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

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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: 1,705 adults with CP were matched to 5,115 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.

Keywords: cerebral palsy, osteoarthritis, osteoporosis, inflammatory musculoskeletal diseases, incidence

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.

Patients and Methods

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 1,000 published studies including studies examining the incidence of OA, OP and inflammatory arthritis.[19-21]

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.

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).

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.

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.

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 relate to current smokers, and recategorising alcohol consumption as current drinkers and non-current drinkers with missing records assumed to pertain to non-current drinkers. 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 Schoenfeld residuals against time and including interaction terms between time and each predictor variable, respectively, for all models. Martingale residuals were plotted 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).

Results

1,705 patients with CP who met the inclusion criteria were identified and matched to 5,115 patients without CPfor 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 51.0 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 2.32 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 visitsfor 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 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 missing data on alcohol consumption recategorised as non-current drinkers resulted in effect estimates and 95% CI that were very similar to those obtained from the primary analysis (Table 3).

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 dietetic 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 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.[31] 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,[32] 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 into effective management of these conditions in adults with CP.

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Table 1. Patient characteristics at start of follow-up

Variable	**Patients with CP (n=1,705)**	**Patients without CP (n=5,115)**	**Total (n=6,820)**
Sex			
Males	907 (53.2)	2,721 (53.2)	3,628 (53.2)
Age, yr			
Median (IQR)	29 (20 to 42)	29 (20 to 42)	29 (20 to 42)
<30	877 (51.4)	2,631 (51.4)	3,508 (51.4)
30-39	336 (19.7)	1,008 (19.7)	1,344 (19.7)
40-49	223 (13.1)	669 (13.1)	892 (13.1)
50-59	135 (7.9)	405 (7.9)	540 (7.9)
≥60	134 (7.9)	402 (7.9)	536 (7.9)
Smoking status			
Current smoker	213 (12.5)	1,511 (29.5)	1,724 (25.3)
Ex-smoker	65 (3.8)	424 (8.3)	489 (7.2)
Non-smoker	1,261 (74.0)	2,740 (53.6)	4,001 (58.7)
Missing	166 (9.7)	440 (8.6)	606 (8.9)
Alcohol consumption			
Current drinker	724 (42.5)	3,142 (61.4)	3,866 (56.7)
Ex-drinker	15 (0.9)	40 (0.8)	55 (0.8)
Non-drinker	527 (30.9)	640 (12.5)	1,167 (17.1)
Missing	439 (25.8)	1,293 (25.3)	1,732 (25.4)
Practice region[a]			
North England and Scotland	473 (27.7)	1,419 (27.7)	1,892 (27.7)
Midlands and Wales	603 (35.4)	1,809 (35.4)	2,412 (35.4)
South England	587 (34.4)	1,761 (34.4)	2,348 (34.4)
Northern Ireland	42 (2.5)	126 (2.5)	168 (2.5)
Wrist fracture			
Presence of	17 (1.0)	69 (1.4)	86 (1.3)
Average yearly GP visits (OA)			
Median (IQR)	7.97 (4.04 to 14.45)	3.48 (1.39 to 6.99)	4.28 (1.73 to 8.74)

range	0 to 154.70	0 to 97.40	0 to 154.70
0 - 1.9 visits	199 (11.7)	1704 (33.3)	1903 (27.9)
2 - 11.9 visits	942 (55.3)	2916 (57.0)	3858 (56.6)
≥ 12 visits	564 (33.1)	495 (9.7)	1059 (15.5)
Average yearly GP visits (RA)			
Median (IQR)	8.48 (4.47 to 14.82)	3.77 (1.55 to 7.52)	4.71 (1.94 to 9.35)
Range	0 to 154.70	0 to 97.40	0 to 154.70
0 - 1.9 visits	164 (9.6)	1573 (30.8)	1737 (25.5)
2 - 11.9 visits	952 (55.8)	2964 (58.0)	3916 (57.4)
≥ 12 visits	589 (34.6)	578 (11.3)	1167 (17.1)
Average yearly GP visits (OP)			
Median (IQR)	8.37 (4.38 to 14.74)	3.79 (1.56 to 7.52)	4.70 (1.95 to 9.34)
Range	0 to 154.70	0 to 97.4	0 to 154.70
0 - 1.9 visits	167 (9.8)	1565 (30.6)	1732 (25.4)
2 - 11.9 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
CP: cerebral palsy; IQR: interquartile range; BMI: ; SD: standard deviation
[a]North England and Scotland: North East England, North West England, Yorkshire, Scotland; Midlands and Wales: East Midlands, West Midlands, East of England, Wales; South England: South West England, South Central England, London, South East England

