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Knee osteoarthritis is greatest in obesity with cardiometabolic clustering

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Abstract

Objective—To assess the role of obesity and metabolic dysfunctionality with knee osteoarthritis (OA), knee joint pain and physical functioning performance, adjusted for joint space width (JSW) asymmetry.

Methods—Knee OA was defined with a Kellgren-Lawrence (K-L) score≥2 on weight-bearing radiographs. Obesity was defined as a body mass index≥30 kg/m^2. Cardiometabolic clustering classification was based on having two or more of the following factors: low high-density lipoprotein cholesterol or elevated levels of low density lipoprotein cholesterol, triglycerides, blood pressure, c-reactive protein, waist:hip ratio, or glucose or diabetes. The difference between lateral and medial knee JSW was used to determine joint space asymmetry.

Results—In a sample of women (n=482, mean age 47 years), prevalences of knee OA and persistent knee pain were 11% and 30%, respectively. The knee OA prevalence in non-obese women without cardiometabolic clustering was 4.7% as compared to 12.8% in obese women without cardiometabolic clustering and 23.2% in obese women with cardiometabolic clustering. Non-obese women without cardiometabolic clustering were less likely to perceive themselves as limited compared to women in all other obesity/cardiometabolic groups (P<0.05). Similar associations were seen with knee pain and physical functioning measures. The inclusion of a joint space asymmetry measure was associated with knee OA but not with knee pain or physical functioning.

Conclusion—Knee OA was twice as frequent in obese women with cardiometabolic clustering compared to those without, even when considering age and joint asymmetry. Obesity/ cardiometabolic clustering was also associated with persistent knee pain and impaired physical functioning.

Keywords

knee osteoarthritis; pain; physical functioning; obesity; cardiometabolic clustering; joint space asymmetry

Osteoarthritis (OA), based on radiographs, is a highly prevalent joint disease affecting 30–50% of adults aged 65 years or greater (1,2). Age, female sex, obesity, and previous injury

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are consistently reported risk factors for OA (3). Obesity is the most conspicuous risk factor (4–7) and of great interest because it is potentially modifiable. Further, there is concern that with the increasing frequency of obesity, including the escalating frequency of morbid obesity worldwide, there will be an arthritis epidemic.

There is debate about how obesity contributes to the initiation and progression of osteoarthritis; resolution of this debate could inform the selection of viable interventions. Candidate mechanisms for the contribution of obesity to joint health status include 1) an excessive and/or misdirected biomechanical load that stimulates excess osteoblast or chondrocyte biosynthesis in the bone or cartilage (8); 2) a generalized negative metabolic environment reflecting a systemic inflammatory response (9–13) or response to the secretory products of adipose tissues; or 3) both biomechanical and metabolic effects.

Hart and Spector (4) hypothesized that the association between obesity and OA in non-weight bearing joints includes a metabolic mechanism, but the data associating osteoarthritis with obesity-related metabolic factors is mixed. Some studies have reported significant associations between knee OA or hand/wrist OA and cardiovascular risk factors (hypertension, uric acid, cholesterol) (10,11) while other knee OA studies have failed to identify significant relationships (12,13). While some studies have related higher concentrations of C-reactive protein to both greater prevalence and incidence of knee osteoarthritis (9,14,15), not all studies have reported this (16,17).

The patterns (10,11,16,18) of associations between metabolic factors and osteoarthritis has led some to declare that the primary contribution of obesity to OA may be joint-specific and dependent upon the degree to which obesity contributes to the mechanical loading of articular cartilage at a specific site (19–21). For example, varus knee alignment is thought to place mechanical loads, including those loads generated by excess body mass, mostly on the medial tibiofemoral compartment (22). The impact of excess body mass at this site could generate both mechanical and metabolic contributions whereas the impact of excess body mass on hand OA may be more reflective of the metabolic contribution.

