

Comorbidities in osteoarthritis

Note: this is the final draft submitted to the journal of the article:

Muckelt PE, Roos EM, Stokes M, McDonough S, Grønne DT, Ewings S, Skou ST.

Comorbidities and their link with individual health status: a cross-sectional analysis of 23,892 people with knee and hip osteoarthritis from primary care *Journal of Comorbidity* 2020; In press.
Open Access

Accepted: 8th March 2020

The final, fully proofed and peer-reviewed journal article will be available from the publisher online,
via the following link:

<https://journals.sagepub.com/home/cob>

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Comorbidities and their link with individual health status: a cross-sectional analysis of 23,892 people with knee and hip osteoarthritis from primary care

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GLA:D® has received funding from the Danish Physiotherapy Association's fund for research, education and practice development; the Danish Rheumatism Association; and the Physiotherapy Practice Foundation. Mr Muckelt is funded by the Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis (Grant reference 21595). Dr. Skou is currently funded by a grant from Region Zealand and a grant from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement No 801790).

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Conflict of interest

Dr. Roos is deputy editor of Osteoarthritis and Cartilage, the developer of the Knee injury and Osteoarthritis Outcome Score (KOOS) and several other freely available patient-reported outcome measures and co-founder of Good Life with Osteoarthritis in Denmark (GLA:D®), a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

Dr. Skou is associate editor of the Journal of Orthopaedic & Sports Physical Therapy, has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all of which are outside the submitted work. He is co-founder of GLA:D®.

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Word count: 4773

Keywords: Osteoarthritis, Multimorbidity, Comorbidity, Health status

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Abstract

Objectives: Robust data on the impact of comorbidities on health in people with OA is lacking, despite its potential importance for patient management. Objectives were to determine coexisting conditions in people with OA in primary care, and whether more comorbidities were linked with individual health status.

Methods: A retrospective analysis of 23,892 patients with knee and hip OA was conducted to determine comorbidities present (number/clusters), and how these linked with pain intensity (0-100), widespread pain (site numbers), medication usage (paracetamol, NSAIDs, opioids), quality of life (EQ-5D) and physical function (walking speed) using independent t-tests or chi-square test.

Results: 62% of people with OA treated in primary care had at least one comorbidity; hypertension (37%), heart disease (8%) and diabetes (7%) being most common. Outcome measures worsened with more comorbidities (0 to 4+ comorbidities); Pain intensity [mean (SD)] 46(22) to 57(21); number of painful sites 3.7(3.0) to 6.3(5.4); quality of life 0.73(0.10) to 0.63(0.15); walking speed 1.57m/s(0.33) to 1.24m/s(0.31), while the proportion of people using pain medication increased from 0 to 2 comorbidities (58% to 69%; $P<0.001$), with an increase in opioid use from 4.6% to 19.5% with more comorbidities (0 to 4+ comorbidities).

Conclusion: Most people with knee or hip OA in primary care have at least one other long-term condition. A greater number of comorbidities is linked with worsening health, highlighting the importance of screening for comorbidities when treating patients with OA. It is important for clinicians to consider how OA treatments will interact and affect other common comorbidities.

Introduction

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Multimorbidity, defined as the co-occurrence of at least two long-term conditions [1, 2], affects up to a fifth of the world population [3, 4] and accounts for 78% of all consultations in primary care [5]. A recent report from the Academy of Medical Sciences [6] highlighted the urgent need to address multimorbidity through a range of research priorities, including increased knowledge about common clusters of conditions and their impact on health-care utilization and health status.

Although osteoarthritis (OA) is the disease with the highest occurrence of comorbidities [7], robust large-scale data on common clusters of long-term conditions in OA and their impact on individual health status in primary care is missing. Previous smaller cohort studies including patients through advertisements [8] and from secondary care [9] suggest that at least two out of three people with OA have one or more other comorbidities [8, 9] with hypertension, heart disease, type 2 diabetes mellitus and lung disease being some of the most common comorbidities [8, 10].

People with OA and comorbidities, as well as other people affected by multiple long-term conditions, are treated using multiple single-disease guidelines [4]. However, the recent NICE guidelines on multimorbidity question this single-disease care approach and highlights the importance of accounting for all conditions when informing the patient about available treatment options and treating the individual patient [1]. In order to best inform patients with OA it is important to understand what other conditions coexist in primary care, and how these conditions effect the patient's health status [1].

Therefore, the aim of this study was to determine, which diseases typically cluster in people with knee or hip OA in a large-scale registry in primary care and to identify

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whether the number of comorbidities present is linked with symptom severity, usage of pain medication, widespread pain, quality of life, physical activity level and walking speed.

We hypothesized, that people with a higher number of long-term conditions, would have worse health status, including poorer quality of life and physical function, than those with fewer long-term health conditions.

