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Appendix C

Meta-Analysis of Olive Oil Studies

EFFECTS OF OLIVE OIL ON BLOOD LIPIDS:

RESULTS OF A META-ANALYSIS OF HUMAN CLINICAL TRIALS

Final report

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Nutrition Impact, LLC

INTRODUCTION

Death from coronary heart disease is significantly lower in Mediterranean countries than in other developed countries even though overall fat intake is relatively high (~40% of calories) (Keys, 1970). Olive oil is primarily composed of the monounsaturated fatty acid oleic acid, and has been consumed as part of the Mediterranean Diet for hundreds of years. Several meta-analyses have reported beneficial effects on blood lipids of replacing saturated fats with unsaturated fats (Mensink and Katan, 1992; Clarke et al., 1997). The Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) identifies low-density lipoprotein (LDL) cholesterol as the primary target for cholesterol lowering in America. Reduction of saturated fat in the diet is the first dietary modifications recommended to reduce LDL levels (NCEP, 2001). A number of human clinical trials have been conducted to evaluate the effects of olive oil on blood lipids, in particular LDL. Several of these compared the effects of adding olive oil in place of carbohydrate, saturated or polyunsaturated fat in the diet. Because many of these trials were relatively small, we conducted a meta-analysis to pool results from the randomized controlled clinical trials that have evaluated the effects of incorporating olive oil into various dietary regimes. In particular, we were interested in the effects of olive oil as compared to 1) low fat/high carbohydrate diets, 2) high saturated fat diets, and 3) high polyunsaturated fat diets. This is the first meta-analysis reported on the effects of a particular source of monounsaturated fat on blood lipids.

METHODS

Study Identification and Selection

The life sciences literature was searched to identify human studies that examined the effects of olive oil on blood lipids. A MEDLINE search was conducted using the search terms olive oil, cholesterol, and human. Manuscripts, in English only, were reviewed for eligibility by one author (VLF), who was aware of the study designs or methodologies. The meta-analysis inclusion criteria were as follows:

1. Studies were conducted in humans;
2. Studies were randomized controlled experiments that used either a crossover design or a design with parallel arms for treatment and control;
3. Intervention period was greater than 2 weeks;
4. Reports included data to estimate the mean treatment minus control effect and included appropriate variance estimates.

We were interested in comparing olive oil-containing diets to three diet types: 1) low fat diets (<30% calories from fat and <10% calories from saturated fat); 2) saturated fat diets (>10% calories from saturated fat); and 3) polyunsaturated fat diets (>10% of calories from polyunsaturated fat). We hypothesized that if olive oil has a beneficial effect on blood lipids, then subjects on olive oil diets should have better lipid profiles than those on saturated fat diets and equivalent lipid profiles to subjects consuming low fat or high polyunsaturated fat diets.

Statistical Approach to Meta-analysis

For each individual study, the effects of olive oil on lipid variables were calculated by subtracting the post-treatment lipid concentrations for olive oil from the post-treatment lipid concentrations for the control group (low fat, high saturated fat, or high polyunsaturated fat diets), and dividing by the pooled variance. The result was then multiplied by a bias correction factor, which is a function of the number of subjects in each study. That is, for the i^{th} study, the estimated effect size is

$$d_i = J(N-2)\frac{\overline{Y}^T - \overline{Y}^C}{s}$$

where *J(N-2)* is the bias correction factor, $\overline{Y}^T$ is the mean of the treatment group, $\overline{Y}^C$ is the mean of the control group, and s is the pooled standard deviation (Hedges and Olkin, 1985 [not in ref list]). When the sample sizes for the treatment and control groups are equal, as in crossover designs, d_i is the unique minimum variance unbiased estimator of the true effect size.

The asymptotic distribution of d_i is normal with mean δ_i, the true effect size, and asymptotic variance

$$\sigma_\infty^2(d) = \frac{n^T + n^C}{n^T n^C} + \frac{\delta_i^2}{2(n^T + n^C)}$$

which is estimated by

$$\hat{\sigma}^2(d) = \frac{n^T + n^C}{n^T n^C} + \frac{d_i^2}{2(n^T + n^C)}$$

where n^T and n^C are the sample sizes for the treatment and control groups, respectively.

Then, the weighted estimator of δ_+, the overall effect from all studies, is

$$d_+ = \sum_{i=1}^{k} w_i d_i \Big/ \sum_{i=1}^{k} w_i$$

with weights

$$w_i = \frac{1}{\hat{\sigma}^2(d_i)}$$

Then under general conditions this estimator is asymptotically normal with an estimated variance of

$$\hat{\sigma}^2(d_+) = \left(\sum_{i=1}^{k} \frac{1}{\hat{\sigma}^2(d_i)} \right)^{-1}$$

a 95% confidence interval estimating δ is then calculated as

$$\delta_L = d_+ - z_{\alpha/2} \hat{\sigma}^2(d_+)$$

$$\delta_U = d_+ + z_{\alpha/2}\hat{\sigma}^2(d_+)$$

where $z_{\alpha/2}$ is the two-tailed critical value of the standard normal distribution. A d_i and 95% confidence interval was calculated for each olive oil/control pair.

An overall effect (δ_+) and 95% confidence interval was calculated for three groups of studies: 1) those in which it was possible to compare olive oil diets with low fat diets; 2) those where we were able to compare olive oil diets to high saturated fat diets; and 3) those where we were able to compare olive oil diets to diets high in polyunsaturated fat diets.

The validity of the overall estimates was first confirmed by testing for homogeneity of effect sizes. The statistic Q, defined as

$$Q = \sum_{i=1}^{k} \frac{(d_i - d_+)^2}{\hat{\sigma}^2(d_i)},$$

has an asymptotic chi-square distribution with k-1 degrees of freedom under the null hypothesis that the k studies have the same population effect size. This test determined whether the inter-study differences were from the same distribution of effect sizes. If Q was significant, we attempted to determine the cause for inter-study differences and made a decision to remove studies or to continue with our analyses. With no heterogeneity or understood heterogeneity, effect sizes were then pooled by weighting the individual study effect sizes by the reciprocal of the variance of the individual effect sizes (thus, this also considers the number of subjects in an individual study).

Note that δ_+ are standardized differences in means and as such are not associated with units. To associate these values with units of biological significance (mg/dl), we multiplied δ_+ and 95% confidence limits by the appropriate average standard deviations. Finally, we determined if other variables (gender, age, duration of trial, etc.) identified in the publications affected the observed effect sizes. A very similar statistical approach was taken by Gardner and Kraemer (1995) [not in ref list] to compare the effects of monounsaturated versus polyunsaturated fat on blood lipids.

RESULTS

Study Characteristics

The characteristics of the studies included in this meta-analysis are presented in Table 1a. Studies excluded from the analysis and the reasons for exclusion are shown in Table 1b. We excluded all studies that used olive as a control to evaluate effects of fish oil on blood lipids, because most of these were conducted in individuals with coronary heart disease or they did not meet other inclusion criteria. Overall, 22 studies providing 23 observations, comprising 482 unique subjects, were included in the meta-analysis. Eleven studies were utilized to compare the effects of olive oil to low fat diets. There were a total of 203 adult subjects in the studies comparing low fat diets to olive oil. In seven of these studies, subjects had non-insulin dependent diabetes (NIDDM). The average percent calories from fat and percent calories from saturated fat in the low fat diet studies was 24.7% and 8.4%, respectively. Average total cholesterol while on the low fat diets was 204.3 mg/dl. The average percent calories from fat and percent calories from monounsaturated fat in the olive oil diet studies was 40.3% and 24.8%, respectively.

There were fewer studies to compare the effects of olive oil diets with diets high in either saturated fat or polyunsaturated fat. Six studies were available to compare olive oil to polyunsaturated fat diets. There were a total of 118 adult subjects, none of whom had NIDDM. Average percent calories from fat and from polyunsaturated fat in the high polyunsaturated fat diet studies was 30.4% and 12.2%, respectively. In the olive oil diets in these studies, average percent calories from fat and from monounsaturated fat was 31.0% and 17.9%, respectively. For comparing the effects of olive oil to saturated fat diets, five studies providing data on six interventions met our inclusion criteria. In these studies, there were a total of 194 adult subjects (161 unique), none of whom had NIDDM. Average percent calories from fat and from saturated fat in the high saturated fat diet studies was 34.9% and 18.5%, respectively. In these olive oil diet studies, average percent calories from fat and percent calories from monounsaturated fat was 35.0% and 19.7%, respectively.

