Supplementary Data

Section A

A.1. CARDIA Year-5 and Year-25 Data Collection

The 4,242 original images collected at the Year-5 echocardiography examination were read by seven trained analysts/readers and echocardiograms were recorded using an Acuson cardiac ultrasound machine (Acuson, Inc., Mountain View, Calif.) with a standardized recording protocol.

Of the 4,242 original images acquired at the Year-5 examination with the Acuson machine, 1,516 (36%) randomly selected images were reread at Year-25 by four experienced readers as a part of a reread substudy using the Digisonics analysis software for 2D measures, according to the Year-25 protocol.

A.2. Machine Reproducibility Study Design and Results

To evaluate the comparability of Year-5 and Year-25 data, a machine reproducibility substudy was performed at Year-25. Acuson and Toshiba machines (images read using the new software: Digiview, Digisonics) were compared and standard echocardiography reproducibility was assessed for three 2D 4-chamber parameters and sixteen M-mode parameters.

The machine reproducibility study was conducted at the Johns Hopkins University Reading Center and enrolled 96 normal, healthy volunteers. The median (IQR) age was 52 (47-59) years, 49% were males, and 63% were African-American. The machine study employed a two period cross-over design with replication (median time between visits was 7 days (minimum 5, maximum 44)). As is standard for a cross-over design, half the patients were randomly assigned to receive one of the two machines first and the other half received the alternative ordering. At each visit, two different sonographers measured the patient using the same machine. The ordering of the two sonographers was systematically varied so that each one went first half the time. This design was chosen because the primary interest was the comparison of the two machines. With this design, the estimate of the difference between machines is based on the average of the two measurements at each visit, similar to the standard estimate from a simple two period cross-over with one observation per period. Furthermore, the washout period between visits was sufficiently long that carry-over effects were likely to be absent.

The analysis was based on a linear mixed model with a random subject effect to account for repeated measurements on the same subject. The model included factors for machine, visit, session and reader, and also interactions between machine and the other three factors. Each analysis included a check on the assumptions of normally distributed errors with constant variance. Since we were primarily interested in differences between the two machines, we also considered a model with three two-way interactions, between machine and each of visit, session and reader. There was no consistency in the statistical significance among the various measurements in any of the interactions, nor of the directions of the estimated interaction effects. Therefore, Table A.2.1 shows results of the models without interactions. The results show evidence for a systematic difference between the readers for most measures. There were highly significant differences between readings for the two machines for most of the measures, with the Acuson having lower values in some cases and higher values in other cases.

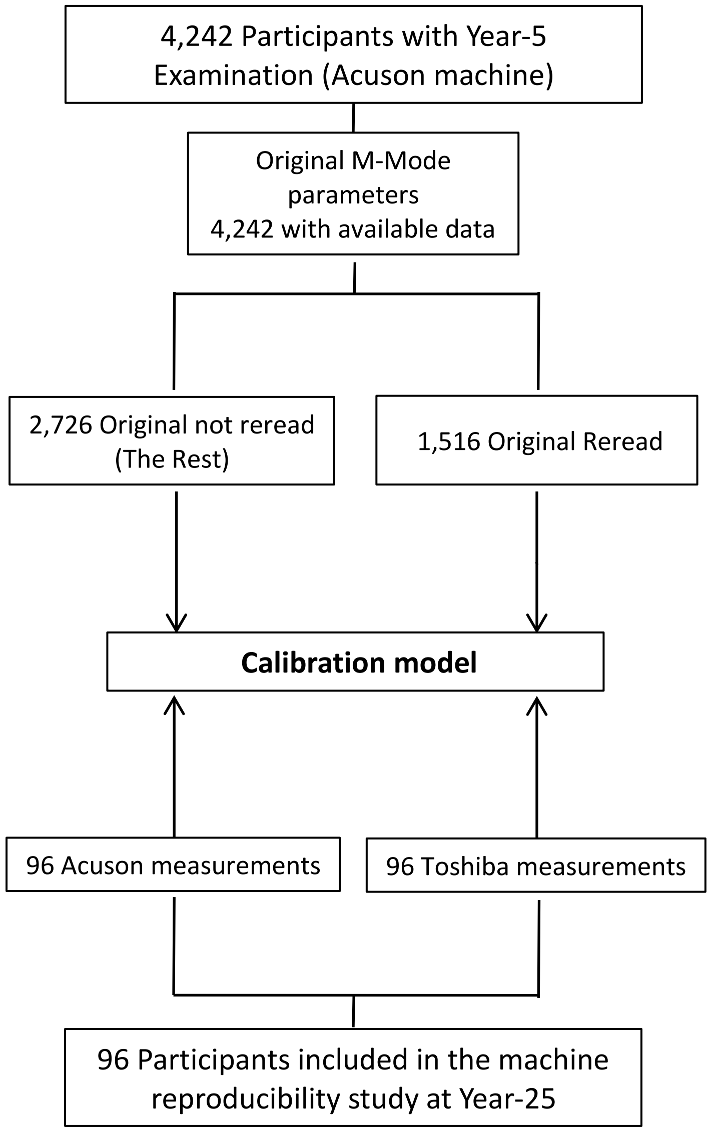
Table A.2.1. Inter- and intra-reader reproducibility assessment, Machine Reproducibility Study, Baltimore, 2010 − 2011.

