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Associations between comorbidities and immediate and one-year outcomes following supervised exercise therapy and patient education – A cohort study of 24,513 individuals with knee or hip osteoarthritis

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SUMMARY

Objective: To investigate if comorbidities are associated with change in health outcomes following an 8-week exercise and education program in knee and hip osteoarthritis (OA).
Methods: We included 24,513 individuals with knee or hip OA from the Good Life with osteoArthritis in Denmark (GLA:D®). GLA:D® consists of two patient education sessions and 12 supervised exercise sessions. Before the program, individuals self-reported having one or more of 11 common comorbidities. Physical function was assessed using the 40-m Fast-Paced Walk Test (FPWT, m/sec) before and immediately after the program. Pain intensity and health-related quality of life was self-reported before, immediately after, and at 12 months post-intervention using a visual analogue scale (VAS, 0–100) and the EQ-5D-5L index (−0.624 to 1.000), respectively. Associations of comorbidity combinations with change in outcomes immediately and at 12 months was estimated using mixed linear regression.
Results: Individuals with OA improved on average 0.12 m/s (95%CI 0.12 to 0.13) in 40-m FPWT, −12.7 mm (95%CI -13.2 to −12.2) in VAS, and 0.039 (95%CI 0.036 to 0.041) in EQ-5D-5L from before to immediately after the intervention with minor additional improvements at 12 months. Despite that individuals with comorbidities had worse baseline scores in all outcomes than individuals without comorbidities, they had similar levels of improvement immediately and 12 months after the intervention.
Conclusion: Comorbidities are not associated with worse nor better health outcomes following an 8-week exercise and education program in individuals with OA, suggesting exercise as a viable treatment option for individuals with OA, irrespective of comorbidities.

Introduction

Two thirds of individuals with knee or hip osteoarthritis (OA) have coexisting chronic conditions[1], including cardiovascular and pulmonary diseases, diabetes, and depression[2–4], and typically report worse pain intensity and physical function compared to those without multiple conditions[1,5,6].

Individuals with knee or hip OA are commonly managed in primary care, and international guidelines recommend exercise therapy as part of the first line treatment[7,8] supported by numerous randomised controlled trials (RCTs) demonstrating that exercise therapy is effective in reducing pain intensity and improving physical function and quality of life[9,10]. However, it is unclear, whether individuals with knee and hip OA and one or more comorbidities have similar improvements following exercise therapy as those without comorbidities. Unfortunately, the majority of published trials either excluded individuals with other conditions

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than OA or did not report results separately for those with comorbidities[9,10].

It is important to determine if outcomes from exercise therapy are suboptimal in individuals with OA and specific comorbidities or combinations of comorbidities in order to optimize outcomes by tailoring treatment programs specific to the needs of different subgroups. Only one recent study, limited by including just six comorbidities and a relatively low number of individuals with some of the comorbidities, has investigated if the presence of comorbidities was associated with pain and function outcome after exercise therapy[11]. They found that obesity and anxiety/depression were predictive of both pain and function outcomes, whereas estimates for pulmonary conditions and diabetes were imprecise due to few cases, precluding any clear interpretations.

Therefore, the main aim of this study was to investigate if presence of the most prevalent comorbidities and combinations of comorbidities were associated with immediate improvements in physical function following an eight-week supervised exercise and patient education program in a large-scale cohort of individuals with knee and hip OA. Additionally, we wanted to investigate any association with immediate and one-year improvements in health-related quality of life and pain relief.

Method

Study design

This study is a comparative cohort study using registry-based data from the Good Life with osteoArthritis in Denmark (GLA:D®) program. GLA:D® is a university-based not-for-profit initiative to facilitate implementation of treatment guidelines and has been implemented nationwide in Denmark for individuals with knee or hip OA. It consists of two patient education sessions followed by 12 60-min sessions of neuromuscular exercise (twice weekly over 6 weeks) supervised by certified physical therapists. The program is evaluated using pre-defined and validated outcomes prior to, immediately after (~3 months), and 12 months after initiating the program. The content of GLA:D® with regard to treatment and outcomes has previously been published[12], including details of the neuromuscular exercise program[13]. The Danish Data Protection Agency has previously approved the GLA:D® registry and all participants have consented to submitting their data to the registry. No ethics approval of GLA:D® is needed according to the local ethics committee of the North Denmark Region.

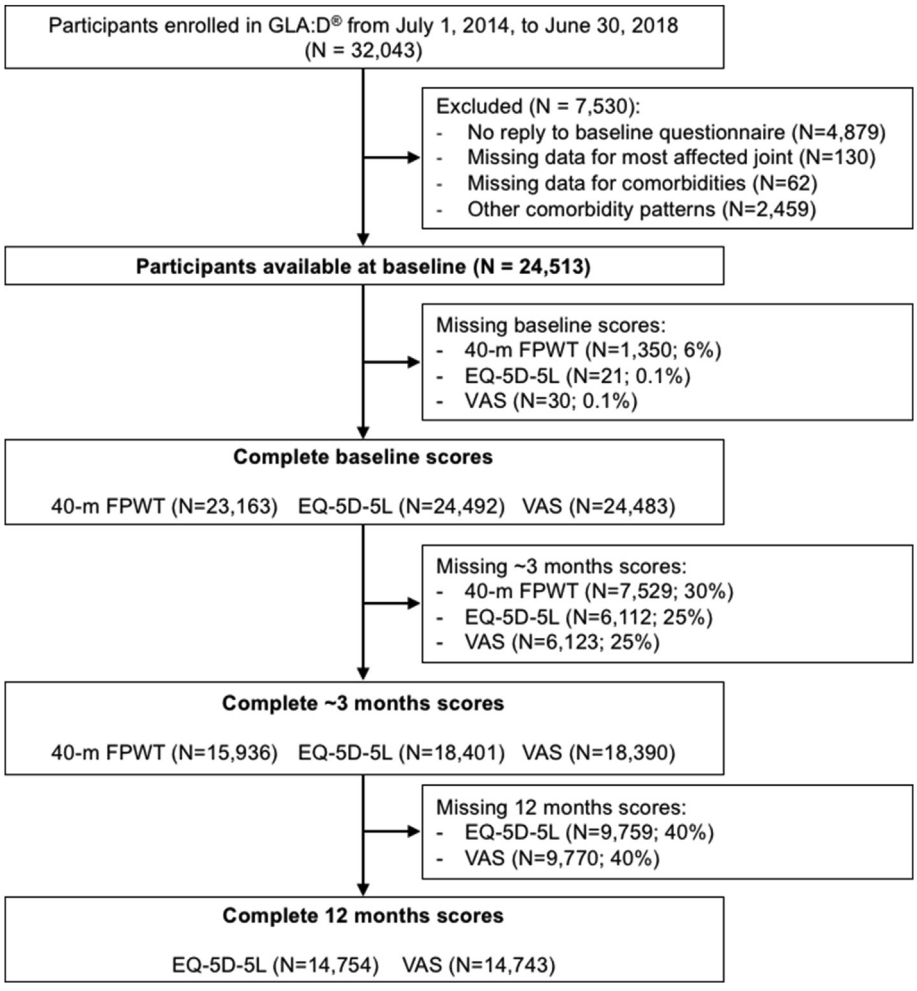

Fig. 1 Flowchart of included participants.

