Quantifying the Association of Radiographic Osteoarthritis in Knee or Hip Joints with Other Knees or Hips: The Johnston County Osteoarthritis Project

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ABSTRACT. ***Objective.*** To quantify the association of radiographic osteoarthritis (ROA) in one knee or hip joint with other knee or hip joints.

Methods. We analyzed baseline data from the Johnston County Osteoarthritis Project (n = 3068). We fit 4 models for left/right knee/hip. The Kellgren-Lawrence (KL) radiographic grade severity scale was KL 0/1 (no/questionable ROA), 2 (mild ROA), or 3/4 (moderate/severe ROA). We estimated associations between KL grade in contralateral joints and other joint sites (e.g., worst hip in knee models), adjusting for sex, race/ethnicity (African American/white), age, and measured body mass index, using cumulative odds logistic regression models. Interactions were investigated: race/ethnicity by sex; race/ethnicity and sex by the 2 explanatory variables.

Results. Contralateral joint KL grade was strongly associated with KL grade, with OR ranging from 9.2 (95% CI 7.1, 11.9) to 225.0 (95% CI 83.6, 605.7). In the left knee model, the contralateral joint association was stronger among African Americans than whites, but for the other models the associations by race/ethnicity were identical. Models examining other joint sites showed weaker but mostly statistically significant associations (OR 1.4 to 1.8).

Conclusion. We found a strong multivariable-adjusted association between KL grades in contralateral knees and hips, and a modest association with the other joint site (e.g., knees vs hips). These results suggest that diagnosis of ROA in 1 large joint may be a marker for risk of multijoint ROA, and warrant interventions to reduce the incidence or severity of ROA at these other joints. (First Release April 15 2010; J Rheumatol 2010;37:1260–5; doi:10.3899/jrheum.091154)

Key Indexing Terms:
POLYARTHRITIS KELLGREN-LAWRENCE GRADE OSTEOARTHRITIS
CONTRALATERAL KNEE HIP

Among US adults, nearly 27 million had clinical osteoarthritis (OA) in 2008 (up from 21 million in 1995)[1]. Being strongly related to age and body mass index (BMI), OA presents an increasing burden in North America and the rest of the world as the population ages and grows heavier[2-5]. The Kellgren-Lawrence (KL) grade, an integer index ranging from 0 to 4, is a standard radiographic measurement of joint degradation used in diagnosing OA[6]. Radiographic OA (ROA) can be defined simply as a KL grade of 2 or higher.

There is a large body of literature suggesting that the occurrence of OA in different joints within an individual is

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associated, and suggesting some biological basis (e.g., genetic factors)[7-15]. Several studies have examined left-side versus right-side prevalence of OA in knees and hips[16-21], primarily measuring differences between the univariate distributions of left-side versus right-side ROA in knees and/or hips. For example, Newton, *et al*[19] suggested that the observed difference in left-side versus right-side distributions was attributable to a difference in impulse loading in right-footed people. Conversely, Stea, *et al*[16] observed a higher prevalence of right-hip OA in left-footed Italians, and concluded that in left-footed patients, the right side was subjected to greater stress. Few studies have sought to study between-joint associations in knees or hips, but one, Vossinakis, *et al*[22], found that preexisting hip OA on one side significantly predicted future development of OA on the other side. Spector, *et al*[23] also studied the incidence of future development of OA in contralateral joints (knees) among those with preexisting unilateral disease; however, their study did not include a control (disease-free) group. They found that obesity was a strong predictor of OA incidence in the contralateral knee.

We approach this subject from a new angle, and study the cross-sectional between-joint distribution of ROA in the knees and hips simultaneously (4 large joints). We aim to answer the question: how is ROA in 1 joint associated with ROA in the other 3 large joints in the body? Odds ratios (OR) are estimated in log-odds regression models to describe the cross-sectional association of hip (or knee) ROA with contralateral joint, and with the other joint site (hips for knee models, or knees for hip models).

MATERIALS AND METHODS

The study was approved by the institutional review boards of the University of North Carolina Schools of Medicine and Public Health and the Centers for Disease Control and Prevention. All participants gave written informed consent at the time of recruitment.

