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Prevalence and course of lower limb disease activity and walking disability over the first five years of juvenile idiopathic arthritis: results from the childhood arthritis prospective study

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Abstract

Objectives. To investigate the time course of lower limb disease activity and walking disability in children with JIA over a 5 year course.

Methods. The Childhood Arthritis Prospective Study (CAPS) is a longitudinal study of children with a new JIA diagnosis. CAPS data includes demographics and core outcome variables at baseline, 6 months and yearly thereafter. Prevalence and transition rates from baseline to 5 years were obtained for active and limited joint counts at the hip, knee, ankle, and foot joints; and walking disability, measured using the Childhood Health Assessment Questionnaire walking subscale. Missing data were accounted for using multiple imputation.

Results. A total of 1,041 children (64% female), with a median age of 7.7 years at first visit were included. Baseline knee and ankle synovitis prevalence was 71% and 34% respectively, decreasing to between 8-20% and 6-12% respectively after 1 year. Baseline hip and foot synovitis prevalence was less than 11%, decreasing to less than 5% after 6 months. At least mild walking disability was present in 52% at baseline, stabilising at 25-30% after 1 year.

Conclusion. Lower limb synovitis and walking disability are relatively common around the time of initial presentation in children and young people with JIA. Mild to moderate walking
disability persisted in approximately 25% of patients for the duration of the study, despite a significant reduction in frequency of lower limb synovitis. This suggests that there is an unmet need for non-medical strategies designed to prevent and/or resolve persistent walking disability in JIA.

Key words: juvenile idiopathic arthritis, epidemiology, lower limb, ankle, foot, knee, hip, synovitis, walking disability, prevalence.

**Rheumatology key messages**

- Prognosis for lower limb disease is good, but walking disability persists for many with JIA.
- There may be unmet need for care to prevent and/or resolve walking disability in JIA.
- Evidence is provided for walking disability trajectories including absence, persistent moderate and fluctuating courses.

**Introduction**

Juvenile idiopathic arthritis (JIA) is the most common form of inflammatory arthritis in childhood with an estimated prevalence of 1 per 1,000 children [1]. In JIA, synovitis is the primary disease pathology, and its clinical signs and symptoms include joint pain, swelling, stiffness, and deformities [2-4].

JIA has a predilection for involvement of the lower limb joints, particularly the knee and ankle [5-7]. Lower limb synovitis has been associated with abnormal function in several small-sample cross-sectional studies of gait and clinical surveys [2,8-10]. Results from these studies suggest that some children with JIA have degraded gait patterns characterised by decreased walking speed, step length, and altered loading characteristics [2,8,10]. Such impairments typically manifest as difficulties undertaking routine functional tasks including walking, and stair climbing. Walking is the most common form of incidental, free-living
physical activity in children and adolescents [11], so further research on the long-term impact of lower limb disease on walking ability in JIA is warranted.

Only one study evaluated the long-term prevalence and course of lower limb disease activity in children with JIA [5]. It found that almost all children with JIA will experience lower limb joint synovitis at some point over the course of their disease [5]. Early in the post-diagnosis stage, approximately 75% and 60% of those with JIA will experience knee or ankle joint synovitis respectively, decreasing to 50% at 1-year post-diagnosis with the introduction of first-line disease-modifying therapies, and 30-40% thereafter [5]. Physical functional impairments, such as walking disability, associated with lower limb synovitis [2,9,12-13] were not evaluated.

Composite measures of disease activity are considered to be potentially reversible with appropriate pharmacological therapies [14,15]. In contrast, outcome measures for the physical function domain incorporate both reversible and irreversible components [3,16]. Functional disability scores appear to be highly correlated with active joint counts in early disease, while limited joints counts are highly correlated with disability and radiographic joint damage with longer disease durations [3,16]. These findings suggest some children with JIA may be vulnerable to a persistent or progressive course of disability, despite disease activity suppression.

Relative to the prevalence and course of general disability in JIA which has been well described [3,16], walking disability has not been studied. Greater understanding of the patterns of lower limb joint impairments and how they relate to walking disability over time may facilitate more effective rehabilitative management strategies. The objectives of this
study are to investigate the prevalence and time course of lower limb disease activity and walking disability in patients with JIA over the first 5 years following diagnosis and to identify walking disability trajectories over this 5-year course.

