Incidence of osteoarthritis, osteoporosis and inflammatory musculoskeletal diseases in adults with cerebral palsy: A population-based cohort study

Neil E. O’Connella,⁎, Kimberley J. Smithb, Mark D. Petersonc, Nicola Ryand,e, Silvia Liveranif, Nana Anokyea, Christina Victora, Jennifer M. Rya,g

a Institute of Environment, Health and Societies, Brunel University London, Kingston Lane, Uxbridge, UB8 3PH, United Kingdom
b Department of Psychological Sciences, Faculty of Health and Medical Sciences, University of Surrey, United Kingdom
c Department of Physical Medicine and Rehabilitation, University of Michigan Medicine, USA
d Department of Cardiology, Aberdeen Royal Infirmary, United Kingdom
e Department of Interventional Cardiology, Hospital Clínico San Carlos, Spain
f School of Mathematical Sciences, Queen Mary University of London, United Kingdom
g Department of Epidemiology and Public Health Medicine, Royal College of Surgeons in Ireland, Ireland

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ABSTRACT

Background: People with cerebral palsy (CP) may be at increased risk of musculoskeletal conditions due to various factors including malnutrition and abnormal levels of skeletal loading. This study aimed to compare the incidence of osteoporosis, osteoarthritis and inflammatory musculoskeletal diseases between adults with and without CP.

Methods: A population based cohort study was conducted using data from the Clinical Practice Research Datalink collected between 1987 and 2015. Adults with CP were matched to adults without CP for age, sex and general practice. Cox models, stratified by matched set and adjusted for potential confounders, were fitted to compare the risk of osteoporosis, osteoarthritis and inflammatory musculoskeletal diseases.

Results: 1705 adults with CP were matched to 5115 adults without CP. Adults with CP had an increased risk of osteoporosis in unadjusted (Hazard Ratio (HR) 3.67, 95% Confidence Interval (CI) 2.32 to 5.80, p < 0.001) and adjusted (HR 6.19, 95% CI 3.37 to 11.39, p < 0.001) analyses. No evidence of increased risk of inflammatory musculoskeletal diseases was observed in unadjusted or adjusted analyses. For osteoarthritis no evidence of increased risk was seen in the unadjusted analysis, but evidence of an increased risk was seen when the analysis was adjusted for alcohol consumption, smoking status, and mean yearly general practice (GP) visits (HR 1.54, 95% CI 1.17 to 2.02, p < 0.001).

Conclusions: After accounting for potential confounding variables, we found that CP is associated with increased risk of osteoporosis and osteoarthritis. These findings provide the strongest epidemiological evidence to date for increased risk of osteoporosis and osteoarthritis in people with CP, and highlight need for clinical awareness of such conditions in this population.

1. Introduction

Cerebral palsy (CP) is considered the most common cause of childhood physical disability with a prevalence of approximately 2–3 per 1000 live births [1]. CP is defined by abnormal fine and gross motor functioning that results in activity limitations and reduced participation [1,2]. People with CP commonly experience musculoskeletal disorders, including spasticity, contractures and bony deformities [1]. Although CP is considered to be a non-progressive disorder, people with CP often report that musculoskeletal disorders and function worsen with age [3]. Notably, nearly one-third of adults with CP report experiencing musculoskeletal pain that is associated with deteriorating physical function [4,5].

Longstanding abnormalities in the amount and pattern of loading of musculoskeletal tissues are potential risk factors for various musculoskeletal conditions. It is widely considered that people with CP are at increased risk of osteoporosis (OP) due in part to the impact of decreased weight bearing on bone mineral density throughout childhood.
Peak bone mass is established through childhood to early adulthood [6] and clinically significant osteopenia appears to be common in children and adolescents with CP [7]. A number of small studies have indicated abnormal bone microarchitecture in adults with cerebral palsy [8–10] and a recent systematic review found evidence to suggest this is also present in ambulatory people with CP [11]. Moreover, there is recent cross-sectional evidence that adults with CP have higher prevalence of fractures as compared to adults without CP, even after adjusting for osteoporosis [12]. There is a dearth of high quality evidence however relating to the prevalence of OP in the adult CP population. Abnormal loading and movement throughout childhood development can also impact the morphology and health of joints [13], raising the risk of developing arthropathies such as osteoarthritis (OA).

