

# Biochemical, immunochemical and serology analytes validation of the lithium heparin BD Barricor blood collection tube on a highly automated Roche COBAS8000 instrument

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**Summary.** *Background:* Recently developed blood tubes with a barrier to provide plasma are becoming widespread. We compared 43 biochemical, 35 immunochemical and 7 serology analytes in a BD-Vacutainer® Barricor tube for local clinical validation of this lithium-heparin tube with a barrier. *Methods:* Samples from 70 volunteers were collected in different BD-tubes: a clot-activator tube with gel (SST), a lithium-heparin tube with gel (PST), and a lithium-heparin tube with barrier (BAR). Biases from Bland-Altman plots and 95% confidence intervals were compared with the desirable specification from the Ricos database in order to verify whether measurements from different tubes were significantly different. *Results:* For most of the analytes tested, the measurements using SST, PST or BAR tubes were equivalent. Only BIC, GLU, K, LAD, LPA, P, TP, CTX, Ferritin, HGH, vitD3 and ANTIS showed statistically significant, between-tubes, differences which might have clinical implication. *Conclusions:* The study demonstrates that SST, PST and BAR can be used interchangeably for most of the analytes tested, including serology analytes. This allows the use of the same tube for assaying multiple analytes, increasing the laboratory efficiency while decreasing patients discomfort by minimizing blood withdrawal. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** blood collection tube, mechanical separator, plasma, serum, serology

## 1. Introduction

The preanalytical phase plays a crucial role in laboratory diagnostic and blood collection is probably its most important aspect (1). Heparin plasma and serum are commonly used matrices. The latter is the preferred specimen for the analysis of biochemical parameters (2,3), nevertheless plasma has some important laboratory advantages like a shorter turnaround time (TAT) due to both the absence of the 30-60 minutes time interval needed for the coagulation process (4) and to a shorter centrifugation step, and allows to obtain a

larger volume of sample (about 15-20% more) which increases the number of analysis that can be made on one sample (5). According to the World Health Organization, plasma is preferred to serum because it reflects better the patients' physiological condition (6) by preventing the changes induced by the coagulation process which causes an increase in some analytes (e.g. potassium) and a decrease of others (e.g. total proteins) (7). In addition, the use of anticoagulant prevents the variations induced by the coagulation factors activated when the needle is inserted. The use of plasma also minimizes the formation of fibrin networks found

very frequently in serum tubes for several reasons: the sample arrived quickly in the laboratory (e.g. through pneumatic mail systems) and is centrifuged before clot formation, or because the sample was from patients taking oral anticoagulants or heparin which delayed the formation of the clot (8). The presence in serum of soluble fibrin clots causes, on highly automated analytical lines, frequent sampling alarms requiring re-centrifugation or manual re-run of the sample leading to a large increase of the TAT.

Blood collection tubes (BCT) with a gel separator are often the preferred choice because serum (plasma) is physically separated from clotted whole blood (blood cells) (3). However, some drawbacks may still occur like the non-specific adsorption of the molecule to be analyzed or the release of interfering substances (9). A new BCT, the BD-Barricor tube (BAR), containing lithium heparin as anticoagulant and an innovative mechanical separator has been recently developed. According to the manufacturer BAR will improve the quality of laboratory routine analysis in term of TAT and analytes stability. A few studies comparing BAR with standard plasma or serum tubes have been published (10-13) but they still do not cover the wide range of analytes tested in routine analysis. Furthermore, to the best of our knowledge, the BD-Barricor tube has never been tested before for serological analytes. Given this lack of data, 43 biochemical analytes, 35 immunochemical analytes and 7 serology analytes were tested on a fully automated Roche COBAS8000 instrumentation. The study aimed at verify whether plasma (either standard or BAR tubes) can replace serum for high throughput routine analysis without affecting the normal clinical ranges suggested by the manufacturer or selected by the Laboratory.

## 2. Materials and methods

### 2.1. Subjects and blood sampling

A total of 70 apparently healthy volunteers, 29 males and 41 females from the San Raffaele Hospital in Milan, Italy were included in the study during the period April-June 2017. Volunteers were aged between 18 and 70 and had no pregnancy status. During blood

collection from the volunteers, no exclusion criteria were applied with the exception of difficulties in blood withdrawal like inability to find a suitable vein. Blood samples were collected after overnight fasting (8-10 hours), between the hours of 08:00 and 10:00 am. Smoking and the consumption of tea or coffee were forbidden from midnight until blood collection. Alcohol consumption was not allowed for 3 days prior to blood sampling. Volunteers were seated in an upright position 1 minute before venipuncture and remained seated during the whole procedure. Blood samples were collected, as described elsewhere (14, 15), into three different BCTs from BD (Becton, Dickinson and Company, NJ): a clot-activator gel-containing tube BD-SST II Advance tube, 3.5 mL, 13x75 mm (SST); a lithium heparinized gel-containing tube BD-PST II, 3.0 mL, 13x75 mm (PST); a lithium heparinized tube with a barrier BD-Barricor, 3 mL, 13x75 mm (BAR). PST and BAR were processed immediately after sample collection whereas SST was incubated for at least 30' to allow appropriate clotting. Samples were separated by centrifugation at 3000xg for 10' at 4°C. No visible hemolysis was detected in any sample. Concentration measurements were performed within 4 hours after blood collection.

A total of 85 parameters were measured on a Roche COBAS 8000 device (Roche Diagnostic, Basel, Switzerland). Among them 43 were routine biochemical analytes including albumin (ALB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), amylase (AMS), pancreatic amylase (AMSP), anti-streptolysin O (ASO), aspartate aminotransferase (AST), beta-2 microglobulin (B2MICR), bicarbonate (BIC), total bilirubin (BILT), complement C3 (C3), complement C4 (C4), calcium (Ca), cholinesterase (CHE), creatine kinase (CK), chloride (CL), cholesterol (CHO), creatinine (CREA), C-reactive protein (CRP), iron (Fe), gamma-glutamyl transferase (GGT), glucose (GLU), high-density lipoprotein (HDL), homocysteine (HOM), immunoglobulin A (IGA), immunoglobulin G (IGG), immunoglobulin M (IGM), potassium (K), lactate dehydrogenase (LAD), lipase (LIP), lipoprotein A (LPA), low-density lipoprotein (LDL), magnesium (MG), mucoproteins (MUCO), sodium (NA), procalcitonin (PCT), phosphate (P), rheumatoid factor (RF), total protein (TP), transfer-

rin (TRF), triglyceride (TG), urea (UREA), uric acid (UA). The 35 routine immunochemical analytes include: alpha-fetoprotein (AFP), vitamin B12 (B12), beta human chorionic gonadotropin (BHCG), cancer antigen 125 (CA125), cancer antigen 15-3 (CA153), carcinoembryonic antigen (CEA), creatine kinase-muscle/brain (CKMB), cortisol (CORT), peptide-C (CPEP), calcitonin (CA), serum C-telopeptide (CTX), estradiol (E2), ferritin, folate, follicle-stimulating hormone (FSH), free triiodothyronine (FT3), free thyroxine (FT4), cancer antigen 19-9 (GICA), osteocalcin (GLA), growth hormone (HGH), human prolactin (HPRL), insulin (INS), Luteinizing hormone (LH), myoglobin (MIOG), N-terminal-pro BNP (PROBNP), progesterone (PROG), total prostate-specific antigen (PSA), triiodothyronine (T3), thyroxine (T4), testosterone (TESTO), thyroglobulin antibodies (TGAB), anti-thyroid peroxidase (TPO), high-sensitivity cardiac troponin T (hs-CTnT), thyroid stimulating hormone (TSH), and vitamin D3 (vitD3). A total of 7 routine serology analytes were also measured: anti-hepatitis B antibodies (ANTIS), Cytomegalovirus IgG antibodies (CMVG), Cytomegalovirus IgM antibodies (CMVM), Rubella IgG antibodies (RUBEOG), Rubella IgM antibodies (RUBEOM), Toxoplasma gondii IgG antibodies (TOXOG) and Toxoplasma gondii IgM antibodies (TOXOM).

Table 1 shows a brief description of the method used for each analyte.

Individuals signed an informed consent authorizing the use of their anonymously collected data for retrospective observational studies (article 9.2.j; EU general data protection regulation 2016/679 [GDPR]), according to the San Raffaele Hospital policy (IOG075/2016).

## 2.2. Statistical analyses

Statistical analyses and graphs were performed with the software Sigmaplot (Systat-Software, Inc. San Jose, CA, USA) and Excel (Microsoft, Redmond, WA, USA). Comparisons between SST, PST and BAR were assessed by the Bland-Altman (BA) plot (17). To avoid disproportionate weights due to analytes having wide concentration ranges the calculated

mean bias, and the corresponding 95% confidence interval (95%CI) were expressed as percentage. The latter was compared with the desirable specification (B%) obtained from the Ricos database (18). ASO, MUCO, PCT, UA, BHCG, CT, vitD3 and serological analytes, for which B% was not available, were compared with a 5% arbitrary threshold. The 95CI% was calculated as:  $\text{bias} \pm t(0.025; df=n-1)SE$ , where bias is the calculated % mean bias, SE the standard error of the n differences, with t from the t distribution with n-1 degrees of freedom. The mean %bias was considered statistically significant if its calculated 95%CI did not include the zero; if the 95%CI also exceeded the B%, the mean %bias was considered clinically significant. However, if the 95CI% exceeded the B% but contained also the zero, we cautiously preferred not to make any statement.

## 3. Results

Collected blood was first tested for hemolysis by measuring the free hemoglobin (fHb), using the hemolysis index (HI). The Roche instrumentation estimates the HI by dichromatic wavelength paired measurement, providing results as absolute numbers, where one unit corresponds to 0.01 g/L. PST and BAR tubes showed fHb of 0.045 and 0.040 g/L, respectively whereas the SST tubes exhibit slightly higher hemolysis (0.070 g/L). However, after a one way ANOVA test, only SST and BAR showed a statistically significant difference.

Table 2-4 show the summary of the BA comparisons between the three BCTs and the corresponding B%.

### 3.1. Biochemical analytes

BIC, K, LAD, LPA, P, and TP showed 95CI% clinically significant only when serum was compared to plasma. Within the same analyte, the 95CI% were similar regardless of the type of plasma tube used. In contrast Ca (which was associated to a rather small B%) and GLU, showed significantly different 95CI% in all of the three comparisons. Na and TRF, also associated to small B%, showed significantly different

**Table 1.** List of the analytes measured in this study and their corresponding methodology

<b>Biochemical</b>		<b>Immunochemical</b>	
<b>Analyte</b>	<b>Method</b>	<b>Analyte</b>	<b>Method</b>
ALB	Immunoturbidimetric assay	AFP	electrochemiluminescence
ALP	Colorimetric assay	B12	electrochemiluminescence
ALT	Spettrophotometric assay	BHCG	electrochemiluminescence
AMS	Enzymatic-colorimetric	CA125	electrochemiluminescence
AMSP	Enzymatic-colorimetric	CA153	electrochemiluminescence
ASO	Immunoturbidimetric assay	CEA	electrochemiluminescence
AST	Spettrophotometric assay	CKMB	electrochemiluminescence
B2MICR	Immunoturbidimetric assay	CORT	electrochemiluminescence
BIC	Enzymatic assay	CPEP	electrochemiluminescence
BILT	Colorimetric assay	CT	electrochemiluminescence
C3	Immunoturbidimetric assay	CTX	electrochemiluminescence
C4	Immunoturbidimetric assay	E2	electrochemiluminescence
Ca	Colorimetric assay	Ferritin	electrochemiluminescence
CHE	Colorimetric assay	Folate	electrochemiluminescence
CK	Spettrophotometric assay	FSH	electrochemiluminescence
CL	Potentiometric assay	FT3	electrochemiluminescence
CHO	Enzymatic/colorimetric assay	FT4	electrochemiluminescence
CREA	Colorimetric assay	GICA	electrochemiluminescence
CRP	Immunoturbidimetric assay	GLA	electrochemiluminescence
FE	Colorimetric assay	HGH	electrochemiluminescence
GGT	Enzymatic/colorimetric assay	HPRL	electrochemiluminescence
GLU	Enzymatic assay	HS-CTnT	electrochemiluminescence
HDL	Enzymatic/colorimetric assay	INS	electrochemiluminescence
HOM	Enzymatic assay	LH	electrochemiluminescence
IGA	Immunoturbidimetric assay	MIOG	electrochemiluminescence
IGG	Immunoturbidimetric assay	PROPNB	electrochemiluminescence
IGM	Immunoturbidimetric assay	PROG	electrochemiluminescence
K	Potentiometric assay	PSA	electrochemiluminescence
LAD	Spettrophotometric assay	T3	electrochemiluminescence
LIP	Enzymatic/colorimetric assay	T4	electrochemiluminescence
LPA	Turbidimetric assay	TESTO	electrochemiluminescence
LDL	Enzymatic/colorimetric assay	TGAB	electrochemiluminescence
MG	Colorimetric assay	TPO	electrochemiluminescence
MUCO	Immunoturbidimetric assay	TSH	electrochemiluminescence
NA	Potentiometric assay	VitD3	electrochemiluminescence
PCT	Immunoturbidimetric assay	<b>Serology</b>	
P	Spettrophotometric assay	ANTIS	electrochemiluminescence
RF	Immunoturbidimetric assay	CMVG	electrochemiluminescence
TP	Colorimetric assay	CMVM	electrochemiluminescence
TRF	Immunoturbidimetric assay	RUBEOG	electrochemiluminescence
TG	Enzymatic/colorimetric assay	RUBEOM	electrochemiluminescence
UREA	Enzymatic assay	TOXOG	electrochemiluminescence
UA	Enzymatic/colorimetric assay	TOXOM	electrochemiluminescence

**Table 2.** Biochemical analytes. For each comparison is shown the number of tests (n), the BA Bias calculated as percentage (%bias), the confidence interval (95CI%) and the biological variation expressed as desirable specification for inaccuracy (B%) (18). Analytes with a 95CI% exceeding B% are highlighted in grey

Analyte	n	SST vs Barricor		SST vs PST		Barricor vs PST		B%
		%bias	95CI%	%bias	95CI%	%bias	95CI%	
ALB	69	0.9	0.32, 1.39	0.8	0.16, 1.37	-0.2	-0.75, 0.37	1.4
ALP	69	2.0	1.39, 2.92	2.7	2.41, 3.67	0.7	0.16, 1.63	6.7
ALT	70	3.9	1.39, 5.96	-1.4	-3.80, 0.64	-5.3	-7.52, -2.97	11.5
AMS	70	-0.7	-1.20, 0.22	-0.4	-0.91, 0.00	0.3	-0.24, 0.77	7.4
AMSP	70	-0.5	-1.34, 0.25	0.0	-0.74, 0.74	-0.5	-0.04, 1.12	8.0
ASO	70	-2.0	-4.51, 0.61	-0.9	-3.30, 1.48	1.1	-1.48, 3.30	5*
AST	62	1.2	-1.61, 4.02	-1.2	-4.52, 1.98	-2.4	-0.27, 5.14	6.5
B2MICR	66	0.6	0.07, 1.22	0.7	0.16, 1.33	0.2	-0.29, 0.62	4.1
BIC	68	-5.9	-7.79, -3.77	-5.9	-7.91, -4.00	-0.3	-1.78, 1.19	1.6
BILT	69	-0.6	-1.91, 0.79	-0.7	-1.98, 0.85	-0.2	-1.64, 1.29	8.9
C3	70	-3.1	-4.04, 0.75	-0.3	-1.13, 0.37	2.8	0.45, 3.58	4.1
C4	68	0.0	-0.81, 0.74	0.8	0.06, 1.49	0.8	0.02, 1.47	8.6
Ca	69	0.8	0.08, 1.73	-0.8	-1.58, -0.25	-1.8	-2.51, -1.10	0.8
CHE	70	0.5	-0.08, 1.18	0.8	0.21, 1.40	0.3	-0.28, 0.81	4.8
CK	69	2.2	1.19, 3.19	1.6	0.70, 2.39	-0.6	-1.62, 0.34	11.5
CL	70	0.3	-0.14, 0.46	-0.1	-0.38, 0.25	-0.4	-0.48, -0.08	0.5
CHO	69	0.1	-0.43, 0.72	1.0	0.37, 1.68	0.8	0.22, 1.45	4.1
CREA	70	-1.5	-2.45, -0.50	-1.0	-1.81, -0.03	0.5	-0.49, 1.61	4.0
CRP	70	-2.1	-3.87, -0.13	-0.3	-1.47, 0.96	1.7	-3.98, 0.48	21.8
FE	69	1.3	0.50, 2.00	1.6	0.85, 2.19	0.3	-0.10, 0.75	8.8
GGT	70	2.2	0.53, 5.13	0.9	-0.87, 2.50	-1.3	-0.37, 4.41	11.1
GLU	70	3.9	2.42, 5.45	2.3	0.53, 4.20	-1.6	-2.72, -0.47	2.3
HDL	70	-0.1	-0.74, 0.59	0.0	-0.43, 0.47	0.1	-0.71, 0.47	5.6
HOM	63	0.1	-0.94, 1.17	-0.9	-2.07, 0.23	-1.2	0.23, 2.09	8.6
IGA	70	-0.2	-1.08, 0.70	0.5	-0.67, 1.65	0.6	-1.59, 0.29	9.1
IGG	69	0.5	0.06, 0.95	0.7	0.23, 1.13	0.1	-0.62, 0.32	4.3
IGM	69	0.4	-0.12, 1.02	1.6	0.67, 2.47	1.1	-2.01, -0.24	11.9
K	70	7.6	6.47, 8.62	7.2	6.25, 8.23	-0.4	-1.21, 0.46	1.8
LAD	70	-3.9	-6.09, -1.40	-3.9	-6.24, -1.24	0.1	-2.38, 2.39	4.3
LIP	68	0.1	-0.52, 0.69	0.3	-0.37, 0.84	0.1	-0.67, 0.53	11.3
LPA	54	-4.7	-8.24, -1.22	-4.4	-7.70, -1.03	-0.3	-1.87, 2.48	3.7
LDL	68	0.3	-0.19, 0.88	0.6	0.06, 1.19	0.3	-0.83, 0.23	5.5
MG	69	0.1	-0.61, 0.82	0.3	-0.31, 0.92	0.2	-0.83, 0.40	1.8
MUCO	70	0.2	-0.87, 0.90	0.9	0.09, 1.61	0.6	-1.45, 0.23	5*
NA	69	0.0	-0.19, 0.19	0.2	0.01, 0.39	0.2	-0.47, -0.09	0.2
PCT	64	-4.9	-19.19, 7.69	-34.3	-50.87, -17.69	-33.5	-15.51, -51.39	5*
P	70	7.6	6.67, 8.31	5.0	3.96, 6.05	-2.6	-1.42, -3.28	3.4
RF	69	0.5	-0.02, 0.66	0.7	-0.01, 1.27	0.3	-0.15, 0.66	6.5
TP	69	-4.5	-5.20, -3.70	-4.1	-4.95, -3.25	-0.4	-0.98, 0.25	1.4
TRF	68	0.1	-0.70, 0.98	1.3	0.42, 2.04	-1.2	-1.91, -0.41	1.3
TG	70	0.8	-0.01, 1.56	3.5	2.59, 4.40	2.7	3.46, 1.90	9.6
UREA	70	-1.5	-2.49, -0.57	-0.5	-1.41, 0.26	1.0	-1.76, 0.01	5.6
UA	70	0.3	-0.58, 1.10	0.0	-0.69, 0.57	-0.3	-0.93, 0.50	5*

**Table 3.** Immunochemical analytes. For each comparison was shown: the number of tests (n), the BA Bias calculated as percentage (%bias), the confidence interval (95CI%) and the biological variation expressed as desirable specification for inaccuracy (B%) (18). Analytes with a 95CI% exceeding B% are highlighted in grey.

Analyte	n	SST vs Barricor		SST vs PST		Barricor vs PST		B%
		%bias	95CI%	%bias	95CI%	%bias	95CI%	
AFP	63	0.4	-0.39, 1.20	0.2	-0.89, 1.28	-0.2	-1.25, 0.80	11.8
B12	68	0.9	-0.31, 2.11	1.5	0.31, 2.66	0.8	-0.23, 1.84	17.7
BHCG	70	-1.2	-3.04, 0.61	-0.7	-2.27, 0.79	0.5	-0.50, 1.46	5*
CA125	65	1.6	0.88, 2.37	2.4	1.68, 3.06	0.7	-0.11, 1.60	15.0
CA153	65	1.7	-0.06, 3.43	2.7	0.88, 4.46	1.0	-0.80, 2.78	15.8
CEA	65	2.0	1.03, 2.93	2.5	1.42, 3.47	0.5	-0.64, 1.58	14.3
CKMB	64	2.3	-0.09, 4.73	1.5	-2.3, 3.49	0.1	-2.05, 2.26	7.8
CORT	64	-1.1	-4.02, 1.74	1.2	-1.89, 4.35	2.1	-0.93, 5.19	7.6
CPEP	64	-1.3	-3.52, 0.98	-0.9	-2.83, 1.05	0.4	-1.47, 2.22	7.1
CT	65	-0.4	-2.09, 1.30	-3.8	-4.91, 1.66	-3.5	-4.98, -1.50	5*
CTX	64	-8.3	-9.92, -6.40	-5.2	-6.92, -3.46	3.1	1.77, 4.41	8.1
E2	68	-2.4	-12.2, 7.49	8.7	-1.99, 19.32	9.1	-0.68, 18.6	8.3
Ferritin	70	-3.9	-6.80, -1.18	-0.2	-2.11, 1.31	3.7	1.04, 6.17	5.2
Folate	69	-3.2	-6.36, 0.04	-3.7	-7.19, 0.05	-0.5	-3.27, 2.25	19.2
FSH	66	1.0	0.60, 1.40	0.9	0.35, 1.35	-0.1	-0.58, 0.32	12.1
FT3	68	-0.4	-2.51, 1.78	-0.6	-2.74, 1.48	-0.3	-1.58, 2.12	4.8
FT4	68	0.5	-0.10, 1.01	0.7	0.25, 1.29	0.3	-0.19, 0.83	3.3
GICA	64	0.4	-0.15, 0.91	0.6	-0.02, 1.12	0.2	-0.81, 0.32	32.9
GLA	57	-1.6	-3.34, 0.21	-1.3	-2.96, 1.29	0.3	-1.94, 1.31	7.9
HGH	64	13.4	4.38, 21.18	12.9	4.01, 20.94	-0.3	-0.31, 0.96	12.2
HPRL	62	-1.1	-1.74, -0.51	-0.7	-1.03, 0.01	0.3	-1.02, 0.38	10.5
HS-CTnT	70	-0.6	-4.27, 3.01	-3.1	-5.17, 0.06	-2.4	-0.73, 5.67	7.0
INS	65	2.9	-0.71, 6.53	5.4	2.65, 8.15	2.5	-5.08, 0.10	15.5
LH	64	-3.8	-4.55, 2.97	-3.5	-4.23, -2.85	-0.2	-0.71, 0.36	8.9
MIOG	64	-3.3	-5.44, -1.18	-2.9	-4.44, -1.43	0.4	-2.25, 0.80	8.2
PROBNP	66	0.2	-2.01, 2.33	0.6	-1.41, 2.59	0.5	-1.87, 2.93	4.7
PROG	66	-10.3	-19.39, 0.25	-2.0	-14.83, 10.90	6.9	-16.47, 2.63	13.5
PSA	26	0.1	-2.23, 2.30	-0.7	-3.19, 1.83	-0.	-1.04, 2.48	18.7
T3	64	0.6	-0.25, 1.39	0.4	-0.50, 1.13	-0.3	-0.52, 1.02	5.2
T4	65	1.7	1.16, 2.30	2.4	1.86, 2.92	0.7	-1.21, -0.10	3.0
TESTO	28	-1.7	-3.78, 0.34	0.6	-1.91, 3.13	2.3	-5.31, 0.66	6.0
TGAB	63	-32.8	-39.40, -26.26	-28.2	-34.54, -21.85	5.3	-10.21, 0.23	20.6
TPO	61	-2.5	-17.95, 13.03	-18.5	-31.25, 0.28	-16.6	-0.65, 25.44	5.7
TSH	68	2.2	1.23, 3.22	-0.2	-1.12, 0.64	-2.5	1.54, 3.39	9.7
vitD3	65	1.2	-0.65, 3.75	-3.2	-5.30, -0.94	-4.4	-6.49, -2.39	5*

95CI% only when PPT was used whereas SST and BAR were equivalent.

