



Causal association between subtypes of osteoarthritis and common comorbidities: A Mendelian randomisation study



Will Thompson^a, Subhashisa Swain^{a,b}, Sizheng Steven Zhao^c, Anne Kamps^d, Carol Coupland^e, Changfu Kuo^f, Sita Bierma-Zeinstra^d, Jos Runhaar^d, Michael Doherty^a, Weiya Zhang^{a,*}

^a Academic Rheumatology, Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham, NG5 1PB, United Kingdom

^b Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, United Kingdom

^c Centre for Epidemiology Versus Arthritis, Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, Manchester, United Kingdom

^d Department of General Practice, Erasmus MC University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, Netherlands

^e Centre for Academic Primary Care, School of Medicine, University Park, Nottingham, NG7 2RD, United Kingdom

^f Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital, 5, Fu-Hsing Street, Taoyuan, 333, Taiwan

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ABSTRACT

Objective: To investigate the causal association between Osteoarthritis (OA) and five comorbidities: depression, tiredness, multisite chronic pain, irritable bowel syndrome (IBS) and gout.

Design: This study used two-sample Mendelian Randomisation (MR). To select the OA genetic instruments, we used data from the largest recent genome-wide association study (GWAS) of OA (GO Consortium), with a focus on OA of the knee (62,497 cases, 333,557 controls), hip (35,445 cases, 316,943 controls) and hand (20,901 cases, 282,881 controls). Genetic associations for comorbidities were selected from GWAS for depression (246,363 cases, 561,190 controls), tiredness (449,019 participants), multisite chronic pain (387,649 participants), IBS (53,400 cases, 433,201 controls) and gout (6543 cases, 456,390 controls). We performed a bidirectional MR analysis using the inverse variance weighted method, for both joint specific and overall OA.

Results: Hip OA had a causal effect on multisite chronic pain (per unit change 0.02, 95% CI 0.01 to 0.04). Multisite chronic pain had a causal effect on knee (odds ratio (OR) 2.74, 95% CI 2.20 to 3.41), hip (OR 2.12, 95% CI 1.54 to 2.92), hand (OR 2.24, 95% CI 1.59 to 3.16) and overall OA (OR 2.44, 95% CI, 2.06 to 2.86). In addition, depression and tiredness had causal effects on knee and hand, but not hip, OA.

Conclusions: Apart from Hip OA to multisite chronic pain, other joint OA did not have causal effects on these comorbidities. In contrast, multisite chronic pain had a causal effect on any painful OA.

1. Introduction

Osteoarthritis (OA) is the most common cause of arthritis worldwide and affects 10% of adults in the UK [1]. It is the second most common cause of musculoskeletal pain after back pain [2], and is a major health burden within the UK [3].

OA is a commonly diagnosed comorbidity with other chronic health conditions such as cardiovascular, musculoskeletal, and neuropsychiatric conditions in the UK and other European countries [4]. In our previous research, we performed latent class analysis with electronic health data from the Clinical Practice Research Database (CPRD) to identify categories (or clusters) of comorbidities among patients with existing OA. We were able to classify people with OA into four broad clusters (cardio

vascular, musculoskeletal and mental health, musculoskeletal and cardiovascular, and metabolic) based on their comorbidities, as well as a “relatively healthy” cluster [5]. One of the emerging clusters found was musculoskeletal and/or chronic pain with mental illness. The cluster includes conditions such as fibromyalgia, depression, chronic fatigue, irritable bowel syndrome (IBS) and gout. We have also previously investigated the association of chronic conditions with incident OA recording in primary care using data from the CPRD (using age, sex and practice matched controls without OA), finding that individuals with pre-existing comorbidities were more likely to develop OA within the following 20 years (an association being found for 40 of the 49 comorbidities assessed) [6]. It was discovered that fibromyalgia and poly-myalgia were the leading comorbidities associated with knee OA within

* Corresponding author.

E-mail address: weiya.zhang@nottingham.ac.uk (W. Zhang).

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Table 1
Summary of data sets contributing to the Two-Sample MR analysis.

Phenotype	N	Ethnicity	Country/s ^b	Recruited	GWAS type	% UKBB ^a	Phenotype definition	Phenotype description	Unit	Access site (code)	Ref
Knee OA	396,054	European (1% East Asian)	UK, IS, EE, JP, NL, GR, US, NO	1984–2021	Meta-analysis (fixed effect IVW)	25	Self-report, hospital diagnosed, radiographic	16% cases	logOR	Musculoskeletal Knowledge Portal (KP.Format.GO.FILTER.GW.KneeOA.FULL.09052019.txt.gz)	[12]
Hip OA	353,388	European	UK, IS, EE, NL, GR, US, NO	1984–2021	Meta-analysis (fixed effect IVW)	16	Self-report, hospital diagnosed, radiographic	10% cases	logOR	Musculoskeletal Knowledge Portal (KP.Format.GO.FILTER.GW.HipOA.FULL.09052019.txt.gz)	[12]
Hand OA	303,789	European	UK, IS, EE, NL, US, NO	1984–2021	Meta-analysis (fixed effect IVW)	2	Self-report, hospital diagnosed, radiographic	7% cases	logOR	Musculoskeletal Knowledge Portal (KP.Format.GO.FILTER.GW.HandOA.FULL.09052019.txt.gz)	[12]
Knee OA (no UKBB ^a)	298,274	European (1% East Asian)	UK, IS, EE, JP, NL, GR, US, NO	1984–2021	Meta-analysis (fixed effect IVW)	0	Self-report, hospital diagnosed, radiographic	14% cases	logOR	NA	[12]
Hip OA (no UKBB ^a)	296,748	European	UK, IS, EE, NL, GR, US, NO	1984–2021	Meta-analysis (fixed effect IVW)	0	Self-report, hospital diagnosed, radiographic	8% cases	logOR	NA	[12]
Hand OA (no UKBB ^a)	296,202	European	UK, IS, EE, NL, US, NO	1984–2021	Meta-analysis (fixed effect IVW)	0	Self-report, hospital diagnosed, radiographic	7% cases	logOR	NA	[12]
Depression	807,553	European	UK, US	2006–2016	Meta-analysis (fixed effect IVW)	45	Self-report	31% cases	logOR	IEU Open GWAS project (ieu-b-102)	[15]
Tiredness	449,019	European	UK	2006–2010	Primary GWAS	100	Self-report	Tired: Not at all (46%), Several days (39%), More than half the days (6%), Every day (6%)	Per unit change	IEU Open GWAS project (ukb-b-929)	[16]
Multisite Chronic Pain	387,649	European	UK	2006–2010	Primary GWAS	100	Self-report	Sites of pain: 0 (56%), 1 (24%), 2 (12%), 3 (5%), 4 (2%), 5 (0.7%), 6 (0.2%), 7 (0.03%)	Per unit change	University of Glasgow Enlighten (chronic_pain-bgen.stats.gz)	[17]
Irritable Bowel Syndrome	486,601	European	UK, US, IT, NL, EE, SE, BE, NO, DE	1995–2016	Meta-analysis (fixed effect IVW)	69	Self-reported, hospital diagnosed	11% cases	logOR	NHGRI-EBI GWAS catalog (GCST90016564)	[18]
Gout	456,390	European	UK	2006–2010	Primary GWAS	100	Hospital diagnosed	1% cases	logOR	IEU Open GWAS project (ukb-b-13251)	[16]

^a UKBB, UK Biobank.