We hypothesized that obesity was associated with both a metabolic component and with joint asymmetry in relation to radiograph-defined knee OA. We also hypothesized that these metabolic and biomechanical components would be associated with knee joint pain and measures of physical functioning.

MATERIALS AND METHODS

Study population

The Michigan Bone Health and Metabolism Study (MBHMS) is a longitudinal, population-based study conducted among women living in and around Tecumseh, Michigan. MBHMS enrollees were the daughters of the Tecumseh Community Health Study participants who, in 1988, were between the ages of 20 and 40 years, not pregnant and premenopausal. These women were contacted using letters, telephone calls and in-person visits and more than 80% agreed to participate. In 1992, a second sampling frame based on a community census of Tecumseh was developed to include women whose parents had not participated in the TCHS. As a result, an additional 121 women in the desired age range of 24–44 years (of a possible 135 eligible) were recruited (90% participation rate). The total MBHMS cohort consists of 664 participants, aged 24–44 years in 1992. All women in the MBHMS study are Caucasian.

While MBHMS participants have been followed annually since 1992, this report is based on data collected at the MBHMS follow-up visit 11 (in 2002/2003). Included in this report is

follow-up visit 11 data from 482 MBHMS women with (1) readable knee radiographs (to characterize OA status); (2) physical measures assessment and blood/urine for assay of cardiometabolites (to characterize cardiometabolic obesity group) and (3) performance-based and self-reported physical functioning information.

The University of Michigan Institutional Review Board approved the study protocol, and written informed consent was obtained from each participant.

Osteoarthritis measures

Knee radiographs were taken using semi-flexed positioning (23) using General Electric radiographic equipment (model X-GE MPX-80; General Electric Medical Systems, Milwaukee, WI) and Kodak film (X-DA with Kodak rare earth-intensifying screens, Eastman Kodak, Rochester, NY). The source-film distance was 40 inches and standard radiographic techniques were used. Radiographs were evaluated by two readers with a third consensus reader for the presence of OA defined by the Kellgren and Lawrence (K-L) scale depicted in the Atlas of Standard Radiographs of Arthritis (0=normal, 1=doubtful OA, 2=minimal OA, 3=moderate OA, and 4=severe OA) (24). This scale is based on the degree of osteophyte formation, joint space narrowing, sclerosis, and joint deformity. OA was defined as the presence of at least one knee with a grade of 2 or higher. Apart from the K-L criteria, joints were classified as showing changes consistent with rheumatoid arthritis, missing, or uninterpretable.

As a part of the quality assurance program, readers reviewed the K-L grading criteria and evaluated films that were representative of each K-L level. Then 25 knee radiographs were evaluated independently by each reader and their results were compared for consistency. After completing standardization procedures, readers independently evaluated radiographs of both knees. The scores from two readers were compared and any discordant scores were reread and, if necessary, subjected to consensus evaluation. Further, a sample of 110 knee radiographs, selected for use in evaluations, were interleaved with newly acquired films to be re-read to identify potential drift in scoring over time.

Joint space width (JSW) was measured on the medial and lateral aspects of each knee radiograph with electronic calipers. Measurement locations were ascertained by identifying the centerline of each joint using the medial and lateral tibial condyle margins and then establishing points that were 50% and 75% between the centerline and the condylar margin. Two readers measured the JSW independently and if the difference between the two readers was greater than 0.4 mm, the JSW was re-measured by the two readers. The absolute difference between the medial and lateral JSW at the 75% location was used as a proxy of joint asymmetry. Long films were not available to estimate the degree of varus at the knee.

Pain and physical functioning measures

Pain and physical functioning questionnaires are completed by MBHMS participants. The pain questions ask if there has been persistent knee joint pain during the antecedent three years and, if so, the participant is asked if there has been pain at least half the time in the previous month.