PCT showed 95CI% significantly different from the arbitrary adopted B% when PPT was used, however, the 95CI% amplitudes were very large. In contrast, when SST was compared to BAR the 95CI% became almost ten time smaller, but still exceeded the B%.

### 3.2. Immunochemical analytes

HGH and TGAB showed 95CI% significantly different from B% only when serum was compared to plasma. It must be noted that very large %bias were observed for TGAB on these two comparisons. In contrast, Ferritin showed significant differences only

**Table 4.** Serological analytes. For each comparison was shown: the number of tests (n), the BA Bias calculated as percentage (%bias), the confidence interval (CI95%) and the biological variation expressed as desirable specification for inaccuracy (B%) (18). Analytes with a 95CI% exceeding B% are highlighted in grey.

Analyte	n	SST vs Barricor		SST vs PST		Barricor vs PST		B%
		%bias	CI95%	%bias	CI95%	%bias	CI95%	
ANTIS	64	10.4	6.23, 14.64	9.9	6.60, 13.46	-1.2	-2.82, 0.33	5*
CMVG	64	2.0	-0.90, 3.01	2.3	-1.53, 3.04	0.4	-1.95, 1.14	5*
CMVM	60	1.9	1.05, 2.79	2.2	1.07, 3.30	0.2	-0.52, 1.01	5*
RUBEOG	63	-0.1	-0.72, 0.61	-0.4	-1.11, 0.35	-0.3	-0.36, 0.85	5*
RUBEOM	61	0.0	-0.72, 0.72	0.1	-0.69, 0.93	0.1	-0.59, 0.54	5*
TOXOG	66	0.1	-0.39, 1.78	0.1	-2.39, 1.87	0.0	-0.88, 2.73	5*
TOXOM	58	-0.3	-0.97, 0.38	-0.8	-1.39, 0.01	-0.6	-0.06, 1.20	5*

when BAR was used whereas, for vitD3, only when PST was used. CTX showed a 95CI% significantly different from B% only when SST was compared to BAR. E2, TPO and PROG showed 95CI% exceeding B%, and containing the zero, in all of the three comparisons.

### 3.3. Serological analytes

All of the analytes showed 95CI% smaller than the arbitrary adopted 5% threshold, with the exception of ANTIS which showed a 95CI% significantly different from B% when serum was compared to either PST or BAR.

## 4. Discussion

Among the biochemical analytes BIC, K, LAD, LPA, P and TP are clearly associated to a matrix effect which was considered clinically significant (table 5). The TP and K differences between plasma and serum were expected and attributed to the coagulation process (19). Calcium and GLU showed both a matrix effect and an influence of the new BAR mechanical separator. In the case of GLU the two effects add up when SST is compared to BAR whereas for Ca they have opposite signs. Furthermore the B% for Ca was so small (0.8%) that, although the %bias were significant, we considered them clinically irrelevant (table 5). The same was true for Na and TRF (B%: 0.2 and 1.3%

respectively) which showed matrix effects and influences of the new mechanical separator so small as to be considered clinically irrelevant (Table 5).

PCT showed %biases higher than 30% in the SST vs PST and BAR vs PST comparisons (likely arising from the low concentration data associated with the healthy condition of the individuals tested) whereas a %bias lower than the arbitrary adopted 5% was observed in the SST vs BAR comparison. However, in the latter comparison the 95CI% contained the zero and exceeded the desirable specification interval. Thus, we cautiously did not state whether the two measurements were equivalent or not (Table 5).

Among the immunochemical analytes HGH and TGAB were associated to a matrix effect only. Because of the very large %biases and 95CI% observed for TGAB, we prudently did not draw any conclusion for these measurements. We might speculate that the large %biases were consistent with the Roche recommendation for the exclusive use of serum for TGAB determination (table 5). For CTX the matrix effect (SST vs PST) and the mechanical separator effect were both insignificant. However the two effects adds up resulting in a significant difference between SST and BAR (Table 5). A significant difference was observed for Ferritin as well which showed no matrix effect but a pronounced effect of the mechanical separator (Table 5). In contrast, the matrix effect and the effect of the mechanical separator (both significant) observed for vitD3 were of the opposite sign. As a result SST and BAR can be used interchangeably, for vitD3 measurements, whereas re-

**Table 5.** Differences observed when comparing SST, PST and BAR tubes. NS: no statistically significant difference; SS-CLI: statistically significant difference and likely clinically relevant (highlighted in grey); SS: statistically significant difference only, clinically irrelevant

Analyte	SST vs BAR	SST vs BAR	BAR vs PST
<b>Biochemical:</b> ALB, ALP, ALT, AMS, AMSP, ASO, AST, B2MICR, BILT, C3, C4, CHE, CK, CL, CHO, CREA, CRP, FE, GGT, HOM, HDL, IGA, IGG, IGM, LIP, LDL, MG, MUCO, RF, TG, UA, UREA	NS	NS	NS
BIC	SS-CLI	SS-CLI	NS
Ca	SS <sup>a</sup>	SS <sup>a</sup>	SS <sup>a</sup>
GLU	SS-CLI	SS-CLI	SS-CLI
K	SS-CLI	SS-CLI	NS
LAD	SS-CLI	SS-CLI	NS
LPA	SS-CLI	SS-CLI	NS
NA	NS	SS <sup>a</sup>	SS <sup>a</sup>
PCT	?? <sup>b</sup>	?? <sup>b</sup>	?? <sup>b</sup>
P	SS-CLI	SS-CLI	NS
TP	SS-CLI	SS-CLI	NS
TRF	NS	SS <sup>a</sup>	SS <sup>a</sup>
<b>Immunochemical:</b> AFP, B12, BHCG, CA125, CA153, CEA, CKMB, CORT, CPEP, Folate, FSH, FT3, FT4, GICA, GLA, HPRL, HS-CTnT, INS, LH, MIOG, PROPNB, PSA, T3, T4, TESTO, TSH	NS	NS	NS
CTX	SS-CLI	NS	NS
E2	?? <sup>b</sup>	?? <sup>b</sup>	?? <sup>b</sup>
Ferritin	SS-CLI	NS	SS-CLI
HGH	SS-CLI	SS-CLI	NSD
PROG	?? <sup>b</sup>	?? <sup>b</sup>	?? <sup>b</sup>
TGAB	?? <sup>b</sup>	?? <sup>b</sup>	NS
TPO	?? <sup>b</sup>	?? <sup>b</sup>	?? <sup>b</sup>
vitD3	NS	SS-CLI	SS-CLI
<b>Serology:</b> CMVG, CMVM, RUBEORG, RUBEOM, TOXOG, TOXOM	NS	NS	NS
ANTIS	SS-CLI	SS-CLI	NS

<sup>a</sup>Because of the relatively small desirable specification (B%), the %bias, although significantly different, was considered clinically irrelevant.

<sup>b</sup>We, cautiously, did not state whether the two measurements were equivalent or not.

placing SST with PST might have significant clinical implications (Table 5). For E2, PROG and TPO the plasma vs serum comparisons all gave confidence intervals which exceeded B% and, at the same time, contained the zero. This was likely the consequence of the many results falling in the low concentration range and associated with the healthy condition of the individuals tested (Figure S2A-B). Thus we, cautiously, did not state whether the measurements were equivalent or not.

B% was not available for the serology analytes thus an arbitrary 5% threshold was adopted. Among them only ANTIS showed a significant matrix effect which was considered clinically significant (table 5).

## 5. Conclusion

We demonstrated that plasma tubes, including the new BAR tube, can be used interchangeably with SST for most of the standard biochemical and immunochemical analytes as well as for serology analytes. This is of particular importance because using the same tube for assaying multiple analytes significantly increases the efficiency and effectiveness of the laboratory while decreasing patient discomfort.

For the few analytes showing clinically significant between-tubes differences (Table 5), a new normal clinical range should be calculated in order to guaran-



tee the patients' safety. It must be also noted that the results showed in this study refers to a Roche COBAS 8000 device and its related assays. Thus, laboratory equipped with different instrumentations might show different outcomes.

**Conflict of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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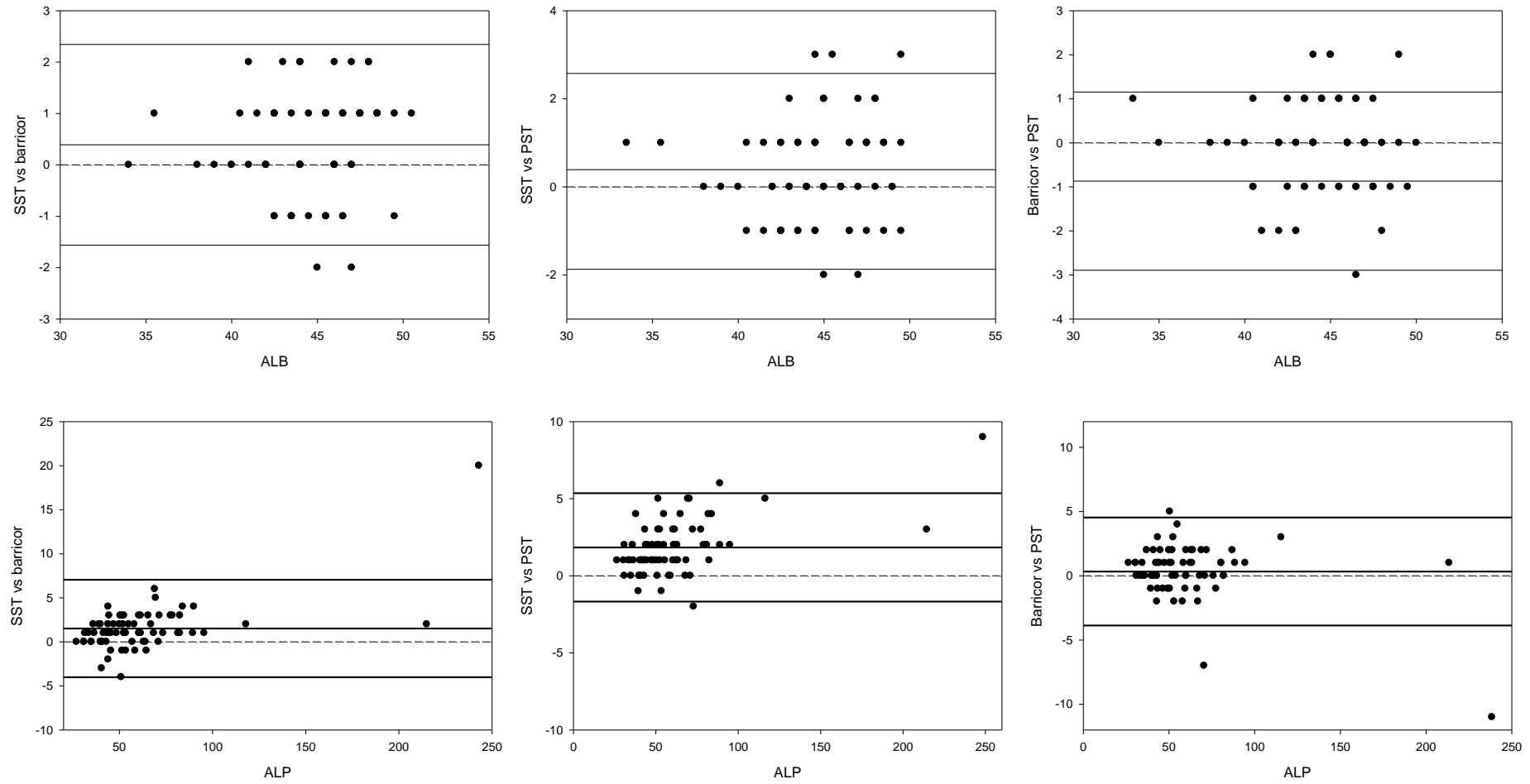
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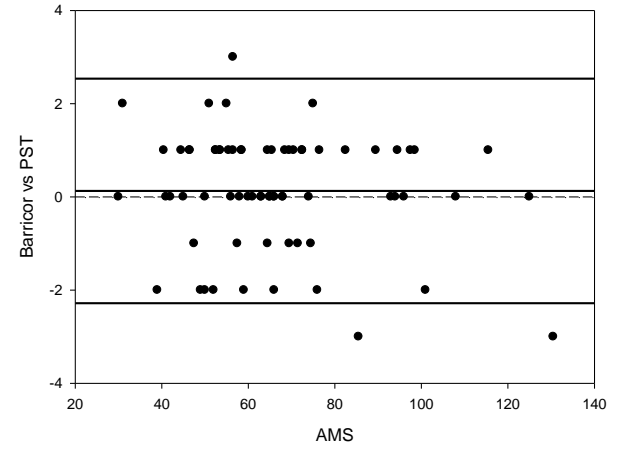
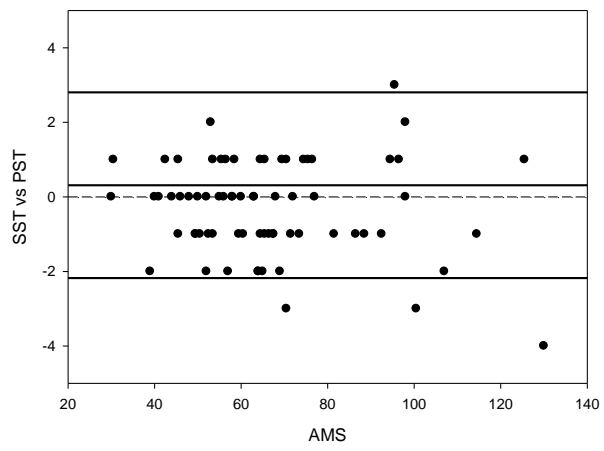
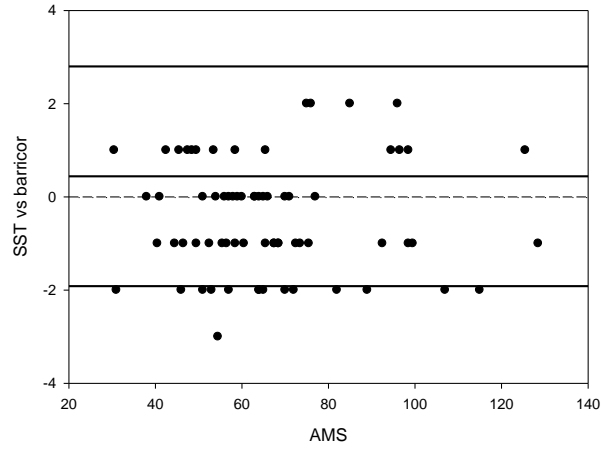
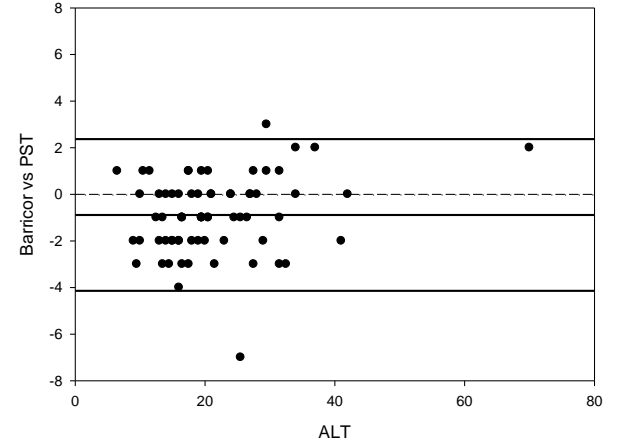
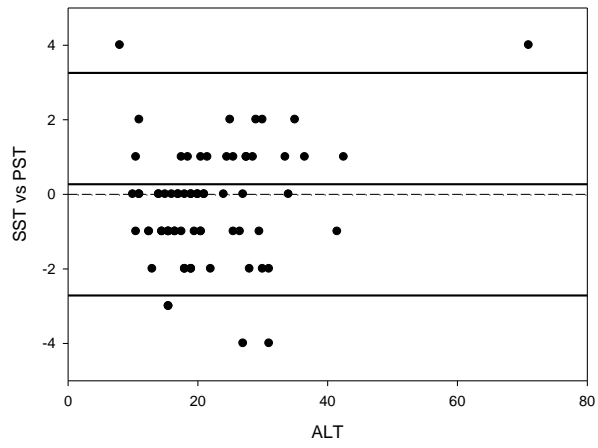
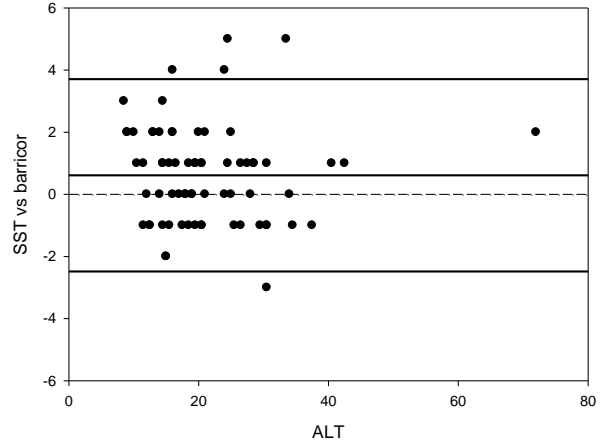
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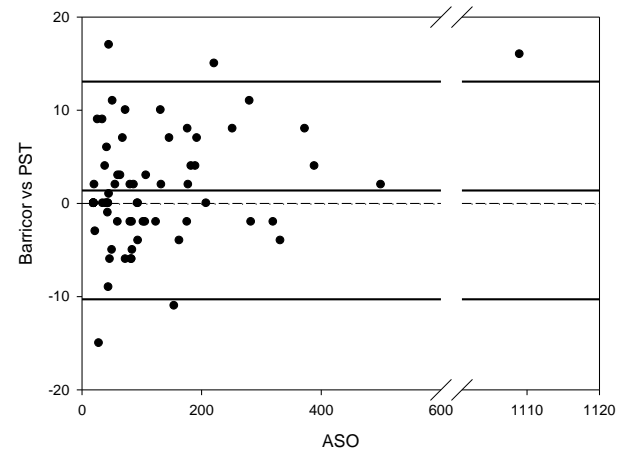
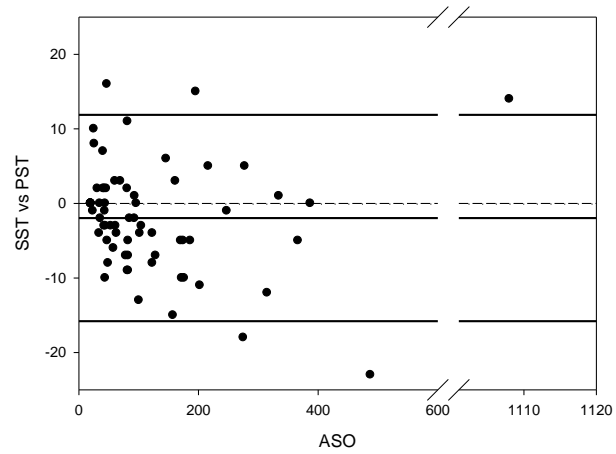
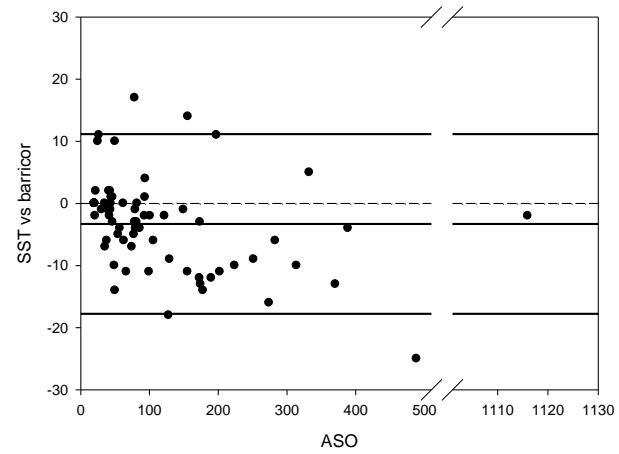
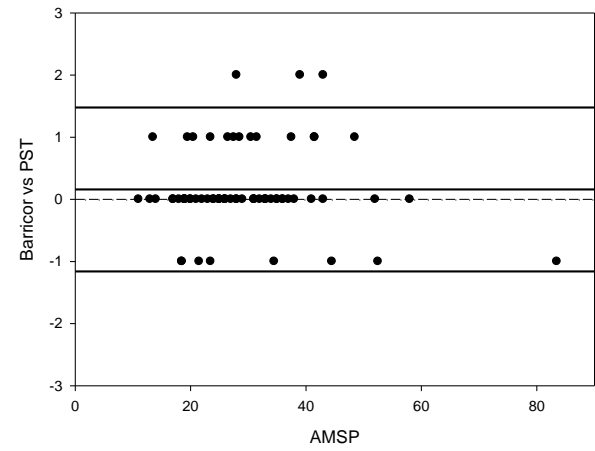
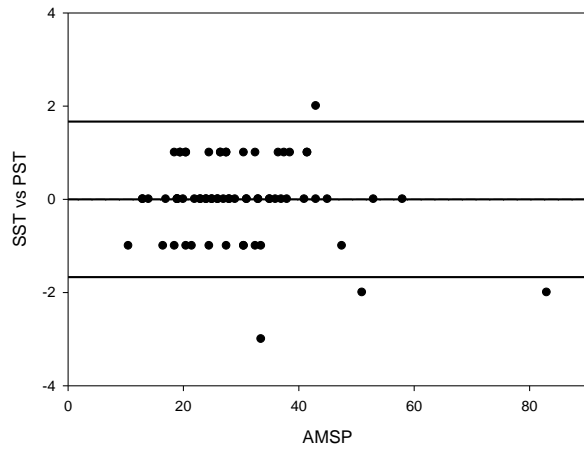
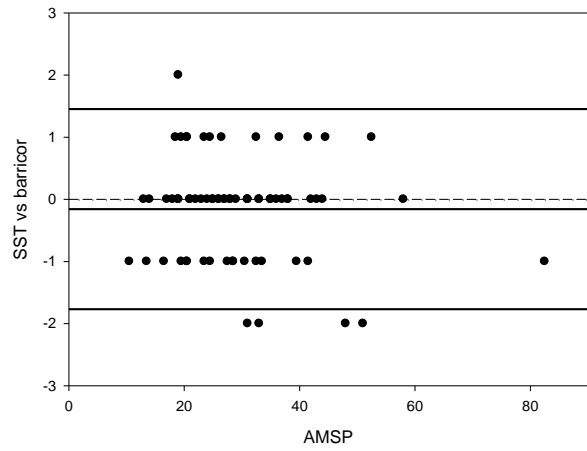
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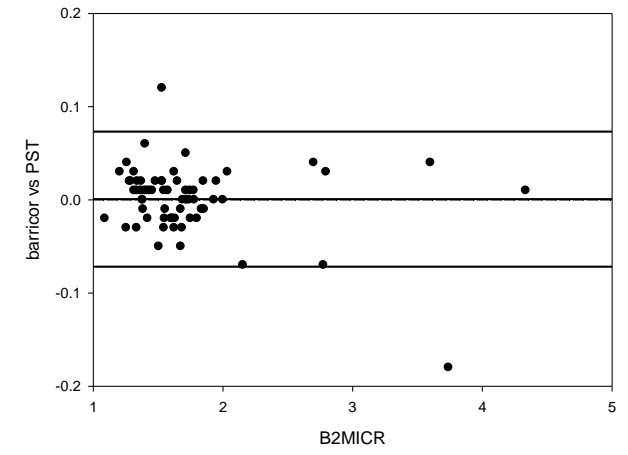
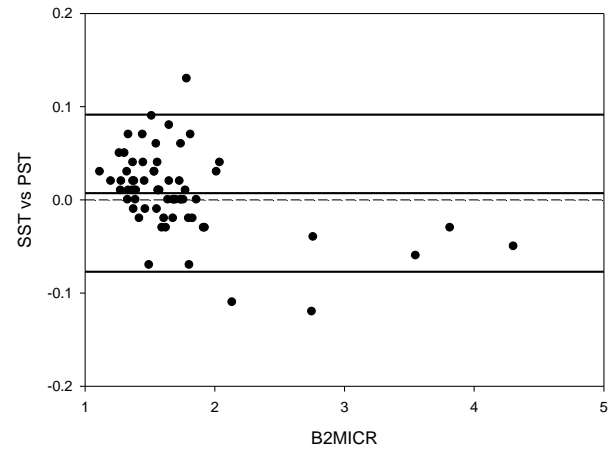
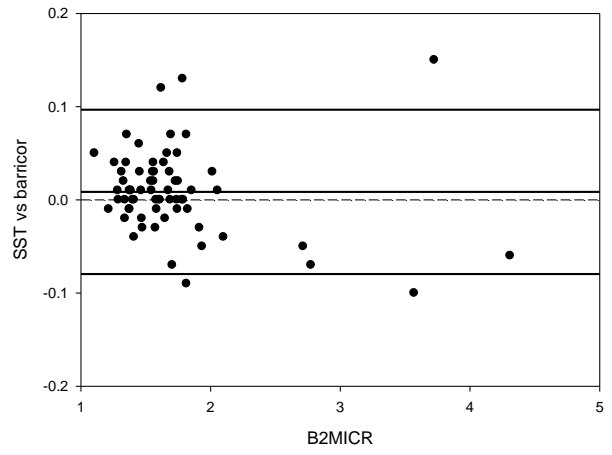
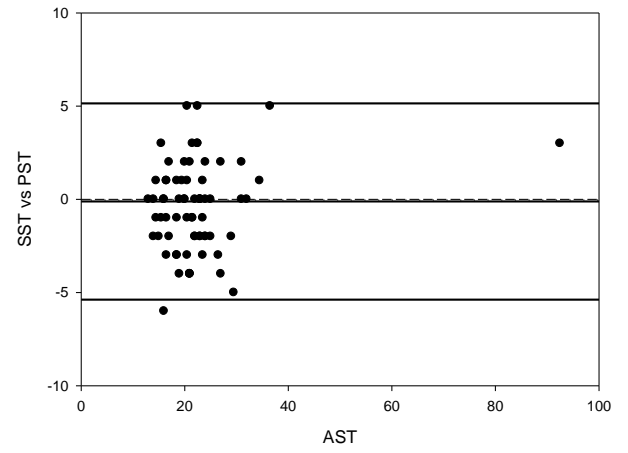
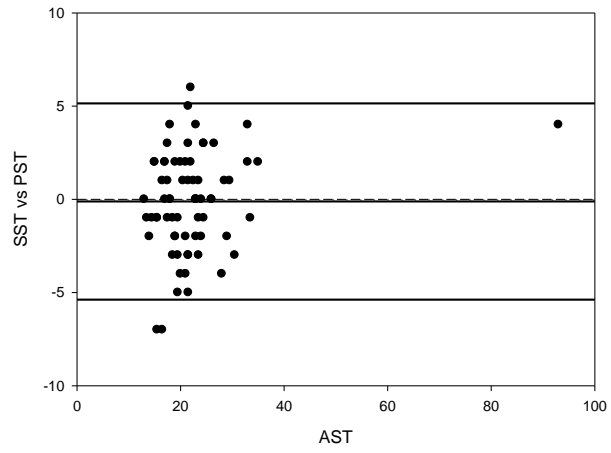
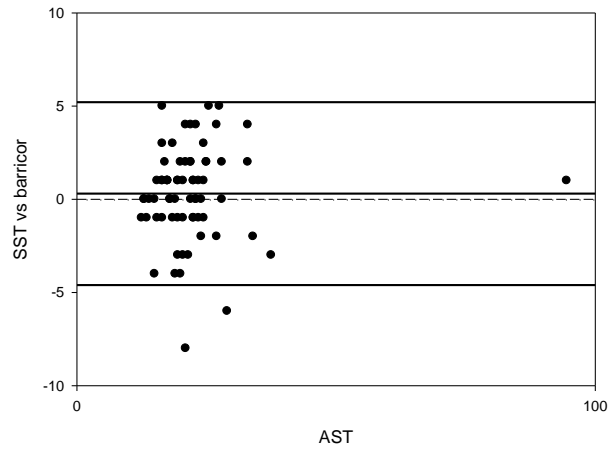
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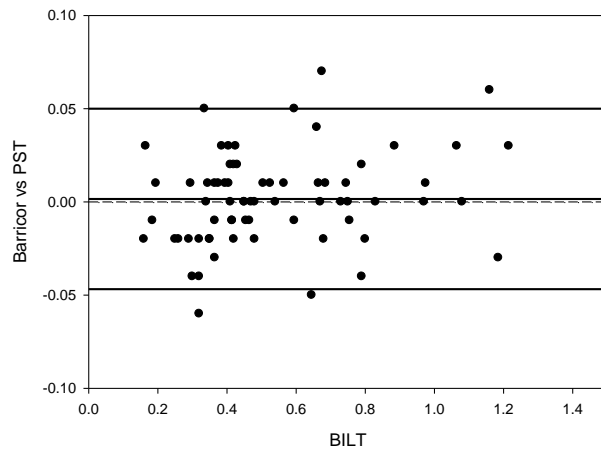
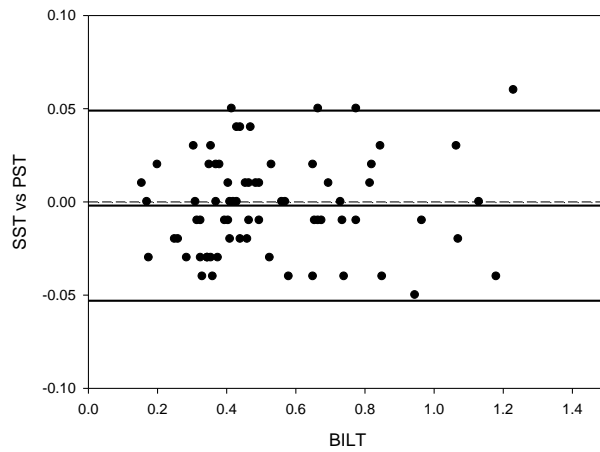
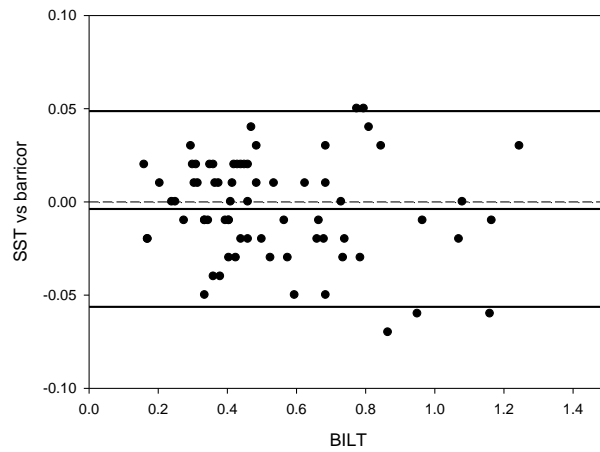
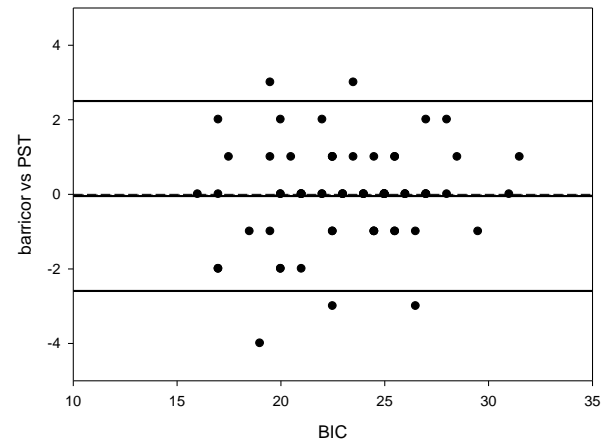
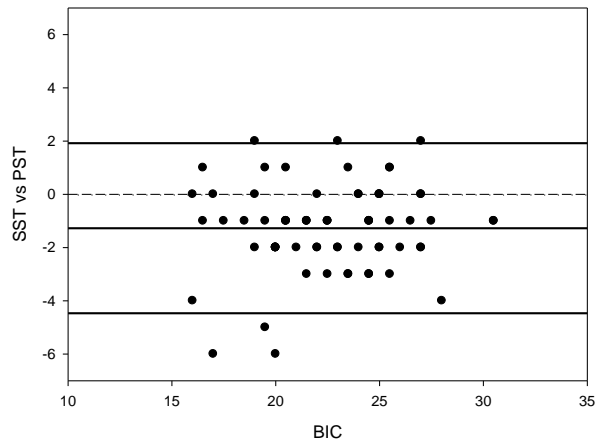
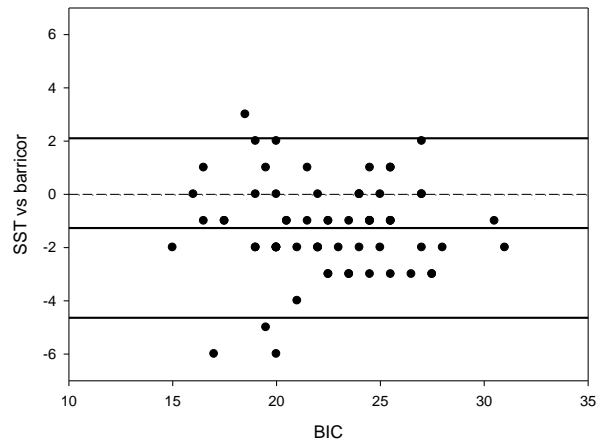
**Figure S1A:** B&A plots for chemical analytes: the pair value differences were expressed as real values.