METHOD

Design

This was a registry-based study from the Good Life with osteoArthritis in Denmark (GLA:D®) program – an ongoing nationwide initiative focusing on the implementation of treatment guidelines for knee and hip OA in clinical practice [11]. GLA:D® consists of two sessions of patient education followed by twice weekly 1-hour sessions of neuromuscular exercise for 6 weeks supervised by primary care physiotherapists certified to deliver the treatment program. The treatment effects are evaluated using pre-defined and validated outcomes at baseline, immediately after the treatment program and at 12 months. A detailed description of GLA:D®, including patient characteristics, treatment and outcomes, is available elsewhere [11].

The current report conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for reporting observational studies. Ethics approval of GLA:D® was not needed, according to the local ethics committee of the North Denmark Region. The GLA:D® registry has previously been approved by the Danish Data Protection Agency and all patients consented to submit their data to the GLA:D® registry.

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Participants

Participants with pain or functional limitation from knee or hip joints that consult their primary care physiotherapist are eligible for GLA:D® if they do not meet one or more of these exclusion criteria : 1) reason for the joint symptoms other than OA as evaluated by the physiotherapist, e.g. inflammatory joint disease or patellar tendinopathy; 2) other symptoms that are more pronounced than the OA symptoms, e.g. chronic, generalized pain, or fibromyalgia; 3) do not understand Danish.

Participants were assigned to the hip or knee group by whichever was their primary OA, but some participants had both.

For the current report, all participants in GLA:D® with available data at baseline were included. All data were collected prior to participants taking part in the GLA:D® program.

Outcomes

Grouping variable

Comorbidities that participants had along with OA were self-reported (via questionnaire) and included: hypertension, heart disease, diabetes, lung disease, rheumatoid arthritis, diseases in the stomach, neurological disease, depression, cancer, diseases in the kidney or liver, anemia or another blood disease, and miscellaneous medical conditions, defined as any conditions other than those mentioned above [11]. Participants were asked if they any of the diseases above, and were required to tick a yes/no box for each condition. For some conditions such as lung disease and heart disease there were examples e.g. COPD (lung disease) and ischemic heart disease.

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Health status variables

Health status variables were collected via a combination of patient form, and physiotherapist forms. The majority of variables were collected via the patient forms with the exception of symptom duration, pain medication, and the functional test; 40-meter walk test, use of walking aid, sit to stand, which were all conducted under supervision of a physiotherapist and entered by them into the database. Age and gender were retrieved from the personal identification number (CPR). BMI was also calculated from weight and height collected by the therapist.

Demographics

Age, gender, BMI, and self-reported educational level (1=primary school, 2=secondary school, 3=short term education (under 3 years after secondary school), 4= middle term education (3-4 years after secondary school), 5=long term education (minimum 5 years after secondary school)) were recorded as demographic measures.

Symptoms

Symptom duration was recorded. Patients marked the total number of body areas (out of 56) where they had felt pain in the last 24 hours on a pain mannequin to assess bodily pain [11]. Mean pain intensity during the last month of the most affected joint was evaluated on a 100mm visual analogue scale (VAS), with a descriptor of “no pain” (0mm) and “maximum pain” (100mm). The VAS score is a widely used measure of pain for people with OA, and is valid and reliable [12].

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Patients were asked about the frequency of their hip/knee pain using an item from the Knee Injury and Osteoarthritis Outcome Score (KOOS) or Hip disability and Osteoarthritis Outcome Score (HOOS) on a scale of 0-4 (0=never, 1=monthly, 2=weekly, 3=daily, 4=always) [13, 14] . Participants were asked if they had problems walking due to their hip/knee (“yes” or “no”).

Pain medication

Patients were asked if they had been using pain medication within the last three months and asked to indicate what kind of medication, with several options (Paracetamol, NSAID (oral or topical), Morphine or other opioids). The answers were recoded “yes” (any pain medication used) and “no” (no pain medication used). For analysing each drug separately, the answers were recoded into a binary variable for the use of each type of drug.

Fear of movement

Patients were asked to indicate if they were afraid that their joint would be damaged from physical activity and exercise (“yes” or “no”).

Quality of life

Joint-related quality of life was evaluated using the subscale quality of life from the self-reported questionnaires: KOOS (Knee injury and Osteoarthritis Outcome score), and the HOOS (Hip injury and Osteoarthritis Outcome score), with scores ranging from 0 (worst) to 100 (best). KOOS and HOOS are valid, reliable and responsive patient-reported outcome measures previously applied in studies of OA [13, 14].

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Generic quality of life was evaluated by using the EQ-5D-5L questionnaire (scored using Danish crosswalk value set) and the EQ VAS. The EQ-5D-5L has been shown to be valid and reliable when used within an OA population [15].