The Medical Outcomes Study Short Form (MOS SF-36) 10-item scale was used to describe women's perception of their physical functioning (PF) limitations. This is a widely used questionnaire which has been extensively evaluated for construct validity, internal consistency, and test-retest reliability (25–28) in diverse ethnic groups and age ranges. It includes a 3-item response of “limited a lot”, “limited a little”, or “not limited at all” to the following items: vigorous activities; moderate activities; lifting or carrying groceries; climbing several flights of stairs; climbing one flight of stairs; bending, kneeling, or

stooping; walking more than one mile; walking several blocks; walking one block; or requiring assistance in bathing or dressing. It is scored using norm-based methods and transformed to have a mean of 50 (standard deviation=10) and range 1–100 in the general US population, with a score of 100 indicating the best physical functioning. Scores were categorized into three groups as follows: ≤50 points classified as having substantial limitations, 51–85 classified as having moderate limitations, and 86–100 points classified as not limited. Women categorized as having substantial limitations (≤50 points) could have reported no limitations on, at most, five of the 10 activities. Those classified as having moderate limitations (score of 51–85) could have reported no limitations on, at most, eight of 10 activities, thus allowing for some limitations in vigorous and moderate activities.

Velocity assessment and timed 40-foot walk—Gait and walking ability were assessed with a timed 40-foot walk, measured in seconds, that includes passage over an instrumented gait mat. The gait mat provided data to characterize velocity. Women may walk with assistive devices.

Sit-to-rise—Chair-rise performance was measured when participants rose from a standard-height, armless chair. Participants were asked to fold their arms over their chest and to rise as quickly as possible. Movement time was measured by stop watch from onset of trunk motion on the chair to achievement of upright standing position. If a participant was unable to rise from the chair or sat back down before achieving full upright stance, the rise was so noted. Results from five separate repetitions were averaged.

Grip and leg strength—To measure grip strength, participants were seated in a chair with their lower arm placed at a right angle to the body's sagittal plane with the elbow in 90 degrees of flexion. The hands were placed so that fingers and thumb were parallel to the legs and the wrist was slightly extended to hold the dynamometer. Each participant performed three consecutive grip strength trials with both the dominant and non-dominant hands, squeezing the dynamometer with maximum effort. Results from the three trials were averaged, and the participant's average dominant grip strength was used for analysis.

A portable instrumented chair was used to measure lower leg isometric strength, measured as torque or the product of force and the torque arm length. Torque arm length is equal to the length measured between the lateral joint line of the knee and the bottom surface of the heel plus 0.0251 m, the distance from the top surface of the foot trolley platform and the transducer axis. Participants were encouraged to produce maximum effort for each trial, and torque (Nm) for three successful trials was averaged.

2-pound lift—Participants were timed as they lifted a 2-pound box from the floor to waist height. The box was placed at a standard distance (8”) forward of the toes. Participants could either bend at the knee or waist and the modality was recorded. Inability to lift the box successfully to waist height was flagged.

Timed stair climb—Each participant was asked to climb up and down a set of three standard stairs three times, beginning with the right leg. The amount of time that each participant required to ascend the stairs, turn, and descend the stairs three consecutive times was measured for total movement time (29). In addition, inability to complete the stair climb (i.e., unable because of wheelchair) and the amount and type of assistance needed (e.g., handrails or personal assistant) was recorded.

Functional reach—In the standing posture, participants were asked to do an arm's length forward reach, and then to reach as far as possible without moving their feet. Participants held a marking pen in their hand while doing the arm's length and forward reach, and placed

a mark on a sheet of paper with each reach. The distance between the two marks was measured to determine the forward reach distance.