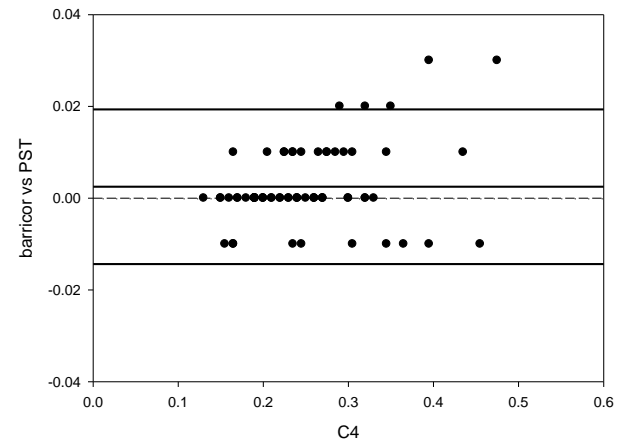
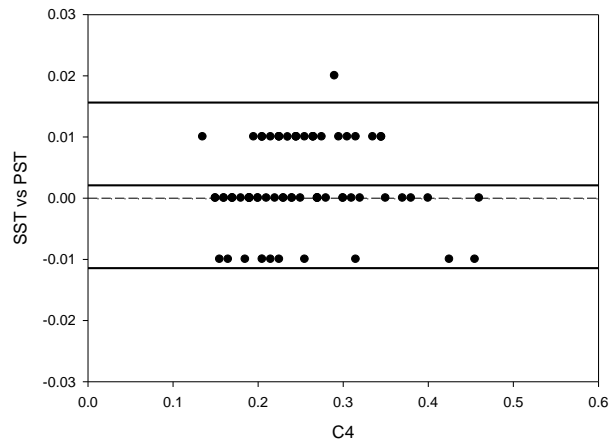
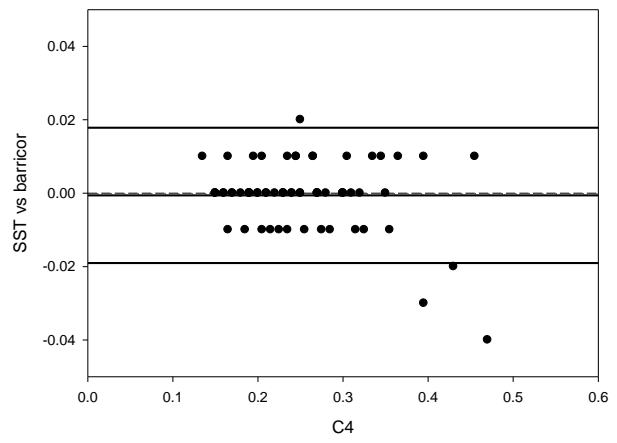
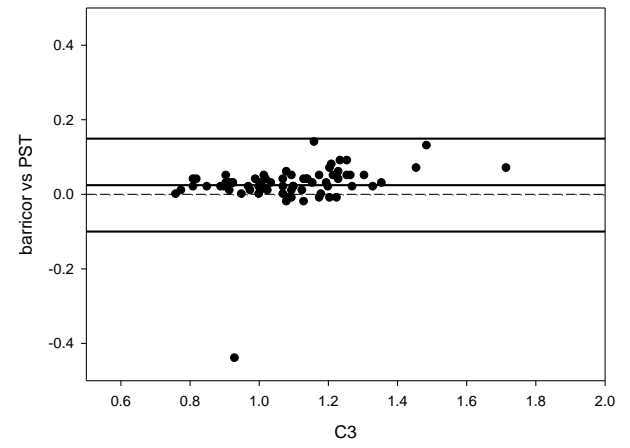
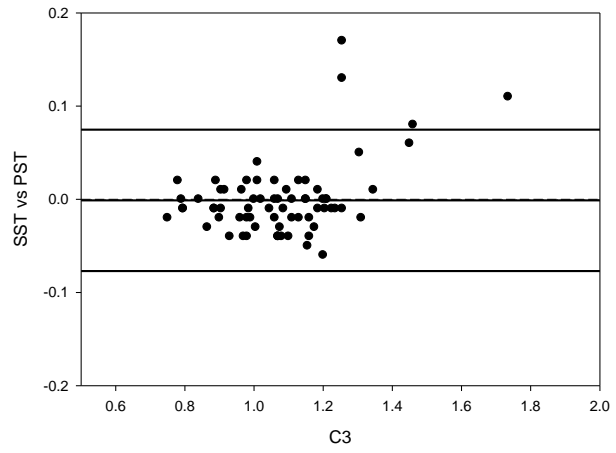
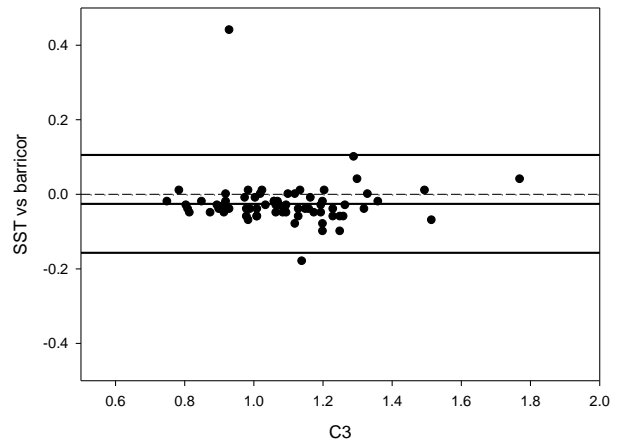


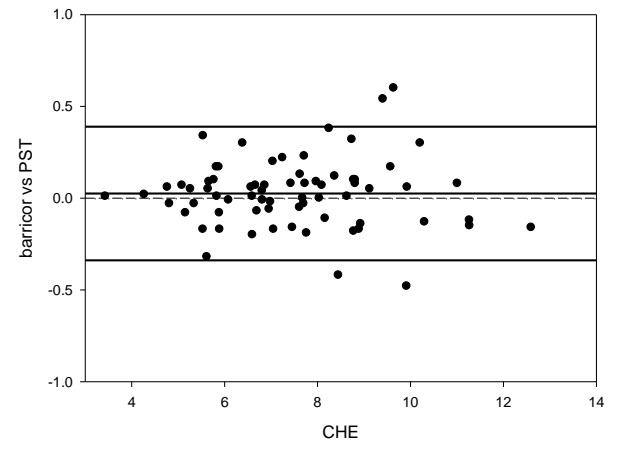
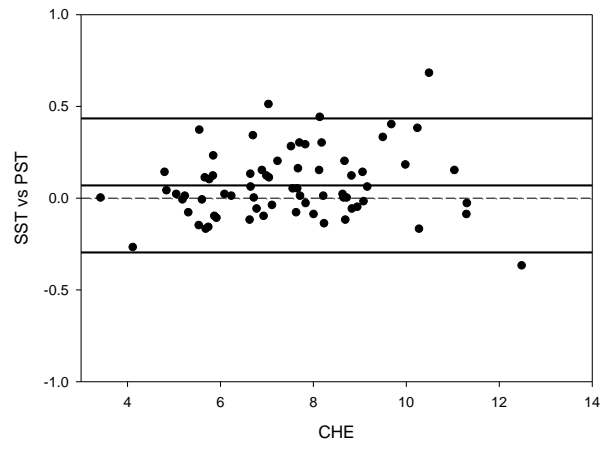
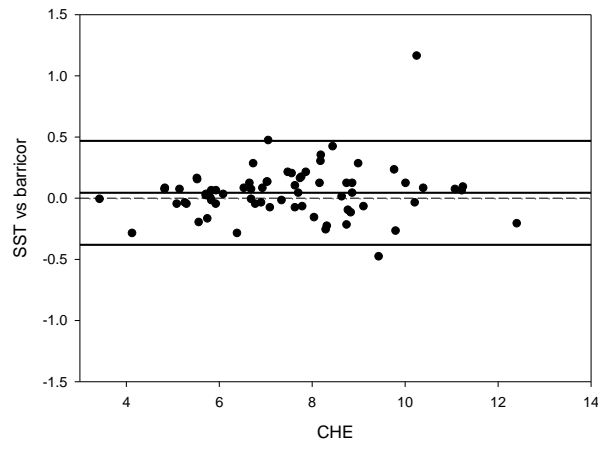
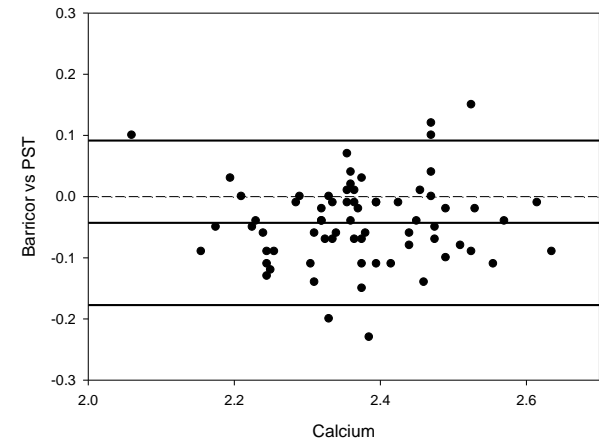
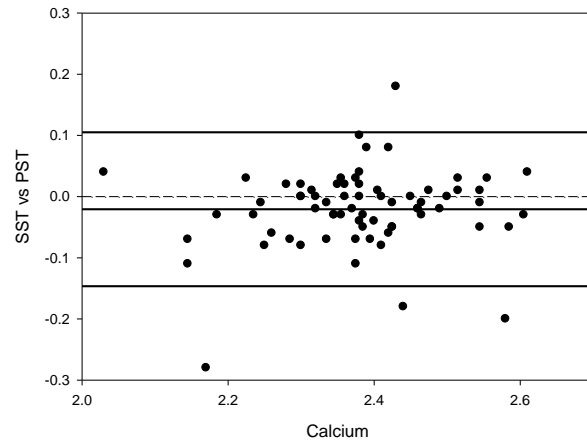
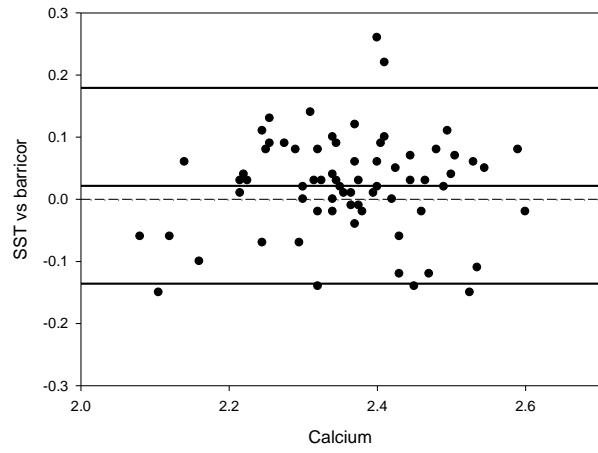




