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Permalink

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Journal

The American Journal of Cardiology, 99(6)

ISSN

0002-9149

Authors

Reid, Cheryl L
Anton-Culver, Hoda
Yunis, Carla
[et al.](#)

Publication Date

2007-03-01

DOI

10.1016/j.amjcard.2006.10.048

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Peer reviewed

Prevalence and Clinical Correlates of Isolated Mitral, Isolated Aortic Regurgitation, and Both in Adults Aged 21 to 35 Years (from the CARDIA Study)

Cheryl L. Reid, MD^a, Hoda Anton-Culver, PhD^a, Carla Yunis, PhD^b, and Julius M. Gardin, MD^{c,*}

Aortic regurgitation (AR) and mitral regurgitation (MR) can result in serious clinical complications and death. The physiologic and clinical correlates of AR and MR in a free-living young adult population, however, have not been well defined. The prevalence and correlates of AR and MR were investigated in Coronary Artery Risk Development in Young Adults (CARDIA), a multicenter National Heart, Lung, and Blood Institute study of 4,352 men and women aged 21 to 35 years who had 2-dimensionally directed M-mode echocardiographic and spectral and color Doppler examinations. Isolated MR by color Doppler was detected in 10.4% (90.4% with trivial or mild severity). Isolated AR by color Doppler was present in 0.8% (37.7% with mild severity). Combined AR and MR occurred in 0.5%. There was no association between body mass index and the prevalence or severity of MR or AR. Left ventricular mass was greater in subjects with isolated AR (mean \pm SD 172 \pm 49 g) than in those with MR (155 \pm 48 g) and greater in both groups than in subjects without MR and AR (148 \pm 44 g). AR was associated with increased aortic root diameter, whereas subjects with isolated MR and those with AR and MR had increased left atrial dimensions and greater left ventricular internal dimensions. In conclusion, MR and AR detected by color Doppler echocardiography are relatively uncommon in a healthy young adult population, but both are associated with evidence of increased left ventricular dimensions and mass. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99: 830–834)

Coronary Artery Risk Development in Young Adults (CARDIA) is a prospective, multicenter epidemiologic study of healthy young adults aged 23 to 35 years at the time of their initial echocardiographic examinations.¹ The purposes of the present study were to determine in this population (1) the prevalence and severity of left-sided valvular regurgitation; (2) the relation of valvular regurgitation to other clinical variables, such as age, gender, ethnicity, and weight; (3) the frequency and severity of morphologic abnormalities associated with mitral regurgitation (MR) and aortic regurgitation (AR); and (4) whether minimal or mild degrees of valvular regurgitation are associated with differences in left ventricular (LV) systolic function and anatomy (dimension and mass) compared with young adults without valvular regurgitation.

Methods

Study population: The overall design and objectives of CARDIA have been described elsewhere.² The initial CARDIA cohort comprised 5,115 participants aged 18 to 30 years at the time of enrollment (1985 to 1986), 5 years before the first echocardiographic examination. The sample was approximately balanced by race (black and white), gender, age (18 to 24 and 25 to 30 years), and education (high school and more than high school). The CARDIA cohort included participants recruited and examined at 4 field centers located in Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Echocardiograms were initially obtained from 4,352 participants aged 21 to 35 years as part of the third CARDIA examination (1990 to 1991). This cohort comprised 905 black men, 1,054 white men, 1,214 black women, and 1,179 white women. At the time of the echocardiographic examinations, participants underwent detailed clinical evaluations, including measurements of height, weight, and systolic and diastolic blood pressures.

Echocardiography: Two-dimensionally directed M-mode echocardiography was attempted in all participants using a protocol similar to that used in the Cardiovascular Health Study (CHS), a multicenter study of free-living elderly subjects sponsored by the National Heart, Lung, and Blood Institute (Bethesda, Maryland).¹ The echocardiograms were obtained using an Acuson ultrasound machine (Mountain View, California) with a 2.5-MHz transducer. A baseline M-mode, 2-dimensional, spectral, and color Doppler echo-

^aDepartment of Medicine, Division of Epidemiology, University of California, Irvine, Irvine, California; ^bHypertension and Vascular Disease Center, Wake Forest University School of Medicine, Winston-Salem, North Carolina; and ^cDepartment of Medicine, Division of Cardiology, St. John Hospital & Medical Center, Detroit, Michigan. Manuscript received April 25, 2006; revised manuscript received and accepted October 11, 2006.

