Title

Association of Serum Low-Density Lipoprotein, High-Density Lipoprotein, and Total Cholesterol With Development of Knee Osteoarthritis

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Is there an association of serum low density lipoprotein, high density lipoprotein or total cholesterol with development of knee osteoarthritis?

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Abstract

Objectives: Studies suggest an association between elevated total serum cholesterol (TC), particularly low-density lipoprotein cholesterol (LDL), and osteoarthritis (OA). We evaluated the association between total cholesterol, LDL, and high-density lipoprotein (HDL) and risk of knee OA.

Methods: We studied participants from the Multicenter Osteoarthritis study (MOST) cohort at risk of developing knee OA. From baseline through 7 years, repeated knee x-rays and MRIs were obtained and knee symptoms were queried. From baseline fasting blood samples, lipids and lipoproteins were analyzed using standard assays. After excluding participants with baseline OA, we defined two sets of cases: those developing radiographic OA and those developing symptomatic OA (knee pain and radiographic OA). Controls did not develop these outcomes. Additionally, we examined worsening of: cartilage loss and synovitis on MRI and of knee pain using the WOMAC scale. We carried out logistic regression adjusting for age, sex, BMI, education, baseline pain, and depressive symptoms, testing total cholesterol and lipoproteins as continuous measures and did sensitivity analyses examining whether commonly used thresholds for high cholesterol, LDL or low HDL increased risk.

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Results: We studied 337 cases with incident symptomatic OA and 283 cases with incident radiographic OA. Mean age at baseline was 62 years (55% women). Neither total, LDL, nor HDL showed a significant association with radiographic or symptomatic OA. Additionally, we found no association of these lipid measures with cartilage loss, worsening synovitis or worsening knee pain.

Conclusion: Our data do not support an association between total cholesterol, LDL or HDL with OA outcomes.

Keywords

Body composition; osteoarthritis; pain; lipids

Osteoarthritis (OA) is the most common form of arthritis and is a leading cause of disability in the United States (1). Its prevalence is estimated at around 30 million in the U.S. and 240 million worldwide, with increasing disease burden attributed to the obesity epidemic and an aging population (1,2). Current treatment focuses on management of pain and improvement of function. Thus far, therapies aimed at delaying structural deterioration of the joint have been unsuccessful in both modifying the course of the disease and reducing pain.

Osteoarthritis has been viewed traditionally as a disease caused by excessive mechanical loading, e.g. “wear and tear,” leading to degeneration of articular cartilage over time. Over the past decade, the understanding of processes underlying the pathology of osteoarthritis have, in addition to loading, increasingly included a model of synovial inflammation driven by a complex interplay of cytokines, metalloproteinases, and reactive oxygen species causing cartilage degeneration and bone loss (2). Studies evaluating OA have identified a link between obesity and OA of hand joints (3–5) suggesting that OA could be caused, in part, by factors unrelated to mechanical load. These findings support current research focusing on the hypothesis that OA is not only a localized joint disease, but an inflammatory disease involving both metabolic and mechanical factors.

Several experimental studies have suggested an association between dyslipidemia and OA. Proposed mechanisms by which this may occur include anti-inflammatory effects of elevated serum high density lipoprotein (HDL) and pro-inflammatory effects of elevated serum low density lipoprotein (LDL) and oxidized LDL. DeMunter et al showed that mice fed a cholesterol-rich diet had LDL accumulation in synovial cells, synovitis and increased ectopic bone formation; they propose a mechanism by which increased levels of oxidized LDL activate synovial macrophages, fibroblasts, and endothelial cells, leading to local inflammation, cartilage loss, and ectopic bone formation (5). (6, 7). Busso, et al showed that synovial fluid and plasma total cholesterol, HDL and LDL were highly correlated with synovial fluid levels of these lipoproteins suggesting that circulating serum lipids are able to freely move into the joint, further strengthening the hypothesis that altered lipid levels in the blood may have a direct effect on joint homeostasis (8).