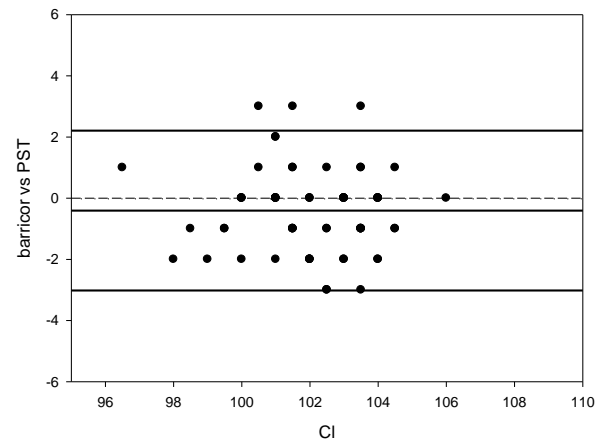
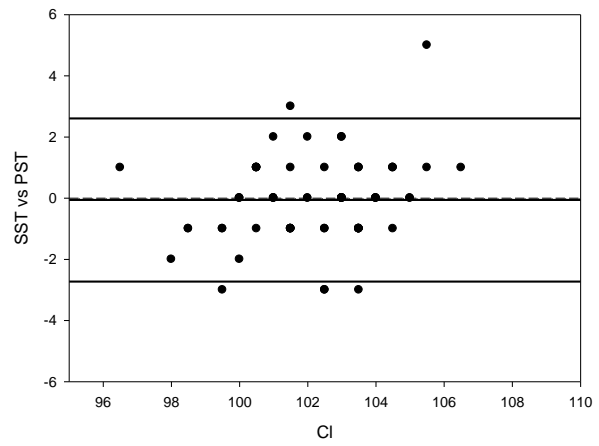
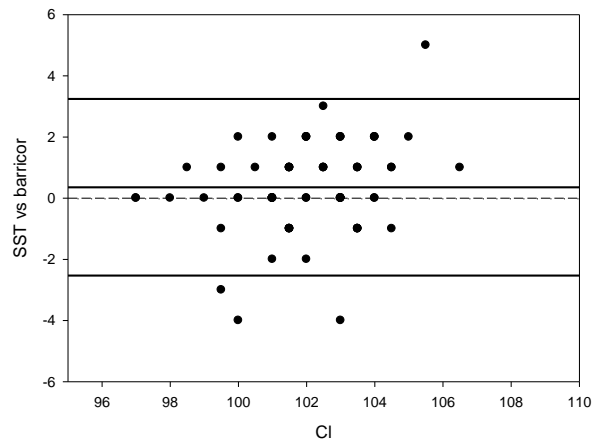
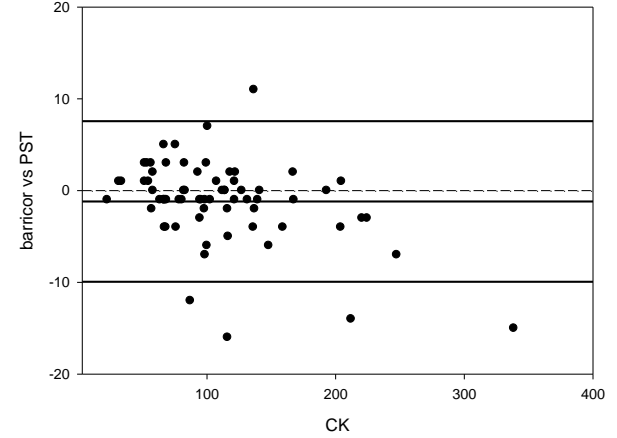
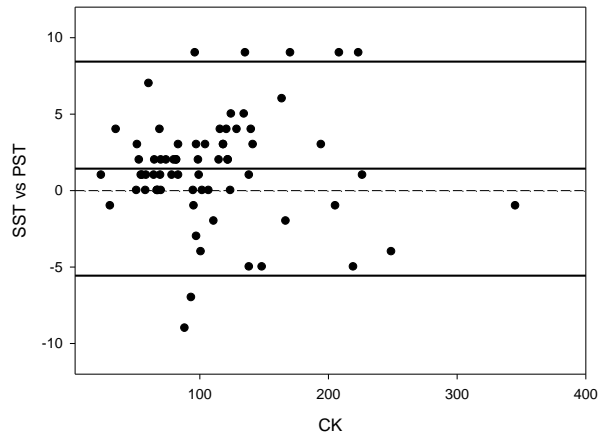
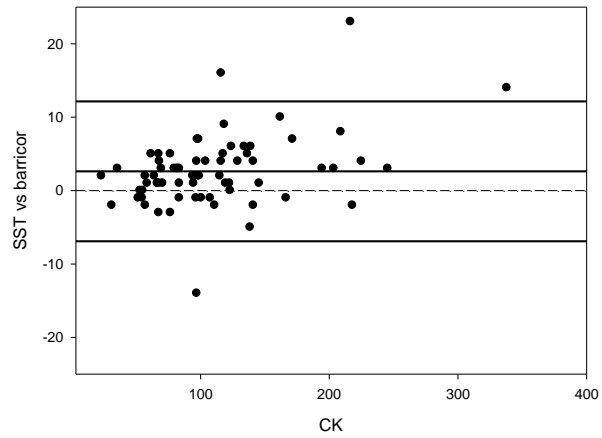


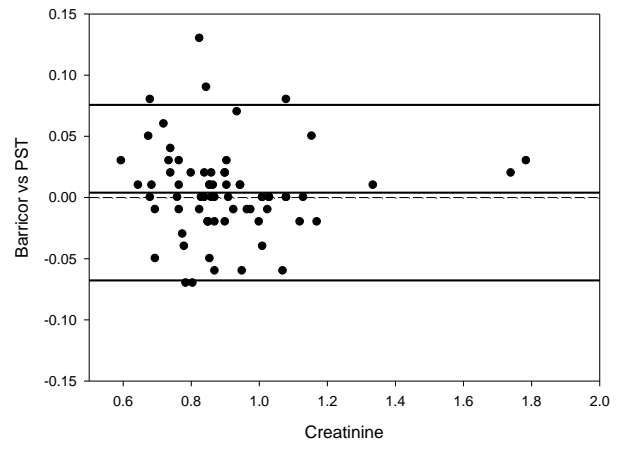
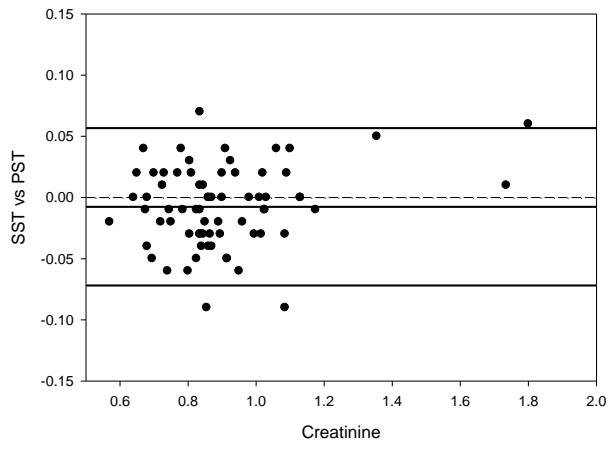
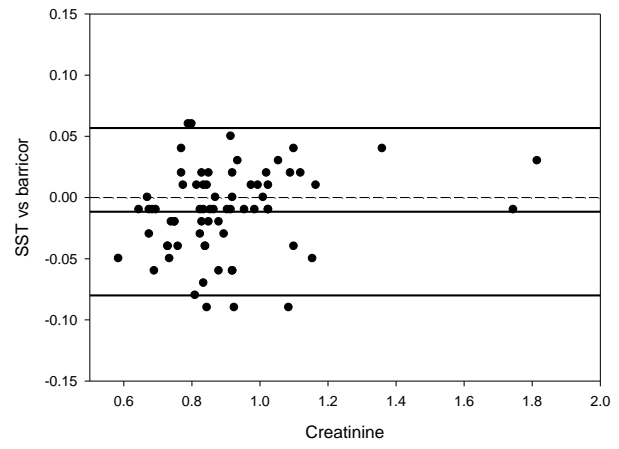
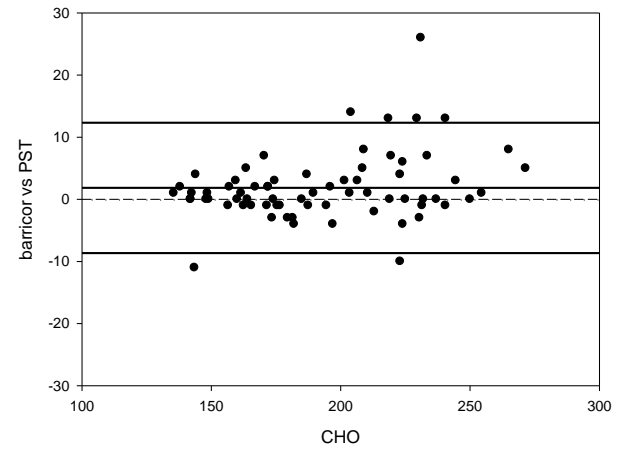
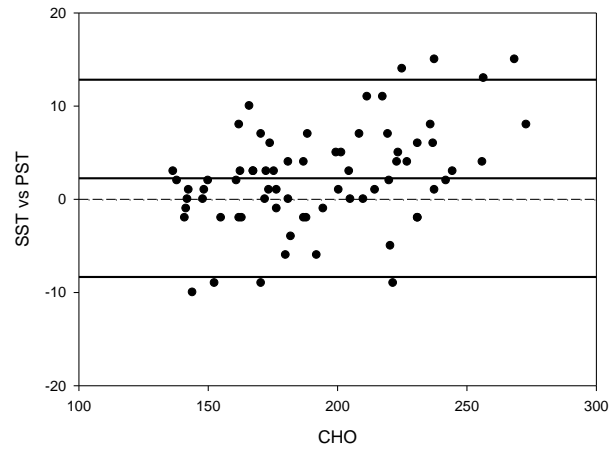
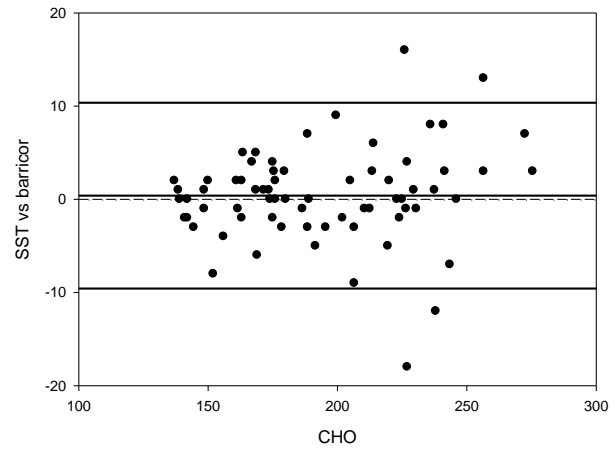


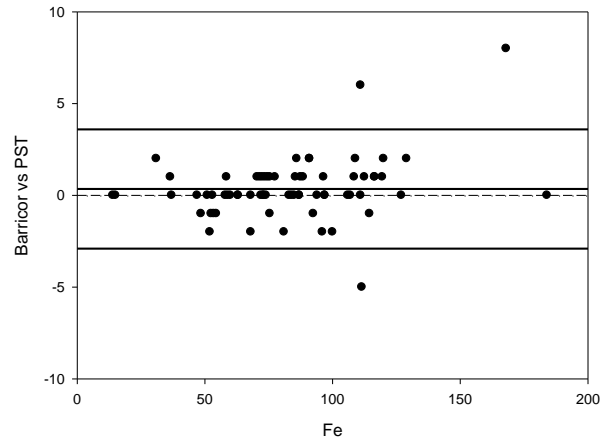
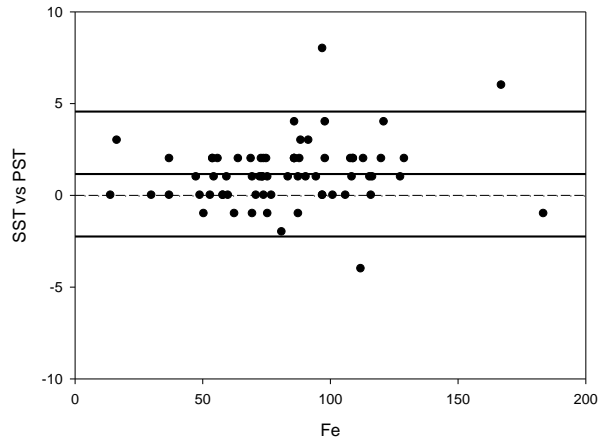
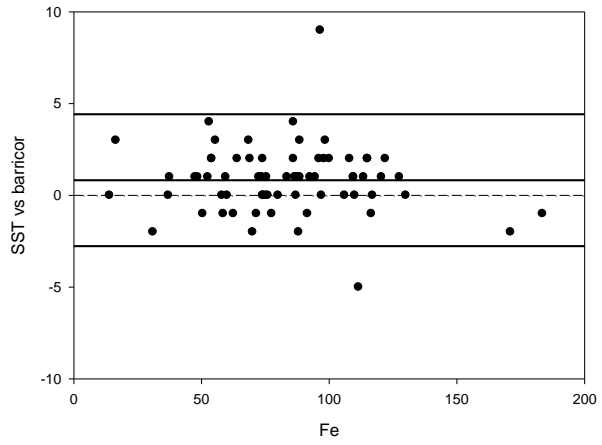
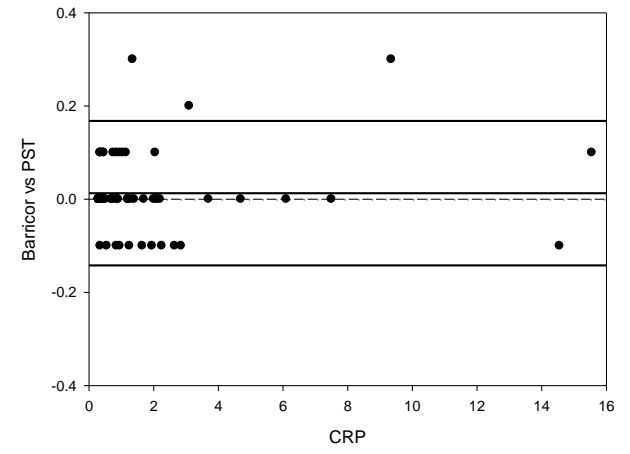
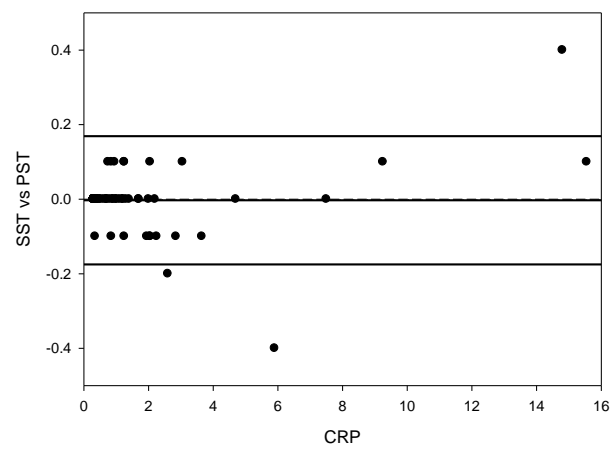
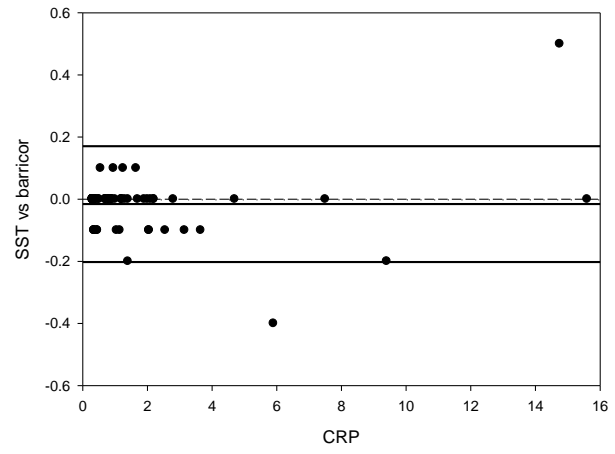


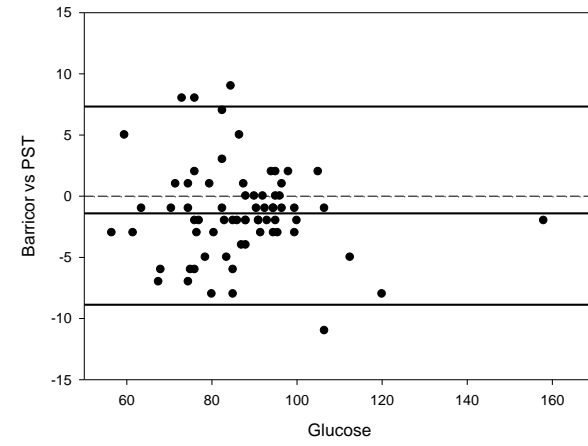
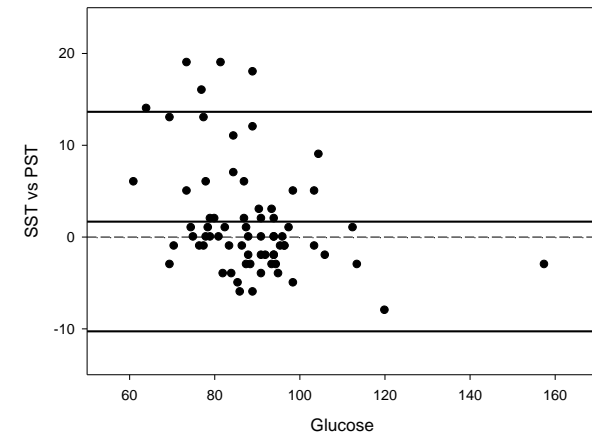
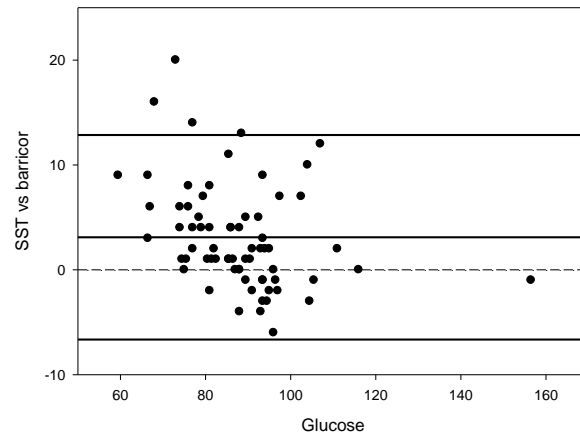
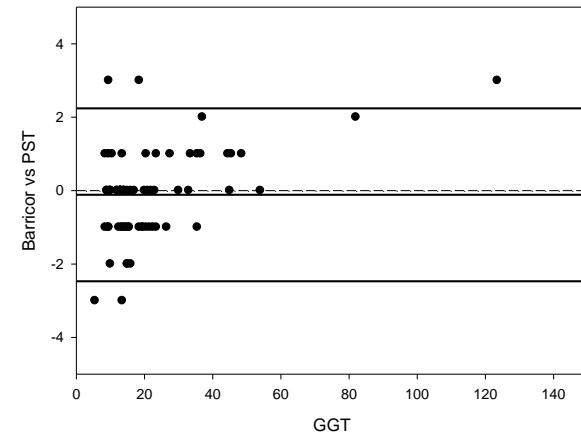
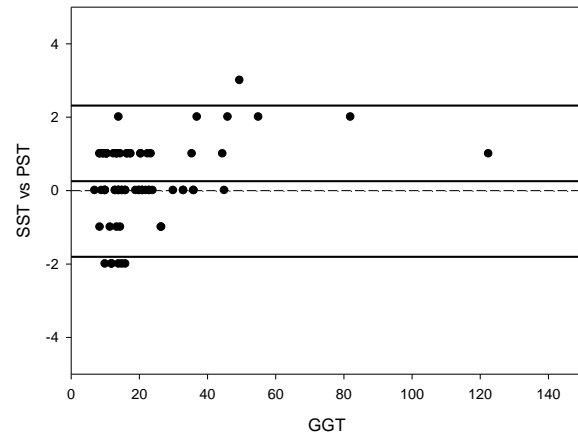
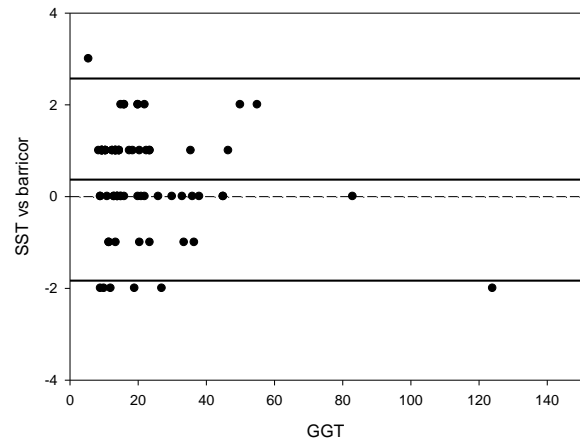


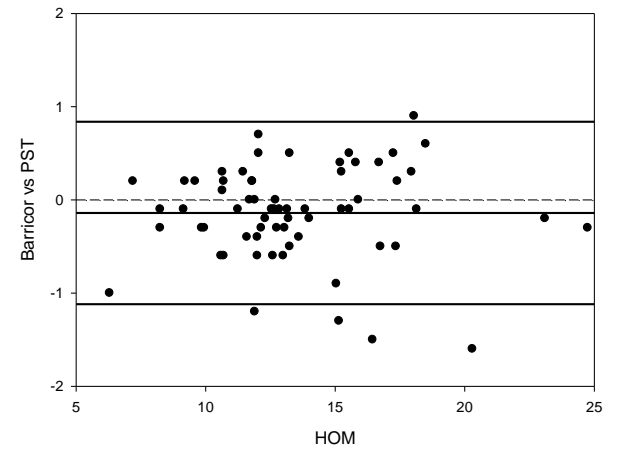
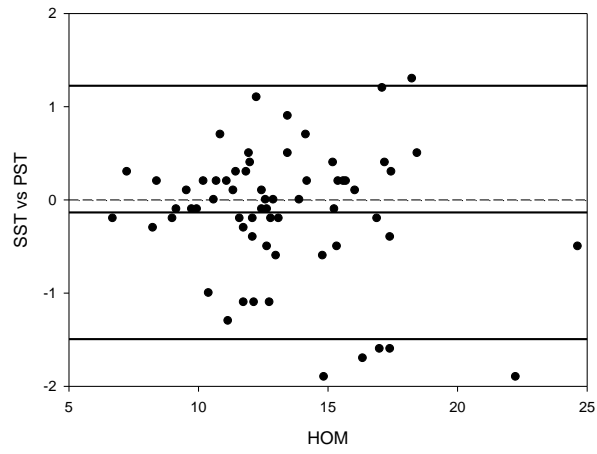
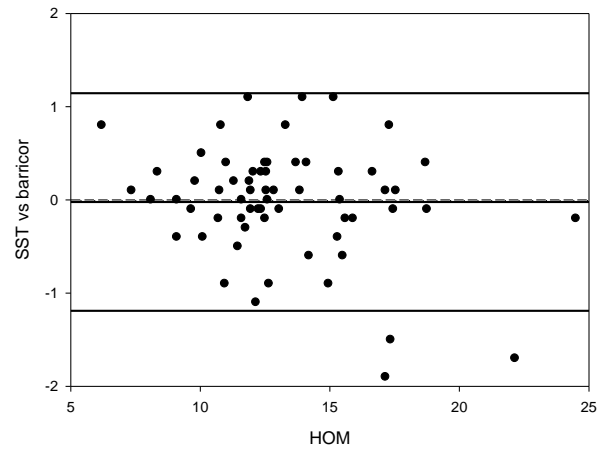
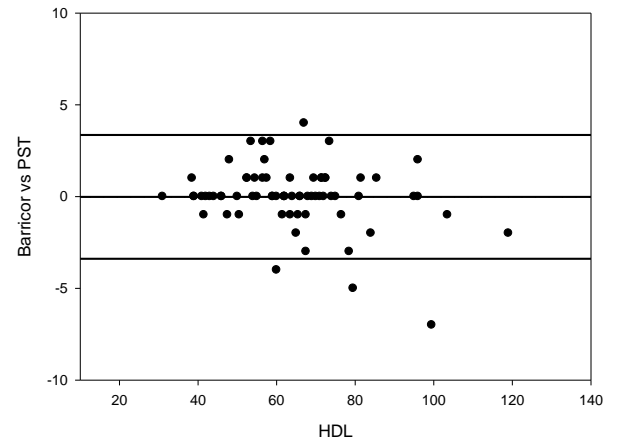
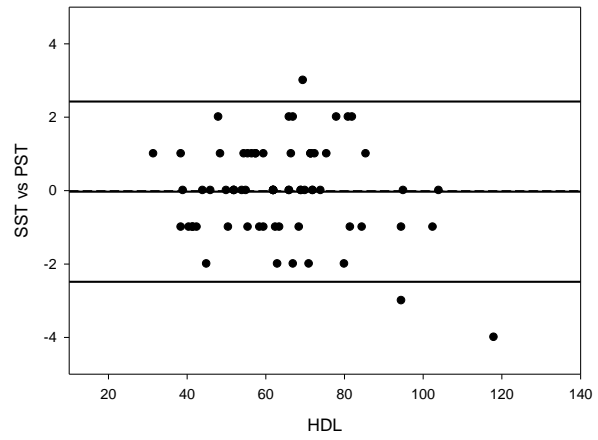
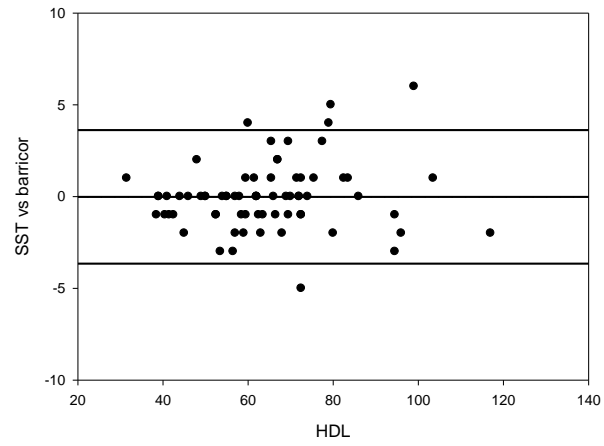