Lipid Effects

Olive oil versus low fat diets. The eleven individual study effect sizes for total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides comparing low fat diets to diets containing olive oil are presented in Figures 1a-d, respectively. Significant findings are those where the 95% confidence interval does not include zero. For total, LDL and HDL cholesterol, none of the individual study effects were significantly different from zero. For triglycerides, the effect size for only one of the individual studies was significantly different from zero. The Q-statistic indicated that these studies all came from the same effect size for all lipid variables. Pooling of the effect sizes to determine the best estimate of the overall effect, represented as OVERALL in Figures 1a-d and Table 2a, indicates there were no differences in total and LDL cholesterol when low fat diets were compared with higher fat diets containing olive oil. However, there was a significant ($p < 0.05$) increase in effect size for HDL cholesterol and a significant ($p < 0.05$) decrease in effect size for triglycerides in diets containing olive oil as compared to low fat diets. The magnitudes of these pooled effect sizes were determined by multiplying the effect size by the relevant average standard deviations, and are presented in Table 2a. Thus, the significant increase in HDL cholesterol was equivalent to 3.0 mg/dl (7.2% increase) significant decrease in triglycerides was equivalent to 20.0 mg/dl (12.21% decrease).

Olive oil versus saturated fat diets. The individual study effect sizes for total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides in comparisons of olive oil diets with saturated fat diets are presented in Figure 2a-d, respectively. The Q-statistic was significant for total and LDL cholesterol, indicating there was more than one set of effect sizes in these data. Subsequent analyses indicated that the study by Choudhury et al. (1995) and one of the interventions by Ng et al. (1992), both of which used palm oil as the saturated fat source, yielded different effect sizes ($p<0.05$; Figures 2a and b). However, rather than eliminating these studies, we decided to keep them in the overall analyses, and thus yield a conservative estimate of the effects of olive oil containing diets as compared to diets high in saturated fat.

Total and LDL cholesterol effect sizes (Figures 2a and 2b) for three individual studies were significantly ($p < 0.05$) different from zero (lower on olive oil diets). One of the individual study effect sizes for HDL cholesterol (Figure 2c) was significantly different from zero; none of the individual study effect sizes for triglycerides was different from zero (Figure 2d). After pooling of the effect sizes (Figures 2a-d and Table 2b), there were significant ($p<0.05$) reductions in total and LDL cholesterol with no changes in HDL cholesterol or triglycerides when diets high in saturated fat were compared with diets containing olive oil. The magnitude of these pooled effect sizes (Table 2a) was equivalent to a 17.7 mg/dl decrease in total cholesterol (8.8% reduction) and a 15.5 mg/dl decrease in LDL cholesterol (11.3% reduction).

Olive oil versus polyunsaturated fat diets. The six individual study effect sizes for total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides comparing diets high in polyunsaturated fat to diets containing olive oil are presented in Figures 3a-d, respectively. None of the individual study effect sizes for total, LDL, HDL cholesterol, or triglycerides were significantly different from zero. After pooling of the effect sizes (Figures 2a-d and Table 2b), only the overall effect sizes for triglycerides was significantly different from zero. The magnitude of the pooled effect on triglycerides was an increase of 12.5 mg/dl on olive oil diets (11.8% increase).

Additional Statistical Analyses

We also examined whether other characteristics of the studies influenced effect sizes for each lipid variable. In general, these variables (gender, age, study duration, baseline lipid variables, and when appropriate, presence of diabetes) were not related to effect sizes. For total cholesterol, higher control levels resulted in larger negative effect sizes ($p < 0.05$), and this same trend was indicated for LDL cholesterol ($p < 0.10$). Control values for HDL cholesterol and triglycerides had no relationship on effect sizes.

DISCUSSION

Meta-analysis pools results from similar studies, allowing greater statistical sensitivity. The present analysis has shown that diets containing olive oil resulted in total and LDL cholesterol levels similar to those of low fat diets. However, HDL cholesterol was higher and triglycerides were lower with diets containing olive oil as compared to low fat diets. The effects on triglycerides may be related to the fact that low fat diets are also [typically?] high in carbohydrates. Numerous studies have reported that triglycerides are higher when consuming low fat diets rich in carbohydrates [refs?]. The Dietary Reference Intake panel indicated there was some evidence that increased sugar intake is associated with increased plasma triglycerides (DRI, 2002). In this meta-analysis, we included subjects with NIDDM. We believe this was justified for at least two reasons: 1) the Q-statistic showed that the effect sizes pooled were similar, indicating the results of the individual studies were from the same distribution of effect sizes, and 2) post-pooling regression analyses indicated that the presence of subjects with NIDDM in our analyses was unrelated to effect sizes.

The effects of comparing diets containing olive oil with diets high in saturated fat, i.e., significant reductions in total and LDL cholesterol with no effects on HDL cholesterol or triglycerides, were fully expected. Reduction in saturated fat continues to be the key dietary change recommended to lower LDL cholesterol. The percentage reductions we observed were quite large (8.8 % and 11.3% for total and LDL cholesterol, respectively), and thus may reduce heart disease risk 16-22% (Law et al., 1994 [not in ref list]; NCEP, 2001) from reductions in total and LDL cholesterol alone. Other components of olive oil may also have an impact on the risk for heart disease.

When comparing diets high in polyunsaturated fat to diets containing olive oil, we observed no differences in total, LDL or HDL cholesterol, but did see an increase in triglycerides. The reason(s) for this is unclear. The average percentage of calories from total fat was similar for both diets (34.9 vs. 35.0), suggesting that total carbohydrates were not a factor in the triglyceride increase. It is possible that the quality of the carbohydrates may have had a role in the effect on triglycerides. As reported previously, higher intake of sugars may result in an increase in triglycerides. However, data were not provided in the publications to evaluate whether the increase noted in triglycerides was related to total sugar intake.

CONCLUSION

We have shown that diets containing olive oil significantly raised HDL cholesterol and lowered triglycerides as compared to low fat diets, and significantly reduced total and LDL cholesterol compared to diets high in saturated fat. This analysis also revealed that total and LDL cholesterol levels in diets containing olive oil are similar to those in low fat diets or diets high in polyunsaturated fats. Finally, we noted an unexplained increase in triglycerides in diets containing olive oil as compared to diets high in polyunsaturated fat. Overall, it appears that diets containing olive oil lead to better lipid profiles and may be helpful in reducing the risk of heart disease, especially as compared to diets high in saturated fat.

Table 1b. Studies Excluded from the Meta Analysis

Reference	Reason study excluded
Baggio, et al., 1988	Not a randomized trial; sequential dietary periods
Gimeno, et al., 2002	Intervention period only one week
Kris-Etherton, et al., 1993	Only pooled standard errors available; individual treatment variances not reported
Mata, et al., 1992	Not a randomized trial; sequential dietary periods
Morgan, et al., 1993	Not a randomized trial; sequential dietary periods; intervention period only two weeks
Nicolaiew, et al., 1998	Both treatments high oleic acid diets (one from olive oil the other from sunflower oil)
Sanders, et al., 1994	Not a randomized trial; sequential dietary periods; intervention period only two weeks
Seppanen-Laakso, et al., 1993	Not a randomized trial
Madiagn, et al., 2000	Intervention period only two weeks
Wagner, et al., 2001	Intervention period only two weeks
Bairati, et al., 1991	Fish oil study; subjects with coronary heart disease
Connor, et al., 1993	Fish oil study; not a randomized trial
Donnelly, et al., 1992	Fish oil study; subjects on dialysis
Flaten, et al., 1992	Fish oil study
Mori, et al., 1992	Fish oil study; subjects with peripheral vascular disease
Puiggros, et al., 2002	Fish oil study; not a randomized trial
Ramiez-Tortosa, et al., 1999	Fish oil study; subjects with peripheral vascular disease
Sacks, et al., 1995	Fish oil study; subjects with coronary artery disease

