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Association of Decrease in Body Mass Index With Reduced Incidence and Progression of the Structural Defects of Knee Osteoarthritis: A Prospective Multi-Cohort Study

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Objective. To define the association between change in body mass index (BMI) and the incidence and progression of the structural defects of knee osteoarthritis as assessed by radiography.

Methods. Radiographic analyses of knees at baseline and at 4–5 years of follow-up were obtained from the following 3 independent cohort studies: the Osteoarthritis Initiative (OAI) study, the Multicenter Osteoarthritis Study (MOST), and the Cohort Hip and Cohort Knee (CHECK) study. Logistic regression analyses using generalized estimating equations, with clustering of both knees within individuals, were used to investigate the association between change in BMI from baseline to 4–5 years of follow-up and the incidence and progression of knee osteoarthritis.

Results. A total of 9,683 knees (from 5,774 participants) in an "incidence cohort" and 6,075 knees (from 3,988 participants) in a "progression cohort" were investigated. Change in BMI was positively associated with both the incidence and progression of the structural defects of knee osteoarthritis. The adjusted odds ratio (OR) for osteoarthritis incidence was 1.05 (95% confidence interval [95% CI] 1.02–1.09), and the adjusted OR for osteoarthritis progression was 1.05 (95% CI 1.01–1.09). Change in BMI was also positively associated with degeneration (i.e., narrowing) of the joint space and with degeneration of the femoral and tibial surfaces (as indicated by osteophytes) on the medial but not on the lateral side of the knee.

Conclusion. A decrease in BMI was independently associated with lower odds of incidence and progression of the structural defects of knee osteoarthritis and could be a component in preventing the onset or worsening of knee osteoarthritis.

INTRODUCTION

Knee osteoarthritis is a debilitating degenerative disease affecting 22.9% of individuals ages ≥40 years globally (1). Overweight and obesity are risk factors for both the incidence and progression of knee osteoarthritis (2), with nearly 25% of cases of new-onset knee pain or osteoarthritis attributable to excess weight (3). A critical question is whether weight loss can

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mitigate these problems. Clinically, weight loss in those with knee osteoarthritis reduces knee pain, improves knee function, and enhances quality of life (4–10), but it is unclear whether weight loss mitigates the structural defects of knee osteoarthritis (7,11–23). If it does, then weight loss could be used to protect against the incidence and progression of structural degeneration of the knee due to osteoarthritis.

To our knowledge, 2 observational studies have investigated the association between weight loss and incidence of the structural defects of knee osteoarthritis, and both showed that weight loss was significantly associated with reduced incidence of knee osteoarthritis (11,12). These findings were applicable to female participants, as 1 of the 2 studies found the association with weight loss only in female participants due to the limited number of incident cases in male participants (n = 24) (11), and the other study involved female participants exclusively (12). While the prevalence of knee osteoarthritis is higher in female than in male adults (1), it is relevant to understand the effect of weight loss on the incidence of knee osteoarthritis in male adults given the number of individuals affected (e.g., 10% of male adults and 13% of female adults ages 60 years or older have symptomatic knee osteoarthritis in the USA [24]).

Like the small number of studies on incidence, studies on progression of the structural defects of knee osteoarthritis in people who already have knee degeneration at baseline are also scant. We know of only 1 study that investigated this, by following up knees that already had definite osteoarthritis at baseline (as indicated by a Kellgren-Lawrence [KL] grade of ≥2 [25]) (13). That study showed no association between weight loss and the progression of some key structural defects of knee osteoarthritis (13).

Based on the findings of these previous studies (11–13), we can hypothesize that weight loss may reduce the incidence of the structural defects of knee osteoarthritis (i.e., weight loss may be preventative), but that once knee degeneration is present, weight loss may not reduce its progression. However, the existing literature does not allow further examination of this hypothesis, because to our knowledge all of the 11 other studies that have investigated the association between weight loss and the structural defects of knee osteoarthritis (7,14–23) investigated knees both without and with structural degeneration of the knee at baseline (i.e., a KL grade of <2 and a KL grade of ≥2), meaning that both incidence and progression were being investigated in those studies without distinction. This could be a potential contributor to the mixed findings from these 11 studies (7,14–23). Specifically, 6 of the studies had shorter follow-up durations (i.e., <18 months) (7,14–16,19,21), and 5 had longer follow-up durations (i.e., ≥48 months) (17,18,20,22,23). The 6 studies with shorter follow-up durations had mixed findings: 2 of the 6 studies found an association between weight loss and structural degeneration of the knee (15,19), while the remaining 4 did not (7,14,16,21). The 5 studies with longer follow-up durations found an association between either weight loss (17,18,22,23) or weight gain (20) and the structural degeneration of the knee. However, the data used in these 5 studies with longer follow-up came from the same single cohort study (the Osteoarthritis Initiative [OAI] study). Therefore, it is unknown whether data from different cohort studies would produce findings that differ from those of the studies which used only data from the OAI study. Moreover, a recent systematic review did not present any consistent evidence of an association between weight loss and change in knee structure (as imaged by radiography or magnetic resonance imaging) in individuals with osteoarthritis and overweight or obesity (26). The authors of that systematic review called for a longitudinal study involving a large sample of participants (either at risk of or with osteoarthritis) with variations in weight change (e.g., weight loss, weight stability, weight gain) over a longer follow-up, to gain further understanding as to whether and which structural changes of knee osteoarthritis are sensitive to weight change.