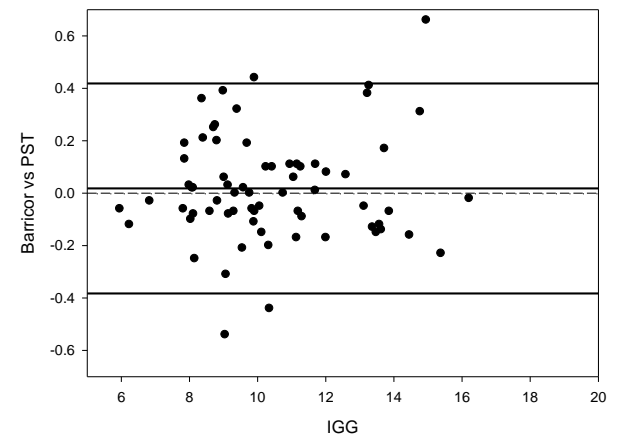
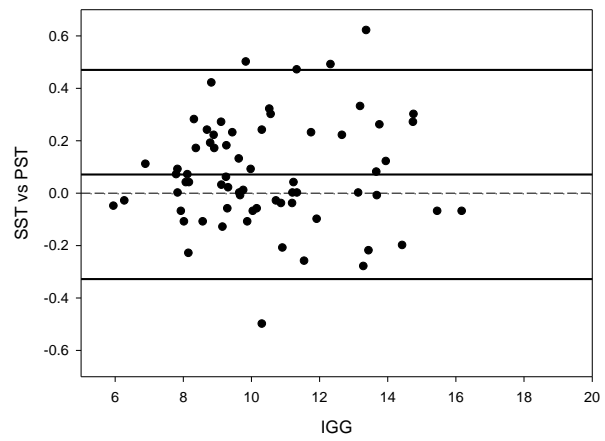
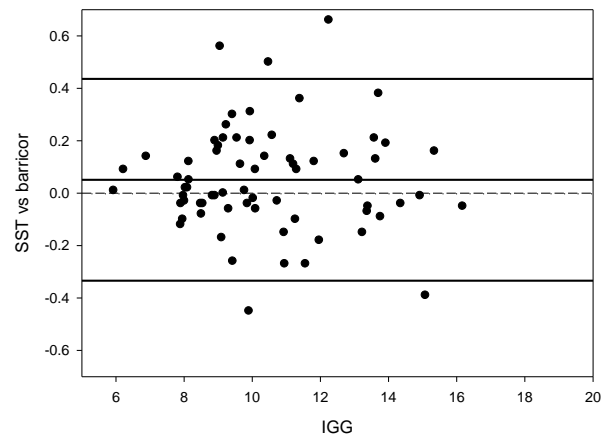
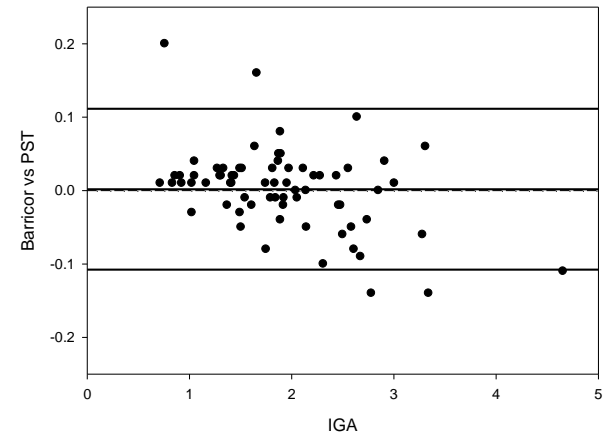
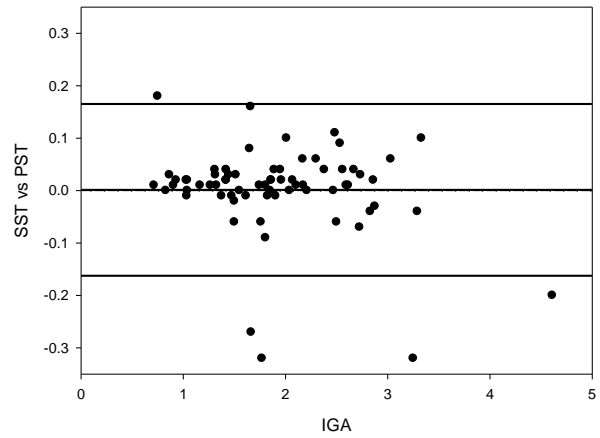
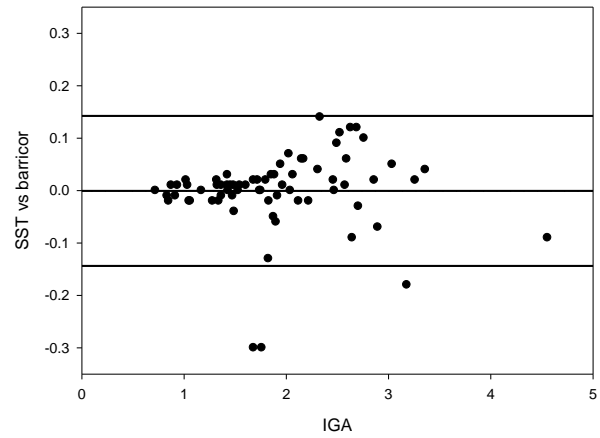


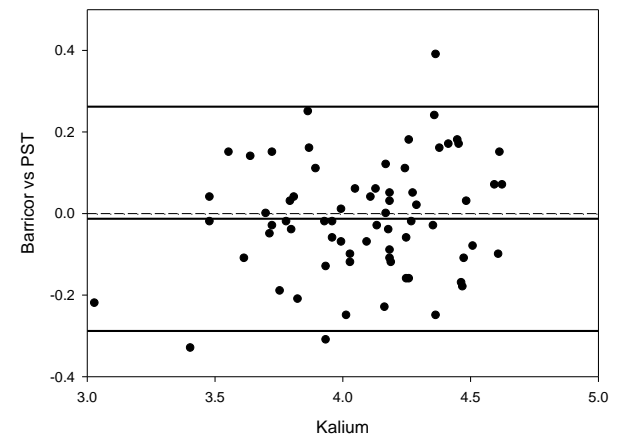
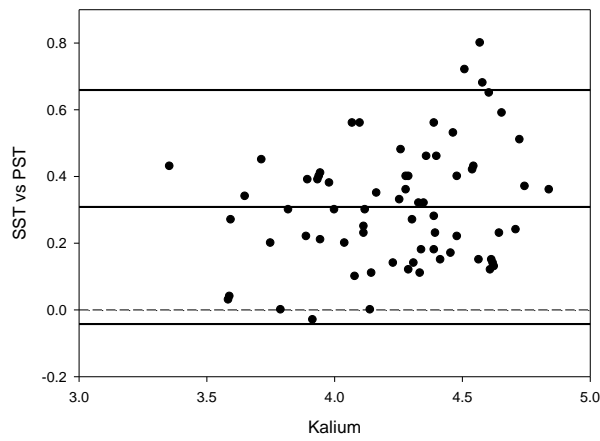
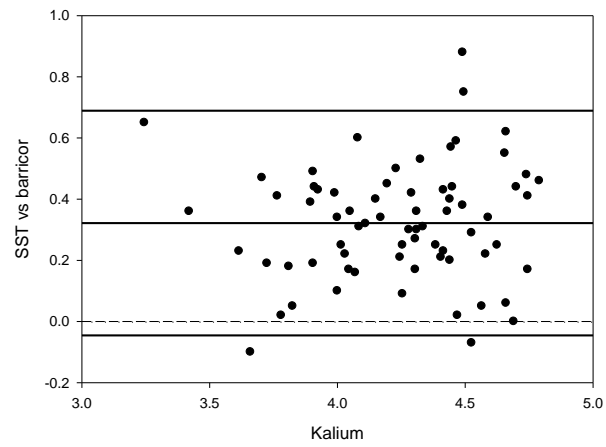
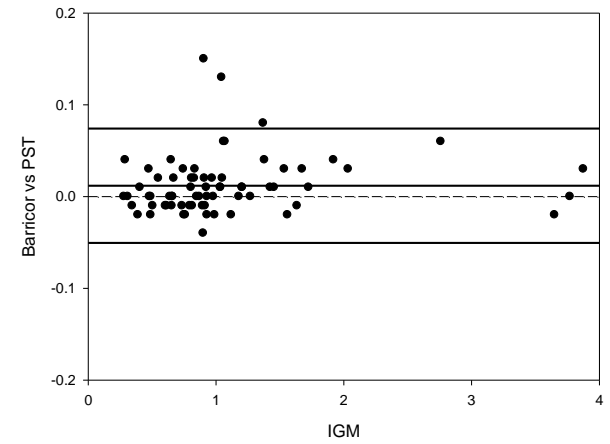
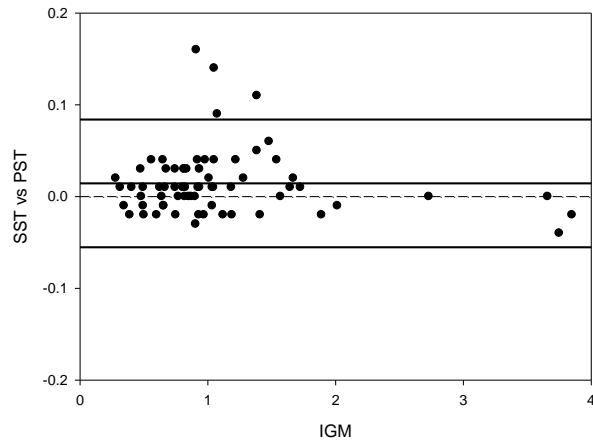
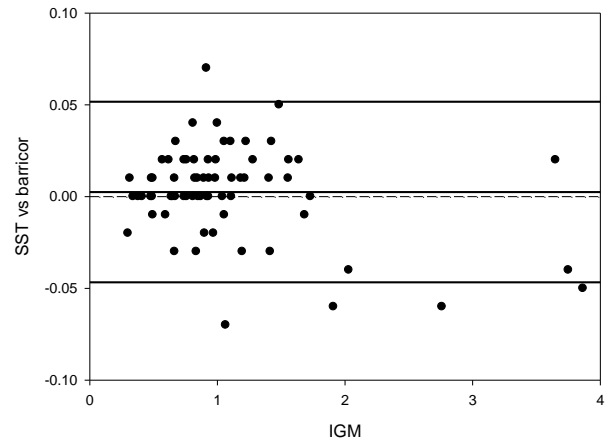


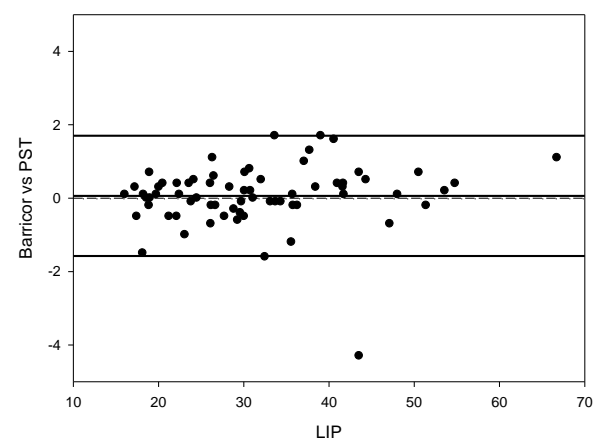
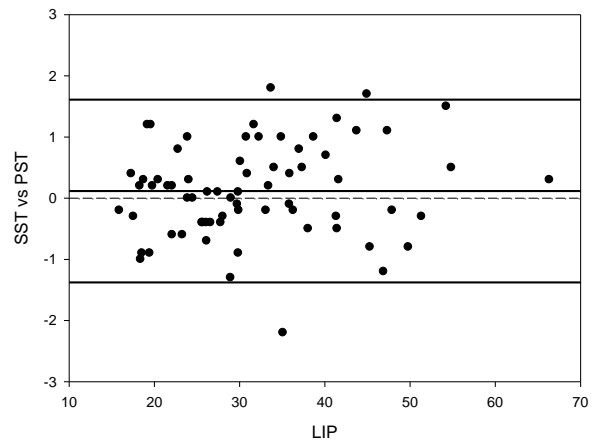
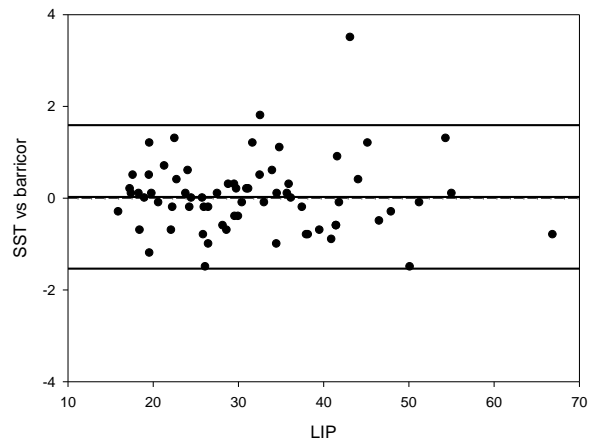
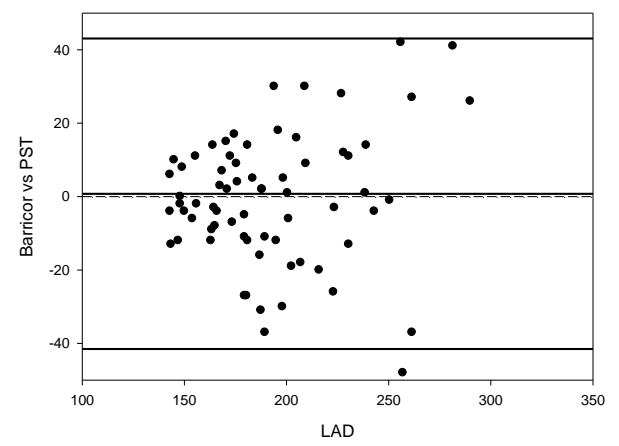
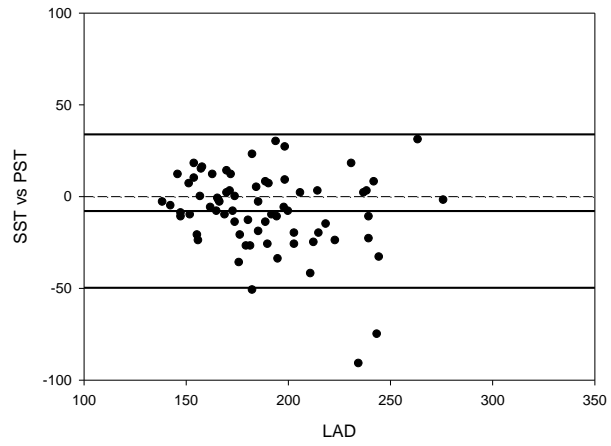
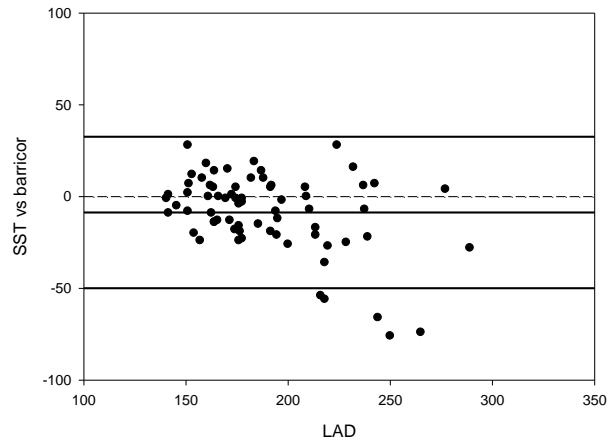




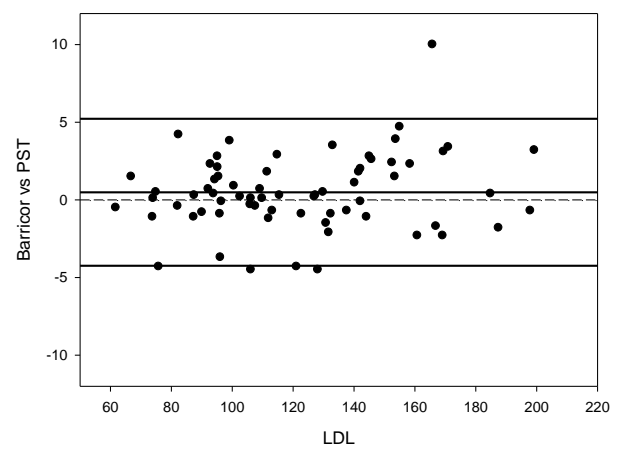
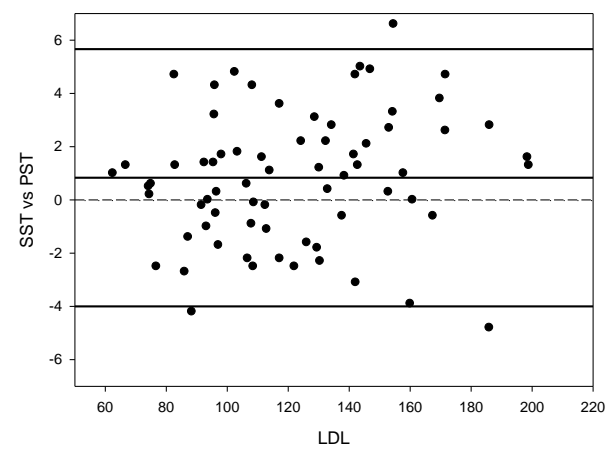
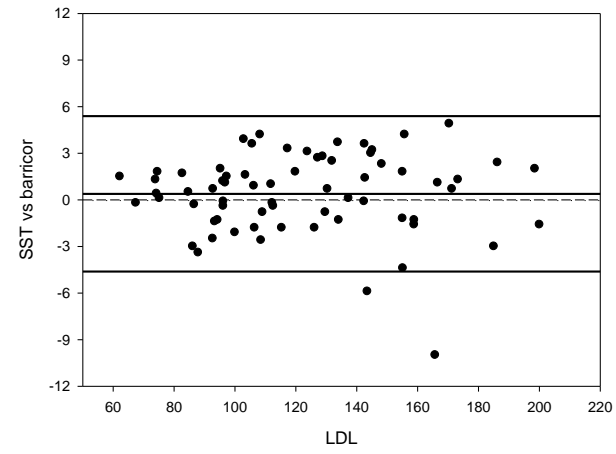
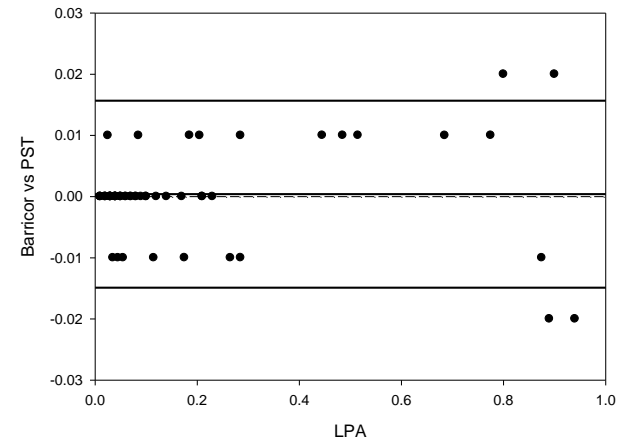
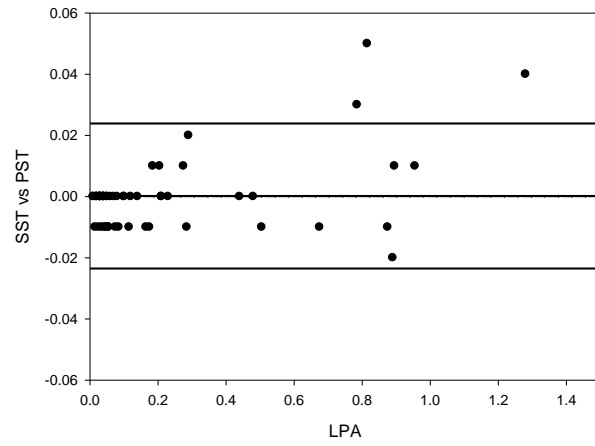
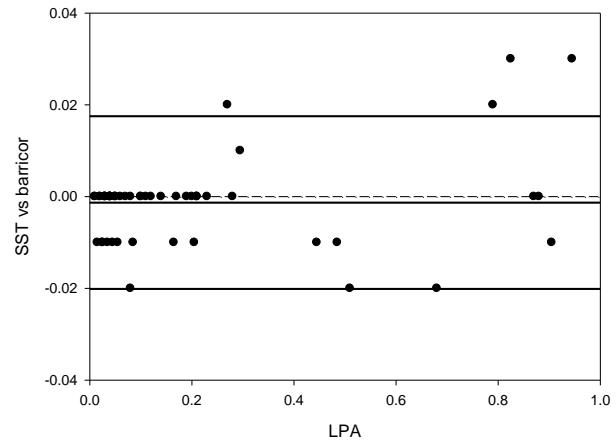


