SUPPLEMENTARY MATERIAL

Researcher List of SOC Study Group

Leading Principal Instructor

Changqing Zhang - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Contributing Principal Instructor

Qirong Qian - Department of Orthopaedics, Shanghai Changzheng Hospital, Shanghai, People’s Republic of China

Zhenjun Yao - Department of Orthopaedics, Zhongshan Hospital Fudan University, Shanghai, People’s Republic of China

Guodong Li - Department of Orthopaedics, Shanghai Tenth People's Hospital, Shanghai, People’s Republic of China

Yong Feng - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Yigang Huang - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Chenyi Jiang - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Weitao Jia - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Guangyi Li - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Xiaochun Peng - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Hao Shen - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Huipeng Shi - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Yunchao Shao - Department of Orthopaedics, Zhongshan Hospital Fudan University, Shanghai, People’s Republic of China

Kun Tao - Department of Orthopaedics, Shanghai Tenth People's Hospital, Shanghai, People’s Republic of China

Bo Wang - Department of Orthopaedics, Shanghai Changzheng Hospital, Shanghai, People’s Republic of China

Xuetao Xie - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Zongping Xie - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Ting Yuan - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Xiaowei Yu - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Xiaoyu Yan - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People’s Republic of China

Yi Yang - Department of Orthopaedics, Zhongshan Hospital Fudan University, Shanghai, People's Republic of China
Zhenzhong Zhu - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China
Qianying Cai - Shanghai Institute of Microsurgery on Extremities, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China
Shengbao Chen - Shanghai Institute of Microsurgery on Extremities, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China
Kai Fu - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China
Kaiyuan Liu - Department of Orthopaedics, Shanghai Tenth People's Hospital, Shanghai, People's Republic of China
Huan Wang - Department of Orthopaedics, Shanghai Changzheng Hospital, Shanghai, People's Republic of China
Shengcheng Wan - Department of Orthopaedics, Zhongshan Hospital Fudan University, Shanghai, People's Republic of China
Hongyi Zhu - Department of Orthopaedics, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China
Yiqin Zhou - Department of Orthopaedics, Shanghai Changzheng Hospital, Shanghai, People's Republic of China
Principal Instructor for Statistical analysis and methodology
Yanyan Song - Department of Biostatistics, Clinical Research Institute, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China

Brief protocol of Shanghai Osteoarthritis Cohort (SOC)

Design

This multicentre, prospective, observational cohort was initiated by the SOC Study Group which consists of researchers from four academic hospitals in Shanghai on clinically diagnosed knee/hip OA, aiming at identifying prognostic factors for incident progression of clinically diagnosed OA. Participants were routinely followed up once per year by phone call. Radiographic and therapeutic data and other clinically relevant information were extracted from institutional Health Information System (HIS) and reported by participants. The study was approved by the medical ethics committees of all participating centres (Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine; Shanghai Changzheng Hospital; Zhongshan Hospital Fudan University; Shanghai Tenth People's Hospital) and informed consent was obtained from all participants. Patients were encouraged to choose SOC centres and/or our collaborated GPs as their primary choices for OA management.

Study population

From January 2011, patients who visited the four medical centres with a clinical diagnosis of HOA/KOA by orthopedic specialists were assessed for eligibility. Inclusion criteria: (1) clinically diagnosed KOA and/or HOA; (2) age > 45 years at enrollment; (3) willing to be followed up at least once per year. Exclusion criteria: (1) any other rheumatic diseases; 2) previous hip or knee joint replacement; (3) osteochondritis dissecans; (4) history of intraarticular lower limb fractures; (5) history of lower limb septic arthritis; (6) malignancy in the past 5 years; (7) understand neither written nor spoken Mandarin.

Criteria for ending follow up: (1) did not complete annual follow-up in two consecutive years; (2) voluntarily withdraw from the study; (3) receiving hip or knee joint replacement.