Data collection. We conducted a cross-sectional analysis using population-based data from the baseline Johnston County Osteoarthritis Project[24] in rural North Carolina (n = 3068). At the time this study was designed in 1990, Johnston County, North Carolina, a rural area of about 800 square miles, had a population of about 81,000. A majority of residents (66%) lived in completely rural areas, with the remainder in small towns[25]. African American residents and residents 60 years of age or older constituted 20% and 17% of the population, respectively. The baseline sampling occurred from May 1991 through December 1997 and involved 2 stages of stratified random sampling. Details about the Johnston County Osteoarthritis Project are described in Jordan, *et al*[24].

Race/ethnicity was self-reported. All participants had radiographic examination of the knees with the anterior-posterior (AP) view with weight-bearing and foot map positioning, and of the hips with an AP pelvis view. Knee and hip radiographs were read without knowledge of participant clinical status, by a single bone and joint radiologist using the KL radiographic atlas for overall knee radiographic grades[6]. This scale defines ROA in 5 categories. Radiographs scored as KL grade 0 (normal) showed no radiographic features of OA; KL grade 1 (questionable) included a minute radiographic osteophyte of doubtful pathologic significance; KL grade 2 (mild) showed an osteophyte but no joint space narrowing; KL grade 3 (moderate) showed moderate diminution of joint space; and KL grade 4 (severe) was defined by severe joint space narrowing with subchondral bone sclerosis[6]. Interrater reliability assessed with another trained radiologist and intrarater reliability for the radiologist were high (weighted kappa for interrater reliability was 0.86; kappa for intrarater reliability was 0.89), as described[26].

Because of a skewed and sparse distribution, we categorized KL grade groups as follows: KL 0/1 means no/questionable ROA; KL 2 means mild ROA; and KL 3/4 means moderate/severe ROA. ROA as used in this analysis refers to KL grade ≥ 2. Other variables included in our models were age, sex, race/ethnicity (African American or white), and measured BMI.

Data analysis. All analyses used weighted data to represent the population of Johnston County. The models were fit as "partial proportional odds" cumulative logistic regression models, using generalized estimating equations (GEE) methods[27]. When analyzing data with an ordinal outcome, a proportional odds model assumes that the cumulative odds of each level of an ordinal outcome is in constant proportion with the explanatory variable. When the OR for a particular explanatory variable varies across the level of outcome KL grade being considered (in this analysis, varied between outcomes of KL grade ≥ 2 and ≥ 3), a model allowing nonproportional odds (NPO) is required. NPO terms were formally tested and allowed into the models (when statistically significant) on a per-variable basis (hence, "partial" proportional odds model). A practical example of NPO can be found in a study by Campbell, *et al*[28], looking at racial and ethnic disparities in breast cancer. They found that women in high-poverty areas are at substantially greater risk for late-stage diagnosis of breast cancer, but the disparity was less for early stage diagnoses (NPO).

We fit 4 separate models, 1 each for the left and right knees and hips. The 2 main explanatory variables of interest were contralateral joint KL grade and maximum KL grade in the other joint site (that is, maximum KL grade in hips for left and right knee models, and vice versa). Thus, what we label as a left knee ROA outcome model has the main explanatory variables of right knee ROA and maximum KL grade for the hips. All models were adjusted for age, sex, race/ethnicity (African American or white), and measured BMI. According to standard model development, several 2-way statistical interactions were investigated: race/ethnicity by sex; race/ethnicity by each of the 2 main explanatory variables; and sex by each of the 2 main explanatory variables. Interactions refer to statistical interactions. Nonproportionality terms for all main effects were tested in unadjusted models based on the generalized score test for GEE models[29] at a significance level (i.e., alpha) of 0.10. From the multivariable model that resulted (nonsignificant NPO terms were excluded), interactions and any remaining nonproportionality terms were then selected out with backwards elimination at a significance level of 0.05. The 2 main explanatory variables and the main effects for age, sex, race/ethnicity, and BMI were included in the model regardless of significance. Bootstrap replication was used to accommodate design effects associated with the complex survey design[30]. All statistical analyses were done using SAS version 9.1.3.