^b Standard two letter country codes were used to describe each country included in the study.

20 years, and gout and irritable bowel syndrome were the leading comorbidities associated with ankle/foot OA within 20 years. The association between OA and fibromyalgia and the aforementioned conditions (with the exception of gout) is consistent with a central pain sensitisation hypothesis of OA (where OA diagnosis is driven by pain perception) as opposed to a peripheral mechanism hypothesis (where OA is due to accumulated damage to the joints) [7].

The reason for the frequent co-occurrence of OA with comorbidities remains largely unknown. It may be because of shared risk factors such as ageing, or because of OA itself, the comorbidities themselves or the medication used. However, using observational studies to investigate such concurrence always runs the risk of bias due to unmeasured confounding. An alternative method for estimating causal effects is Mendelian Randomisation (MR), where genetic variants are used as instrumental variables for a given exposure, which are randomly assigned and are not influenced by later environmental confounders. However, this rests on the assumption that the genetic variants used are valid instrumental variables for the exposure being measured [8]. OA is represented differently at different joints, for example OA in the hand is different from knee OA. The association of different joint specific OA with comorbidities is not yet well studied.

Even though we previously explored the bidirectional association between OA and different comorbidities using an epidemiological observational study design, the causal relationship is difficult to explain [6]. We therefore decided to perform a bidirectional MR analysis to investigate the causal relationship between three subtypes of symptomatic OA (Knee, Hip and Hand OA) and the five least studied comorbidities, namely fibromyalgia (which we proxied with multisite chronic

pain, a core symptom of fibromyalgia [9]), depression, fatigue (which we proxied with self-reported tiredness [10]), IBS and gout (which we included in order to proxy peripheral mechanisms of OA).

2. Materials and methods

This study used a Two-Sample MR framework, where genetic variants proxying the exposure are identified in one population sample, and their effects on an outcome are tested in a separate sample, as well as making use of available summary statistics from GWAS. MR hinges on three core assumptions, specifically: (i) the genetic variants are robustly associated with the exposure being measured; (ii) the genetic variants are not associated with known confounding variables; and (iii) the genetic variants only affect the outcome through the exposure (i.e., no horizontal pleiotropy) [8]. This study is part of an international collaborative project on Comorbidities in Osteoarthritis (ComOA) [11].

2.1. Main analysis

2.1.1. Data sources

2.1.1.1. OA. This analysis used the most recent and largest GWAS of OA to identify the genetic instruments used, which to date is the Genetics of OA (GO) Consortium meta-analysis [12]. GO Consortium includes UK Biobank as a contributing cohort. The consortium data includes participants from European and East Asian (1% of the Knee OA sample, independent of UK Biobank) ancestry populations from the UK, Iceland, Estonia, Japan, the Netherlands, Greece, China, the USA and Norway

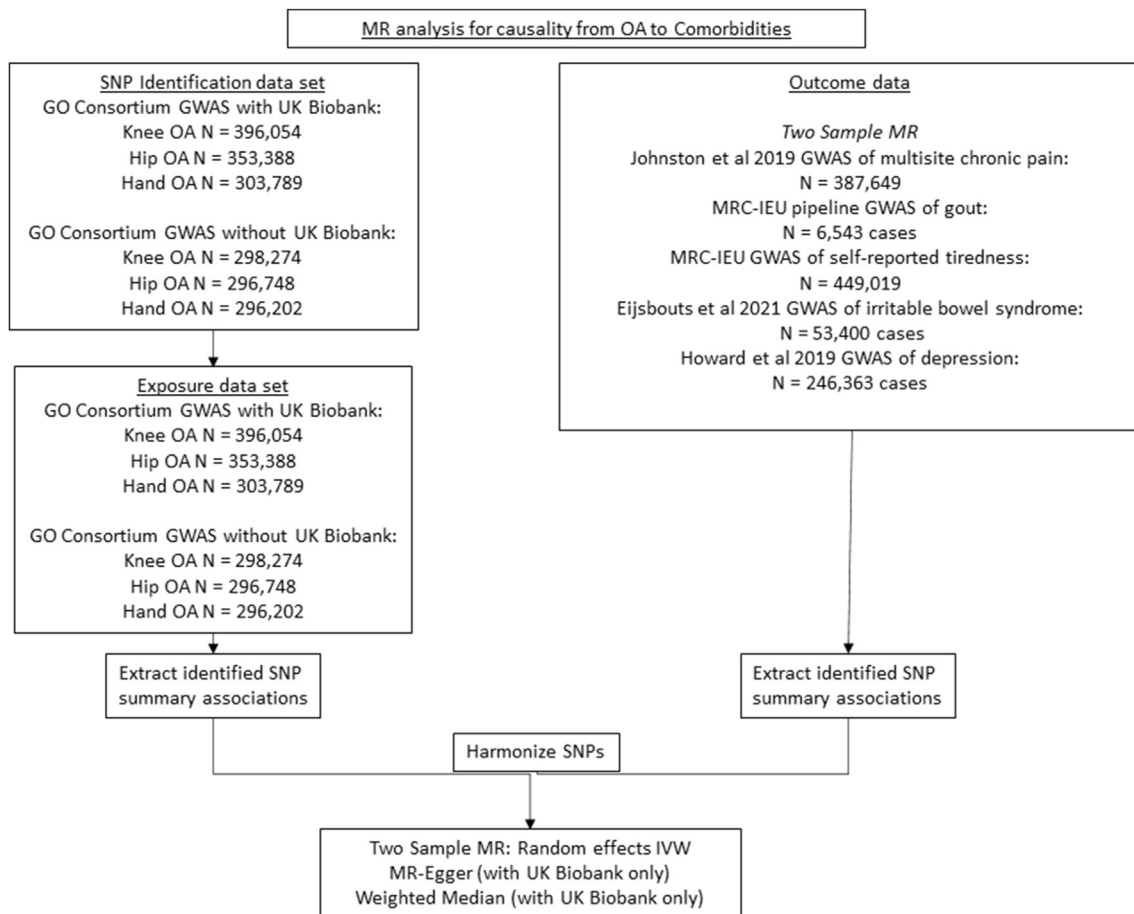


Fig. 1. MR analysis for causality from OA to comorbidities

GO, Genetics of Osteoarthritis, GWAS, Genome Wide Association Study, OA, Osteoarthritis, MRC-IEU, Medical Research Council-Integrative Epidemiology Unit, IVW, Inverse-Variance Weighted (analysis).

from 1984 onwards. Participants were selected from a range of cross-sectional and longitudinal studies and registries, and OA cases were defined as symptomatic (i.e., self-reported joint pain), radiographic and hospital diagnosed (i.e., ICD-10 codes) OA. In total, GWAS from 13 cohorts contributed to the meta-analysis, with the summary single nucleotide polymorphism (SNP) values being pooled using a fixed effects inverse variance weighting (IVW) method. All studies were approved by local research ethics committees. The GO Consortium performed GWAS for multiple OA phenotypes, and this analysis used the following as exposures: Knee OA (62,497 cases, 333,557 controls), Hip OA (N = 35,445 cases, 316,943 controls) and Hand OA (20,901 cases, 282,881 controls; defined as OA in the carpometacarpal joints) [12]. We chose not to use results from the All OA (N = 177,517 cases, 649,173) GWAS, which included patients with any OA phenotype as cases [12], as OA pathology is mechanistically different per joint site [13], potentially leading to causal effects cancelling each other out.