Physical activity and function

Physical activity was assessed using the UCLA questionnaire, where participants were asked to rate their physical activity on a scale from 1 to 10 (10=Regularly participates in impact sports; 9=Sometimes participates in impact sports; 8=Regularly participates in active events; 7=Sometimes participates in active events; 6=Regularly participates in moderate activities; 5=Sometimes participates in moderate activities; 4=Regularly participates in mild activities; 3=Sometimes participates in mild activities; 2=Mostly inactive or restricted to minimum activities of daily living; 1=Wholly inactive, dependent on others, and cannot leave residence). The UCLA has been found to be a useful measure of physical activity in people with OA [16].

Physical function was assessed using the 40-meter walk test (converted to meters per second for the purposes of this report), and the 30 second sit to stand test. Both tests are recommended by the Osteoarthritis Research Society International as components of core sets of performance based physical function tests for knee and hip [17]. Physiotherapists were asked to indicate if participants used a walking aid during the 40 meter walk test [11].

Patient involvement

Patients and patient organizations have been involved in the development and the ongoing update of GLA:D® and its materials.

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Data analysis

For the present analysis, data collected in GLA:D® between June 30, 2014 (start of data collection on comorbidities) and end of December 31, 2017 were used.

In line with the aims of this study, the analysis was designed to identify how comorbidities cluster in people with hip or knee OA, and whether there is an association between number of comorbidities and outcomes, such as symptom severity, usage of pain medication and quality of life. In addition, patient characteristics across comorbidity group are reported to help understand the demographics of these groups. Finally, hip and knee OA patients are compared to understand if there are differences in the number of comorbidities present with the two different sites of OA.

Potential differences in the number of present comorbidities between patients with hip and knee OA were examined using a Mann-Whitney U test (as the outcome being tested is ordinal data), with the significance level set to 0.05.

Cross tabs of the number of participants with each condition were generated, and used to establish the top five pairs and trios of conditions that cluster together. The percentage of participants within each of these clusters was then calculated against the entire cohort to ascertain the prevalence of each cluster.

Frequencies for number of other conditions were calculated, and for the purposes of analysis these were grouped with 0 representing those with OA only; 1, OA and one other condition; 2, OA and two other conditions; 3, OA and three other conditions; 4+, OA and four or more other conditions. Groups were compared on each of the health status variables using independent samples t-tests. Each group were tested in comparison with the next number of comorbidities, so zero comorbidities compared

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to one comorbidity, one to two etc. The significance level was set to 0.0125 between groups as four t-tests were conducted on each variable ($0.05/4=0.0125$). Education level, expressed as an ordinal variable, was compared between comorbidity groups using Mann-Whitney U test with the significance level set to 0.0125 (due to the Bonferroni adjustment). Gender, Medication usage (including breakdown), problems walking, fear of walking, and use of walking aid in 40-meter walk test were assessed using Chi squared (significance set to 0.0125). Confidence intervals were set to 98.75 due to the number of tests conducted. All analyses were conducted using SPSS (version 24).

The purpose of the paper was to describe the differences between comorbidity groups; as number of comorbidities is not an experimental variable and due to the cross-sectional design, the study did not attempt to explore a cause and effect relationship with health status. Hence, methods such as multivariable models designed to control for confounders were not used.

RESULTS

Of 27,513 patients who attended GLA:D®, 24,029 (87.3 %) completed the patient form containing information on comorbidities and 12.7 % did not complete the form (69.8% females, mean [SD] age = 65.9 [11.1], BMI = 28.4 [5.3]).

Participants with missing data on other conditions were also removed, leaving 23,892 (72.4% females, age = 64.9[9.5], BMI = 28.3 [5.3]).

Participants were characterised as having hip or knee OA based on their primary concern. However, 2,441 (40.44%) out of 6,036 hip OA participants also had knee OA, and 3,620 (20.34%) out of 17,795 Knee OA participants also had hip OA.

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Comorbidities and clusters

62.1% of the participants were affected by at least one condition other than OA (Table 1). The most common condition to present with OA was hypertension (37%; Figure 1).

Table 1. Frequency of number of other conditions in people with knee or hip osteoarthritis

Number of other conditions	Frequency	Percentage
0	9058	37.9
1	8518	35.7
2	4216	17.6
3	1506	6.3
4	409	1.7
5	134	0.6
6	37	0.2
7+	14	0.06

[Insert figure one here]

Figure 1. Percentage of patients with osteoarthritis presenting with each other condition. Miscellaneous medical conditions were defined as any conditions other than those mentioned previously

The most common two conditions to cluster together with OA were hypertension and diabetes (4.9% of participants) (Table 2). The top five pairs of conditions that clustered together accounted for 16.2% of the participants, which is over half of all of those with two or more conditions.

The most common trios of conditions that clustered together with OA were hypertension, heart disease, and diabetes (0.6%); The top five trios of conditions that clustered together accounted for 1.7% of the participants, which is about a fifth of all those with three or more conditions.