RESULTS

Table 1 shows the sample-weighted baseline distribution of age group, sex, race/ethnicity, and grouped BMI. Weights were scaled to reflect sample-weighted percentages (for example, the distribution of sex by race/ethnicity is quite different when weighted), while maintaining an accurate sense of sample size. Scaled weights were used to represent population-based percentages while maintaining the scale of our sample size. The sample was between 45 and 93 years old, with two-thirds of the sample age 55 and older. More than half the subjects were women, and close to one-fifth were African American. Thirty-four percent were obese (BMI ≥ 30)[31].

Table 2 and Table 3 show the cross-tabulated KL grade

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Table 1. Weighted distribution of age, sex, race/ethnicity, and BMI (n = 3068). Scaled weighted counts are rounded to the nearest integer.

Variable	n (%)
Age, group, yrs	
45–54	1030 (33.6)
55–64	826 (26.9)
65–74	816 (26.6)
75+	395 (12.9)
Sex	
Men	1308 (42.6)
Women	1760 (57.4)
Race/ethnicity	
African American	566 (18.4)
White	2502 (81.6)
BMI group	
< 25	799 (26.0)
25–29.9	1208 (39.4)
30+	1051 (34.2)
Missing	10 (0.3)

BMI: body mass index.

levels in knees and hips (left side vs right side). Knees show significantly more ROA on the right side (22.1%) than the left (19.5%; Table 2; McNemar's unweighted $p < 0.01$). Hips show more ROA on the left side (20.2%) than the right (18.6%; Table 3), but the difference is not significant at alpha 0.05. Crude (unadjusted) OR for contralateral joint KL grade can also be calculated from these tables, comparing the odds of left-side versus right-side KL grade in knees and hips, using either KL ≥ 2 or KL 3/4 as the definition of ROA for the calculation. The crude OR for contralateral joint KL grade are very high. For the outcome KL ≥ 2 knees, the OR for having a contralateral knee with KL ≥ 2 was 20.1 (95% CI 16.2, 25.1) compared with a knee without ROA; for the outcome KL ≥ 3 knees, the OR for having a contralateral knee with KL ≥ 3 was 62.7 (95% CI 42.3, 93.1). For the outcome KL ≥ 2 hips, the OR for having a contralateral hip with KL ≥ 2 was 11.8 (95% CI 9.4, 14.7); for the outcome KL 3 hips, the OR for having a contralateral hip with KL ≥ 3 was 150.7 (95% CI 72.7, 312.2).

Table 4 lists the adjusted OR for the main explanatory variables from the models. Goodness-of-fit tests for GEE showed adequate fit for these models. Maximum KL grade in the other joint site exhibited proportional odds in all 4 models. But contralateral joint KL grade had NPO in both knee models, and BMI had NPO in the left hip model. A significant interaction term between race/ethnicity and contralateral joint KL grade remained in the left knee model. To ease the interpretation of these models, NPO terms are represented in Table 4 as the calculated effect of the explanatory variable for each cutpoint of the outcome variable. Similarly, the interaction between race/ethnicity and contralateral joint KL grade is listed as the effect of contralateral joint KL grade by race/ethnicity (and by cutpoint level, since the same model had NPO for contralateral joint KL grade). Because of the race/ethnicity interaction and the nonproportional odds in the left knee model, the effect of contralateral joint KL grade in that model requires that one consider race/ethnicity and the outcome level (depending on whether one is interested in effects on the association with mild/moderate/severe ROA, or with moderate/severe ROA). Consider a specific example to illustrate how to interpret the OR in Table 4. In the top left cell, the OR for the association between the explanatory variable contralateral (right) joint KL grade 2 and outcome left-knee KL grade ≥ 2 among whites is 10.2, meaning that a white person with right-knee KL grade 2 is 10.2 times as likely to have left-knee KL grade ≥ 2 than a white person with right-knee KL grade 0/1. In the same cell, the OR for the association between the explana-

Table 2. Weighted distribution of left-side vs right-side Kellgren-Lawrence grade in knees. Scaled weighted counts are rounded to the nearest integer. Total less than 3068 due to missing data and total joint replacement.

