■ KNEE

The associations of implant and patient factors with migration of the tibial component differ by sex

A RADIOSTEREOMETRIC STUDY ON MORE THAN 400 TOTAL KNEE ARTHROPLASTIES

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Aims
Thresholds of acceptable early migration of the components in total knee arthroplasty (TKA) have traditionally ignored the effects of patient and implant factors that may influence migration. The aim of this study was to determine which of these factors are associated with overall longitudinal migration of well-fixed tibial components following TKA.

Methods
Radiostereometric analysis (RSA) data over a two-year period were available for 419 successful primary TKAs (267 cemented and 152 uncemented in 257 female and 162 male patients). Longitudinal analysis of data using marginal models was performed to examine the associations of patient factors (age, sex, BMI, smoking status) and implant factors (cemented or uncemented, the size of the implant) with maximum total point motion (MTPM) migration. Analyses were also performed on subgroups based on sex and fixation.

Results
In the overall group, only fixation was significantly associated with migration ($p < 0.001$). For uncemented tibial components in males, smoking was significantly associated with lower migration ($p = 0.030$) and BMI approached significance ($p = 0.061$). For females with uncemented components, smoking ($p = 0.081$) and age ($p = 0.063$) approached significance and were both associated with increased migration. The small number of self-reported smokers in this study warrants cautious interpretation and further investigation. For cemented components in females, larger sizes of tibial component were significantly associated with increased migration ($p = 0.004$). No factors were significant for cemented components in males.

Conclusion
The migration of uncemented tibial components was more sensitive to patient factors than cemented implants. These differences were not consistent by sex, suggesting that it may be of value to evaluate female and male patients separately following TKA.

Cite this article: ***Bone Joint J*** **2022;104-B(4):444–451.**

Introduction
The screening of designs for total knee arthroplasty (TKA) using short-term implant migration data from radiostereometric analysis (RSA) has been shown to predict longer-term outcomes.[1-3] However, there has been little investigation into the influence of individual patient factors on the migration of the tibial component. Previous studies showing the predictive value of RSA have provided thresholds of acceptable migration for both cemented and uncemented tibial baseplates together,[1-3] despite higher magnitudes of early migration for uncemented components.[3,4] In patients with tibial components that are defined as "well-fixed" by RSA, however, there is significant variation in the pattern of migration during the first two postoperative years. Although some of this variation can probably be attributed to differences in design and fixation, it is likely that individual patient factors would also influence migration.

Cemented fixation depends on an immediate mechanical interlock created by the curing and

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doi:10.1302/0301-620X.104B4.BJJ-2021-1247.R1 $2.00

Bone Joint J
2022;104-B(4):444–451.

Table I. Details of implant designs and patient characteristics by design.

Implant design	Fixation	Insert	n	Mean age, yrs (SD)	Mean BMI, kg/m² (SD)	Sex, M:F
Advance*	Cemented	MP†, PS†	74	64 (7.7)	32 (5.2)	111:47
NexGen‡	Cemented	PS†	33	65 (8.6)	32 (5.5)	20:13
Triathlon§	Cemented	CR, CS, PS†	160	63 (8.3)	34 (7.0)	113:47
Advance Biofoam*	Uncemented (porous-coated, with or without screws)	MP†	46	69 (5.4)	30 (4.1)	20:26
Trabecular Metal Monoblock‡	Uncemented (trabecular metal)	PS†, CR	55	64 (7.5)	32 (5.6)	33:22
Trabecular Metal Modular‡	Uncemented (trabecular metal)	PS†	19	62 (6.7)	35 (4.8)	11:8
Triathlon Peri-Apatite-Coated§	Uncemented (porous-coated + Periapatite)	CR, CS, PS†	32	64 (6.6)	29 (5.0)	10:22

*Wright Medical Technology, USA
†Indicates posterior cruciate ligament resected.
‡Zimmer, USA.
§Stryker, USA.
CR, cruciate-retaining; CS, cruciate-stabilized; MP, medial pivot; PS, posterior-stabilized; SD, standard deviation.

Table II. Sample sizes and data for the whole cohort and subgroups by fixation and sex.