Cardiometabolic and body composition measures

Glucose was measured using a hexokinase-coupled reaction [Boehringer Mannheim Diagnostics, Indianapolis, IN]. Total cholesterol and triglycerides were analyzed by enzymatic methods; HDL-c was isolated using heparin-2M manganese chloride (30) and LDL-c calculated using the Friedwald equation (31). High sensitivity C-reactive protein (hs-CRP) was measured using ultra-sensitive rate immunonephelometry (Dade-Behring, Marburg, Germany). Two blood pressure measurements were taken using a mercury column manometer after a minimum of 5 minutes of rest with participants in the seated position, and the average of the two values was used. Weight and height, measured with a calibrated balance beam scale and stadiometer, were used to calculate BMI [weight (kg)/height $(m)^2$]. Waist circumference (cm) was measured with a non-stretching tape at the narrowest point of the mid-torso at maximum inhalation. Hip circumference was measured at a point approximately 9 inches below the waist.

Women were classified into one of four cardiometabolic-obesity subgroups based upon their obesity status (non-obese, BMI<30 kg/m^2 or obese, BMI≥30 kg/m^2) and the presence or absence of two or more cardiometabolic defects, as described in Table 1. Among those classified as having cardiometabolic defects, obese women had greater numbers of cardiometabolic defects, on average, as compared to non-obese women.

Data analyses—Univariate distributions of the continuous measures of body size, metabolic products, joint space width (JSW), joint space difference, and physical functioning measures were examined for normality. To meet the assumptions of normality and to reduce skewness, natural log transformations were applied, as necessary. The frequencies of the K-L score for osteoarthritis of the knee and categorical covariates, including measures of pain and perception of physical functioning, were examined.

Knee K-L scores, pain and measures of physical functioning were outcome measures while variables representing obesity/cardiometabolic status and the difference between the medial and lateral joint space were explanatory variables. *P*-values for comparisons between obesity/cardiometabolic groups or knee OA groups were based on the non-parametric Wilcoxon signed rank test for continuous variables or chi-square tests for categorical variables. Analysis of variance and analysis of covariance were used to determine the least squared means and standard errors of groups defined by the combinations of the presence or absence of knee OA/cardiometabolic group or physical functioning/cardiometabolic group. Regression analyses were used to evaluate the association of the difference in JSW in models that also included variables for obesity/cardiometabolic status and age.

P-values (two-sided tests) and 95% confidence intervals (95% CI) were used to identify the likelihood of a true association.

RESULTS

The 2002 prevalence of x-ray-defined knee osteoarthritis in the MBHMS population was 11% and the prevalence of having persistent knee pain during the previous three years was 30%. As seen in Table 2, women with knee OA were 3 years older, 32% heavier, and had more compromised metabolic measures than women without knee OA, with the exception of low density lipoprotein cholesterol (LDL-c) where there was no difference. The two non-obese groups with [(median, inter-quartile range (IQR)), 26.81, 3.72) and without (23.76, 4.66)] cardiometaboic (CM) defects had significantly different median BMI values

($P<0.0001$) but there were no differences in the median BMI values (IQR) between the two obese groups with (34.82, 6.22) and without (32.97, 7.17) CM defects ($P=0.06$).

Cardiometabolic clustering, obesity and knee OA

As seen in Table 3, there was a higher knee OA prevalence in obese women with CM clustering (23.2%) compared to the referent group of non-obese women without CM clustering (4.7%), with an odds ratio of 6.2 (95% CI 2.93, 13.07). Obese women without CM clustering had a knee OA prevalence of 12.8%; the odds of their having knee OA was 3.0 (95% CI 1.03, 8.71) as compared to the referent group. Non-obese women with CM clustering did not have a significantly greater odds of having knee OA than non-obese women without CM clustering.

Cardiometabolic clustering, obesity, and pain

As seen in Table 4, obese women with CM clustering reported significantly more persistent knee pain during the previous 3 years ($P<0.05$) compared to women in the other three cardiometabolic-obesity groups.

Cardiometabolic clustering, obesity, and physical functioning

Non-obese women without CM clustering were significantly more likely to perceive themselves as not limited, based on the SF-36 PF score, compared to women in the other three categories (vs. non-obese with CM clustering $P=0.004$; vs. obese without CM clustering $P=0.03$; vs. obese with CM clustering $P<0.0001$). There were no differences in the distribution of perception of limitation among women in the other three cardiometabolic-obesity groups.