Left Knee KL Grade	Right Knee KL Grade No/Questionable	Mild	Moderate/Severe	Total, n (%)
No/questionable (0/1)	2158	223	28	2409 (80.5)
Mild (2)	155	219	53	427 (14.3)
Moderate/severe (3/4)	20	36	102	157 (5.2)
Total, n (%)	2333 (77.9)	479 (16.0)	182 (6.1)	2994 (100.0)

Table 3. Weighted distribution of left-side vs right-side Kellgren-Lawrence grade in hips. Scaled weighted counts are rounded to the nearest integer. Total less than 3068 due to missing data and total joint replacement.

Left Hip KL Grade	Right Hip KL Grade No/Questionable	Mild	Moderate/Severe	Total, n (%)
No/questionable (0/1)	1961	188	15	2164 (79.9)
Mild (2)	239	251	14	504 (18.6)
Moderate/severe (3/4)	7	9	26	41 (1.5)
Total, n (%)	2207 (81.4)	448 (16.5)	55 (2.0)	2709 (100.0)

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Table 4. Weighted multivariable adjusted final models for radiographic OA in the left/right knee/hip (OR with 95% CI), with contralateral joint data by race/ethnicity. OR are multivariable-adjusted and derived from models that included all the variables in a column: age, sex, race/ethnicity, BMI, contralateral Kellgren-Lawrence (KL) grade, and other joint site maximum KL grade.

Explanatory Variable	4 Models (by outcome variable) Left Knee Model OR (95% CI)	Right Knee Model OR (95% CI)	Left Hip Model OR (95% CI)	Right Hip Model OR (95% CI)
Among Whites				
Contralateral KL grade (for outcome KL grade ≥ 2*)				
2 vs 0/1	10.2 (7.4, 14.0)	12.9 (9.8, 17.1)	9.4 (7.3, 12.2)	9.2 (7.1, 11.9)
3/4 vs 0/1	47.3 (27.0, 82.8)	36.5 (19.9, 67.2)	89.7 (33.6, 239.3)	225.0 (83.6, 605.7)
Contralateral KL grade (for outcome KL grade ≥ 3**)			Same as for outcome	Same as for outcome
2 vs 0/1	5.3 (2.7, 10.6)	9.6 (5.7, 16.1)	KL grade ≥ 2 (above)	KL grade ≥ 2 (above)
3/4 vs 0/1	83.3 (40.7, 170.5)	104.2 (57.5, 188.7)	(odds were proportional)	(odds were proportional)
Among African Americans				
Contralateral KL grade (for outcome KL grade ≥ 2*)		Same As Whites	Same as Whites	Same as Whites outcome
2 vs 0/1	24.0 (14.0, 41.1)	outcome KL grade ≥ 2	outcome KL grade ≥ 2	KL grade ≥ 2 (no
3/4 vs 0/1	64.1 (32.0, 128.4)	(no race/ethnicity interaction)	(no race/ethnicity interaction)	race/ethnicity interaction)
Contralateral KL grade (for outcome KL grade ≥ 3**)		Same as Whites	Same as Whites	Same as Whites
2 vs 0/1	12.5 (5.7, 27.2)	outcome KL grade ≥ 3	outcomeKL grade ≥ 3	outcome KL grade ≥ 3
3/4 vs 0/1	112.8 (52.0, 244.8)	(no race/ethnicity interaction)	(no race/ethnicity interaction)	(no race/ethnicity interaction)
Overall				
Other joint site maximum KL grade***				
2 vs 0/1	1.5 (1.2, 2.0)	1.4 (1.0, 1.8)	1.5 (1.2, 2.0)	1.5 (1.1, 2.0)
3/4 vs 0/1	1.7 (0.9, 3.0)	1.8 (1.0, 3.3)	1.8 (1.2, 2.7)	1.6 (1.0, 2.4)

* Referent is KL grade 0/1. ** Referent is KL grade 0/1/2. *** Odds were proportional for other joint site maximum KL grade. BMI: body mass index.

tory variable contralateral (right) joint KL grade 3/4 and outcome left-knee KL grade ≥ 2 among whites is 47.3, meaning that a white person with right-knee KL grade 3/4 is 47.3 times as likely to have left-knee KL grade ≥ 2 than a white person with right-knee KL grade 0/1.