Variable	n	Mean age, yrs (SD; range)	Mean BMI, kg/m² (SD; range)	Smoker:non-smoker*
All	419	65 (7.8; 32 to 84)	33 (6.1; 20 to 58)	40:360
Uncemented	152	66 (7.0; 42 to 79)	31 (5.2; 20 to 50)	18:118
Female	74	65 (6.8; 47 to 79)	32 (5.9; 20 to 50)	8:65
Male	78	66 (7.3; 42 to 79)	30 (4.4; 22 to 43)	10:53
Cemented	267	64 (8.2; 32 to 84)	33.3 (6.4; 20 to 58)	22:242
Female	183	63 (8.1; 32 to 84)	34.4 (6.7; 20 to 58)	13:167
Male	84	66 (8.0; 42 to 84)	31.2 (5.1; 23 to 45)	9:75

*Smoking status is unknown for 19 patients (5%).
SD, standard deviation.

hardening of polymethylmethacrylate, while uncemented fixation relies on the growth of underlying bone into the implant over a period of weeks or months.[5] Uncemented fixation may be sensitive to individual patient factors, such as the quality of the bone, which may influence ingrowth. The quality of the bone may be of particular concern for uncemented fixation in post-menopausal women.[6] Additional sex-related differences in TKA include higher rates of obesity in female patients,[7] and the appropriate sizing of components for smaller bones.[8] For these reasons, we were interested not only in the relationship between implant and patient factors and migration in successful TKA, but also in examining these associations in subgroups composed of separate cohorts of cemented and uncemented, and female and male patients. Further patient factors that may be important in this context include BMI[9,10] and smoking.[11,12]

The aim of this study was to examine the association between implant factors such as fixation and size, and patient factors such as age, sex, BMI, and smoking status with the migration of the tibial component during the first two postoperative years.

Methods

RSA data were collected prospectively on patients undergoing primary TKA between January 2002 and July 2015 with varying designs of implant. Relevant data were obtained from the Halifax RSA database, which was created to collect RSA data for a wide range of implants for any patient undergoing primary or revision hip or knee arthroplasty.[4] Ethical approval was obtained and the patients provided written consent.

Tantalum RSA markers were inserted into the proximal tibia and the polyethylene component intraoperatively. All patients had a reference RSA examination within the first four postoperative days. Protocols for RSA follow-up, equipment, and software varied according to the time of enrolment.[4] All patients had follow-up RSA examinations at six months, one year, and two years postoperatively. Those who were enrolled after 2008 had additional examinations at six weeks and three months postoperatively. Marker-based analysis was used in all patients, with maximum total point motion (MTPM) calculated for standardized locations to reduce variation by implant design.[13]

Inclusion criteria were patients undergoing TKA for a diagnosis of primary osteoarthritis (OA) who had a reference RSA examination followed by a minimum of two follow-up RSA examinations during the first two postoperative years. Exclusion criteria were: those undergoing revision TKA; revision for any reason within two years or later (to ensure that only successful cases were included); those in whom revision components were used in a primary TKA; and technical problems with RSA analysis including those in whom insufficient markers were visible, the condition number was > 150, or with a mean error of rigid body fitting > 0.35 mm.[14]

Patients. A total of 518 primary TKAs were available from the database. Patients in whom revision components were used were excluded (n = 21; 4%). Nine in whom a revision was performed during the first two postoperative years (for aseptic loosening in two, one cemented and one uncemented; periprosthetic fracture in one; infection in four; avascular necrosis in one; and instability in one) were excluded, and 40 patients with missed reference examinations, insufficient visible markers or RSA errors (8%) were excluded. A total of 24 patients were excluded because they only had a single follow-up RSA examination (6%). A further five TKAs were excluded as they were