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Table 2. Frequency of total participants for top five pairs and trios of other conditions in people with knee and hip osteoarthritis

Name of conditions	Frequency	Percentage of participants
Top five pairs of conditions		
Hypertension and diabetes	1166	4.88
Hypertension and heart disease	1036	4.34
Hypertension and lung disease	611	2.56
Hypertension and stomach diseases	543	2.27
Hypertension and Rheumatoid arthritis	523	2.19
Top five trios of conditions		
Hypertension, heart disease, and diabetes	139	0.58
Hypertension, heart disease, and lung disease	96	0.40
Hypertension, heart disease, and neurological diseases	66	0.28
Hypertension, diabetes, and Rheumatoid arthritis	55	0.23
Hypertension, lung disease, diabetes	50	0.21

Miscellaneous medical conditions were removed from this grouping as it is unknown what conditions make up this group.

Knee vs hip osteoarthritis

Participants with hip OA are slightly less likely to suffer from other comorbidities than those with knee OA. There is a statistically significant difference between the mean number of other conditions between groups (hip OA 0.97 versus knee OA 1.01, mean difference 0.03, 98.75% CI <0.01 to 0.06, $p=0.027$). 39% of participants with hip OA have no other conditions whereas 37.6% of those with knee OA have no other conditions (Table 3).

Table 3. Frequency and percentage of participants with hip and knee osteoarthritis against number of conditions other than osteoarthritis

Osteoarthritis		Number of other conditions								
		0		1		2		3		4+
Effected joint	n	%	n	%	N	%	n	%	n	%

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Hip (n=6036)	2355	39.00	2142	35.50	1026	17.00	377	6.20	137	2.30
Knee (n=17795)	6691	37.60	6354	35.70	3177	17.80	1125	6.30	591	2.60

Link between comorbidities and health status

Demographics

As age increases, the number of comorbidities tend to increase, with participants only suffering from OA being the youngest (mean (98.75% CI) = 62.80 (62.53-63.06)), and participants suffering from four or more conditions in addition to OA being the eldest (mean (98.75% CI) = 67.18, (66.28-67.38)) (Table 4).

BMI significantly increases as the number of other conditions increases with participants with the lowest BMI having OA alone (mean (98.75% CI) = 27.20 (27.08-27.34)), and those with the highest BMI having four or more conditions (mean (98.75% CI) = 31.13 (30.53-31.73)). Education level appear to be linked with the number of comorbidities, with participants affected by OA alone being the highest educated people (mean (98.75% CI) = 3.29 (3= under 3 years after secondary school), (3.25-3.31)), and participants affected by four or more conditions in addition to OA having the lowest education levels (mean (98.75% CI) 2.79 (2= secondary school), (2.67-2.90)) (Table 4).

Symptoms

Significant differences were found in the number of bodily areas participants felt pain in the last 24 hours between each group (OA alone, mean (98.75% CI) = 3.65, (3.56-3.73), 4+ conditions, mean (95% CI) = 6.29, (5.68-6.90)) (Table 4).

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Problems with walking were more common in those with more comorbidities and were significantly higher as the number of additional conditions increased, with the exception of between 3 and 4 or other conditions (OA alone, **percentage** (98.75% CI) = 73.10%, (72.0-74.3), 3 conditions, **percentage** (98.75% CI) = 85.00%, (82.5-87.2)).

Participants had significantly higher pain severity in the last month the more conditions they were affected by (OA alone, mean (98.75% CI) = 45.92, (45.30-47.00.), 4+ conditions, mean (98.75% CI) = 57.24, (54.80-59.68)) (Table 4).

Use of pain medication

Participants who are afflicted by one or two conditions in addition to OA are significantly more likely to use medication for pain management in the last three months, than those with OA alone (OA alone, **percentage** (98.75% CI) = 58.00%, (56.7-59.30), two conditions, **percentage** (98.75% CI) = 66.00%, (64.10-67.80)). However, once participants have two or more additional conditions, then pain medication analysed as a binary variable does not significantly increase (Table 4). Paracetamol was the most used medication at OA only (**percentage** (98.75% CI) = 46.72%, (45.41-48.04)) and steadily increases to four or more conditions (**percentage** (98.75% CI) = 59.05, (54-64.10)). NSAID's usage starts high (**percentage** (98.75% CI) = 37.88, (36.61-39.17)) and decreases steadily to four or more conditions (**percentage** (98.75% CI) = 28.60, (23.95-33.24)). Opioids usage starts low (**percentage** (98.75% CI) = 4.57, (4.02-5.12)) and increases considerably (**percentage** (98.75% CI) = 19.46, (15.39-23.53)) (Table 4).

Quality of life

Quality of life scores from the EQ-5D-5L questionnaire worsen significantly as the number of comorbidities increases (OA alone, mean (98.75% CI) = 0.73, (0.73-0.73),

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4+ conditions, mean (98.75% CI) = 0.63, [0.61-0.64]). This is matched by a significant drop in perceived health levels measured on EQ VAS between groups (OA alone, mean (98.75% CI) = 73.07, (72.60-73.54), 4+ conditions, mean (98.75% CI) = 55.28, [53.29-57.28]) (Table 4).