Baseline variables

At baseline, all demographic and clinical characteristics including current age, age at initial diagnosis of OA, smoking status, weight, height, residential address, phone number, email address (optional), education level (optional), income (optional) and presence of baseline co-morbidities were self-reported by the participants. The baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (normalised to scores within a range of 0–100) was collected. The WOMAC questionnaire is a well-validated instrument consisting of 24 questions with three separate dimensions (pain, physical function, and stiffness) in OA.[1] All participants received blood cell counting, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), antibodies to cyclic citrulline peptide (anti-CCP) tests at enrollment.

All KOA participants underwent weightbearing semi-flexed posteroanterior knee radiographs with a standard protocol. [2] Briefly, each participant was instructed to position their knee facing a vertical table, with their toes touching the table and weight evenly distributed between both legs. The feet were rotated externally by approximately 10° and images were captured using a horizontal X-ray beam that was centred on the joint line. The captured image was assessed by a senior radiologist. If necessary, the participant was then instructed to reposition his or her knee and receive one or more replicate exposures until obtaining a satisfactory image. All hip radiographs for HOA patients were obtained with the patient in a weight-bearing position. The X-ray beam was arranged in an anterior-posterior orientation, parallel to the horizon and at a right angle to the table. Pelvis radiographs were

executed with approximately 15° of internal foot rotation and with the X-ray beam aimed at the upper border of the pubic symphysis. In the case of hip anterior-posterior views, approximately 15° of internal foot rotation was likewise necessary, but the X-ray beam was targeted at the joint space.[3] The K-L grades were then reviewed and rated by an independent radiographic evaluation committee consisting of three radiologists specialising in musculoskeletal radiology.

MRI Scanning and Measurement

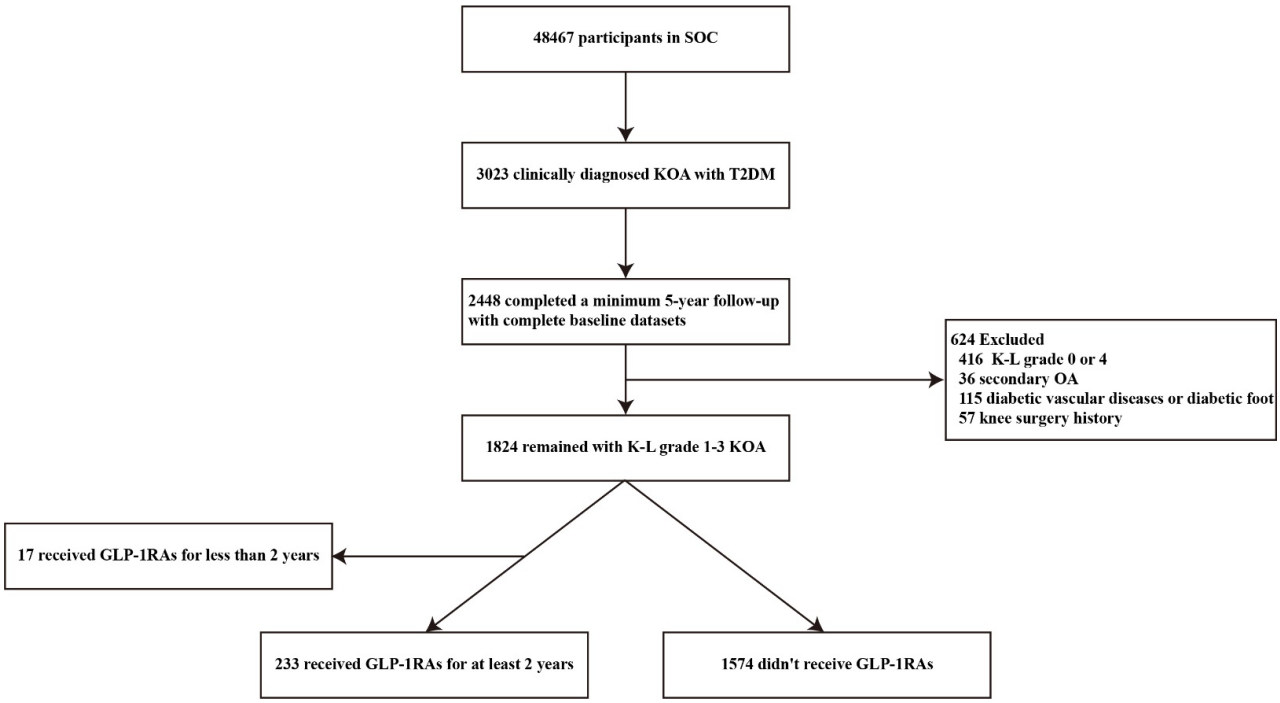
We did not perform routine MRI scanning for each participant. All MRI scanning in this study was performed by the decision of patient after consulting with his or her treating physician. To obtain qualified MRI data for our research purpose, the participants were requested to contact the researchers when they planned to receive an MRI scanning. The researchers would arrange an appropriate time and site for the participant to receive the MRI scanning. All the imaging data were acquired using 3.0T clinical MRI scanners from Siemens. The pulse sequence parameters for the protocol of double-echo steady-state (DESS) MRI series of knee were 384×307 (phase) matrix; 140 (mm) field of view; 0.7 (mm) slice thickness; 25° flip angle; 16.3/4.7 (ms/ms) repetition time/echo time; 185 (kHZ) bandwidth. The pulse sequence parameters for the protocol of DESS MRI series of hip were flexible body-matrix; 192 (mm) field of view; 0.6 (mm) slice thickness; 25° flip angle; 14.8/5 (ms/ms) repetition time/echo time; 260 (kHZ) bandwidth.