Obese women with CM clustering had a consistent 10% deficit in physical performance capacity compared to non-obese women without CM clustering. Obese women with CM clustering had significantly greater stair climb times and 2-pound lift times than those in any other category (shown in Table 5). Among non-obese women, those with CM clustering had significantly greater walk times and less gait velocity than those without CM clustering. Not surprisingly, the obese women tended to have significantly less quadriceps torque than those who were not obese. The association of grip strength and obesity status varied by cardiometabolic status (Table 6).

Women with CM clustering (both obese and non-obese groups) had significantly shorter forward reach distances compared to non-obese women without CM clustering.

Competitive modeling of biomechanical and metabolic components

To examine the potential effect of obesity generating biomechanical and metabolic components simultaneously, statistical models included variables representing obesity-cardiometabolic status and the lateral-medial JSW difference; all models were adjusted for age. Both JSW difference and obesitycardiometabolic status were associated with knee OA. After adjustment for age, a 1 mm increase in JSW difference was associated with 2.1 times greater odds of having knee OA (95% CI 1.59–2.89) and those who were obese with CM clustering had 4.5 times greater odds of having knee OA (95% CI 1.88–11.00) compared to the referent group of non-obese women without CM clustering.

While obesity-cardiometabolic status was associated with persistent knee joint pain, JSW difference was not. Those who were obese with CM clustering had 2.5 times greater odds of having persistent knee pain (95% CI 1.50–4.16) compared to the referent group. In models of physical functioning, those who were obese with CM clustering consistently had

significantly poorer functioning, but there was no association with the JSW difference measure (data not shown).

DISCUSSION

We identified obesity as being highly associated with radiograph defined knee OA, knee joint pain, perceived physical functioning and multiple measures of physical functioning performance. However, while both OA and obesity are highly prevalent in this sample, it is the co-presence of cardiometabolic clustering accompanying obesity that exacerbates the association with radiograph-defined knee OA, knee pain, and physical performance measures. The presence of cardiometabolic clustering among obese women is important because we identified that the prevalence of knee OA is almost twice as great in these women compared to obese women without cardiometabolic clustering. Further, there was no significant association of obesity in the pain measures or many of the physical functioning performance measures unless obesity was accompanied by cardiometabolic clustering. The presence of the same patterns of association of obesity with cardiometabolic clustering in relation to pain and physical performance suggests that there is internal validity in this association.

It is important to note, however, that being obese is not synonymous with clustering of cardiometabolic risk factors. Twenty-five percent of obese women in this sample did not have cardiometabolic clustering. Likewise, we have previously reported that approximately one-third of obese men and women of the NHANES III sample, representative of the US population, did not have evidence of cardiometabolic clustering (37).

There is substantial opportunity for obesity to have a physiological role in the development and subsequent progression of knee osteoarthritis. Recognition of the potential for this key role has emerged over the past 10 years with the understanding that adipose tissue secretes hormones with receptor-mediated action like other endocrine organs. We hypothesize that the observed relationship between cardiometabolic abnormalities and obesity is a reflection of the relationships between products secreted by adipose tissue and cardiovascular disease risk factors. We (38) have published data from a subset of this population in which greater increases in leptin over the menopause transition were associated with greater decreases in high-density lipoprotein cholesterol (HDL-c) and greater increases in diastolic blood pressure, and glucose, insulin and insulin resistance (all $P<0.05$). Larger decreases in adiponectin over the menopause transition were associated with greater increases in systolic blood pressure, insulin and insulin resistance and with greater decreases in HDL-c.

