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Current preclinical testing of new hip replacement technologies does not reflect real world loadings: capturing patient-specific and activity-related variation in hip contact forces

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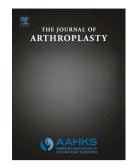
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- 1 Current preclinical testing of new hip replacement technologies does not
- 2 reflect real world loadings: capturing patient-specific and activity-related
- 3 variation in hip contact forces

32 33	Abstract
34	Background: Total hip replacement (THR) implants are routinely tested for their tribological
35	performance through regulatory pre-clinical wear testing (e.g. ISO-14242). The standardized loading
36	conditions defined in these tests consist of simplified waveforms, which do not specifically represent
37	in vivo loads in different groups of patients. The aim of this study was to investigate, through
38	musculoskeletal modelling, patient-specific and activity-related variation in hip contact forces (HCFs)
39	in a large cohort of THR patients during common activities of daily living (ADLs).
40	Methods: 132 THR patients participated in a motion-capture analysis while performing different
41	ADLs, including walk, fast walk, stair ascent and descent (locomotor); sit-to-stand, stand-to-sit, squate
42	and lunge (non-locomotor). HCFs were then calculated using the AnyBody Modelling System and
43	qualitatively compared across all activities. The influence of gender on HCFs was analysed through
44	statistical parametric mapping (SPM) analysis.
45	Results: Systematic differences were found in HCF magnitudes and individual components in both
46	locomotor and non-locomotor ADLs. The qualitative analysis of the ADLs revealed a large range and
47	a large variability of forces experienced at the hip during different activities. Significant differences in
48	the three-dimensional loading patterns were observed between males and females across most
49	activities.
50	Conclusions: THR patients present a large variability in the forces experienced at the hip joint during
51	their daily life. The inter-patient variation might partially explain the heterogeneity observed in
52	implant survival rates. A more extensive pre-clinical implant testing standard, under clinically
53	relevant loading conditions has been advocated to better predict and avoid clinical wear problems.
54	Keywords: Total hip replacement, hip contact force, functional outcomes, activities of daily living,
55	biomechanics
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Introduction

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Total hip replacement (THR) is the most effective form of treatment for severe hip osteoarthritis [1-3], reducing pain and restoring mobility in arthritic patients [4-6]. Monitoring of implant survivorship revealed survival rates greater than 95% at ten years, but with this number falling to 58% after 25 years [7]. However the overall demand for THR is expected to increase in the future as a consequence of a demographic shift towards an ageing population [8, 9].

The ever-improving survivorship of joint replacements is evidence of the important continued innovation and improvement in implant design and surgical techniques, which has led to better implant fixation options, improved wear performance, and reduction in peri- and post-operative complication rates [2, 3]. The outcomes of novel implant design are not however always better than for existing implants [10, 11]. Occasionally, innovation leads to unforeseen problems such as early implant failure, as exemplified by the ASR hip implant, which failed because of higher than anticipated wear between the two metal bearing surfaces [12-14]. One lesson to be learned from the ASR was the differential in failure rates for population-level factors such as gender, which had not been identified during preclinical testing but which resulted in significantly higher failure rates in women for the ASR implant [15]. These demographic-dependent design shortcomings are not only associated with frank and widespread early failures but can be observed, albeit more subtly, in broader registry data, with younger patients and, in contrast to the ASR hip, male patients typically having an increased lifetime risk of revision [16, 17]. It has also become apparent that different implant combinations perform better in different patient groups [18]. While such information is useful when gathered retrospectively and is well suited to monitoring performance of tried and tested combinations such as metal on polyethylene bearings, it would be better to be able to predict the likely outcomes of novel designs during any pre-clinical testing.

The majority of hip replacement failures are caused by wear [19] which is a consequence of load and motion as determined by the amount and type of physical activity undertaken by the patient [20]. Additionally, different patient factors such as age, gender, weight, activity level and patient-specific kinematic patterns have shown a correlation with wear [20-22]. Therefore the differential failures due to wear are potentially predictable and testable.

Joint replacements are routinely tested for their tribological performance before being introduced to the market by means of standardized tests [23]. Current regulatory pre-clinical testing standards, such as the ISO 14242-1, define standardized loading conditions consisting of simplified and stylised waveforms, which do not directly represent *in-vivo* loads and motion in different groups of patients. The loading profile defined in the ISO 14242-1 pre-clinical testing standard is given in Figure 1. A

more extensive implant testing under clinically relevant loading conditions [23] has been suggested to be warranted to predict and avoid clinical wear problems, which could have been better anticipated in the case of the ASR implant system [14].