Images of the target knee were imported into Stradview (University of Cambridge Department of Engineering, Cambridge, UK), which was used for semi-automatic cartilage segmentation. Two trained readers independently and manually drew initial contours for the tibia and femur every three slices, from which a 3D isosurface was generated for each bone separately. The cartilage surfaces were then automatically measured in every slice and checked manually. To calculate the mean cartilage thickness, the minimum Euclidean distance of each point at the bone–cartilage interface towards the cartilage surface was averaged. The imaging readers were blinded to treatment and order of the image acquisition. The final readout was obtained by averaging the two independent readouts.

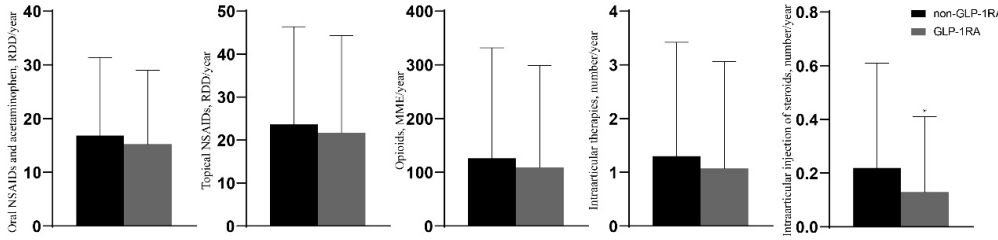
Other Information Collected during Routine follow up

Participants were routinely followed up once per year by phone call to obtain following information: (1) any incident knee/hip surgery; (2) any incident knee/hip surgery in purpose of treating OA; (3) WOMAC score; (4) body weight; (5) drug consumption in treatment of OA (recorded and reported by patients); (6) any physical therapies for OA management (optional); (7) any alternative treatments for OA management (optional).

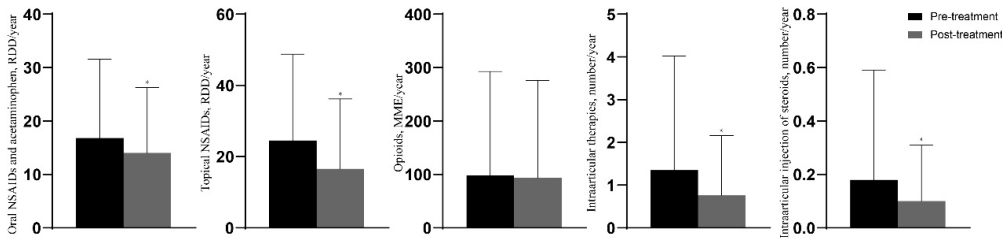
Supplemental figure S1. Flow chart of the study



Supplemental figure S2: Comparison of symptom-relieving medication use between the non-GLP-1RA and GLP-1RA groups. *, P<0.05.