2.1.1.2. Comorbidities. We reported findings of five comorbidities, namely fibromyalgia (which we proxied with multisite chronic pain, a core symptom of fibromyalgia [9]), depression, fatigue (which we proxied with self-reported tiredness [10]), IBS and gout in this manuscript. The ComOA consortium is also exploring associations with other conditions, not of interest to this manuscript.

To test the effect of comorbidities on OA, we selected genetic instruments from the largest available GWAS that had published its results in a peer reviewed journal, or was made available for external analysis, up until July 2022.

A summary of the different data sources used for this study can be found in Table 1. For depression, the largest published GWAS did not report the summary statistics, so the identified SNPs could not be used for

MR directly [14]. Therefore, to select genetic instruments, we used the Howard et al., 2019 GWAS (246,363 cases, 561,190 controls) [15] which was a meta-analysis of three earlier GWAS, including UK Biobank [15]. To proxy fatigue, we used frequency of tiredness [10]. The largest published GWAS of frequency of tiredness only reported one genome-wide significant SNP [10], hence we instead used an unpublished GWAS of frequency of tiredness from the Medical Research Council-Integrative Epidemiology Unit (MRC-IEU) GWAS pipeline [16]. To proxy fibromyalgia, we used multisite chronic pain [9]. The largest available GWAS for multisite chronic pain was Johnson et al., 2019 [17]. For IBS the largest available GWAS was the Eijsbouts et al., 2021 GWAS (53,400 cases, 433,201 controls) [18], which was a meta-analysis of three GWAS from two cohorts, including UK Biobank. The UK Biobank cohort was split between IBS questionnaire responders and non-responders to reduce confounding [18]. For gout, we used the unpublished 2018 GWAS of gout based on self-reported non-cancer illness codes from the MRC-IEU GWAS pipeline [16].

2.2. Statistical analysis methods

2.2.1. Instrumental variable selection

We extracted the genetic instruments from the genome-wide data set for the exposure being measured. Of the genome wide significant ($p < 5e^{-8}$) SNPs extracted from the data set, we used LD clumping to identify the lead SNPs, excluding all non-independent SNPs at a threshold of $r^2 \leq 0.001$ within an LD window of 1000 kb. For datasets accessible on the MRC IEU database, this was achieved in R (version 4.1.2) using the TwoSampleMR R package [16]. For publicly available datasets that were not available on the MRC IEU database, this was achieved using the "ieugwas-r" package [19].

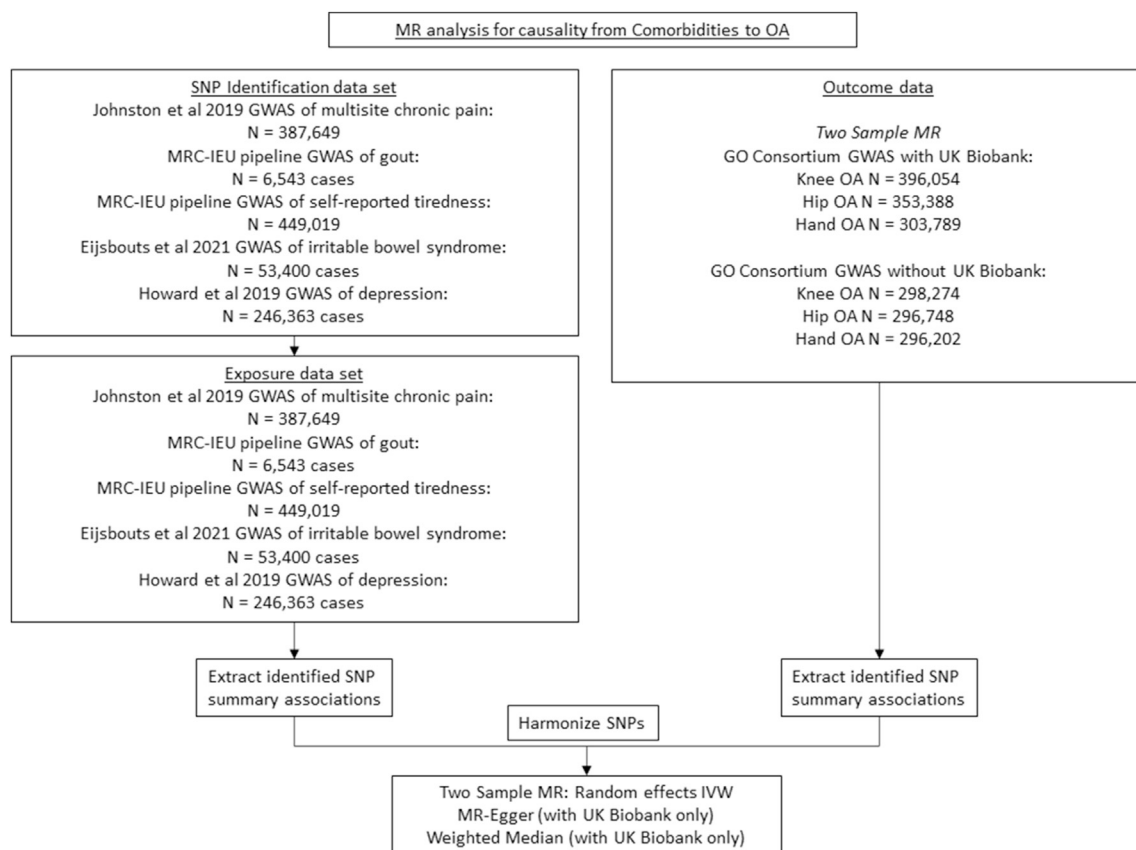


Fig. 2. MR analysis for causality from comorbidities to OA

GO, Genetics of Osteoarthritis, GWAS, Genome Wide Association Study, OA, Osteoarthritis, MRC-IEU, Medical Research Council-Integrative Epidemiology Unit, IVW, Inverse-Variance Weighted (analysis).

