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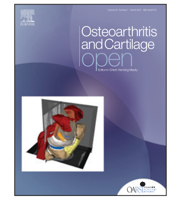

Predominant lifetime occupation and associations with painful and structural knee osteoarthritis: An international participant-level cohort collaboration

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SUMMARY

Objective: With adults working to older ages, occupation is an important, yet less modifiable domain of physical activity to consider in the risk of knee osteoarthritis (OA). This study aimed to investigate the association between predominant lifetime occupation and prevalent knee OA.
Design: Participant-level data were used from five international community-based cohorts: Johnston County Osteoarthritis Project, the Hertfordshire Cohort Study, the Multicenter Osteoarthritis Study, the Tasmanian Cohort Study and Framingham Osteoarthritis Study. Self-reported predominant occupation was categorized into sedentary, light, light manual and heavy manual levels. Cross-sectional associations between predominant lifetime occupation and knee OA outcomes including prevalence of radiographic knee OA (RKOA), symptomatic RKOA and knee pain, were assessed using logistic regression, accounting for cohort clustering.
Results: Data for 7391 participants were included. 24.7% reported sedentary lifetime occupation, 30.0% light, 35.9% light manual and 9.4% heavy manual. 43.3% presented with RKOA, 52.1% with knee pain and 29.0% with symptomatic RKOA. There was over a two-fold increase in the odds of having RKOA, knee pain and symptomatic

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RKOA in those whose with heavy manual compared to sedentary occupations ((odds ratio (OR): 2.14; 95% confidence interval (CI): 1.79, 2.58), (OR: 2.19; 95% CI: 1.78, 2.70), (OR: 2.41; 95% CI: 1.94, 2.99) respectively). *Conclusion:* This large international multi-cohort study demonstrated an association of heavy manual work with RKOA, symptomatic RKOA and knee pain. Measures that protect workers and are designed to reduce heavy manual related activities remain a priority to reduce the risk of knee OA.

1. Introduction

Adult prevalence rates for symptomatic radiographic knee osteoarthritis (OA) have been estimated between 8.5 and 22% [1–3], and as life expectancy is increasing the number of people living with severe OA is expected to grow [4]. In order to address the burden of knee OA it is important to have an understanding of the risk factors for knee OA, considering the lack of reliable therapies that are currently available. Occupational physical activity has been shown to be associated with knee OA in both population-based studies [5–9] and systematic reviews [10–12], particularly in association with tasks such as kneeling, squatting, heavy lifting, climbing stairs and ladders. Whilst other studies have focused on specific occupations and have observed varying degrees of risk for specific occupations including, but not limited to farming, mining, building and construction and health care assistants [13–16]. The Standard Occupational Classification (SOC) System is a common classification of occupational information, which at its most detail level contains at least 840 potential occupational types [17]. There is currently no evidence to quantify the association between occupation and knee OA, based on such an extensive list. A number of population cohorts include occupation data with similar extensive list of occupations available. This provides an opportunity to consider a wide range of occupations in the investigation of the association between occupation and knee OA. Such information would be useful to confidently inform health care policy making within the workforce and produce guidelines based on the detail of occupational type as well as broader categories such as sedentary/light/light manual/heavy manual work.

There are a number of methodological issues when trying to synthesize the results of occupational research in relation to chronic disease such as OA. Palmer (2012) highlights the challenges of healthy survivor selection bias, diagnostic bias and recall bias in such studies, which may lead to both over and underestimation of relative risk [12]. As an example, in a systematic review and meta-analysis, McWilliams et al. (2011) estimated higher risks from physical work in retrospective case–control than in prospective studies, and also in studies from health care compared with community settings [11].

There is also substantial variability in the measurement of occupation related exposures between studies, for example occupational activities, related tasks and job type have all previously been used as exposures. There are also differences in the definition of OA as an outcome, with the majority of studies focusing on radiographic OA. McWilliams et al. (2011) showed that whilst some occupational activities increase the risk of knee OA, the influence of publication bias and heterogeneity in the measures of occupation are key limitations in synthesizing results [11]. Whilst heterogeneous exposure and outcome definitions may not necessarily be a weakness on a study by study basis, they are a challenge when comparing findings for one common scientific question.