To extend the findings of the research mentioned above, we conducted this study using the combined data sets of the following 3 prospective cohort studies: the OAI study from the USA (27), the Multicenter Osteoarthritis Study (MOST) from the USA (28), and the Cohort Hip and Cohort Knee (CHECK) study from The Netherlands (29). The current multi-cohort study thus included a large total possible number of participants (n = 8,824), both male and female, without and with the structural defects of knee osteoarthritis at baseline. Finally, we investigated KL grades (which assess overall structural defects of knee osteoarthritis) as well as all commonly studied individual structural defects of knee osteoarthritis, in order to gain complete understanding of any potential association with weight change. Because weight change data were not available from all 3 cohorts, we investigated change in body mass index (BMI)—which was available from all 3 cohorts—as a proxy measure of weight change.

PARTICIPANTS AND METHODS

Data sources and selection of participants and knees. The data used in this study were obtained from the OAI (27), MOST (28), and CHECK (29) cohort studies. From the above 3 cohort studies (8,824 participants), we created 2 cohorts of knees: the incidence cohort, which included only knees that did not have the structural defects of osteoarthritis at baseline, and the progression cohort, which included knees that did have the structural defects of osteoarthritis at baseline. Before creating these 2 cohorts, we applied selection criteria first at the level of the participant and then at the level of the knee (Figure 1). After applying the participant-level exclusion criteria, there were 8,318 participants (16,636 knees) remaining. Of these 16,636 knees, we excluded knees that had undergone knee replacement surgery prior to baseline, then sorted the remaining knees into our 2 cohorts (incidence and progression) as follows. The incidence

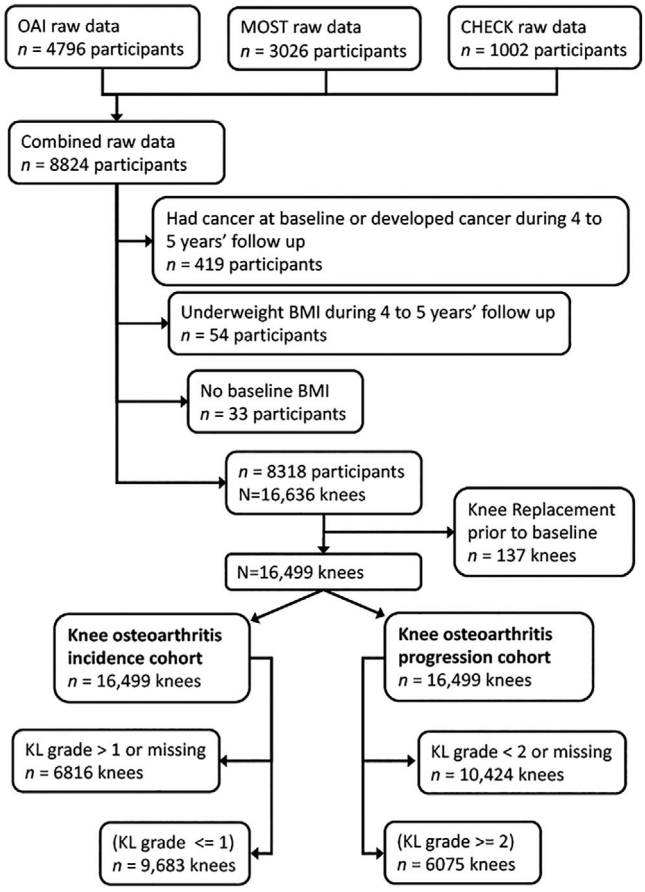

Figure 1. Selection of knees for investigations of the incidence and progression of the structural defects of knee osteoarthritis. OAI = Osteoarthritis Initiative; MOST = Multicenter Osteoarthritis Study; CHECK = Cohort Hip and Cohort Knee; BMI = body mass index; KL = Kellgren-Lawrence.

cohort consisted of only knees that had an osteoarthritis status at baseline of "none" or "doubtful" (i.e., a KL grade of 0 or 1, respectively, of which there were 9,683 knees from 5,774 participants). The progression cohort consisted of only knees that had an osteoarthritis status at baseline of "minimal," "moderate," or "severe" (i.e., a KL grade of 2, 3, or 4, respectively, of which there were 6,075 knees from 3,988 participants).

Baseline and follow-up radiographic data. We used radiographic data from baseline and 4 years of follow-up from the OAI study, and from baseline and 5 years of follow-up from the MOST and CHECK studies. The OAI study had limited radiographic data at any other time points beyond 4 years. The MOST and CHECK studies did not have radiographic data at 4 years, and that is why the 5-year data were used.

Exposure. Our exposure of interest was change in BMI (in kg/m^2) from baseline to follow-up of 4 or 5 years. We used change in BMI instead of change in weight because BMI data—unlike weight data—were available in all 3 cohorts used in this multi-cohort study.

Outcomes. The outcomes for this study were the incidence and progression of the structural defects of knee osteoarthritis as assessed by radiography. These were defined in the following 2 ways: overall structural defects as assessed by KL grade, and structural defects in 3 individual features of the knee (i.e., joint space narrowing, osteophytes on the femoral surface, and osteophytes on the tibial surface) on both the medial and the lateral side of the knee, as assessed by Osteoarthritis Research Society International (OARSI) grade (30). The incidence of overall structural defects of knee osteoarthritis was defined as moving from a KL grade of 0 or 1 at baseline to a KL grade of 2 or more at follow-up (in the incidence cohort). The progression of overall structural defects of knee osteoarthritis was defined as moving from a KL grade of 2 or 3 at baseline to a K/L grade at least 1 unit greater at follow-up (in the progression cohort). While we used distinct criteria to investigate the incidence and progression of overall structural defects of knee osteoarthritis, we investigated structural defects of the 3 individual features of the knee by determining the number of knees that showed an increase of at least 1 OARSI grade within the incidence and the progression cohorts. OARSI grades are as follows: 0 = normal, 1 = mild defect, 2 = moderate defect, and 3 = severe defect (30). Because the incidence and progression cohorts were defined based on overall structural defects of the knee as determined by KL grade at baseline and not on individual structural defects as determined by OARSI grade at baseline, an increase by 1 or more OARSI grades within the incidence or progression cohorts was neither exclusively "incidence" nor "progression", and so is referred to nonspecifically as "degeneration of individual structural features".