Variable	Visit 1	Session 1	Reader (ref. Reader 1)			Acuson
			2	3	P-value	
2D Four Chamber LV End Diastolic Volume (ml)	-0.08 (0.86), {0.93}[1]	-0.89 (0.76), {0.24}	-1.64 (1.03)	4.60 (1.51)	{<0.0001}	-2.38 (0.86), {0.007}
2D Four Chamber LV End Systolic Volume (ml)	-0.29 (0.64), {0.66}	-0.06 (0.54), {0.91}	-0.51 (0.73)	6.01 (1.07)	{<0.0001}	-0.96 (0.64), {0.14}
2D Four Chamber LV Ejection Fraction (%)	0.45 (0.39), {0.25}	-0.12 (0.37), {0.74}	-0.40 (0.48)	-4.03 (0.67)	{<0.0001}	-0.12 (0.39), {0.76}
Aortic Root (cm)	0.02 (0.02), {0.30}	0.07 (0.02), {0.002}	-0.08 (0.03)	-0.06 (0.04)	{0.04}	0.00 (0.02), {0.83}
Left atrial internal dimension in systole (cm)	0.01 (0.03), {0.75}	-0.04 (0.03), {0.21}	0.09 (0.04)	0.02 (0.06)	{0.03}	-0.05 (0.03), {0.098}
Inter-ventricular septal thickness in diastole (cm)	0.00 (0.01), {0.57}	0.01 (0.01), {0.28}	-0.01 (0.01)	0.09 (0.01)	{<0.0001}	0.01 (0.01), {0.051}
LV posterior wall thickness in diastole (cm)	0.01 (0.01), {0.07}	0.01 (0.01), {0.17}	0.02 (0.01)	0.03 (0.01)	{0.10}	0.03 (0.01), {<0.001}
LV internal dimension in diastole (cm)	-0.02 (0.02), {0.28}	-0.04 (0.02), {0.04}	-0.01 (0.03)	-0.12 (0.04)	{0.0004}	-0.07 (0.02), {0.001}
LV internal dimension in systole (cm)	0.01 (0.03), {0.72}	-0.06 (0.03), {0.02}	0.01 (0.04)	0.09 (0.05)	{0.10}	-0.09 (0.03), {0.002}
Inter-ventricular septal thickness in systole (cm)	0.00 (0.01), {0.74}	0.02 (0.02), {0.18}	-0.06 (0.02)	0.09 (0.03)	{<0.0001}	0.05 (0.01), {0.002}
LV posterior wall thickness in systole (cm)	-0.01 (0.01), {0.36}	0.02 (0.02), {0.22}	-0.02 (0.02)	0.03 (0.03)	{0.04}	0.05 (0.01), {0.001}
LV fractional shortening (%)	-0.44 (0.46), {0.34}	0.75 (0.45), {0.10}	-0.05 (0.59)	-2.70 (0.82)	{0.0002}	0.82 (0.46), {0.076}
LV End Diastolic Volume (ml)	-1.16 (1.07), {0.28}	-2.13 (1.05), {0.05}	-0.74 (1.42)	-7.18 (2.08)	{0.0002}	-3.63 (1.07), {0.001}
LV End Systolic Volume (ml)	0.39 (0.92), {0.67}	-2.08 (0.84), {0.01}	0.25 (1.13)	2.48 (1.63)	{0.18}	-2.86 (0.92), {0.003}
LV Stroke Volume (ml)	-1.62 (0.98), {0.10}	-0.07 (1.00), {0.94}	-1.37 (1.34)	-10.5 (1.94)	{<0.0001}	-0.79 (0.98), {0.42}
LV Ejection Fraction (%)	-0.56 (0.60), {0.35}	0.93 (0.58), {0.11}	-0.10 (0.76)	-3.38 (1.07)	{0.0004}	0.99 (0.60), {0.10}
Heart Rate (bpm)	0.15 (0.80), {0.85}	2.51 (0.48), {<0.001}	0.35 (0.65)	0.56 (0.94)	{0.82}	1.20 (0.80), {0.14}
LV Cardiac Output (l/min)	-0.14 (0.10), {0.17}	0.24 (0.08), {0.003}	-0.08 (0.11)	-0.62 (0.15)	{<0.0001}	0.06 (0.10), {0.56}
LV Mass (g)	0.63 (0.99), {0.53}	-0.07 (0.96), {0.94}	0.79 (1.30)	7.80 (1.91)	{<0.0001}	2.18 (0.99), {0.030}

[1] Values are Estimate (SE), {p-value}. LV: Left Ventricular; 2D: Two Dimensions