Table 4 shows that contralateral joint KL grade is strongly associated with KL grade in knees and hips, with all effects highly significant in all models. Contralateral joint KL grade 2 (vs 0/1) OR for associations with higher KL grade in the outcome joint range from 9.2 (right hip; both races/ethnicities; both cutpoints) to 24.0 (left knee; African American; cutpoint KL grade ≥ 2 vs KL grade 0/1). Contralateral joint KL grade 3/4 (vs 0/1) OR for associations with higher KL grade in the outcome joint range from 36.5 (right knee; both races/ethnicities; cutpoint KL grade ≥ 2 vs KL grade 0/1) to 225.0 (right hip; both races/ethnicities; both cutpoints). Maximum KL grade in the other joint site showed a weaker effect in all 4 models, but 6 of the 8 coefficients were statistically significant and all OR exceeded 1. OR ranged from 1.4 to 1.5 for other joint site KL grade 2 (vs 0/1), and from 1.6 to 1.8 for other joint site KL grade 3/4.

To simplify Table 4, we present the NPO terms and race/ethnicity interactions for contralateral joint KL grade here in the following text only. In the right knee model, the OR for the association between contralateral joint KL grade 2 and mild/moderate/severe ROA (KL grade ≥ 2) was 1.4 times (95% CI 0.8, 2.3) stronger than the association between contralateral joint KL grade 2 and moderate/severe ROA (KL grade 3). Conversely, the association between contralateral joint KL grade 3/4 and KL grade ≥ 2 was only 0.4 times (95% CI 0.2, 0.7) the association between contralateral joint KL grade 3/4 and KL grade ≥ 3. Similar to the right knee model, in the left knee model, the association between contralateral joint KL grade 2 and outcome KL grade ≥ 2 was 1.9 times (95% CI 1.0, 3.6) the association between contralateral joint KL grade 2 and the outcome of KL grade ≥ 3. Also similar to the right knee model, the association between contralateral joint KL grade 3/4 and an outcome of KL grade ≥ 2 was less (0.6 times, 95% CI 0.3, 1.1) than the association between contralateral joint KL grade 3/4 and an outcome of KL grade ≥ 3. The NPO terms in these models suggest that the effects of contralateral joint KL grade are stronger when associated with ROA of a similar level in the outcome joint than ROA of a dissimilar level.

We found the contralateral associations to vary across race/ethnicity: in the left knee model, the association for KL grade 2 was 2.4 times stronger (95% CI 1.3, 4.4) among African Americans than whites, and the association for KL grade 3/4 was 1.4 times stronger (95% CI 0.6, 2.9). Statistically significant interactions were not observed in the right knee models.

DISCUSSION

The association between moderate/severe ROA in the contralateral knee and moderate/severe ROA was stronger than the association between moderate/severe ROA and mild/

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moderate/severe ROA. We also found that the association between mild ROA in the contralateral knee and mild/moderate/severe ROA was stronger than the association between mild ROA and moderate/severe ROA. We found evidence of only 1 interaction, race/ethnicity and right-knee KL grade, in the left knee model. The interaction suggests that African Americans experienced a stronger association than whites between outcome and contralateral joint KL grades. We found no other interactions between sex or race/ethnicity and contralateral joint KL grade or maximum KL grade in the other joint site.

We did not explicitly compare ROA prevalence according to left or right side beyond the basic comparison of marginal distributions made earlier from Table 2 and Table 3. However, this topic has been studied on large joints previously, with somewhat inconsistent results[16-21]. For example, Neame, *et al*[17] found that OA in the tibiofemoral (knee) joint was more prevalent on the right side, and that the minimum joint space in hips was smaller on the left side (consistent with our data). On the other hand, Chitnavis, *et al*[18] reported that patients undergoing total joint replacement surgeries had more right-side replacements than left-side, in both knees and hips.