To ensure that our effect estimates represented the effect of increased exposure risk on an outcome, all SNP associations were harmonized to the exposure increasing allele before analysis [20]. SNPs that are both palindromic and indistinguishable allele frequencies (MAF >0.499) were excluded from the analyses, as were SNPs that were not available in all data sets. When MR was performed, SNPs were weighted by their reported exposure association, Steiger filtering was applied to remove SNPs that explained greater variance for outcome than exposure [21]. To perform Steiger filtering, we estimated the F-statistic for each SNP association.

After performing the analysis, we estimated the minimal detectable odds ratio for an effect on the outcome, given 80% power, p-value of 0.05, the exposure GWAS sample size and the total variance explained by the genetic instruments [22].

2.2.2. Inverse variance weighted (IVW) method

Once the instrumental variables were selected, we independently extracted individual SNP-outcome associations and individual SNP-exposure associations from the data sets. These associations were measured either in the natural-log odds ratio (logOR), or per unit change. We then calculated the ratio of the SNP-outcome association over the SNP-exposure association (i.e., Wald ratios) and pooled the results by joint site (Knee OA, Hip OA and Hand OA). In addition, we also pooled

the Wald ratio results by each comorbidity (i.e., all OA SNPs effect on the comorbidity, and the comorbidity SNPs effect on all joint sites simultaneously) to get the Average Causal Effect of/on OA. We used the Two-SampleMR package [16] to estimate both the individual and the overall causal effects using random effects IVW analysis (the random effects model being used to control for between SNP heterogeneity). For the individual Wald ratios, we presented them on forest plots to examine the heterogeneity visually and to present I² values that we estimated from the IVW analyses Q statistics. Where the exposure was in logOR, the overall causal estimate was multiplied by 0.693 (i.e., log(2)), to be equivalent to the change per 2-fold increase in the binary exposure [23]. Where the exposure was per unit change, the original measure was used, hence equivalent to the change per 1 unit change increase in the exposure.

2.2.3. Sensitivity analysis

In Two Sample MR, there is a risk that if the two samples have an overlapping population, the MR result will be biased towards the confounded association when using weak instruments. This is an issue when the GO Consortium GWAS includes UK Biobank, and the selected comorbidity GWAS datasets are 45–100% UK Biobank participants. However, if the genetic instruments are strong (F-statistic >10) then this bias is less likely to be an issue [24], therefore we used the GO Consortium meta-analysis with UK Biobank (which produced more

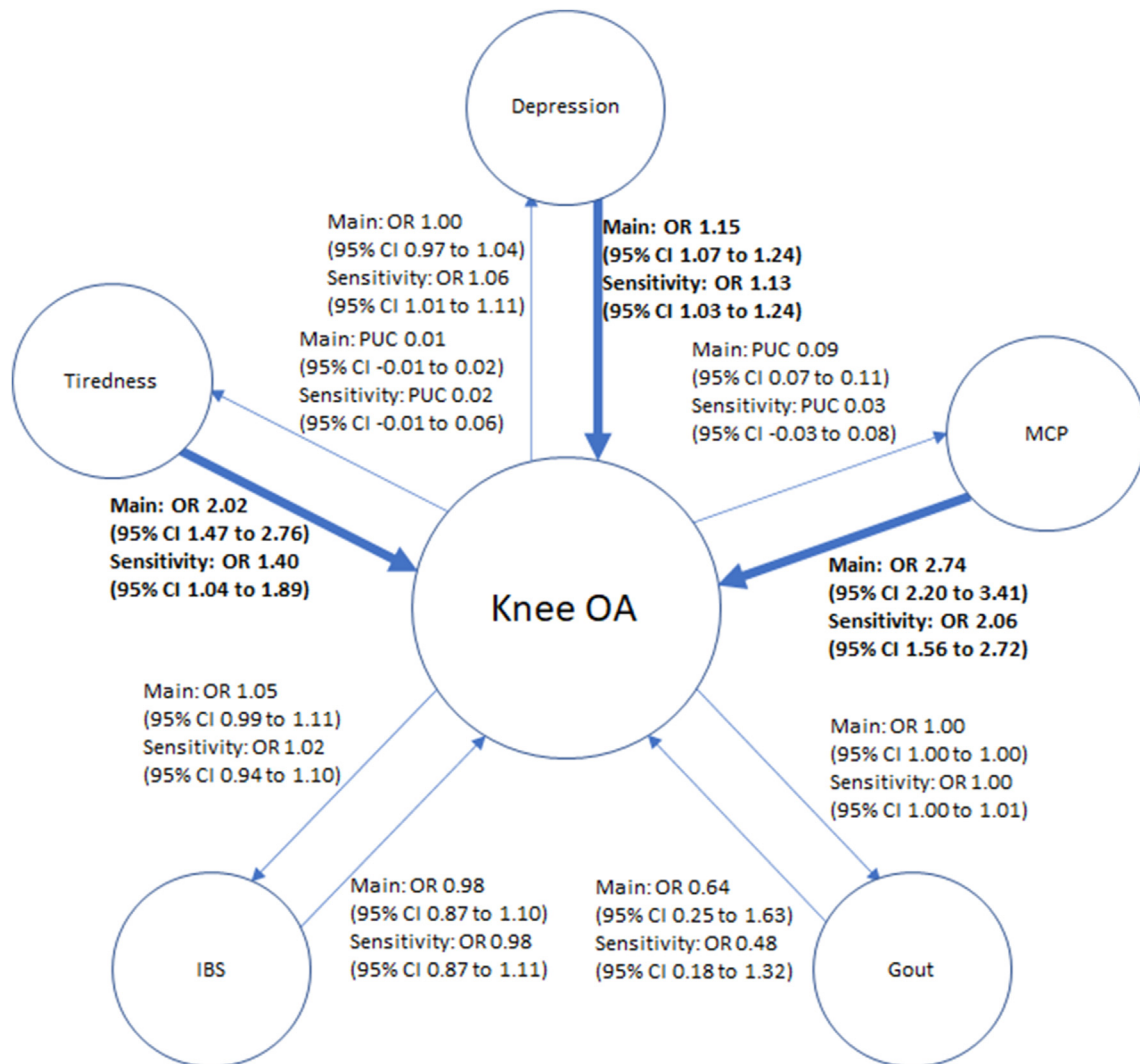


Fig. 3. Causal estimates between comorbidities and Knee OA

- a) OR, Odds Ratio, PUC, Per Unit Change, CI, confidence interval, MCP, multisite chronic pain, IBS, irritable bowel syndrome, OA, osteoarthritis
- b) Darker line and text mean p < 0.05 for both main and sensitivity.

genome-wide significant hits) as the main result. Nonetheless, as a sensitivity analysis, we independently used GWAS data sets from the GO Consortium meta-analysis GWAS *without* UK Biobank (Knee OA, 42,996 cases, 255,278 controls; Hip OA, 25,159 cases, 271,589 controls; Hand OA, 19,385 cases, 276,817 controls) [12] for both the OA to comorbidities and comorbidities to OA MR analyses. Note, as this was a sensitivity analysis for the main IVW estimates, we chose not to present the MR-Egger and weighted median estimates for this analysis.