Given the experimental evidence supporting an association between dyslipidemas and the development of OA, several authors have attempted to evaluate this relationship through observational studies. However, these studies have reported mixed results, highlighting

the need for further research in this area (9, 10). Few of these reports have focused on serum HDL and LDL concentrations, and to our knowledge, only three studies reported longitudinal data. In one longitudinal study, results suggested an increased risk of hand OA with higher levels of HDL, but the sample size was small and confidence intervals wide. The other studies were not about painful OA per se, but focused on MRI bone marrow lesions (BML) and their relation to lipids (11, 12). While these data serve as a starting point in understanding the role that plasma lipids may play in the development of OA, there exists a paucity of literature directly evaluating the relationship between serum lipid and lipoprotein concentrations and incident osteoarthritis, particularly incidence of disease in the knee, the site of most disabling OA.

Using longitudinal data from the MOST cohort, the goal of this study was to comprehensively and longitudinally determine whether circulating total cholesterol, LDL, and HDL were associated with the risk of radiographic and symptomatic knee OA in the MOST cohort.

Subjects and Methods

Study sample

MOST is a large NIH-funded longitudinal observational study focused on symptomatic and radiographic knee OA in a cohort of community dwelling older adults with or at high risk for knee OA (13). The study enrolled 3026 participants age 50–79 years from 2003–2006 at two clinical sites (Iowa City, Iowa and Birmingham, Alabama). Participants' demographic, medical, and lifestyle information as well as imaging were collected at baseline. Participants were followed with repeated examinations at 30, 60 and 84 months.

Weight-bearing, semi-flexed posteroanterior (PA) and lateral views of the knees were obtained at baseline and at each exam according to the MOST radiograph protocol (14). Two readers interpreted and graded all radiographs according to Kellgren-Lawrence (KL) grade and if they disagreed, readings were adjudicated by a panel of three readers (15). MRIs of the knee were acquired at each visit using a 1.0 T magnet (OrthOne, ONI Inc., Wilmington, MA, USA) and a circumferential extremity coil. All images were acquired without contrast. As in previous work (16) we read one randomly selected knee MRI per person. This was done for budgetary reasons and because of the high rate of symmetry in knee MRIs. The MRIs were read by two experienced musculoskeletal radiologists using the Whole Organ MRI Score (WORMS) (17). Synovitis and cartilage morphology were scored in MRIs at baseline, 30, and 60 months. There was good interobserver agreement for each of the features reported (18). At each examination, participants completed the WOMAC questionnaire, reporting on the amount of pain experienced during activities in each knee.

Anthropometric measurements—BMI

Weight was measured to the nearest 0.1 kg on a standard medical balance beam scale, and height was measured on full inspiration to the nearest 1 mm with a wall-mounted Harpenden stadiometer by certified MOST personnel following a written protocol. BMI was calculated as weight in kilograms divided by the height in meters squared.

Assessment of OA structure and pain symptoms

We defined two primary knee outcomes: incident radiographic OA and incident symptomatic OA both up to 7 years after baseline and created two separate nested case control studies. In the first of these, outcome was incident radiographic knee OA among the subset of participants who had no radiographic OA in either knee (both knees with Kellgren and Lawrence grade <2) at baseline. Those participants who developed either radiographic knee OA (KL≥2) or had a knee arthroplasty in either knee by follow-up were defined as having incident radiographic knee OA. In the second case control study, we focused on symptomatic OA. It was defined in a person when they had the combination of frequent knee pain (saying yes to the question, Do you have pain, aching or stiffness in either knee on most days?) and had concurrent radiographic OA in that knee. Persons with symptomatic OA at baseline in either knee were excluded from both case control studies, and for each of these studies, we followed participants for 7 years to identify incident cases. For each of these case groups, we used risk set sampling to select controls randomly from eligible participants at baseline who did not become cases during follow-up. One risk set took 30-month follow-up and randomly selected controls who were not cases then, a second set of cases at 60 months and a third set of cases at 84 months. For incident x-ray OA, we selected 1 control per case. To increase the likelihood that we would detect an association for the clinically important outcome of symptomatic OA, we selected 2 controls per case.