A cross-sectional study of multimorbidity in a sample of middle aged adults with CP found a 40% prevalence of osteopenia/OP and a 27% prevalence of OA [14]. The co-existence of osteoarthritis and osteopenia/OP was present in 17% of participants. However the absence of a comparable control group without CP in this study precluded estimation of the increased risk of these conditions in adults with CP. A further cross-sectional study from a single clinical centre [15] in the US found an increased prevalence of osteopenia, osteoporosis and musculoskeletal morbidity in adults with CP compared to adults without CP.

In a study of national survey data in the USA, Peterson et al. [16] found a 15.3% increase in the prevalence of joint pain and a 14% increase in the prevalence of arthritis in people with CP compared to people without CP, though the study did not differentiate the type of arthritis studied or the cause of joint pain. In a cross-sectional study of adults with CP from a single clinical centre in the USA, Whitney et al. [17] reported a higher prevalence of OP, OA and rheumatoid arthritis (RA) than those reported from population based estimates. They also reported a greater odds of these conditions with increased age. While there is no clear mechanism by which CP might increase the risk of rheumatoid arthritis, or other systemic inflammatory musculoskeletal conditions those authors suggested putative mechanisms including an “accelerated ageing” clinical phenotype leading to immunosenescence as well as immunosuppression related to CP. Any such mechanism is currently speculative. However, this study also lacked any direct comparison with a sample without CP, was cross-sectional, took its sample from a single clinical centre and did not include a broader spectrum of inflammatory musculoskeletal diseases.

Our aim was to assess if the risk of OA, OP and inflammatory musculoskeletal diseases among adults with CP differs from people without CP by comparing the incidence of these conditions in a population-based sample using longitudinal data from routinely collected UK primary care records. These conditions were the chosen focus of the study as it is widely considered that at increased risk of OP and OA exists, but there is a paucity of high quality evidence to estimate the size of that risk, and because a prior cross-sectional study suggested an increased risk of RA in this group.

2. Patients and methods

2.1. Study design and data source

A matched cohort study was conducted using data from the UK Clinical Practice Research Datalink (CPRD). The CPRD contains primary care data routinely collected via electronic health records from general practices in the UK. Data collection began in 1987 and we used data obtained during the period 1 January 1987 to 30 November 2015. The CPRD includes data on clinical events, prescriptions, preventative care, referrals and hospital admissions and data are largely representative of the UK population [18]. Data from the CPRD have been used to conduct approximately 1000 published studies including studies examining the incidence of OA, OP and inflammatory arthritis [19–21].

2.2. Participants

Read codes are used to record clinical diagnoses in primary care in the UK. All patients, aged 18 years and older, with at least one record of CP (as identified by Read codes in Supplementary material S1) occurring during the study period with data that met the definition for research-standard follow-up were included in the study. The CPRD performs quality checks to determine if data are acceptable for use in research. Firstly, an “up to standard date” is identified for each practice, which indicates the date at which the practice is considered to have continuous high quality data fit for use in research. Secondly, patient data is checked for a number of issues and excluded if they have non-continuous follow-up or poor data recording. The start of follow-up (hereafter the “index date”) for patients with CP was the latest of: the date the patient registered with the general practice, the date the data were considered research-standard, or the 1st January of the year in which the patient turned 18 years of age. Patients with a record of CP were matched to three control patients without CP on age (within 3 years in either direction), sex and general practice (GP). The index date for control patients was set to be the same as that of their matched case. Controls had a complete history for the duration of their case’s follow-up. Patients were followed to the earliest of: (1) transfer out of CPRD; (2) end of the study period; (3) practice last collection date; (4) death; or (5) first event of the outcome.

2.3. Outcomes

A first event of OA, OP, and inflammatory musculoskeletal diseases was identified using Read code lists for OA, “rheumatoid arthritis, other inflammatory polyarthropathies and systemic connective tissue disorders” and OP (code lists available in supplementary information S2–4).

2.4. Other characteristics

Smoking status (current smoker, ex-smoker, non-smoker) and alcohol consumption (current drinker, ex-drinker, or non-drinker) were identified. Where multiple records of smoking status and alcohol consumption were available the earliest record after the patient turned 18 years of age was used for the analyses. We also identified mean yearly GP visits, calculated as total number of face-to-face or telephone consultations from start of follow-up to censoring, or first event of OA, OP, and inflammatory musculoskeletal diseases, respectively, divided by total years of follow-up. Finally, we identified people who had experienced a wrist fracture during the follow-up period, prior to the first event of OP if applicable.