Section B

Figure B.1. Flow Chart

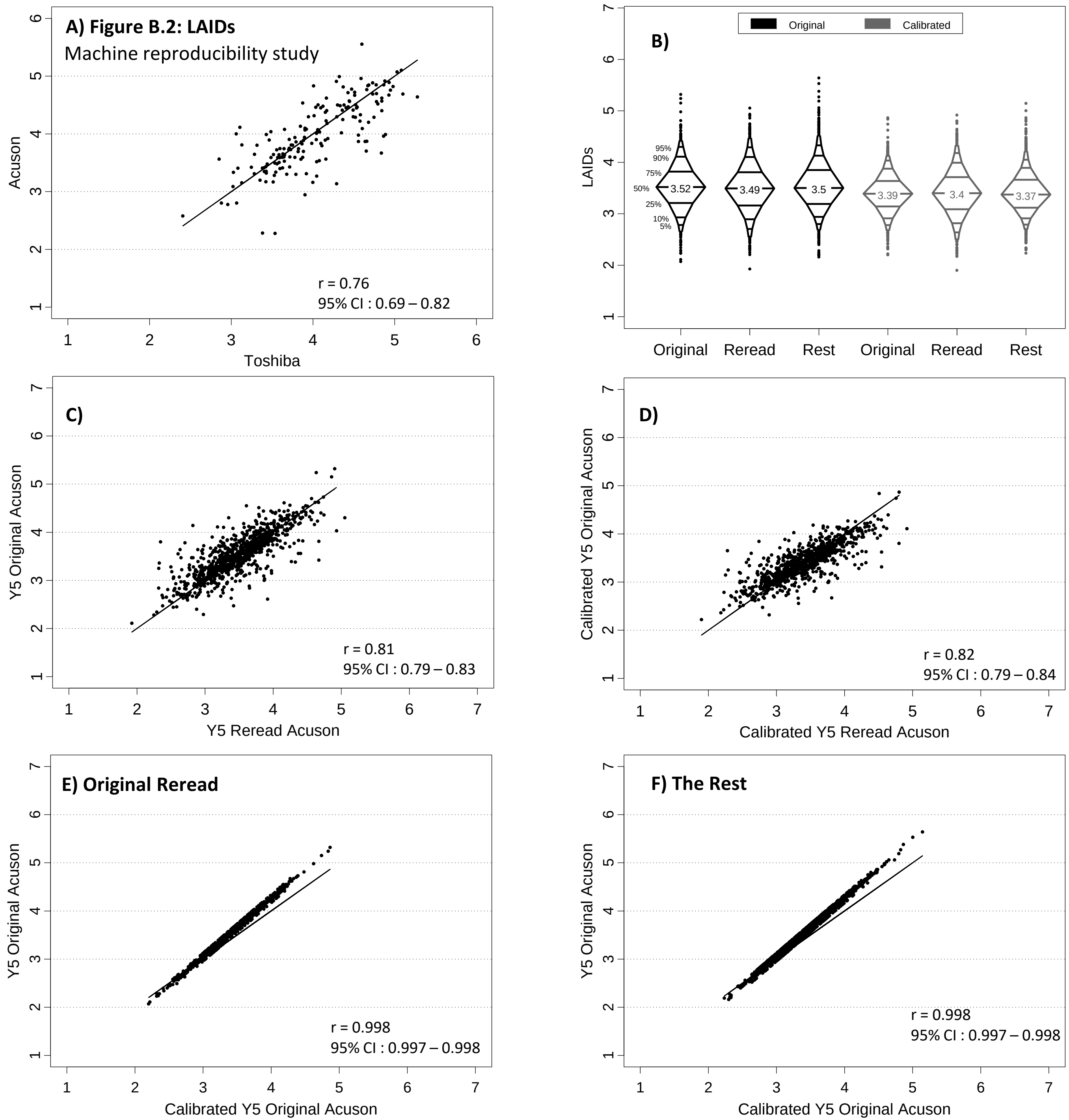


Figures B.2 to B.9

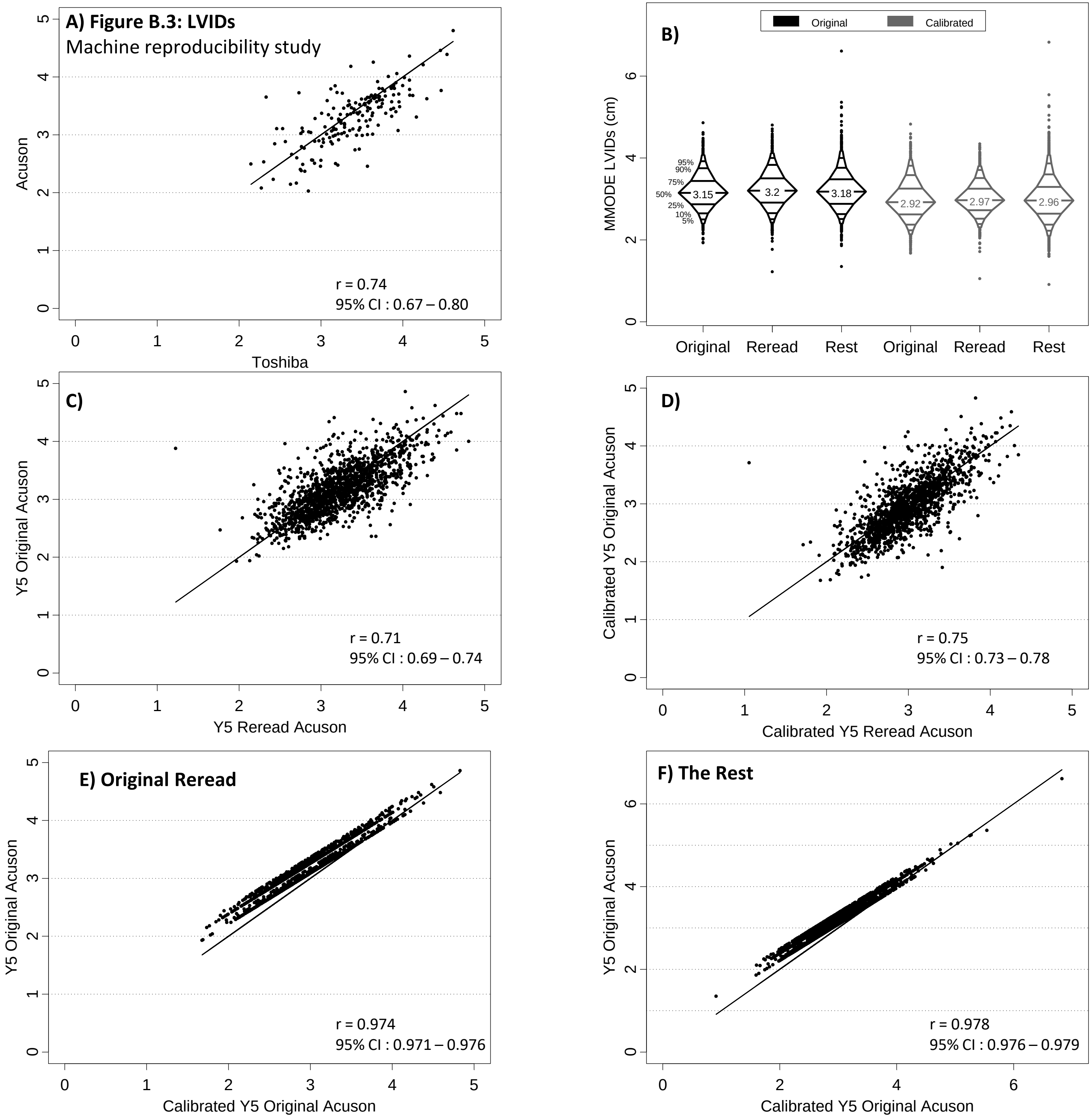
These figures all exhibit similar features, although sometimes to a different extent. We summarize instances where there are distinctive features of the various panels that differ noticeably from the overall pattern just described and illustrated by Figure 1 (LVMASS). In Figure B.2 (LAIDS), the linearity between Acuson and Toshiba is not as strong, but still good. Interestingly, the correlations between both the original and calibrated values in panels C and D of Figure B.2 are higher than those in Figure 1, clearly because of the variability of the original measurements seen in panel C. Finally, the slope of the regression of the original values on the calibrated values has a slope larger than one; this is driven by the regressions of the original (reread sample) on the predicted reread values. Similar comments apply for Figures B.3 and B.4 for LVIDs and LVIDd, respectively. In Figures B.5 to B.8 (IVS and LVPW) there is systematic disagreement between the original reads at 5 years and the subsequent reread, as shown in Panel C. This suggests a possible change in the way that the measurement was made. Judging from the graphs (compare panels C and E), the linear model was able accommodate these differences. Finally, Figure B.9 depicts estimated LVFS that was derived from two other calibrated measurements (LVIDs and LVIDd), without assistance from the calibration model. Both LVIDs and LVIDd were derived from the model, which in the case appeared to work well.