To further investigate potential associations of lipid and lipoprotein levels with outcomes, we assessed several secondary outcomes, including cartilage loss and change in synovitis based on MRI readings (17). These analyses were performed in the combined sample of all cases and controls. Within each of 14 subregions in each knee, cartilage morphology was scored 0–6 using the WORMS scale (17). We defined worsening cartilage morphology by analyzing each sub-region and characterizing each as worsening when the score increased by 1 point. Sub-regions with baseline scores of 6 were excluded. Second, we examined change in synovitis. Each region (infrapatellar, intercondylar and suprapatellar) was scored 0–3 based on volume at each timepoint, and the scores were then summed (0–9). We defined worsening synovitis as an increase in the summed score of one or more, excluding knees with synovitis scores of 9 at baseline (20). We assessed one knee pain outcome (change in WOMAC pain) and calculated changes in pain as the difference of WOMAC pain score from baseline to the end of follow-up in each knee.

Lipid and Lipoprotein Profile

Blood draws were performed at the time of the baseline visit following an overnight fast. Blood samples were allowed to clot at room temperature for 30 minutes, and serum was separated by centrifugation at 1,500 g at 4 °C for 20 minutes. Aliquots were stored at −80° C in the MOST repository. For the determination of lipid profiles, matched case-control samples (N=994) were shipped overnight on dry ice to the Cardiovascular Nutrition Laboratory at the Jean Mayer USDA Human Nutrition Research Center of Aging at Tufts University. Serum total cholesterol and HDL concentrations were measured on an AU400e automated analyzer (Beckman Coulter, Brea, CA; intra-assay CV< 3%; inter-assay CV <4%) using enzymatic reagents (Beckman-Coulter). LDL concentration was calculated using the Friedewald equation (19) except when triglycerides were above 400mg/dl. For

those samples, a direct LDL method was used (AU400e automated analyzer, Beckman Coulter, Brea, CA; intra-assay CV< 2.4%; inter-assay CV <3.6%).

Potential Confounders

As indicated for each analysis, the data were adjusted for participants' demographic, lifestyle, and medical history reported on the baseline questionnaire, age, sex (men, women), education (college or above, yes vs. no), physical activity (Physical Activity Scale for the Elderly [PASE], continuous), smoking (never, past, current), BMI (kg/m^2, continuous) and statin use (yes/no). We used an indicator variable to adjust for race (white vs. non-white) and clinic site. For all pain outcomes, we included depressive symptom score (Center for Epidemiologic Studies Depression [CES-D], scale score ≥16, yes vs. no as a covariate). For knee pain analyses, we adjusted for baseline WOMAC pain score (continuous).

Statistical Analyses

Our analytic sample consisted of MOST participants who were either selected as cases or controls in one of our case control studies (incident x-ray OA or incident symptomatic OA) and who had an archived baseline fasting serum sample. They had to be followed until at least the second MOST exam at 30 months.

Our analyses looked at the range of lipids on OA outcomes, testing each on a continuous basis and examining risk per s.d. increase. To avoid not missing potential associations between total cholesterol, LDL or HDL on OA outcomes, we tested commonly used thresholds for high total cholesterol (≥200 mg/dL), high LDL (≥130 mg/dL), and low HDL (≤60 mg/dL).

Analyses of radiographic OA and incident symptomatic OA were at the level of the person. For each case control study, we used logistic regression to analyze the association of the lipid or lipoprotein level at baseline with the OA outcome. The dependent variable for each of these analyses was cumulative incidence of the OA outome over 7 years. For analyses of MRI findings and of WOMAC pain, we combined data from all cases and controls from the primary case control studies, creating one large sample. Analyses of MRI findings and of WOMAC pain were at the level of the knee, or knee subregion for cartilage loss; to adjust for the correlation between knees (or subregions of knees), we performed generalized estimating equations.