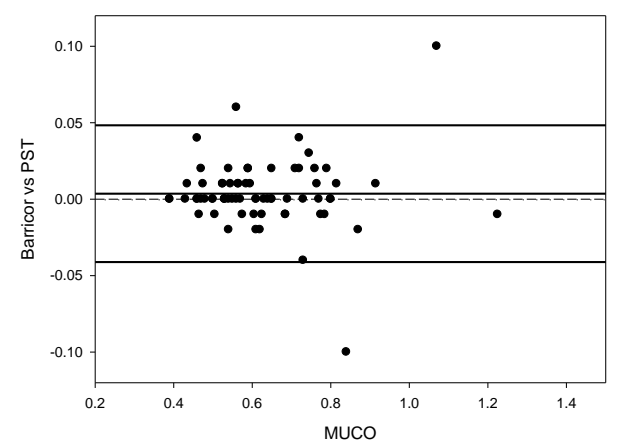
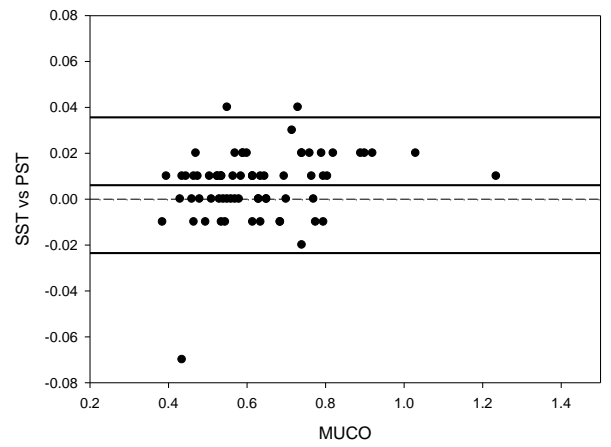
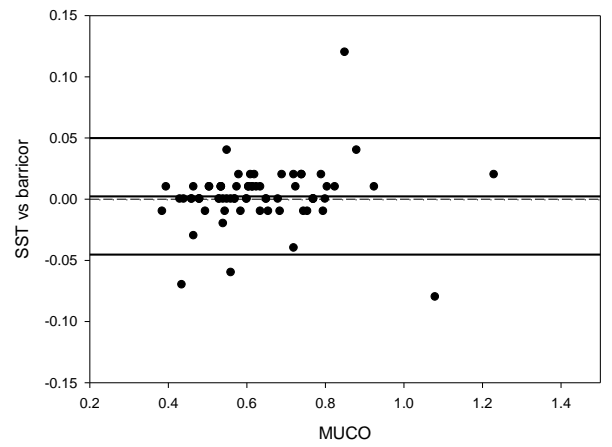
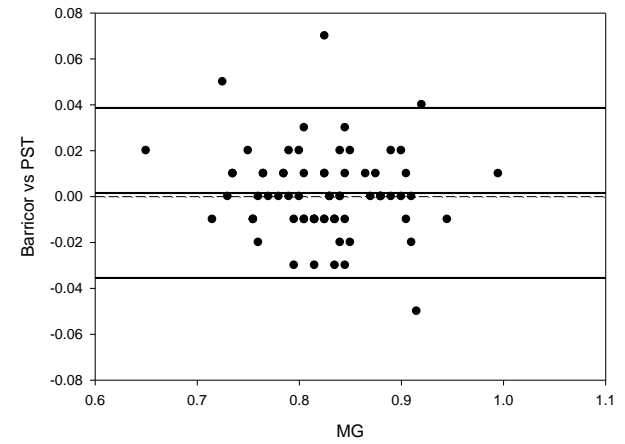
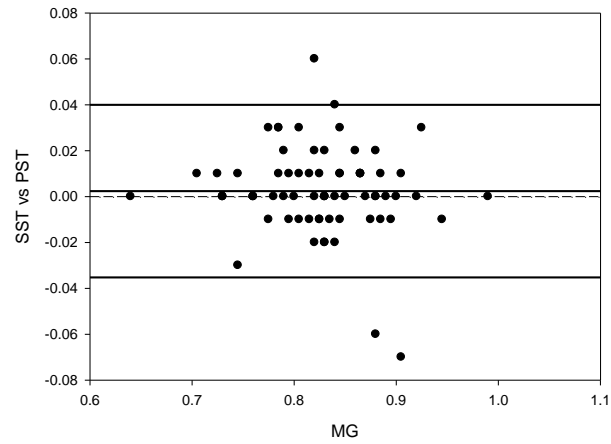
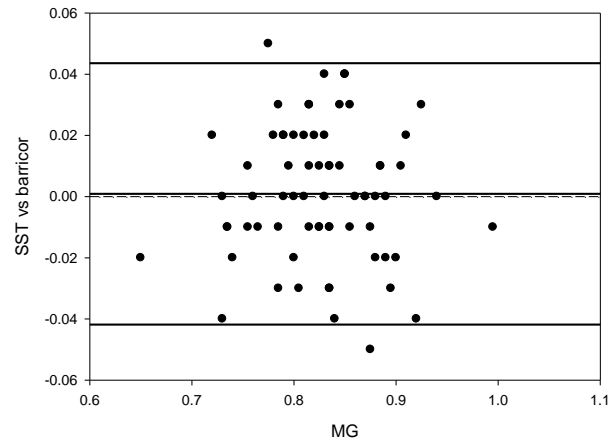


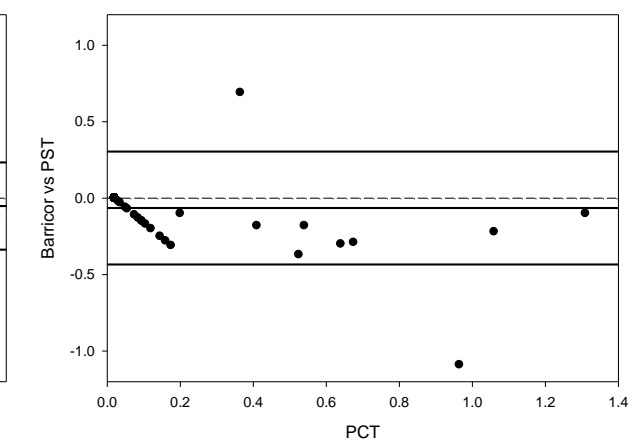
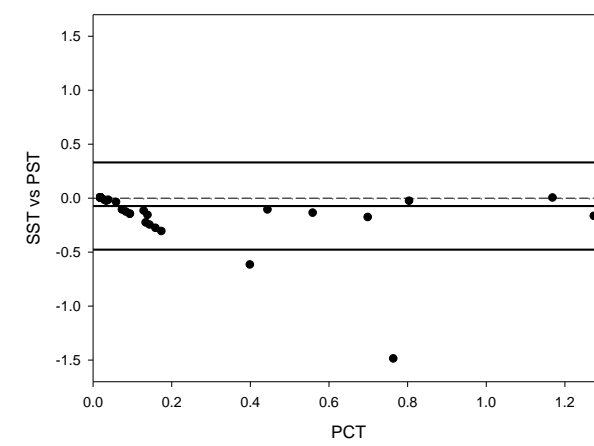
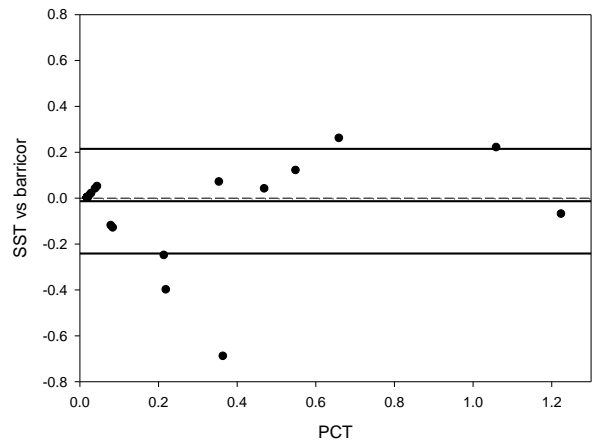
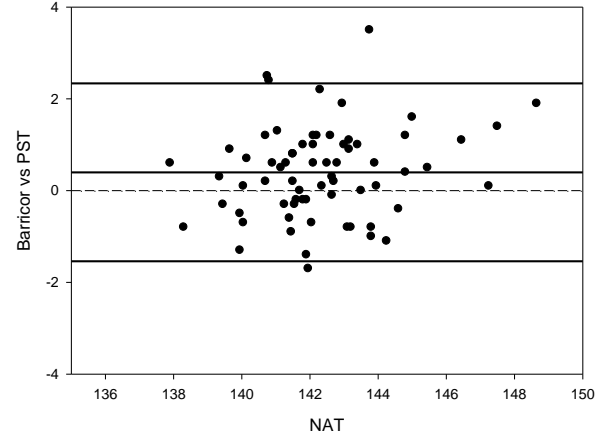
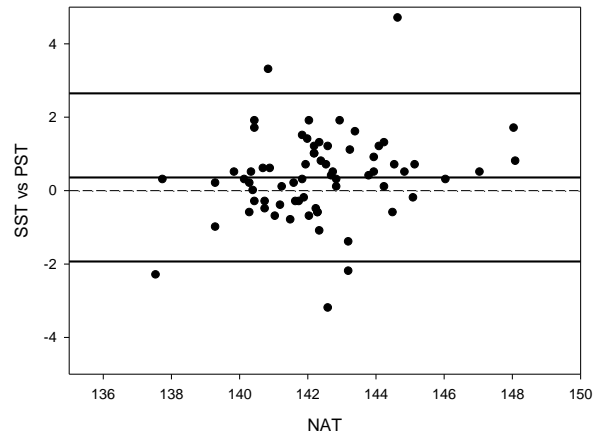
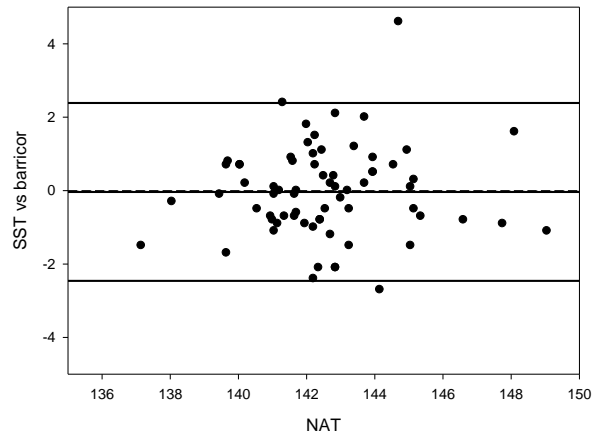


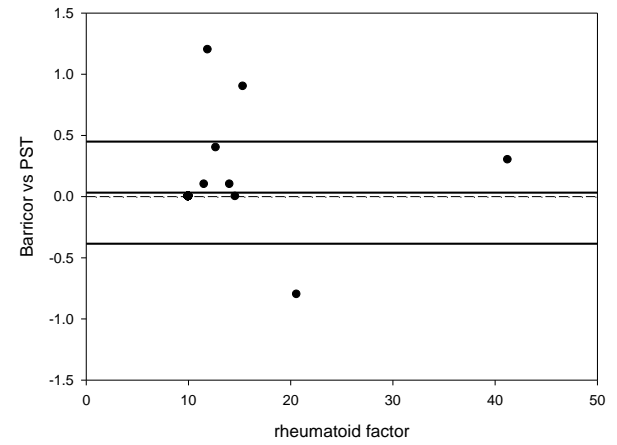
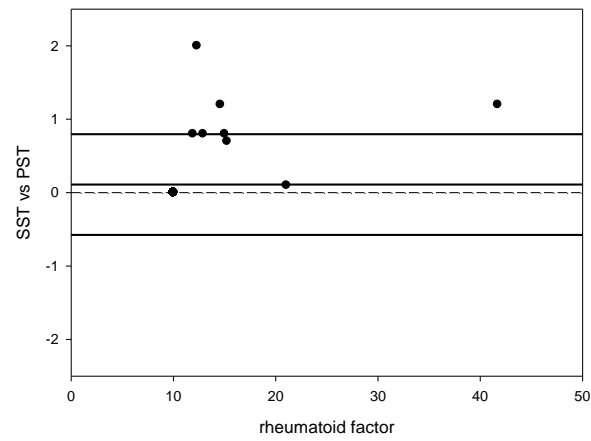
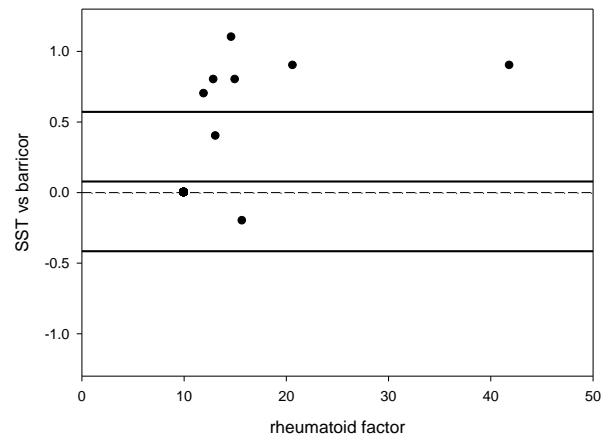
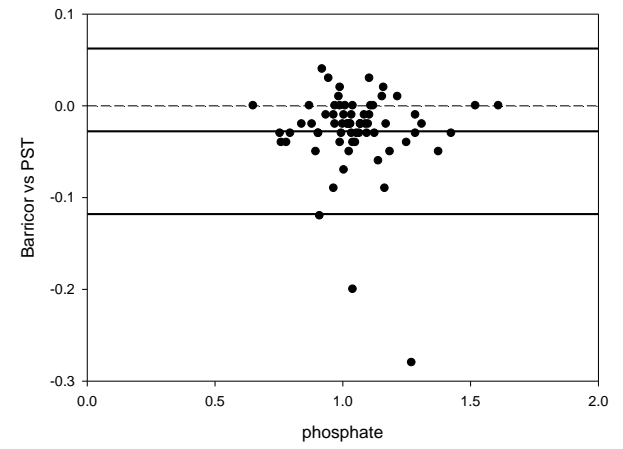
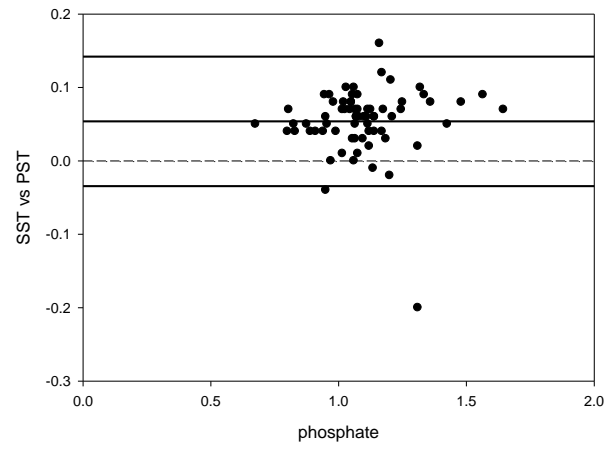
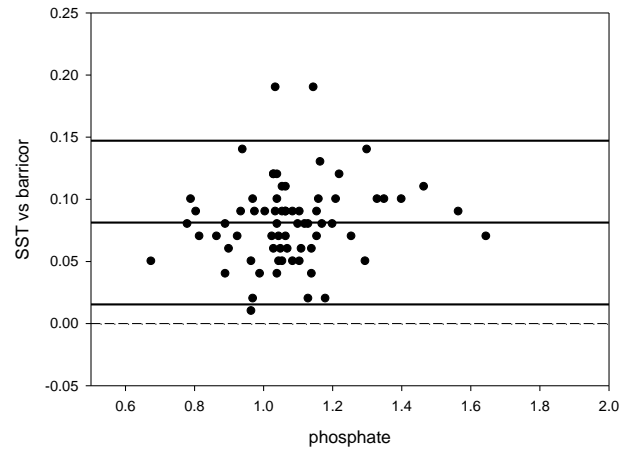


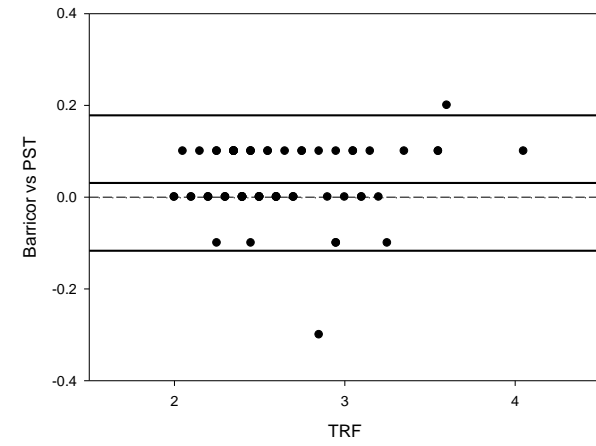
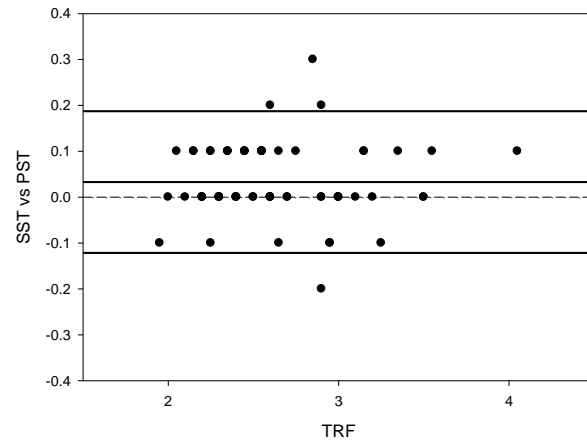
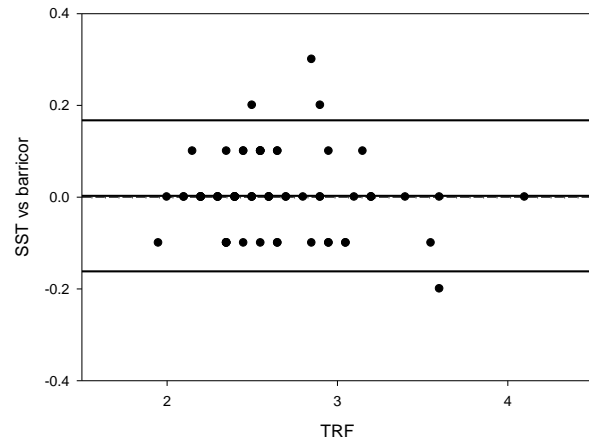
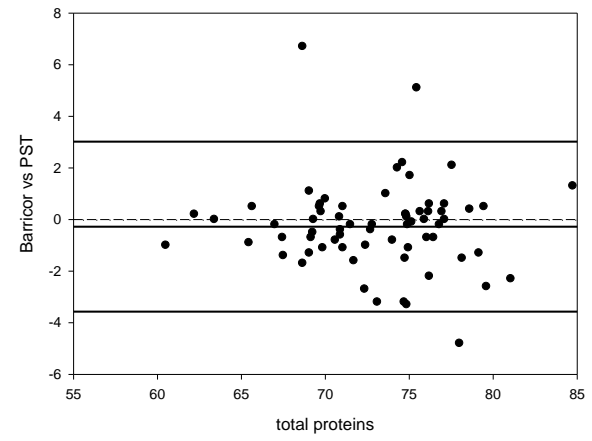
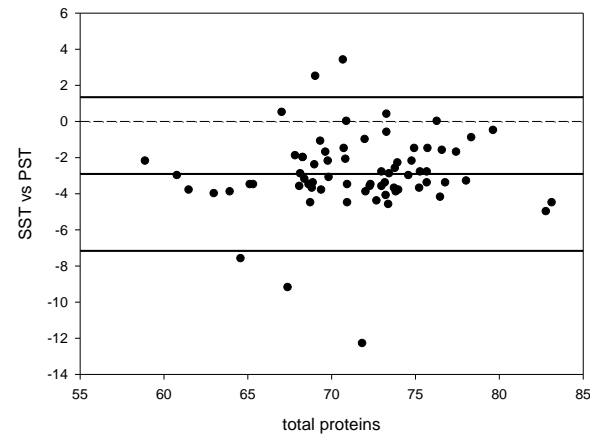
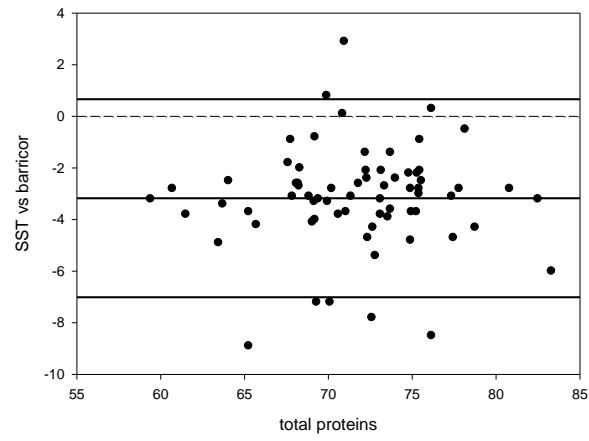