The reporting of this study conforms to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline[14].

Participants

Individuals with knee or hip pain and/or functional impairments, resulting in contact with the health care system are assessed for eligibility in GLA:D®. Individuals are ineligible if they have other reasons for their joint symptoms than OA as evaluated by the physical therapist, e.g., inflammatory joint disease or patellar tendinopathy, if they have other symptoms that are more pronounced than the OA symptoms, e.g., chronic, generalized pain, or fibromyalgia, or if they do not understand Danish.

In the present study, only participants with complete baseline data for the most affected joint and comorbidities were included (Fig. 1). Furthermore, only data from participants enrolled in GLA:D® in the period from July 1, 2014 to June 30, 2018 were used as no information about comorbidities were included before this period.

Comorbidities (exposure)

The exposure of interest in the present study was the presence of one or more comorbidities. Before entering GLA:D®, participants were asked to indicate if they had any of the following comorbidities (yes/no), some of them with explanations to guide the participants when answering: 'hypertension (HT)', 'heart diseases (HD) (e.g., narrowing of the heart's blood vessels)', 'ulcer or other bowel diseases', 'respiratory diseases (e.g., chronic obstructive pulmonary disease (COPD))', 'diabetes mellitus (DM, type 1 or 2)', 'kidney or liver diseases', 'anemia (i.e., reduced number of red blood cells) or other blood diseases', 'cancer', 'depression', 'rheumatoid arthritis (RA) (NB not the same as osteoarthritis)', or 'neurological diseases (e.g., blood clots in the brain, Parkinson's, or migraine)'. For analytic purposes, including having a sufficient number of participants in each comorbidity group, only the 20 most prevalent comorbidity combinations in GLA:D® were included in this study.

Outcomes

The main outcome was change in physical function from before to immediately after the treatment program assessed by the physical therapist (40-m Fast-Paced Walk Test (FPWT) (m/sec)). The FPWT is recommended by the Osteoarthritis Research Society International (OARSI) as a performance-based functional test for knee and hip OA[15]. A difference of minimum 0.20 m/s was considered as clinically important[16].

Secondary outcomes included change in quality of life and mean pain intensity from before to immediately after, and at 12 months after the program. Participants self-reported health-related quality of life using the EuroQol-5 dimensions five level index questionnaire (EQ-5D-5L), which is a generic quality of life measurement tool[17]. It was scored using the Danish crosswalk value set, and ranges from −0.624 to 1.000 corresponding to 'worst' and 'best' health, respectively. Change in self-reported mean pain intensity during the last month in the most affected knee was assessed on a 100-point visual analogue scale (VAS), which ranges from 0 corresponding to 'no pain' to 100 corresponding to 'maximum pain'[18]. For EQ-5D-5L and VAS differences of minimum 0.05 and 15 mm, respectively, were considered clinically important[17,19].

As an additional outcome, adherence to the supervised exercise sessions were reported by the physical therapist immediately after the program by replying to the question: 'How many exercise sessions did the patient attend?' with the reply options: 'more than 12 sessions', '10–12 sessions', '7–9 sessions', '1–6 sessions', and 'did not attend at all'. In the analyses, response options were dichotomized into 'less than 10 sessions' and '10 or more sessions'.

Statistical analyses

Multiple imputation

The proportion of missing data for the main outcome (40-m FPWT) at baseline and at follow-up (i.e., immediately after the GLA:D® program) was 6% and 30%, respectively, while the proportions for VAS at baseline, immediately after the program, and 12 months were 0.1%, 25% and 40%, respectively, which were the same for EQ-5D-5L (Fig. 1). For the additional outcome (adherence to exercise sessions) the proportion of missing data was 34% ($n = 8,247$). Under the assumption of data being missing at random (MAR)[20], missing values for the outcomes at all time points were imputed using multiple imputation with chained equations[21]. For the main and secondary outcomes, the multiple imputation model included all outcomes (i.e. 40-m FPWT, EQ-5D-5L, and VAS) at each time point, the exposure (i.e., comorbidity groups), confounders in the primary analysis (see under 'main analyses'), and as auxiliary variable the most affected joint. The same confounders and auxiliary variables were included in the imputation model for adherence to exercise sessions, whereas only the baseline scores for 40-m FPWT, EQ-5D-5L, and VAS were included in this model. Linear regression was used to impute 40-m FPWT, while predictive mean matching (PMM) was used for EQ-5D-5L and VAS, and logistic regression for adherence to exercise. A total of 30 imputed data sets approximately equal to the proportion of missing observations for the main outcome were generated[21].

Main analyses

The main outcome (between-group difference in 40-m FPWT change score from baseline to immediately after GLA:D®) was analyzed using linear mixed regression (restricted maximum likelihood estimation (REML)) with participants nested within clinics as random effects and group (no comorbidities vs different comorbidities) and time (baseline and immediately after GLA:D®) as fixed effects. Both unadjusted and adjusted differences with 95% confidence intervals were estimated across imputed data sets using Rubin's rules[22]. Included confounders in the adjusted analysis were age (continuous), sex (male/female), BMI (continuous), educational level (ordered categorical), not born in Denmark (yes/no – proxy of ethnicity), living alone (yes/no), pain in other joints (hip or knee – yes/no), use of analgesics within recent 3 months (yes/no), number of bodily pain sites (ordered categorical), and self-reported physical activity level (ordered categorical). A complete directed acyclic graph (DAG) of the assumed causal relationships is available in Supplementary Fig. S1. The same analysis approach was used for pain intensity and health-related quality of life, with the addition of 12 months follow-up.

Because bodily pain, pain in the other knee than the most affected joint or hip joints, physical activity level, and use of analgesics may be considered intermediate factors (see DAG in Supplementary Fig. S2), sensitivity analyses excluding these four variables as confounders were conducted. Furthermore, all analyses were repeated stratified for most affected joint (knee or hip), and lastly, the impact of missing data was explored by repeating all analyses using only participants with complete data at all time points (i.e., complete-case analysis). Assumptions underlying all models were examined using quantile–quantile plots and scatter plots of residuals and predicted values.