Table 2. Incidence rate of eachcondition , unadjusted and adjusted hazard ratios for each condition comparing patients with cerebral palsy to patients without cerebral palsy (n=6,820)

	Events, No. (%)	Total person-years (1,000s)	Incidence, per 1,000 person-years	Unadjusted hazard ratio (95% CI)	p value	Adjusted hazard ratio[a] (95% CI)	p value
Osteoarthritis							
CP	104 (6.1)	13.9	7.46	1.07 (0.85 to 1.35)	0.552	1.54 (1.17 to 2.02)	0.002
non-CP	370 (7.2)	53.8	6.88				
Inflammatory musculoskeletal diseases							
CP	13 (0.8)	14.5	0.89	0.76 (0.41 to 1.40)	0.376	0.89 (0.45 to 1.75)	0.731
non-CP	62 (1.2)	56.4	1.10				
Osteoporosis							
CP	41 (2.4)	14.4	2.85	3.67 (2.32 to 5.80)	<0.001	6.19 (3.37 to 11.39)	<0.001
non-CP	53 (1.0)	56.5	0.94				

CP: cerebral palsy; CI: confidence interval

[a]adjusted for alcohol, smoking, GP visits

Table 3. Adjusted hazard ratios from sensitivity analyses, for each condition comparing patients with cerebral palsy to patients without cerebral palsy

	Osteoporosis model adjusted for wrist fracture (n=6,820)		**Complete case analysis (n=5,075)**		**Reclassified smoking status and alcohol consumption[a] (n=6,820)**	
	Adjusted HR[b] (95% CI)	p value	Adjusted HR[c] (95% CI)	p value	Adjusted HR[d] (95% CI)	p value
OA	-	-	2.05 (1.60 to 2.62)	<0.001	1.65 (1.25 to 2.19)	<0.001
IMD	-	-	0.76 (0.38 to 1.51)	0.434	0.96 (0.48 to 1.91)	0.904
OP	7.24 (3.79 to 13.82)	<0.001	3.03 (1.89 to 4.87)	<0.001	5.85 (3.19 to 10.72)	<0.001

CI: confidence interval

[a]missing data for smoking status and alcohol consumption classified as current smokers and non-current drinkers, respectively

[b]adjusted for alcohol, smoking, GP visits, and wrist fracture

[c]adjusted for age, sex, region, alcohol, smoking and GP visits

[d]adjusted for alcohol, smoking and GP visits

OA osteoarthritis, OP osteoporosis, IMD inflammatory musculoskeletal diseases

Supplementary information

S1 Text. Read codes indicating cerebral palsy

Read code	Read term
F23y400	Ataxic diplegic cerebral palsy
F23y000	Ataxic diplegic cerebral palsy
F137.11	Athetoid cerebral palsy
F137000	Athetoid cerebral palsy
F2B..00	Cerebral palsy
F2Bz.00	Cerebral palsy NOS
F230100	Cerebral palsy with spastic diplegia
F23..00	Congenital cerebral palsy
F23y300	Dyskinetic cerebral palsy
F23..12	Infantile cerebral palsy
F23y200	Spastic cerebral palsy
F230111	Spastic diplegic cerebral palsy
F2B1.00	Spastic hemiplegic cerebral palsy
F2B0.00	Spastic quadriplegic cerebral palsy
F23yz00	Other infantile cerebral palsy NOS
Fyu9000	[X]Other infantile cerebral palsy
F23y.00	Other congenital cerebral palsy
F23y100	Flaccid infantile cerebral palsy
F2By.00	Other cerebral palsy
Fyu9.00	X]Cerebral palsy and other paralytic syndromes
F23z.00	Congenital cerebral palsy NOS
F23..11	Congenital spastic cerebral palsy
F23y600	Choreoathetoid cerebral palsy

S2 Read Codes for Osteoporosis (adapted from https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/1/codelist/osteoporosis/)