2.5. Statistical analysis

Descriptive statistics were used to report patient characteristics at start of follow-up.

For each outcome, a separate Cox model with an underlying age timescale, stratified by matched set, was fitted to examine the association between CP and incidence of each MSK condition [22]. Initially, unadjusted hazard ratios were calculated. All Cox models were then adjusted for smoking status, alcohol consumption, and mean yearly GP visits. We adjusted for mean yearly GP visits, as patients with CP may have more GP visits, and patients who consulted their GP more frequently may be more likely to receive a diagnosis of the respective conditions. As the mechanism underlying missing records for smoking status and alcohol consumption in primary care data is likely to be missing not at random, as opposed to missing at random [23,24], multiple imputation is not appropriate for these data. Smoking status and alcohol consumption were dichotomised as current smokers and non-current smokers, and current drinkers and non-current drinkers, respectively. As Marsden [23,24] identified that missing data for
smoking status most likely pertain to ex-smokers and non-smokers, and missing data for alcohol consumption most likely pertain to current drinkers [23,24], missing data were assumed to relate to non-current smokers and current drinkers, respectively.

2.5.1. Model checking and sensitivity analyses

For the analysis relating to OP, we conducted a sensitivity analysis by further adjusting the model for wrist fracture. Wrist fracture is a potential confounding factor for the association between CP and OP as people who experience a wrist fracture may be more likely to receive a diagnosis of OP, and people with CP may be more likely to experience a fracture due to an increased risk of falls. Further, sensitivity analyses were conducted to examine the impact of assumptions regarding the mechanisms of missing data on conclusions by: (1) excluding missing data for smoking status and alcohol consumption (i.e. performing complete case analysis); and (2) recategorising smoking status as current smokers and non-current smokers, with missing data assumed to pertain to non-current smokers. As each patient with CP may not be matched for age, sex and general practice to three patients without CP in complete case analysis, for this analysis we used Cox models with an underlying age timescale adjusted for age, sex, region, smoking status, alcohol consumption and GP visits. The validity of the assumption of proportional hazards was assessed by plotting scaled Martingale residuals against mean yearly GP visits and age, where applicable, to examine if there was a linear association between each variable and the outcome.

The CPRD has obtained research ethics approval from a National Research Ethics Service Committee for purely observational research using anonymised CPRD data. The protocol was approved by the Independent Scientific Advisory Committee for MHRA Database Research (protocol no. 16_077R2A).

3. Results

1705 patients with CP who met the inclusion criteria were identified and matched to 5115 patients without CP for age, sex and practice. The characteristics of patients with and without CP at start of follow-up are reported in Table 1. The distribution of exposures, outcomes and potential confounders across patients with complete and incomplete data is presented in Supplementary material S5. The distribution of data relating to smoking status and alcohol status, before and after imputation, is reported in Supplementary material S6. For patients with CP, median follow-up time was 6.72 yr (range 0.003 yr to 27.94 yr) for osteoarthritis, 7.11 yr (range 0.04 yr to 27.94 yr) for inflammatory musculoskeletal diseases, and 7.08 yr (range 0.003 yr to 27.94 yr) for osteoporosis. For patients without CP, median follow-up time was 10.23 yr (range 0.01 yr to 28.01 yr) for OA, 10.91 yr (range 0.10 yr to 28.01 yr) for people without CP for inflammatory musculoskeletal diseases, and 10.92 yr (range 0.14 yr to 28.01 yr) for OP. The median (IQR) age of first diagnosis of osteoporosis was 55.1 years (47.9 years to 63.8 years) in people with CP, and 68.6 years (55.9 years to 77.8 years) in people without CP. For OA the median (IQR) age of first diagnosis was 53.0 years (46.2 years to 66.2 years) in people with CP and 59.1 years (49.5 years to 70.0 years) in people without CP. The median (IQR) age of first diagnosis of inflammatory musculoskeletal diseases was 38.9 years (36.1 years to 50.1 years) in people with CP and age was 52.7 years (40.1 years to 63.8 years) in people without CP.