These deficiencies in preclinical testing have been highlighted when comparing the ISO 14242-1 testing waveforms to real world hip joint contact forces (HCFs) measured through instrumented implants [24], particularly when comparing the ISO model to the larger and varied loading pattern observed when performing real-world activities of daily living (ADLs) [25]. Due to the inherently invasive nature of in vivo HCFs measurement via instrumented implants, data is only available for a small number of patients and thus has not captured the variation which exists in larger populations. Advances in computational techniques such as musculoskeletal modelling have shown potential for estimating accurate HCFs non-invasively [26] and these techniques are much better suited to describing the load variability observed in larger populations [27].

The aim of the current study was to explore differences in hip contact forces between patient groups in a relatively large sample of hip replacement cases and to further investigate these differences during a selection of the real-world ADLs to which a hip implant is typically exposed *in vivo*.

Methods

132 THR patients were recruited into the study through a clinical database of surgical cases as part of the LifeLongJoints (LLJ) patients' cohort. Inclusion criteria for the hip replacement group were; between 1-5 years THR post-surgery, older than 18 years of age, no lower limb joint replaced other than hip joint(s), fully pain free and not suffering from any other orthopaedic or neurological problem which may compromise gait. Ethical approval was obtained via the UK national NHS ethics (IRAS) system and all participants provided informed, written consent.

Motion-capture data acquisition

Patients undertook a series of ADLs during which lower-limb kinematics and kinetics were acquired using a ten camera Vicon system (Vicon MX, Oxford Metrics, UK) sampling at 100Hz, integrated with two force plates (AMTI, Watertown, MA, USA) capturing at 1000Hz. The CAST marker set was used to track lower limb segments kinematics in six degrees of freedom. A more detailed description can be found in [28]. For the THR group, the operated limb (or in bilateral cases, the most recently operated limb) was used for analysis.

126	Patient characteristics
127	This patient cohort has been previously shown to demonstrate a large variability in hip loadings
128	during gait, which were shown to be dependent on patient characteristics, particularly on BMI and
129	the patients' functional ability determined by their self-selected walking speed [27]. To further
130	investigate the load variability in this patients' cohort, we stratified the patients by gender, which
131	$represents \ an \ important \ differentiator \ of \ implant \ survivorship. \ Patients \ were \ allowed \ to \ individually$
132	exclude activities that they were not able to perform relatively comfortably. Patient demographics
133	for each activity are reported in Table 1.
134	Activities of daily living
135	The ADLs are grouped into two categories: locomotor tasks (walk, fast walk, stair ascent and stair
136	descent) and non-locomotor tasks (sit to stand, stand to sit, squat and lunge). Information regarding
137	the protocol of each task can be found at (https://doi.org/10.5518/319), while a brief description is
138	provided below.
139	Walking tasks
140	Patients undertook two walking conditions i) at a self-selected walking speed (hereafter referred to
141	as a normal walk) and ii) a fast walk, where patients were instructed to walk "as fast as possible
142	without running" along a 10m walkway. All trials were time-normalized from heel-strike (0%), to
143	heel strike (100%) and interpolated to 1% steps (101 points).
144	Stair Negotiation
145	Patients were asked to ascend and descend three steps at self-selected comfortable speed, without
146	the use of a handrail. The stair case was mounted and bolted to the force plates [29] to collect
147	ground reaction force data. All trials were time-normalized from foot-strike (0%), to foot-strike
148	(100%) and interpolated to 1% steps (101 points).
149	Standing and Sitting
150	During the sitting and standing trials, patients sat on a platform with the feet shoulder-width apart,
151	each foot positioned on a separate force plate in a fixed position. The seat height was matched to
152	the level the patient's tibial plateau. Patients were then asked to stand and return to a seated
153	position without use of the arms which were held out straight ahead, to avoid any occlusion of the
154	markers.

155	Lunge

- Lunge was chosen to replicate relevant sports activities such as lawn green bowls and tennis.
- 157 Patients were asked to stand with both feet on one force plate and lunge forward, leading with the
- study limb, onto the adjacent force plate return to standing.