In addition to investigating incidence and progression, we estimated population attributable fractions (i.e., the proportion of cases of incidence and progression of the overall structural defects of knee osteoarthritis that would have been avoided if all knees in that population has been exposed to a particular decrease in BMI) (31). To this end, we selected a decrease in BMI of 1 unit (kg/m^2) from baseline to follow-up at 4 or 5 years, both in participants from all BMI categories collectively, as well as in participants from the following distinct BMI categories separately: normal (defined as a BMI between 18.5 kg/m^2 and <25.0 kg/m^2), overweight (defined as a BMI between 25.0 kg/m^2 and <30.0 kg/m^2), and obese (defined as a BMI of <30.0 kg/m^2).

Statistical analyses. We used generalized estimating equations with a logistic link function (i.e., logistic regression with clustering of the left and right knee within individuals) (32) to investigate the association between change in BMI between baseline and 4–5 years of follow-up and the incidence or progression of the structural defects of knee osteoarthritis. Univariate (unadjusted) and multivariable (adjusted) analyses were performed. All

of the multivariable analyses were adjusted for the following 13 variables: sex, BMI category at baseline, age at baseline, race, KL grade or OARSI grade at baseline for analyses of overall structural defects or individual structural defects, respectively, walking (seldom, sometimes, or often) or not walking for physical activity at baseline, knee pain at baseline as assessed by the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index (33), smoking status at baseline, marriage status at baseline, number of comorbidities at baseline, employment status at baseline, education status at baseline, and cohort study from which

Table 1. Baseline characteristics of participants and knees in the incidence cohort, stratified by decrease in BMI, stable BMI, and increase in BMI*

	Decrease in BMI	Stable BMI	Increase in BMI	Total	*P*
At the participant level					
No. of participants	1,101	2,130	1,611	4,842	–
Age, mean ± SD years	59.9 ± 8.5	60.4 ± 8.4	58.3 ± 7.7	59.6 ± 8.3	<0.01
Sex					<0.01
Male	400 (36.3)	942 (44.2)	577 (35.8)	1,919 (39.6)	–
Female	701 (63.7)	1,188 (55.8)	1,034 (64.2)	2,923 (60.4)	–
Race					0.38
White	951 (86.4)	1,876 (88.1)	1,411 (87.6)	4,238 (87.5)	–
Other	150 (13.6)	254 (11.9)	200 (12.4)	604 (12.5)	–
BMI, mean ± SD kg/m^2	29.6 ± 5.1	27.4 ± 4.4	28.4 ± 4.8	28.2 ± 4.8	<0.01
BMI category†					<0.01
Normal	196 (17.8)	666 (31.3)	413 (25.6)	1,275 (26.3)	–
Overweight	429 (39.0)	918 (43.1)	643 (39.9)	1,990 (41.1)	–
Obese	476 (43.2)	546 (25.6)	555 (34.5)	1,577 (32.6)	–
Walking or not walking for physical activity					0.39
Never	124 (11.3)	267 (12.6)	181 (11.3)	572 (11.8)	–
Seldom, sometimes, or often	975 (88.7)	1,858 (87.4)	1,425 (88.7)	4,258 (88.2)	–
Smoking status					0.01
Currently or formerly	413 (37.8)	729 (34.4)	622 (38.8)	1,764 (36.6)	–
Never	679 (62.2)	1,392 (65.6)	980 (61.2)	3,051 (63.4)	–
Marital status					0.47
Never married	76 (6.9)	127 (6.0)	120 (7.5)	323 (6.7)	–
Widowed, divorced, or separated	206 (18.8)	405 (19.1)	306 (19.1)	917 (19.0)	–
Married	816 (74.3)	1,590 (74.9)	1,174 (73.4)	3,580 (74.3)	–
Number of comorbidities					<0.01
0	703 (64.1)	1,548 (73.1)	1,108 (69.2)	3,359 (69.8)	–
1	205 (18.7)	371 (17.5)	291 (18.2)	867 (18.0)	–
2 or more	188 (17.2)	198 (9.4)	202 (12.6)	588 (12.2)	–
Employment status					0.12
Not working	445 (40.5)	803 (37.8)	591 (36.7)	1,839 (38.0)	–
Working	653 (59.5)	1,324 (62.2)	1,019 (63.3)	2,996 (62.0)	–
Education status					<0.01
High school or below	316 (28.9)	426 (20.1)	437 (27.2)	1,179 (24.4)	–
Above high school	779 (71.1)	1,698 (79.9)	1,167 (72.8)	3,644 (75.6)	–
Cohort study					<0.01
OAI	494 (44.9)	1,202 (56.4)	711 (44.1)	2,407 (49.7)	–
MOST	363 (33.0)	693 (32.5)	602 (37.4)	1,658 (34.2)	–
CHECK	244 (22.1)	235 (11.1)	298 (18.5)	777 (16.1)	–
At the knee level					
No. of knees	1,837	3,554	2,739	8,130	–
Kellgren-Lawrence grade‡					0.03
None (grade 0)	1,238 (67.4)	2,518 (70.9)	1,916 (69.9)	5,672 (69.8)	–
Doubtful (grade 1)	599 (32.6)	1,036 (29.1)	823 (30.1)	2,458 (30.2)	–
Knee pain, mean ± SD WOMAC score (range 0–20)	2.4 ± 3.2	1.8 ± 2.7	2.3 ± 3.2	2.1 ± 3.0	<0.01