Leptin, encoded by the obesity gene (ob) (39) to reduce food intake and increase energy expenditure (40) thereby indirectly mediating body fat stores (41), was initially thought to be limited to the adipocytes, but it has been shown that osteoblasts and chondrocytes are capable of leptin synthesis and secretion (41,42) and leptin receptors have been found in articular cartilage (43). Leptin concentrations found in the synovial fluid of people with OA correlated with their BMI. In animal models, leptin stimulated anabolic activity in chondrocytes, including induction of IGF-1 and TGFβ synthesis at both the messenger RNA and protein levels. IGF-1 and TGFβ are activated in response to cartilage damage (44–46), and the anabolic activity of chondrocytes serve as a repair mechanism for damaged cartilage.

Levels of adiponectin, an adipokine associated with insulin sensitivity regulation (47,48), are low in obese individuals and in those with cardiovascular disease. Adiponectin is present in synovial fluid (49,50) cartilage, osteophytes, infrapatellar fat pad, and menisci (51,52) of OA patients, and functional adiponectin receptors have been expressed in chondrocytes (53).

Because of the decreased levels of adiponectin among those with cardiovascular disease, adiponectin has been hypothesized to have anti-inflammatory effects (47); however, recent work among those with joint diseases suggests that adiponectin may, in fact, have pro-inflammatory effects and be involved with cartilage matrix degradation (53–55). Lago et al. (53) recently demonstrated that adiponectin induced the expression of NOS2 and stimulated IL-6, MMP-3, MMP-9 and MCP-1 release.

As recently reviewed, the additional loading associated with obesity is almost universally believed to produce aberrant mechanics, raising stress within connective-tissue structures, generating malalignment and resulting in musculoskeletal injury (56). There are numerous mechanical theories as to how obesity can impact movement, but the evidence directly linking musculoskeletal injury to altered biomechanics in the obese is not extensive. It is thought that obesity leads to both increased gravitational and muscle forces across the knee joint, and that once cartilage degradation is present, knee OA progresses more rapidly in the presence of larger-than normal knee loads during gait (22). Further, Messier et al. (57) have reported that the peak vertical ground-reaction forces (GRF) increased in almost direct proportion with body weight in obese adults who were walking. Recent work by Browning and Kram in young adults (58) demonstrated that net muscle moments were significantly greater in obese versus normal-weight subjects and were due to greater GRF in the obese group. Obesity greatly increases the biomechanical loads involved in walking, a frequently proposed therapy for obesity, and these loads increase with walking speed.

BMI has been related to knee OA severity in those with varus knees but not in those with valgus knees (59). While these investigators concluded that much of the effect of BMI on the severity of medial tibiofemoral OA was explained by varus malalignment, the investigators statistically controlled for gender rather than reporting the association stratified by gender. The impact of obesity on alignment of the tibiofemoral compartment may be different in men vs. women because of the inherent gender difference in pelvic alignment.

We found that our proxy measure of tibiofemoral joint asymmetry (the difference between lateral and medial joint space width) was significantly associated with having knee OA as a main effect concurrently with cardiometabolic status as a main effect. Interestingly, however, knee joint asymmetry was not associated with pain or physical functioning measures whereas the cardiometabolic obesity was associated with more pain and poorer physical functioning. This may have occurred because this joint asymmetry proxy measure is directly associated with the radiograph defined OA, and only indirectly associated with the pain and functioning measures.

This study has several strengths and limitations. The study includes a direct measure of radiograph-defined knee OA along with measures of persistent knee pain and physical performance/functioning. Further, because this population-based sample is limited to women, our findings are not complicated by the increasing evidence of differences in body composition and cardiometabolic measures between men and women. Thus, our findings may have a greater impact on women – the group that is greatest at risk for knee osteoarthritis. Likewise, the restricted age of our population (less than 60 years of age) allows us to minimize the effects of aging, the primary risk factor for knee OA, on the cardiometabolic results. Nevertheless, the impact of cardiometabolic obesity and tibiofemoral joint asymmetry in those older than 60 is yet to be revealed. The major limitation of our study is that it does not include long films to assess varus alignment and so we relied instead upon a proxy joint asymmetry measure, the difference between medial and lateral joint space.