Read code	Read term
585O.00	Quantitative ultrasound scan of heel - result osteoporotic
58E4.00	Forearm DXA scan result osteoporotic
58EA.00	Heel DXA scan result osteoporotic
58EG.00	Hip DXA scan result osteoporotic
58EM.00	Lumbar DXA scan result osteoporotic
58EV.00	Femoral neck DEXA scan result osteoporotic
N330.00	Osteoporosis
N330000	Osteoporosis, unspecified
N330100	Senile osteoporosis
N330200	Postmenopausal osteoporosis
N330300	Idiopathic osteoporosis
N330400	Dissuse osteoporosis
N330500	Drug-induced osteoporosis
N330600	Postoophorectomy osteoporosis
N330700	Postsurgical malabsorption osteoporosis
N330800	Localized osteoporosis - Lequesne
N330900	Osteoporosis in multiple myelomatosis
N330A00	Osteoporosis in endocrine disorders
N330B00	Vertebral osteoporosis
N330C00	Osteoporosis localized to spine
N330D00	Osteoporosis due to corticosteroids
N330z00	Osteoporosis NOS
N331200	Postoophorectomy osteoporosis with pathological fracture
N331300	Osteoporosis of disuse with pathological fracture
N331400	Postsurgical malabsorption osteoporosis with path fracture
N331500	Drug-induced osteoporosis with pathological fracture
N331600	Idiopathic osteoporosis with pathological fracture
N331800	Osteoporosis + pathological fracture lumbar vertebrae
N331900	Osteoporosis + pathological fracture thoracic vertebrae

N331A00	Osteoporosis + pathological fracture cervical vertebrae
N331B00	Postmenopausal osteoporosis with pathological fracture
N331M00	Fragility fracture due to unspecified osteoporosis
N331N00	Fragility fracture
NyuB000	[X]Other osteoporosis with pathological fracture
NyuB100	[X]Other osteoporosis
NyuB200	[X]Osteoporosis in other disorders classified elsewhere
NyuB800	[X]Unspecified osteoporosis with pathological fracture
N330z00	Osteoporosis NOS
66a5.00	Osteoporosis - no treatment

S3 Read Codes for inflammatory Arthoparthies (adapted from http://www.phpc.cam.ac.uk/pcu/cprd_cam/codelists/)

Read code	**Read term**
N04z.00	inflammatory polyarthropathy nos
M154100	discoid lupus erythematosus
N241z00	myalgia or myositis nos
N040E00	rheumatoid arthritis of tibio-fibular joint
N044.00	chronic post-rheumatic arthropathy
N043.00	juvenile rheumatoid arthritis - still's disease
N040M00	rheumatoid arthritis of ip joint of toe
N04X.00	seropositive rheumatoid arthritis, unspecified
M154700	subacute cutaneous lupus erythematosus
N042200	rheumatoid nodule
N04y000	rheumatoid lung
N040700	rheumatoid arthritis of wrist
N040P00	seronegative rheumatoid arthritis
N043200	pauciarticular juvenile rheumatoid arthritis
N042000	rheumatic carditis
N001100	crest syndrome

N040L00	rheumatoid arthritis of lesser mtp joint
M160.00	psoriatic arthropathy
N10..00	inflammatory spondylopathies
N004.00	polymyositis
M160z00	psoriatic arthropathy nos
N040300	rheumatoid arthritis of sternoclavicular joint
N043300	monarticular juvenile rheumatoid arthritis
Nyu1500	[x]other juvenile arthritis
N045300	juvenile arthritis in crohn's disease
N040N00	rheumatoid vasculitis
N003X00	dermatopolymyositis, unspecified
N045500	juvenile rheumatoid arthritis
N001000	progressive systemic sclerosis
M160.11	psoriatic arthritis
N000.00	systemic lupus erythematosus
N042.00	other rheumatoid arthropathy + visceral/systemic involvement
N040200	rheumatoid arthritis of shoulder
N040G00	rheumatoid arthritis of subtalar joint
N241200	fibromyositis nos
N04..11	inflammatory polyarthropathy
N043000	juvenile rheumatoid arthropathy unspecified
N040400	rheumatoid arthritis of acromioclavicular joint
M160000	psoriasis spondylitica
M154.00	lupus erythematosus
N041.00	felty's syndrome
N045200	juvenile arthritis in psoriasis
N065.00	unspecified polyarthropathy or polyarthritis
N241100	myositis unspecified
N241.00	myalgia and myositis unspecified
N040900	rheumatoid arthritis of pip joint of finger
N040S00	rheumatoid arthritis - multiple joint
N040C00	rheumatoid arthritis of sacro-iliac joint
N040J00	rheumatoid arthritis of other tarsal joint