In addition, we undertook two other methods to verify the results, specifically: i) MR-Egger, which uses the SNP-exposure and SNP-outcome associations as equivalent to points for linear regression, with the intercept value being used to determine the presence of horizontal pleiotropy [25]; and ii) weighted median analysis, where the median value for all the estimates is selected to reduce the impact of weak instruments (providing less than 50% of the variants are weak instruments) [26].

2.3. Patient and public involvement

Three PPI representatives with OA were involved in this study through group meetings. They provided their inputs at each step of the study, including discussions about the struggles of living with multiple conditions, the lack of research in causal relationship and management of multimorbidity, and the importance for this study. The results of the

study were shared with the members in lay-person language and their inputs were considered in writing the manuscript.

3. Results

We performed bi-directional MR, estimating the causal effects both of OA on comorbidities (Fig. 1) and comorbidities on OA (Fig. 2). Of the participants included in our analysis, >99% came from European ancestry backgrounds in developed countries. At maximum there was a 25% overlap between the exposure and outcome (main Knee OA with tiredness, multisite chronic pain and gout). Details of the minimum odds ratios and mean F statistics for each analysis can be found in Supplementary Table 1. All the analysis performed had a mean F statistic greater than 10 (range = 33.49 to 133.78; Supplementary Table 1).

3.1. Effect of OA on comorbidities

There was inconsistent evidence of a causal effect of Knee OA on depression, multisite chronic pain, and gout (Fig. 3). There was no causal effect of any subtype of OA on tiredness or IBS. However, there was consistent evidence (i.e., p-value <0.05 for both the main and sensitivity analyses) of a causal effect of Hip OA on multisite chronic pain (Fig. 4). No evidence of causal effects was seen for Hand OA (Fig. 5), and there

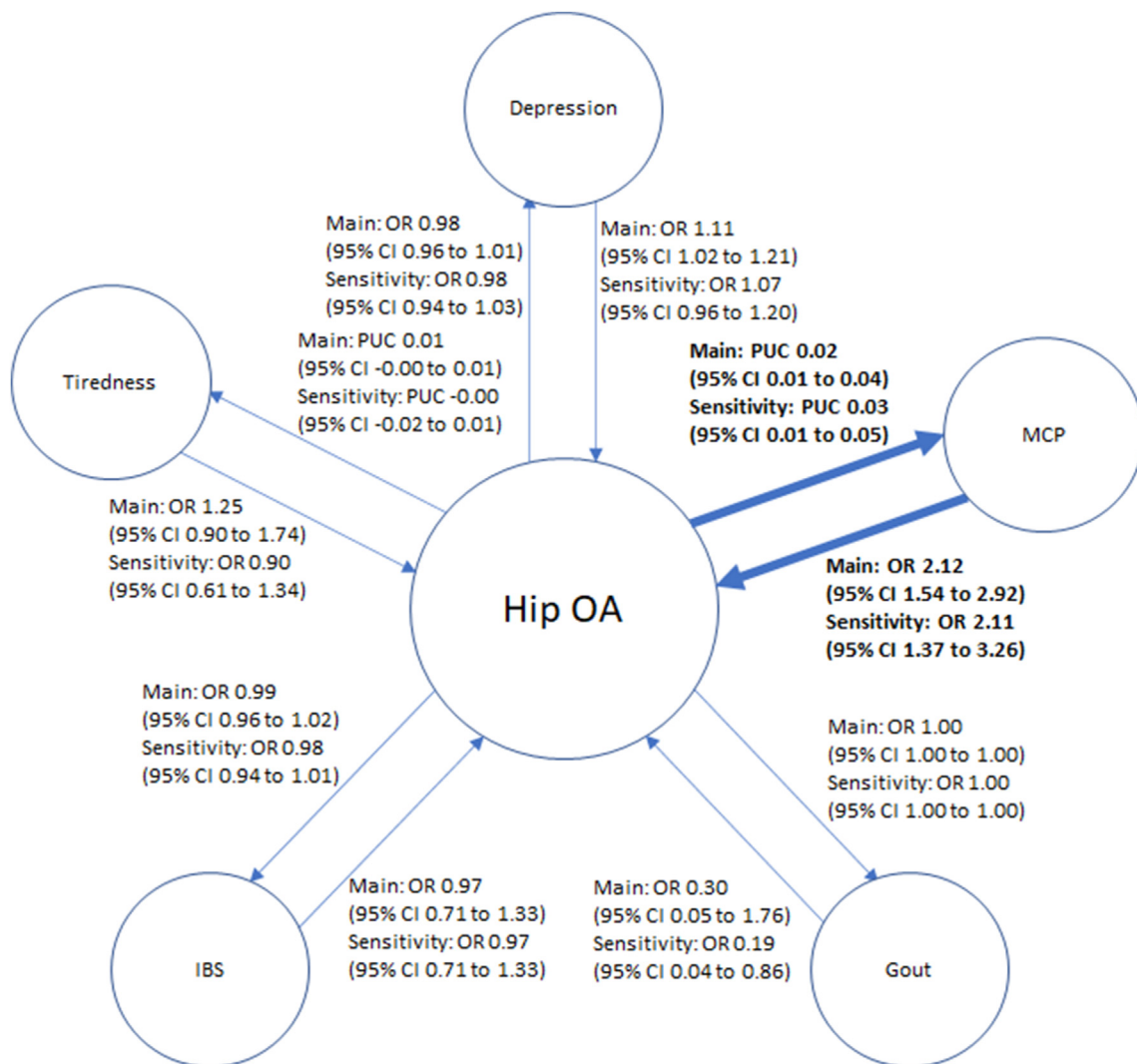


Fig. 4. Causal estimates between comorbidities and Hip OA

a) OR, Odds Ratio, PUC, Per Unit Change, CI, confidence interval, MCP, multisite chronic pain, IBS, irritable bowel syndrome, OA, osteoarthritis
 b) Darker line and text mean p < 0.05 for both main and sensitivity.

was a consistent Average Causal Effect of OA on multisite chronic pain and inconsistent evidence for a causal effect on tiredness (Fig. 6).

Supplementary Table 2 presents the SNP-associations for this analysis, Supplementary Figs. 1–5 present additional forest plots of the causal effects and Supplementary Figs. 6–15 present the Wald ratio effects for the SNPs used.

3.2. Effect of comorbidities on OA

There was consistent evidence of a causal effect of depression on Knee OA, Hand OA, and Pooled OA, but inconsistent evidence of a causal effect on Hip OA (Figs. 3–6). There was consistent evidence of a causal effect of tiredness on Knee OA, Hand OA, and an Average Causal Effect on OA (Figs. 3, 5 and 6). There was consistent evidence of a causal effect of multisite chronic pain on all OA subtypes and an Average Causal Effect on OA (Figs. 3–7). There was no causal effect of IBS on any subtype of OA. There was inconsistent evidence of a protective effect of gout on Hip OA and an Average Causal Effect on OA (Figs. 4 and 6).