We had hypothesized that obesity was associated with both metabolic and biomechanical alignment in relation to radiograph defined osteoarthritis of the knee. We also hypothesized that these metabolic and biomechanical components would be associated with knee joint pain and measures of physical functioning. While obesity was strongly associated with knee OA, the most prominent associations with knee OA, pain, or functioning occurred when obese women also demonstrated clustering of cardiometabolic patterning. This observation has important ramifications for the selection of both behavioral and therapeutic treatments of knee osteoarthritis.

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Table 1

Measures of cardiometabolic status. Participants with two or more of the criterion were classified as having cardiometabolic defects.

- Self-reported diabetes, use of diabetes medications, or glucose > 126 mg/dL*
- CRP ≥ 2 mg/L†
- HDL-c ≤ 45 mg/dL or LDL-c > 160 mg/dL‡
- Triglycerides ≥ 200 mg/dL‡
- Waist:Hip ratio ≥ 0.81 cm:cm¶
- Systolic blood pressure > 135 mmHg, diastolic blood pressure > 85 mmHg, or use of high blood pressure medications//

*Per the American Diabetes Association recommendation (32)

†Per the previously used cut point for elevated high sensitivity C-reactive protein (33,34)

‡Per Adult Treatment Panel III recommendations (35) for high/very high LDL-c and high triglycerides. Note: ATP-III recommendations are for HDL-c < 40 mg/dL but given recent evidence of the importance of high HDL-c values, we chose a slightly higher cutpoint.

¶Per the World Health Organization clinical risk categories of waist:hip ratio (36)

//Values represent the upper-end of the range considered `pre-hypertensive' by the American Heart Association

Table 2

Age, cardiometabolic factors and joint space width measurements (median, interquartile range) in women with and without x-ray defined knee osteoarthritis (OA), MBHMS Visit 11

	No Knee OA		Knee OA		
	Median	**IQR**	**Median**	**IQR**	***P*-value***
	N=429		**N=53**		
Age (years)	47.0	8.0	50.0	5.0	**<0.0001**
Weight (kg)	70.6	23.2	92.9	24.8	**<0.0001**
Body mass index (kg/m^2)	27.3	8.4	35.6	11.1	**<0.0001**
Waist:hip ratio (cm:cm)	0.81	0.10	0.86	0.08	**0.0001**
Glucose (mg/dL)	95.0	13.0	100.0	14.0	**0.02**
CRP (mg/L)	0.19	0.33	0.33	0.36	**0.002**
Lipids					
HDL-c (mg/dL)	54.0	18.0	49.0	14.0	**0.03**
LDL-c (mg/dL)	138.0	45.0	132.5	43.0	0.27
Triglycerides (mg/dL)	117.0	79.0	141.0	116.0	**0.01**
Blood pressure (mmHg)					
Systolic	117.5	19.0	126.0	17.5	**<0.0001**
Diastolic	78.0	12.0	80.0	9.0	**0.0004**
Joint space width (mm)					
Medial	4.27	1.02	4.39	1.27	0.67
Lateral	5.55	1.12	6.28	1.61	**<0.0001**
Difference	1.32	1.11	2.01	1.81	**<0.0001**

**P*-value for between group comparison

Arthritis Rheum. Author manuscript; available in PMC 2010 October 15.

Table 3

At MBHMS Visit 11, the odds (with 95% confidence intervals) of having knee OA (K-L score ≥ 2) according to the presence or absence of cardiometabolic clustering within obesity category

	Cardiometabolic Clustering	N	N (%) with knee OA	OR (95% CI)*
Non-obese				
< 30 kg/m^2	No	212	10 (4.7%)	Reference group
< 30 kg/m^2	Yes	85	5 (5.9%)	1.28 (0.43, 3.87)
Obese				
≥ 30 kg/m^2	No	47	6 (12.8%)	3.00 (1.03, 8.71)†
≥ 30 kg/m^2	Yes	138	32 (23.2%)	6.20 (2.93, 13.07)‡

*Odds ratios and 95% CI are from an unadjusted logistic regression models with non-obese without cardiometabolic clustering group as the referent category.