Additional analyses

As additional analyses, between group differences in change in all outcomes were analyzed using the same approach as for the main analyses, however substituting the group with number of comorbidities (i.e. 0 vs 1, 2, 3, or >3) instead of the specific comorbidity groups. Unadjusted and adjusted relative risks (RR) with 95% confidence interval for difference in risks of not adhering to exercise sessions between the different comorbidity groups were estimated from logistic regression[23] across imputed data sets using Rubin's rules[22]. Also, here the impact of missing data was explored by repeating the analyses using only participants with complete data at all time points (i.e., complete-case analysis).

All analyses were conducted using Stata V.16.1. Before any analyses commenced, the statistical analysis plan was uploaded to the Open Science Framework where the statistical codes used for the main analyses are also available (https://osf.io/8vdhq/).

Results

A total of 24,513 participants were included in the analyses, of whom 70% had complete data on the main outcome (40-m FPWT) at 3 months follow-up, while 75% and 60% had complete data for the secondary outcomes (EQ-5D-5L and VAS) at three and 12 months, respectively (Fig. 1). Among included participants, approximately two thirds were women and reported the knee as

	All (n = 24,513)	No comorbidities (n = 12,128)	Comorbidities (n = 12,385)
Most affected joint, *n* (%)			
Knee	18,271 (75)	8,923 (74)	9,348 (75)
Hip	6,242 (25)	3,205 (26)	3,037 (25)
Age, years (SD)	64.7 (9.7)	62.9 (10.1)	66.5 (9.0)
Female, *n* (%)	17,799 (73)	9,052 (75)	8,747 (71)
BMI, kg/m^2 (SD)*	28.2 (5.2)	27.3 (4.9)	29.1 (5.4)
Educational level, *n* (%)†			
Primary school	4,243 (17)	1,738 (14)	2,505 (20)
Secondary school	2,736 (11)	1,329 (11)	1,407 (11)
Short-term education‡	4,819 (20)	2,373 (20)	2,446 (20)
Middle-term education§	9,870 (40)	5,145 (42)	4,725 (38)
Long-term education‖	2,834 (12)	1,541 (13)	1,293 (10)
Born outside Denmark, *n* (%)¶	917 (4)	466 (4)	451 (4)
Living alone, *n* (%)#	6,216 (25)	2,751 (23)	3,465 (28)
Physical activity level, *n* (%)**			
Inactive	524 (2)	200 (2)	324 (3)
Low (e.g., walking and limited housework)	7,114 (29)	3,046 (25)	4,068 (33)
Moderate (e.g., swimming and unlimited housework)	8,104 (33)	4,007 (33)	4,097 (33)
High (e.g., prolonged biking and fitness)	7,125 (29)	3,870 (32)	3,255 (26)
Very high (e.g., running, tennis and skiing)	1,627 (7)	995 (8)	632 (5)
Pain in other knee or hip joints, *n* (%)			
No	10,535 (43)	5,387 (44)	5,148 (42)
Bilateral joint (from most affected joint)	8,696 (35)	4,294 (35)	4,402 (36)
Hip or knee††	4,200 (17)	1,966 (16)	2,234 (18)
Bilateral joint and hip or knee††	1,082 (4)	481 (4)	601 (5)
Number of bodily pain areas, *n* (%)			
0	679 (3)	356 (3)	323 (3)
1-2	10,966 (45)	5,656 (47)	5,310 (43)
3-4	6,732 (27)	3,290 (27)	3,442 (28)
5-6	2,838 (12)	1,370 (11)	1,468 (12)
seven or more	3,298 (13)	1,456 (12)	1,842 (15)
Use of analgesics within recent 3 months, *n* (%)‡‡	15,415 (63)	7,267 (60)	8,148 (66)
Quality of life (EQ-5D-5L, −0.624 to 1.000), mean (SD)§§	0.714 (0.112)	0.724 (0.107)	0.703 (0.115)
Pain intensity (VAS, 0-100 mm), mean (SD)‖‖	47.4 (21.9)	45.9 (21.8)	48.9 (21.9)
40 m Fast-Paced Walk Test, m/s (SD)¶¶	1.50 (0.33)	1.56 (0.33)	1.43 (0.32)

n: Number, SD: Standard Deviation, BMI: Body Mass Index (kg/m^2), VAS: Visual Analogue Scale.

* 69 missing observations.

† 11 missing observations.

‡ Under 3 years after secondary school.

§ 3-4 years after secondary school.

‖ At least 5 years after secondary school.

¶ 7 missing observations.

7 missing observations.

** 19 missing observations.

†† Hip if most affected joint is knee and vice versa.

‡‡ At least one of the following: Acetaminophen, oral or topical Non-Steroidal Anti-inflammatory Drug (NSAID), Morphine, Tramadol, or Codeine.

§§ 21 missing observations.

‖‖ 30 missing observations.

¶¶ 1,350 missing observations.

Table I Baseline characteristics of participants with and without comorbidities

the most affected joint, while the average age was 64.7 years (Table I). The most frequent comorbidities were HT alone (23%) and HT in combination with either DM or HD (6%), while the least frequent included anaemia and HT in combination with kidney/liver disease (<1%) (Table II and Supplementary Table S2). Participants with comorbidities were on average a little older and slightly more overweight than those with no comorbidities (Table I). Baseline characteristics in the specific comorbidity groups are available in Supplementary Table S2. Participants lost to follow-up had slightly poorer baseline scores in all outcome measures, while other characteristics were comparable to those with complete follow-up (Supplementary Table S1).

Main outcome (40-m FPWT)

Compared to participants without comorbidities, those with comorbidities had worse physical function (40-m FPWT) at baseline, which became more pronounced with increasing number of comorbidities (Table II). The average improvement from before to immediately after the treatment program was 0.12 m/s (95% CI 0.12 to 0.13) in participants without comorbidities. For all comorbidities but one, the average improvement did not statistically significantly differ from those without comorbidities. Only individuals with anaemia had significantly less improvement, however, all differences in improvements were close to 0.00 m/s with 95% confidence intervals excluding the predefined minimal clinically important difference of 0.20 m/s (Table II).

Secondary outcomes (EQ-5D-5L & VAS)

Participants with comorbidities had worse pain intensity (VAS) and quality of life (EQ-5D-5L) at baseline than those without comorbidities (Tables III and IV). In participants without comorbidities, pain intensity declined on average −12.7 mm (95% CI -13.2 to −12.2) and −13.8 mm (95% CI-14.3 to −13.4) immediately after the treatment and at 12 months, respectively, while quality of life improved by 0.039 (95% CI 0.036 to 0.041) and 0.051 (95% CI 0.048 to 0.053). In both outcomes, only six out of twenty single or combined comorbidities, including HD and HT in combination with different other conditions, had a statistically significant difference in change at either three or 12 months than those without comorbidities (Tables III and IV). Yet, for all comorbidities the point differences were only minor and all less than the predefined clinically important differences (15 mm for VAS, and 0.05 for EQ-5D-5L). Only for quality of life, participants with HT plus depression or neurologic disease, and participants with HT plus HD and DM confidence intervals included clinically important differences (Tables III and IV).