The high variation in exposure and outcome definitions across studies makes it difficult to confidently advocate a clear public health message. In order to overcome the difficulties in synthesizing aggregate data which use a variety of definitions for both occupation related exposures and OA outcomes, original cohort data can be analysed in a participant-level data analysis, where exposures, confounders and outcomes are harmonised and pooled according to a stringent methodical process. This method also provides the opportunity to gain a better clinical understanding of the degree to which different components of knee OA (pain and/or structure) are affected by occupation-related factors.

It is important to identify the role of occupation in disabling diseases such as OA, particularly with respect to the need for people to remain in employment to older ages, and to inform prevention strategies targeted to reduce the global burden of OA. Having a better understanding of these factors will provide valuable information to inform occupational health policies and agendas. This study therefore aims to investigate the cross-sectional associations between levels of physically-demanding occupational activities (based on a wide range of occupation types and activities) with the prevalence of structural and symptomatic knee OA. It also aims to overcome the limitations introduced when using aggregated results by gathering participant-level data collected from five international prospective community-based cohorts.

2. Methods

2.1. Study design

This study was designed to examine the cross-sectional relationship between predominant lifetime occupation and the prevalence of knee OA in multiple, population-based cohort studies from around the world. Due to the novel aspect of combining these types of data, a process of variable harmonisation was undertaken to establish a common outcome (knee OA and knee pain), exposure (predominant lifetime occupation) and confounder variables.

2.2. Cohort selection

Cohorts were selected based on the presence of lifetime occupational history and knee pain/radiographic data. Five cohorts were identified with appropriate data and were available for analysis: Johnston County Osteoarthritis Project (JoCoOA; United States [USA]) [1], Hertfordshire Cohort Study (HCS; United Kingdom [UK]) [18], Multicenter Osteoarthritis Study (MOST; USA) [19], the Tasmanian Older Adult Cohort (TasOAC; Australia) [20] and Framingham Offspring Study (USA) [21, 22].

Each cohort has been described in detail previously, however, in brief, JoCoOA is a population-based prospective cohort study assessing the occurrence and natural history of OA in residents of Johnston County, North Carolina (USA) [1]. Men and women were recruited between 1991 and 1997, and the study protocol ensured that the study sample was representative of noninstitutionalised civilians in the US. The HCS is a large, prospective population-based cohort study of the lifecourse origins of adult disease among community-dwelling men and women in the UK. HCS study participants were born in the UK county of Hertfordshire between 1931 and 1939 and were still living in the county between 1998 and 2004 during baseline recruitment. MOST is a US-based longitudinal observational study of participants with, or at high risk for, knee OA. In this enhanced risk factor cohort, community-dwelling men and women were recruited to MOST in 2003, based on the presence of knee symptoms, history of knee injury or surgery or being overweight. TasOAC is another prospective, population-based study based in Tasmania (Australia). All participants were recruited randomly from the southern Tasmanian electoral rolls, with equal numbers of men and women attending a baseline clinical assessment between 2002 and 2004. Framingham is a population-based study based in the city of Framingham, Massachusetts (US), participants were recruited between 1983 and 1985, with all cohort participants being evaluated for the presence of OA of the knee.