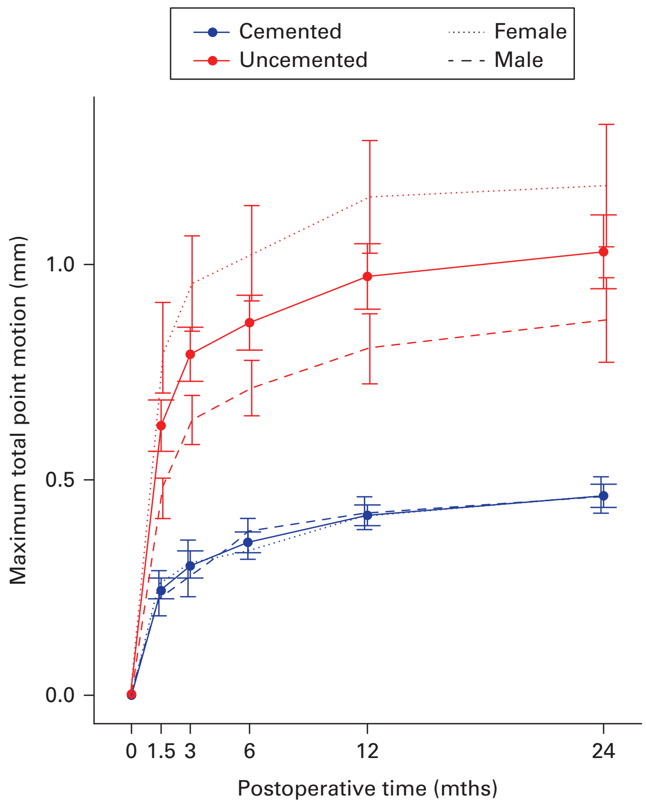

Fig. 1

Longitudinal implant maximum total point motion (MTPM) migration by fixation, and by fixation and sex. Error bars represent the standard error of the mean.

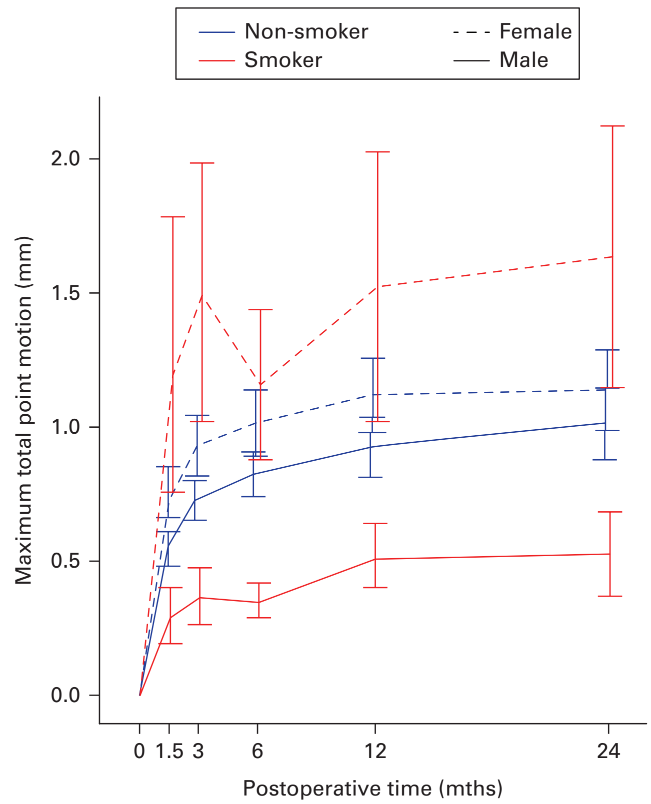

Fig. 2

Longitudinal maximum total point motion (MTPM) migration by sex and smoking status for uncemented tibial components. Smoking status was significant in male patients (p = 0.030) and approached significance in female patients (p = 0.081). Error bars represent the standard error of the mean.

revised > two years postoperatively: one for infection, two for instability and two for pain, at a median of 2.5 years postoperatively (2.2 to 4.7); giving a 3% overall revision rate; eight revisions (57%) were of cemented components.

A total of 419 TKAs in 381 patients, with 1,646 follow-up RSA examinations, were analyzed. Seven implant designs were included (Table I). No tibial components had mobile bearing inserts. There were 267 cemented and 152 uncemented components in 257 female and 162 male patients (Table II). Simplex P cement (Stryker, USA) was used for all cemented components with antibiotics in 201 cemented TKAs (75%). The patella was resurfaced in 334 TKAs (80%). Most operations were performed by six surgeons, with 15 (4%) being recruited by a single surgeon as part of a multicentre study on a single design of implant.[15] The median follow-up was seven years (2.2 to 15); 307 (73%) had follow-up of > five years.