Similarly, KOOS QOL score worsens as the number of conditions increases (OA only, mean (98.75% CI) = 46.83, (46.38-47.29), one other condition, mean (98.75% CI) = 38.11, (36.38-39.82). However, there were no significant differences between two other conditions and three other conditions. HOOS QOL score also worsens as the number of conditions increases, however, only two of these changes are statistically significant (0-1 mean (98.75% CI) 48.81 (48.02-49.59) to 47.34 (46.51-48.17); and 2-3 mean (98.75% CI) 45.96 (44.74-47.17) to 42.74 [40.71-44.71]) (Table 4).

Physical activity and function

The highest physical activity levels were found in the OA only group (mean (98.75% CI) = 6.08, [6.03-6.12]) and the lowest levels in the four or more conditions group (mean (95% CI) 4.82, (4.62-5.02); Table 4).

There is a significant decrease in the walking speed achieved during the 40-meter walk test between each group, with participants with more conditions walking significantly slower (OA alone, mean (98.75% CI) = 1.57m/s, (1.56-1.58), 4+ conditions, mean (98.75% CI) = 1.24m/s, (1.21-1.27); Table 4).

With increasing number of conditions, there is a small increase in the percentage of participants using a walking aid to complete the test between each group. However, there is only a significant increase in the use of walking aids between those with one

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(percentage (98.75% CI) = 1.8%, [1.5%-2.2%]) and two (percentage (98.75% CI) = 2.7%, [2.1%-3.4%]) other conditions (Table 4).

The amount of sit to stands that participants achieved during the 30 second sit to stand test decreases significantly as the number of other conditions increases.

Those with OA only average 12.82 (CI 98.75%= 12.72-12.92) sit to stands and those with 4+ additional conditions averaging 10.18 (CI 98.75%= 9.83-10.53) (Table 4).

Three hundred and twelve (1.4%) participants were unable to perform the sit to stand test, 86 with OA alone (1% of group), 108 with OA and one other condition (1.3% of group), 63 with OA and two other conditions (1.6% of group, 35 with OA and three other conditions (2.4% of group), and 20 with OA, and four or more other conditions (3.5% of the group).

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Table 4. Health status in people with knee and hip osteoarthritis and one or more other long-term conditions

Number of conditions other than osteoarthritis										
0		1		2		3		4+		
Variable	Mean /percentage	CI (98.75%)	Mean /percentage	CI (98.75%)	Mean /percentage	CI (98.75%)	Mean /percentage	CI (98.75%)	Mean /percentage	CI (98.75%)
Demographics										
Age (years)(n=23725)	62.80†	62.53-63.06	65.58†	65.34-65.83	66.71	66.37-67.06	67.00	66.42-67.58	67.18	66..28-67.38
Gender (percentage of females)(n=23809)	73.30%	72.1%-74.5%	73.00%	71.7%-74.2%	71.10%	69.3%-72.8%	68.30%	65.2%-71.2%	68.40%	63.3%-73.0%
BMI(n=23750)	27.20†	27.08-27.34	28.42†	28.28-28.55	29.40†	29.18-29.61	30.04†	29.66-30.42	31.13	30.53-31.73
Education level(n=23879)	3.29†	3.25-3.32	3.14†	3.11-3.18	3.04†	2.99-3.09	2.94†	2.85-3.03	2.79	2.64-2.93
Symptoms										
Symptom duration (months)(n=19533)	41.7	39.83-43.56	42.27	40.34-44.23	44.87	42.03-47.71	48.93	43.70-54.16	50.94	42.41-59.46
Pain mannequin (max 56) (n=23892)	3.65†	3.56-3.73	3.91†	3.82-4.01	4.39†	4.24-4.55	4.91†	4.61-5.21	6.29	5.68-6.90
Frequency of knee or hip pain (n=23883)	2.86†	2.84-2.88	2.92†	2.90-2.94	2.99†	2.95-3.02	3.09	3.03-3.14	3.14	3.06-3.22
Percentage who had walking problems (n=23876)	73.10%†	72.0%-74.3%	77.40%†	76.2%-78.5%	81.80%†	80.3%-83.3%	85.00%	82.5%-87.2%	88.70%	84.9%-91.6%
Mean pain in last month (n=23859)	45.92†	45.30-47.00	47.80†	47.17-48.45	50.37†	49.42-51.31	53.83†	52.25-55.41	57.24	54.80-59.68
Medication										
Percentage who used pain medication in the last 3 months (n=23809)	58.00%†	56.7%-59.3%	63.10%†	61.7%-64.4%	66.00%	64.1%-67.8%	68.70%	66.3%-71.6%	68.90%	63.8%-73.5%
Paracetamol	46.72%†	45.41-48.04	52.54 %†	51.18-53.89	55.41 %	53.49-57.32	58.80%	55.64-61.97	59.05%	54.00-64.10
NSAIDs	37.88 %	36.61-39.17	36.54 %	35.23-37.84	35.64 %	33.79-37.48	32.23%	29.22-35.23	28.60%	23.95-33.24
Opioids	4.57 %†	4.02-5.12	6.98 %†	6.29-7.57	9.95 %†	8.80-11.11	14.55%†	12.28-16.82	19.46%	15.39-23.53
Psychological										
Percentage who had fear of movement (n=23885)	14.80%	13.9%-15.8%	13.60%	12.7%-14.6%	13.10%	11.9%-14.5%	15.20%	13.0%-17.7%	19.20%	15.4%-23.6%
Quality of life										
EQ-5D-5L questionnaire (n=23870)	0.73†	0.73-0.73	0.71†	0.71-0.71	0.69†	0.69-0.70	0.66†	0.66-0.67	0.63	0.61-0.64
EQ-5D-5L VAS (n=23878)	73.07†	72.60-73.54	69.95†	69.45-70.44	65.58†	64.87-66.29	61.55†	60.31-62.79	55.28	53.29-57.28
KOOS QOL Score (n=17795)	46.83†	46.38-47.29	45.11†	44.64-45.57	43.18	42.52-43.84	42.02†	40.89-43.16	38.11	36.38-39.82
HOOS QOL Score (n=6036)	48.81†	48.02-49.59	47.34	46.51-48.17	45.96†	44.74-47.17	42.74	40.71-44.77	41.01	37.57-44.45
Physical function and activity										
UCLA activity level (n=23871)	6.08†	6.03-6.12	5.76†	5.71-5.81	5.43†	5.36-5.50	5.23†	5.11-5.35	4.82	4.62-5.02
40 meter walk test (meters per second)(n=22509)	1.57†	1.56-1.58	1.47†	1.46-1.48	1.40†	1.39-1.42	1.35†	1.33-1.37	1.24	1.21-1.27
Percentage who used a walking aid in walk test (n=22923)	1.40%	1.1%-1.7%	1.80%†	1.5%-2.2%	2.70%	2.1%-3.4%	3.40%	2.3%-4.8%	4.20%	2.5%-6.9%
Sit to stand (n=22591)	12.82†	12.72-12.92	12.10†	12.01-12.20	11.53†	11.39-11.66	10.92†	10.70-11.14	10.18	9.83-10.53