2.3. Harmonisation of primary risk factor: predominant lifetime occupation

A variety of questions were used to assess occupation within each cohort. Therefore, a method to harmonise predominant lifetime occupation was derived, ultimately resulting in the assignment of one of four occupation levels: sedentary; light; light manual and heavy manual for each individual (see supplementary file 1 for methods of occupation harmonisation). Where studies (such as MOST) used questions based on occupation related tasks in relation to the type of work competed for most of adult life (i.e., mainly sitting with slight arm movements), these tasks were categorised directly into one of the four occupational levels (sedentary; light; light manual and heavy manual), according to categorisation methods established in previous work [23]. HCS, JoCoOA and TaSOAC captured an extensive list of free text occupation titles. In order to assign each free text title to one of the four occupation levels (sedentary; light; light manual and heavy manual) we undertook a process in which firstly the Computer Assisted Structured Coding Tool (CASCOT) [17] was used to assign a SOC 2010 [24] for each free-text occupation. This reduced the free text titles down into the 369 broad occupational level classification codes. Each of the 369 SOC 2010 codes were then categorised into one of the four occupational levels using a process of agreement between two leading investigators (LG and CP), plus an expert in occupational rheumatology (KWB) (see supplementary file 1 for original and harmonised occupation measures). Occupation data collected spanned 1995–2004, with specific cohort time points being detailed in supplementary file 1. Only current occupation was available within the Framingham data, however given the categories of occupations provided it is likely that most of the occupations listed are predominant lifetime occupations. Therefore, within Framingham, retired participants were excluded from the analysis, likewise were those who answered ‘other’ as their type of occupation was unknown.

2.4. Harmonisation of primary outcome: knee osteoarthritis

Three outcomes were considered: radiographic knee OA, knee pain only and symptomatic radiographic knee OA. Time points for data collection in each cohort are shown in supplementary file 1.

In all cohorts participant-level knee pain was defined by using either an NHANES-type question (i.e. ‘have you had pain in or around a knee on most days for at least a month’) or a threshold on the WOMAC pain subscale [25]. Radiographic knee OA was defined at the person level using a validated scoring method (Kellgren and Lawrence (K/L)), as a grade 2 or above in either knee. Alternatively, an equivalent combination of radiographic features (osteophytes and joint space narrowing) from other validated scoring methods (such as the OARSI atlas) [26,27] was used (see supplementary file 2 for original and harmonized outcome measures). Symptomatic radiographic knee OA was defined as the presence of knee pain and radiographic knee OA.

2.5. Harmonisation of confounders

The confounders considered within this study were: age; sex; race/ethnicity; BMI; cohort. Age and BMI were collected at the time of the clinic visit when knee outcomes were assessed. Race/ethnicity was included in the analysis for any cohort which had more than one race/ethnicity category reported (see supplementary file 1 for original and harmonized outcome measures).

2.6. Statistical analysis

Characteristics of study participants were described using means and standard deviations (SD) for continuous, normally distributed variables, and median and inter-quartile ranges (IQR) for skewed variables. Frequencies and percentages were used to summarise binary and categorical variables. Study population descriptive, predominant lifetime occupation and clinical knee descriptive statistics were presented for the whole study population and by cohort.

All available data were used in logistic regression analysis to explore cross-sectional associations between predominant lifetime occupational levels and radiographic knee OA, knee pain and symptomatic knee OA. Results are presented as odds ratios (OR) with associated 95% confidence intervals (95% CI). Two sets of models were run: 1) univariate models assessing knee outcomes accounting for cohort clustering and, 2) models adjusted for age, sex, race/ethnicity and BMI at knee outcome assessment.

Statistical significance was defined at the 5% level and all analyses were undertaken using Stata 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP) [28].

3. Results

Data for 7391 participants in the five cohorts were harmonised and included within this study. The average age of all study participants at the time the radiographic image was taken was just under 62 years, with the mean ranging from 52.1 to 65.6 in the five cohorts (Table 1). The proportion of females in each cohort varied from 49.5% in HCS to 67.4% in JoCoOA. The majority of study participants in the study were Caucasian white (86.5%) and the overall average BMI was 28.4 (kg/m^2).

Table 2 describes predominant lifetime occupation levels. Just under 25% of the study sampled were categorised as having a sedentary occupation. The majority of study participants (35.9%) were categorised as having a light manual occupation, while just under 10% had a heavy manual occupation.

Twenty-nine percent of study participants had a diagnosis of symptomatic knee OA (Table 2). Over half (52.1%) reported having knee pain and radiographic knee OA was present in 43.3% of all study participants.