Of all the studies cited, Neame, *et al*[17] and Vossinakis, *et al*[22] have reported on associations somewhat similar to a contralateral joint OR (in terms of "right-side vs left-side" OA). Neame, *et al* reported unadjusted OR for left-side versus right-side OA of 0.89 (95% CI 0.62, 1.28) in hips, 1.24 (95% CI 1.01, 1.52) in tibiofemoral knee radiographs, and 1.02 (95% CI 0.84, 1.24) in patellofemoral knee radiographs. These results differ completely from ours. The OR reported by Neame, *et al* actually related to the ratio of left-side versus right-side univariate distributions, and therefore do not represent the effect of contralateral joint OA on the odds of OA in a joint. In a study more similar to ours, Vossinakis, *et al* found that preexisting hip OA on 1 side significantly predicted future development of OA on the other side. They reported an OR of 3.99 (95% CI 1.28, 12.39), adjusted for age and sex[22]. This result is substantially different from ours (lower), which is likely attributable to the differences in study design: for example, at study inception, Vossinakis, *et al* examined unilateral hip OA only (excluding bilateral hip disease), with followup of 2 to 31 years when/if symptoms developed in the contralateral joint, or between 10 and 35 years among those who remained symptom-free. Our study design differs substantially from these 2 studies, which prevents direct comparisons of the quantitative results. Nevertheless, the Vossinakis, *et al* study does provide some support for the notion that OA in the contralateral joint is associated with OA in the outcome joint. While the OR for contralateral joint KL grade in our study are relatively very high, comparisons with raw OR calculated from Table 2 and Table 3 suggest a biologically consistent relationship. It may also be noted that large OR are common when the reference category has a very small probability. Table 2 and Table 3 show that the marginal probabilities of KL grade 3/4 in left/right knees/hips are all very low.

Although our study used cross-sectional data, results suggest that diagnosis of OA in 1 large joint may be a marker for risk of multijoint ROA. This information could prove beneficial to people with newly diagnosed unilateral ROA. Knowing the increased risk of OA in other joints, they could be counseled to avoid high-risk activities (e.g., occupational or recreational heavy weight-lifting involving the at-risk joints) and offered interventions (e.g., weight loss, or exercises designed to strengthen joints such as targeted physiotherapy) that would avoid or delay the onset of symptomatic OA (if not ROA) in the at-risk joint(s)[32,33].

Our study has a number of strengths. First, the sample is large and population-based (sample-weighted), providing precise results that are generalizable to 6 townships of Johnston County, and possibly to a wider population because the sociodemographic characteristics of the US population are comparable (e.g., BMI) to the Johnston County population at baseline. Second, we have obtained radiographs of both knees and both hips simultaneously for all subjects, giving us the relatively rare opportunity to study associations between ROA occurring in different large joints within the body. Third, having recorded race/ethnicity (African American vs white), sex, and BMI allowed us to investigate possible effect modification (interactions) with the contralateral joint and other joint site, as well as to control for potentially confounding factors.

Our study also has a number of limitations. First, the sample was collected in a rural part of North Carolina that had a relatively high proportion of African Americans and a relatively high prevalence of obesity at baseline. Study results may be less generalizable to people in urban centers, although controlling for BMI and investigating interactions with sex and race/ethnicity would most likely have mitigated this problem. In addition, as mentioned, BMI in the US today is higher than previously, further mitigating this problem. Second, the baseline data analyzed in this study were collected over a relatively long time (1991 to 1997) for a cross-sectional sample. While it is possible that some drift in the population distribution of ROA could have occurred during that time, it is unlikely that this would be substantial enough to affect our results, particularly since the data on 4 joints within each person were collected simultaneously. Finally, results are based on cross-sectional data and therefore we do not know the temporal sequence of the associations we have studied.

We found a very strong cross-sectional association between KL grade in a knee or hip joint and KL grade in the contralateral knee or hip, even after controlling for age, sex, BMI, race/ethnicity, and maximum KL grade in the other joint site. The OR for contralateral joint KL grade can be in

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the tens or even hundreds depending on which cutpoint and joint are being considered. The biggest effect was found in African Americans and associations with knee ROA. Maximum KL grade in the other joint site showed a weaker but mostly significant effect on the odds of higher KL grade in the outcome joint, after controlling for age, sex, BMI, race/ethnicity, and contralateral joint KL grade. The strength of the association between ROA in the outcome and contralateral joints far exceeds the strength of any other known risk factor. Our results magnify the critical importance of the multijoint OA phenotype in studies of OA etiology, and also illustrate the need for etiologic studies of contralateral associations.

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