A total of 38 patients (10%) underwent bilateral TKA. Of these, 18 had the same combination of components, fixation, and insert in both knees, while the remaining 20 had different implants bilaterally. Three patients underwent simultaneous bilateral TKA; the remainder had TKAs at a mean 1.7 years apart (four months to eight years).

Statistical analysis. Longitudinal analysis using marginal models[16–18] was undertaken to examine the association of patient and implant variables with MTPM migration, with $\log_{10}$(MTPM) being taken as the outcome variable.[10,19] The following variables were included as covariates in the analysis: sex, age, BMI, and smoking status at the time of surgery (smoker or non-smoker), fixation (cemented or uncemented), and size of the implants (tibial baseplate area in cm^2, estimated as the area of an ellipse based on the anteroposterior and mediolateral dimensions of every size of each design of tibial component). All analyses were performed in R v. 3.5.1 (R Foundation for Statistical Computing, Austria) using our own code to apply a robust estimation procedure to generalized estimating equations (GEE).[20] An autoregressive correlation structure was used. In order to investigate the influence of patients with bilateral TKAs, the analysis was repeated with one randomly selected TKA. The level of significance was set at $p < 0.05$.

All analyses were repeated for the following subgroups: females with uncemented components; males with uncemented components; females with cemented components; and males with cemented components.

Table III. Results of longitudinal data analyses for the associations of patient variables with implant migration for various tibial components

Variable*	Estimate (SE; 95% CI)	p-value
All components		
Follow-up exam time†	0 (0; 0 to 0)	< 0.001
Fixation	0.34 (0.03; 0.27 to 0.40)	< 0.001
Sex	0.04 (0.05; -0.05 to 0.14)	0.354
Age	0 (0; 0.00 to 0.01)	0.251
BMI	0 (0; 0.00 to 0.01)	0.335
Tibial component area	0.01 (0.01; 0.00 to 0.02)	0.220
Smoking status	-0.01 (0.05; -0.11 to 0.1)	0.925
Uncemented components, female patients		
Follow-up exam time	0 (0; 0 to 0)	0.012
Age	0.01 (0.01; 0.00 to 0.03)	0.063
BMI	0.01 (0.01; -0.01 to 0.02)	0.323
Tibial component area	-0.02 (0.02; -0.05 to 0.02)	0.395
Smoking status	0.26 (0.15; -0.03 to 0.56)	0.081
Uncemented components, male patients		
Follow-up exam time	0 (0; 0 to 0)	< 0.001
Age	0 (0.01; -0.01 to 0.01)	0.802
BMI	0.02 (0.01; 0.00 to 0.04)	0.061
Tibial component area	0.01 (0.01; -0.02 to 0.04)	0.481
Smoking status	-0.25 (0.12; -0.48 to -0.02)	0.030
Cemented components, female patients		
Follow-up exam time	0 (0; 0 to 0)	< 0.001
Age	0 (0; 0.00 to 0.01)	0.556
BMI	0 (0; -0.01 to 0.00)	0.794
Tibial component area	0.02 (0.01; 0.01 to 0.04)	0.004
Smoking status	-0.03 (0.08; -0.19 to 0.12)	0.676
Cemented components, male patients		
Follow-up exam time	0 (0; 0 to 0)	< 0.001
Age	0 (0.01; -0.01 to 0.01)	0.969
BMI	0 (0.01; -0.01 to 0.01)	0.907
Tibial component area	0 (0.01; -0.02 to 0.02)	0.997
Smoking status	0.05 (0.09; -0.14 to 0.23)	0.610

Independent variable: $\log_{10}$(MTPM).
*Reference levels for factor variables: fixation, cemented; sex, male; smoking status, non-smoker.
†Follow-up exam time is included in each of the models to account for repeated measures on individuals.
CI, confidence interval; SE, standard error.

One-year MTPM migration data were summarized for groups based on patient and implant factors that were significant or approaching significance in the longitudinal analyses for the overall group and subgroups, in order to allow comparison with existing thresholds.[1]

Results

Investigating the association of patient and implant factors with the overall longitudinal MTPM migration of all the tibial components revealed that only fixation was significant (p < 0.001; Figure 1; Table III). The mean migration at one year was 0.42 mm (standard deviation (SD) 0.36) in the cemented group and 0.97 mm (SD 0.91) in the uncemented group, with additional differences by sex (Table IV).