Supplemental figure S3 Before-and-after comparison of symptom-relieving medication use within the GLP-1RA group. *, P<0.05.



Supplemental table S1. List of acetaminophen, oral NSAIDs, topical NSAIDs and their recommended daily doses (RDD)

Drug		
Acetaminophen	Acetaminophen	1250 mg
Oral NSAID	Aceclofenac	125 mg
Oral NSAID	Acemetacin	90 mg
Oral NSAID	Celebrex	200 mg
Oral NSAID	Choline Magnesium Trisalicylate	3275 mg
Oral NSAID	Dexibuprofen	800 mg
Oral NSAID	Dexketoprofen	68.75mg
Oral NSAID	Diacerein	75 mg
Oral NSAID	Diclofenac Sodium	112.5 mg
Oral NSAID	Diflunisal	375 mg
Oral NSAID	Etoricoxib	45 mg
Oral NSAID	Etodolac	800 mg
Oral NSAID	Fenbufen	800 mg
Oral NSAID	Flurbiprofen	175 mg
Oral NSAID	Ibuprofen	600 mg
Oral NSAID	Imidazole salicylate	1875 mg
Oral NSAID	Imrecoxib	200 mg
Oral NSAID	Indometacin	62.5 mg
Oral NSAID	Ketoprofen	200 mg
Oral NSAID	Lornoxicam	24 mg
Oral NSAID	Loxoprofen sodium	270 mg
Oral NSAID	Meloxicam	11.25 mg
Oral NSAID	Nabumetone	1500 mg
Oral NSAID	Naproxen	875 mg
Oral NSAID	Nimesulide	150 mg
Oral NSAID	Oxaprozin	400 mg
Oral NSAID	Piroxicam	20 mg
Oral NSAID	Rofecoxib	18.75mg
Oral NSAID	Sulindac	400 mg
Topical NSAID	Diclofenac Sodium	110 mg
Topical NSAID	Etofenamate	150 mg
Topical NSAID	Flurbiprofen	80 mg
Topical NSAID	Ibuprofen	212.5 mg
Topical NSAID	Ketoprofen	60 mg
Topical NSAID	Loxoprofen sodium	100 mg
Topical NSAID	Piroxicam	36 mg

Supplemental table S2. List of opioid analgesics and morphine milligram equivalents (MME)[4]

Opioid analgesic	MME conversion factor
Bezitramide	60
Codeine	0.15
Dextromoramide	4
Dextropropoxyphene	0.1
Diamorphine (Injection)	3
Diamorphine (Oral formulation)	1
Dihydrocodeine	0.25
Dipipanone	0.5
Fentanyl (Film)	180
Fentanyl (Nasal spray)	160
Fentanyl (Patch)	100
Fentanyl (Tablet)	130
Hydrocodone	1
Hydromorphone	5
Ketobemidone	2
Levorphanol	11
Meptazinol	0.03
Morphine (Injection)	2
Morphine (Oral formulation)	1
Nalbuphine	1
Nicomorphine	1
Oxycodone	1.5
Oxymorphone	3
Pentazocine	0.37
Pethidine (Injection)	0.24
Pethidine (Oral formulation)	0.1
Piritramide	0.75
Tapentadol	0.4
Tilidine	0.1
Tramadol	0.1
Trimeperidine	0.5

Supplemental table S3. Enrollment year for participants in the GLP-1RA and non-GLP-1RA groups

	2011	2012	2013	2014	2015	2016	Total	P value
GLP-1RA (n)	54	51	44	37	38	9	233	0.55
Non-GLP-1RA (n)	315	303	291	296	283	86	1574	

Supplemental table S4. The year of initial incident exposure to GLP-1RAs of participants in the GLP-1RA group

	2011	2012	2013	2014	2015	2016	2017	2018	2019	Total
Number	5	17	19	35	45	45	44	19	4	233

Data of GLP-1RA exposure before enrollment is missing.