Table 2a. Overall Effect of Olive Oil as Compared to Low-Fat Diets

Variable	Pooled Effect Size	95% Confidence Interval	Magnitude of Effect Size, mg/dl [Mean (95% CI)]	Mean Control Values, mg/dl	Percentage Change, %
Total Cholesterol	-0.017	0.178 -0.212	-0.63 (6.60, -7.86)	198.7	-0.3
LDL-Cholesterol	-0.000	0.155, -0.195	0 (6.56, -6.56)	125.6	0.0
HDL-Cholesterol	0.252*	0.448, 0.056	3.01 (5.36, 0.67)	42.0	7.2
Triglycerides	-0.316*	-0.119, -0.512	-20.0 (-7.53 -32.4)	165.4	-12.1

* Statistically significant, $p < 0.05$

Table 2b. Overall Effect of Olive Oil as Compared to Saturated Fat Diets

Variable	Pooled Effect Size	95% Confidence Interval	Magnitude of Effect Size [Mean (95% CI)]	Mean Control Values, mg/dl	Percentage Change, %
Total Cholesterol	-0.470*	-0.267, -0.674	-17.7 (-10.0 –25.3)	200.5	-8.8
LDL-Cholesterol	-0.460*	-0.257, -0.664	-15.5 (-8.64, -22.3)	137.0	-11.3
HDL-Cholesterol	-0.179	0.021, -0.379	-1.97 (0.23, -4.17)	45.3	-4.4
Triglycerides	-0.062	0.138, -0.261	-3.22 (7.15, -13.5)	104.5	-3.1

* Statistically significant, $p < 0.05$

Table 2c. Overall Effect of Olive Oil as Compared to Polyunsaturated Fat Diets

Variable	Pooled Effect Size	95% Confidence Interval	Magnitude of Effect Size [Mean (95% CI)]	Mean Control Values, mg/dl	Percentage Change, %
Total Cholesterol	0.242	0.500, -0.016	7.22 (14.9, -0.48)	191.8	3.8
LDL-Cholesterol	0.185	0.442, -0.072	4.93 (11.8, -1.92)	127.4	3.9
HDL-Cholesterol	0.053	0.309, -0.202	0.49 (2.84, -1.85)	42.6	1.1
Triglycerides	0.287*	0.544, 0.030	12.5 (23.6, 1.30)	105.4	11.8

* Statistically significant, $p < 0.05$

Figure 1a. Effect of Olive Oil on Total Cholesterol as Compared to Low-Fat Diets

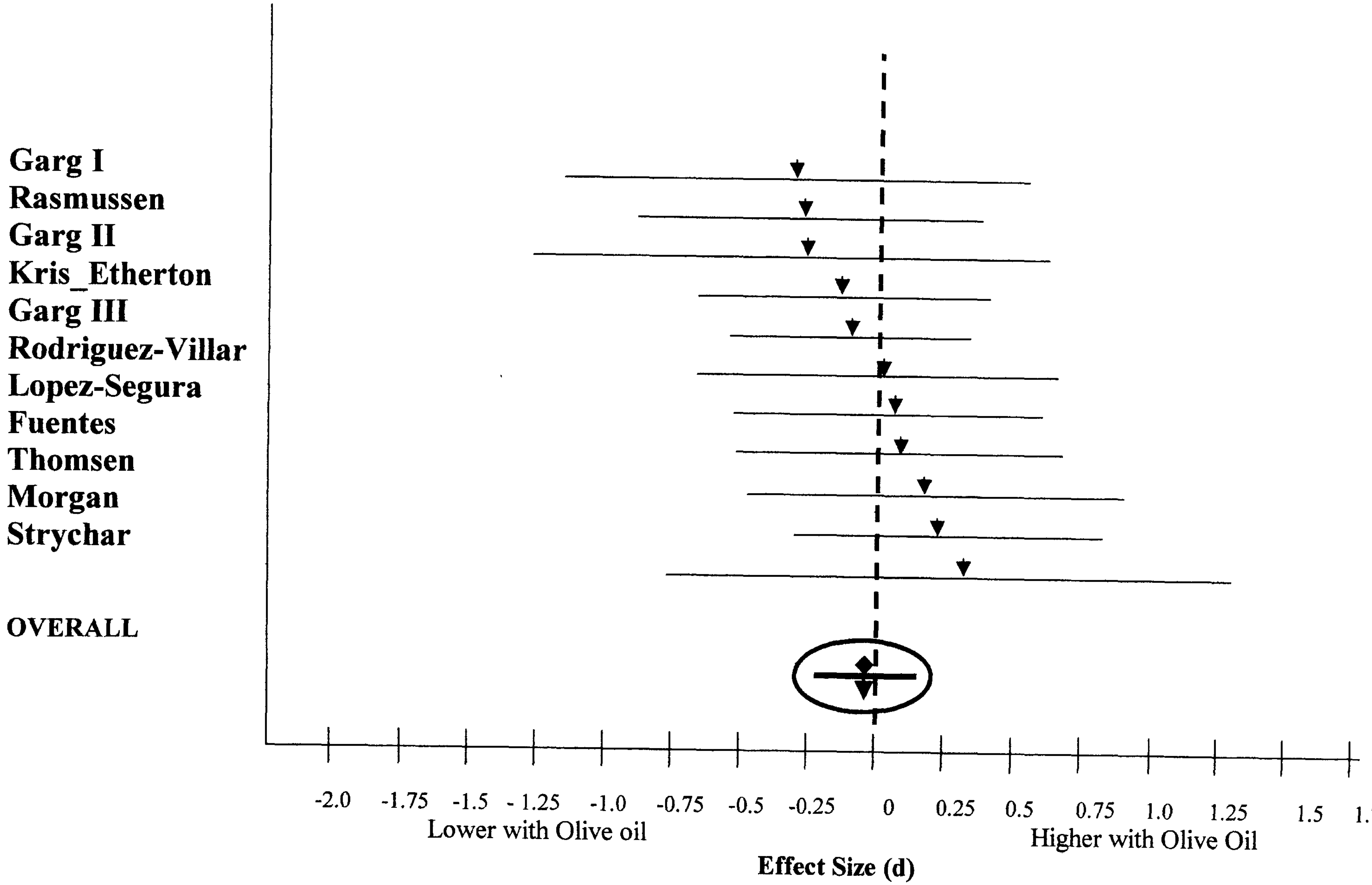


Figure 1b. Effect of Olive Oil on Low-Density Lipoprotein Cholesterol as Compared to Low-Fat Diets