Table IV. One-year tibial component maximum total point motion (MTPM) migration (mm) for groups of interest.

Group	n*	Mean (SD; 95% CI)
All tibial components by fixation and sex		
Uncemented, female	69	1.16 (1.10; 0.89 to 1.42)
Uncemented, male	76	0.81 (0.71; 0.65 to 0.97)
Cemented, female	168	0.41 (0.37; 0.36 to 0.47)
Cemented, male	77	0.43 (0.31; 0.35 to 0.50)
Uncemented tibial components by sex and smoking status		
Female, non-smoker	61	1.12 (1.08; 0.84 to 1.40)
Female, smoker	7	1.52 (1.32; 0.30 to 2.75)
Male, non-smoker	51	0.93 (0.80; 0.70 to 1.15)
Male, smoker	10	0.52 (0.38; 0.25 to 0.79)
Uncemented tibial components in females by age		
60+ yrs	56	1.27 (1.17; 0.95 to 1.58)
< 60 yrs	13	0.67 (0.42; 0.41 to 0.92)
Uncemented tibial components in males by BMI		
< 30 kg/m²	43	0.62 (0.45; 0.48 to 0.75)
≥ 30 kg/m²	33	1.06 (0.89; 0.74 to 1.38)
Cemented tibial components by sex and tibial component size†		
Female, small tibia areas	42	0.36 (0.24; 0.29 to 0.44)
Female, medium tibia areas	126	0.43 (0.41; 0.36 to 0.50)
Male, medium tibia areas	38	0.48 (0.34; 0.37 to 0.59)
Male, large tibia areas	39	0.37 (0.27; 0.28 to 0.46)

*Individual missed follow-up visits at one year account for different sample sizes from Table II.
†Tibial component size areas: 19.2 cm² ≤ small < 23.2 cm² (found in females only); 23.2 cm² ≤ medium ≤ 30 cm² (found in females and males); 30 cm² > large ≤ 40.1 cm² (found in males only).
CI, confidence interval; SD, standard deviation.

Uncemented components in female patients (n = 74) showed the highest migration overall (Figure 1) and at one year (Table IV). For this subgroup, no variables had a significant association with migration (Table III), but both age (p = 0.063) and smoking status (p = 0.081) approached significance, with increasing age being associated with higher migration, and smokers having greater migration than non-smokers (Figure 2; Table IV). The relationship between age and migration suggests that migration may differentiate at approximately 60 years of age, with lower migration one year postoperatively in younger patients (Figure 3; Table IV).

Smoking status was significant for migration in uncemented components in males (n = 78; p = 0.030), but with the opposite effect in females. Male smokers had lower migration compared with male non-smokers (Figure 2; Table IV). No other variables were significant (Table III), although BMI approached significance (p = 0.061). Migration one year postoperatively did not show a clear relationship to BMI (Figure 4; Table IV).

In females with cemented components (n = 183), the area of the baseplate was significant for migration (p = 0.004) with larger components associated with increased migration (Tables III and IV, Figure 5).

No patient or additional implant variables were statistically significant for migration in males with cemented components (n = 84) (Table III).

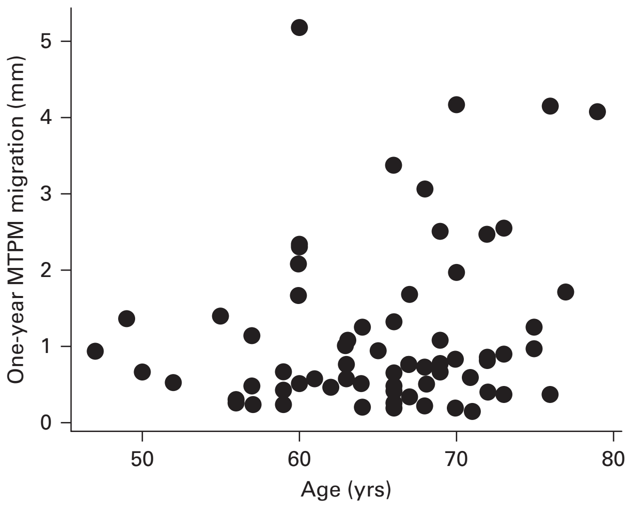

Fig. 3

One-year maximum total point motion migration (MTPM) migration for uncemented components in female patients relative to age at the time of surgery. Age approached significance for migration (p = 0.063).