Supplemental table S5. Clinically relevant change on weight in patients of the GLP-1RA and non-GLP-1RA groups

	GLP-1RA (n = 233)	**Non-GLP-1RA (n = 1574)**	***P* value**
Clinically relevant change on weight*			
Gain	43 (18.5%)	722 (45.9%)	<0.001
Stable	55 (23.6%)	641 (40.7%)	
Reduction	135 (57.9%)	211 (13.4%)	

* A weight change greater than 5% is considered as clinically relevant.

Supplemental table S6. Comparison of treatment, PROs and incident knee surgery between participants who achieved a clinically significant reduction in weight and those who did not.

	Reduction in weight (n = 346)	**Non-reduction in weight (n = 1461)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Weight, kg					
Baseline	64.5 (12.5)	65.4 (12.2)		0.22	
Change	-7.35 (4.31)	3.90 (4.31)	-11.26 (-11.77, -10.76)	<0.001	<0.001
WOMAC total score					
Baseline	19.6 (9.2)	19.8 (9.7)		0.76	
Change	2.65 (13.26)	3.65 (14.18)	-1.17 (-2.35, 0.006)	0.23	0.051
WOMAC pain subscore					
Baseline	17.8 (13.1)	17.4 (12.3)		0.60	
Change	1.21 (18.56)	1.69 (17.63)	-0.58 (-2.65, 1.49)	0.65	0.58
WOMAC stiffness subscore					
Baseline	18.8 (14.3)	18.2 (15.3)		0.50	
Change	4.37 (19.81)	6.71 (20.66)	-2.42 (-4.37, -0.46)	0.057	0.016
WOMAC function subscore					
Baseline	20.2 (11.3)	20.7 (12.2)		0.55	
Change	2.87 (16.27)	3.87 (17.53)	-1.20 (-2.69, 0.30)	0.34	0.12
Follow-up, years	7.7 (1.6)	7.8 (1.6)	..	0.68	..
Knee surgery	4 (1.7%)	91 (6.2%)	..	0.001	0.002

Data are shown as means (SDs) unless otherwise indicated. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. WOMAC questionnaire and all its subscales were normalised to scores within a range of 0–100.

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

Supplemental table S7. Comparison of structural outcomes between participants who achieved a clinically significant reduction in weight and those who did not

	Reduction in weight (n = 287)	**Non-reduction in weight (n = 1168)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Interval of MRI scanning, years	4.2 (2.2)	4.3 (2.3)	..	0.52	..
Cartilage loss, mm	-0.19 (0.20)	-0.20 (0.20)	..	0.29	..
Cartilage loss velocity, mm/year	-0.06 (0.09)	-0.07 (0.10)	0.01 (-0.005, 0.02)	0.25	0.25

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

Supplemental table S8. History use of GLP-1RAs during study period

	No.
Liraglutide	168 (72.1%)
Dulagopeptide	95 (40.8%)
Semaglutide	171 (73.4%)
Other (e.g. Losenatide, Risenatide, Exenatide)	45 (19.3%)

Supplemental table S9. Sensitivity analysis of PROs between the GLP-1RA (based on the latest follow-up before GLP-1RA usage) and non-GLP-1RA groups

	GLP-1RA (n = 233)	**Non-GLP-1RA (n = 1574)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Weight, kg					
Baseline	66.5 (12.2) †	65.1 (12.3)		0.11	
Change	-5.10 (6.93)	2.69 (5.23)	-7.78 (-8.54, -7.03)	<0.001	<0.001
WOMAC total score					
Baseline	19.9 (8.2) †	19.8 (9.6)		0.90	
Change	2.06 (11.97)	3.58 (13.99)	-2.03 (-3.41, -0.65)	0.077	0.004
WOMAC pain subscore					
Baseline	18.9 (11.8) †	17.4 (12.3)		0.071	
Change	-1.76 (15.25)	2.01 (17.60)	-3.93 (-6.29, -1.56)	0.001	0.001
WOMAC stiffness subscore					
Baseline	18.7 (11.0) †	18.3 (15.5)		0.68	
Change	5.31 (16.43)	6.33 (20.43)	-1.49 (-3.75, 0.77)	0.39	0.20
WOMAC function subscore					
Baseline	20.5 (11.0) †	20.7 (11.9)		0.78	
Change	2.65 (15.17)	3.72 (17.25)	-1.68 (-3.43, 0.078)	0.33	0.061
Follow-up, years	5.4 (1.7) ††	7.8 (1.6)	..	<0.001	..
Interval time††† , years	0.46 (0.28)	..	..	..	..