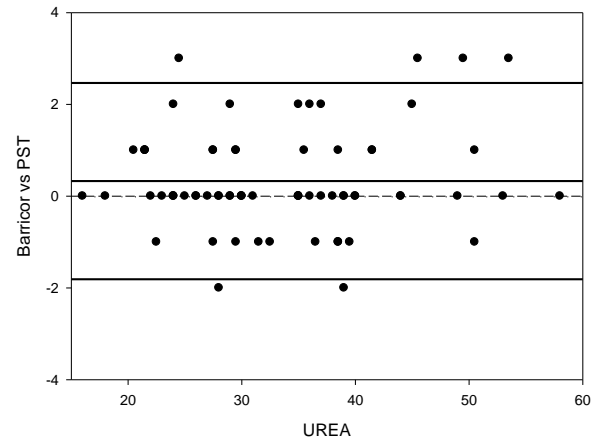
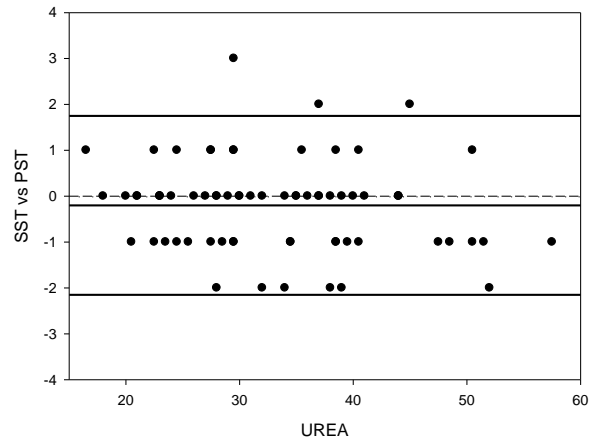
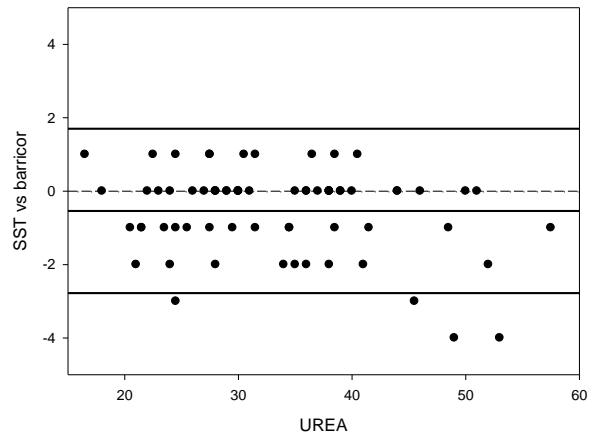
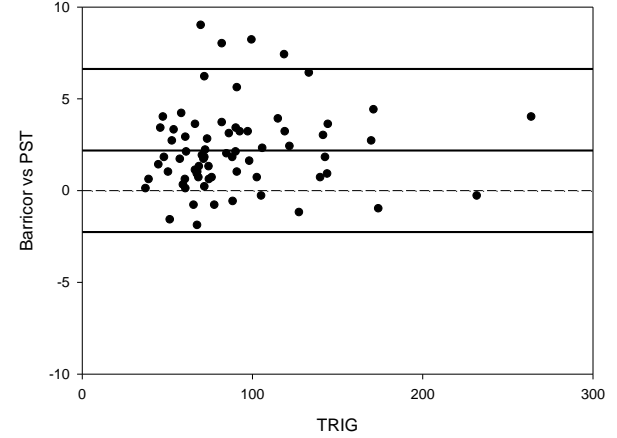
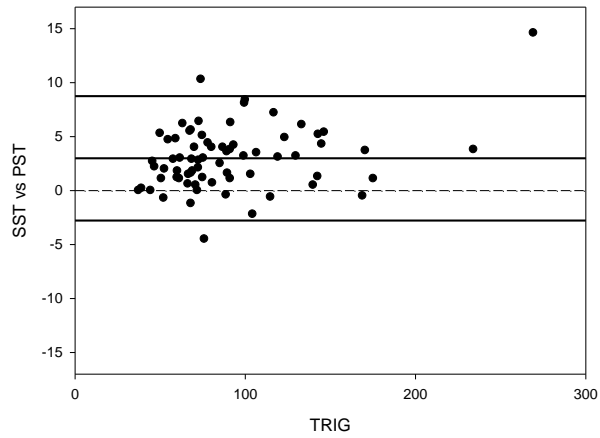
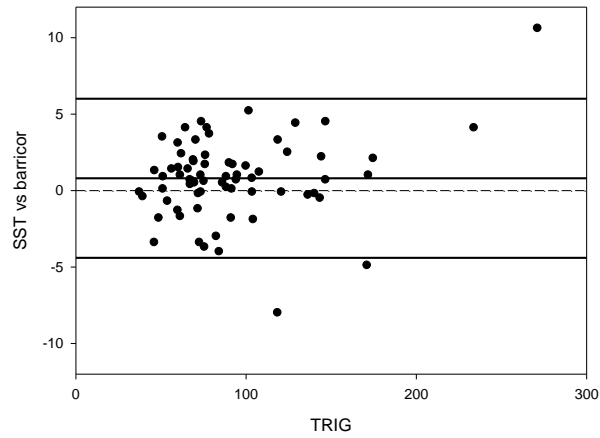


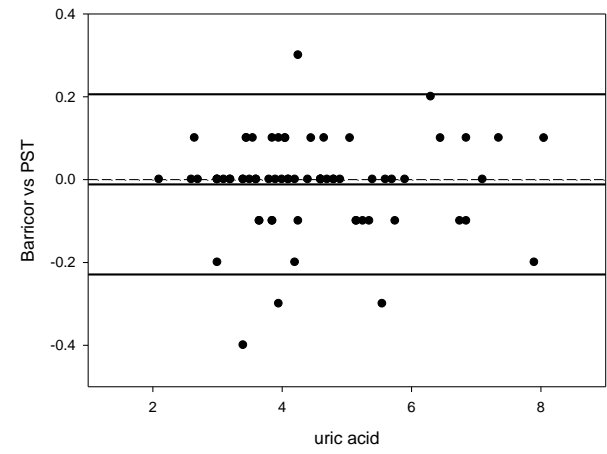
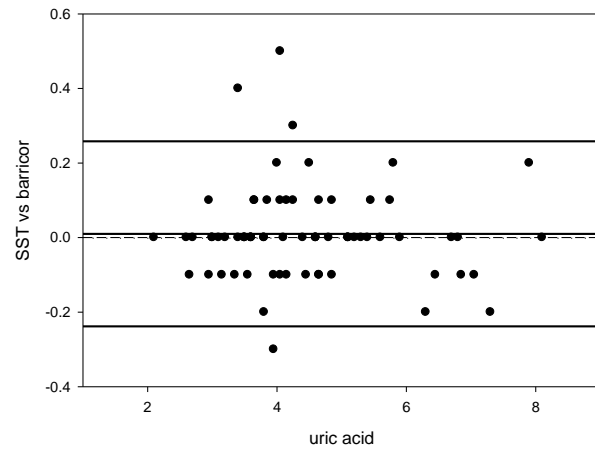
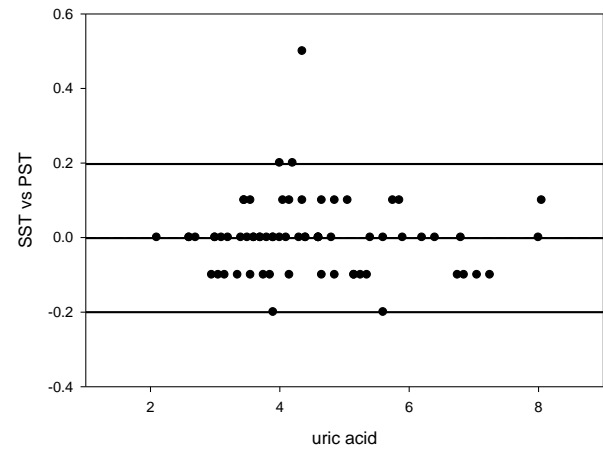




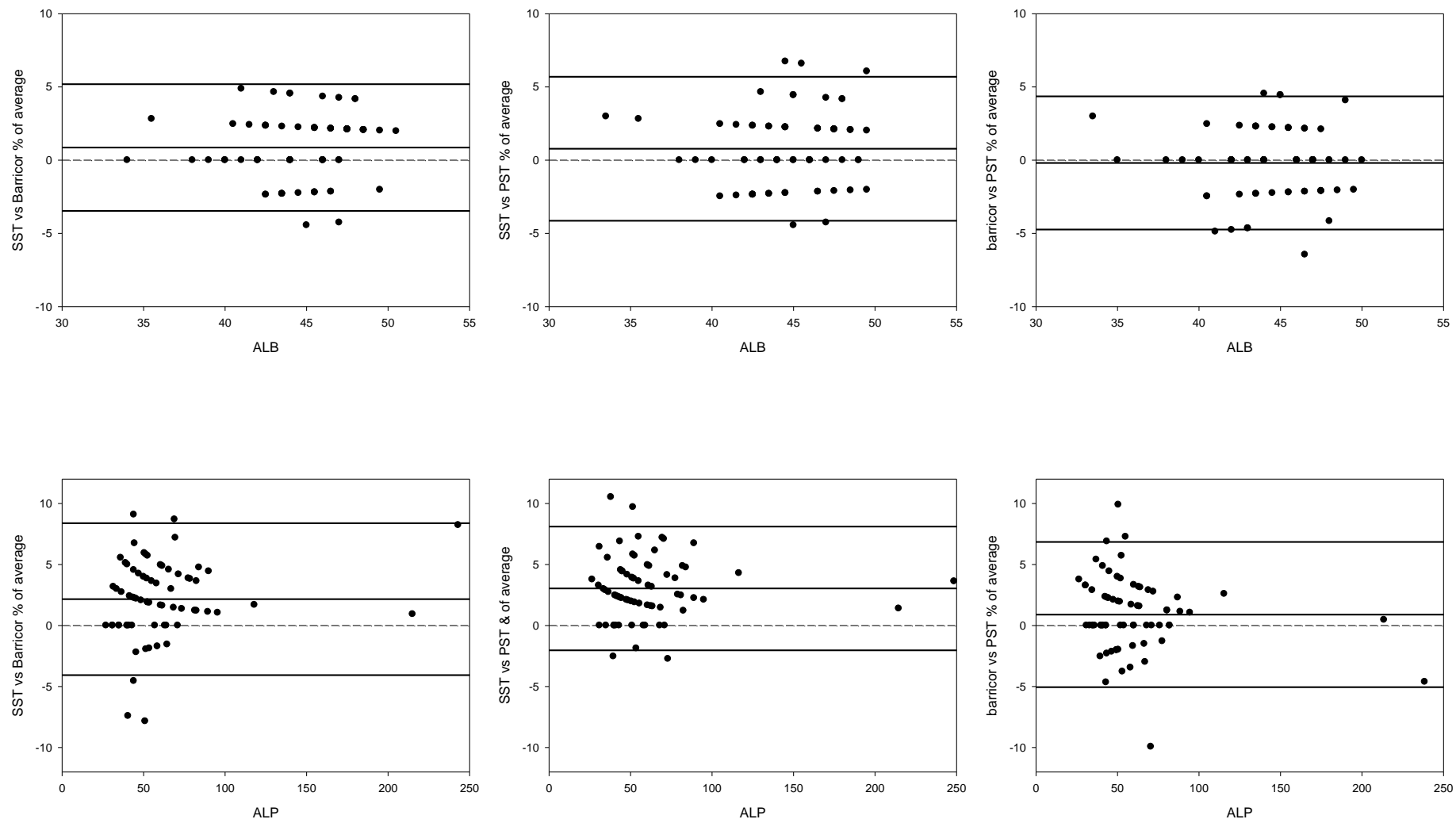




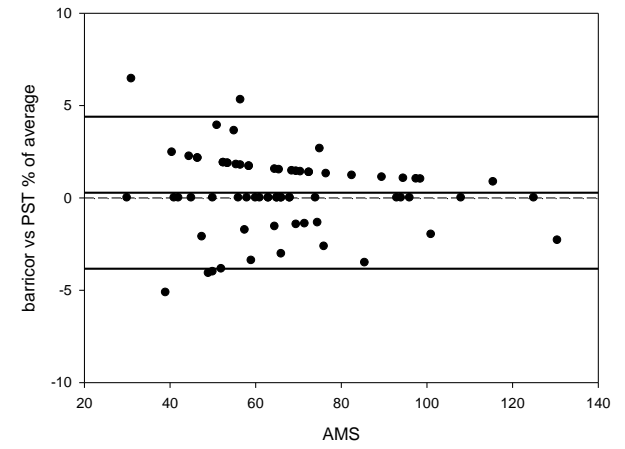
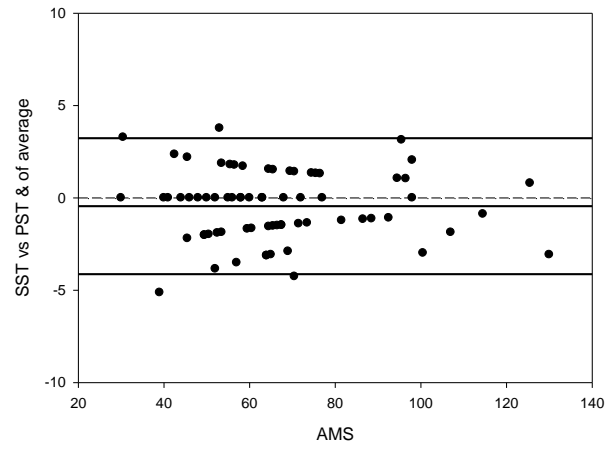
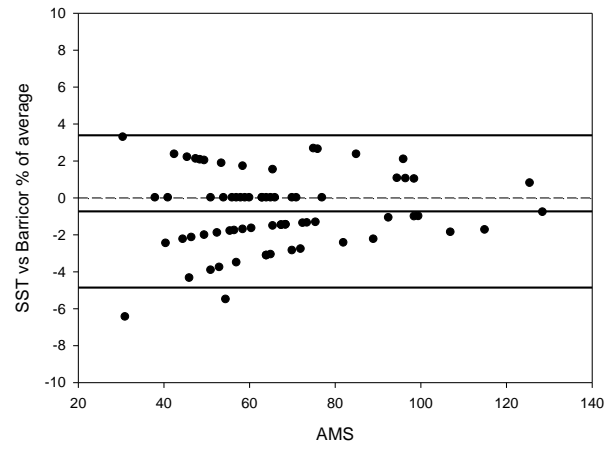
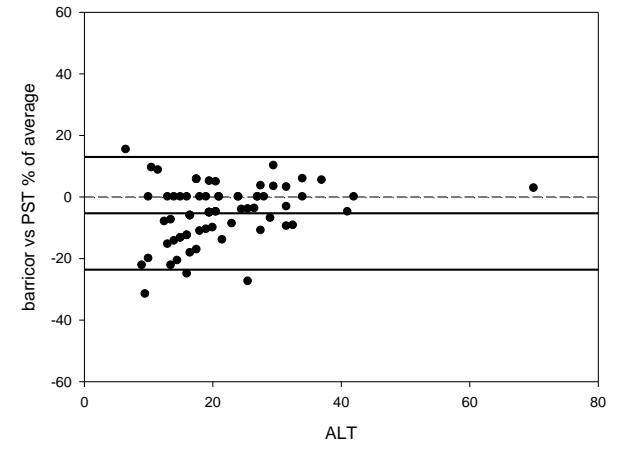
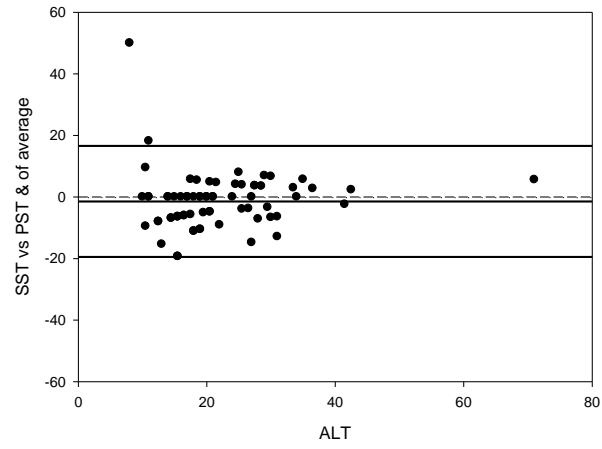
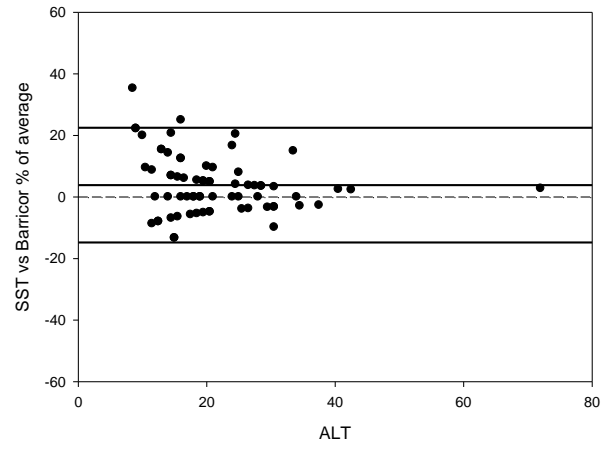


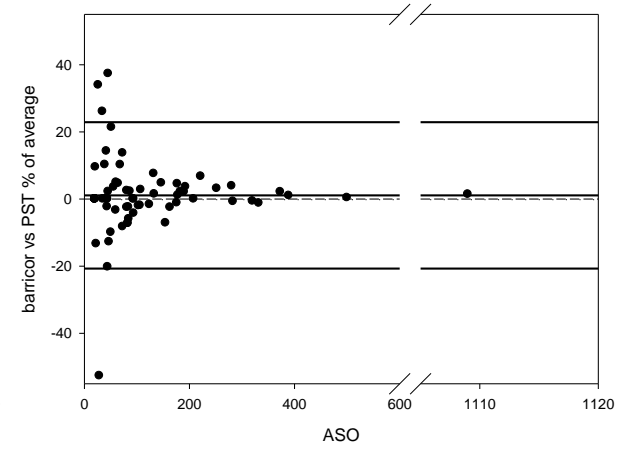
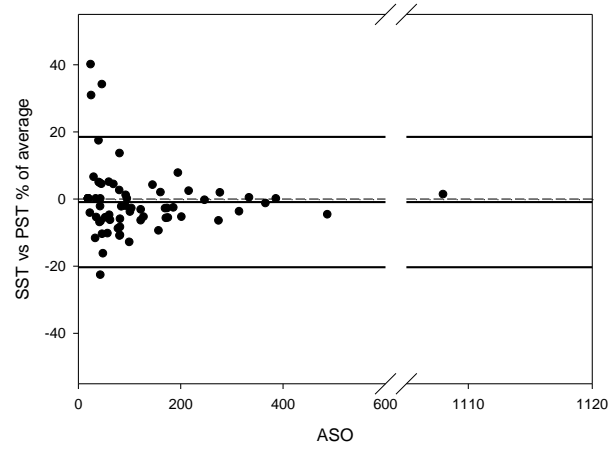
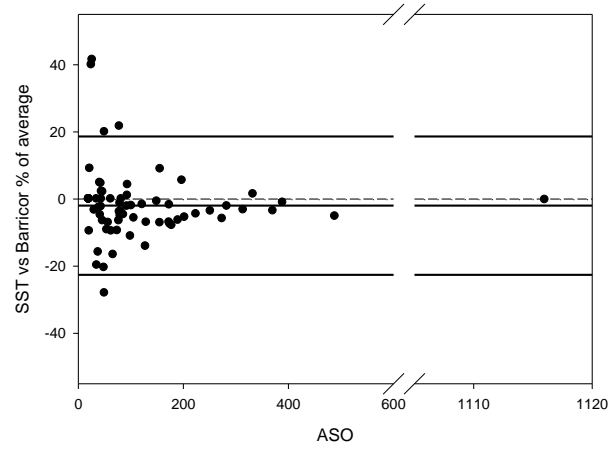
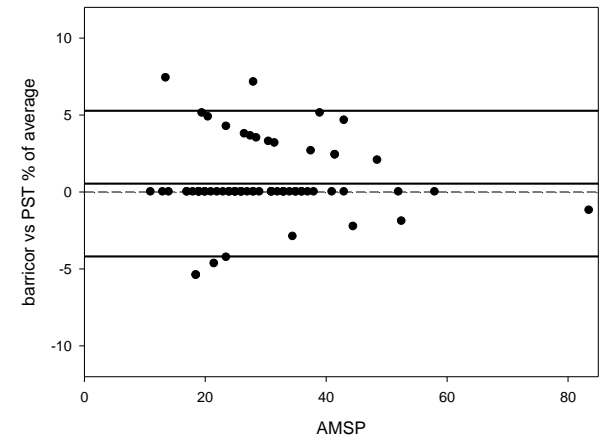
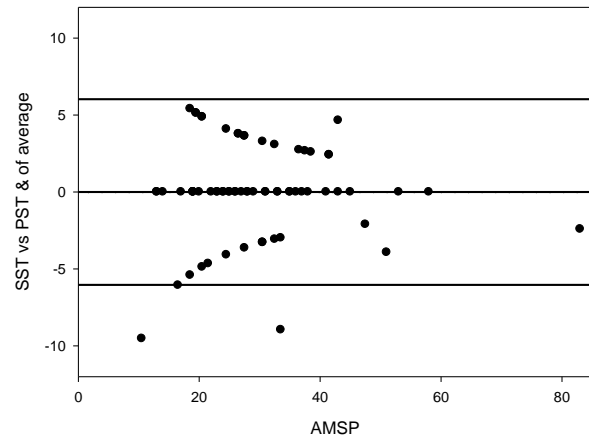
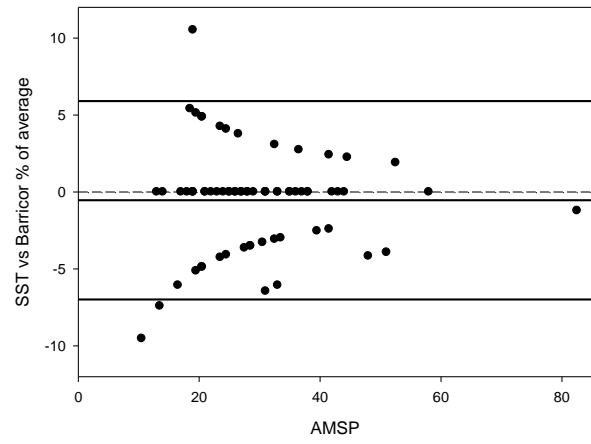


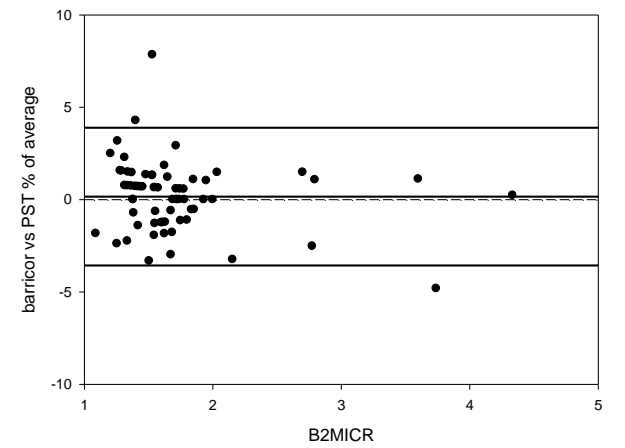
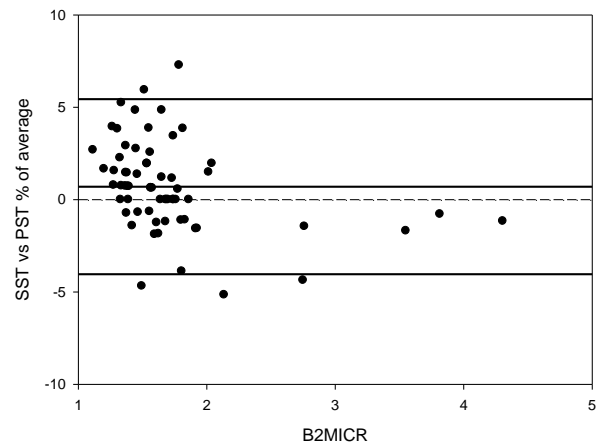
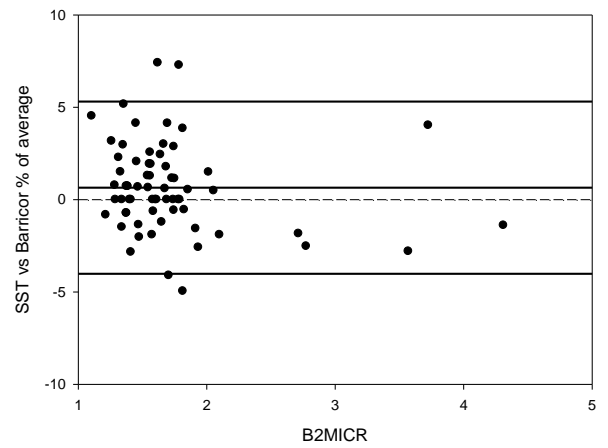
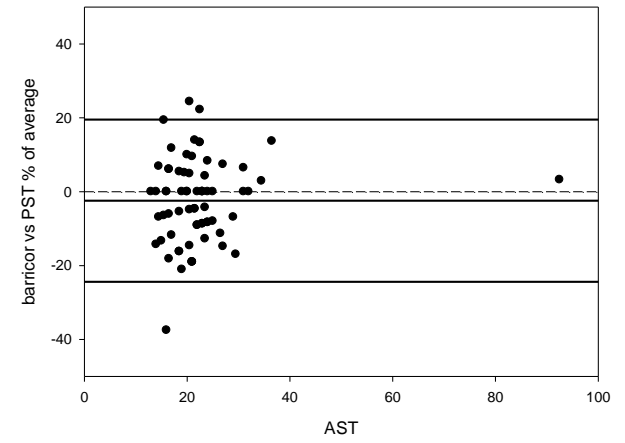
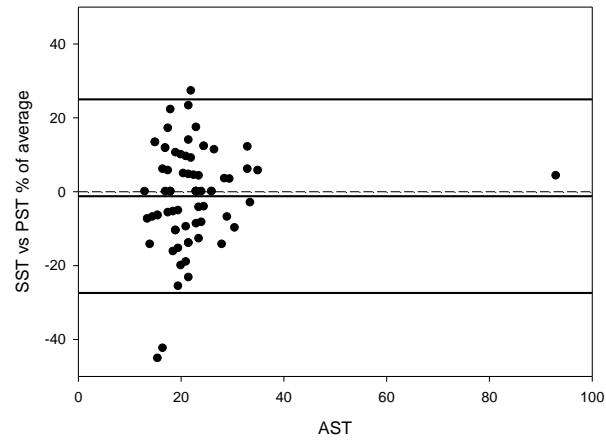
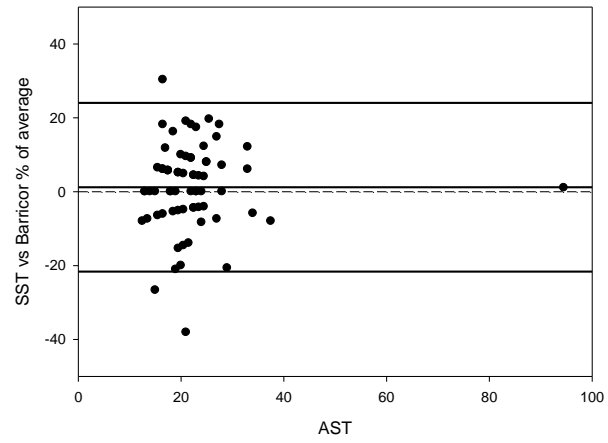
**Figure S1B:** B&A plots for chemical analytes: the pair value differences were expressed as percentage.