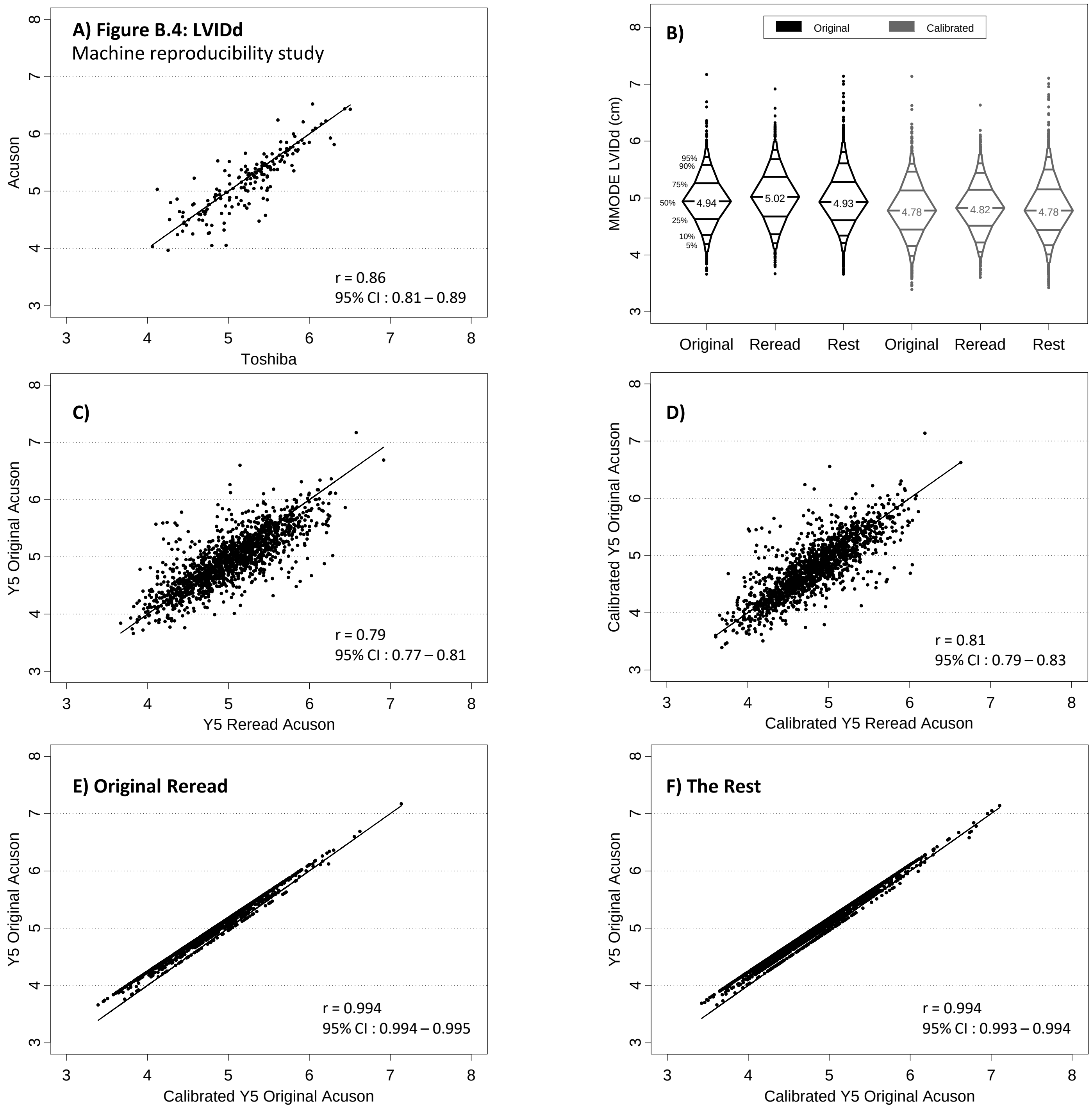
Figures Legend

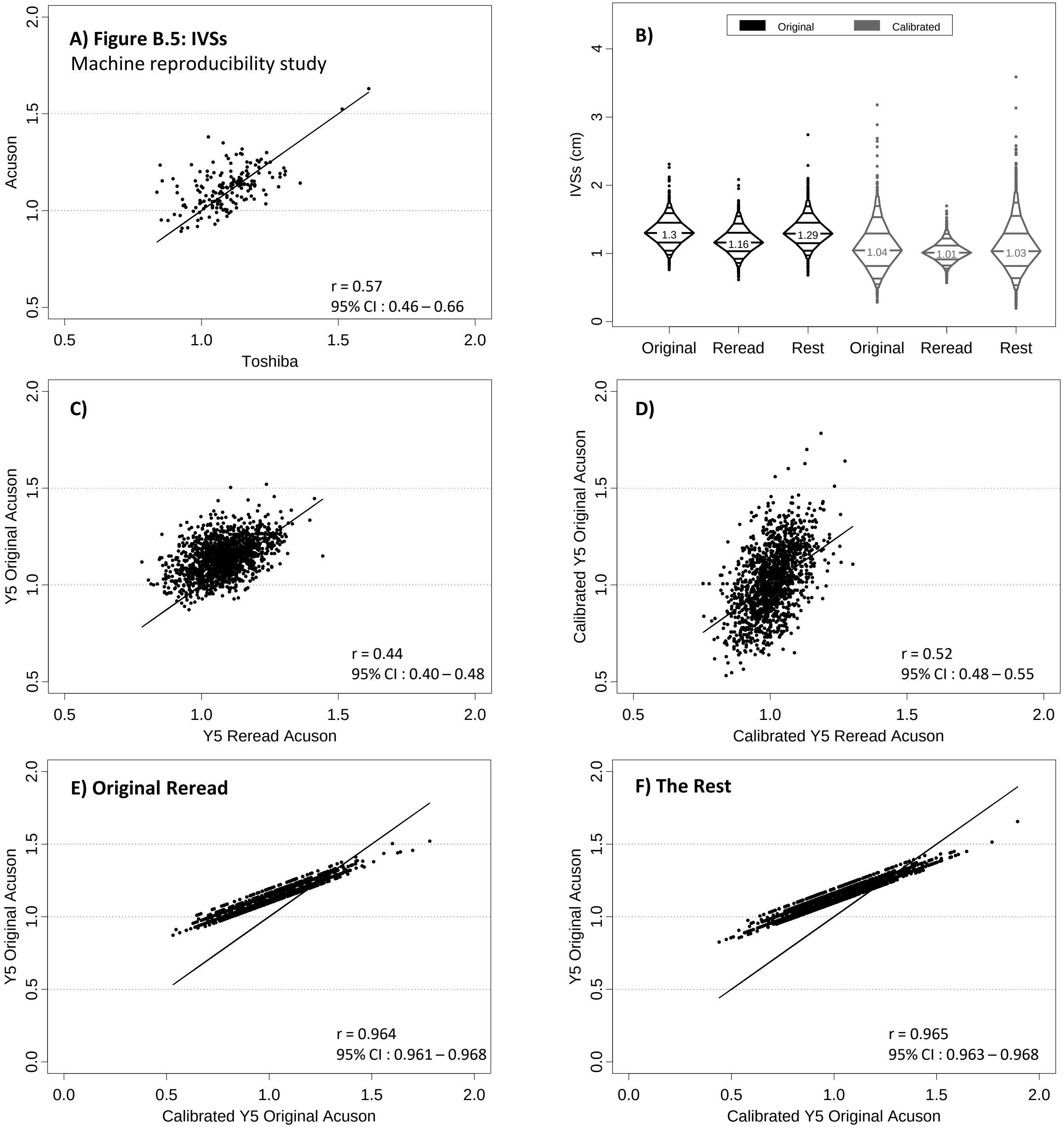
Panel A shows a scatterplot of the Acuson (y-axis) and corresponding Toshiba (x-axis) measurements from the machine reproducibility substudy, together with the line of identity. Panel B shows percentile boxplots of the distributions of original and calibrated Year-5 Acuson measurements for the three sets of Year-5 data. Panel C is a scatterplot of the Year-5 original Acuson vs. Year-5 reread Acuson measurements from the reread substudy. Panel D is a scatterplot of the calibrated Year-5 original Acuson vs. calibrated Year-5 reread Acuson measurements from the reread substudy. Both panels include the line of identity. Panel E is a scatterplot of the Year-5 original Acuson vs. Year-5 calibrated original Acuson measurements from the reread substudy. Panel F is a scatterplot of the original Year-5 Acuson vs. Year-5 calibrated original Acuson measurements for the remaining Year-5 reads.