Data are shown as means (SDs) unless otherwise indicated. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. WOMAC questionnaire and all its subscales were normalised to scores within a range of 0–100.

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

†The baseline weight and PROs were defined as the data collected at the latest follow-up before the administration of GLP-1RA for the GLP-1RA group.

†† The interval between the initiation of GLP-1RA usage and the latest follow-up for the GLP-1RA group.

††† The interval between the latest follow-up before the initial exposure of GLP-1RA and the initiation of GLP-1RA usage.

Supplemental table S10. Sensitivity analysis of PROs and incident knee surgery after excluding patients with WOMAC total score lower than 7 at baseline

	GLP-1RA (n = 214)	**Non-GLP-1RA (n = 1459)**	**Adjusted mean difference * (95% CI)**	**P value**	**Adjusted p value***
Weight (Change from baseline), kg	-4.40 (8.04)	2.63 (5.21)	-7.02 (-7.83, -6.20)	<0.001	<0.001
HbA1c (Change from baseline), %	0.01 (1.16)	0.07 (1.23)	-0.05 (-0.23, 0.13)	0.55	0.58
WOMAC total score (Change from baseline)	1.27 (13.59)	2.35 (13.50)	-1.49 (-2.93, -0.05)	0.27	0.043
WOMAC pain subscore (Change from baseline)	-1.91 (19.03)	1.29 (17.56)	-3.31 (-5.85, -0.77)	0.014	0.011
WOMAC stiffness subscore (Change from baseline)	4.21 (20.87)	5.12 (20.29)	-1.31 (-3.72, 1.11)	0.54	0.29
WOMAC function subscore (Change from baseline)	1.86 (17.16)	2.33 (16.76)	-0.97 (-2.80, 0.86)	0.70	0.30
Follow-up, years	7.7 (1.5)	7.8 (1.6)	..	0.32	..
Knee surgery	4 (1.9%)	83 (5.7%)	..	0.019	0.026

Data are shown as means (SDs) unless otherwise indicated. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. WOMAC questionnaire and all its subscales were normalised to scores within a range of 0–100.

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

Supplemental table S11. Sensitivity analysis of structural outcomes after excluding patients with WOMAC total score that lower than 7 at baseline

	GLP-1RA (n = 173)	**Non-GLP-1RA (n = 1175)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Interval of MRI scanning, years	4.5 (2.1)	4.3 (2.3)	..	0.31	..
Cartilage loss, mm	-0.18 (0.20)	-0.21 (0.20)	..	0.077	..
Cartilage loss velocity, mm/year	-0.05 (0.08)	-0.07 (0.10)	0.02 (0.001, 0.03)	0.009	0.038

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

Supplemental table S12. Comparison of patients who reaching the MCID improvement of WOMAC total score in the GLP-1RA and non-GLP-1RA groups *

	GLP-1RA (n = 233)	**Non-GLP-1RA (n = 1574)**	**P value**
Improvement	61 (26.2%)	347 (22.0%)	0.16
No improvement	172 (73.8%)	1227 (78.0%)	

*The MCID for the WOMAC total score was 7.

Supplemental table S13. Comparison of patients who reaching the MCID improvement of WOMAC pain subscore in the GLP-1RA and non-GLP-1RA groups *

	GLP-1RA (n = 233)	**Non-GLP-1RA (n = 1574)**	**P value**
Improvement	81 (34.8%)	443 (28.1%)	0.038
No improvement	152 (65.2%)	1131 (71.9%)	

*The MCID for the WOMAC pain subscore was 9.