For descriptions of variables and statistical methods see method section

†significant difference of 0.0125 or less to the group above (with more comorbidities) as calculated by the Bonferroni adjustment.

In the view of clarity, it was decided to show mean and CI for education level instead of median and range, as this is easier to see and understand.

DISCUSSION

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Our large-scale study of people in primary care, confirms and extends findings from previous similar cohort studies from secondary care [2-4, 7] by demonstrating that most people (62%) with knee and hip OA studied in primary care have at least one other long-term condition with the most common coexisting conditions being hypertension, heart disease, diabetes mellitus and lung disease. We found that symptom severity, usage of pain medication, widespread pain, quality of life, physical activity level and walking speed gradually worsen with more comorbidities. The current single-disease framework is associated with an increased burden from consultations and treatments in people with more long-term conditions. Our study highlights the importance of accounting for all coexisting conditions and points to including treatments [18], such as exercise therapy [19], that are able to improve individual health status across conditions.

Education and health

The positive association between education level and health is well established [4, 20] [21]; well educated people experience better health than poorly educated people. The current study adds to this evidence, as those with OA alone had a significantly higher education level, than those with more conditions.

Medication usage

Pain medication to help cope with OA is common [22], and is also common in the treatment of chronic pain. Unsurprisingly, in the current study medication usage is high with over half the participants with OA alone taking medication (58%), the most commonly used is paracetamol. As the number of comorbidities increases so does the use of pain medication, this itself is not surprising, there is however a potential cause for concern in the rapid increase in opioid usage from 4.6% to 19.5% going from zero to four plus comorbidities, considering the recent focus of opioid overuse

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[23], with further suggestion that there is considerable use in a OA setting [24]. This raises long term concerns especially when the analgesic effects of physical activity are so widely known [25, 26].

Physical activity and function with long-term health conditions

The present study found that the more long-term conditions a person had, the lower physical activity level and physical function. Physical inactivity, excessive fat levels, and pain, all of which increase in this cohort as the number of conditions increase, are connected with systemic low-grade inflammation, independent of BMI [27], which is part of the pathogenesis of a range of long-term, painful musculoskeletal and non-musculoskeletal conditions, which might explain their co-occurrence [28, 29]. The long-term conditions could lead to reduced physical function and decreased physical activity levels, which could worsen the inflammation and lead to the development of other long-term conditions, thereby creating a 'vicious cycle' of long-term low-grade inflammation [26, 30]. Maintaining or improving physical function is of particular importance for improving functional independence in later life [31].