The majority of study participants with radiographic knee OA (38.3%) were categorised as having a light manual occupation (supplementary Table 3). Twenty-percent of study participants with radiographic knee OA were categorised as having a sedentary occupation, 30% a light occupation and 11.6% a heavy manual occupation. Similarly patterns were seen for knee pain and symptomatic knee OA, with the majority of participants reporting knee pain or having symptomatic knee OA were also categorised as having a light manual occupation (36.5% and 37.5% respectively).

Results of individual participant-level meta-analysis are contained in Fig. 1. When compared to a sedentary predominant lifetime occupation, there was over a two-fold increase in the odds of an individual having symptomatic radiographic knee OA if participants reported heavy manual work (OR: 2.41; 95% CI: 1.94, 2.99). Increased odds of having symptomatic radiographic knee OA were also seen in those who reported light (OR: 1.89; 95% CI: 1.61, 2.22) and light manual (OR: 1.58; 95% CI: 1.35, 1.84) occupations compared with those in sedentary occupations.

Results also indicated that heavy manual occupations were associated with over a two-fold increase in the odds of having both knee pain and radiographic knee OA ((OR: 2.19; 95% CI 1.78, 2.70) and (OR: 2.14; 95% CI 1.79, 2.58) respectively). All relationships remained robust to adjustment for age and BMI at knee assessment, sex and race/ethnicity.

In order to further explore predominant lifetime occupation and radiographic knee OA, an ordinal logistic model was run to assess severity of radiographic knee OA, defined by K&L grade 0, 1, 2 and 3 plus, by occupation categorisation. TasOAC was not included within this analysis as radiographic knee OA was captured using the Altman Atlas Grading. Results indicated that light, light manual and heavy manual occupations were each associated with increased odds of having more

Table 1
Demographics for all 7391 individual study participants and stratified by cohort.

	All (max = 7391)		JoCoOA (max = 1529)		HCS (max = 987)		MOST (max = 2995)		TasOAC (max = 1020)		Framingham (max = 860)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (Years)	61.7	8.6	62.1	9.0	65.6	2.6	62.5	8.1	63.0	7.5	52.1	8.9
	Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Age (Years)	26	89	45	89	60	72	50	79	51	81	26	77
	N	**%**	**N**	**%**	**n**	**%**	**N**	**%**	**n**	**%**	**n**	**%**
Sex, Female	4324	58.5	1031	67.4	489	49.5	1801	60.1	521	51.1	482	56.00
Race/Ethnicity												
Caucasian white	9210	86.5	1073	70.2	987	100.0	2493	83.2	797	98.3	860	100.0
African American	915	12.7	456	29.8	0	0.0	459	15.3	0	0.0	0	0.0
Asian	7	0.1	0	0.0	0	0.0	0	0.0	7	0.9	0	0.0
Indigenous Australian	7	0.1	0	0.0	0	0.0	0	0.0	7	0.9	0	0.0
Other	43	0.6	0	0.0	0	0.0	43	1.4	0	0.0	0	0.0
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
BMI (kg/m^2)	28.4	25.4–32.4	29.6	26.1–34.0	26.5	24.1–29.4	29.9	26.7–33.8	27.3	24.6–30.5	26.6	23.8–29.3

JoCoOA – Johnston County Osteoarthritis Project; HCS – Hertfordshire Cohort Study; MOST – Multicenter Osteoarthritis Study; TasOAC – The Tasmanian Older Adult Cohort.

serve radiographic knee OA compared to sedentary occupations ((OR: 1.62; 95% CI 1.44, 1.84), (OR: 1.49; 95% CI 1.32, 1.68) and (OR: 2.41; 95% CI 2.02, 2.88) respectively).