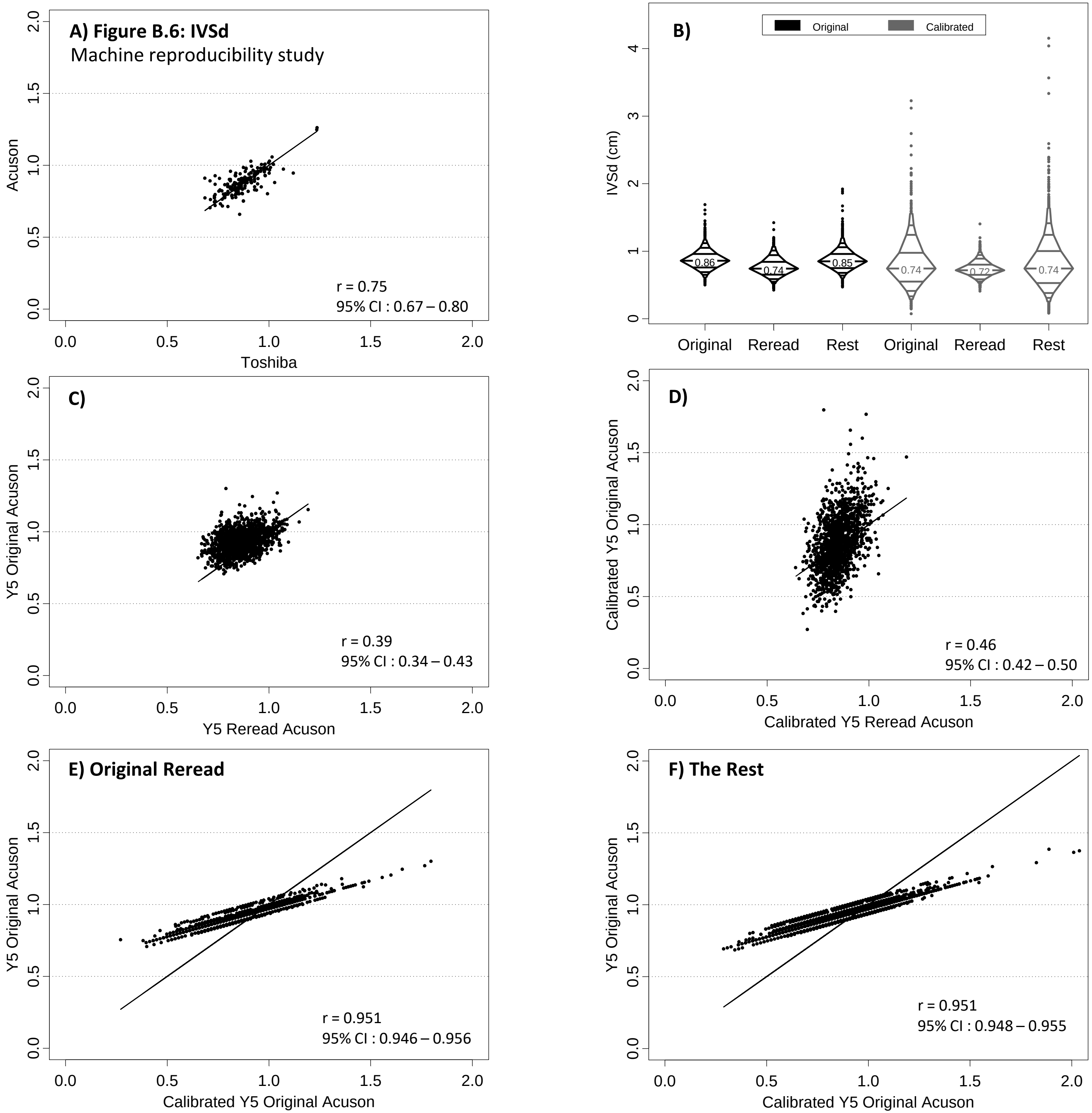


A) Figure B.2: LAIDs
Machine reproducibility study
Acuson
Toshiba
r = 0.76
95% CI : 0.69 – 0.82
B)
Original
Calibrated
LAIDs
95%
90%
75%
50%
25%
10%
5%
3.52
3.49
3.5
3.39
3.4
3.37
Original
Reread
Rest
Original
Reread
Rest
C)
Y5 Original Acuson
Y5 Reread Acuson
r = 0.81
95% CI : 0.79 – 0.83
D)
Calibrated Y5 Original Acuson
Calibrated Y5 Reread Acuson
r = 0.82
95% CI : 0.79 – 0.84
E) Original Reread
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.998
95% CI : 0.997 – 0.998
F) The Rest
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.998
95% CI : 0.997 – 0.998