Unadjusted hazard ratios (HR) [Table 2] showed no evidence that patients with CP had a higher risk of OA (HR: 1.07, 95% CI 0.85 to 1.35, p = 0.552) or inflammatory musculoskeletal diseases (HR: 0.76, 95% CI 0.41 to 1.40, p = 0.376). There was evidence from the unadjusted analysis that patients with CP had increased risk of OP (HR: 3.67, 95% CI 2.53 to 5.36, p < 0.001) compared to patients without CP. After adjusting for smoking, alcohol consumption, and mean yearly GP visits (Table 2), there was evidence that people with CP had increased risk of OA (HR: 1.54, 95% CI 1.17 to 2.02, p = 0.002) and OP (HR: 6.19, 95% CI 3.37 to 11.39, p < 0.001) compared to patients without CP, but no evidence of increased risk of inflammatory musculoskeletal diseases among patients with CP (HR: 0.89, 95% CI 0.45 to 1.75, p = 0.731).

Table 1

| Variable | Patients with CP (n = 1705) | Patients without CP (n = 5115) | Total (n = 6820) |
|----------|-----------------------------|-------------------------------|---------------|
| Sex      |                             |                               |               |
| Males    | 907 (53.2)                  | 2721 (53.2)                   | 3628 (53.2)   |
| Females  | 798 (46.8)                  | 2394 (46.8)                   | 3192 (46.8)   |
| Age, yr  |                             |                               |               |
| Median (IQR) | 7.97 (4.04 to 14.45) | 7.52 (3.77 to 14.82) | 7.74 (4.28 to 15.04) |
| Range    | 0 to 1.9 visits              | 0 to 1.9 visits               | 0 to 1.9 visits |
| 0-19 visits | 199 (11.7)                 | 194 (3.7)                     | 393 (5.9)     |
| 2-11 visits | 942 (55.3)                 | 1285 (24.6)                   | 2227 (33.1)   |
| ≥12 visits | 564 (33.1)                  | 1410 (27.7)                   | 2074 (30.5)   |
| Average yearly GP visits (OA) |                   |                               |               |
| Median (IQR) | 3.77 (1.55 to 7.52) | 3.79 (1.56 to 7.52) | 3.80 (1.55 to 7.52) |
| Range    | 0 to 1.9 visits              | 0 to 1.9 visits               | 0 to 1.9 visits |
| 0-19 visits | 164 (9.6)                  | 157 (3.0)                     | 321 (4.7)     |
| 2-11 visits | 952 (55.6)                 | 2964 (58.0)                   | 3916 (57.4)   |
| ≥12 visits | 589 (34.6)                  | 1734 (32.4)                   | 2323 (35.9)   |
| Average yearly GP visits (OP) |                   |                               |               |
| Median (IQR) | 3.79 (1.56 to 7.52) | 3.79 (1.56 to 7.52) | 3.80 (1.55 to 7.52) |
| Range    | 0 to 1.9 visits              | 0 to 1.9 visits               | 0 to 1.9 visits |
| 0-19 visits | 167 (9.8)                  | 1565 (30.6)                   | 1732 (25.4)   |
| 2-11 visits | 955 (56.0)                 | 2969 (58.0)                   | 3924 (57.5)   |
| ≥12 visits | 583 (34.2)                  | 581 (11.4)                    | 1164 (17.1)   |

Data reported as no. (%) unless stated otherwise.

| Variable | Patients with CP | Patients without CP | Total |
|----------|------------------|---------------------|-------|
| CP       |                  |                     |       |
| n        | 1705             | 5115                | 6820  |
| p        | 0.731            |                     |       |

CI 2.32 to 5.80, p < 0.001 compared to patients without CP. After adjusting for smoking, alcohol consumption, and mean yearly GP visits (Table 2), there was evidence that people with CP had increased risk of OA (HR: 1.54, 95% CI 1.17 to 2.02, p = 0.002) and OP (HR: 6.19, 95% CI 3.37 to 11.39, p < 0.001) compared to patients without CP, but no evidence of increased risk of inflammatory musculoskeletal diseases among patients with CP (HR: 0.89, 95% CI 0.45 to 1.75, p = 0.731).