* Except where indicated otherwise, values are the number (%). The percentage calculations are based on complete case (i.e., excluding missing values). A decrease in body mass index (BMI) was defined as a decrease of ≥1 BMI unit; stable BMI was defined as a decrease or increase of <1 BMI unit; and an increase in BMI was defined as an increase of ≥1 BMI unit. Chi-square and Kruskal-Wallis tests were used for comparisons between BMI change groups. OAI = Osteoarthritis Initiative study; MOST = Multicenter Osteoarthritis Study; CHECK = Cohort Hip and Cohort Knee study; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

† Normal BMI was defined as a BMI between 18.5 kg/m^2 and <25.0 kg/m^2, overweight as a BMI between 25.0 kg/m^2 and <30.0 kg/m^2, and obese as a BMI of ≥30.0 kg/m^2. Participants who had a BMI in the underweight category (BMI <18.5 kg/m^2) were excluded from the cohort.

‡ Knees with a Kellgren-Lawrence grade of minimal (grade 2), moderate (grade 3), or severe (grade 4) were excluded from these analyses.

the data were sourced (i.e., OAI, MOST, or CHECK). Data on these variables were available from all 3 of the cohort studies we used. The method for selection of variables is explained in the Supplementary Variable Selection and References, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42307.

We performed 5 sensitivity analyses (see Supplementary Sensitivity Analyses for details). STATA/BE version 17.0 for Windows (64-bit x86-64) was used for our analyses. *P* values of less than 0.05 by 2-tailed test were considered significant. Missing data were not replaced by any imputation method. The punaf package in STATA (34) was used to estimate population attributable fractions (31).

RESULTS

Characteristics of the incidence and progression cohorts. Of the 9,683 knees (from 5,774 participants) in the incidence cohort (i.e., knees with a KL grade of 0 or 1 at baseline), 1,217 (12.6%) developed overall structural defects of knee osteoarthritis over the 4–5 years of follow-up (i.e., a KL grade of ≥2 at follow-up). There were 1,826 knees with missing data on KL grade at the 4–5 years of follow-up in the incidence cohort (i.e., 18.9%). Of the 6,075 knees (from 3,988 participants) in the progression cohort (i.e., knees with a KL grade of ≥2 at baseline), 908 knees (15.0%) had progressed by 1 or more KL grades in overall structural defects of knee osteoarthritis over the 4–5 years of follow-up. There were 1,800 knees with missing data on KL grade at 4–5 years of follow-up in the progression cohort (i.e., 29.6%).

In the incidence and progression cohorts, 36.7% and 34.8% of the knees, respectively, were exposed to a BMI change of <1 BMI unit (i.e., 1 kg/m^2) in either direction between baseline and 4–5 years of follow-up (Supplementary Figure A, http://onlinelibrary.wiley.com/doi/10.1002/art.42307). In the incidence cohort, 19.0% of the knees were exposed to a decrease in BMI of ≥1 BMI unit, 44.3% of the knees were exposed to an increase of ≥1 BMI unit, and 4.2% of the knees were exposed to a decrease in BMI of ≥3 BMI units. In the progression cohort, 20.0% of the knees were exposed to a decrease in BMI of ≥1 BMI unit, 45.2% of the knees were exposed to an increase of ≥1 BMI unit, and 5.6% of the knees were exposed to a decrease in BMI of ≥3 BMI units (Supplementary Figure A, https://doi.org/10.1002/art.42307).

Tables 1 and 2 show the baseline characteristics of participants in the incidence and progression cohorts, respectively, stratified by chang in BMI: decrease in BMI (decrease of ≥1 BMI unit), stable BMI (decrease or increase of <1 BMI unit), and increase in BMI (increase of ≥1 BMI unit). Sex and BMI categories at baseline were statistically significantly different between the BMI change groups in both the incidence and progression cohorts. Specifically, the group showing an increase in BMI had the highest percentage of female participants in both the incidence and progression cohorts (64.2% and 65.1%, respectively) compared to the groups showing a decrease in BMI (63.7% and 62.3%, respectively) and stable BMI (55.8% and 55.3%, respectively). The group showing a decrease in BMI had the highest proportion of participants with obesity in both the incidence and progression cohorts (43.2% and 58.3%, respectively), compared to the groups showing stable BMI (25.6% and 40.0%, respectively) and an increase in BMI (34.5% and 52.2%, respectively).

Incidence and progression of the overall structural defects of knee osteoarthritis as assessed by radiography over 4–5 years. We evaluated the association between change in BMI from baseline to 4–5 years of follow-up and the odds in that time of the incidence and progression, respectively, of the overall structural defects of knee osteoarthritis as assessed by KL grade, using both unadjusted (univariate) and adjusted (multivariable) models (Tables 3 and 4). In the unadjusted models, there was a positive but not statistically significant association between change in BMI and the odds of incident knee osteoarthritis, and a positive and statistically significant association between change in BMI and the progression of knee osteoarthritis. In the adjusted models, change in BMI between baseline and 4–5 years of follow-up was positively and statistically significantly associated with both the incidence and progression of the overall structural defects of knee osteoarthritis. Specifically, the adjusted odds ratio (OR) of incidence was 1.05 (95% confidence interval [95% CI] 1.02–1.09), and the adjusted OR of progression was 1.05 (95% CI 1.01–1.09). As an aside, it is coincidental that the results appear almost identical when expressed to 2 decimal places. These results suggest that each 1-unit decrease in BMI was associated with a 4.76% reduction (i.e., 1 – exp (-log (1.05)) = 0.0476) in the odds of the incidence and progression of the overall structural defects of knee osteoarthritis as assessed by KL grade from baseline to 4–5 years of follow-up. As another example, a 5-unit decrease in BMI, which is an amount that can lead to a reduction in BMI category (e.g., from overweight to normal), was associated with a 21.65% reduction (i.e., 1–exp (log (1.05) * 5) = 0.2165) in the odds of the incidence and progression in these outcomes from baseline to 4–5 years.