N001.12	systemic sclerosis
N040.00	rheumatoid arthritis
N040600	rheumatoid arthritis of distal radio-ulnar joint
N003000	juvenile dermatomyositis
N003.00	dermatomyositis
N04y200	adult-onset still's disease
N042100	rheumatoid lung disease
N04y.00	other specified inflammatory polyarthropathy
N043100	acute polyarticular juvenile rheumatoid arthritis
N045400	juvenile arthritis in ulcerative colitis
M154z00	lupus erythematosus nos
N042z00	rheumatoid arthropathy + visceral/systemic involvement nos
N040800	rheumatoid arthritis of mcp joint
N045100	juvenile seronegative polyarthritis
N040H00	rheumatoid arthritis of talonavicular joint
N040A00	rheumatoid arthritis of dip joint of finger
N040D00	rheumatoid arthritis of knee
N040Q00	rheumatoid bursitis
N040500	rheumatoid arthritis of elbow
N045600	pauciarticular onset juvenile chronic arthritis
N045.00	other juvenile arthritis
N040B00	rheumatoid arthritis of hip
N04yz00	other specified inflammatory polyarthropathy nos
N043z00	juvenile rheumatoid arthritis nos
N04y100	sero negative arthritis
N20..00	polymyalgia rheumatica
N040K00	rheumatoid arthritis of 1st mtp joint
N040F00	rheumatoid arthritis of ankle
N04..00	rheumatoid arthritis and other inflammatory polyarthropathy
N045000	juvenile ankylosing spondylitis
N047.00	seropositive errosive rheumatoid arthritis
N040T00	flare of rheumatoid arthritis

S4. Read codes for osteoarthritis (adapted from http://www.phpc.cam.ac.uk/pcu/cprd_cam/codelists/)

Read code	Read term
N05zS00	osteoarthritis nos, of 1st mtp joint
N11z.11	osteoarthritis spine
N11D300	osteoarthritis of spine nos
N05z713	toe osteoarthritis nos
N05zF00	osteoarthritis nos, of mcp joint
N03xF00	arthritis associated with other disease, talonavicular joint
N05..00	osteoarthritis and allied disorders
N03x600	arthritis associated with other disease, mcp joint
N051.00	localised, primary osteoarthritis
N053400	localised osteoarthritis, unspecified, of the hand
N05zz00	osteoarthritis nos
N05zN00	osteoarthritis nos, of ankle
N053.00	localised osteoarthritis, unspecified
N05zJ00	osteoarthritis nos, of hip
N03x000	arthritis associated with other disease, shoulder
N05z300	osteoarthritis nos, of the forearm
N11..12	osteoarthritis of spine
N05zK00	osteoarthritis nos, of sacro-iliac joint
N051z00	localised, primary osteoarthritis nos
N03x800	arthritis associated with other disease, dip joint of finger
N06z411	hand arthritis nos
N051F00	localised, primary osteoarthritis of elbow
N05z412	thumb osteoarthritis nos
N05z900	osteoarthritis nos, of shoulder
N06z712	foot arthritis nos
N051D00	localised, primary osteoarthritis of the wrist
N053600	localised osteoarthritis, unspecified, of the lower leg

N06z711	ankle arthritis nos
N06zA00	acute arthritis
7P20400	delivery of rehabilitation for osteoarthritis
N052600	localised, secondary osteoarthritis of the lower leg
N05z511	hip osteoarthritis nos
N052800	localised, secondary osteoarthritis of other specified site
N052200	localised, secondary osteoarthritis of the upper arm
N06zB00	chronic arthritis
N050200	generalised osteoarthritis of multiple sites
N051G00	osteoarthritis of spinal facet joint
N054900	oligoarticular osteoarthritis, unspecified, multiple sites
N05zM00	osteoarthritis nos, of tibio-fibular joint
14G2.00	h/o: osteoarthritis
N05zH00	osteoarthritis nos, of dip joint of finger
N05z800	osteoarthritis nos, other specified site
N052300	localised, secondary osteoarthritis of the forearm
N06z611	knee arthritis nos
N05z100	osteoarthritis nos, of shoulder region
N052z00	localised, secondary osteoarthritis nos
N053200	localised osteoarthritis, unspecified, of the upper arm
N110.12	osteoarthritis cervical spine
N054700	oligoarticular osteoarthritis, unspecified, of ankle/foot
N065A00	generalised arthritis
N03xD00	arthritis associated with other disease, ankle
N051500	localised, primary osteoarthritis of the pelvic region/thigh
N05zL00	osteoarthritis nos, of knee
N051600	localised, primary osteoarthritis of the lower leg
N05z500	osteoarthritis nos, pelvic region/thigh
N05z311	wrist osteoarthritis nos
N054200	oligoarticular osteoarthritis, unspecified, of upper arm
N05zD00	osteoarthritis nos, of distal radio-ulnar joint
N05z712	foot osteoarthritis nos
14G..11	h/o: arthritis