We carried out several sensitivity analyses. First, because of concerns that baseline levels of lipids and lipoproteins might not accurately reflect levels up to 7 years later, we carried out analyses limiting incidence to 5 years. Second, some incident OA is caused by injury which would tend to cause unilateral disease. We wanted to focus on those with systemic factors affecting disease, so in another sensitivity analysis, we defined cases as those who during follow-up developed incidence in both knees, either contemporaneously (e.g both at 30 months) or sequentially (e.g. one knee at 30 months, the other at 60 months). In addition, we examined quartiles of cholesterol, HDL and LDL to see if high (or low) levels affected risk of disease. Lastly, we added visceral adiposity (21) as a covariate in our analysis to see if the relationships of lipids with OA outcomes were altered. Analyses were carried out using SAS version 9.4.

Institutional review board approvals were obtained from University of California, San Francisco, Boston University, University of Alabama at Birmingham and The University of Iowa. All participants provided written consent for study participation.

Results

Mean age at baseline was 62 years and 55% were women, more than 20% took statins (see Table 1 for description of study participants) with 614 participants in the case control study of radiographic OA and 898 in the study of symptomatic OA. There were no associations of incident radiographic OA and incident symptomatic OA with total cholesterol, LDL, and HDL cholesterol levels (see Table 2). We also found no association of total cholesterol, LDL and HDL with cartilage loss, worsening synovitis or worsening knee pain (see Table 3). Lastly, we examined whether persons with high cholesterol, LDL or low HDL had an increased risk of OA, and found no suggestive associations (see Figure 1).

In sensitivity analyses, we found no associations of cholesterol, LDL or HDL with incident OA if we limited incidence to the first 5 years after baseline and also found no association with lipids or lipoproteins when we restricted cases to those who developed bilateral disease. In analyses examining quartiles of cholesterol, HDL and LDL, we similarly found no associations with incident radiographic or symptomatic OA. Lastly adjusting for visceral adiposity in our main analyses shown in table 2 did not affect results of these analyses (data not shown).

Discussion

In this longitudinal nested case control study, we examined the relationship between lipid and lipoprotein levels and OA within the Multicenter Osteoarthritis study (MOST) cohort. Although there is a growing body of experimental and epidemiologic evidence that suggest an association between elevated serum total cholesterol and LDL, and low HDL, with the development of OA, our data did not support such an association. We also did not find an association between serum lipid and lipoprotein levels with either cartilage loss, worsening synovitis or worsening knee pain.

Advances in the understanding of the pathogenesis of OA indicate that it involves not only “wear and tear” related to age and mechanical loading, but also synovial inflammation. This knowledge has led to a growing body of research evaluating the mechanisms by which metabolic factors that affect inflammation may contribute to OA. Several experimental studies evaluating the relationship of dyslipidemia and OA suggest that alterations in lipids play a role in the development of OA. De Munter et al showed that in mice with increased levels of LDL via cholesterol-rich diet or ApoE deficiency, there was increased synovial thickening and ectopic bone formation (6, 7). Additionally, Triantaphyllidou et al (23) showed that mice with low HDL levels and high LDL levels (based on a lecithin cholesterol acyltransferase (LCAT) knockout and apoA-I knockout) who were placed on a Western diet developed OA in their joints, whereas control mice did not. In these mice, the Western diet activated enzymes that break down cartilage (5). Busso et al showed that total cholesterol,

LDL and HDL levels were all similar in plasma and synovial fluid, suggesting easy transit between compartments (22).