This research was supported by Contracts NO1-HC 48047, 48048, 48049, 48050, 95095, and 95100 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland.

*Corresponding author: Tel: 313-343-6390; fax: 313-343-3912.

E-mail address: julius.gardin@stjohn.org (J.M. Gardin).

Table 1
Blood pressure and echocardiographic characteristics of mitral and aortic regurgitation in the Coronary Artery Risk Development in Young Adults cohort

Variable	Isolated MR (n = 455)	Isolated AR (n = 33)	Combined MR and AR (n = 20)	No MR/No AR (n = 3,844)	p Trend (overall p Value)
Systolic blood pressure (mm Hg)	108.2 ± 11.5	110.7 ± 15.9	110.1 ± 16.4	107.7 ± 11.5	0.31
Diastolic blood pressure (mm Hg)	69.1 ± 10.0	70.7 ± 12.1	67.1 ± 10.0	69.3 ± 10.2	0.63
Pulse pressure (mm Hg)	39.2 ± 8.3	40.0 ± 9.3	43.0 ± 10.0	38.5 ± 8.4	0.027
LV internal dimension, diastole (mm)	5.0 ± 0.5	5.2 ± 0.6	5.4 ± 0.7	4.9 ± 0.5	<0.0001
LV internal dimension, systole (mm)	3.3 ± 0.5	3.3 ± 0.7	3.4 ± 0.8	3.2 ± 0.4	<0.0001
Interventricular septum, diastole (mm)	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.1	0.9 ± 0.2	0.55
LV posterior wall, diastole (mm)	0.9 ± 0.2	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.089
Left atrial size (mm)	3.6 ± 0.5	3.5 ± 0.5	3.8 ± 0.7	3.5 ± 0.5	0.0004
Aortic root (mm)	2.8 ± 0.4	3.1 ± 0.5	2.9 ± 0.4	2.8 ± 0.4	0.0001
LV fractional shortening (%)	34.5 ± 5.9	37.1 ± 7.0	36.5 ± 8.9	35.8 ± 5.9	0.0001
LV mass (g)	155.0 ± 47.9	172.2 ± 48.9	170.0 ± 55.9	148.5 ± 44.1	0.0001

cardiogram was recorded on super-VHS videotape during a 30-minute examination of each subject. Videotapes were forwarded from the field centers to the Echocardiography Reading Center at the University of California, Irvine, where images were digitized and measurements made using a Dextra D-200 off-line image analysis system (Dextra Medical, Inc., Lakewood, California). M-mode measurements were performed of the left atrial and aortic root dimensions and of ventricular septal thickness, LV posterior wall thickness, and LV internal dimension, all in systole and diastole. M-mode measurements were made using the recommendations of the American Society of Echocardiography.³ Derived measurements included (1) LV fractional shortening, calculated as $[(LVIDd - LVIDs)/LVIDd] \times 100\%$, and (2) LV mass (in grams) derived as described by Devereux et al.,⁴ calculated as $0.80 \{1.04 [(VSTd + LVIDd + PWTd)^3 - LVIDd^3]\} + 0.6$, where LVIDs is LV internal dimension at end-systole, LVIDd is LV internal dimension at end-diastole, PWTd is posterior wall thickness at end-systole, PWTd is posterior wall thickness at end-diastole, and VSTd is ventricular septal thickness at end-diastole.

Morphologic abnormalities: After review of the 2-dimensional echocardiograms, valvular abnormalities associated with AR were coded as bicuspid aortic valve, dilated aortic root, vegetations, and thickened aortic valve. Valve thickening was defined by visual inspection as increased thickness of ≥ 1 valve leaflet. Valvular abnormalities associated with MR were coded as increased leaflet thickness, vegetations, subvalvular calcification, rheumatic valve, and mitral valve prolapse. Data describing the presence of mitral valve prolapse in CARDIA have been previously reported and are summarized only in relation to other morphologic abnormalities.⁵ There were no subjects with mechanical or bioprosthetic aortic or mitral valves.