Patient education is essential to ensure that people increase and maintain their physical function, activity level, and to reduce risk of secondary conditions especially in a younger cohort, who can implement longer term lifestyle changes. Education should include causes and the disease process of OA [26], importance of physical activity, and self-help tools in order for them to self-manage their conditions. It is also crucial to reassure patients that the belief that exercise therapy will damage their joints is a myth [26].

OA and comorbidity

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It is well established that low physical activity levels can contribute to the development of long term conditions [31] and slower walking pace is a predictor of mortality [32]. OA is an important factor in this, as it can cause pain in the joints, making movement and therefore activity painful and difficult for those who need it [26], coupled with a fear of movement itself, seen as a risk of causing more damage [26]. This in turn increases the risk of further development of other long term condition, which can make pain worsen and thereby even further reduce physical activity [33]. Even in the OA only group, problems walking was reported by 73% of the participants. This problem increases as the number of conditions increases but suggests that OA is one of the key barriers to walking [34]. With walking as one of the easiest ways of increasing physical activity, this can be very detrimental, although it must be noted that in this study it is unknown if OA or other morbidities came first. A recent study by Pereira [35] found that around 35% of people with one long term condition had problems walking compared to 77.4% in the present study. They further found that 68% of people with three long-term health conditions had problems walking compared to the 80% found in this study. OA not only includes physical problems but is often linked with psychological effect, with psychological distress more frequently experienced in patients with OA when compared to other chronic conditions [36]. This is seen in the present study with increased fear of movement and lower quality of life scores.

Prevalence within the general population

It is important to understand the present results in some context against the general population. OA is thought to be one of the most prevalent of all musculoskeletal

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diseases, affecting an estimated 10% of the world's population over the age of 60 [35]. Hypertension is also very prevalent within the population, and therefore it was not surprising that it was the most common disease found with OA in this study. It is important to note however, that hypertension prevalence is considerably higher in the current study (37%) than previous studies of the general population that found a prevalence of around 14% [37]. When split by age groups, prevalence in the general population was 13% in 60-69 year olds and 16% in 70-79 year olds. Diabetes has a prevalence in the general population of 6.8% [37], 8% in 60-69 year olds and 10% in 70-79 year olds [38], which is similar to the levels found in the same age group in the present study. Heart disease has a prevalence in the general population of 3.1 [37] and 10% prevalence in 60-69 year olds and 13% in 70-79-year olds [38], which is consistent with the present study. The prevalence of depression in the present study (4.3%) appears to be smaller than in the general population (9.9) aged 18 or over [38].

Clinical implications

Most research so far has excluded people with multimorbidity [39, 40], and most of the health care sector applies a single-disease framework focusing on the individual disease instead of focusing on the person most often having more than one long-term condition [41, 42]. This has an extensive negative impact on the quality of care in clinical practice and is inconvenient, inefficient and unsatisfactory for the individual with the long-term conditions and their health care provider [43-45].

In this large-scale study in primary care, we found that most people with OA have at least one other long-term condition and that the number of comorbidities is linked with the individual patient's health status. Therefore, patients with more than one

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long-term condition may require a more individualized treatment approach, e.g. require further supervision or lower intensity levels of the exercise due to cardiorespiratory conditions [46, 47], as well as needing additional time and support to overcome higher levels of pain, fear of pain and disability. Hence, clinicians are required to offer care adapted to the goals, needs and preferences of the individual patient and address the complexity and interaction of all the long-term conditions and treatments of the patient with multiple conditions. It is important to note that physical activity is an important part of this individualised care of patients with OA and comorbidities, as physical inactivity is a risk factor for at least 35 long-term conditions[31] and as exercise therapy is an effective treatment of at least 26 long-term conditions [29], including those commonly found in patients with OA. This highlights exercise therapy, supported by self-management and weight loss (if needed), as a treatment that might be particularly feasible and effective in patients with more than one chronic condition as it is able to improve health across different long-term conditions. Although this reflects current OA treatment recommendations [48, 49], it is important to recognize that the presence of other conditions may lower a patients baseline levels of physical function and require adaptations of the treatment, which would therefore potentially change the initial goals and expectation they should be setting.

Limitations

Some limitations of the study must be mentioned. First, all of the participants in this study are part of a preselected group; they are the population with OA who are

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actively seeking patient education and exercise therapy (GLA:D®) as treatment for OA (after referral from their general practitioner). Those who could not/would not seek this treatment may be different in some of the health status measures. It could well be that some of those who did not take part were worse off and had more long-term conditions. Second, 18% of participants reported having miscellaneous medical conditions and details on the individual conditions are unknown. Participants were asked if they had any other conditions not already included. Therefore, participants could have thought that this included conditions that may not have been diagnosed or were unrelated to the ongoing study, such as eczema. This feeds into another limitation, which is that all the comorbidities were self-reported, which may have led to inaccuracies in actual presence of long-term conditions [50]. This may have been the case with rheumatoid arthritis; before a supplementary text was added to explain that rheumatoid arthritis is different from OA in 10th July 2015, the prevalence was 10.43% (437 out of 4191), once the supplementary text was in place this dropped to 4.09% (805 out of 19661). It can therefore be questioned if those who filled in the questionnaire before this time understood the difference.