Plots of Martingale residuals suggested that a linear association existed between each outcome and GP visit for all models. There was no evidence that the proportional hazards assumption was violated for any model. Sensitivity analyses did not change the conclusions of the

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study. Adjusting the final model for wrist fracture resulted in an increase in the HR for OP (HR: 7.24, 95% CI 3.79 to 13.82, \( p < 0.001 \); Table 3). However, the confidence interval included the estimate obtained from the primary analysis. Complete case analysis resulted in similar effect estimates and identical conclusions to the primary analysis for OP and inflammatory musculoskeletal diseases. For osteoarthritis, complete case analysis resulted in a larger hazard ratio for CP compared to the primary analysis (HR: 2.05, 95% CI 1.60 to 2.62; Table 3). Conducting the analysis with missing data on smoking status recategorised as current smokers and non-current drinkers resulted in effect estimates and 95% CI that were very similar to those obtained from the primary analysis (Table 3).

### 4. Discussion

The principal finding of this population-based cohort study was that adults with CP had a higher incidence of OP and OA as compared to adults without CP, after accounting for age, sex, general practice, alcohol consumption, smoking status, and GP visits; however, no differences were observed in the incidence of inflammatory musculoskeletal diseases.

This is the largest study to date to investigate the incidence of MSK conditions in adults with CP. There is a dearth of epidemiological evidence in relation to this topic, though reduced bone mass has been observed in children with spastic quadriplegia [25], and there is some evidence of raised fracture rates in children and adults with CP [12,26]. These findings have implications for the clinical management of people with CP. Osteoporosis and its sequelae might be prevented or mitigated using various approaches including dietician intervention, weight-bearing physical activities, clinical screening, or pharmacological interventions. In the UK the National Institute of Health and Care Excellence (NICE) guideline on CP in children and young people [27] recommend awareness of the risk of low bone mineral density and low-impact fractures, assessment of dietary calcium/vitamin D intake in those with risk factors, and the creation of individualized treatment plans to reduce the risk. The 2019 NICE guideline on CP in adults [28] recognizes the potential increased risk of osteoporosis and arthritis, and recommends monitoring adults with CP for these conditions, despite identifying minimal and very low quality evidence relating to the incidence of OP and no evidence relating to the incidence of OA. Our findings provide more robust evidence to support these recommendations.

It is a commonly held view that chronic abnormal joint loading in people with CP increases the risk of OA via impact on joint development and accelerated wear and tear [13,29]. Previous studies have suggested a rise in the prevalence of joint pain and arthritis in people with CP [16,17]. It is likely that OA may be influenced by factors such as mobility status and, potentially, obesity. In terms of mobility status, it is likely that its relationship with OA risk might not be linear. There is some exploratory evidence for higher prevalence of OA in non-ambulatory versus ambulatory people with CP [15] but it is also plausible that risk of OA might be raised in ambulatory people with high BMI. In our study, the low proportion of patients with CP with overweight or obesity, compared to patients without CP, and our inability to adjust for ambulatory status might have contributed to the rather marginal results seen for OA. Although there is substantial variation in the prevalence of obesity among adults with CP across studies (7.3% to 41.4%) [30], the prevalence of 9.6% reported herein is not unusually low nor dissimilar to that found in a small cross-sectional study of adults with CP in Ireland [31]. It is also possible that people with CP may be less likely to be attributed a diagnosis of OA from their clinician despite reporting symptoms consistent with the diagnosis. Clinicians may be less inclined to specifically identify symptoms as an issue that they presume to be the

### Table 3

| Osteoarthritis model adjusted for wrist fracture \((n = 6820)\) | Complete case analysis \((n = 5075)\) | Reclassified smoking status and alcohol consumption \((n = 6820)\) |
|-------------------------|---------------------------------|---------------------------------|
| **Adjusted HR** \(95\% \text{ CI}\) \(p\) value | **Adjusted HR** \(95\% \text{ CI}\) \(p\) value | **Adjusted HR** \(95\% \text{ CI}\) \(p\) value |
| OA – \(-\) – \(-\) | 2.05 \((1.60 \text{ to } 2.62)\) \(< 0.001\) | 1.65 \((1.25 \text{ to } 2.19)\) \(< 0.001\) |
| IMD – \(-\) – \(-\) | 0.76 \((0.38 \text{ to } 1.51)\) \(0.434\) | 0.96 \((0.48 \text{ to } 1.91)\) \(0.904\) |
| OP \(7.24 \text{ (3.79 to 13.82)}\) \(< 0.001\) | 3.09 \((1.89 \text{ to } 4.87)\) \(< 0.001\) | 5.85 \((3.19 \text{ to } 10.72)\) \(< 0.001\) |