Methods

Study population

Participants in this study are from the Childhood Arthritis Prospective Study (CAPS), with details of the study described elsewhere [17]. In short, CAPS is a multicentre study in the UK that commenced in 2001, to identify predictors of short-term and long-term outcomes of inflammatory arthritis. CAPS participants were children (aged ≤16 years at onset) with inflammatory arthritis of at least 1 joint persisting for at least 2 weeks who were recruited following first presentation to paediatric rheumatology. Exclusion criteria are septic arthritis, haemarthrosis, arthritis caused by malignancy, trauma, or connective tissue disorders. CAPS complied with the Declaration of Helsinki and was approved by the North-West Multi-Centre Research Ethics Committee. Written informed consent was obtained from the parent(s)/guardian for participating children, and children considered able provided age-appropriate assent.

Data collection

At baseline, the rheumatologist clinically examined the joints, recording the number of limited and active joints (out of 71 joints), completed a 10 cm physician’s global assessment (PGA) visual analogue scale (VAS; range 0–10 cm, where 10 is the worst score) and assigned an International League Against Rheumatism (ILAR) subtype of JIA based on the disease characteristics at presentation [18]. A joint was considered active if there was swelling due to active synovitis or in the absence of swelling, limited motion accompanied by heat, pain or
tenderness [19]. A limited joint was a joint limited in motion. The parents and child were interviewed by a rheumatology research nurse, and medical records were reviewed to extract data on demographics. The parent or child, where appropriate, completed childhood health assessment questionnaire (CHAQ), a measure of functional disability (range 0–3, where 3 is the worst) [20], a 100-mm VAS pain scale, and a 10-cm parent/patient global health measure (parent general evaluation [PGE]). The CHAQ was completed by the parent if the child was ≤10 years or optionally by the parent or child if age ≥11 years. The active joint count, PGA, and PGE were used to calculate the clinical Juvenile Arthritis Disease Activity Score based on a 27 joint count (cJADAS-27, which excludes ESR) [14].

**CAPS follow up data collection**

Follow-up study data were captured at 6 months following first presentation and then annually for 5 years. Data were extracted from the medical record and included the most recent rheumatological examination, PGA, PGE, CHAQ and pain VAS.

**Statistical analysis**

Patient data between 2001 and December 2015 were available for analysis. This analysis was limited to children who presented to paediatric rheumatology prior to September 2010, who were diagnosed with JIA [18], and who had both active and limited joint counts recorded and/or had completed the CHAQ on at least 1 occasion over a 5-year follow-up period.

Demographic and disease characteristics (active and limited joint count, PGA, PGE, CHAQ score, excluding ESR), pain, cJADAS-27 and ILAR subtype as recorded at 1 year were summarised using descriptive statistics.
Local joint impairments were determined using active and limited joint counts recorded at the hip, knee, ankle, subtalar, inter-tarsal, metatarsophalangeal (MTP) and interphalangeal (IP) joints and dichotomised as present (≥1 limb affected) or absent (0). Walking disability was measured using the CHAQ walking subscale (Is your child able to: 1) walk outside on flat ground?, and 2) climb up 5 steps; possible responses include: without any difficulty, with some difficulty, with much difficulty, or unable to do). CHAQ walking disability is reported in terms of severity (0=no disability, 1=mild disability, 2=moderate disability, 3=severe disability), as well as present (≥1, at least mild disability) or absent (0, no disability). The prevalence of lower limb synovitis and walking disability, and severity of walking disability were calculated as absolute frequencies (n) and percentages (%) of participants. Change between consecutive follow-ups was calculated as percentages of participants with new, stable or resolved synovitis (knee and ankle joints only) and walking disability. Analyses were undertaken using SPSS 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) and STATA 13 (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Analyses of prevalence for active lower limb joints assumed that some data were missing-not-at-random (MNAR). Children with missing data were split into seven groups: those discharged well, transferred to other clinics (excluding those who have likely moved to adult services), transferred to adult services, moved home address, lost to follow up in CAPS, follow-up completed but with incomplete data, and follow-up missed but with subsequent return to follow-up. Assumptions were made regarding these groups based upon the approach by Shoop-Worrall et al [21]: participants had no active lower limb joints at follow-up if they belonged to groups one, three, five and seven. All other data were assumed to be missing-at-random (MAR) and were imputed via multiple imputation over 20 iterations using STATA.
13. Missing data for prevalence of limited joints, and walking disability were all assumed to be MAR and thus were imputed via multiple imputation over 20 iterations (see supplementary data, section methods for handling missing data, available at Rheumatology Advances in Practice online). Multiple imputations were not undertaken where the observed prevalence for individual affected joints was low (<5% at follow-up). Secondary analyses included graphical explorations of complete (referred to as closed cohort), incomplete (open cohort) and imputed case analyses for active/limited joints and presence/absence of walking disability (see supplementary figures S1-8, available at Rheumatology Advances in Practice online).