Valvular regurgitation: Color Doppler recordings were performed in the apical 4-chamber and long-axis views. The severity of AR was quantitated on the basis of the ratio of the jet width (measured in the apical long-axis view directly below the aortic valve leaflets) to LV outflow height (measured in the parasternal long-axis view) times 100%. On the basis of this ratio, severity was divided into 4 grades: (1) trivial (<6%), (2) mild (6% to <25%), (3) moderate ($\geq 25\%$ to <47%), and (4) severe ($\geq 47\%$).⁶ The severity of

MR was quantitated in the apical 4-chamber view as the ratio of jet area to left atrial area times 100%. On the basis of this ratio, severity was graded as (1) trivial (<6%), (2) mild ($\geq 6\%$ to <20%), (3) moderate ($\geq 20\%$ to <41%), and (4) severe ($\geq 41\%$).⁷

Covariates analyzed: Clinical and physical characteristics either caused by or suspected of association with left-sided valvular regurgitation were analyzed in relation to the presence and severity of valvular regurgitation. Factors selected a priori included (1) age; (2) gender; (3) race; (4) systolic and diastolic blood pressure (in millimeters of mercury), corresponding to the average of the second and third seated cuff pressures at rest in systole and diastole, measured after 1 minute of rest; and (5) body mass index (BMI), calculated as weight in kilograms divided by height in square meters. To assess the effect of the presence and severity of valvular regurgitation on cardiac function, the following factors were analyzed: (1) pulse pressure in subjects with AR (calculated as the difference between systolic and diastolic blood pressure and measured in millimeters of mercury), (2) LV mass (in grams), (3) LV internal dimension at end-diastole and end-systole (in centimeters), (4) LV fractional shortening (in percent), (5) aortic root dimension (in centimeters), and (6) left atrial dimension (in centimeters).

Statistical analysis: All values are reported as mean \pm 1 SD. The statistical significance of continuous variable comparisons was determined using Student's *t* test. Physiologic covariates were adjusted for BMI. Subjects were classified into 4 categories (see Table 1): isolated MR, isolated AR, combined MR and AR, and no MR or AR. To avoid the effects of concomitant regurgitation present in both valves, statistical analysis for AR was performed after subjects with moderate or greater MR had been excluded. For analysis of MR covariates, subjects with AR were excluded. The statistical significance of categorical variable comparisons was assessed using the chi-square test. Differences were considered significant at an α level of <0.05.

Relation of BMI to valvular regurgitation: A nested case-control design was used to examine the relation between MR or AR and BMI. For the purposes of this analysis, only patients identified as having mild, moderate, or

Table 2
Prevalence of valvular regurgitation by body mass index

BMI (kg/m ²)	MR	No MR	AR	No AR
Men: ≤22.9, women: ≤21.6	98 (28.1%)	84 (23.9%)	17 (32.7%)	16 (30.2%)
Men: 22.9–28, women: 21.6–29.2	179 (51.3%)	179 (50.9%)	28 (53.9%)	29 (54.7%)
Men: 28–31.8, women: 29.2–34.5	41 (11.8%)	52 (14.8%)	5 (9.6%)	6 (11.3%)
Men: ≥31.8, women: 35.5	31 (8.9%)	37 (10.5%)	2 (3.9%)	2 (3.8%)
Total	349	352	52	53

severe MR and/or AR were selected and compared with a group of 406 controls from the CARDIA cohort randomly selected to match for age and gender.

Patients and controls were assigned to 4 categories using gender-specific percentiles of BMI as cut points: (1) low body mass: ≤25th percentile of BMI in the CARDIA cohort (men ≤22.9 kg/m², women ≤21.6 kg/m²); (2) average body mass: BMI between the 25th and 75th percentiles (men 22.9 to 28 kg/m², women 21.6 to 29.2 kg/m²); (3) moderately high body mass: BMI between the 75th (inclusive) and 90th percentiles (men 28 to 31.8 kg/m², women 29.2 to 34.5 kg/m²); and (4) very high body mass: BMI ≤90th percentile (men ≥31.8 kg/m², women ≥35.5 kg/m²). From these categories, 3 dummy variables were created, with the category of average body mass as the reference group. The 2 categorical variables, gender and age (21 to 24, 25 to 29, 30 to 34, and 35 to 41 years), were controlled for in the analyses. Analyses for AR and MR were conducted separately. Logistic regression was used to compute odds ratios for regurgitation within each level of BMI, controlling for gender and age.