We investigated the possibility of interactions between change in BMI from baseline to 4–5 years of follow-up with other variables in our analyses, namely BMI category at baseline, KL grade at baseline, and sex, for both the incidence and progression cohorts, but there were no statistically significant interactions. This suggests that the associations between change in BMI and the incidence and progression of knee osteoarthritis as assessed by KL grade are independent of BMI category at baseline, KL grade at baseline, and sex.

Table 2. Baseline characteristics of participants and knees in the progression cohort, stratified by decrease in BMI, stable BMI, and increase in BMI*

	Decrease in BMI	Stable BMI	Increase in BMI	Total	*P*
At the participant level					
No. of participants	798	1,410	1,008	3,216	–
Age, mean ± SD years	63.0 ± 8.7	63.1 ± 8.5	60.6 ± 8.0	62.3 ± 8.5	<0.01
Sex					<0.01
Male	301 (37.7)	630 (44.7)	352 (34.9)	1,283 (39.9)	–
Female	497 (62.3)	780 (55.3)	656 (65.1)	1,933 (60.1)	–
Race					<0.01
White	606 (75.9)	1,180 (83.7)	799 (79.3)	2,585 (80.4)	–
Other	192 (24.1)	230 (16.3)	209 (20.7)	631 (19.6)	–
BMI, mean ± SD kg/m^2	31.9 ± 6.2	29.3 ± 5.0	30.7 ± 5.5	30.4 ± 5.6	<0.01
BMI category†					<0.01
Normal	88 (11.0)	260 (18.4)	132 (13.1)	480 (14.9)	–
Overweight	245 (30.7)	586 (41.6)	350 (34.7)	1,181 (36.7)	–
Obese	465 (58.3)	564 (40.0)	526 (52.2)	1,555 (48.4)	–
Walking or not walking for physical activity					0.86
Never	117 (14.7)	197 (14.0)	148 (14.7)	462 (14.4)	–
Seldom, sometimes, or often	680 (85.3)	680 (85.3)	858 (85.3)	2,747 (85.6)	–
Smoking status					0.75
Currently or formerly	239 (30.1)	444 (31.7)	315 (31.4)	998 (31.2)	–
Never	554 (69.9)	959 (68.3)	687 (68.6)	2,200 (68.8)	–
Marital status					0.02
Never married	53 (6.7)	91 (6.5)	84 (8.4)	228 (7.1)	–
Widowed, divorced, or separated	219 (27.7)	314 (22.4)	241 (24.0)	774 (24.2)	–
Married	518 (65.6)	996 (71.1)	678 (67.6)	2,192 (68.6)	–
Number of comorbidities					<0.01
0	531 (67.0)	1,042 (74.4)	728 (72.6)	2,301 (72.0)	–
1	162 (20.4)	237 (16.9)	174 (17.4)	573 (17.9)	–
2 or more	100 (12.6)	122 (8.7)	100 (10.0)	322 (10.1)	–
Employment status					0.01
Not working	338 (42.4)	626 (44.4)	387 (38.5)	1,351 (42.0)	–
Working	460 (57.6)	784 (55.6)	619 (61.5)	1,863 (58.0)	–
Education status					0.16
High school or below	193 (24.3)	311 (22.1)	255 (25.4)	759 (23.7)	–
Above high school	601 (75.7)	1,095 (77.9)	749 (74.6)	2,445 (76.3)	–
Cohort study					<0.01
OAI	464 (58.1)	892 (63.3)	558 (55.4)	1,914 (59.5)	–
MOST	296 (37.1)	477 (33.8)	405 (40.2)	1,178 (36.6)	–
CHECK	38 (4.8)	41 (2.9)	45 (4.4)	124 (3.9)	–
At the knee level					
No. of knees	1,218	2,114	1,525	4,857	–
Kellgren-Lawrence grade‡					0.43
Minimal (grade 2)	689 (56.6)	1,176 (55.6)	1,176 (55.6)	2,716 (55.9)	–
Moderate (grade 3)	417 (34.2)	699 (33.1)	699 (33.1)	1,623 (33.4)	–
Severe (grade 4)	112 (9.2)	239 (11.3)	239 (11.3)	518 (10.7)	–
Knee pain, mean ± SD	3.7 ± 3.9	3.1 ± 3.6	3.7 ± 3.9	3.4 ± 3.8	<0.01
WOMAC score (range 0–20)					

* Except where indicated otherwise, values are the number (%). The percentage calculations are based on complete case (i.e., excluding the missing values). A decrease in body mass index (BMI) was defined as a decrease of ≥1 BMI unit; stable BMI was defined as a decrease or increase of <1 BMI unit; and an increase in BMI was defined as an increase of ≥1 BMI unit. Chi-square and Kruskal-Wallis tests were used for comparisons between BMI change groups. OAI = Osteoarthritis Initiative study; MOST = Multicenter Osteoarthritis Study; CHECK = Cohort Hip and Cohort Knee study; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† Normal BMI was defined as a BMI between 18.5 kg/m^2 and <25.0 kg/m^2, overweight as a BMI between 25.0 kg/m^2 and <30.0 kg/m^2, and obese as a BMI of ≥30.0 kg/m^2. Participants who had a BMI in the underweight category (BMI <18.5 kg/m^2) were excluded from the cohort.
‡ Knees with a Kellgren-Lawrence grade of none (grade 0) or doubtful (grade 1) were excluded from these analyses.