4. Discussion

4.1. Key results

This individual-level meta-analysis of over seven thousand people from three countries found that working in light, light manual or heavy manual occupations was associated with symptomatic radiographic OA, independent of age, sex, BMI and race/ethnicity when compared with sedentary occupations. In particular heavy manual occupations were associated with a greater than two-fold increase in symptomatic radiographic OA. This study also demonstrated over a two-fold increase in knee pain and radiographic knee OA in those study participants reporting heavy manual occupations, and just under a 1.5-fold increase in both the risk of radiographic and symptomatic knee OA and light manual occupations.

4.2. Results in context of other studies

To the best of our knowledge, this is the first study to provide a comprehensive methodology for the classification of multiple measures of occupation resulting in the harmonisation of occupation data across studies. Results of this study confirm previous findings that manual occupations are associated with a higher risk of knee OA compared with sedentary occupations. Previous studies have examined the relationship between knee OA and occupation by observing either particular physically demanding occupations such as construction and farming [14] or specific biomechanical occupation related stressors such as kneeling or squatting, heavy lifting [6,29,30].

Holmberg et al. found that men working long term in the building and construction industry had a 3.7-times (95% CI: 1.2, 11.3) increased risk of knee OA and women, but not men, who had worked long term in farming also tended to have an increased risk of knee OA (OR: 2.1; 95% CI: 1.0, 4.5) [14]. While this study found no associations with other particular occupations such as forestry, postal work, cleaning and healthcare work and knee OA.

Sandmark et al. found high levels of exposure to lifting heavy items at work was associated with a three-fold increase in men (OR: 3.0; 95% CI: 1.6, 5.5) and nearly two-fold increase in women (OR: 1.7; 95% CI: 1.0, 2.9) in the risk of knee OA leading to joint replacement compared to individuals with no or low exposure [29]. Likewise, Klussman et al. found occupational kneeling/squatting was related to an increased OR for knee OA (women, OR: 2.52 (>8934 h/life); men, OR: 2.16 (574–12,244 h/life)) [30]. Similarly a study by Allen et al. showed several occupational tasks including lifting >10 pounds, crawling, doing heavy work while standing, walking and less sitting were associated with increased odds of symptomatic knee OA (OR: 1.4–2.1) [8]. Additionally one study observing the frequency of exposures to occupational tasks found that greater exposure to these tasks at the longest job and the current job were associated with greater WOMAC knee pain scores ($p < 0.01$) [9].

A number of recent systematic reviews have identified that frequent performance of physically demanding occupation related tasks such as kneeling, squatting and heavy lifting were associated with both the development and progression of knee OA [31,32]. These reviews however rely on aggregated results and often rely on published studies so therefore suffer from publication bias. Aggregate data are often derived and presented differently across studies and most studies vary in their

Table 2
Harmonised occupational categories and knee outcomes for all 7391 individual study participants and stratified by cohort.

	All		JoCoOA		HCS		MOST		TasOAC		Framingham	
	n	%	n	%	N	%	N	%	n	%	n	%
Predominant lifetime occupation												
Sedentary	1717	24.7	477	31.6	335	34.0	452	15.1	210	21.3	243	51.6
Light	2082	30.0	348	23.0	247	25.1	1264	42.2	108	10.9	115	24.4
Light Manual	2497	35.9	575	38.1	348	35.3	914	30.5	562	56.9	98	20.8
Heavy Manual	654	9.4	111	7.3	56	5.7	365	12.2	107	10.8	15	3.2
Phenotypic manifestation of knee OA												
Radiographic knee OA only	3198	43.3	469	30.7	396	40.1	1576	52.6	695	68.1	62	7.2
Knee pain only	3207	52.1	692	46.7	328	40.1	1602	80.9	379	37.3	206	24.0
Symptomatic knee OA	1786	29.0	283	19.1	174	21.3	1027	51.9	277	27.2	25	2.9

JoCoOA – Johnston County Osteoarthritis Project; HCS – Hertfordshire Cohort Study; MOST – Multicenter Osteoarthritis Study; TasOAC – The Tasmanian Older Adult Cohort.