Another factor that has been implicated in leading to OA is oxidative stress and reactive oxygen species within the joint, particularly oxidized LDL. The complex mechanisms by which oxidative stress contribute to the pathogenesis of OA was recently reviewed by Lepetsos et al, and include overproduction of reactive oxygen species within chondrocytes leading to increased chondrocyte apoptosis and synovial inflammation, cartilage degradation, and subchondral bone dysfunction (24–27). Oxidized LDL, a lipid peroxidation product produced mainly by reactive oxygen species, has been shown to play a role in the pathogenesis of OA. Shen et al found increased levels of oxidized LDL in the synovial fluid as well as increased lectin-type oxLDL receptor (LOX-1) expression in the cartilage of OA patients in comparison to controls (28). Erturk et al investigated the relationship of Paraoxonase-1 (PON-1), an enzyme that protects LDL and HDL from oxidative damage, with oxLDL and oxidative stress in OA (29). They found increased levels of oxLDL, higher markers of oxidative stress, and significantly lower levels of PON-1 in the sera of participants with OA in comparison to controls. There was also a correlation between serum ox-LDL and knee OA grade utilizing the Kellgren-Lawrence scoring system and pain via WOMAC score.

The results of these experimental studies suggest that elevated levels of lipids and/or lipoproteins are major contributors to the pathogenesis of OA. Despite this strong experimental evidence, this study showed a null association with incident symptomatic and radiographic knee OA and elevated serum LDL levels.

Although there have been cross sectional studies reporting possible associations between lipid levels and OA as recently evaluated in the systematic review and meta-analysis by Baudart et al (10), caution must be used when drawing conclusions regarding causation based on the results of cross sectional studies. To date, only three longitudinal studies have specifically assessed the relationship between certain features of OA (cartilage loss) and lipid and lipoprotein profiles. The results have been mixed.

Garcia-Gil et al evaluated whether serum lipid levels were associated with incident radiographic hand OA in 277 participants without OA at baseline. Hand radiographs were repeated 11 years after baseline. No statistically significant associations between serum lipids and radiographic hand OA were observed, but a trend toward high HDL levels being associated with a lower risk of hand OA was reported. Despite the longitudinal nature of this study and the analysis of serum lipids as both continuous and categorical set of variables, a significant limitation of this study was that it was underpowered. Additionally, the patient population included only women who were younger (mean age 50) with lower levels of obesity than the average population.

Davies-Tuck et al evaluated 148 female participants without a history of OA for the development of bone marrow lesions (BML) of the knee; they obtained baseline lipids and followed up with knee MRI two years later (11). Results showed an association between BML incidence and higher total cholesterol levels, but no association with LDL or HDL.

They did not find an association between presence of BMLs at baseline with any lipid parameter, nor with change in cartilage volume over two years. This study's results were at odds with a longitudinal study published three years later by Dore, et al, who evaluated the development of BMLs of the knee in 394 male and female participants (12). Baseline lipids and knee MRI were evaluated at baseline, and BMLs were assessed by MRI 2.7 years later. They found no significant cross-sectional or longitudinal association between total cholesterol and BMLs but did report an inverse association of BML change and HDL.

In this study, we did not find any significant associations between incident symptomatic knee OA and lipid levels. It is unlikely that this null association was attributable to sample size, as our confidence bounds were narrow. For example, increasing levels of LDL were associated with a modest reduction in risk of OA, but the upper border of that confidence bound stretched only to 1.12, consistent with a 12% increase in the odds of disease. If an association does exist, there may be other factors which have not yet been identified contributing to the correlation between lipids and OA. Among these other factors may be metabolic syndrome and a component of it, visceral adioposity. A recent review has strongly suggested that metabolic syndrome is not associated with knee OA, especially after adjustment for BMI (30). We carried out additional analyses testing visceral adiposity as a confounder and it did not affect the associations we report, suggesting it does not account for a spurious null associations. Despite the strong evidence that lipids enter the joint freely and intraarticular oxLDL leads to joint damage, perhaps another mechanism exists within the joint which disturbs this relationship, making measured serum lipids unrelated to intraarticular oxLDL. Lastly, although our data showed a small protective association of elevated total cholesterol and elevated LDL on symptomatic OA, this was not statistically significant and was likely due to chance.