CI: confidence interval.
OA osteoarthritis, OP osteoporosis, IMD inflammatory musculoskeletal diseases.
* \(\times\) Missing data for smoking status and alcohol consumption classified as current smokers and non-current drinkers, respectively.
\* \(\times\) Adjusted for alcohol, smoking, GP visits, and wrist fracture.
\* \(\times\) Adjusted for age, sex, region, alcohol, smoking and GP visits.
\* \(\times\) Adjusted for alcohol, smoking and GP visits.
inevitable sequelae of living with CP or may not prioritise joint pain over other problems that the patient is reporting. It is also possible that clinicians may classify joint pains using other descriptors. As such our results might underestimate the incidence of OA in this group.

That we observed no increase in the incidence of inflammatory musculoskeletal diseases is at odds with the findings of Whitney et al. [17], who showed an increased prevalence of RA in a clinic based sample people with CP compared to general population estimates. That study [17] was not population-based, did not make a direct comparison with an equivalent sample of people without CP and looked specifically at rheumatoid arthritis rather than the broader scope of systematic inflammatory MSK conditions. As we included rheumatoid arthritis within a broader category of inflammatory musculoskeletal diseases, it is possible that an effect may have been missed.

This is the first study to compare the incidence of OA, OP and inflammatory musculoskeletal diseases between adults with and without CP using a relatively large cohort of adults with CP. We were able to adjust for several potential confounding factors, and our findings were robust to sensitivity analyses. It should be acknowledged that residual confounding may still be present as we were unable to adjust for mobility status or physical activity. However, caution should be taken when adjusting for these factors as they are likely to be mediators of the association between CP and both OA and OP, and conditioning on them may itself induce bias [32]. Exploration of mobility status as an effect modifier is warranted in future studies to improve our understanding of the impact of severity of disability on risk for these conditions. In our analyses, we did not adjust for BMI. It has been shown that BMI is an imperfect estimation of body composition in people with CP [33], as it overestimates fat free mass and underestimates fat mass. This inaccuracy is increased in people with more severe CP, due to diminished lean mass. As we did not have measure of the severity of CP, we were unable to account for this in our analyses which may have led to error. In addition, there was a large amount of missing data for BMI and imputation of missing values may have compounded this inaccuracy. In the analysis relating to osteoporosis we conducted a sensitivity analysis by adjusting for wrist fracture as a potential confounding factor, as people who experience a wrist fracture may be more likely to receive a diagnosis of OP, and people with CP may be more likely to experience a fracture due to an increased risk of falls. However, we did not adjust for other specific fragility fractures or fragility fractures in general due to concerns surrounding the consistent use of read codes for these events. As a result of matching patients on practice, practice-level rather than patient-level socioeconomic status was adjusted for in the analysis. Although the Index of Multiple Deprivation scores may be used to categorise patients in CPRD according to patient- and practice-level socioeconomic status, it is only available for approximately half of patients in CPRD and these data were not obtained.

Further limitations include the possibility that the diagnostic code lists were incomplete, identification of cases is dependent on the quality of original recording in the database, and a substantial proportion of data were missing for smoking status, alcohol consumption. To assess the impact of the potentially strong assumptions that we made when imputing missing data, we conducted two sensitivity analyses; a complete case analysis and analysis recategorising missing data relating to smoking status and alcohol consumption as smokers and non-drinkers, respectively. These sensitivity analyses did not change the conclusions of the study and support the robustness of these findings to different underlying mechanisms of missing data.

This is the first population-based cohort study examining the incidence of OA, inflammatory musculoskeletal diseases and OP in adults with CP. Our study demonstrated that adults with CP have a higher incidence of OP and OA compared to adults without CP after accounting for potential confounding variables. Despite previous studies identifying a high prevalence of joint pain and functional deterioration among people with CP, there is a dearth of literature on the burden of musculoskeletal disorders in this population. These findings support the need for clinical awareness of OA and OP as potential comorbidities in adults with CP. Further research is required to effectuate effective management of these conditions in adults with CP.

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Contributors

All authors were involved in study design and approved the final manuscript. JR conducted the statistical analysis. NOC wrote the first draft of the manuscript.

Declarations of interest

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.05.007.

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