	Baseline 40-m FPWT Mean m/s (95% CI)	**3 mo. 40-m FPWT** Mean m/s (95% CI)	**Change 3 mo. 40-m FPWT** Mean m/s (95% CI)
No comorbidities, $n = 12{,}128$	1.56 (1.56–1.57)	1.69 (1.68–1.69)	0.12 (0.12–0.13)
	Difference at baseline	**Difference in change at 3 months**	
	Mean m/s (95% CI)	Unadjusted mean m/s (95% CI)	Adjusted* mean m/s (95% CI)
HT, $n = 5{,}716$	−0.12 (−0.13 to −0.11)	−0.00 (−0.01 to 0.01)	−0.00 (−0.01 to 0.01)
HT + DM, $n = 729$	−0.22 (−0.25 to −0.20)	−0.00 (−0.03 to 0.01)	0.00 (−0.02 to 0.02)
HT + HD, $n = 630$	−0.17 (−0.19 to −0.14)	−0.01 (−0.03 to 0.01)	−0.01 (−0.03 to 0.01)
Resp, $n = 558$	−0.07 (−0.10 to −0.04)	−0.01 (−0.03 to 0.01)	−0.01 (−0.03 to 0.01)
HD, $n = 551$	−0.09 (−0.11 to −0.06)	−0.01 (−0.03 to 0.01)	−0.01 (−0.03 to 0.01)
Neu, $n = 508$	−0.05 (−0.08 to −0.03)	0.00 (−0.02 to 0.02)	0.00 (−0.02 to 0.02)
RA, $n = 501$	−0.06 (−0.09 to −0.04)	0.02 (−0.00 to 0.04)	0.02 (−0.00 to 0.04)
Ulcer, $n = 447$	−0.05 (−0.08 to −0.02)	−0.01 (−0.03 to 0.01)	−0.01 (−0.04 to 0.01)
Dep, $n = 408$	−0.09 (−0.12 to −0.06)	0.01 (−0.02 to 0.04)	0.01 (−0.02 to 0.04)
DM, $n = 358$	−0.15 (−0.18 to −0.11)	−0,01 (−0.04 to 0.01)	−0.01 (−0.04 to 0.01)
HT + Resp, $n = 323$	−0.20 (−0.24 to −0.17)	−0.02 (−0.05 to 0.00)	−0.03 (−0.05 to 0.00)
HT + RA, $n = 275$	−0.14 (−0.18 to −0.10)	−0.03 (−0.06 to 0.00)	−0.03 (−0.06 to 0.00)
HT + Neu, $n = 274$	−0.14 (−0.18 to −0.10)	0.01 (−0.02 to 0.04)	0.01 (−0.02 to 0.04)
HT + Ulcer, $n = 254$	−0.16 (−0.20 to −0.12)	0.02 (−0.01 to 0.05)	0.02 (−0.01 to 0.05)
Cancer, $n = 234$	−0.06 (−0.10 to −0.02)	0.01 (−0.02 to 0.04)	0.01 (−0.02 to 0.04)
HT + Dep, $n = 203$	−0.21 (−0.26 to −0.17)	0.01 (−0.02 to 0.05)	0.01 (−0.02 to 0.05)
HT + Cancer, $n = 137$	−0.16 (−0.22 to −0.11)	−0.01 (−0.05 to 0.04)	−0.01 (−0.05 to 0.04)
HT + HD + DM, $n = 117$	−0.26 (−0.32 to −0.20)	0.01 (−0.04 to 0.06)	0.01 (−0.04 to 0.06)
Anemia, $n = 83$	−0.04 (−0.11 to 0.03)	**−0.06 (-0.11 to -0.1)**	**−0.06 (-0.11 to -0.01)**
HT + Ren/Liv. $n = 79$	−0.09 (−0.16 to −0.02)	−0.03 (−0.08 to 0.02)	−0.03 (−0.08 to 0.02)
Number of comorbidities			
1 comorbidity, $n = 9{,}441$	−0.10 (−0.11 to −0.9)	−0.00 (−0.01 to 0.01)	−0.00 (−0.01 to 0.01)
2 comorbidities, $n = 3{,}838$	−0.17 (−0.19 to −0.17)	−0.01 (−0.01 to 0.00)	−0.01 (−0.01 to 0.00)
3 comorbidities, $n = 1{,}173$	−0.23 (−0.25 to −0.21)	−0.00 (−0.02 to 0.01)	−0.00 (−0.02 to 0.01)
≥4 comorbidities, $n = 392$	−0.31 (−0.34 to −0.28)	0.01 (−0.02 to 0.03)	0.01 (−0.02 to 0.03)

n: Number, CI: Confidence interval. HT: Hypertension, DM: Diabetes mellitus one or 2, Resp: Respiratory disease, HD: Heart disease, Neu: Neurologic disease, RA: Rheumatoid arthritis, Dep: Depression, Ren/Liv: Renal and/or liver disease.

* Adjusted for age, sex, BMI, educational level, not born in Denmark, civil status, physical activity, problems in other joints, use of analgesics, and number of bodily pain areas. Estimates in bold reflect statistical significance ($P < 0.05$).

Table II 40-meter Fast-Paced Walk Test (40-m FPWT) differences at baseline, and changes immediately after exercise therapy and education between participants with and without comorbidities