This study has several strengths. This is one of the few studies evaluating the temporal relationship between serum lipid levels and incident knee OA using a longitudinal design. We evaluated participants using indices which account for both symptoms (pain) and radiographic changes, whereas previous longitudinal studies have assessed only radiographic changes; therefore we are able to identify participants which meet ACR criteria for knee OA, which includes the presence of pain. The nested case control design of this study reduces selection bias, since cases and controls are selected from the same population. Finally, we tested cholesterol as both a continuous measure and did sensitivity analyses examining whether commonly used lipid thresholds for increased risk, thereby evaluating the data from several angles to ensure robustness.

One limitation of this study is that participants within the MOST cohort are primarily older, Caucasian Americans, and therefore our results may not be generalizable to a more diverse population. Additionally, we focused on incident knee OA, and it is possible that the metabolic factors affecting non-weight bearing joints such as the hand may differ from those affecting large, weight-bearing joints such as the knee. Also, our analyses of secondary outcomes such as cartilage loss may be affected by selection bias in that these outcomes were correlated with case status. While we adjusted in analyses for statin use at baseline, statin use may take decades to influence the occurrence of OA and we did not know the duration of statin use in our participants. Further, we did not examine the effect of other lipid

lowering agents which were rarely used by MOST participants. Finally, lipid levels were taken at at single point in time, and therefore we cannot rule out whether additional factors such as lifestyle modifications affected the lipid levels later, modifying OA risk.

In conclusion, we did not find an association between total cholesterol, LDL, or HDL levels with incident OA or other OA outcomes. While LDL may have local deleterious effects on joint structure, elevated systemic levels probably do not confer risk of disease.

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Significance and Innovations:

- Recent data have suggested an association between elevated serum cholesterol levels, particularly low density lipoprotein (LDL), and the development of osteoarthritis, however there is a paucity of literature directly evaluating the relationship between serum lipid and lipoprotein concentrations and incident osteoarthritis
- This is the first study to comprehensively and longitudinally determine whether circulating total cholesterol, LDL, and HDL are associated with the risk of developing radiographic and symptomatic knee OA