N06z511	hip arthritis nos
N052.00	localised, secondary osteoarthritis
N11..11	arthritis of spine
N053z00	localised osteoarthritis, unspecified, nos
N054500	oligoarticular osteoarthritis, unspecified, of pelvis/thigh
N11D000	osteoarthritis of cervical spine
N05zE00	osteoarthritis nos, of wrist
N06z.11	arthritis
N051400	localised, primary osteoarthritis of the hand
N03x200	arthritis associated with other disease, acromioclavic joint
66H..11	arthritis monitoring
N05z611	knee osteoarthritis nos
N051100	localised, primary osteoarthritis of the shoulder region
N03x400	arthritis associated with other disease, dist rad-uln joint
N05z211	elbow osteoarthritis nos
N054100	oligoarticular osteoarthritis, unspecified, of shoulder
N05zG00	osteoarthritis nos, of pip joint of finger
N03xE00	arthritis associated with other disease, subtalar joint
N05z600	osteoarthritis nos, of the lower leg
N03x700	arthritis associated with other disease, pip joint of finger
N11D100	osteoarthritis of thoracic spine
N03x100	arthritis associated with other disease, sternoclavic joint
N05zR00	osteoarthritis nos, of other tarsal joint
N051700	localised, primary osteoarthritis of the ankle and foot
N063800	climacteric arthritis of other specified site
N05z411	finger osteoarthritis nos
N05z700	osteoarthritis nos, of ankle and foot
N06z211	elbow arthritis nos
N11D.00	osteoarthritis of spine
N03x900	arthritis associated with other disease, hip
N11D200	osteoarthritis of lumbar spine
N050z00	generalised osteoarthritis nos
N050100	generalised osteoarthritis of the hand

N05z400	osteoarthritis nos, of the hand
N053611	patellofemoral osteoarthritis
N05z200	osteoarthritis nos, of the upper arm
N05zQ00	osteoarthritis nos, of talonavicular joint
N06z311	wrist arthritis nos
N03xH00	arthritis associated with other disease, 1st mtp joint
N052500	localised, secondary osteoarthritis of pelvic region/thigh
N05zT00	osteoarthritis nos, of lesser mtp joint
N05zP00	osteoarthritis nos, of subtalar joint
N054000	oligoarticular osteoarthritis, unspec, of unspecified sites
N054.00	oligoarticular osteoarthritis, unspecified
N051800	localised, primary osteoarthritis of other specified site
N05zB00	osteoarthritis nos, of acromioclavicular joint
N05z000	osteoarthritis nos, of unspecified site
N054z00	osteoarthritis of more than one site, unspecified, nos
N050.00	generalised osteoarthritis - oa
N051E00	localised, primary osteoarthritis of toe
N054800	oligoarticular osteoarthritis, unspecified, other spec sites
N053300	localised osteoarthritis, unspecified, of the forearm
N03x500	arthritis associated with other disease, wrist
N051300	localised, primary osteoarthritis of the forearm
Nyu1B00	[x]other specified arthritis
N03xJ00	arthritis associated with other disease, lesser mtp joint
N05z.00	osteoarthritis nos
N051200	localised, primary osteoarthritis of the upper arm
N053800	localised osteoarthritis, unspecified, of other spec site
N03xG00	arthritis associated with other disease, other tarsal joint
N054600	oligoarticular osteoarthritis, unspecified, of lower leg
N05zC00	osteoarthritis nos, of elbow
N05zU00	osteoarthritis nos, of ip joint of toe
N050000	generalised osteoarthritis of unspecified site
N051000	localised, primary osteoarthritis of unspecified site
ZV13400	[v]personal history of arthritis