Transition rates for walking disability states for the entire sample between follow-ups were explored using the TraMineR categorical sequence data package for R [22] and are expressed as absolute frequencies and percentages. A transition is defined as the sequence of walking disability states between any two successive follow ups (for example, an improvement from severe to moderate walking disability). Longitudinal trajectories for walking disability states from closed and open cohort data were explored graphically by constructing a riverplot using the riverplot R package.

Results

Study population
A total of 1,041 children, of which 64% were female, with a median age at baseline of 7.7 years (interquartile range [IQR] 3.5-11.5 years) were included in the study (Table 1). A flowchart of study participant recruitment is provided in supplementary figure S9, available at Rheumatology Advances in Practice online.
Lower limb joint impairments

Active and limited joint counts were available for 999 children at baseline, reducing to 841 (84%) at 6 months, 916 (92%) at 1 year, 852 (85%) at 2 years, 747 (75%) at 3 years, 666 (67%) at 4 years, and 576 (58%) at 5-year follow-up. A total of 204 children had complete baseline and all subsequent follow-ups over 5 years (closed cohort). The children in the closed cohort differed significantly from the open cohort in terms of age (closed: median 5.8 years [IQR 2.8-8.7]; open: 8.8 years [3.8-12.1], p<0.01), symptom duration (closed: 3 months [1-6]; open: 4 months [2-9], p=0.02), and PGA (closed: 3.5cm [1.8-6.1]; open: 2.8cm [1.5-5], p=0.01). For the open cohort, baseline knee joint synovitis prevalence was 71%, decreasing to 26% at 6 months and between 8-20% after 1 year (Figure 1A). Baseline ankle joint synovitis was 34%, decreasing to 18% at 6 months and between 6-12% after 1 year. Baseline hip and foot joints synovitis prevalence was less than 11%, decreasing to 2-4% at 6 months and 1-3% after 1 year. Baseline limited joint prevalence at the knee was 53%, decreasing to 22% at 6 months and between 9-19% after year 1 (Figure 1B). Baseline limited joint prevalence at the ankle was 21%, decreasing to 12% at 6 months and 6-8% after year 1. Baseline limited joint prevalence at the hip and foot joints was less than 10%, reducing to between 2-6% at 6 months and approximately 0-5% after year 1. Open cohort prevalence estimates were consistent with closed cohort estimates (see supplementary figures S1-8, available at *Rheumatology Advances in Practice* online). Imputed prevalence estimates were highly consistent (to within 2.5%) with the original data (open cohort) at each time point.

Change in active joint synovitis state between follow-ups

The hip joint remained largely quiescent between each subsequent follow-up, with over 91% of participants having stable inactive hip joints, 0.5-1% having stable active disease, and 0.5-2% developing new active disease (Figure 2A). At the knee, 23% had stable active synovitis
from 0-6 months, decreasing to 9% from 6 months to 1 year and 5-6% thereafter (Figure 2B). New instances of knee synovitis were observed for between 7-12% of participants at subsequent follow ups. After year 1, between 70-75% of participants had stable inactive knee joints. At the ankle, 13% had stable active synovitis from 0-6 months, decreasing to 5% from 6 months to 1 year and 3-5% thereafter (Figure 2C). New instances of ankle synovitis were observed for approximately 5-11% of participants at subsequent follow ups. After year 1, approximately 80% of participants had stable inactive ankle joints. The subtalar joint remained largely quiescent, with over 86% of participants having stable inactive subtalar joints, 0-1.5% having stable active disease, and 2-3% developing new active disease (Figure 2D). Imputed estimates consistently exceeded original data for inactive stable disease by up to 10%.