Conclusion

This is the first large-scale study of comorbidities in people with OA in primary care demonstrating that most people (62%) have at least one other long-term condition, with the most common being hypertension and the most common to cluster together being hypertension and diabetes. In patients with OA, more comorbidities are linked with lower education levels, higher pain frequency, and severity, more widespread pain, fear of pain, lower quality of life, higher use of pain medication (particularly opioids) physical activity levels and physical function. In educating and treating

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patients with OA, screening for comorbidities is important as these may affect the individual patient health status and treatment choices. Along with this, it is important for clinicians to consider and give information on how the treatments for OA will interact and help other common comorbidities, e.g. exercise which is an important treatment and prevention of many other long-term health conditions.

Acknowledgements

The authors would like to thank the clinicians and patients involved in collecting data for GLA:D®.

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Table and figure legends

Table 1. Frequency of number of other conditions in people with knee and hip osteoarthritis

Figure 1. Percentage of patients with osteoarthritis presenting with each other condition. Miscellaneous medical conditions were defined as any conditions other than those mentioned previously

Table 2. Frequency of total participants for top five pairs and trios of other conditions in people with knee and hip osteoarthritis

Table 3. Frequency and percentage of participants with hip and knee osteoarthritis against number conditions other than osteoarthritis

Table 4. Health status in people with knee and hip osteoarthritis and one or more other long-term conditions

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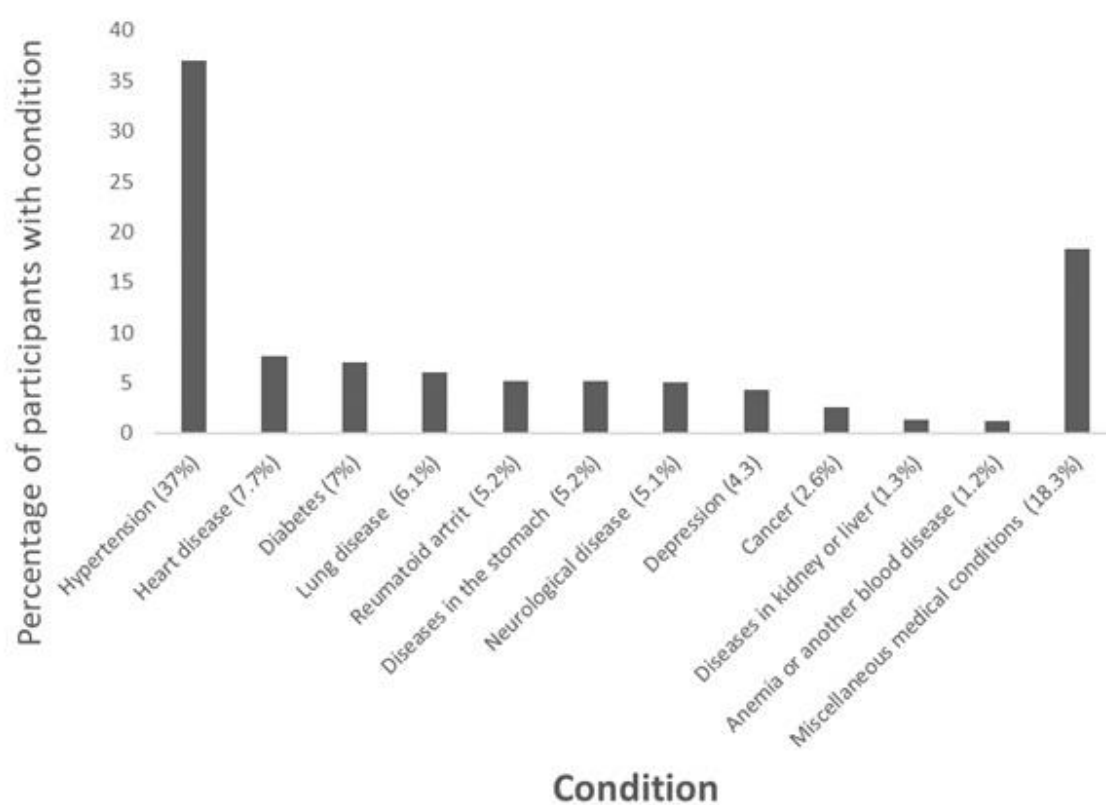


Figure 1. Percentage of patients with osteoarthritis presenting with each other condition. Miscellaneous medical conditions were defined as any conditions other than those mentioned previously