Results

Prevalence and severity of valvular regurgitation: No AR or MR was noted in 88.3% of the total cohort. Isolated AR of any severity was present in 0.8%, isolated MR was present in 10.4%, and combined MR and AR were present in 0.5%, for a total prevalence of valvular regurgitation of 11.7%. There were no differences in the prevalence of AR or MR on the basis of gender (AR: 1.4% in men vs 1.0% in women; MR: 11.2% in men vs 10.7% in women) or race (AR: 1.1% in blacks vs 1.3% in whites; MR: 11.0% in blacks vs 10.9% in whites).

The severity of AR on the basis of color Doppler recordings was mild in 37.7% and moderate in 62.3%. There were no cases of trivial or severe AR. The severity of MR was trivial in 25.7%, mild in 64.0%, moderate in 10.1%, and severe in 0.2% of subjects with MR.

Physiologic abnormalities associated with valvular regurgitation: The direct and derived M-mode echocardiographic measurements for the 4 MR and AR categories are listed in Table 1. In participants with any degree of AR, there was a small but significant increase in LV internal dimension in diastole (5.3 ± 0.6 vs 4.9 ± 0.5 cm, $p < 0.0001$) after adjustment for BMI. The increase in LV internal dimension was associated with an increase in LV mass, without a concomitant increase in end-diastolic ventricular septal or LV posterior wall thickness. Aortic root dimension was significantly increased in subjects with AR compared with those without AR (3.0 ± 0.5 vs

2.8 ± 0.4 cm, $p < 0.0001$). Pulse pressure was significantly greater in subjects with AR because of slightly greater systolic blood pressure.

In participants with mild or greater MR compared with those without MR, there was a similar modest increase in LV internal dimension after adjustment for BMI during diastole (5.0 ± 0.5 vs 4.9 ± 0.5 cm, $p < 0.0001$) and systole (3.3 ± 0.4 vs 3.2 ± 0.4 cm, $p = 0.001$), which was associated with an increase in LV mass. There was no significant difference in LV diastolic dimensions between the group with mild MR and no AR and the group with moderate to severe MR and no AR (5.0 ± 0.5 cm in the 2 groups, $p = \text{NS}$). Left atrial dimension was only slightly greater in participants with MR (3.6 ± 0.5 vs 3.5 ± 0.5 cm, $p < 0.0001$). When the variables listed in Table 1 were compared with the severity of MR (mild vs moderate to severe), no significant differences were found.

Echocardiographic morphologic abnormalities: Abnormalities of the aortic valve or root were present in only 0.3% of the entire cohort. Of the 53 participants with AR (20 with concomitant MR), no echocardiographic abnormality of the aortic valve or root was noted in 46 (86.8%). Bicuspid aortic valves were detected in 4 subjects (7.5%): 2 with mild AR and 2 with moderate AR. In the entire cohort, bicuspid aortic valves were detected in 0.14%. Other abnormalities visualized included a thickened valve in 1 subject and dilated aortic roots in 2 subjects. In those subjects without AR, bicuspid aortic valves were detected in 2 (a total prevalence of 0.14%), thickened valves in 3, and dilated aortic roots in 2.

Morphologic abnormalities of the mitral valve were noted in 6.3% of the total cohort. Of the 475 participants with MR (20 with concomitant AR), 405 (85.3%) had no echocardiographic abnormalities recorded. Thickened mitral leaflets were noted in 10 (2.1% of subjects with MR and 0.09% of those without MR), and rheumatic mitral disease, defined as thickened mitral leaflets with apparent restricted leaflet tip motion, was present in 1 subject.

Mitral valve prolapse by any definition was present in 262 participants in the total cohort (6.0%); 26 were classified as having “definite” mitral valve prolapse (0.6%), and the remainder of the subjects had “possible” mitral valve prolapse.⁵ The cause of MR was definite mitral valve prolapse in 9 subjects (1.9% of those with MR; 6 with mild and 3 with moderate severity) and possible mitral valve prolapse in 51 subjects (10.7%).