159 **Squat**

- Squatting or a variation of a squat is performed on a daily basis [30] and therefore is important to
- assess. Patients were positioned with one foot on each force plate shoulder width apart, and were
- asked to squat as low as comfortably possible with arms out in front of them to avoid marker
- 163 occlusion.

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Data processing

- All markers were labelled and gap-filled using the spline fill function in Vicon Nexus 2.5 (Vicon MX,
- Oxford Metrics, UK), before the labelled marker coordinates and kinetic data were exported to
- 167 Visual 3D modelling software (C-motion, USA) for further analysis. Kinematic data were filtered using
- a low-pass (6Hz) Butterworth filter. Ground reaction force (GRF) data were filtered using a low-pass
- 169 Butterworth filter (25Hz).

Musculoskeletal Modelling

- 171 Musculoskeletal simulations were performed using a commercially available software (AnyBody
- 172 Modeling System, Version 7.1, Aalborg, Denmark). A detailed musculoskeletal model of the lower
- limb [26] based on a cadaveric dataset [31], was scaled to match the anthropometrics of each
- patient based on marker data collected during a static trial [32]. Marker trajectories and GRF data
- 175 from each gait trial served as input to an inverse dynamics analysis, based on a third-order-
- polynomial muscle recruitment criterion, to calculate muscle forces and HCFs. A total of 2148 trials
- were processed and analyzed through the toolkit AnyPyTools [33]. The HCF components were
- defined in a common femur-based reference frame [24] and averages for each patient during each
- individual ADL were computed.

Hip contact force analysis

- 181 The mean resultant HCFs, with relative ranges of variation, predicted across this cohort were
- 182 qualitatively compared to measurements from instrumented implants reported in the Orthoload
- database [34] for matching ADLs.
- 184 Mean resultant HCFs and their individual components, with associated 95% confidence intervals, are
- also qualitatively compared across different ADLs and the peak values are reported.

Additionally, individual patients' loading profiles across activities were investigated and the data from one representative low-functioning and one high-functioning patient were reported in relation to the cohort as a whole. Functional level was defined by the self-selected gait speed as reported previously [27, 28].

Statistical Parametric Mapping (SPM) analysis

The mean computed HCFs for each patient and activity were then normalized to each patient's body mass. The normalized HCFs were analysed using Statistical Parametric Mapping (SPM, www. spm1D.org, v0.4). The three individual force components were regarded as a vector field, describing the three-dimensional variation over time of the HCF vector trajectory. A two-sample Hotelling's T² test, the vectorial analog of a scalar t-test [35], was carried out to evaluate the influence of gender on the contact forces. The use of vector field analysis takes into consideration covariance between force components, thus reducing errors due to covariation bias. Technical details and practical examples are provided elsewhere [35]. The output test statistic SPM{ T²} was evaluated at each point in the time series of each activity. Significance level was set at α =0.05, and the corresponding T²* critical threshold was calculated based on the temporal smoothness of the input data through Random Field Theory. Finally, the probability that similar suprathreshold regions would have occurred from equally smooth random waveforms was calculated. Post-hoc scalar field t-tests were also conducted using SPM on each force component separately, with Bonferroni-corrected significance threshold levels set at α =0.05/3=0.017. Only differences which were statistically significant for more than 2% of the gait cycle are discussed.

Results

Hip contact forces during activities of daily living

The predicted resultant contact forces for the new LLJ patients' cohort showed comparable trends and mean absolute values with previous HCF data derived from the small-sample instrumented prosthesis Orthoload studies for all the compared activities (Figure 2). Standing up from a chair presented a lower peak HCF value compared to the patients fitted with instrumented prostheses, although one of the instrumented implant patients was reported to have confounding contralateral hip pain. Stair ascent and descent showed similar trends and peak values, although with a shift in the temporal frame. The ranges of variation of the predicted HCF were generally wider, particularly for the locomotive activities, as might be expected from a larger cohort of patients.

The comparison of individual force components across ADLs (Figure 3) reveals qualitative differences between the waveform profiles. The different locomotive tasks (Figure 3a) show higher resultant mean peak values for fast walk (3086.1N), stair ascent (2822.7N), and stair descent (2897.5N) compared to level walking (2449.1N). Additionally, stair ascent and descent demonstrated an extended and higher HCF from heel strike to toe off compared to level walking, while fast walking in our cohort is characterized by a more pronounced excursion in HCF magnitude, with higher peak values and a lower force during mid-stance. Similar trends emerged for the proximo-distal component (Figure 3b). Fast walk and stair ascent present mean peak medial forces approximately 25% higher compared to level walking and stair descent (Figure 3d). Similarly, fast walk and stair ascent HCF are also characterized by a concurrent higher peak posterior force compared to level walking, while stair descent present an extended posterior load throughout the loaded phase (Figure 3c).