Walking disability

CHAQ walking disability scores were available for 737 children at baseline, reducing to 669 (91%) at 6 months, 727 (99%) at 1 year, 663 (90%) at 2 years, 592 (80%) at 3 years, 519 (70%) at 4 years, and 454 (62%) at 5-year follow-up. A total of 173 (23%) children completed baseline and all subsequent follow-ups over 5 years (closed cohort). These patients differed significantly from those with missing data for age (closed: 6.3 years [2.8-10.1]; open 8.1 years [3.8-11.9], p<0.01), and overall CHAQ score (closed 0.5 [0.125-1.125]; open 0.75 [0.125-1.5], p=0.01). For the open cohort, at least mild walking disability was present in 52% at baseline, reducing to 37% at 6 months, 33% at 1 year, and stabilising at 25-31% thereafter. Moderate walking disability was more frequently observed at each time point relative to mild and severe walking disability (Figure 3A), with 33% of participants having moderate walking disability at baseline, reducing to 25% at 6 months, 23% at 1 year and 17-23% thereafter. Mild walking disability was observed in 15% at baseline, reducing to 10% at 6 months, 9% at
1 year and 6-9% thereafter. Severe walking disability was relatively infrequent and was observed in 5% of participants at baseline, 2% at 6 months, and less than 1% thereafter. Open cohort prevalence estimates were consistent with closed cohort estimates (see supplementary figures S1-8, available at *Rheumatology Advances in Practice* online). Imputed prevalence estimates were highly consistent (to within 1%) with the original data (open cohort) at each time point.

**Change in walking disability ‘states’ between follow-ups**

Proportional increases were observed for participants with a stable absence of walking disability, from 41% at baseline to 6 months, to 54-67% thereafter. Stable walking disability was frequently observed, affecting 30% of participants between baseline and 6 months, decreasing to 23% between 6 months and 1 year, and between 16-21% thereafter. New instances of walking disability were less frequently observed, affecting between 7-10% of participants. Proportional decreases were observed for resolution of walking disability, from 23% for baseline to 6 months, 13% at 6 months to 1 year, reducing to 7% at 4-5 years. Imputed estimates consistently exceeded original data for resolved walking disability.

**Transitions and trajectories of walking disability**

For all follow-ups over the full 5-year study period there were a total of 3,907 transitions for walking disability states observed for the entire sample (Table 2). The most frequently observed sequences were maintenance of ‘no walking disability’ (n=2243, 57.4%) and maintenance of ‘moderate walking disability’ (n=518, 13.2%) between two consecutive follow ups. A total of 485 (12.4%) transitions were observed for at least ‘mild walking disability’ to no walking disability.
The riverplots (Figure 4A and B) reveal two main concentrations of participants, one with a stable absence of walking disability, and the other with persistent moderate walking disability over 5-years of follow-up. The plots also reveal a frequent fluctuating course of walking disability, with deterioration and improvement between absent, mild and moderate walking disability states. There are also concentrations of trajectories to and from missing data to absent disability across the 5-year follow up period (Figure 4A).

**Discussion**

This study represents the first large-scale longitudinal evaluation of lower limb joint involvement and walking disability from the point of diagnosis in children with JIA. These results suggest that prevalence rates for knee and ankle joint synovitis and joint limitation of motion are high at initial presentation and then stabilise with the initiation of medical therapies. Joint impairments at the hip, subtalar and small foot joints were infrequently observed over the 5-year study and somewhat contrary to previous study findings [2,9,12,13].

Assessment of active and limited joint counts have been shown to frequently underestimate lower limb synovitis relative to more sensitive imaging techniques [23-27]. Expert consensus guidance on imaging in JIA concluded that ultrasound and MRI are superior to clinical examination in the evaluation of joint inflammation [28]. The entity of ‘sub-clinical’ synovitis is not currently well understood, but evidence suggesting its presence may predict future JIA relapses [29]. The low prevalence of hip, sub-talar and foot synovitis in this study suggests that the role of imaging requires further consideration.

Persistent synovitis may be problematic at the knee and ankle for a small proportion of children with JIA. This finding is in agreement with previous studies that demonstrated
several distinct disease activity courses exist, including ‘moderate increasing’ and ‘persistent moderate’ trajectories, which account for approximately 25% of patients with JIA [30,31]. This is an important finding since previous studies have demonstrated that persistent disease activity is associated with radiographic progression and reduced physical function [32,33]. Ankle joint synovitis appears to be associated with unfavourable disease outcome characterised by failure to achieve remission [34,35]. Prognosis for lower limb disease activity overall appears to be good, with low prevalence of lower limb disease activity observed for all lower limb joints after 1-year.