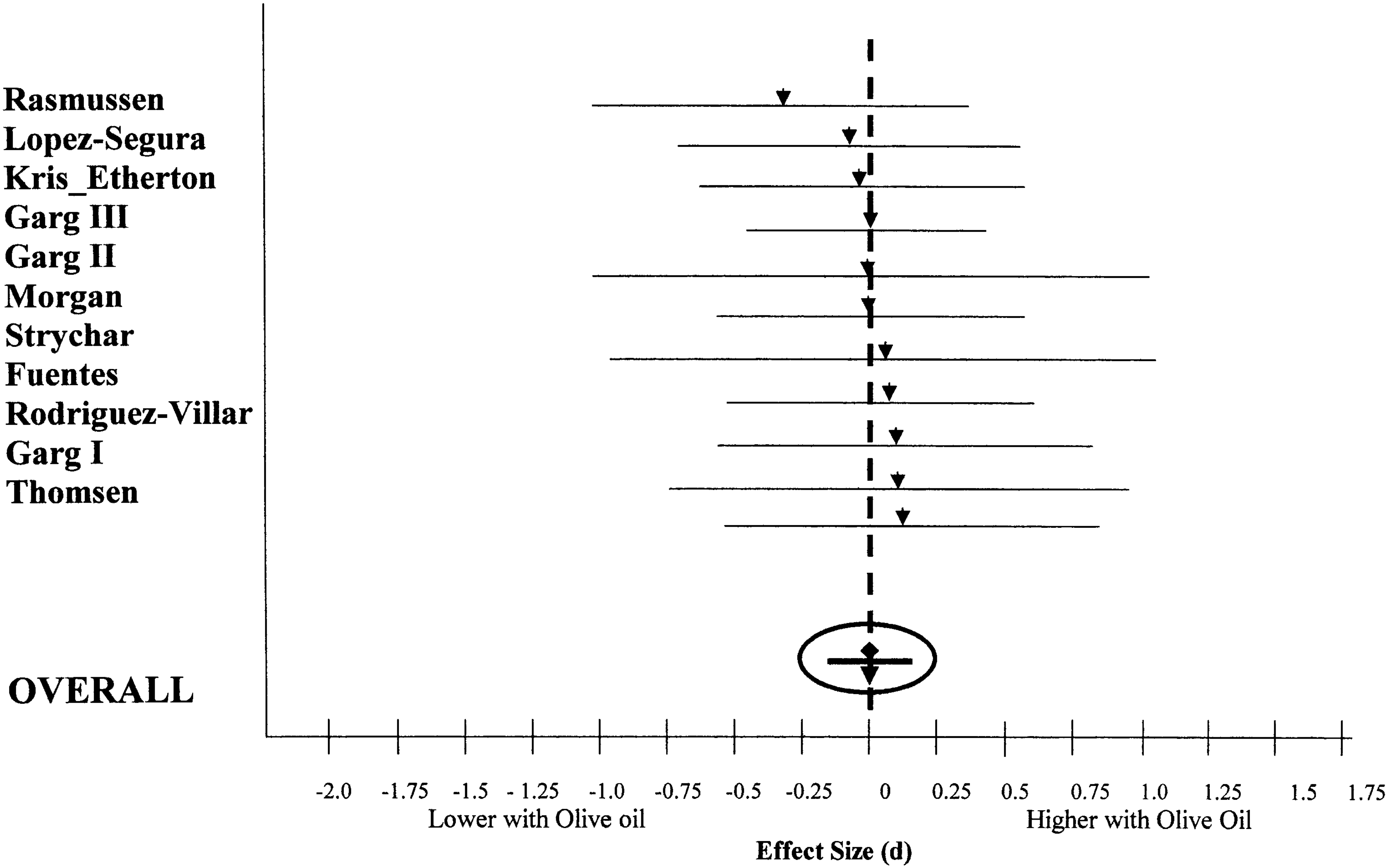
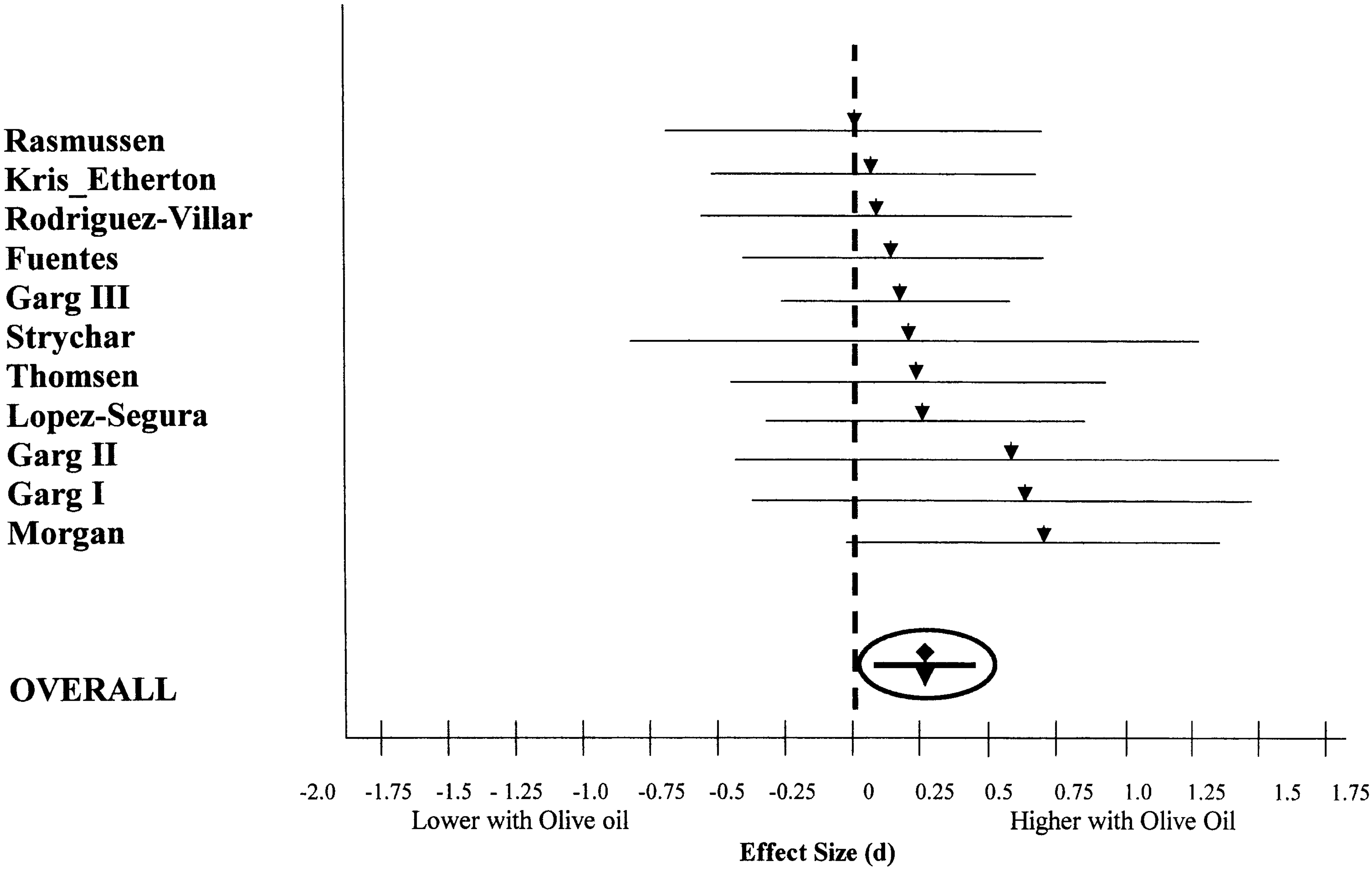
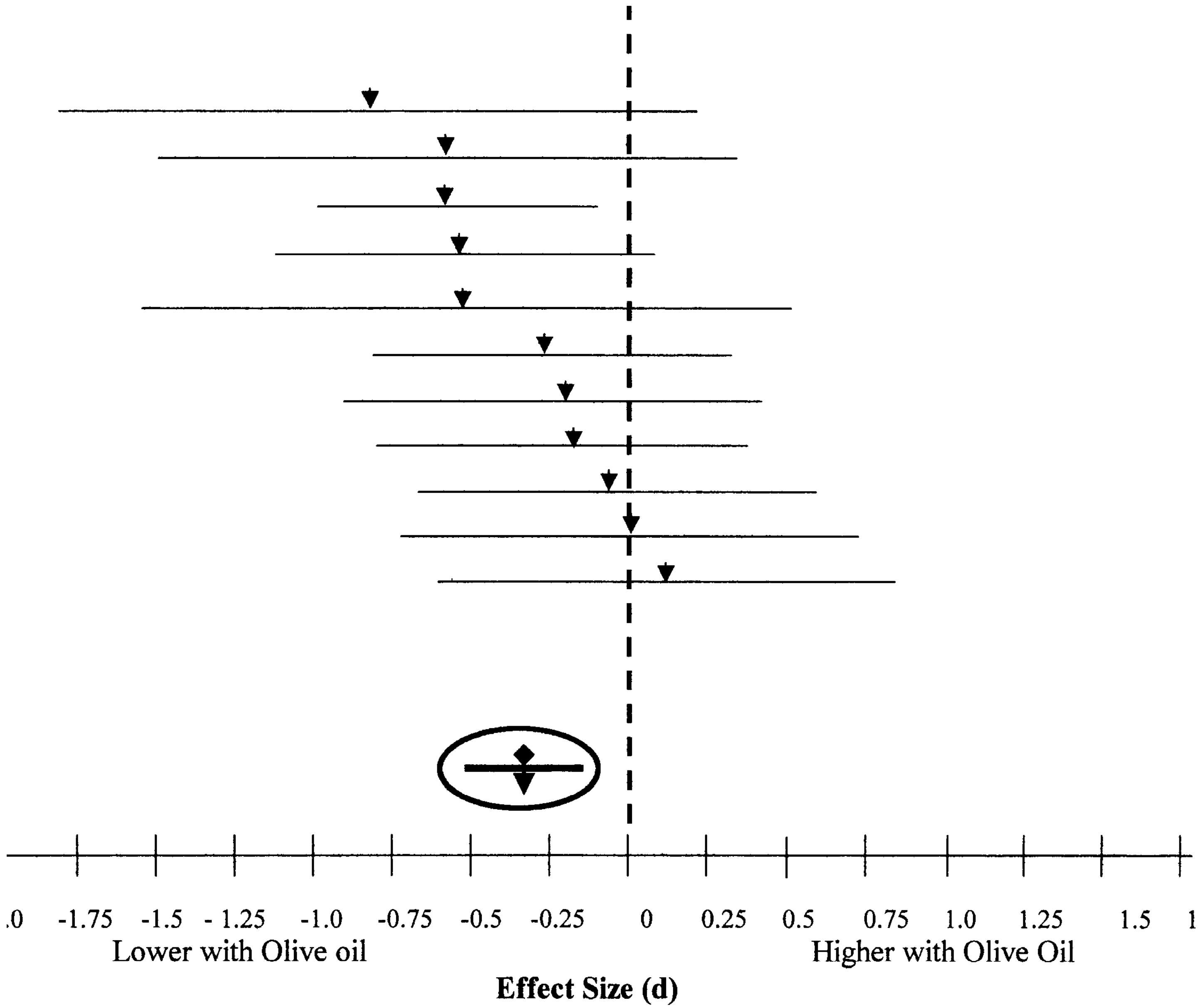