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	Baseline VAS Mean mm (95% CI)	**3 mo. VAS** Mean mm (95% CI)	**Change 3 mo. VAS** Mean mmm (95% CI)	**12 mo. VAS** Mean mm (95% CI)	**Change 12 mo. VAS** Mean mm (95% CI)
No comor, $n = 12,128$	45.9 (45.5–46.3)	33.2 (32.7–33.6)	−12.7 (−13.2 to −12.2)	32.0 (31.6–32.5)	−13.8 (−14.3 to −13.4)
	Difference at baseline	**Difference in change at 3 months**		**Difference in change at 12 months**	
	Mean mm (95% CI)	Unadjusted mean mm (95% CI)	Adjusted* mean mm (95% CI)	Unadjusted mean mm (95% CI)	Adjusted* mean mm (95% CI)
HT, $n = 5,716$	2.1 (1.4–2.9)	0.3 (−0.6 to 1.1)	0.3 (−0.6 to 1.1)	1.2 (0.3–2.1)	**1.3 (0.4 to 2.2)**
HT + DM, $n = 729$	4.5 (2.8–6.2)	1.5 (−0.5 to 3.5)	1.5 (−0.5 to 3.5)	2.5 (0.4–4.7)	**2.6 (0.4 to 4.8)**
HT + HD, $n = 630$	3.2 (1.4–5.0)	−0.0 (−2.1 to 2.1)	0.0 (−2.1 to 2.1)	1.2 (−1.2 to 3.6)	1.2 (−1.2 to 3.6)
Resp, $n = 558$	2.7 (0.8–4.6)	0.2 (−2.1 to 2.5)	0.2 (−2.1 to 2.5)	1.5 (−1.0 to 4.1)	1.6 (−1.0 to 4.1)
HD, $n = 551$	−0.6 (−2.5 to 1.4)	3.5 (1.3–5.8)	**3.5 (1.3 to 5.8)**	4.0 (1.4–6.6)	**4.0 (1.4 to 6.6)**
Neu, $n = 508$	3.9 (1.9–5.9)	−1.5 (−3.8 to 0.9)	−1.3 (−3.6 to 1.1)	−0.6 (−3.8 to 0.9)	−0.6 (−3.2 to 2.0)
RA, $n = 501$	3.5 (1.5–5.5)	−1.2 (−3.8 to 1.3)	−1.1 (−3.7 to 1.4)	−0.8 (−3.4 to 1.9)	−0.7 (−3.4 to 2.0)
Ulcer, $n = 447$	5.7 (3.6–7.9)	−1.1 (−3.7 to 1.6)	−1.0 (−3.7 to 1.6)	−0.1 (−3.0 to 2.8)	−0.2 (−3.1 to 2.7)
Dep, $n = 408$	6.6 (4.4–8.9)	0.4 (−2.5 to 3.2)	0.3 (−2.5 to 3.2)	2.7 (−0.8 to 6.2)	2.7 (−0.8 to 6.2)
DM, $n = 358$	2.5 (0.2–4.9)	0.3 (−2.5 to 3.2)	0.3 (−2.5 to 3.2)	−0.6 (−3.9 to 2.8)	−0.5 (−3.9 to 2.8)
HT + Resp, $n = 323$	3.0 (0.5–5.5)	3.0 (0.0–5.9)	**3.0 (0.0 to 5.9)**	0.4 (−3.0 to 3.9)	0.4 (−3.0 to 3.8)
HT + RA, $n = 275$	3.9 (1.2–6.6)	1.9 (−1.4 to 5.1)	1.9 (−1.4 to 5.1)	2.4 (−1.2 to 6.0)	2.4 (−1.2 to 6.0)
HT + Neu, $n = 274$	2.2 (−0.5 to 4.9)	5.1 (1.8–8.4)	**5.0 (1.7 to 8.3)**	7.2 (3.7–10.7)	**7.1 (3.6 to 10.6)**
HT + Ulcer, $n = 254$	7.5 (4.7–10.3)	−0.5 (−4.0 to 3.0)	−0.3 (−3.8 to 3.3)	2.7 (−1.1 to 6.6)	2.9 (−0.9 to 6.8)
Cancer, $n = 234$	1.4 (−1.5 to 4.3)	2.5 (−1.1 to 6.0)	2.5 (−1.1 to 6.0)	2.9 (−0.8 to 6.7)	2.9 (−0.8 to 6.7)
HT + Dep, $n = 203$	7.7 (4.5–10.8)	−1.3 (−6.0 to 2.6)	−1.3 (−5.2 to 2.7)	2.3 (−2.3 to 6.9)	2.4 (−2.3 to 7.0)
HT + Cancer, $n = 137$	1.0 (−2.8 to 4.8)	5.3 (0.8–9.9)	**5.4 (0.9 to 10.0)**	0.2 (−4.9 to 5.3)	0.3 (−4.8 to 5.4)
HT + HD + DM, $n = 117$	6.6 (2.5–10.7)	0.2 (−5.5 to 5.1)	0.1 (−5.5 to 5.2)	−1.4 (−8.4 to 5.6)	−1.4 (−8.4 to 5.6)
Anemia, $n = 83$	2.7 (−2.1 to 7.6)	−1.2 (−7.0 to 4.6)	−1.2 (−7.0 to 4.6)	−2.8 (−9.2 to 3.6)	−2.7 (−9.1 to 3.6)
HT + Ren/Liv. $n = 79$	2.9 (−2.1 to 7.9)	−0.2 (−6.4 to 5.9)	−0.2 (−6.4 to 5.9)	3.0 (−3.7 to 9.8)	3.1 (−3.7 to 9.8)
Number of comorbidities					
1 comorbidity, $n = 9,441$	2.6 (1.9–3.2)	0.2 (−0.5 to 0.0)	0.2 (−0.5 to 0.9)	1.1 (0.3–1.9)	**1.1 (0.4 to 1.9)**
2 comorbidities, $n = 3,838$	4.5 (3.7–5.4)	1.4 (0.4–2.3)	**1.4 (0.4 to 2.3)**	1.9 (0.9–2.9)	**1.9 (0.9 to 2.9)**
3 comorbidities, $n = 1,173$	7.5 (6.1–8.8)	0.5 (−1.1 to 2.0)	0.5 (−1.1 to 2.1)	1.3 (−0.6 to 3.1)	1.3 (−0.6 to 3.1)
≥4 comorbidities, $n = 392$	11.8 (9.5–14.1)	2.6 (−0.2 to 5.4)	2.7 (−0.1 to 5.5)	0.3 (−3.1 to 3.7)	0.3 (−3.1 to 3.8)

n: Number, CI: Confidence interval. Comor: Comorbidities, HT: Hypertension, DM: Diabetes mellitus one and 2, Resp: Respiratory disease, HD: Heart disease, Neu: Neurologic disease, RA: Rheumatoid arthritis, Dep: Depression, Ren/Liv: Renal and/or liver disease.

* Adjusted for age, sex, BMI, educational level, not born in Denmark, civil status, physical activity, problems in other joints, use of analgesics, and number of bodily pain areas. Estimates in bold reflect statistical significance ($P < 0.05$).

Table III Knee and hip pain (VAS) differences at baseline, and changes immediately after, and 12 months after exercise therapy and education between participants with and without comorbidities

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For both the main and secondary outcomes, results from sensitivity analyses did not alter the interpretation from the main analyses (Supplementary Tables S3–S11).