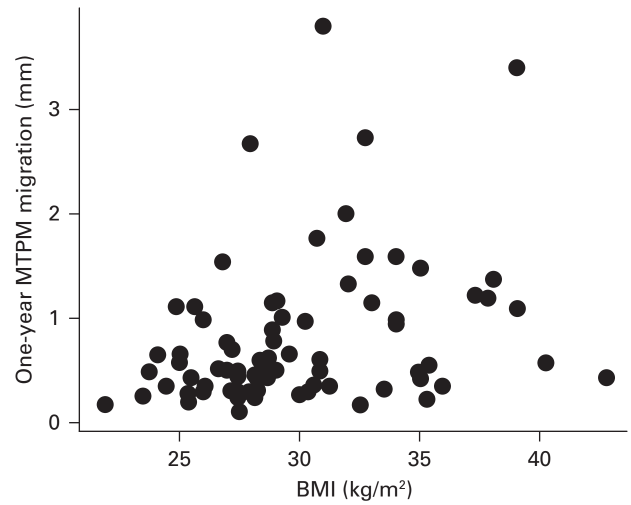

Fig. 4

One-year maximum total point motion migration (MTPM) for uncemented components in males relative to BMI at the time of surgery. BMI approached significance for migration (p = 0.061).

Discussion

The compilation of a large dataset of RSA migrations in primary TKA has allowed the examination of the association between patient and implant factors, and migration of well-fixed tibial components. The method of fixation had the greatest overall association, with significantly increased migration for uncemented components. This difference in magnitude, and greater variation, does not necessarily reflect less favourable outcomes, as both cemented and uncemented groups were revision-free at a median of four years after surgery. Neither do cemented and uncemented components have different proportions of components with migration between one and two years postoperatively of > 0.2 mm (13% for cemented components, 15% for uncemented components).[4] Stable fixation in uncemented components, despite higher initial migration, has been reported in previous RSA studies. Stabilization between three months and one year postoperatively has generally been described.[2,3,19,21–34]

It is important to emphasize that while the overall magnitudes of migration differed according to sex for uncemented components, this does not imply worse uncemented fixation in female patients, as the migration stabilized in both sexes by one year. As with uncemented components in males, those in females had stable fixation between one and two years with minimal migration after one year. Initial high migration may be related to less robust bone stock in post-menopausal women, but the perioperative bone deficits seem to be independent of the ability to generate a biological interface postoperatively.

While fixation had the greatest association with migration in the first two postoperative years, analyzing subgroups defined by fixation and sex revealed other significant relationships. As smoking has been shown to compromise healing, and has been associated with higher revision rates,[12,35,36] the significant decrease in migration of uncemented components in male smokers was an unanticipated finding and one that we have been unable to corroborate from the existing literature. The effect of smoking was reversed for females, with uncemented components having greater migration for smokers (approaching statistical significance). Critically, the significance of smoking on the migration of uncemented components was masked when males and females were analyzed together, because of the opposite effect by sex. We noted that BMI was not signifcantly different between smokers and non-smokers.

While initially counterintuitive, the finding of lower migration in male smokers with uncemented components is in accordance with research into the effects of smoking on OA of the knee. There is evidence that smoking is protective against severe OA and the need for TKA,[37–42] although this finding is not universal.[43–47] It has been suggested in various studies that the effect of nicotine on bone cells, including osteoblasts, osteoclasts, and mesenchymal stem cells, in vitro is biphasic, with low concentrations being stimulatory while high concentrations are detrimental.[48,49] However, negative effects of smoking on the outcome of arthroplasties have been reported, with smoking associated with higher early revision rates due to poor wound-healing and infection.[12,35,36] Particularly relevant for post-menopausal women, smoking is also associated with decreased bone mineral density,[50,51] which may explain the higher initial migration for the female smokers in this study.