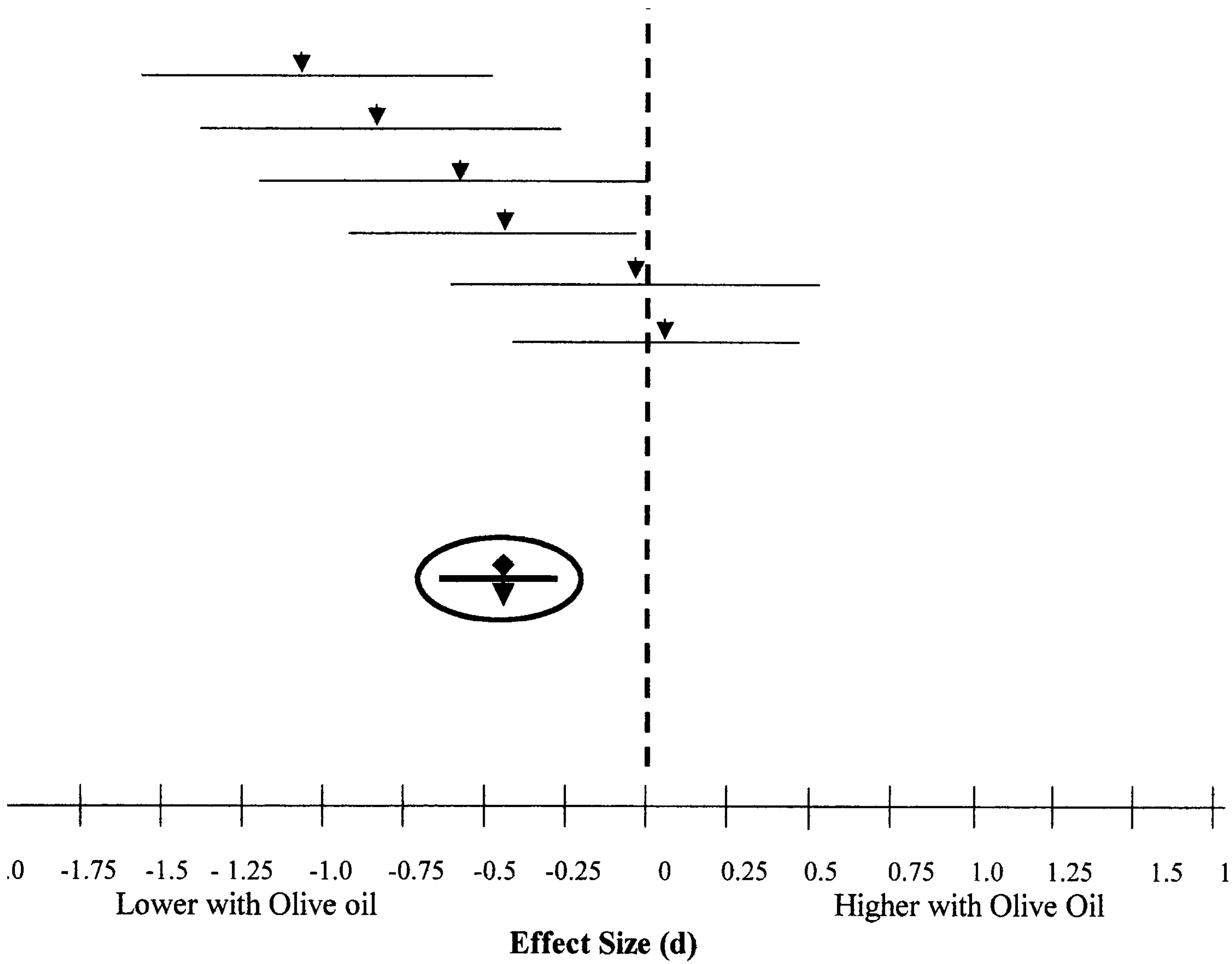
Figure 1c. Effect of Olive oil on High-Density Lipoprotein Cholesterol as Compared to Low-Fat Diets



il on Triglycerides as Compared to Low-Fat Diets



ʼlive Oil on Total Cholesterol as Compared to Saturated-Fat Diets



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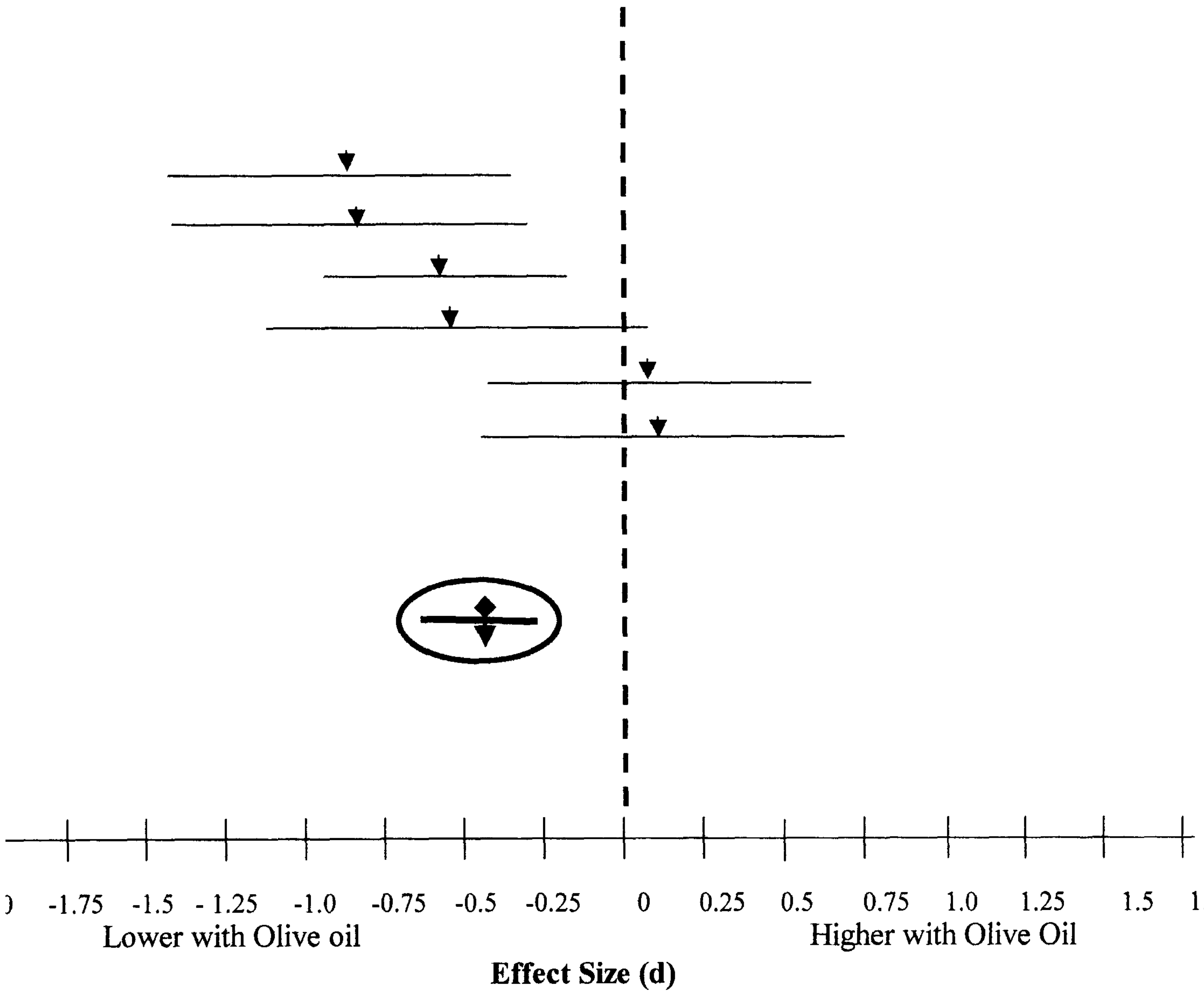