Adherence to exercise sessions

The overall proportion of participants not attending 10 or more exercise sessions were 17% (95% CI 17–18%). Most comorbidity groups were not associated with adherence to exercise sessions (Table V). Participants with HT plus DM, and those with HT plus cancer were more likely to attend 10 or more sessions, while those with depression or DM alone, HT plus RA, HT plus neurologic disease, HT plus depression, and with two, four or more comorbidities were less likely to attend 10 or more exercise sessions than individuals without comorbidities. However, for most associations the lower or upper limit of the 95% confidence interval was close to 1.00 (i.e., no association) (Table V). In the complete-case analysis, all observed associations in the primary analysis diminished and the associations observed for depression, HT plus RA, HT plus neurologic disease, HT plus cancer, and those with two comorbidities became inconclusive with 95% confidence intervals that include 1.00 (Supplementary Table S12).

Discussion

We found that individuals with knee and hip OA and comorbidities had worse function, pain, and quality of life prior to participating in an 8-week exercise and education, as compared to individuals without comorbidities. However, they experienced comparable improvements in walking speed, pain intensity and health-related quality of life and, largely, adhered to the exercise therapy program to the same extent as those without comorbidities. Our findings indicate that presence of comorbidities is not associated with clinically important differences in outcomes after exercise therapy and suggest that individuals with knee or hip OA may be offered supervised exercise therapy and patient education regardless of having comorbidities or not.

	Baseline EQ-5D-5L Mean (95% CI)	3 mo. EQ-5D-5L Mean (95% CI)	Change 3 mo. EQ-5D-5L Mean (95% CI)	12 mo. EQ-5D-5L Mean (95% CI)	Change 12 mo. EQ-5D-5L Mean (95% CI)
No comor, $n = 12{,}128$	0.724 (0.722–0.726)	0.763 (0.760–0.765)	0.039 (0.036–0.041)	0.775 (0.773–0.778)	0.051 (0.048–0.053)
	Difference at baseline	**Difference in change at 3 months**		**Difference in change at 12 months**	
	Mean (95% CI)	Unadjusted mean (95% CI)	Adjusted* mean (95% CI)	Unadjusted mean (95% CI)	Adjusted* mean (95% CI)
HT, $n = 5{,}716$	−0.010 (−0.013 to −0.006)	−0.004 (−0.008 to 0.001)	−0.004 (−0.008 to 0.001)	−0.008 (−0.012 to −0.003)	**−0.008 (-0.012 to -0.003)**
HT + DM, $n = 729$	−0.025 (−0.031 to −0.016)	−0.007 (−0.017 to 0.004)	−0.007 (−0.017 to 0.004)	−0.019 (−0.031 to −0.007)	**−0.019 (-0.031 to -0.008)**
HT + HD, $n = 630$	−0.022 (−0.031 to −0.012)	0.000 (−0.011 to 0.011)	0.000 (−0.012 to 0.011)	−0.023 (−0.037 to −0.009)	**−0.023 (-0.038 to -0.009)**
Resp, $n = 558$	−0.016 (−0.027 to −0.006)	0.000 (−0.011 to 0.012)	0.000 (−0.011 to 0.012)	−0.008 (−0.022 to 0.005)	−0.008 (−0.022 to 0.005)
HD, $n = 551$	−0.005 (−0.016 to 0.005)	- 0.014 (−0.025 to −0.003)	**−0.014 (-0.025 to -0.003)**	−0.016 (−0.029 to −0.002)	**−0.015 (-0.029 to -0.002)**
Neu, $n = 508$	−0.024 (−0.035 to −0.013)	0.002 (−0.011 to 0.014)	0.001 (−0.011 to 0.014)	−0.001 (−0.015 to .013)	−0.001 (−0.015 to 0.013)
RA, $n = 501$	−0.029 (−0.040 to −0.018)	0.010 (−0.003 to 0.023)	0.010 (-0.003 to 0.022)	−0.001 (−0.015 to 0.013)	−0.001 (−0.015 to 0.013)
Ulcer, $n = 447$	−0.036 (−0.047 to −0.024)	0.004 (−0.010 to 0.018)	0.004 (−0.010 to 0.018)	−0.010 (−0.027 to 0.006)	−0.010 (−0.027 to 0.006)
Dep, $n = 408$	−0.112 (−0.124 to −0.100)	0.014 (−0.001 to 0.029)	**0.014 (0.000 to 0.029)**	0.000 (−0.017 to 0.017)	0.000 (−0.017 to 0.017)
DM, $n = 358$	−0.018 (−0.031 to −0.005)	0.000 (−0.017 to 0.017)	−0.002 (−0.017 to 0.012)	0.010 (−0.007 to 0.027)	0.010 (−0.007 to 0.028)
HT + Resp, $n = 323$	−0.024 (−0.038 to −0.010)	−0.003 (−0.018 to 0.012)	−0.007 (−0.022 to 0.009)	−0.002 (−0.019 to 0.015)	−0.002 (−0.019 to 0.015)
HT + RA, $n = 275$	−0.024 (−0.039 to −0.010)	0.010 (−0.007 to 0.027)	−0.002 (−0.019 to 0.015)	−0.008 (−0.027 to 0.011)	−0.008 (−0.028 to 0.011)
HT + Neu, $n = 274$	−0.019 (−0.034 to −0.005)	−0.007 (−0.022 to 0.009)	−0.012 (−0.030 to 0.005)	−0.032 (−0.051 to −0.012)	**−0.032 (-0.051 to -0.012)**
HT + Ulcer, $n = 254$	−0.030 (−0.046 to −0.015)	−0.002 (−0.019 to 0.015)	−0.001 (−0.019 to 0.016)	−0.015 (−0.034 to 0.005)	−0.014 (−0.034 to 0.005)
Cancer, $n = 234$	−0.014 (−0.030 to 0.002)	−0.003 (−0.020 to 0.014)	−0.008 (−0.026 to 0.010)	−0.015 (−0.033 to 0.004)	−0.015 (−0.033 to 0.004)
HT + Dep, $n = 203$	−0.109 (−0.126 to −0.092)	−0.008 (−0.027 to 0.011)	0.014 (−0.008 to 0.036)	0.024 (−0.004 to 0.053)	0.024 (−0.005 to 0.053)
HT + Cancer, $n = 137$	−0.009 (−0.029 to 0.012)	−0.012 (−0.030 to 0.005)	−0.023 (−0.045 to 0.000)	−0.003 (−0.028 to 0.022)	−0.003 (−0.028 to 0.022)
HT + HD + DM, $n = 117$	−0.048 (−0.071 to −0.026)	−0.002 (−0.019 to 0.016)	−0.012 (−0.039 to 0.016)	0.022 (−0.011 to 0.054)	0.022 (−0.010 to 0.054)
Anemia, $n = 83$	−0.003 (−0.024 to 0.029)	−0.008 (−0.026 to 0.010)	−0.002 (−0.032 to 0.029)	0.010 (−0.023 to 0.043)	0.010 (−0.023 to 0.043)
HT + Ren/Liv. $n = 79$	−0.018 (−0.045 to 0.009)	0.015 (−0.007 to 0.037)	0.002 (−0.030 to 0.034)	−0.001 (−0.036 to 0.035)	−0.001 (−0.036 to 0.035)
Number of comorbidities					
1 comorbidity, $n = 9{,}441$	−0.017 (−0.021 to −0.014)	−0.002 (−0.005 to 0.002)	−0.002 (−0.005 to 0.002)	−0.006 (−0.011 to −0.002)	**−0.006 (-0.011 to -0.002)**
2 comorbidities, $n = 3{,}838$	−0.036 (−0.040 to −0.031)	−0.002 (−0.007 to 0.003)	−0.002 (−0.007 to 0.003)	−0.011 (−0.017 to −0.006)	**−0.011 (-0.017 to -0.006)**
3 comorbidities, $n = 1{,}173$	−0.060 (−0.068 to −0.053)	−0.006 (−0.014 to 0.003)	−0.006 (−0.015 to 0.003)	−0.013 (−0.024 to −0.003)	**−0.014 (-0.024 to -0.003)**
≥4 comorbidities, $n = 392$	−0.111 (−0.124 to −0.098)	−0.005 (−0.011 to 0.022)	0.005 (−0.011 to 0.022)	−0.004 (−0.024 to 0.017)	−0.004 (−0.024 to 0.017)