Supplementary Table 3 presents the SNP-associations for this analysis, Supplementary Figs. 16–18 present additional forest plots of the causal effects and Supplementary Figs. 19–27 the Wald ratio effects for the SNPs.

3.3. Other sensitivity analyses

For the MR-Egger analysis, there was no evidence of horizontal pleiotropy for most of the consistent causal effects in the main analysis, apart from the effect of multisite chronic pain on Hand OA, where pleiotropy was detected, and the direction of effect changed. There was also evidence of a protective effect of Hand OA on depression and multisite chronic pain when adjusting for pleiotropy, and a protective effect of IBS on all OA subtypes.

For the weighted median analysis, all the consistent causal effects from the main analysis were replicated, apart from the effect of depression and tiredness on Hand OA (though the point estimates were still consistent with the main causal effects). Evidence was also found for an effect of Knee OA on multisite chronic pain, IBS and gout, Hand OA on tiredness and gout on Hip OA.

Supplementary Table 4 presents the results for fixed effects IVW, MR-Egger and the weighted median analysis.

4. Discussion

We used two sample MR methods to investigate bidirectional causal relationships between subtypes of symptomatic OA and five common

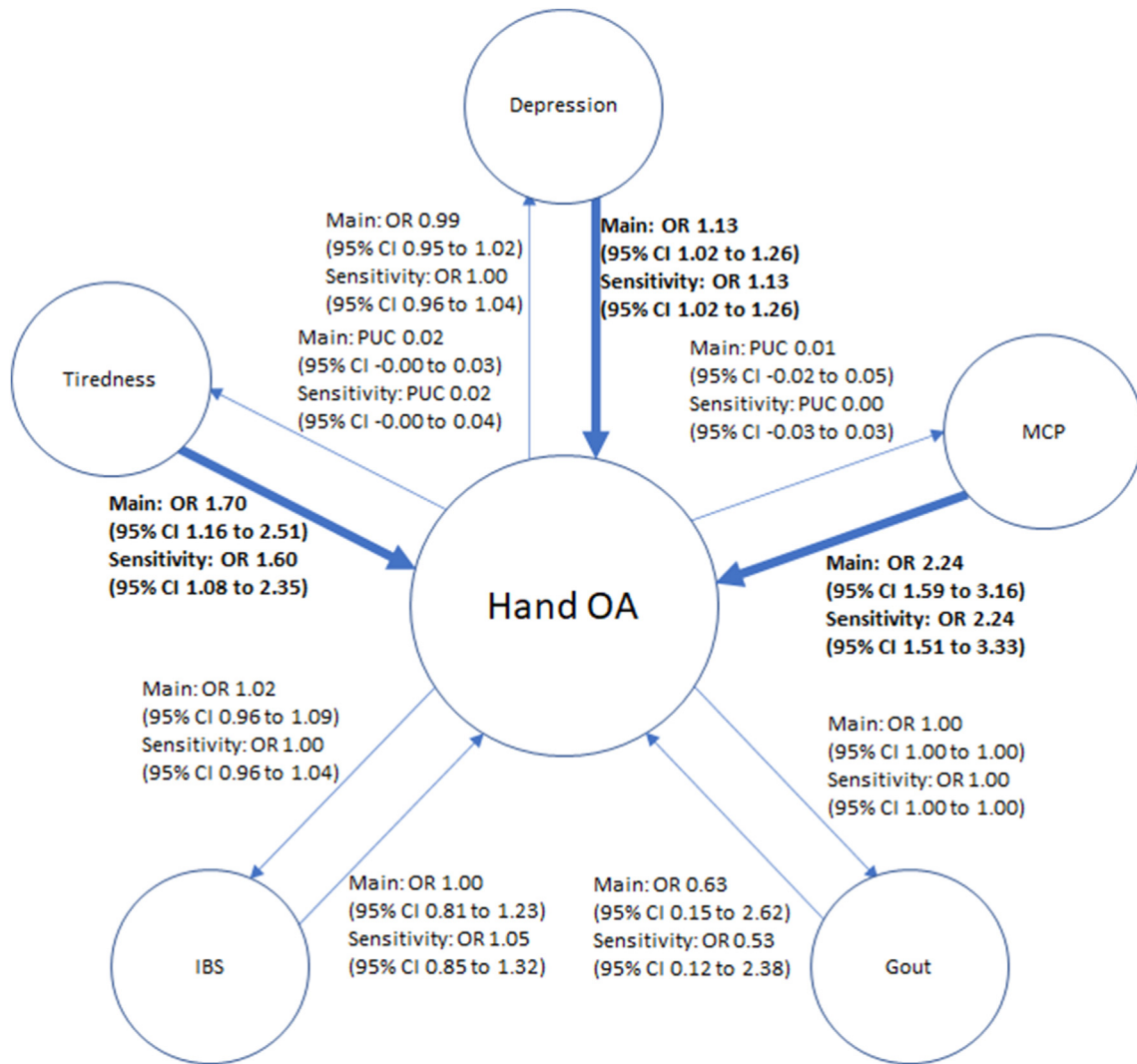


Fig. 5. Causal estimates between comorbidities and Hand OA

a) OR, Odds Ratio, PUC, Per Unit Change, CI, confidence interval, MCP, multisite chronic pain, IBS, irritable bowel syndrome, OA, osteoarthritis
 b) Darker line and text mean $p < 0.05$ for both main and sensitivity.