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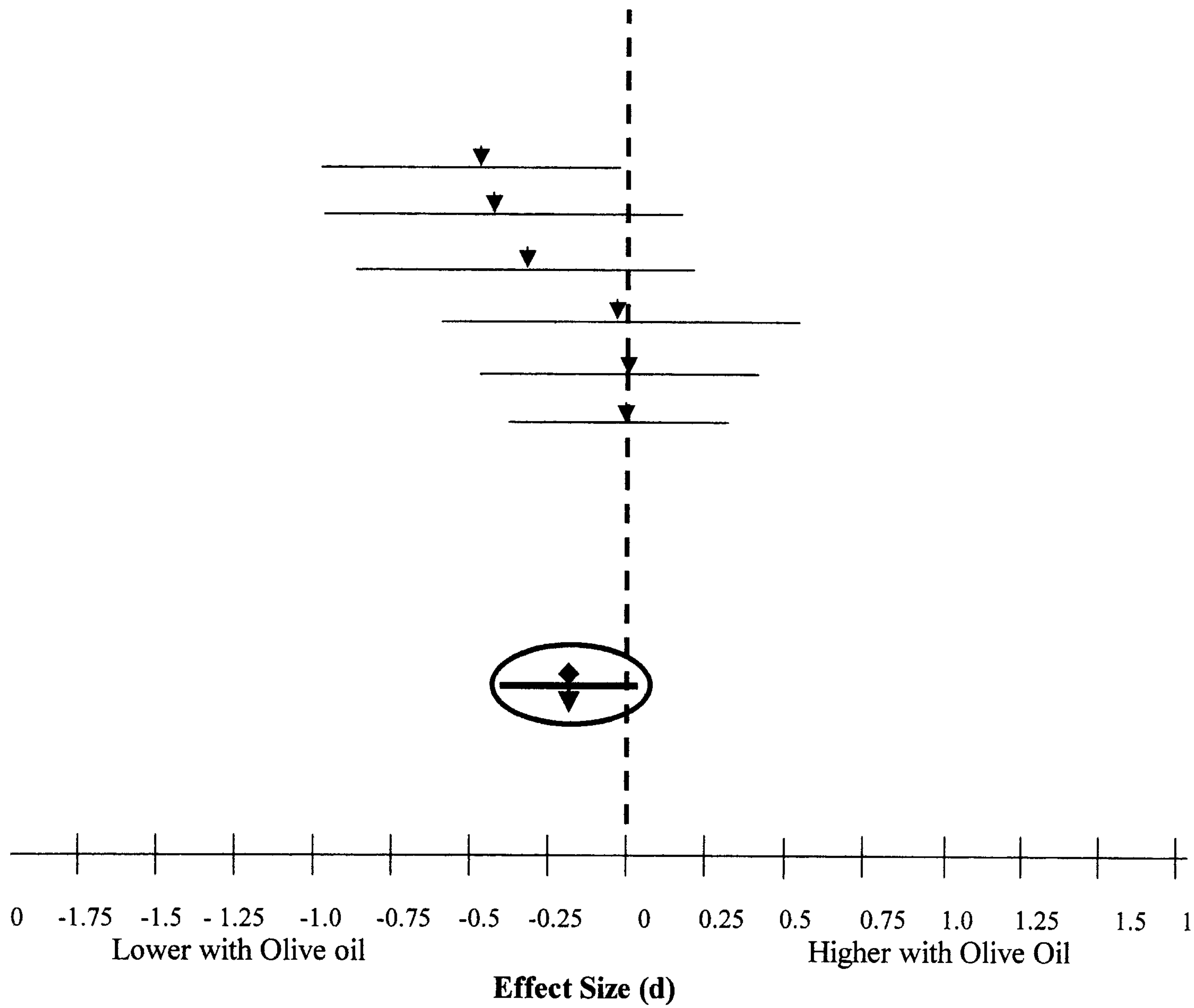

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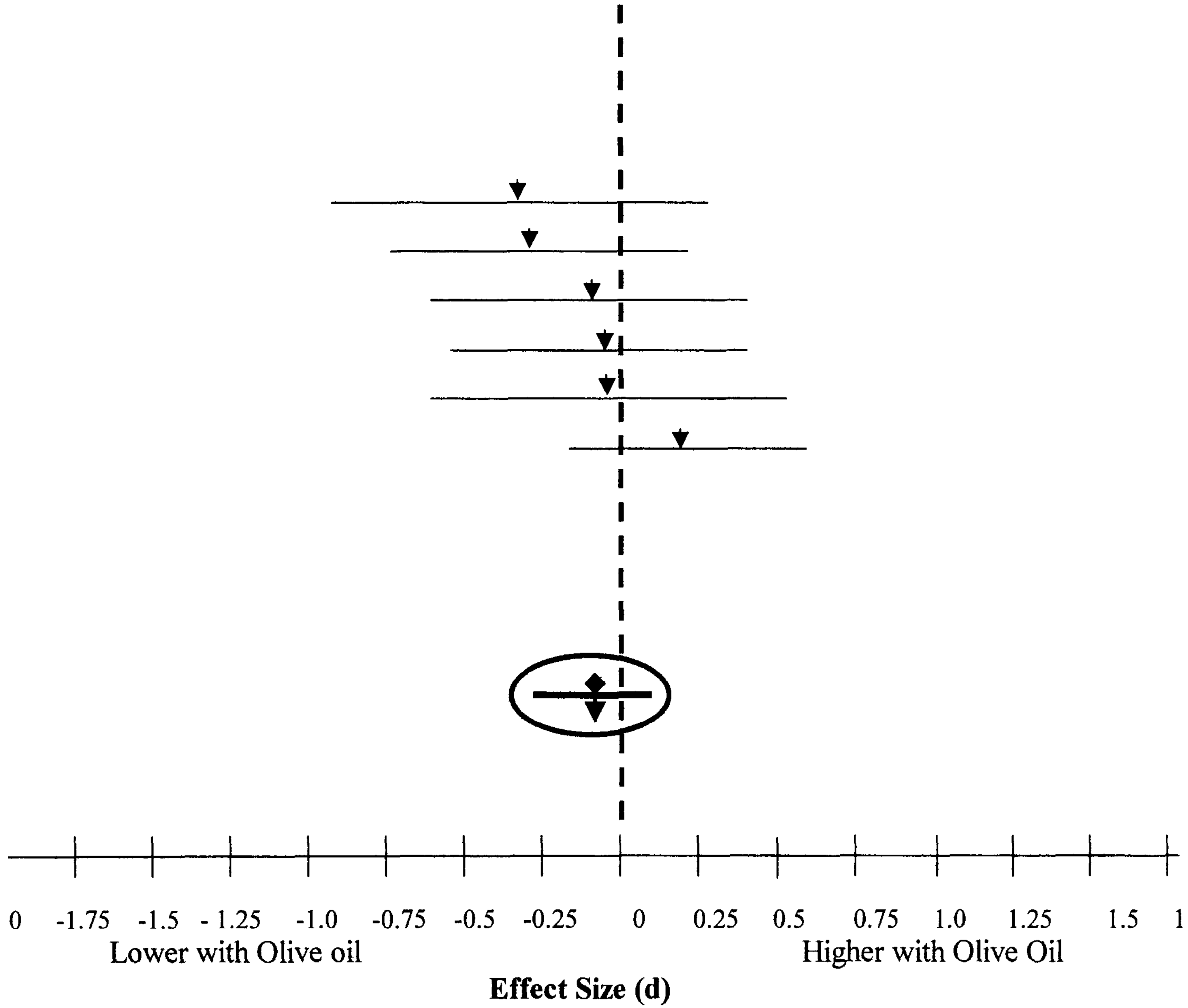