n: Number, CI: Confidence interval. Comor: Comorbidities, HT: Hypertension, DM: Diabetes mellitus one and 2, Resp: Respiratory disease, HD: Heart disease, Neu: Neurologic disease, RA: Rheumatoid arthritis, Dep: Depression, Ren/Liv: Renal and/or liver disease.

* Adjusted for age, sex, BMI, educational level, not born in Denmark, civil status, physical activity, problems in other joints, use of analgesics, and number of bodily pain areas. Estimates in bold reflect statistical significance ($P < 0.05$).

Table IV Quality of life (EQ-5D-5L) differences at baseline, and changes immediately after, and 12 months after exercise therapy and education between participants with and without comorbidities

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	Attending <10 exercise sessions, *n* (%)	Unadjusted RR (95% CI)	Adjusted* RR (95% CI)
No comor, $n = 12,128$	2,161 (18)	1 (reference)	1 (reference)
HT, $n = 5,716$	925 (16)	0.91 (0.85–0.97)	1.02 (0.95–1.09)
HT + DM, $n = 729$	85 (12)	0.65 (0.53–0.80)	**0.74 (0.61 to 0.91)**
HT + HD, $n = 630$	100 (16)	0.89 (0.74–1.07)	1.06 (0.88–1.27)
Resp, $n = 558$	94 (17)	0.94 (0.78–1.14)	1.02 (0.85–1.23)
HD, $n = 551$	74 (13)	0.75 (0.61–0.94)	0.88 (0.71–1.09)
Neu, $n = 508$	95 (19)	1.05 (0.87–1.26)	1.06 (0.88–1.28)
RA, $n = 501$	95 (19)	1.06 (0.88–1.28)	1.09 (0.91–1.31)
Ulcer, $n = 447$	82 (18)	1.03 (0.85–1.326)	1.03 (0.85–1.26)
Dep, $n = 408$	106 (26)	1.46 (1.23–1.73)	**1.32 (1.11 to 1.57)**
DM, $n = 358$	80 (22)	1.26 (1.03–1.53)	**1.36 (1.12 to 1.65)**
HT + Resp, $n = 323$	55 (17)	0.96 (0.75–1.22)	1.16 (0.92–1.46)
HT + RA, $n = 275$	56 (20)	1.15 (0.90–1.45)	**1.27 (1.01 to 1.60)**
HT + Neu, $n = 274$	56 (20)	1.14 (0.90–1.45)	**1.27 (1.00 to 1.60)**
HT + Ulcer, $n = 254$	34 (13)	0.75 (0.55–1.03)	0.89 (0.66–1.21)
Cancer, $n = 234$	38 (16)	0.91 (0.68–1.22)	1.01 (0.76–1.35)
HT + Dep, $n = 203$	61 (30)	1.69 (1.37–2.09)	**1.75 (1.41 to 2.17)**
HT + Cancer, $n = 137$	9 (7)	0.37 (0.20–0.70)	0.45 (0.24–0.84)
HT + HD + DM, $n = 117$	23 (20)	1.10 (0.76–1.59)	1.30 (0.92–1.86)
Anemia, $n = 83$	15 (18)	1.01 (0.64–1.60)	1.09 (0.69–1.71)
HT + Ren/Liv. $n = 79$	9 (11)	0.64 (0.34–1.18)	0.70 (0.38–1.29)
Number of comorbidities			
1 comorbidity, $n = 9,441$	1,575 (17)	0.93 (0.87–0.98)	1.01 (0.95–1.08)
2 comorbidities, $n = 3,838$	665 (17)	0.96 (0.89–1.04)	**1.09 (1.01 to 1.18)**
3 comorbidities, $n = 1,173$	174 (15)	0.82 (0.71–0.95)	0.94 (0.81–1.08)
≥4 comorbidities, $n = 392$	79 (20)	1.12 (0.91–1.36)	**1.24 (1.02 to 1.52)**

n: Number, CI: Confidence interval. Comor: Comorbidities, HT: Hypertension, DM: Diabetes mellitus one and 2, Resp: Respiratory disease, HD: Heart disease, Neu: Neurologic disease, RA: Rheumatoid arthritis, Dep: Depression, Ren/Liv: Renal and/or liver disease.

* Adjusted for age, sex, BMI, educational level, not born in Denmark, civil status, physical activity, problems in other joints, use of analgesics, and number of bodily pain areas. Estimates in bold reflect statistical significance ($P < 0.05$).

Table V Relative risks (RR) for not adhering to ten or more exercise sessions during an exercise therapy and education program for individuals with comorbidities compared to individuals without comorbidities

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To our knowledge, this is the first study to investigate the association of a large number of possible comorbidities with health outcomes after an exercise and education program for individuals with knee and hip OA. Only Legha *et al.* has recently made the attempt, however only included six different conditions with a smaller sample size and without investigating the association of different combinations of comorbidities[11]. They found an association between obesity and anxiety/depression with patient-reported pain and function after exercise therapy at 6 months follow-up, but no associations between diabetes, cardiac or pulmonary conditions, or pain in other body parts and the outcomes. Our results are generally in line with their findings, although presence of depression were not associated with outcomes in the present study and that obesity was not included as a comorbidity, but a possible confounder for the association of other conditions with outcomes. The contrasting results may partly be explained by the deviating methods used for determining depression in Legha *et al.* and the present study. Where participants in GLA:D® were asked specifically with a binary reply option (yes/no) if they had depression, presence of depression in the previous study was assessed using a single item from the EQ-5D questionnaire, which is intended for assessing severity of anxiety/depression symptoms and not for diagnosing depression. The confidence in our findings is strengthened by similar immediate and 1-year results and by the objectively measured physical function, which supported the findings in the patient-reported outcomes (pain and quality of life) between individuals with and without comorbidities.