Whilst prevalence of walking disability decreased from 52% to 32% at 1-year follow-up, an important finding was that at least mild walking disability affected 25-31% of cases after one year despite low prevalence rates of lower limb synovitis. In addition, the majority of those reporting walking disability were in the ‘moderate’ category, which is indicative of ‘much difficulty’ walking or climbing steps. Persistent walking disability also appeared to be problematic for some participants, where 16-22% reported walking disability at two consecutive follow-ups on at least one occasion after 1 year. Together with analyses of transitions and trajectories of walking disability in this cohort, these findings support the theory that walking disability incorporates both reversible and irreversible components which have been confirmed in studies of overall physical function [3,16].

Walking disability in children and young people with JIA is likely multifactorial and may be influenced by reduced muscle strength and endurance, as well as impaired motor function, balance and proprioception [36-39]. Gait compensations are often consistent with the avoidance of pain, stiffness, and exacerbations of disease whereby children walk more slowly, less often, and less far, followed by deconditioning due to reductions in physical
activity [40]. There is strong evidence demonstrating that children with JIA are significantly less active than healthy children [41,42]. Low levels of physical activity in childhood are not trivial and have been associated with poor body composition (e.g., increased fat, decreased lean muscle, poor bone health) and elevated cardiovascular disease risk in later life [43,44]. In addition, walking disability may occur as a result of the presence of disease-related extra-articular features such as tenosynovitis, enthesitis in participants with the enthesitis-related arthritis or dactylitis in psoriatic arthritis. Data on extra-articular features were not routinely collected for each study participant and therefore were not included in this study’s analyses.

There was no specific measure of lower limb function collected as part of the CAPS inception cohort study. As such, we used the CHAQ walking subscale for these analyses. A similar approach has been adopted in adults with rheumatoid arthritis where no tool designed specifically to measure lower limb function was available [45]. This novel approach has some advantages in that the CHAQ is commonly administered as part of routine care for JIA, and it has excellent validity, reliability and responsiveness to change [46]. Moreover, normative data is available from 221 controls for comparison, and this suggests that healthy children will have a mean (standard deviation) score of 0 (0.2) on the CHAQ walking subscale [20]. Given the simplicity of the CHAQ walking subscale, which is derived from only two items (Are you/is your child able to: walk outside on flat ground, and; climb up five steps), it is probable that other important aspects of walking (such as the ability to run or walk on uneven ground) are not captured using this subscale. Individual measurement properties of the CHAQ walking disability subscale remain largely unknown; however previous studies have demonstrated that this subscale has high internal consistency (Cronbach’s alpha 0.7-0.93) [20,46].
There are some limitations of this study concerning the analyses of an open cohort. This cohort was subject to high drop-out rates and missing data as data items were collected as part of routine clinical visits, which may result in selection bias. Moreover, the CAPS study recruited from tertiary centres of paediatric rheumatology, which may be more likely to include the most severe cases. A strength of this study is that potential for selection bias was minimised in three different ways. First, prevalence estimates and transitions for lower limb impairments and walking disability at baseline and over the 5-year follow-up periods were compared by computing both open, closed cohort and imputed data (for selected variables). These estimates remained largely consistent across all analyses, suggesting a low risk of selection bias. Second, baseline characteristics between closed and open cohorts were compared and revealed only modest differences for age, symptom duration, PGA and disability score. Lastly, MI was adopted according to previously accepted assumptions [21]. Selection bias in patients with full follow-up is concluded to be minimal; however, the possibility of a slight overestimation of lower limb impairments and disability is acknowledged.

Given the length of time between annual follow-ups, it is likely that several fluctuations in joint impairments or walking disability may have taken place between measurements that may not have been captured. Indeed persistent disease as observed over two follow-ups separated by one year may in fact be more reflective of two flares in a joint separated by periods of relative quiescence. Therefore, it is acknowledged that careful interpretation is required for persistence of outcomes over time as presented in this study.

Conclusion
Prevalence rates for lower limb synovitis and walking disability are initially high and then stabilise. The prognosis for lower limb impairments is generally good over 5-years; however, walking disability often persists in spite of low prevalence of lower limb disease activity. This study provides evidence of both persistent walking disability, and three distinct trajectories of walking disability including persistent moderate and fluctuating. The results necessitate further research to clarify the relationships between lower limb impairments and walking disability in JIA. There may be an unmet need for non-medical strategies designed to prevent and/or resolve persistent walking disability in JIA.