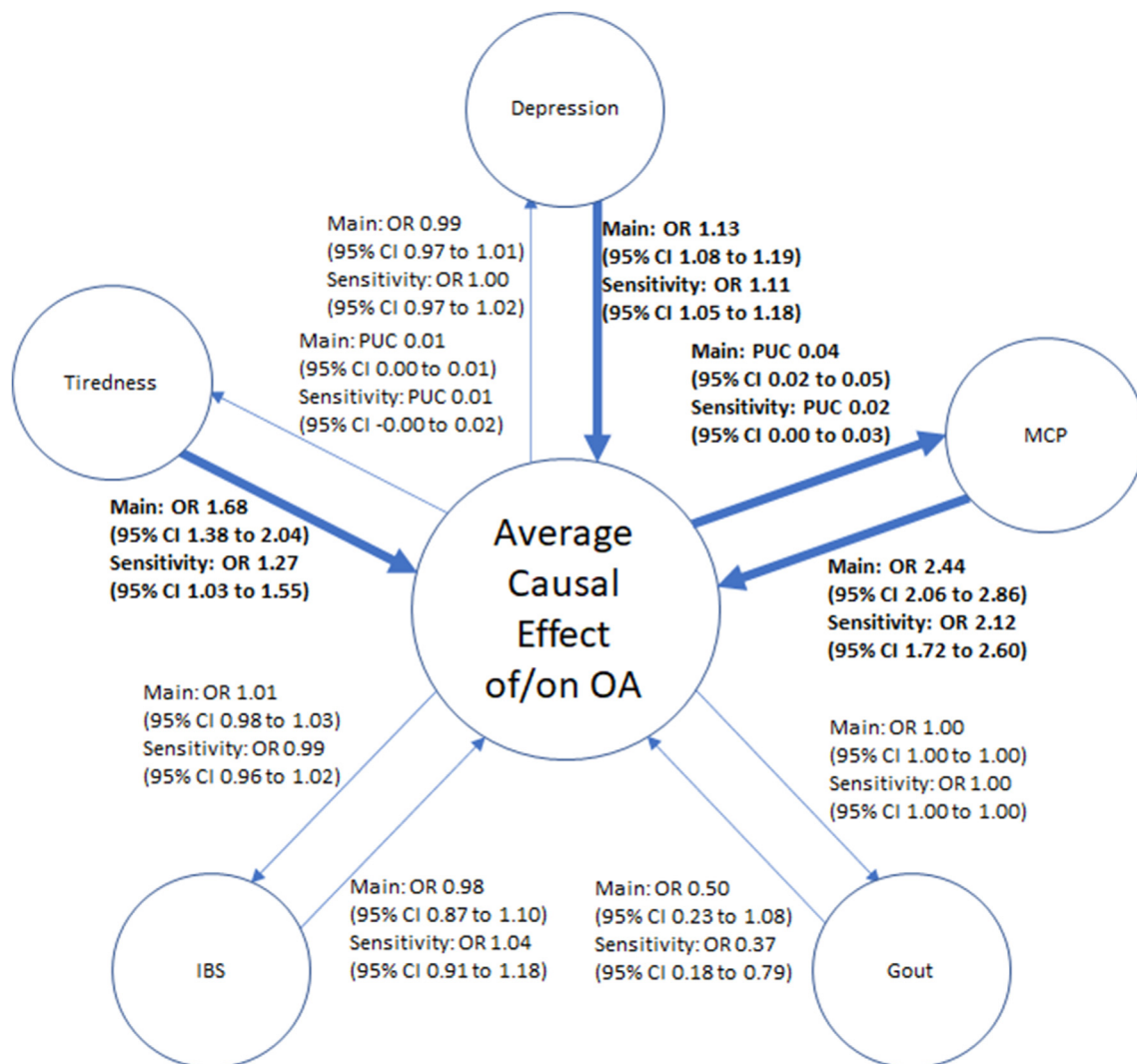


Fig. 6. Average Causal Effects between OA and comorbidities

a) OR, Odds Ratio, PUC, Per Unit Change, CI, confidence interval, MCP, multisite chronic pain, IBS, irritable bowel syndrome, OA, osteoarthritis
 b) Darker line and text mean $p < 0.05$ for both main and sensitivity.

comorbidities. The key findings are: (i) there was a bidirectional causal association between Hip OA and multisite chronic pain, (ii) there was consistent evidence of causal effect of multisite chronic pain on all types of OA, and (iii) there was a causal effect of depression and tiredness on Knee OA and Hand OA. The findings were supported by the sensitivity analysis with and without the UK Biobank data, as well as supported by the other two MR analyses, apart from the horizontal pleiotropy bias observed for Hand OA. Some consistent evidence was also observed for an Average Causal Effect on OA for depression, tiredness and multisite chronic pain, but that needs to be taken with caution due to the heterogeneity between, and double counting SNPs for the different phenotypes of OA.

The general finding of the effects of comorbidities on OA being stronger than the effects of OA on comorbidities is consistent with a previous study by Barowsky et al., 2021 [27] for depression. The evidence of a causal effect of Hip OA on multisite chronic pain is consistent with cross-sectional research which found that 58% of patients diagnosed with radiographic Hip or Knee OA (rather than purely symptomatic OA) reported low back pain and pain at peripheral sites [28]. Further evidence of a causal effect of Hip OA on chronic pain comes from the observation that hip replacement is associated with long term change in brain structures linked to pain processing [29]. The relatively weak evidence of a causal relationship in our study between Hip OA and tiredness

contrasts with earlier observations of an association between fatigue and Hip OA [30]. The finding of multisite chronic pain having a stronger effect on OA than of OA on multisite chronic pain is counter to studies which suggest that OA (particularly Knee OA) occurs before diagnosis of fibromyalgia [6,31]. Similarly, previous studies have observed that prior diagnosis of Knee OA is associated with later diagnosis of depression [32], which was contradicted by our findings. However, these are all observational studies, either cross-sectional or cohort design. The former can only define association whereas the latter can only define temporality, and none can define causality.

Large estimates detected for depression, tiredness and multisite chronic pain on OA is consistent with an important role of central pain sensitisation in symptomatic OA and the association with depression and anxiety and other pain traits [33]. Pain sensitisation has been shown to have a genetic component [17,34], meaning it varies between individuals. It is hypothesized that people with more pain sensitisation are more likely to be diagnosed earlier than those with less pain sensitisation [7]. A central pain sensitivity mechanism could potentially be explained with the delta-sleep deprivation hypothesis, leading to pain sensitisation and an increased diagnosis of fibromyalgia and OA [35]. However, other studies have suggested that general sleep quality is more strongly associated with fibromyalgia and OA than any specific pattern of sleep [36]. Another possible mediator of the effects of depression, tiredness and