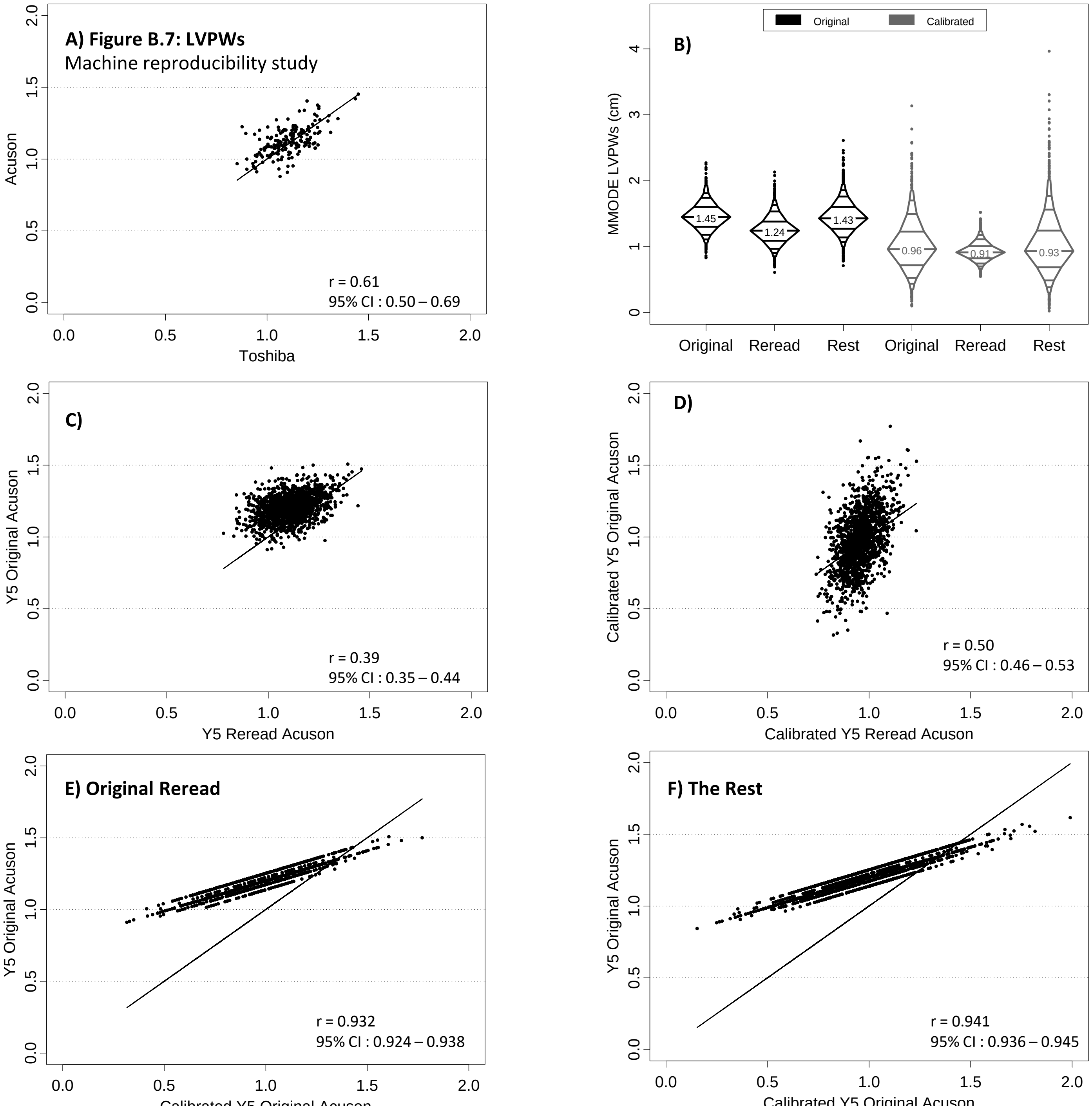

A) Figure B.3: LVIDs
Machine reproducibility study
Acuson
Toshiba
r = 0.74
95% CI : 0.67 – 0.80
B)
Original
Calibrated
MMODE LVIDs (cm)
95%
90%
75%
50%
25%
10%
5%
3.15
3.2
3.18
2.92
2.97
2.96
Original
Reread
Rest
Original
Reread
Rest
C)
Y5 Original Acuson
Y5 Reread Acuson
r = 0.71
95% CI : 0.69 – 0.74
D)
Calibrated Y5 Original Acuson
Calibrated Y5 Reread Acuson
r = 0.75
95% CI : 0.73 – 0.78
E) Original Reread
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.974
95% CI : 0.971 – 0.976
F) The Rest
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.978
95% CI : 0.976 – 0.979