Prevalence of valvular regurgitation by BMI: Table 2 shows the prevalence of AR by BMI. The odds ratios for each level of BMI were not significant (all confidence in-

tervals included 1.0). Logistic regression analysis was not performed within each gender and age subgroup because of the small (or zero) numbers of subjects within the subgroups.

Table 2 lists the prevalence of MR by BMI. The odds ratios for each level of BMI were not significant (all confidence intervals included 1.0). In addition, the logistic regression models were analyzed within each gender and age subgroup. None of the odds ratios was significant, except for that in men aged 25 to 29 years with moderately high BMIs. In this instance, the odds ratio was 0.122 (95% confidence interval 0.024 to 0.61), indicating that men aged 25 to 29 years with moderately high BMIs are significantly less likely to have MR. This isolated finding, however, should be interpreted with caution, because the data do not support a graded relation between BMI and MR severity. Specifically, men aged 25 to 29 years in the highest BMI group were slightly, but not significantly, more likely to have MR. Furthermore, this finding was not replicated in any other gender or age subgroup, or in the overall analysis with adjustments for gender and age.

Discussion

The most significant finding in this large study is that most (88.3%) healthy, young adults have no left-sided valvular regurgitation by color Doppler echocardiography. Either AR or MR, or both, occurred in only 11.7% of the total cohort. Isolated AR was extremely uncommon (0.8%), whereas MR was significantly more frequent (10.4%). In a previous report of a much smaller, healthy cohort (61 patients), the prevalence of left-sided valvular regurgitation detected by color Doppler echocardiography in those <50 years of age was 39%; all cases were considered trivial in severity and confined to the mitral valve.⁸ In a similar study of subjects in whom valvular regurgitation was excluded by physical examination, color Doppler flow studies detected MR in 44% of those <40 years of age.⁹ The severity of MR was not classified, although the mean jet area for the group was 0.26 cm², which would generally be considered mild or trivial. No AR was detected.

The incidence of left-sided valvular regurgitation has been shown to increase with age.⁸ In patients >50 years of age, the prevalence in 1 report of AR by color Doppler was 23% (all mild or trivial) and of MR was 58% (all mild or trivial). AR was seen exclusively in older subjects.⁸ In a large, National Institutes of Health–sponsored study of free-living elderly subjects aged ≥65 years, the prevalence of AR detected by color Doppler echocardiography was 20% (mild: 44% of AR) and of MR was 30% (mild: 73% of MR).¹⁰ From these large studies, it is apparent that age is a primary determinant of “normal” prevalence of left-sided valvular regurgitation and should be considered when interpreting echocardiograms.

The diagnosis and estimation of the severity of valvular regurgitation in our study were based on the quantitative measurement of the regurgitant jets recorded by color Doppler echocardiography. These techniques have been previously validated for AR and MR.^{6,7} One difficulty in comparing large population studies that use color Doppler echocardiography is the variability among studies of the

criteria for the classification of trivial regurgitation, especially of the mitral valve. Regurgitation of the mitral valve may occur in relation to valve closure (“physiologic”) and be of short duration, occurring only during midsystole.^{11,12} The incidence, therefore, of small degrees of valvular regurgitation in a population will depend on many factors, including the criteria used in the detection and the sensitivity of the ultrasound machine.⁷ In the CARDIA study, trivial MR was considered to be a well-defined jet, with a jet area/left area ratio of <6%. For the purposes of further analyses, these subjects were excluded. Regardless of the definition of trivial or physiologic regurgitation, small amounts of closure leakage of the mitral valve are unlikely to have hemodynamic consequences. Mild MR was present in 6.8% of the total CARDIA population, whereas moderate to severe MR, which is the most clinically significant, occurred in only 1.3% of this large young, healthy cohort. There was no difference in LV internal dimension in diastole in these 2 MR groups, possibly because in this young adult cohort, the duration of the MR was relatively short, thus allowing less time for LV remodeling occur (e.g., in the group with moderate to severe MR).