There are limitations to the smoking data in our study, as the information was self-reported and did not permit the analysis of a dose effect. Overall smoking rates in Nova Scotia were 23% (22% for females, 24% for males) and specifically 26% in the 45- to 64-year age group, and 16% for the > 65-year age group.[52] The low percentage of smokers in our study (10%) may reflect under-reporting. The small proportion of smokers may also lead to issues of differences in sample sizes in the statistical

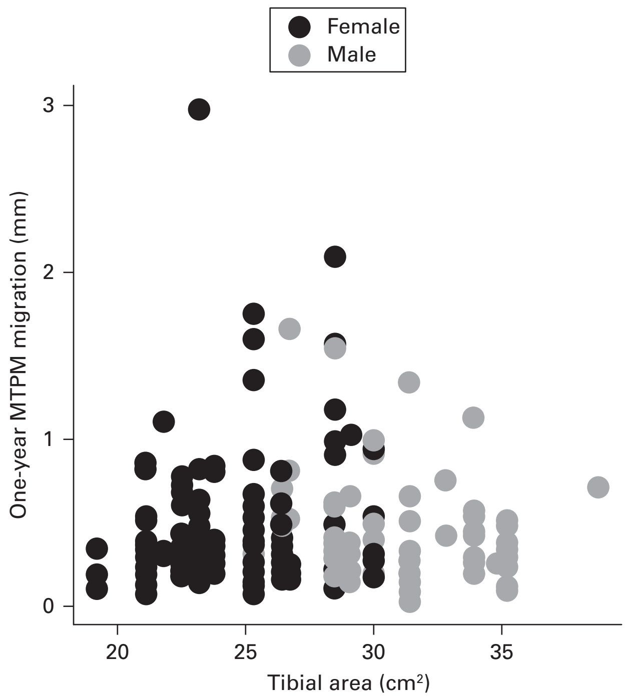

Fig. 5

One-year maximum total point motion migration (MTPM) for cemented components relative to the area of the baseplate. The area was significant for migration in females (p = 0.004), but was not significant in males (p = 0.997).

analysis. The non-smoking group was randomly sampled to achieve equal sample sizes and the statistical analyses were repeated. With matched sample sizes, the factors found to be significant were unchanged, which supports the findings, but does not eliminate the need to interpret them with caution. We suggest that documenting smoking status, history, and detailed use of tobacco may be warranted in future RSA studies, especially when screening new uncemented designs of implants in small groups of patients.

The trend of increased migration with increased age in females with uncemented components may be related to the effects of decreased oestrogen production on bone in post-menopausal women, resulting in loss of bone mass and detrimental structural changes.[6,53] Age alone is also a factor in decreasing bone mineral density, as well as the effects of reduced oestrogen, especially over the age of 75.[53] Acknowledging a small sample size of patients aged > 60 years, our data suggest that this age may represent a discontinuity in one-year migration of uncemented tibial components in females, coinciding with the end of maximum bone loss related to the menopause. However, there was no significant increase in migration after one year postoperatively, indicating that higher initial migration does not preclude successful fixation. This finding is not confounded by the smoking status as there was not a higher proportion of smokers in those aged > 60 years.

BMI approached significance for males with uncemented components, with higher BMI being associated with greater migration. BMI was not significant in any other subgroup. The provision of TKA to obese patients is a contentious issue.[54] Our findings support previous studies reporting that higher BMI is not associated with adverse outcomes after TKA,[55–58] including specifically for uncemented TKA.[59,60] BMI was treated as a continuous variable in our analyses and a wide range of BMIs, between 20 kg/m^2 and 58 kg/m^2, was included.

For cemented components, the only statistically significant factor for migration was the area of the baseplate of the tibial component in the cemented female subgroup, with increased migration associated with larger components. This finding was independent of BMI. Although not statistically significant, the trend was reversed for cemented components in males, with the greatest migration occurring with the smallest sizes which were used in men (these being in the middle of the range of the available sizes.) In contrast, mid-sized components were the largest sizes used in women, indicating that overall, mid-sized components had the greatest migration. One possible explanation is that this was related to the ratio of the size of the keel to the size of the baseplate. In the most commonly used cemented component in this study, the size of the keel did not match in a linear fashion with size of the implant, resulting in some sizes of implant having wider keels relative to the width of the baseplate. An oversized keel may compromise the underlying bone stock and lead to increased migration. Other potential mechanisms are that the proportion of cortical bone contact relative to the surface area of the baseplate is lower in females with larger components, or that the geometry of the component is associated with suboptimal cover in mid-sized bones, due to differing ratios of anteroposterior to mediolateral dimensions in females and males.[8]