Supplemental table S14. Mediation effects for knee outcomes: association of GLP-1RA therapies with WOMAC pain subscore

Exposure: GLP-1RA	**Mediator: Weight change from baseline** **Change of WOMAC pain subscore from baseline* (95% CI)**	***P* value**	**Mediator: HbA1c change from baseline** **Change of WOMAC pain subscore from baseline** (95% CI)**	***P* value**
Controlled direct effect	-3.76 (-6.58, -0.98)†	0.005	-3.34 (-5.94, -0.76)†	0.012
Indirect effect	0.45 (-0.59, 1.50)	0.40	0.007 (-0.061, 0.010)	0.85
Total effect	-3.31 (-5.84, -0.78)	0.008	-3.33 (-5.94, -0.75)	0.012
Proportion mediated	Proportion too small to calculate--not a mediator	0.41	Proportion too small to calculate--not a mediator	0.85

*The model adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

**The model adjusted for age, sex, baseline HbA1c, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

†Values are unstandardised regression coefficients representing change of WOMAC pain subscore from baseline.

Supplemental table S15. Incident knee surgery between the GLP-1RA and non-GLP-1RA Groups

	GLP-1RA (n = 233)	**Non-GLP-1RA (n = 1574)**
TKA	2 (0.9%)	30 (1.9%)
UKA	0 (0.0%)	1 (0.1%)
HTO	0 (0.0%)	6 (0.4%)
Arthroscopic procedures	2 (0.9%)	53 (3.4%)
TKA following arthroscopic procedures	0 (0.0%)	3 (0.2%)

TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty; HTO, high tibial osteotomy.

Supplemental table S16. Subgroup comparison of PROs and incident knee surgery among participants who reached clinically relevant reduction on weight* between the GLP-1RA and non-GLP-1RA groups

	GLP-1RA (n = 135)	**Non-GLP-1RA (n = 211)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value****
WOMAC total score (Change from baseline)	2.17 (13.48)	2.96 (13.14)	-2.10 (-4.29, 0.09)	0.59	0.060
WOMAC pain subscore (Change from baseline)	-0.48 (18.69)	2.30 (18.44)	-3.27 (-7.25, 0.71)	0.17	0.11
WOMAC stiffness subscore (Change from baseline)	4.63 (20.30)	4.21 (19.54)	-0.87 (-4.60, 2.86)	0.85	0.65
WOMAC function subscore (Change from baseline)	2.67 (16.74)	3.00 (15.99)	-1.90 (-4.67, 0.87)	0.85	0.18
Follow-up, years	7.8 (1.5)	7.7 (1.6)	..	0.69	..
Knee surgery	0 (0.0%)	6 (2.8%)	..	0.085	Not applicable†

Data are shown as means (SDs) unless otherwise indicated. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. WOMAC questionnaire and all its subscales were normalised to scores within a range of 0–100.

* A weight change greater than 5% is considered as clinically relevant.

** Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

† Lack of fitting in the regression mode.

Supplemental table S17. Sensitivity analysis of PROs and incident knee surgery after excluding patients had GLP-1RA exposure within the initial six months after enrollment

	GLP-1RA (n = 206)	**Non-GLP-1RA (n = 1574)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Weight (Change from baseline), kg	-4.54 (8.11)	2.69 (5.23)	-7.23 (-8.05, -6.41)	<0.001	<0.001
HbA1c (Change from baseline), %	0.02 (1.25)	0.08 (1.23)	-0.05 (-0.23, 0.13)	0.53	0.56
WOMAC total score (Change from baseline)	2.84 (14.11)	3.58 (13.99)	-1.57 (-3.03, -0.12)	0.48	0.034
WOMAC pain subscore (Change from baseline)	-0.87 (18.81)	2.01 (17.60)	-3.15 (-5.70, -0.60)	0.028	0.016
WOMAC stiffness subscore (Change from baseline)	5.83 (20.71)	6.33 (20.43)	-1.34 (-3.76, 1.08)	0.74	0.28
WOMAC function subscore (Change from baseline)	3.58 (17.46)	3.72 (17.25)	-1.14 (-2.99, 0.72)	0.92	0.23
Follow-up, years	7.8 (1.6)	7.8 (1.6)	..	0.69	..
Knee surgery	4 (1.9%)	93 (5.9%)	..	0.014	0.027

Data are shown as means (SDs) unless otherwise indicated. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. WOMAC questionnaire and all its subscales were normalised to scores within a range of 0–100.