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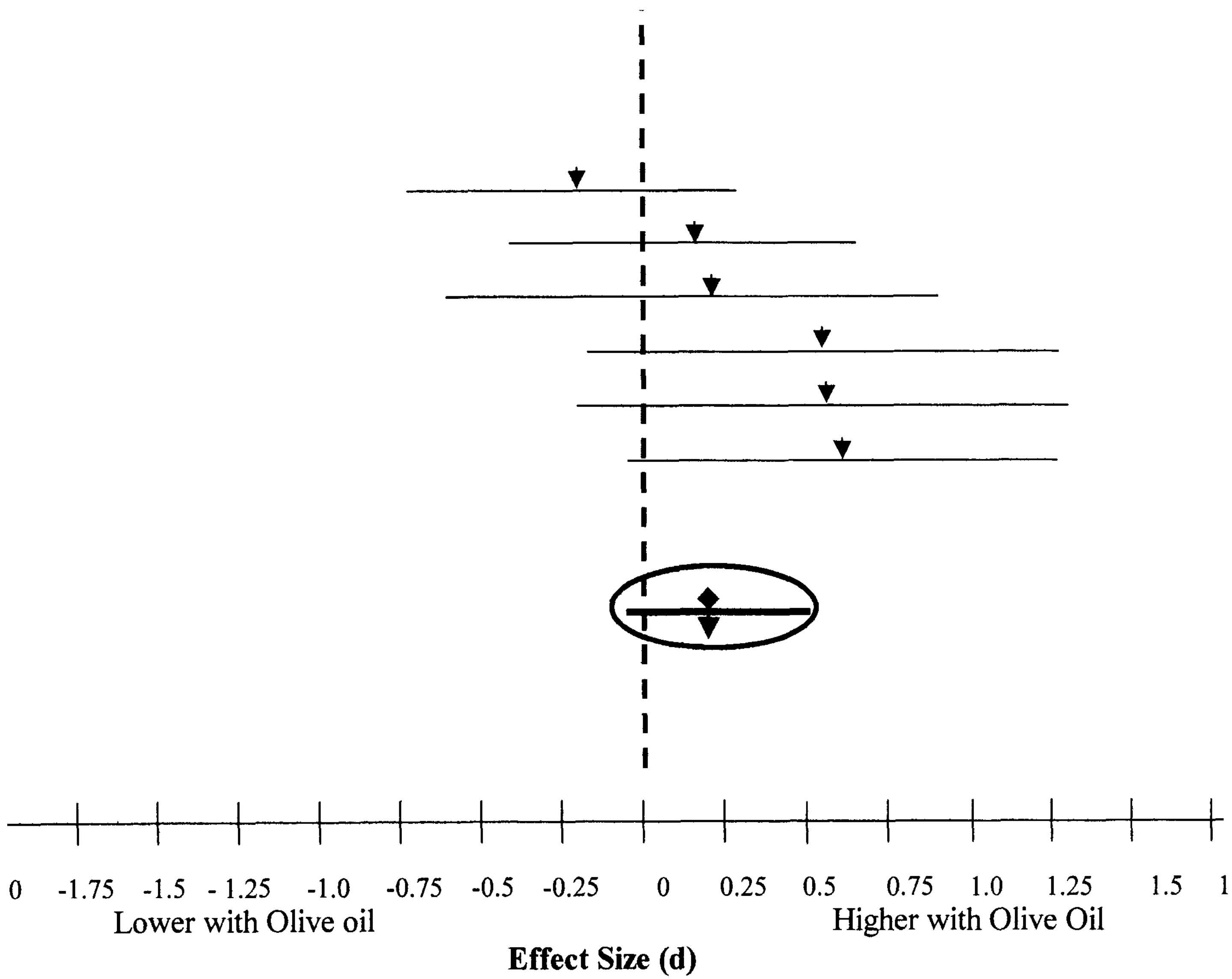

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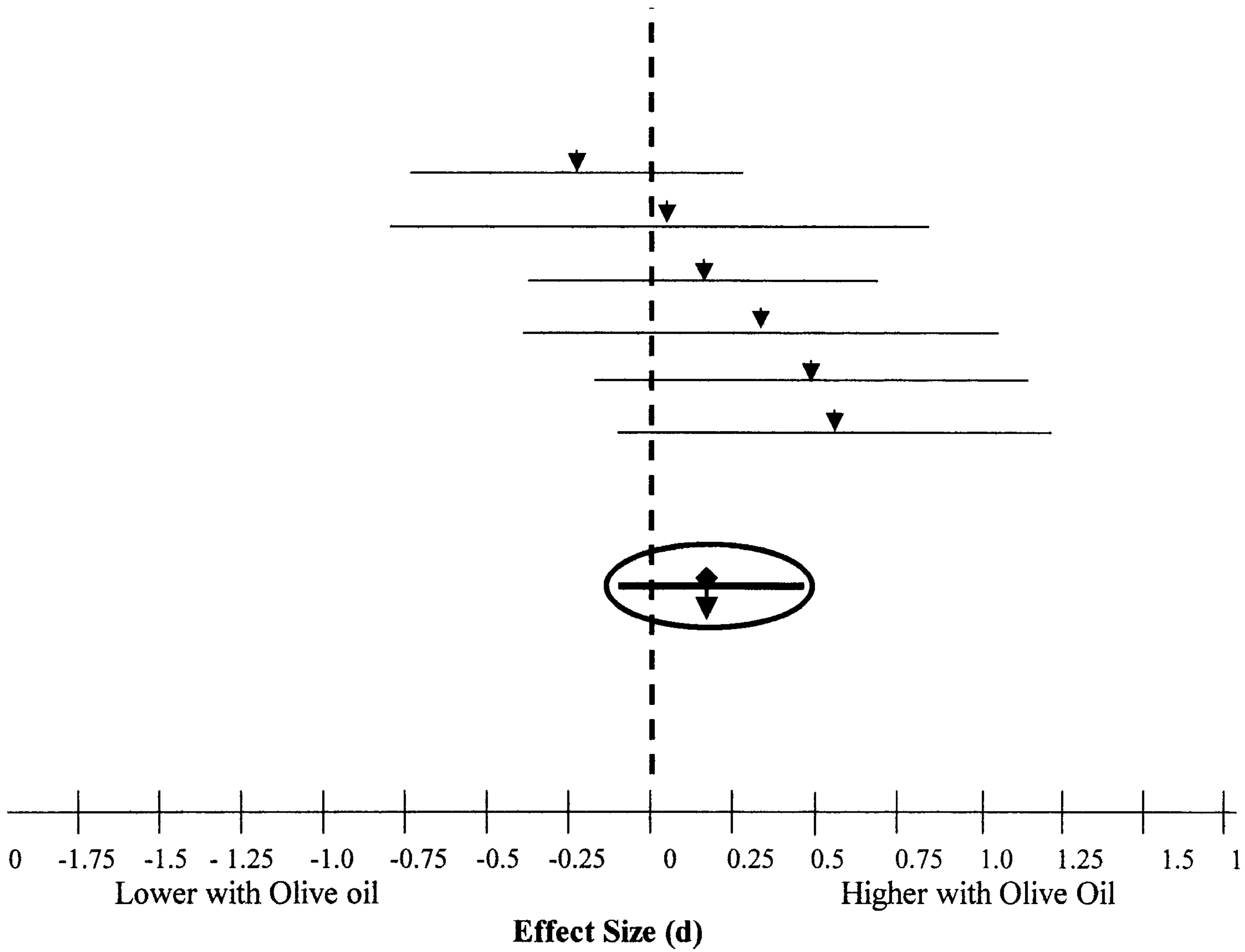