N054400	oligoarticular osteoarthritis, unspecified, of hand
N053500	localised osteoarthritis, unspecified, pelvic region/thigh
N03xB00	arthritis associated with other disease, knee
N06z111	shoulder arthritis nos
N05z711	ankle osteoarthritis nos
N052100	localised, secondary osteoarthritis of the shoulder region
N053700	localised osteoarthritis, unspecified, of the ankle and foot
N05..11	osteoarthritis
N03xA00	arthritis associated with other disease, sacro-iliac joint
N053100	localised osteoarthritis, unspecified, of shoulder region
N03xK00	arthritis associated with other disease, ip joint of toe
N052400	localised, secondary osteoarthritis of the hand
N052700	localised, secondary osteoarthritis of the ankle and foot

S5 The distribution of exposures, outcomes and potential confounders across patients with complete and incomplete data

Variable	Complete records (n=5,075)	Incomplete records (n=1,745)
Exposure (presence of)		
Cerebral palsy	1263 (24.9)	442 (25.3)
Presence of		
Wrist fracture	71 (1.4)	15 (0.9)
Sex		
Males	2533 (49.9)	1095 (62.3)
Age, yr		
Median (IQR)	32 (22 to 45)	21 (18 to 31)
<30	2242 (44.2)	1266 (72.6)
30-39	1132 (22.3)	212 (12.2)
40-49	771 (15.2)	121 (6.9)
50-59	494 (9.7)	46 (2.6)
≥60	436 (8.6)	100 (5.7)
Smoking status		
Current smoker	1416 (27.9)_	308 (17.7)
Ex-smoker	418 (8.2)	71 (4.1)
Non-smoker	3241 (63.9)	760 (43.6)
Missing	0 (0)	606 (34.7)
Alcohol consumption		
Current drinker	3855 (76.0)	11 (0.6)
Ex-drinker	55 (1.1)	0 (0)
Non-drinker	1165 (23.0)	2 (0.1)
Missing	0 (0)	1732 (99.3)
Practice region[a]		
North England and Scotland	1442 (28.4)	450 (25.8)
Midlands and Wales	1705 (33.6)	707 (40.5)
South England	1795 (35.4)	553 (31.7)
Northern Ireland	133 (2.6)	35 (2.0)
Outcome (presence of)		
OA	440 (8.7)	34 (2.0)
RA	68 (1.3)	7 (0.4)
OP	85 (1.7)	11 (0.6)
Average yearly GP visits (OA)		
Median (IQR)	4.96 (2.26 to 9.37)	2.44 (0.87 to 6.56)
Range	0 to 133.63	0 to 154.70
0 - 1.9 visits	1128 (22.2)	775 (44.4)
2 - 11.9 visits	3088 (60.9)	769 (44.1)
≥ 12 visits	859 (16.9)	201 (11.5)
Average yearly GP visits (RA)		
Median (IQR)	5.42 (2.63 to 10.03)	2.52 (0.90 to 6.71)
Range	0 to 133.63	0 to 154.70
0 - 1.9 visits	974 (19.2)	763 (43.7)
2 - 11.9 visits	3142 (61.9)	776 (44.5)
≥ 12 visits	959 (18.9)	206 (11.8)
Average yearly GP visits (OP)		
Median (IQR)	5.38 (2.64 to 10.00)	2.52 (0.88 to 6.71)

Range	0 to 133.63	0 to 154.70
0 - 1.9 visits	972 (19.2)	763 (43.7)
2 - 11.9 visits	3151 (62.1)	773 (44.3)
≥ 12 visits	952 (18.8)	209 (12.0)

S6 The distribution of data relating to BMI, smoking status and alcohol status, before and after imputation

Variable	Before imputation	After imputation
Smoking status, n (%)		
Current smoker	1,724 (25·3)	1,724 (25·3)
Ex-smoker	489 (7·2)	-
Non-smoker[a]	4,001 (58·7)	5,096 (74·7)
Missing	606 (8·9)	-
Alcohol consumption, n (%)		
Current drinker	3,866 (56·7)	5,598 (82·1)
Ex-drinker	55 (0·8)	-
Non-drinker[b]	1,167 (17·1)	1,222 (17·9)
Missing	1,732 (25·4)	-