A) Figure B.4: LVIDd
Machine reproducibility study
Acuson
Toshiba
r = 0.86
95% CI : 0.81 – 0.89
B)
Original
Calibrated
MMODE LVIDd (cm)
95%
90%
75%
50%
25%
10%
5%
4.94
5.02
4.93
4.78
4.82
4.78
Original
Reread
Rest
Original
Reread
Rest
C)
Y5 Original Acuson
Y5 Reread Acuson
r = 0.79
95% CI : 0.77 – 0.81
D)
Calibrated Y5 Original Acuson
Calibrated Y5 Reread Acuson
r = 0.81
95% CI : 0.79 – 0.83
E) Original Reread
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.994
95% CI : 0.994 – 0.995
F) The Rest
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.994
95% CI : 0.993 – 0.994

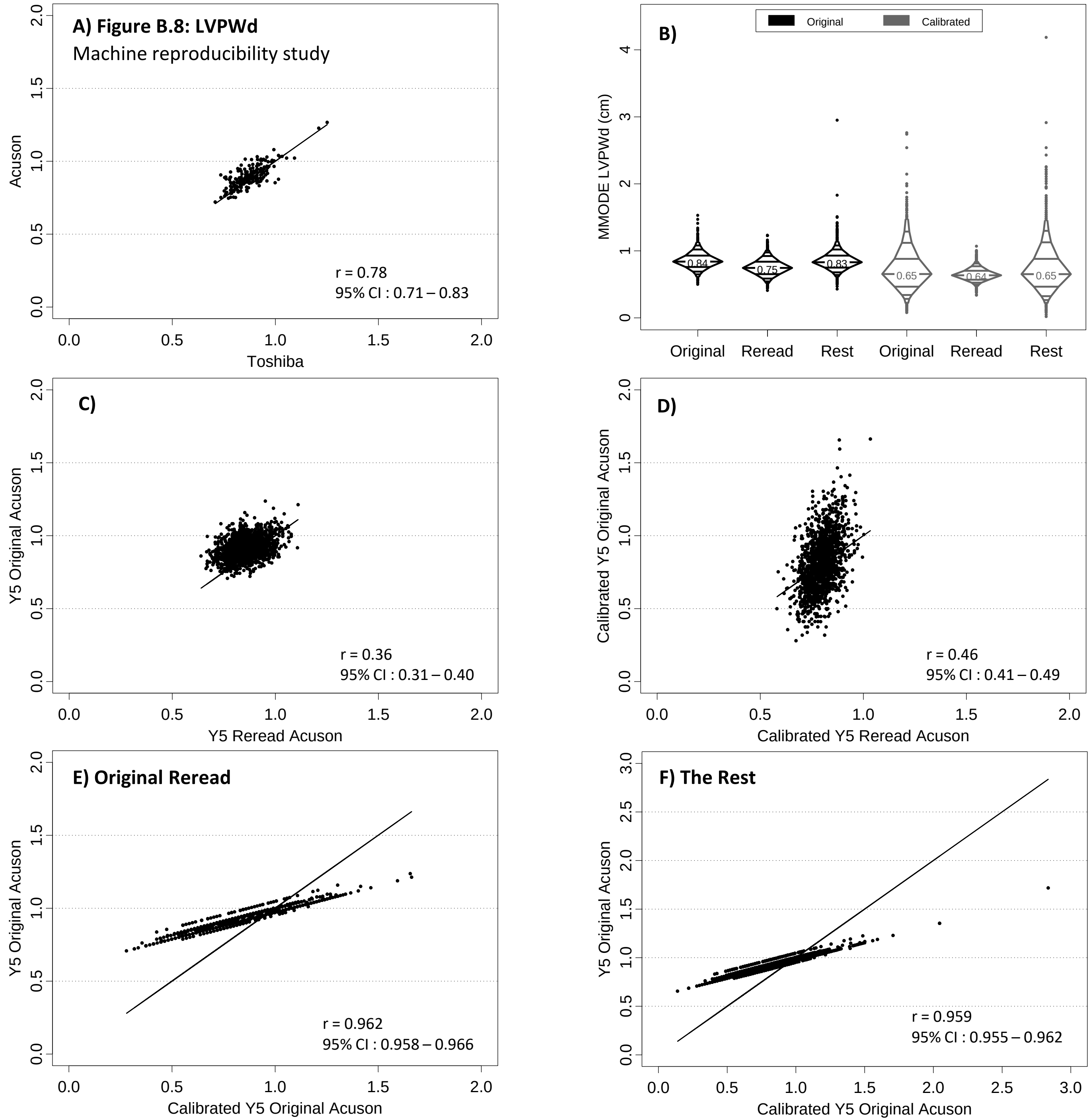

A) Figure B.5: IVSs
Machine reproducibility study
Acuson
Toshiba
r = 0.57
95% CI : 0.46 – 0.66
B)
Original
Calibrated
IVSs (cm)
1.3
1.16
1.29
1.04
1.01
1.03
Original
Reread
Rest
Original
Reread
Rest
C)
Y5 Original Acuson
Y5 Reread Acuson
r = 0.44
95% CI : 0.40 – 0.48
D)
Calibrated Y5 Original Acuson
Calibrated Y5 Reread Acuson
r = 0.52
95% CI : 0.48 – 0.55
E) Original Reread
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.964
95% CI : 0.961 – 0.968
F) The Rest
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.965
95% CI : 0.963 – 0.968