None of the identified differences in change in any of the outcomes in the present study between those with and without comorbidities reached the levels of the pre-defined clinically important differences, which partly may be partially explained by the overall relatively small observed improvements leaving less room for difference in change between the comorbidity groups. However, it should be noted that what constitutes a clinically important difference is not a fixed value[24]. In individuals with OA differences of 0.2–0.3 in 40 m-FPWT have been reported as clinically important[16] and even lower (0.05–0.19) in other populations[25,26]. The same for VAS where values ranging from seven to 37 mm, depending on the baseline pain intensity (low to high, respectively), have been reported as clinically important[19]. Still, taking the different levels of clinically important differences into account does not alter the overall interpretation of important differences between patients with and without comorbidities being absent in the present study.

Previous studies have suggested anxiety and depression as barriers for engagement and adherence to exercise in individuals with OA[27,28], which is supported by our main results, as the proportion of individuals not adhering to 10 or more exercise sessions was highest among individuals with depression (Table V). However, the estimates were inconsistent in the sensitivity analysis with diminished RRs and wide confidence intervals that include 1.00, precluding any clear interpretation. Since adherence is important for the outcome of exercise therapy[29,30], one would assume that anxiety and depression would be associated with outcomes after

exercise therapy, if it had an effect on adherence to exercise therapy. However, this was not demonstrated in our study, as individuals with OA and depression had similar improvements in all outcomes as individuals without depression. A few comorbidity groups did show a small, statistically significant association with higher or lower risk of not attending 10 or more exercise sessions. Given the large number of statistical tests in the present study, caution should be taken when interpreting the importance of these findings, especially as the observed findings may be difficult to explain clinically and would need further investigation.

In the present study, individuals with comorbidities had worse baseline scores in all outcomes, which is similar to findings from other studies[5], and also similar to a recent study from the GLA:D® cohort including a range of other health status outcomes[6]. This was especially evident for physical function and quality of life where particularly those with two or more comorbidities had poorer health status at baseline than individuals without comorbidities. Although it is positive that comorbidities seem not to be associated with worse or better outcomes after exercise therapy and education that also means that the poorer health status at baseline is retained after such a treatment. To reduce the absolute difference in health status between those with and without comorbidities after treatment, it may therefore still be important to screen for and target certain comorbidity groups with further or more individualized treatment. For instance, a recent Dutch trial found that such an individualized, comorbidity-adapted exercise program, taking into account any comorbidity specific restrictions for exercise, was effective in improving physical function and safe in patients with knee OA and severe comorbidities[31]. This supports that exercise therapy may be a viable option for individuals with OA and comorbidities. In relation to this, it should be stressed that the exercise sessions in GLA:D® mainly comprise neuromuscular exercises[13], thus it is unknown if our results may differ if other exercise types were applied, e.g., exercises focusing on aerobic capacity in individuals with OA and comorbidities such as diabetes and cardiovascular diseases[32]. In addition, our findings may only apply to individuals with OA and comorbidities in a less severe state, due to restrictions and contraindications for exercise therapy in individuals with more severe comorbidities (e.g., unstable angina)[33], which may have led doctors not to refer some individuals to GLA:D®.

This study has some limitations. First, due to the observational single-arm design we were unable to assess if presence of comorbidities has an impact on the effect of exercise therapy (i.e., is a moderator) or simply is a prognostic factor regardless of type of treatment[34]. Second, the accuracy of self-reported comorbidities can be debated and has likely resulted in some misclassification. Also, we lack knowledge of the severity of reported comorbidities and were unable to distinguish between what specific conditions the comorbidity categories mainly comprised (e.g., which type of heart disease), however, some of the comorbidity questions included examples or explanations of specific conditions, which possibly have resulted in more uniform replies from participants. As there is no reason to suspect any misclassification to be associated with the outcomes, we believe that misclassifications are most likely to be non-differential. Second, the proportion of missing data for all outcomes was relatively large. However, as missingness and outcome scores were statistically significantly associated with baseline characteristics (data not shown), we assumed data to be missing at random (MAR)[20] and imputed missing data using multiple imputation, which largely showed similar results as complete case analyses. Fourth, the analyses were based on clinical registry data reflecting wider variations in treatment protocols and collection of data than in clinical trials. However, the large sample of individuals with knee or hip OA from a nationwide clinical registry supports the generalizability of the findings to clinical practice. Still, selection bias cannot be ruled out as participants in GLA:D® is a selected group seeking physiotherapy for their OA symptoms where those with severe comorbidities may be detained by physicians from exercise therapy due to restrictions or contraindications for exercise therapy[33], or referred to other suitable therapies, e.g., cardiac or pulmonary rehabilitation programs. This may partly be reflected by fewer individuals reporting having comorbidities and a much lower prevalence of comorbidities such as pulmonary disease and depression than previously reported from primary care in the United Kingdom[2,11]. Some of these discrepancies might be a consequence of different groupings and definitions of conditions but suggest that participants in GLA:D® overall are healthier than individuals with OA in general, which might partially explain the absence of associations between comorbidities and outcomes after exercise therapy in the present study.

In conclusion, we found that individuals with knee or hip OA having one or more comorbidities had worse baseline physical function, pain intensity and quality of life, but improved similarly in the same outcomes after an 8-week exercise therapy and patient education program as compared to individuals without comorbidities, indicating that presence of comorbidities is not associated with clinically important differences in outcomes after exercise and education. This suggests that a combined exercise therapy and patient education program may be recommended as treatment to individuals with knee or hip OA irrespective of whether they have comorbidities or not.

Author contributions

Conception and design: KP, EMR, RST, DTG and STS.
Acquisition of data: STS and EMR.
Analysis and interpretation of data: KP, EMR, RST, DTG and STS.
Drafting manuscript: KP and STS.
Revising manuscript and approving final version of manuscript: All authors.
Obtaining of funding: STS.
All authors take responsibility for the integrity of the data analyses.

Conflict of interest

EMR is deputy editor of Osteoarthritis and Cartilage, the developer of 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 non-for-profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

STS is associate editor of the Journal of Orthopaedic & Sports Physical Therapy and has received a grant from The Lundbeck Foundation and personal fees from Munksgaard, all of which are outside the submitted work. Furthermore, he is co-founder of GLA:D®. The authors report no other conflicts of interests.

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Supplementary data

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