Degeneration of individual structural features of the knee. We assessed the association between change in BMI from baseline to 4–5 years of follow-up and the degeneration of 3 individual structural features of the knee as assessed by radiography (i.e., an increase from baseline of ≥1 OARSI grade) in the incidence and progression cohorts (Tables 3 and 4). These 3 structural features are: the space between the femur and tibia in the knee joint (where degeneration is indicated by joint space

Table 3. Association of change in body mass index between baseline and 4–5 years of follow-up with the risk of incidence of knee osteoarthritis, as shown in univariate and multivariable analyses of the incidence cohort*

Outcome	Univariate analysis		Multivariable analysis†	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Overall structural defects of knee osteoarthritis	1.03 (0.99–1.06)	0.13	1.05 (1.02–1.09)	<0.01
Medial joint space narrowing	1.05 (1.01–1.09)	<0.01	1.08 (1.04–1.12)	<0.01
Medial femoral osteophytes	1.09 (1.04–1.13)	<0.01	1.07 (1.03–1.12)	<0.01
Medial tibial osteophytes	1.03 (1.00–1.06)	0.09	1.05 (1.01–1.08)	<0.01
Lateral joint space narrowing	0.98 (0.94–1.03)	0.50	1.01 (0.96–1.06)	0.69
Lateral femoral osteophytes	1.02 (0.98–1.07)	0.35	1.04 (0.99–1.09)	0.11
Lateral tibial osteophytes	1.00 (0.96–1.04)	0.94	1.02 (0.98–1.06)	0.32

* Incidence of knee osteoarthritis is defined as having a Kellgren-Lawrence (KL) grade of ≥2 at follow-up for those without knee osteoarthritis (i.e., KL grade of 0 or 1) at baseline. The degeneration in individual radiographic features is defined as an increase by ≥1 unit in the Osteoarthritis Research Society International (OARSI) grades from baseline to follow-up. OR = odds ratio; 95% CI = 95% confidence interval.
† Adjusted for KL grade or OARSI grade at baseline for analyses of overall or individual structural defects, respectively, BMI category at baseline, age at baseline, sex, race, walking (seldom, sometimes, or often) or not walking for physical activity at baseline, knee pain at baseline (as assessed by the WOMAC score), smoking status at baseline, marriage status at baseline, number of comorbidities at baseline, employment status at baseline, education status at baseline, and cohort study (i.e., OAI, MOST, or CHECK).

narrowing), the surface of the femur (where degeneration is indicated by femoral osteophytes), and the surface of the tibia (where degeneration is indicated by tibial osteophytes), on the medial and lateral sides of the knee.

For both the incidence and progression cohorts, an association between change in BMI and degeneration of joint space (i.e., narrowing) was only seen for the medial side of the knee, not for the lateral side of the knee. Specifically, the adjusted OR for joint space narrowing was 1.08 (95% CI 1.04–1.12) for the medial side of the knee in the incidence cohort, and, similarly, the adjusted OR was 1.08 (95% CI 1.03–1.12) for the medial side of the knee in the progression cohort (it is coincidental that these results appear almost identical when expressed to 2 decimal places).

The association between change in BMI and degeneration of the femoral and tibial surfaces (as indicated by osteophytes) was also seen on the medial but not the lateral side of the knee in the incidence cohort, with an adjusted OR of 1.07 (95% CI 1.03–1.12) for osteophytes on the femoral surface of the medial side of the knee, and an adjusted OR of 1.05 (95% CI 1.01–1.08) for osteophytes on the tibial surface of the medial side of the knee (Table 3). In the progression cohort, however, there was no significant association between change in BMI from baseline to 4–5 years of follow-up and degeneration of the femoral or tibial surfaces (as indicated by osteophytes) on either the medial or lateral sides of the knee (Table 4).

Sensitivity analyses. The results from all sensitivity analyses were aligned with the conclusions from our primary analyses (above). The first sensitivity analysis showed that our method of variable selection for the multivariable analyses did not alter the

Table 4. Association of change in body mass index between baseline and 4–5 years of follow-up with the risk of progression of knee osteoarthritis, as shown in univariate and multivariable analyses of the progression cohort*

Outcome	Univariate analysis		Multivariable analysis†	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Overall structural defects of knee osteoarthritis	1.05 (1.01–1.09)	<0.01	1.05 (1.01–1.09)	<0.01
Medial joint space narrowing	1.08 (1.04–1.12)	<0.01	1.08 (1.03–1.12)	<0.01
Medial femoral osteophytes	1.03 (1.00–1.07)	0.07	1.04 (1.00–1.08)	0.06
Medial tibial osteophytes	1.01 (0.97–1.04)	0.75	1.01 (0.97–1.04)	0.65
Lateral joint space narrowing	0.99 (0.94–1.05)	0.79	1.00 (0.94–1.06)	0.96
Lateral femoral osteophytes	0.98 (0.94–1.02)	0.26	0.98 (0.95–1.02)	0.40
Lateral tibial osteophytes	1.03 (0.99–1.06)	0.17	1.03 (1.00–1.07)	0.08

* Progression of knee osteoarthritis is defined as an increase by ≥1 unit in the Kellgren-Lawrence (KL) grade for those with knee osteoarthritis (i.e., KL grade ≥2) at baseline. The degeneration in individual radiographic features is defined as an increase by ≥1 unit in the Osteoarthritis Research Society International (OARSI) grades from baseline to follow-up. OR = odds ratio; 95% CI = 95% confidence interval.
† Adjusted for KL grade or OARSI grade at baseline for analyses of overall or individual structural defects, respectively, body mass index category at baseline, age at baseline, sex, race, walking (seldom, sometimes, or often) or not walking for physical activity at baseline, knee pain at baseline (as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]), smoking status at baseline, marriage status at baseline, number of comorbidities at baseline, employment status at baseline, education status at baseline, and cohort study (i.e., OAI, MOST, or CHECK).