†$P < 0.05$

‡$P < 0.0001$

Table 4

At MBHMS Visit 11, number of women with persistent knee joint pain in the last three years and knee pain in the last month, by obesity category and cardiometabolic clustering.

	Non-Obese (BMI < 30 kg/m^2)		Obese (BMI ≥ 30 kg/m^2)	
	No cardiometabolic clustering N=212	Cardiometabolic clustering N=85	No cardiometabolic clustering N=47	Cardiometabolic clustering N=138
	N (%)	N (%)	N (%)	N (%)
Persistent knee joint pain during last 3 years	47 (22.2%)*	24 (28.2%)*	12 (25.5%)*	60 (43.5%)
If yes, knee joint pain during half of last month	34 (16.0%)	17 (20.0%)	6 (13.0%)	49 (35.5%)

*Value significantly different than for those who are obese with cardiometabolic clustering ($P < 0.05$). No other pair-wise differences were statistically significant.

Table 5

At MBHMS Visit 11, N (%) in SF-36 physical functioning categories by obesity category and cardiometabolic clustering

	Non-obese (BMI < 30 kg/m^2)				Obese (BMI ≥ 30 kg/m^2)			
	No cardiometabolic clustering N=212		Cardiometabolic clustering N=85		No cardiometabolic clustering N=47		Cardiometabolic clustering N=138	
	N	%	N	%	N	%	N	%
SF-36 physical functioning category								
Not limited	171	80.7*	53	62.4	29	61.7	71	51.5
Moderately limited	36	17.0	27	31.8	16	34.0	53	38.4
Substantially limited	5	2.4	5	5.9	2	4.3	14	10.1

*Value significantly different than for those in other three cardiometabolic obesity categories ($P < 0.05$).

Table 6

At MBHMS Visit 11, average values (back-transformed) for performance-based physical functioning by obesity and cardiometabolic status

	Non-Obese (BMI<30 kg/m2)				Obese (BMI≥30 kg/m^2)				
	No Cardiometabolic Defects		Cardiometabolic Defects		No Cardiometabolic Defects		Cardiometabolic Defects		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Overall *P*-value
Timed stair climb (sec)	15.80¶	0.21	16.26¶	0.35	16.36¶	0.46	18.10*†‡	0.30	**0.0001**
Timed walk (sec)	7.94†¶	0.07	8.26*¶	0.11	8.24	0.15	8.58*†	0.09	0.0001
Velocity (cm/sec)	174.03†‡¶	1.65	167.64*¶	2.46	164.45*	3.36	159.70*†	1.90	0.0001
2-pound lift (sec)	1.58¶	0.03	1.61¶	0.04	1.58¶	0.05	1.74*†‡	0.04	0.001
Quadriceps strength/average torque (Nm)	71.59‡¶	1.61	68.81‡¶	2.41	84.82*†	4.06	80.77*†	2.22	0.0001
Grip strength (kg)	26.13†	0.52	23.46*¶	0.74	25.92	1.09	26.42†	0.66	0.02
Forward reach (cm)	34.87†¶	0.42	32.98*	0.63	34.54	0.87	33.18*	0.49	0.02
Sit-to-rise time (sec)	1.00	0.02	0.99	0.03	1.01	0.04	1.08	0.03	0.06

*Value significantly different than for those who are non-obese without cardiometabolic clustering ($P < 0.05$)

†Value significantly different than for those who are non-obese with cardiometabolic clustering ($P < 0.05$)

‡Value significantly different than for those who are obese without cardiometabolic clustering ($P < 0.05$)

¶Value significantly different than for those who are obese with cardiometabolic clustering ($P < 0.05$)