The larger kinematic variability of the non-locomotive tasks translated in more evident waveform differences in the contact forces. Lunge, as the only activity that creates an intentional asymmetry in the load distribution between the two limbs, yielded a higher resultant HCF, with a mean peak value of 2506.1N, compared to squat (1694.4N), stand up (1280.4N) and sit down (1247.2N) (Figure 3e). The same trend could be observed for the proximo-distal and medio-lateral force components. Lunges also result in a peak posterior force that is approximately three times higher than the other activities (Figure 3g).

Hip contact forces stratified by gender

The vector-field analysis of HCF revealed significant differences between male and female patients during all locomotive activities, as well as sit down and stand up from a chair (Figure 4). During walking, significant differences of up to 0.49*BW higher in males were observed between 5–14%, 28–44%, 57–72%, and 91–96% of the walking cycle. For fast walking, significant differences of up to 0.56*BW greater in males were observed between 6–16%, 58–69%, and 90–96% of the walking cycle, while stair descent presented significant differences (up to 0.28*BW higher in females) between 25–31% of the activity. Despite males and females presenting similar HCF magnitudes during stair ascent, the vector-field analysis also revealed significant differences between 43–57% of the stair ascent cycle in the order of 0.46*BW, indicating that differences between male and females exist in the three-dimensional trajectory of the force vector (Figure 4c). The test statistics continuum SPM{T²} obtained from the vector-field analysis, as well as the full results of the post-hoc t-tests for the individual force components, are reported for each activity as supplementary material (Figure A1-A8).

Discussion

This study has highlighted the general variability in the magnitudes and patterns of hip loading that might be expected in larger cohort and has identified statistically significant and clinically meaningful differences between males and females following THR, across a range of ADLs. The large interpatient variability might, in vivo, be expected to lead to differing amounts of wear and differing failure rates in sub groups of patients undergoing hip replacement. Full datasets for one representative high functioning patient and one lower functioning patient, demonstrating this variability are available at https://doi.org/10.5518/319. Previous studies have demonstrated that applications of musculoskeletal models can be used to reliably predict contact forces for a large cohort of patients during gait [26, 27]. It was previously shown that different patient characteristics influence both kinematics [28] and loads experienced at hip [27], with patient's overall functionality being a highly influential factor in determining variability in kinematics and kinetics during gait. The present study has also further illustrated the comparability of the computational modelling approach to the Orthoload dataset across five additional ADLs.

It is worth noting however that our methods do have number of limitations which are inherent when using computational modelling. The HCFs predicted in this study were obtained from scaled generic models and a certain level of error in the prediction of forces might persist, due to uncertainty in marker positioning [32] and lack of subject-specific anthropometric imaging data [36]. Additionally, scaled generic models do not account fully for anatomical differences between genders [37] or patient specific implant measures, which could have improved the models' predictions [38].

We found significant differences between males and females in HCFs normalized by body weight across all locomotor activities as well as sit down and stand up from a chair. Differences in the HCF vectorial trajectories indicate that there are functional differences between the two patient groups. The different three-dimensional loading pattern, combined with different absolute load magnitudes, which can be expected in association with weight differences between genders, could affect the implant behaviour and play a role in differing implant survival rates particularly in younger male and female patients. It is notable that while there are gender related differences in risk of revision for people undergoing surgery up to the age of 75 years [16], the risk is comparable between for patients older than 79 years old, suggesting that failure rates are not constant and probably depend on a combination of factors, such as patient-specific kinematics [22, 39]. This lack of clear understanding is highlighted in the failure rates for ASR implants which were unexpectedly higher in

females [15]. One way to predict how these patient-level factors might affect outcomes would be through more representative pre-clinical testing. The current standardization of pre-clinical wear tests does not allow any assessment of the influences that inter-patient variability, specifically in terms of loading, would have on the implant performance *in vivo*.