conclusions from this study (Supplementary Tables A and B, http://onlinelibrary.wiley.com/doi/10.1002/art.42307). The second sensitivity analysis showed that a history of knee injury was not a significant contributor to the outcomes of incidence and progression for the overall structural defects of knee osteoarthritis (Supplementary Tables C and D, http://onlinelibrary.wiley.com/doi/10.1002/art.42307). The third sensitivity analysis, which included participants with cancer or a BMI in the underweight category at baseline or during follow-up, showed that while our findings of significant associations did not change, there were additional significant associations between change in BMI and the incidence and progression of osteophytes. This shows that the inclusion of individuals with cancer or an underweight BMI could have introduced confounding effects in the results (Supplementary Tables E and F, http://onlinelibrary.wiley.com/doi/10.1002/art.42307). The results from the fourth sensitivity analysis showed that there was no confounding effect in the results due to potential alterations in gait biomechanics from having the other knee replaced (Supplementary Tables G and H, http://onlinelibrary.wiley.com/doi/10.1002/art.42307). The final sensitivity analysis showed that decrease in height due to aging was not a confounder for the association between change in BMI and the incidence and progression of knee osteoarthritis (Supplementary Tables I and J, http://onlinelibrary.wiley.com/doi/10.1002/art.42307).

Population attributable fractions. The estimated population attributable fractions suggested that if all knees in the population were exposed to a decrease in BMI of 1 unit (assuming nothing else changed), the risk of incidence of the structural defects of knee osteoarthritis would be reduced by 13% (95% CI 2–22%) (i.e., the risk would be reduced from the mean observed risk of 15.8% to 13.8%), and the risk of progression would be reduced by 10% (95% CI 0–20%) (i.e., from the mean observed risk of 22.8% to 20.5%) (Table 5). Our analysis of subpopulations of participants of different BMI categories showed evidence that a decrease in BMI would be effective in those of all BMI categories for reducing the incidence and progression of the structural defects of knee osteoarthritis (Table 5).

Table 5. Estimated population attributable fraction associated with a one-unit decrease in BMI among participants in the knee osteoarthritis incidence and progression cohorts, in the study population overall and by BMI category*

Group	Estimated population attributable fraction (95% CI)	
	Incidence cohort	Progression cohort
All participants (BMI ≥18.5 kg/m^2)	0.13 (0.02, 0.22)	0.10 (0.00, 0.20)
Participants with normal BMI†	0.15 (0.02, 0.26)	0.12 (−0.01, 0.23)
Participants with overweight BMI†	0.13 (0.02, 0.23)	0.11 (0.00, 0.22)
Participants with obese BMI†	0.11 (0.02, 0.19)	0.09 (0.00, 0.18)

* The estimated population attributable fraction (with 95% confidence interval [95% CI]) represents reduction in the proportions of participants with incidence or progression of structural knee osteoarthritis associated with a 1-unit decrease (i.e., decrease of 1 kg/m^2) in body mass index (BMI).
† Normal BMI was defined as a BMI between 18.5 kg/m^2 and <25.0 kg/m^2, overweight as a BMI between 25.0 kg/m^2 and <30.0 kg/m^2, and obese as a BMI of ≥30.0 kg/m^2.

DISCUSSION

This multi-cohort study demonstrated an association between change in BMI and both the incidence and progression of the structural defects of knee osteoarthritis as determined by evaluation of radiographs. The impact of change in BMI was seen in the medial but not the lateral side of the knee. The size of the associations can be considered weak; a 1-unit decrease in BMI corresponded to a 4.76% reduction in odds of the incidence and progression of knee osteoarthritis. However, a 5-unit decrease in BMI, which is an amount that can lead to a reduction in BMI category (e.g., from overweight to normal), reduced the odds of incidence and progression by 21.65%. Our findings thus suggest that reducing BMI could be an intervention to prevent, delay, or slow the structural defects of knee osteoarthritis.

The current multi-cohort study was strengthened by the use of a large sample from 3 cohorts, with a total of 9,683 knees from 5,774 participants in the incidence cohort and 6,075 knees from 3,988 participants in the progression cohort, followed up over 4–5 years, and with 19.0–20.0% of participants exposed to a decrease in BMI of ≥1 unit in the incidence cohort and 44.3–45.2% exposed to an increase in BMI of ≥1 unit in the progression cohort. In addition to these strengths, we used both knees of participants to avoid bias due to the systematic exclusion of 1 knee from each participant. Lastly, we studied incidence and progression separately, which enabled us to investigate the potential association between change in BMI in participants without or with knee osteoarthritis at baseline. Specifically, our study extends the findings from 2 previous publications that showed an association between weight loss and reduced incidence of the structural defects of knee osteoarthritis in female participants (11,12), by showing this benefit in a mixed cohort of male and female participants.

Our multi-cohort study further advances previous knowledge in that it demonstrated an association between a decrease in BMI and the progression of the overall structural defects of knee osteoarthritis, which had been shown previously in studies with long follow-up in a single cohort (the OAI cohort) (17,18,20,22,23), therefore extending the generalizability of previous findings. With this, we also extend the findings from previous long-term follow-up studies by showing the location of structural compartments in the knee joint that are associated with change in BMI:

specifically medial joint space narrowing and medial femoral and tibial osteophytes (for incidence) and medial joint space narrowing (for progression).