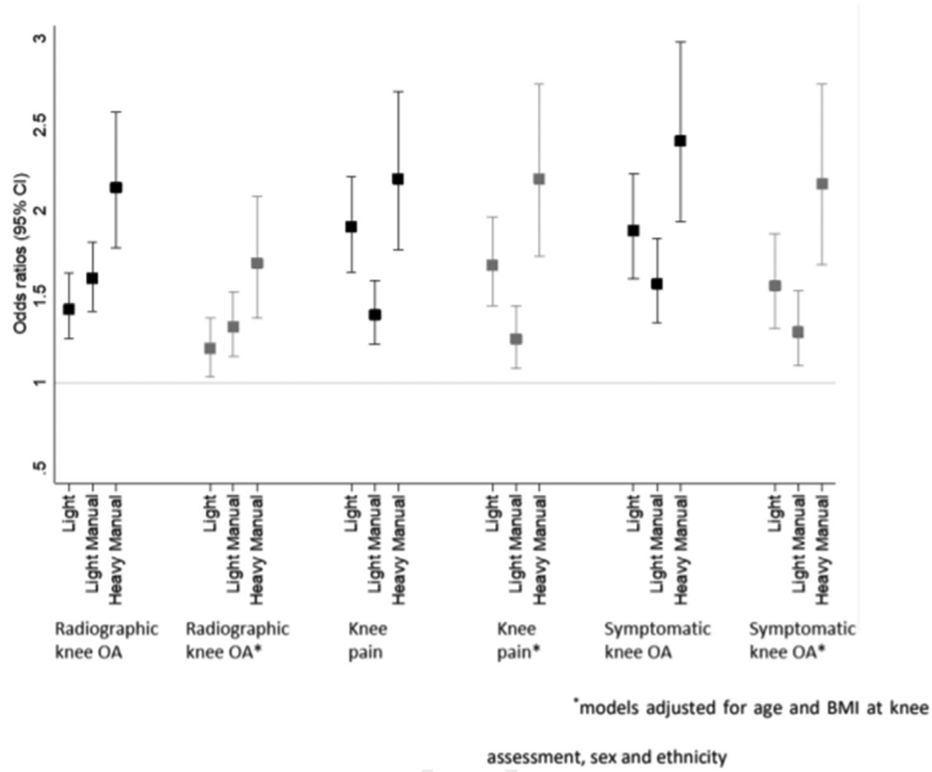

Figure 1. Predominant lifetime occupation associations with knee outcomes.

definitions of occupation, confounders and OA outcomes, which may add to the risk of bias.

The majority of studies have compared heavy manual occupations to sedentary occupations, with little focus on those occupations which may sit in between. Interestingly this study found that even light and light manual occupations were associated with symptomatic radiographic OA. In accordance with these findings one previous study by Rossignol et al. showed that both male and female agriculture workers had the greatest prevalence rate ratio of OA (OR: 2.8; 95% CI: 2.5, 3.2), male masons and other construction workers (OR: 2.9; 95% CI: 2.6, 3.3) along with female cleaners (OR: 6.2; 95% CI: 4.6, 8.0), women in the clothing industry (OR: 5.0; 95% CI: 3.9, 6.3) [33], which may also be classed as light or light manual occupations.

4.3. *Strengths*

Individual level participant data meta-analyses, although time consuming and resource intensive compared with traditional meta-analyses, allows for standardising exposures, outcomes and statistical methods. For example, within this study we were able to use participant-level knee parameters to be able to harmonise three different knee OA outcomes: radiographic knee OA, knee pain and symptomatic radiographic knee OA. This enabled the combined analysis of studies using a variety of knee outcome parameters to explore different knee OA outcomes in relation to occupational activities.

Another important strength to the individual level participant meta-analysis study design is that publication bias can be avoided by not being limited to the inclusion of previously published studies. Neither did we actively seek cohorts who had previously published on the association between occupation and OA. Cohorts were restricted to population-based cohorts, to ensure people without the symptomatic aspects of OA were also captured, therefore limiting selection bias. However, the MOST study participants were recruited for known OA risk factors, therefore presented with a higher prevalence of knee OA.