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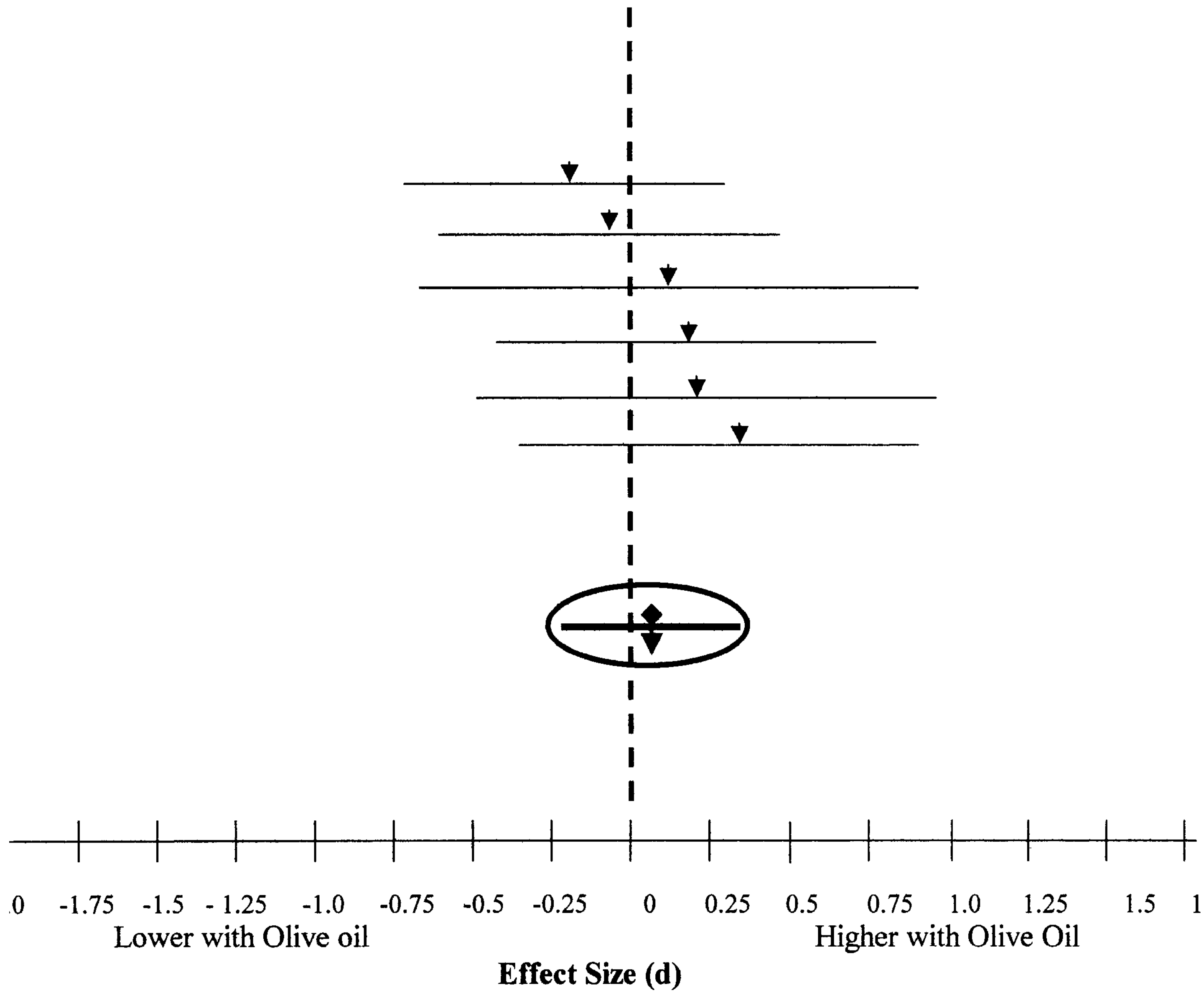
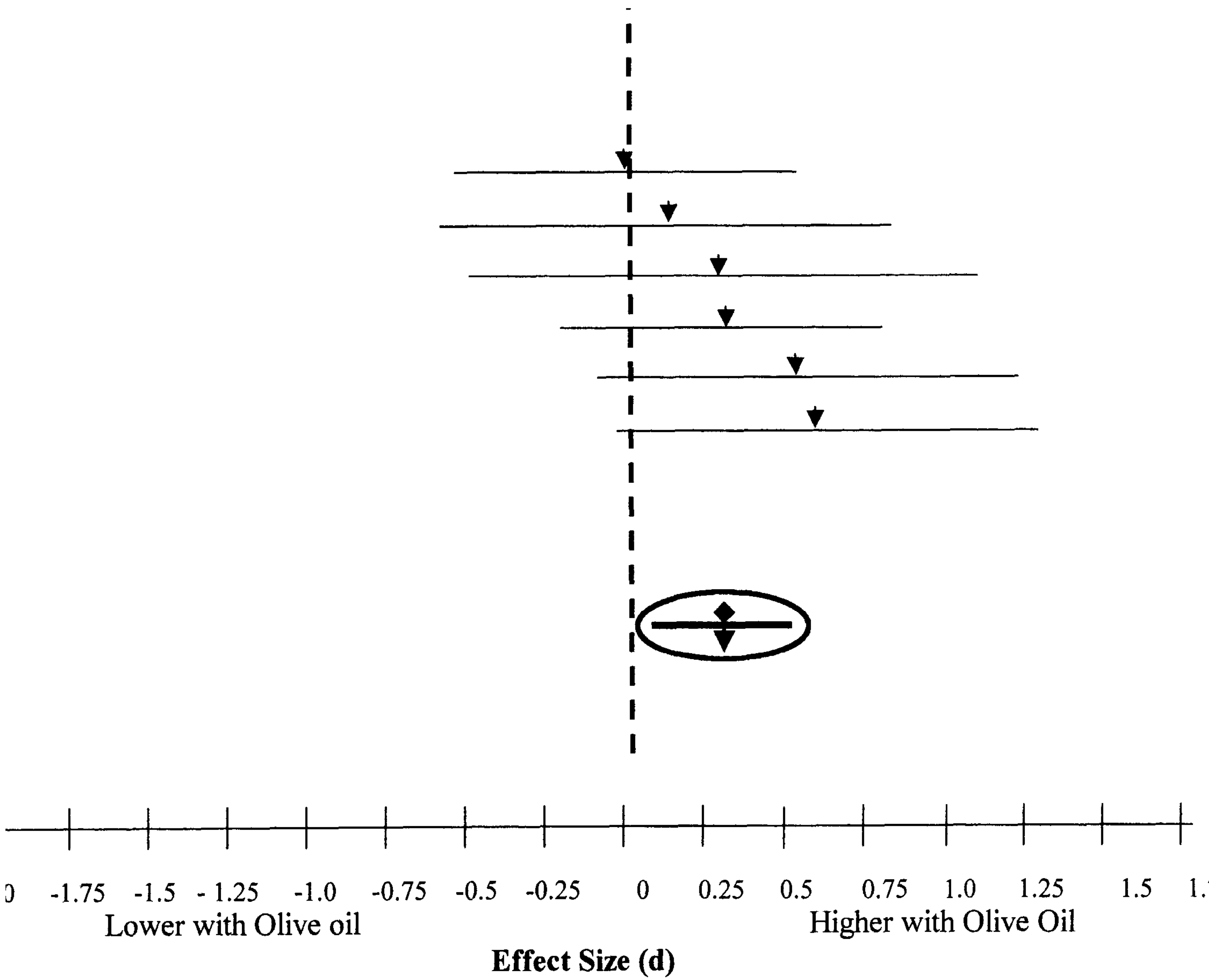


)live Oil on Triglycerides as Compared to Polyunsaturated-Fat Diets



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