Our findings suggest that not only could decreasing BMI prevent or delay the incidence of knee degeneration in individuals who do not have knee defects, it could also prevent, delay, or slow the progression of knee degeneration for those in whom knee degeneration has already commenced. As we treated change in BMI as a continuous variable, a dose-response relationship was found to exist, meaning that greater decreases in BMI would provide more benefit. A dose-response benefit associated with a loss of 5–10% of weight on symptoms of knee osteoarthritis and loading has been shown in several studies (5,7,8,35). Other previous research has shown that compared to individuals who lost less weight in a lifestyle intervention (i.e., decrease of <5%), individuals who lost more weight in the intervention (i.e., decrease of >10% and up to 20%, or decrease of >20%) exhibited greater reductions in both symptoms of knee osteoarthritis and joint inflammation (10). Thus, the above studies demonstrate a dose-dependent association between weight loss and the symptoms of knee osteoarthritis (5,7,8,10,35), and our current study extends this prior knowledge by showing a dose-dependent association between weight loss (as indicated by decrease in BMI) and reduced incidence and progression of the structural defects of knee osteoarthritis.

This multi-cohort study showed that the association between decrease in BMI and reduced incidence and progression of the structural defects of knee osteoarthritis was seen in participants with various characteristics. Notably, the associations between change in BMI from baseline to 4 or 5 years of follow-up and the incidence/progression of knee osteoarthritis were seen regardless of sex (as mentioned above), severity of knee degeneration at baseline, and BMI at baseline. Elaborating on BMI at baseline, the association between change in BMI from baseline to 4–5 years of follow-up and protection against structural degeneration of the knee was not only seen in participants with a status of overweight or obesity (i.e., in those with a BMI ≥25 kg/m^2), but also in participants with a BMI in the normal range (i.e., 18.5 to <25 kg/m^2). Similarly, we previously reported that the association of weight loss with reduced incidence of knee replacement was seen in individuals with overweight or obesity as well as in those with a BMI in the normal range (i.e., 18.5 to <25 kg/m^2) (36). Additionally, our estimated population attributable fractions showed that if all knees in the population—whether from participants with a BMI in the normal, overweight, or obese range—were exposed to a decrease in BMI of 1 unit (assuming nothing else changed), the risk of incidence and progression of the overall structural defects of knee osteoarthritis would be reduced by 13% and 10%, respectively (i.e., mean observed risk of incidence of structural defects of knee osteoarthritis changing from 15.8% to 13.8%; mean observed risk of progression of structural defects of knee osteoarthritis changing from 22.8% to 20.5%). Current international clinical guidelines for the management of osteoarthritis (37–42) recommend weight loss in individuals with osteoarthritis and a BMI in the overweight to obese range. The current findings suggest that reducing BMI could be a useful strategy against knee osteoarthritic degeneration in a wider variety of individuals, not only for delaying or slowing progression of the structural defects of knee osteoarthritis in those in whom knee degeneration has already commenced, but also for preventing knee degeneration in those with intact knees. Our findings also suggest that reducing BMI could be a useful strategy for preventing, delaying, or slowing knee degeneration not only in individuals with overweight or obesity, but also in those with a normal BMI. However, the potential benefits of a decrease in BMI need to be considered alongside the potential dangers of weight loss in those with a normal BMI, especially among elderly adults (43), such as increased risk of hip fracture (44,45) and increased risk of mortality (46). Future research into the effects or associations of change in BMI on osteoarthritis could benefit by including individuals with normal BMI as well as those with overweight or obesity.

Our study demonstrated that the impact of change in BMI is mainly on the medial side of the knee as compared to the lateral side of the knee. This finding is in line with literature reporting that higher rates of cartilage loss generally occur on the medial side of the knee rather than on the lateral side of the knee in those with knee osteoarthritis (47,48), and that the medial side of the knee carries more force from weight than the lateral side (49). Taken together, these findings suggest that reduced mechanical loading on the knee joint—notably on the medial side—is a possible contributor to the association observed between a decrease in BMI and the reduced incidence and progression of the structural defects of knee osteoarthritis, especially given that increased weight bearing contributes to knee degeneration in obesity (50–53). Indeed, research shows that every 1-kg reduction in body weight results in a 2-fold and 4-fold decrease from baseline in joint loads during walking and daily activities, respectively (8,54).

Our study had several limitations. The first limitation comes from the observational nature of the study. The findings of this study are associative rather than causative because it is not a randomized controlled trial. Therefore, future randomized controlled trials are required to demonstrate causality. Second, we did not adjust our primary multivariable analyses for history of knee injury. However, our sensitivity analysis on the subset of participants for whom history of knee injury was available showed that knee injury had no significant effect on the results. Third, there were likely latent confounders in our analyses which were not captured in the 3 cohort studies underpinning our multi-cohort study, such as increased BMI due to a decrease in height with aging. Research shows that the average increase in BMI due to decrease in height (not increase in weight) is 1.4 kg/m^2 for men and 2.6 kg/m^2 for women between the ages of 30 to 80 years

(55). However, our sensitivity analysis showed that decreased height with aging was not a confounding factor in our results. As a fourth limitation, we assessed change in BMI between baseline and 4–5 years of follow-up, but BMI can fluctuate during that time and these changes were not captured in the 3 cohort studies we used. Finally, the cohorts we used in our multi-cohort study were predominantly composed of White and elderly participants; therefore our findings have limited transferability beyond this specific population.

To conclude, this study showed an association between change in BMI and the incidence and progression of structural defects in knee osteoarthritis, notably on the medial side of the knee. While we found evidence of association, not causality, individuals with overweight or obesity—and potentially also those of normal BMI—may benefit from a decrease in BMI to prevent, delay, or slow the structural defects of knee osteoarthritis.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Salis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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