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## TABLES

### Table 1. Demographic and clinical characteristics at first presentation.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>N</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), years</td>
<td>987</td>
<td>7.7 (3.5-11.5)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>999</td>
<td>642 (64.3)</td>
</tr>
<tr>
<td>Active joint count, median (IQR)</td>
<td>999</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Limited joint count, median (IQR)</td>
<td>999</td>
<td>1 (1-3)</td>
</tr>
<tr>
<td>Physician global assessment, mean (SD), cm</td>
<td>803</td>
<td>3.4 (2.3)</td>
</tr>
<tr>
<td>Parent general evaluation, mean (SD), cm</td>
<td>670</td>
<td>2.8 (2.6)</td>
</tr>
<tr>
<td>VAS pain, mean (SD), mm</td>
<td>717</td>
<td>34.8 (28.3)</td>
</tr>
<tr>
<td>CHAQ score, median (IQR)</td>
<td>731</td>
<td>0.625 (0.125-1.375)</td>
</tr>
<tr>
<td>cJADAS-27, mean (SD)</td>
<td>555</td>
<td>10.3 (7.7)</td>
</tr>
<tr>
<td>ILAR subtype, n (%)</td>
<td>1,033</td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
<td>53 (5.1)</td>
</tr>
<tr>
<td>Persistent oligoarthritis</td>
<td></td>
<td>457 (44.2)</td>
</tr>
<tr>
<td>Extended oligoarthritis</td>
<td></td>
<td>22 (2.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>RF negative polyarthritis</td>
<td>152 (14.7)</td>
<td></td>
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<tr>
<td>RF positive polyarthritis</td>
<td></td>
<td>30 (2.9)</td>
</tr>
<tr>
<td>Enthesitis-related arthritis</td>
<td></td>
<td></td>
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<tr>
<td>Psoriatic arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclassifiable</td>
<td></td>
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</tr>
</tbody>
</table>

Data are reported as n (%) unless otherwise stated. VAS: visual analogue scale; CHAQ: childhood health assessment questionnaire; cJADAS: Clinical Juvenile Arthritis Disease Activity Score.

**Table 2.** Transition sequence rates between each walking disability state.

<table>
<thead>
<tr>
<th>Transitions to</th>
<th>Transitions from</th>
<th>-&gt; CHAQ_0</th>
<th>-&gt; CHAQ_1</th>
<th>-&gt; CHAQ_2</th>
<th>-&gt; CHAQ_3</th>
<th>Total (rows)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAQ_0 -&gt;</td>
<td>2243 (57.4)</td>
<td>128 (3.3)</td>
<td>185 (4.7)</td>
<td>1 (0.03)</td>
<td>2557 (65.4)</td>
<td></td>
</tr>
<tr>
<td>CHAQ_1 -&gt;</td>
<td>184 (4.7)</td>
<td>81 (2.1)</td>
<td>95 (2.4)</td>
<td>1 (0.03)</td>
<td>361 (9.2)</td>
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<tr>
<td>CHAQ_2 -&gt;</td>
<td>283 (7.2)</td>
<td>117 (3.0)</td>
<td>518 (13.3)</td>
<td>12 (0.3)</td>
<td>930 (23.8)</td>
<td></td>
</tr>
<tr>
<td>CHAQ_3 -&gt;</td>
<td>18 (0.5)</td>
<td>4 (0.1)</td>
<td>30 (0.8)</td>
<td>7 (0.2)</td>
<td>59 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Total (columns)</td>
<td>2728 (69.8)</td>
<td>330 (8.4)</td>
<td>828 (21.2)</td>
<td>21 (0.5)</td>
<td>3907</td>
<td></td>
</tr>
</tbody>
</table>

Data are reported as n (%). Each row represents the starting sequence of transition from each walking disability state, whereas each column represents the end sequence of transition to each walking state. CHAQ: childhood health assessment questionnaire.