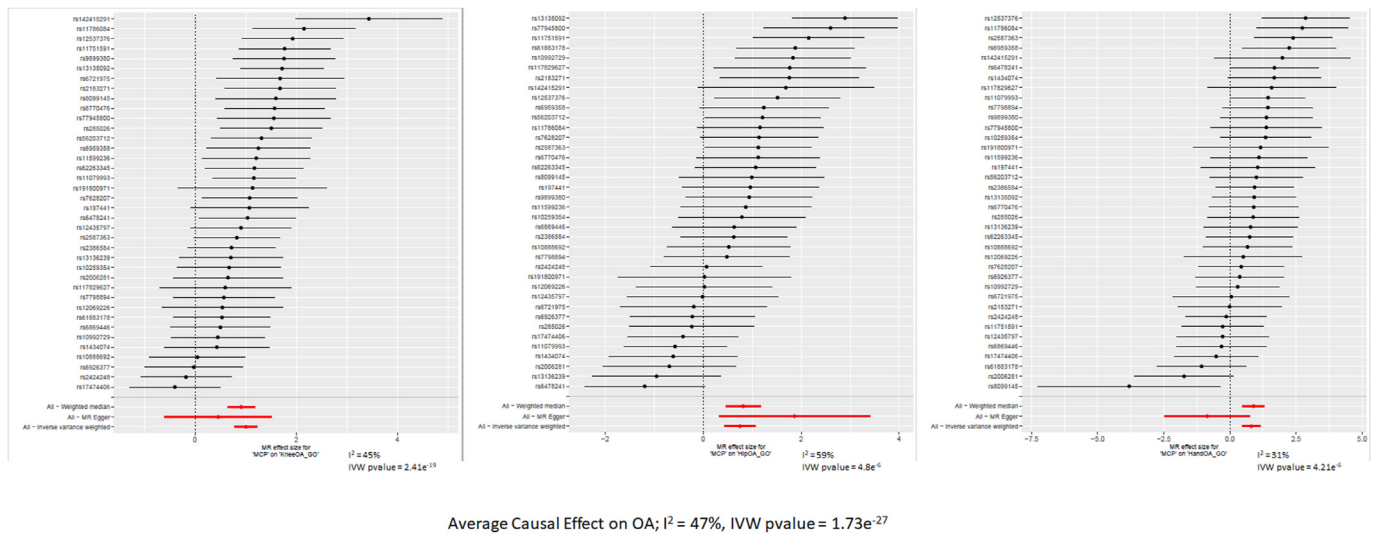


Fig. 7. Multisite chronic pain SNP effects on OA

a) OA, Osteoarthritis, GO, Genetics of Osteoarthritis, MCP, Multisite Chronic Pain, IVW, Inverse Variance Weighted
 b) The scale of the forest plots is untransformed logOR.

multisite chronic pain on OA could be BMI. BMI has been shown to be strongly associated with depression [17,37], fatigue [38] and multisite chronic pain [17,39], as well as having a direct causal effect on Knee OA due to increased joint strain [40].

For the effect of Hip OA on multisite chronic pain, it is possible that pain and biomechanical changes associated with Hip OA cause secondary biomechanical insults to other lower limb joints and to the lumbar spine. This may lead to additional pain at these sites and has been suggested as a likely explanation for the association between Hip OA and lower back pain [41].

4.1. Strengths and limitations

This study used the largest available GWAS of OA, including the largest non-UK Biobank GWAS of OA for the sensitivity analysis [12]. All our genetic instruments had an average F-statistic greater than 10, limiting the risk of weak instrument bias [24]. However, there were numerous estimates that were inconsistent between the full meta-analysis GWAS data set and the data set without UK Biobank. Given that the full GWAS meta-analysis includes UK Biobank (2% for Hand OA, 16% for Hip OA and 25% for Knee OA), there may be bias linked to overlapping samples and weak instruments for these estimates. The only causal effect of OA on a comorbidity was Hip OA on multisite chronic pain. However, more SNPs could be identified for Hip OA than for the other joint sites, meaning a greater amount of variance in Hip OA could be explained, hence the lack of associations could be due to statistical power. There was also some evidence of horizontal pleiotropy in our estimates, namely estimates for Hand OA and irritable bowel syndromes effects on outcomes. The uncertainty in the effect of comorbidities on Hand OA is consistent with the finger, thumb and wrist joints being non-load bearing, making any pain in these regions less noticeable [42], consistent with the central pain hypothesis. For IBS, it should be noted that the IBS variant with the largest negative association with OA (rs12549729; CLDN23) was not reported in the original GWAS due to quality control issues [18]. Whilst there is the possibility that much of the effects detected in this study could be mediated by BMI, it is beyond the scope of this study, which is focussed on specific comorbidities, to investigate. Depression, tiredness and multisite chronic pain are traits that are strongly correlated with each other, thus there is a potential risk of violation of the second assumption of MR. Whilst we did not attempt to identify the effects of these comorbidities independently from each other, this could be achieved using multivariate MR methods [43]. Also, as a

large percentage of the GO consortium GWAS of OA [12] is based on self-reported symptomatic OA, this study is less relevant to understanding the causal relationship of comorbidities with OA pathology. This study was conducted using data derived from predominately (>99%) European ancestry populations, thus the findings (particularly those for depression and OA) may not replicate in African [44] or Asian [45] ancestry populations.

Given the evidence found in this study for a causal effect of comorbidities linked to central pain sensitisation on all types of OA, it is possible that psychological interventions to help patients deal with pain could be effective at reducing the pain due to OA [46]. However, due to the strong correlation between the central pain comorbidities and BMI [17,37–39], further research is needed to differentiate the effects of central mechanisms (i.e., multisite chronic pain, depression, and fatigue) from the genetically correlated peripheral mechanisms (i.e., BMI).

In conclusion, we have found consistent evidence of bidirectional causal effect of Hip OA and multisite chronic pain, consistent evidence of a causal effect of multisite chronic pain on all types of OA, and depression and tiredness on Knee and Hand OA. However, this is just the first step to investigate the causality between OA and five common comorbidities. Further study is needed to confirm the results and to understand the mediating pathways of these causal relationships and potential targets for further treatment.

Author contributions

WZ, MD and WDT designed this study, with further development coming from CFK, SS and SZ. WDT, WZ, SS and AK wrote the statistical analysis plan, based on a previous analysis plan written by AK. WDT undertook most of the analyses with support from WZ, MD, CC, AK, SZ and SS. SBZ and JR supervised AK in her work. WDT wrote the first draft of the paper with support from WZ, MD, CC, SZ and SS; all authors read and made critical revisions to the paper. WDT, WZ, MD, CC, SZ and SS are guarantors of the papers integrity.

Ethics statement

This study used publicly available summary data and did not involve contact with participants; thus, no extra ethical approval or informed consent was required. The research complies with the Declaration of Helsinki.

Data availability statement

This study uses two-sample MR, using summary statistics from predominately publicly available GWAS datasets.

The summary statistics for the main GO Consortium GWAS of osteoarthritis were downloaded from the Musculoskeletal Knowledge Portal (msk.kp.org) in March 2022 from https://msk.hugeamp.org/dinspector.html?dataset=Boer2021_OA_Mixed_Main.

The summary statistics for the sensitivity GO Consortium GWAS without UK Biobank were requested directly from the GO Consortium steering committee via email to go-sc@listen.helmholtz-muenchen.de and the data was downloaded in April 2022.

The summary statistics for depression, tiredness and gout were downloaded using the R package TwoSampleMR from the IEU Open GWAS project between March and August 2022; <https://gwas.mrci.ac.uk/>

The summary statistics for multisite chronic pain from the Johnston et al., 2019 were downloaded via the University of Glasgow Enlighten website from <https://doi.org/10.5525/gla.researchdata.822>.

The summary statistics for irritable bowel syndrome from Eijbsbouts et al., 2021 were downloaded via the NHGRI-EBI GWAS catalog from http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90016001-GCST90017000/GCST90016564/

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Declaration of competing interest

MD has received consultation fees from AstraZeneca, Grunenthal, and Mallinckrodt. WZ has received consultation fees from AstraZeneca, Grunenthal, Eli Lilly and Regeneron advisory boards, and speaker fees from Xiangya Hospital and Shenzhen Rheumatological Meeting. The other authors 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.ocarto.2023.100414>.

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