The analyses of the ADLs have revealed a large range and a large variability of forces experienced at the hip during locomotor and non-locomotor activities. During the locomotive activities (walk, fast walk and stair negotiation), there were similarities in the waveform shapes. During the nonlocomotive ADLs (lunge, sit to stand, stand to sit, and squat) the waveform of the resultant force was, as expected, different to the locomotive activities exhibiting a more uni-modal and less dynamic loading pattern. Additionally, the individual force components also displayed large differences across activities. Higher posterior loads throughout the weight bearing phase of the activity characterize stair descent when compared to other locomotive activities, and these would be expected to alter the 3-dimensional loading pattern at the bearing surface and potentially lead to different wear behaviour. These differences are profound when comparing individual activities and they could potentially be magnified when considering the much greater variety of activities that the wider THR population engages in [40, 41]. Including contrived ADLs or adverse loading conditions in pre-clinical wear tests has previously produced higher levels of wear [42, 43], and the interaction between patient kinematics and surgical factors such as cup placement [44], has demonstrated that wear is a multifactorial phenomenon. The complexity of the interplay between all these factors, would be better explored through more extensive testing of implant performance, particularly under more demanding and clinically relevant conditions such as multiple ADLs [23, 25].

Our data has shown large patient-specific and activity-related variations in the forces experienced at the hip joint, which differ from the standardized loading waveform currently used in pre-clinical testing standards, such as ISO 14242-1. Pre-clinical testing of implants and other orthopaedic implants has come under scrutiny lately both from within the industry, with initiatives such as Beyond Compliance (https://www.beyondcompliance.org.uk/), and through external pressures, such as the recent release of papers by the International Consortium of Investigative Journalists (ref https://www.icij.org/investigations/implant-files/). While more evidence is required to confirm whether using representative waveforms would produce more realistic wear patterns compared to retrievals, [45] further debate about the suitably of current standards is warranted. Future testing protocols should also consider other in vivo loading conditions not studied in the current cohort such as microseparation [46] edge loading or adverse events [23], which could be incorporated into

313	computational models. In the interim using more realistic loading waveforms, such as the ones						
314	identified in this work for pre-clinical hardware simulation would be a progressive step.						
315	To conclude, the LLJ cohort has shown that the testing of hip implants under the current required						
316	standard of ISO 14242 does not represent accurately the in vivo loads, even under a limited set of						
317	activities of daily living. There is a case that implant industry could be more demanding in its						
318	requirements for pre-clinical testing prior to introducing a new implant to market and further work is						
319	obviously needed to explore the consequences of the altered loading patterns on wear and						
320	ultimately the success or otherwise of a hip replacement. As a first step the motion-capture dataset						
321	underpinning this and related studies is available as a public repository at						
322	https://doi.org/10.5518/319, while the associated musculoskeletal models can be obtained through						
323	Zenodo.org under the DOI, DOI:10.5281/zenodo.1254286						
324	Appendices						
325	Full results of the post-hoc t-tests for the individual force components, are reported for each activity						
326	as supplementary material (Figure A1-A8).						
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328	Role of the funding source						
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Tables

Table 1: Patient demographics for each activity of daily living. Values are reported as mean (SD) unless otherwise stated

	No.	Body Mass [kg]	Height [cm]	BMI [kg/m ²]	Male/	Age (y)	Years since
	Patients				Female		THR
Walk	132	78.10(12.79)	166.28 (8.40)	28.20 (3.85)	66/66	71.62(7.61)	2.80(1.42)
Fast	117	78.59(12.81)	167.36 (8.08)	27.99 (3.71)	62/55	70.56(7.31)	2.84(1.43)
Ascent	49	80.13(13.81)	167.55 (9.37)	28.50(4.03)	28/21	69.90(7.70)	3.00 (1.47)
Descent	47	79.87(14.12)	168.01 (9.34)	28.22(3.92)	28/19	70.00(7.87)	3.09 (1.46)
Sit	131	78.08(12.83)	166.25 (8.42)	28.20(3.86)	65/66	71.57(7.61)	2.82 (1.42)
Stand	131	78.08(12.83)	166.25 (8.42)	28.20(3.86)	65/66	71.57(7.61)	2.82 (1.42)
Squat	34	78.45(11.80)	169.74 (6.23)	27.20(3.60)	23/11	67.24(6.28)	3.18 (1.59)
Lunge	35	75.89(11.64)	167.23 (6.41)	27.09(3.53)	22/13	70.29(6.85)	2.57(1.58)