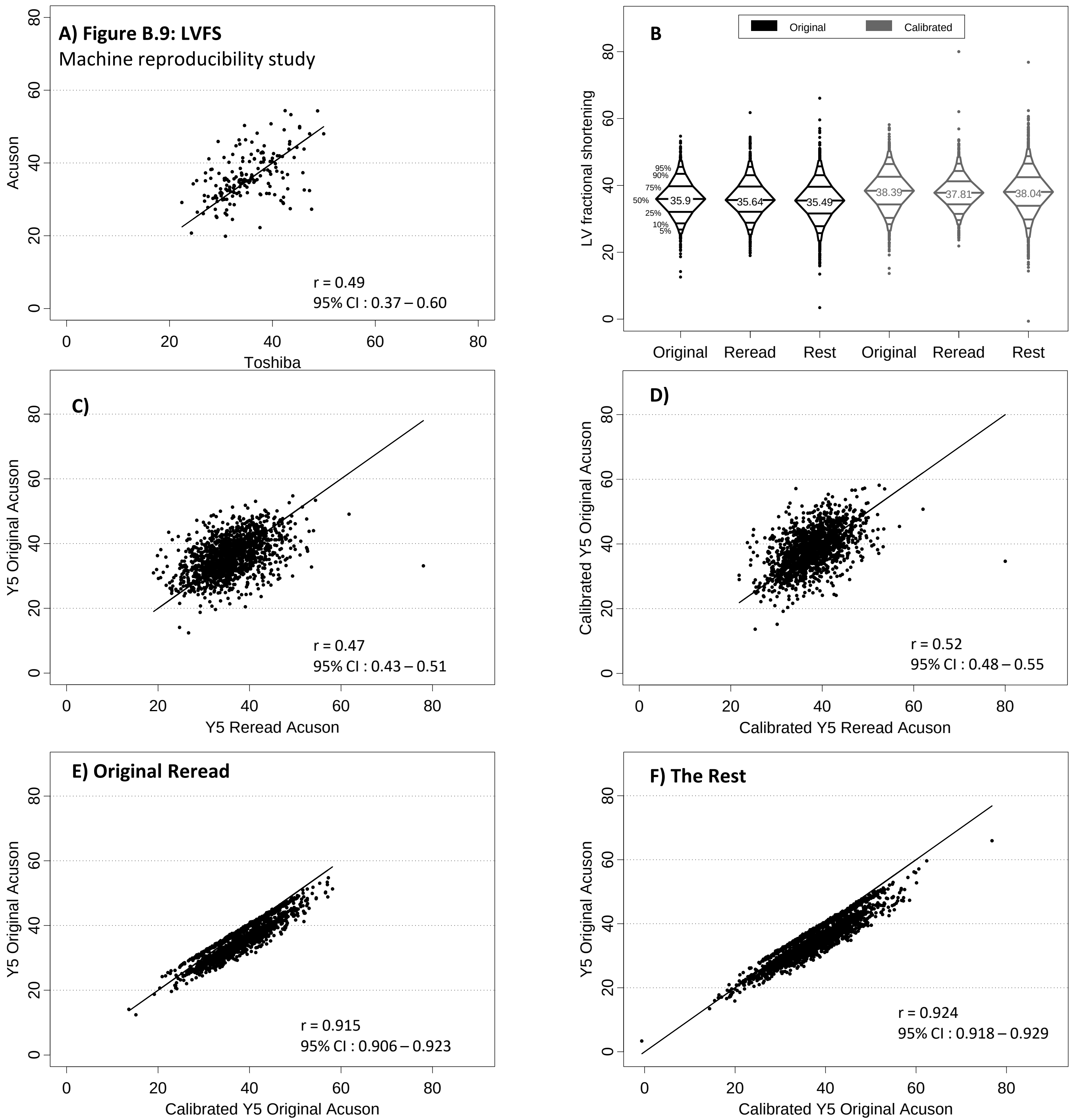


A) Figure B.6: IVSd
Machine reproducibility study
Acuson
Toshiba
r = 0.75
95% CI : 0.67 – 0.80
B)
Original
Calibrated
IVSd (cm)
0.86
0.74
0.85
0.74
0.72
0.74
Original
Reread
Rest
Original
Reread
Rest
C)
Y5 Original Acuson
Y5 Reread Acuson
r = 0.39
95% CI : 0.34 – 0.43
D)
Calibrated Y5 Original Acuson
Calibrated Y5 Reread Acuson
r = 0.46
95% CI : 0.42 – 0.50
E) Original Reread
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.951
95% CI : 0.946 – 0.956
F) The Rest
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.951
95% CI : 0.948 – 0.955



A) Figure B.7: LVPWs
Machine reproducibility study
Acuson
Toshiba
r = 0.61
95% CI : 0.50 – 0.69
B)
Original
Calibrated
MMODE LVPWs (cm)
1.45
1.24
1.43
0.96
0.91
0.93
Original
Reread
Rest
Original
Reread
Rest
C)
Y5 Original Acuson
Y5 Reread Acuson
r = 0.39
95% CI : 0.35 – 0.44
D)
Calibrated Y5 Original Acuson
Calibrated Y5 Reread Acuson
r = 0.50
95% CI : 0.46 – 0.53
E) Original Reread
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.932
95% CI : 0.924 – 0.938
F) The Rest
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.941
95% CI : 0.936 – 0.945


A) Figure B.8: LVPWd
Machine reproducibility study
Acuson
Toshiba
r = 0.78
95% CI : 0.71 – 0.83
B)
Original
Calibrated
MMODE LVPWd (cm)
0.84
0.75
0.83
0.65
0.64
0.65
Original
Reread
Rest
Original
Reread
Rest
C)
Y5 Original Acuson
Y5 Reread Acuson
r = 0.36
95% CI : 0.31 – 0.40
D)
Calibrated Y5 Original Acuson
Calibrated Y5 Reread Acuson
r = 0.46
95% CI : 0.41 – 0.49
E) Original Reread
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.962
95% CI : 0.958 – 0.966
F) The Rest
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.959
95% CI : 0.955 – 0.962


A) Figure B.9: LVFS
Machine reproducibility study
Acuson
Toshiba
r = 0.49
95% CI : 0.37 – 0.60
B
Original
Calibrated
LV fractional shortening
95%
90%
75%
50%
25%
10%
5%
35.9
35.64
35.49
38.39
37.81
38.04
Original
Reread
Rest
Original
Reread
Rest
C)
Y5 Original Acuson
Y5 Reread Acuson
r = 0.47
95% CI : 0.43 – 0.51
D)
Calibrated Y5 Original Acuson
Calibrated Y5 Reread Acuson
r = 0.52
95% CI : 0.48 – 0.55
E) Original Reread
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.915
95% CI : 0.906 – 0.923
F) The Rest
Y5 Original Acuson
Calibrated Y5 Original Acuson
r = 0.924
95% CI : 0.918 – 0.929