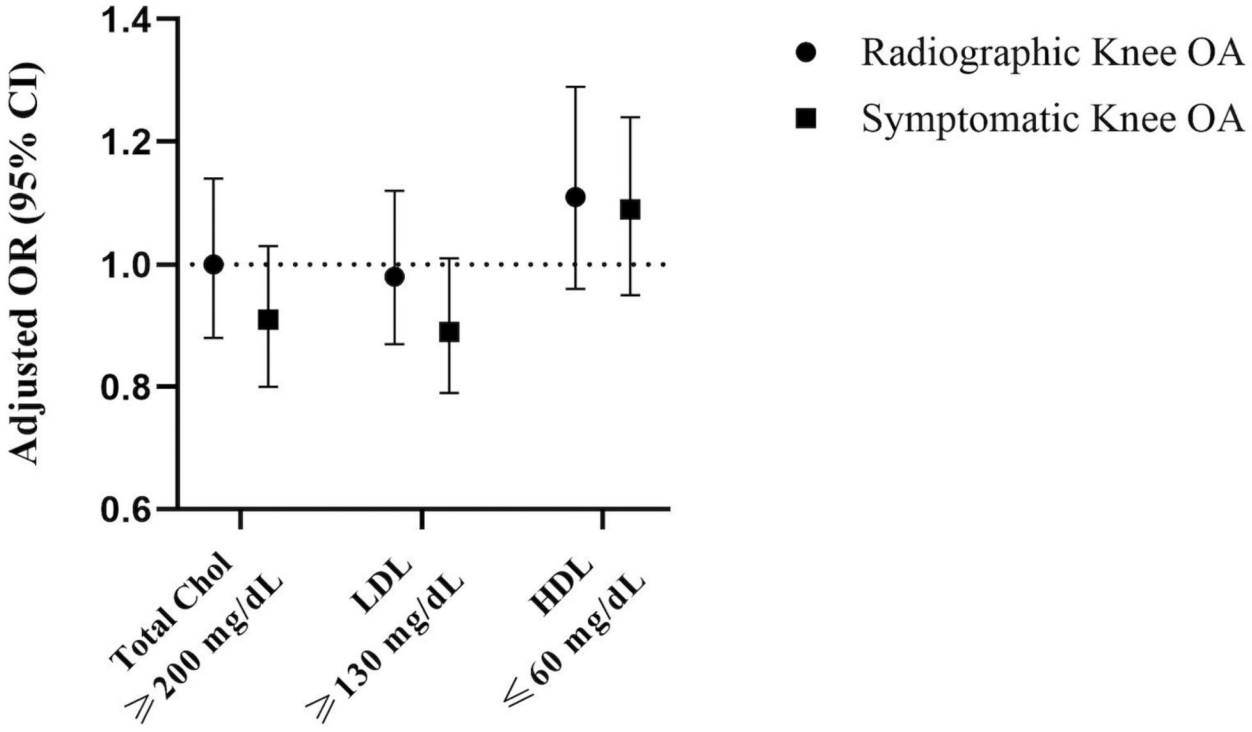

Figure 1:
Association of High Levels of Cholesterol and LDL and Low Levels of HDL with Incident OA Outcomes

Table 1:

Description of Study Participants according to Case Control study

	Incident Radiographic OA		Incident Symptomatic OA	
	Cases (n=285)	**Controls (n=329)**	**Cases (n=338)**	**Controls (n=560)**
Mean Age (years, s.d.)	60.8 (8.0)	59.9 (7.5)	62.4 (8.1)	61.1 (7.8)
Female	62%	59%	63%	57%
Mean BMI (s.d.)	30.5 (5.3)	28.7 (4.5)	30.9 (5.6)	29.3 (4.8)
Some college education	79%	77%	74%	78%
Mean Cholesterol (s.d.)	229 (4.8)	230 (51.2)	225 (47.1)	229 (48.9)
Mean LDL (s.d.)	136 (38.6)	138 (42.9)	133 (38.2)	138 (4.03)
Mean HDL (s.d.)	62 (16.8)	62 (16.7)	62 (17.1)	62 (16.5)
Statin Use	22%	23%	27%	24%

Table 2:

Association of Cholesterol, LDL and HDL with Incident Knee OA : Results of Logistic Regression Analyses*

	Mean (mg/dl)		Adj OR with 95% CI (per SD)	P value
	Cases	Controls		
Incident Knee Radiographic OA(cases/controls=283/329)				
Total Chol	229	229	1.00 (0.88,1.14)	0.97
LDL	136	138	0.98 (0.87, 1.12)	0.80
HDL	62	61	1.11 (0.96, 1.29)	0.16
Incident Symptomatic Knee OA(cases/controls=336/559)				
Total Chol	224	229	0.91 (0.80, 1.03)	0.12
LDL	132	137	0.89 (0.79, 1.01)	0.06
HDL	62	61	1.09 (0.95, 1.24)	0.24

*Logistic regressions adjusted for covariates: age, sex, BMI, educational attainment, race, clinic site and for WOMAC Pain outcome, adjusted also for baseline WOMAC pain score and depressive symptoms (yes/no)

Table 3:

Associations of Cholesterol, HDL and LDL Levels with Change in Worseninig Synovitis or Pain and with Cartilage Loss*

	Worsening Synovitis (218/711)		WOMAC Worsening (300/1654)		Cartilage Loss (4268/10297)	
	adjOR (95% CI)	**P value**	**adjOR (95% CI)**	**P value**	**adjOR (95% CI)**	**P value**
Total Chol	1.03 (0.70–1.52)	0.87	1.02 (0.88–1.20)	0.78	1.02 (0.96–1.10)	0.47
HDL	0.98 (0.81–1.18)	0.81	0.97 (0.83–1.14)	0.73	1.09 (1.02–1.17)	0.02
LDL	0.97 (0.80–1.18)	0.77	1.03 (0.88–1.21)	0.69	1.02 (0.95–1.09)	0.64

* Logistic regressions adjusted for covariates: age, sex, BMI, educational attainment, race, clinic site and for WOMAC Pain outcome, adjusted also for baseline WOMAC pain score and depressive symptoms (yes/no)