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

Supplemental table S18. Subgroup comparison of structural outcomes among participants who reached clinically relevant reduction on weight* between the GLP-1RA and non-GLP-1RA groups

	GLP-1RA (n = 113)	**Non-GLP-1RA (n = 174)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value**
Interval of MRI scanning, years	4.6 (2.2)	4.0 (2.2)	..	0.018	..
Cartilage loss, mm	-0.17 (0.20)	-0.20 (0.19)	..	0.41	..
Cartilage loss velocity, mm/year	-0.05 (0.07)	-0.07 (0.10)	0.01 (-0.008, 0.04)	0.16	0.22

* A weight change greater than 5% is considered as clinically relevant.

Supplemental table S19. Sensitivity analysis of structural outcomes after excluding patients had GLP-1RA exposure within the initial six months after enrollment

	GLP-1RA (n = 165)	**Non-GLP-1RA (n = 1267)**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Interval of MRI scanning, years	4.5 (2.1)	4.3 (2.3)	..	0.25	..
Cartilage loss, mm	-0.17 (0.20)	-0.20 (0.20)	..	0.057	..
Cartilage loss velocity, mm/year	-0.05 (0.08)	-0.07 (0.10)	0.02 (0.001, 0.03)	0.008	0.026

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

Supplemental table S20. Subgroup comparison of structural outcomes with baseline KL grade between the GLP-1RA and non-GLP-1RA groups

	GLP-1RA	**Non-GLP-1RA**	**Adjusted mean difference* (95% CI)**	**P value**	**Adjusted p value***
Interval of MRI scanning, years					
KL grade I†	5.0 (2.2)	4.3 (2.2)	..	0.17	..
KL grade II††	4.6 (2.0)	4.2 (2.3)	..	0.13	..
KL grade III†††	4.1 (2.2)	4.4 (2.3)	..	0.47	..
Cartilage loss, mm					
KL grade I†	-0.16 (0.19)	-0.22 (0.21)	..	0.18	
KL grade II††	-0.18 (0.21)	-0.20 (0.20)	..	0.52	..
KL grade III†††	-0.16 (0.20)	-0.21 (0.20)	..	0.067	..
Cartilage loss velocity, mm/year					
KL grade I†	-0.04 (0.06)	-0.07 (0.11)	0.03 (-0.019, 0.07)	0.21	0.25
KL grade II††	-0.06 (0.08)	-0.07 (0.11)	0.01 (-0.008, 0.04)	0.24	0.21
KL grade III†††	-0.05 (0.07)	-0.07 (0.10)	0.02 (-0.004, 0.05)	0.091	0.090

* Mean difference and P value adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

† GLP-1RA group (n=22) and non-GLP-1RA group (n=179).

†† GLP-1RA group (n=105) and non-GLP-1RA group (n=709).

††† GLP-1RA group (n=61) and non-GLP-1RA group (n=379).

Supplemental table S21. Mediation effects for knee outcomes: association of GLP-1RA therapies with cartilage loss velocity

Exposure: GLP-1RA	**Mediator: Weight change from baseline Cartilage loss velocity* (95% CI)**	***P* value**	**Mediator: HbA1c change from baseline Cartilage loss velocity** (95% CI)**	***P* value**
Controlled direct effect	0.015 (0.001, 0.030)†	0.040	0.018 (0.005, 0.030)†	0.006
Indirect effect	0.003 (-0.004, 0.010)	0.45	0.000 (-0.0003, 0.001)	0.62
Total effect	0.018 (0.006, 0.030)	0.007	0.018 (0.006, 0.030)	0.006
Proportion mediated	Proportion too small to calculate--not a mediator	0.46	Proportion too small to calculate--not a mediator	0.62

*The model adjusted for age, sex, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

**The model adjusted for age, sex, baseline HbA1c, baseline BMI, baseline Kellgren-Lawrence grade, and baseline WOMAC total score.

†Values are unstandardised regression coefficients representing cartilage loss velocity.

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