A further strength of this study is the inclusion of different outcomes (radiographic only, pain only and symptomatic radiographic OA) within the analysis. We know that there is only modest agreement between the radiographic, clinical and self-report methods of diagnosis of knee OA [34], therefore one cannot be used accurately as a proxy for the other.

4.4. *Limitations*

A limitation of this study is that the cohorts included were not originally designed to be directly compared to one another. Therefore, both the occupational exposures and outcomes of OA, along with their components, were assessed differently between cohorts. In order to minimise this variation, we harmonised variables between cohorts, based on previous work for harmonising pain and ROA variables [25] and components of physical activity [23]. By harmonising these, plus individual confounders, and adjusting for them consistently between studies, we have reduced unnecessary heterogeneity between studies. To further ensure that the markedly different profile of the Framingham study sensitivity analysis was completed. Only the effect of light occupation compared to sedentary was attenuated, all other association remained unchanged when Framingham was removed from the analysis.

A further limitation is the lack of specificity of the nature of the occupational exposure activities. Harmonisation of occupational exposures allowed for comparison of broad occupational outcomes among the different cohorts, however from these analyses it is not possible to deduce which specific occupational activities maybe associated with increased risk of knee OA.

The average number of years in the predominant lifetime occupation was not routinely collected, therefore there is potential for bias if the predominant lifetime occupation reported was not the only lengthy occupation undertaken. Due to the cross-sectional nature of this study we are unable to determine the direction of associations, therefore reverse causality cannot be ruled out. For example those who have OA may be more likely to have manual jobs. However, the use of predominant lifetime occupation, rather than only current occupation, strengthens the likely hood of this directional association.

Further work would also be warranted to replicate these findings in cohorts with more diverse populations, as the prevalence of OA has been shown to differ by race/ethnicity. There is also scope to increase the sensitivity of such analyses by undertaking prospective work which identifies the exact tasks within an extensive list of occupations.

5. Conclusions

In this large international multi-cohort study an increase in the odds of having knee pain and knee OA, both radiographic and symptomatic, was demonstrated with light, light manual and heavy manual predominant lifetime occupation when compared with sedentary occupations. This has important implications for the workforce and confirms that manual occupations warrant addressing in public health messaging to reduce the risk of knee OA. It indicates that active industrial measures should be considered to protect manual workers and these measures should be designed to reduce the detrimental effects of heavy manual related activities.

Author contributions

CP, LG, CC and NA were involved in the conception and design of the study. CP and LG processed the data, completed the statistical analysis and drafted the manuscript. CP, LG, DF, MN, GJ, YMG, KDA, LFC, CC and NKA contributed to the acquisition of data. All authors contributed to the interpretation of data, revising the manuscript and the final approval of the manuscript.

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Declaration of competing interest

CP, DW, KWB, MSS and DF has no conflict of interests to report. LG's Institution has received a grant from Versus Arthritis. TP is employed by on a Merck grant. Outside of the submitted work, GJ reports personal fees from BMS, Roche, Abbvie, Amgen, Lilly, Novartis and Jansen, and a grant from Covance. MN Institution received a grant from NIH. YG's Institution has received grants from NIAMS and CDC, and outside of the submitted work has received personal consultancy fees from NIH/NIAMS Data Safety Monitoring Board Member; US Bone and Joint Initiative Faculty member for Young Investigators Workshop. Outside of the submitted work, KA reports speaker fees and travel expenses for committee meetings from American college of Rheumatology, personal fees from Osteoarthritis and Cartilage in regard to associate editor duties and personal fees from University of Seattle for grant review. Outside of the submitted work, LC reports consultancy fees from Abbvie, personal fees from NIH Grant Review, Movement if Life Steering Committee and Balanced Pain Management meetings. LC also reports money to her institution from UNC Chapel Hill and a pending grant from NIDR. Outside CC reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB. NA reports grants and/or personal fees from Marck, Flexion, Regeneron and Pfizer/Lily.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ocarto.2020.100085.

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