AR, in contrast to MR, has not generally been encountered in normal subjects. In 2 previously reported studies, no AR was detected in young, healthy populations.^{8,9} AR was present in only 1.2% of the CARDIA cohort and was considered mild to moderate in severity in all subjects. The small prevalence of AR encountered in this study, compared with previous studies, most likely reflects the difference in recruitment of potential participants. In the CARDIA study, subjects were required only to be free living and able to complete all parts of the examination, such as exercise testing and questionnaires.² No attempt was made to exclude participants on the basis of physical examination or medical history. Therefore, the findings in this study probably more accurately reflect the prevalence of regurgitation in a young, free-living population.

The detection of abnormalities of valve morphology by 2-dimensional echocardiography was unusual in the CARDIA cohort. There were no significant differences in the abnormalities of the aortic valve or root in subjects with or without AR, although aortic root dimensions were greater in those with AR. Bicuspid or congenital aortic valve abnormalities were noted by 2-dimensional echocardiography in only 0.14%. However, this study should not be viewed as definitive regarding the prevalence of bicuspid aortic valves in young adults. The reason for this is that the study was designed a priori to focus on LV and left atrial anatomic and functional measurements and only secondarily to look at anatomic details of the aortic valve. Consequently, it is quite possible that sonographers recording the echocardiograms and echocardiographic readers may not have focused their attention on documenting the presence of bicuspid aortic valves. In comparison, autopsy series have shown an incidence of congenital aortic valve abnormalities of 2.5%.¹³ The sensitivity of 2-dimensional echocardiography for the detection of bicuspid aortic valves in subjects with either surgical or pathologic inspection has been reported to be 78%.¹⁴ The true prevalence of bicuspid aortic valves in an apparently healthy population has not been previously reported. In the Strong Heart Study (SHS), which included

older subjects aged 45 to 74 years, the incidence of bicuspid aortic valves was 0.3%.¹⁵ Bicuspid aortic valves may become either stenotic or regurgitant and lead to death, but the frequency with which this occurs is unclear. Thus, surgical or autopsy series may overestimate the prevalence of this valvular abnormality in the general population.

In contrast, the most common echocardiographic valvular abnormality in this CARDIA cohort was mitral valve prolapse. The reported incidence of mitral valve prolapse detected by echocardiography in the general population has varied from 1% to 13%.^{16,17} This variability results from differences among the studies in the diagnostic method, criteria, and population. Two-dimensionally guided M-mode echocardiography has been reported to increase the specificity of the diagnosis and to avoid some of the false-positive findings caused by holosystolic prolapse present on M-mode echocardiography alone. In the CARDIA study, the criteria for mitral valve prolapse were divided into definite and possible on the basis of the method used (2-dimensionally guided M-mode vs 2-dimensional echocardiography) and the diagnostic criteria. On the basis of the most stringent criteria of definite mitral valve prolapse, the previously reported 0.6% incidence in the CARDIA study is similar to studies reporting much lower incidences in the general population.^{18,19} Although the criteria for definite mitral valve prolapse would result in a high degree of specificity, they may result in an underestimation of the actual prevalence. When all suggested criteria were applied as possible mitral valve prolapse, the overall incidence of 6.0% is similar to the 5.0% reported in the Framingham study, using similar M-mode criteria. The importance of a noninvasive technique with a high degree of sensitivity and specificity results from the known complications associated with mitral valve prolapse, including arrhythmias with sudden death, severe regurgitation requiring valve repair or replacement, endocarditis, and stroke.^{19–22} Furthermore, evidence suggests that patients at increased risk for complications associated with mitral valve prolapse can be identified by 2-dimensional echocardiography.

The CARDIA echocardiographic study was designed primarily to assess factors associated with LV mass. The assessment of valvular regurgitation was not the primary end point, which may have influenced the diligence in detection. For example, the time spent in scanning patients and machine settings were optimized for endocardial border detection. Thus, small degrees of valvular regurgitation may have not been detected or noted during the recordings of the studies and in their interpretation. As noted previously, the prevalence of morphologic abnormalities (e.g., bicuspid aortic valves) may also represent an underestimation compared with that reported in other studies, because this study was not specifically designed to detect such morphologic abnormalities.

Acknowledgment: We would like to acknowledge our appreciation to Debra Brunner, MS, and Sha Zhu, MSc, PhD, for their valuable contributions to the statistical analysis.

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