Compared with the published thresholds of the migration of implants at one year,[1] all uncemented groups were in the 0.5 mm to 1.6 mm range for 'at-risk' migration, requiring longer follow-up to make an assessment. In contrast, all the cemented groups had one-year migrations of < 0.5 mm, putting them in the 'not at risk' category. Further refinement of the one-year threshold, which may also be applied at six months,[3] may increase the precision of the threshold.

The study had limitations, including the fact that the selection of implant designs was affected by both the tendering arrangements of the institutions and industry-funded research studies on specific designs. This may limit the generalizability of the findings to other designs. However, seven designs were included, and the differences in the patients who were selected are accounted for in the statistical models. Bilateral cases were included because different components were used in left and right knees in most cases and patient variables, specifically age and weight, were not constant. The inclusion of patients with bilateral TKAs as independent samples may underestimate the variation and result in narrower confidence intervals,[61,62] but there was no effect on the significance of the factors when the analysis was repeated with only one knee per patient. TKAs which were revised were excluded to provide an assessment of the influence of patient and implant factors in successful fixation, and to allow an evaluation of the migration in subgroups relative to the published thresholds for acceptable migration. Later revisions for any reason were excluded to provide a conservative estimate of successful fixation. Small numbers of revised cases, including only two due to aseptic loosening, prevented an analysis of the patient or implant factors associated with revision. Repeating the analyses with all revision cases included did not alter the conclusions. We acknowledge that there may be other factors that influence migration, such as additional implant factors, alignment, and activity levels. The variables were chosen after preliminary analyses and considering the completeness of the data, statistical independence, and an appropriate number of variables relative to the sample sizes. With larger sample sizes from collaborative efforts, a wider number of variables may be evaluated for their influence on the patterns of migration in both stable fixation and TKAs which undergo revision.

In summary, acknowledging the small number of self-reported smokers, smoking in males with uncemented tibial components was associated with reduced migration of the tibial component compared with non-smokers. In contrast, there was a trend towards higher migration related to the initial settling of the components in females with uncemented components who were older and smoked; however, this did not appear to impair the long-term fixation. With cemented fixation, larger size of the tibial component was related to increased migration only in females. Analyzing migration of primary TKA by subsets of sex and fixation revealed significant factors that were not apparent when the data were treated as a single cohort. More granular analysis of RSA data, including patient and implant factors, may provide additional insights into the mechanisms of fixation and its failure in future studies, and may improve the resolution of early thresholds of acceptable migration, motivating the compilation of larger, multicentre RSA datasets.

Take home message

- Considerable variation exists in longitudinal two-year migration of well-fixed tibial components, especially for uncemented components.
- Evaluation of implant migration in female and male patients separately found that different factors were significantly associated with longitudinal migration, indicating that disaggregation of data by sex should be considered.
- The compilation of larger, multicentre radiostereometric datasets may permit refinement of thresholds for successful early implant migration by including patient and implant design factors.

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Funding statement:
The author(s) disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: Atlantic Canada Opportunities Agency.

ICMJE COI statement:
J. L. Astephen Wilson reports consulting fees from Stryker, unrelated to this study. M. J. Dunbar reports consulting fees and royalties from Stryker, unrelated to this study, as well as board membership at *The Bone & Joint Journal*.

Acknowledgements:
The authors gratefully acknowledge the participation of the additional orthopaedic surgeons who performed the surgeries: Glen Richardson, David Amirault, Gerry Reardon, Michael Gross, Michael Biddulph, and Dermot Collopy; the research staff: Allan Hennigar, Sue Moore, Brittany Scott, James Edwards, Michaela Wallace, Jo-Anne Douglas, and Elise McNeill; and the research study participants.

Ethical review statement:
This study was approved by the Nova Scoita Health Authority Research Ethics Board.

This article was primary edited by J. Scott.