**FIGURE LEGENDS**
Figure 1. Relative frequencies of active (A) and limited (B) joints including imputed values.

Figure 2. Relative frequencies for changes in disease activity. A knee open cohort, B knee imputed values, C ankle open cohort and D ankle imputed values. Dark blue, inactive stable; red, active stable; green, new active; purple, active resolved. Total n for closed cohort transitions between time points are: 0-6months, n=819; 6 months-1year, n=734; 1-2years, n=660; 2-3years, n=521; 3-4years, n=376; 4-5years, n=274.

Figure 3. Relative frequencies (% of n) for walking disability over 5 years. (A) open (baseline, n=737; 6months, n=669; 1 year, n=727; 2 years, n=663; 3 years, n=592; 4 years, n=519; 5 years, n=454) and closed (B) cohorts (n=173). Light blue, no disability; red, mild walking disability; green, moderate walking disability; purple, severe walking disability. C. Relative frequencies (% of n) for changes in walking disability ‘state’ between each successive follow-up for (C) open cohort (0-6months, n=502; 6 months-1year, n=537; 1-2years, n=544; 2-3years, n=496; 3-4years, n=426; 4-5years, n=374 and (D) open cohort with imputed data. Dark blue, no disability; red, stable disability; green, new disability; purple, resolved disability.

Figure 4. Trajectories for child health assessment questionnaire (CHAQ) walking disability levels from baseline to 5-year follow-up. The riverplot illustrates the proportion of participants with different levels of walking disability or missing data over time. Each participant’s trajectory is illustrated by a single line. The thickness of the line at a node is proportional to the percentage of participants at that level of walking disability. A. Riverplot depicting individual sequential trajectories for CHAQ walking disability ordinal data (open cohort). Thicker lines for no walking disability (none) suggest a large proportion had no
walking disability, whereas relatively few had severe walking disability. B. Riverplot depicting CHAQ walking disability trajectories for the closed cohort (n=173).
Open cohort

CHAQ walk DI 3
CHAQ walk DI 2
CHAQ walk DI 1
CHAQ walk DI 0

Baseline 6 months 1 year 2 years 3 years 4 years 5 years

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

275x185mm (96 x 96 DPI)
228x119mm (96 x 96 DPI)
Figure 1. Relative frequencies (% of n) of presence of A active and B limited joints for each lower limb joint over 5 years of follow-up including imputed values for knee and ankle joints.
Figure 2. Relative frequencies (\% of n) for changes in disease activity ‘state’ for A knee open cohort, B knee imputed values, C ankle open cohort and D ankle imputed values between consecutive time-points over 5 years. Dark blue, inactive stable; red, active stable; green, new active; purple, active resolved. Total n for closed cohort transitions between time points are: 0-6months, n=819; 6 months-1year, n=734; 1-2years, n=660; 2-3years, n=521; 3-4years, n=376; 4-5years, n=274.
Figure 3. Relative frequencies (% of n) for levels of walking disability at each time point over 5 years for (A) open (baseline, n=737; 6 months, n=669; 1 year, n=727; 2 years, n=663; 3 years, n=592; 4 years, n=519; 5 years, n=454) and closed (B) cohorts (n=173). Light blue, no disability; red, mild walking disability; green, moderate walking disability; purple, severe walking disability. C. Relative frequencies (% of n) for changes in walking disability ‘state’ between each successive follow-up for (C) open cohort (0-6 months, n=502; 6 months-1 year,
n=537; 1-2 years, n=544; 2-3 years, n=496; 3-4 years, n=426; 4-5 years, n=374 and (D) open cohort with imputed data. Dark blue, no disability; red, stable disability; green, new disability; purple, resolved disability.
Figure 4. Trajectories for CHAQ walking disability levels from baseline to 5-year follow-up. The riverplot illustrates the proportion of participants with different levels of walking disability or missing data over time. Each participant’s trajectory from one level to another is illustrated by a single line. The thickness of the line at a node (i.e. a level at a specific point in time) is proportional to the percentage of participants at that level of walking disability. A. Riverplot depicting individual sequential trajectories for CHAQ walking disability ordinal data (no disability; mild walking disability; moderate walking disability; severe walking
disability; and missing values) for the full open cohort. The thicker lines for no walking
disability (none) suggest a relatively large proportion of participants had no walking
disability over the course of the study, whereas relatively few had severe walking disability,
particularly towards the final follow-up. B. Riverplot depicting CHAQ walking disability
trajectories for the closed cohort (n=173). The thicker lines for moderate walking disability
are indicative of a greater proportion of participants having moderate walking disability
relative to mild or severe.