartilage defects, TF‡	11/54 (20%)	3/5 (60%)	36/390 (9%)	**2.4 (95% CI 1.2–4.7)**	–
Osteophytes, TF‡	13/55 (24%)	0/2 (0%)	37/393 (9%)	**2.2 (95% CI 1.1–4.4)**	–
Meniscal pathologies‡	14/117 (12%)	0/8 (0%)	36/323 (11%)	1.1 (95% CI 0.6–2.1)	–
Meniscal extrusion‡	10/83 (12%)	1/11 (9%)	39/345 (11%)	1.1 (95% CI 0.6–2.2)	–
Clinical markers					
Pain severity (change ≥1 point)	14/50 (28%)	5/34 (15%)	32/366 (9%)	**3.1 (95% CI 1.6–6.0)**	–
WOAMC pain§ (change ≥8.3)	11/45 (24%)	6/25 (24%)	22/158 (14%)	2.0 (95% CI 0.9–4.5)	2.0 (95% CI 0.7–5.4)
WOMAC stiffness§ (change ≥8.0)	11/51 (22%)	8/43 (19%)	20/136 (15%)	1.6 (95% CI 0.7–3.6)	1.3 (95% CI 0.5–3.3)
WOMAC function§ (change ≥10.1)	6/32 (19%)	2/9 (22%)	29/186 (16%)	1.3 (95% CI 0.5–3.3)	–

* Odds ratios for incident OA using a three-level determinant (worsening, improvement, and no change), with 'no change' as reference.
† Worsening: ≥1° more varus in varus/neutral aligned knees or more valgus in valgus/neutral aligned knees, improvement: ≥1° less varus in varus aligned knees or less valgus in valgus aligned knees.
‡ As defined by Runhaar *et al.* (OA&C 2014). Bold figures represent significant odds ratios. ~ Any worsening or improvement in the PF, TF medial, and/or TF lateral compartment.
§ Determined on a subject-level.
no odds ratio provided since short-term change in the population was <10% in this direction (see Table II).

Table III Osteoarthritis and Cartilage

Associations of potential surrogate outcomes with ≥10% short-term (2.5 years) change in the population to incident long-term (6.5 years) knee OA incidence

incident OA disease (i.e., radiographic knee OA incidence) could be a surrogate outcome itself for long-term clinical knee OA incidence, but this has not been thoroughly assessed thus far.

The current study has its limitations. Over the follow-up period (6.5 years), drop-out was substantial. Therefore, only 236 of the original 407 participants (58%) were included in the current analyses. Despite significant baseline differences between those included and excluded in the current analyses that potentially limit the generalizability, differences were on average small and of questionable clinical relevance. Moreover, despite the absence of a significant intervention effect in the original PROOF trial, there is a potential for a limited generalizability towards observational data from an identical cohort, due to (small) intervention effects. However, in previous secondary data analyses which treated PROOF data as a cohort, additional adjustments for intervention effects never affected the main results (see e.g., 33–35). The current study evaluated the potential of several individual outcome measures to serve as a surrogate outcome for long-term OA incidence. In light of the multifactorial nature of OA incidence[1,2], a single surrogate outcome measures could very well not be suitable to capture all

Potential surrogate outcome	Change in surrogate outcome	Sensitivity† (95% CI)	Specificity† (95% CI)	PPV† (95% CI)	NPV† (95% CI)
MRI markers	Worsening‡	22% (11–33)	89% (86–92)	20% (10–31)	90% (87–93)
Cartilage defects, TF*					
Osteophytes, TF*	Worsening‡	26% (14–38)	89% (86–92)	24% (12–35)	91% (88–93)
Clinical markers	Worsening‡	27% (15–40)	91% (88–94)	28% (16–40)	91% (88–94)
Pain severity (change ≥1 point)					

* As defined by Runhaar *et al.* (OA&C 2014).
† Calculated for binary change score of the potential surrogate outcome. PPV: positive predictive value. NPV: negative predictive value.
‡ Associated to significant higher incidence of long-term knee OA incidence.

Table IV Osteoarthritis and Cartilage

Diagnostic accuracy measures for potential surrogate outcomes with significant associations to knee OA incidence

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aspects of the disease incidence[36], and rather a combination of outcomes needs to be studied. Moreover, the presented results cannot be used to inform the incidence of new treatment targets, as the analyses focused on surrogate outcomes that numerically captured the incidence of long-term OA, not those that actually mediated the incidence of long-term OA. For that, other analyses and adjustment for important confounders would have been appropriate[17]. Finally, the chosen cut-off of ≥10% progression after 2.5 years is arbitrary. However, lower scores will inevitably hamper the feasibility of such an outcome measure in any future RCTs.

In conclusion, the current study showed that worsening of TF cartilage defects, worsening of TF osteophytes on MRI, and increased pain severity after 2.5 years were associated to long-term knee OA incidence, among high-risk middle-aged, overweight/obese women. With that, these factors could be seen as surrogate outcomes for long-term OA incidence. However, based on the current results, the applicability of these factors in future RCTs is questionable. Therefore, efforts to validate other potential surrogate outcomes are required.

Author contributions

All authors made substantial contributions to analysis and interpretation of data. JR, MvM, and SBZ contributed to the conception and design of the study and acquisition of the data. JR drafted the manuscript, after which all authors revised the manuscript critically for important intellectual content and gave final approval of the version submitted.

Conflict of interest

All authors declare no conflicts of interest.

Role of the funding source

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Data statement

Data are available at reasonable request.

Supplementary data

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