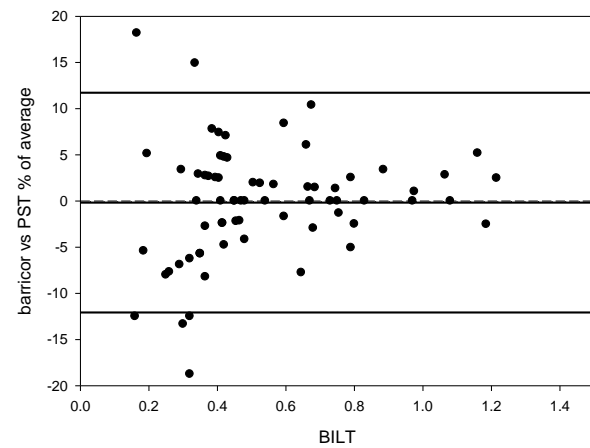
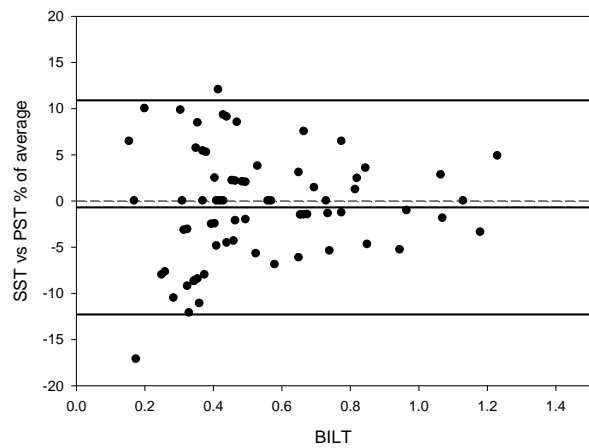
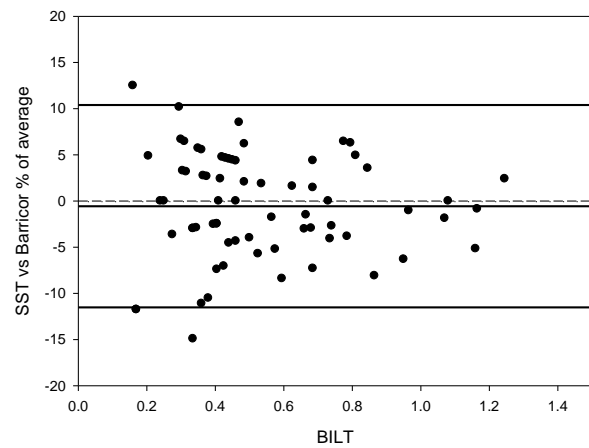
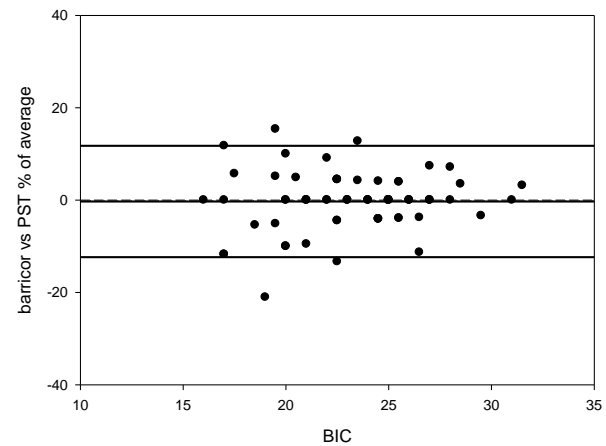
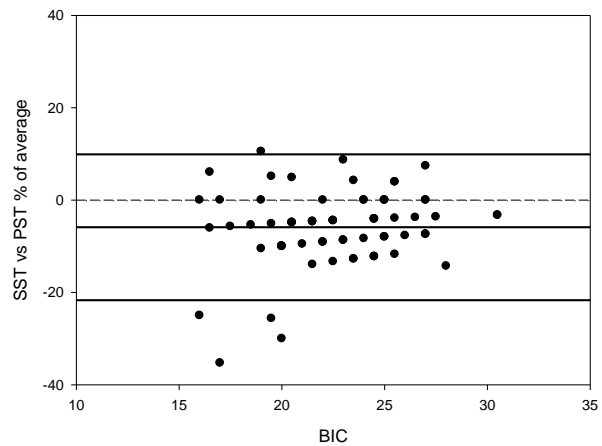
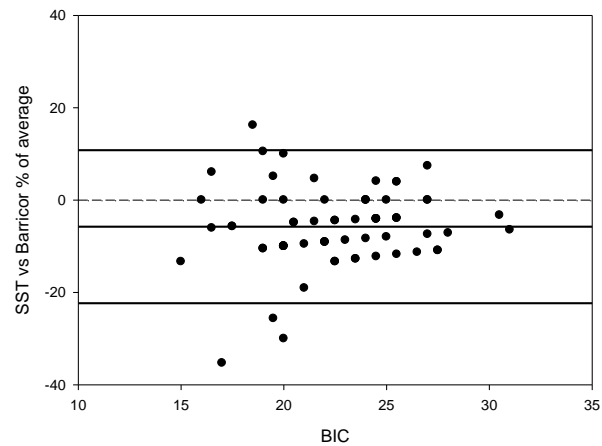


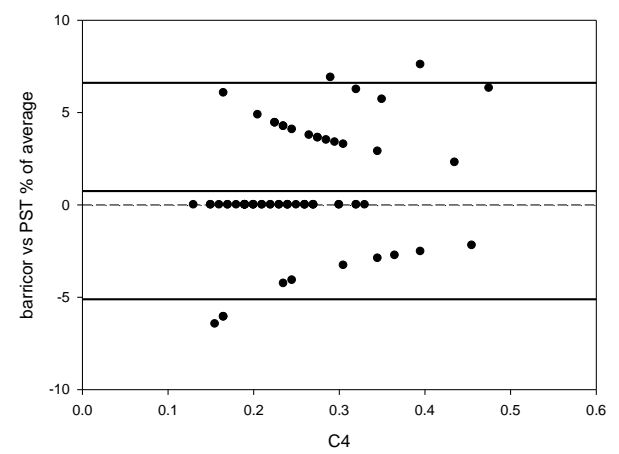
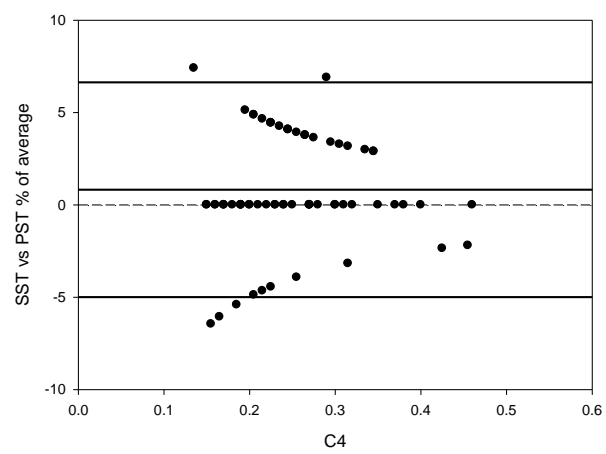
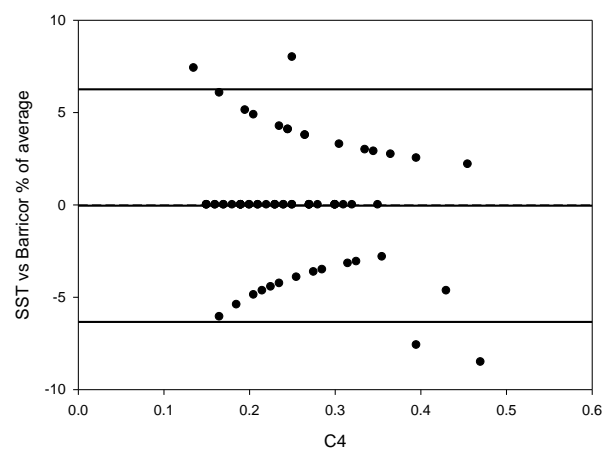
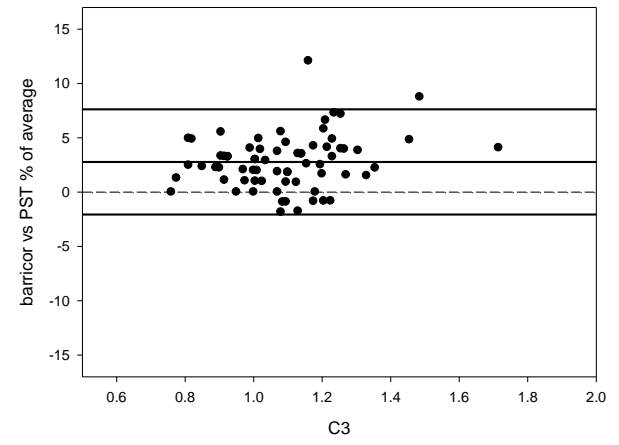
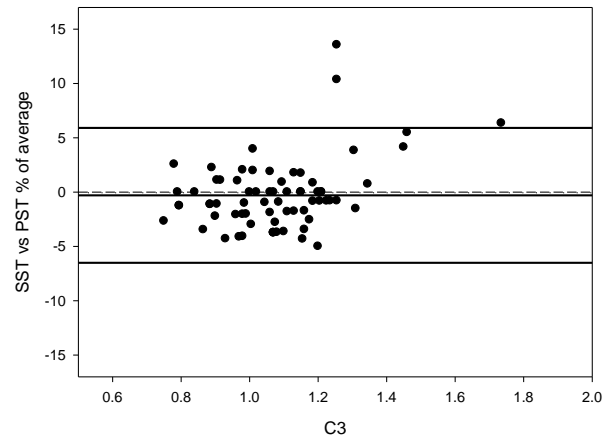
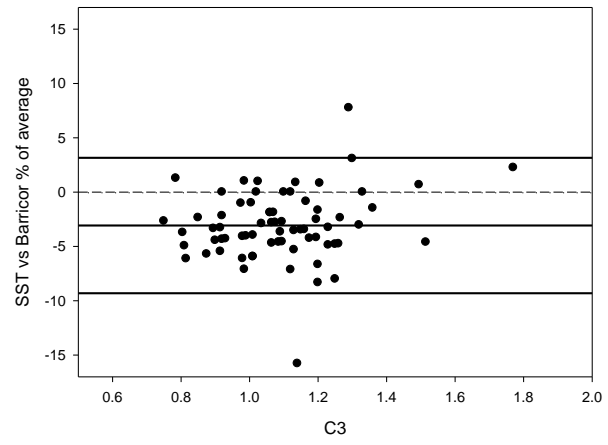


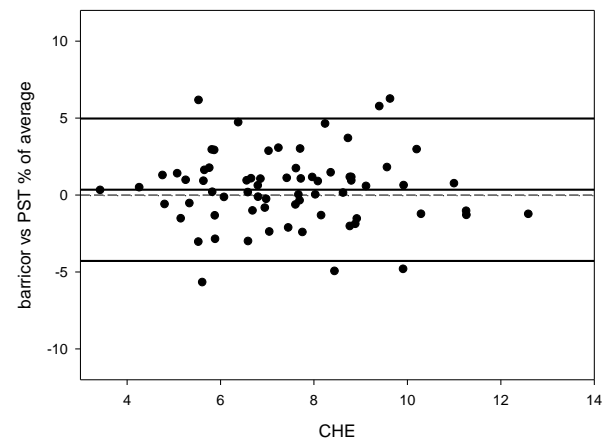
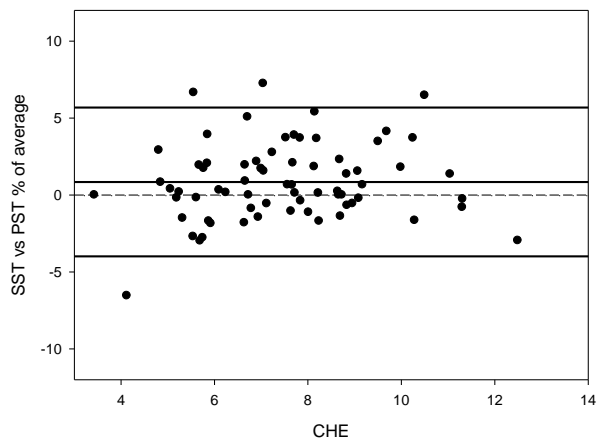
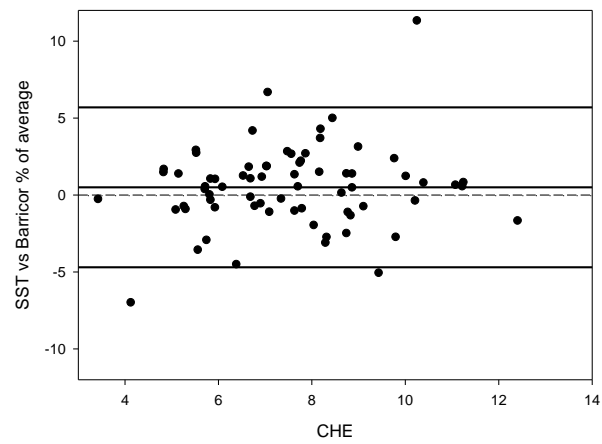
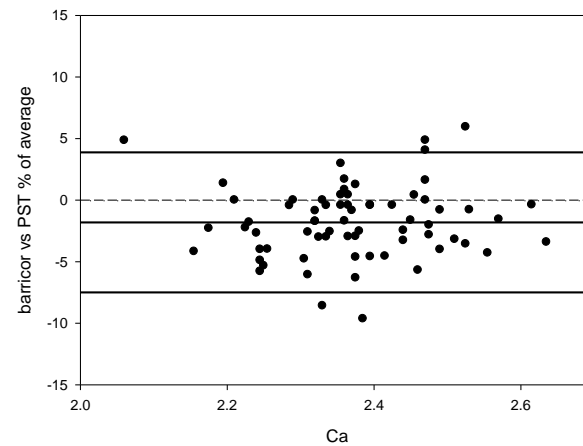
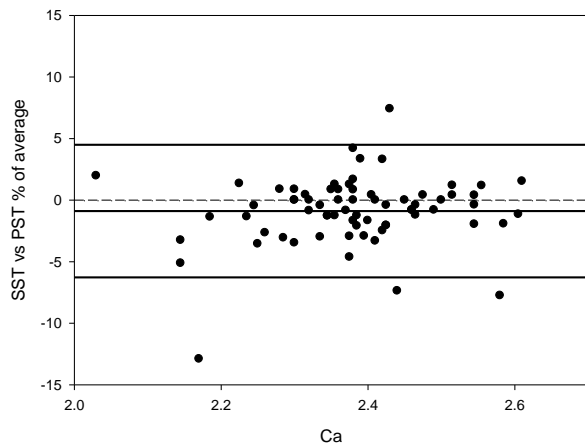
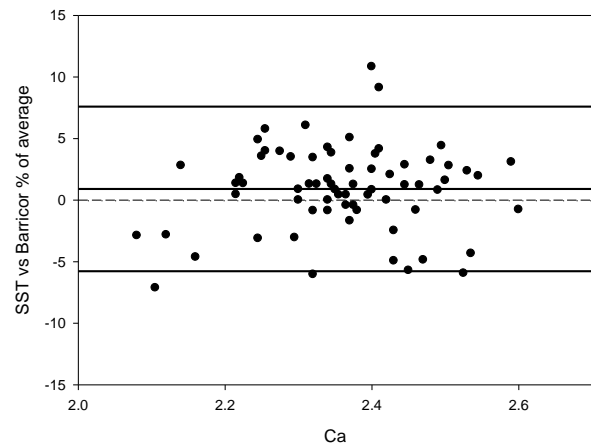


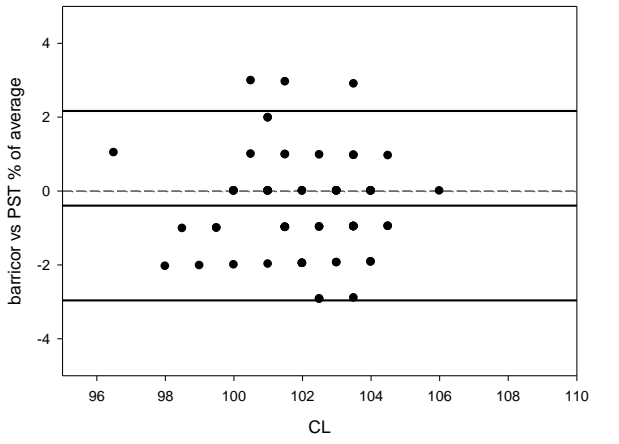
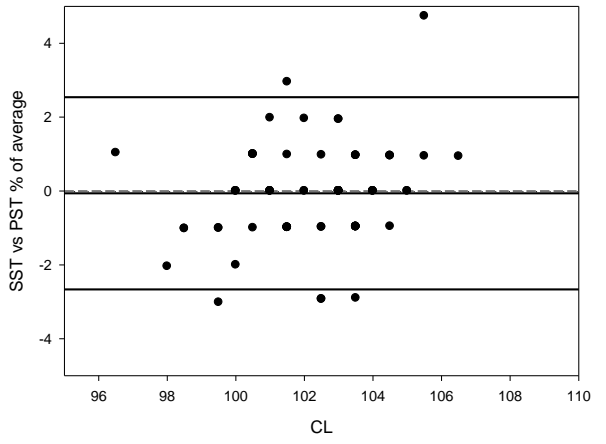
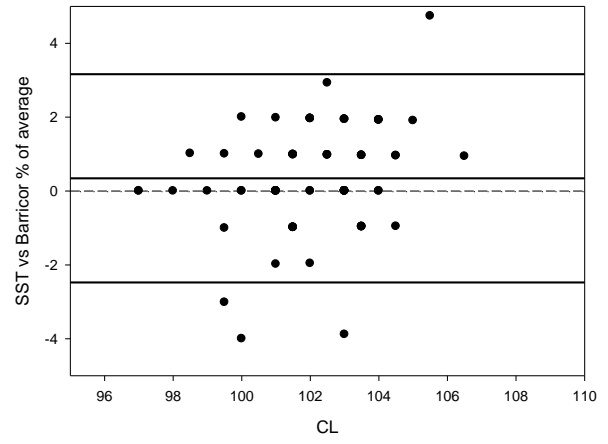
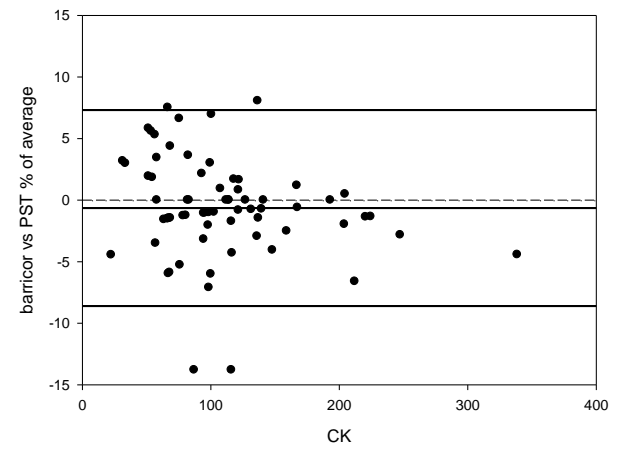
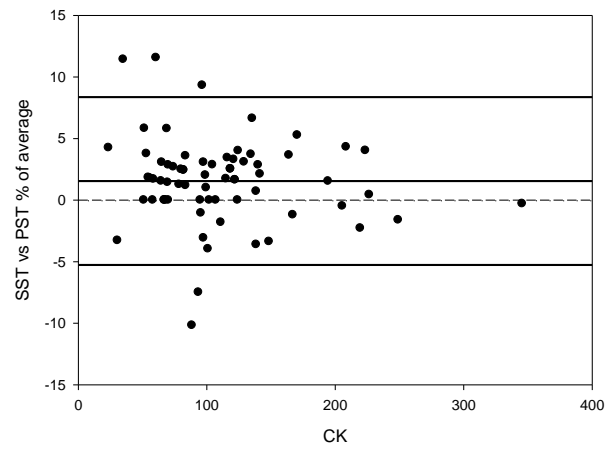
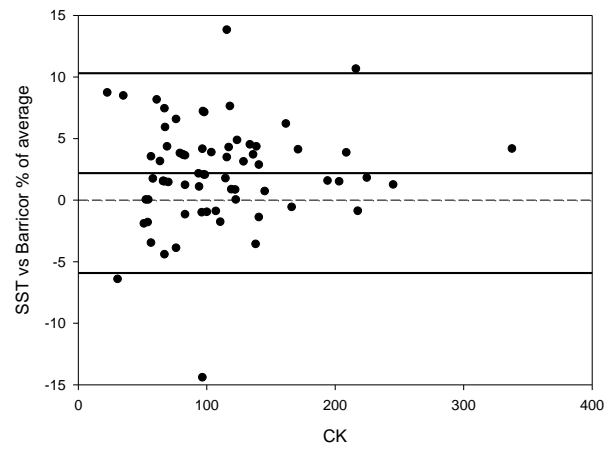


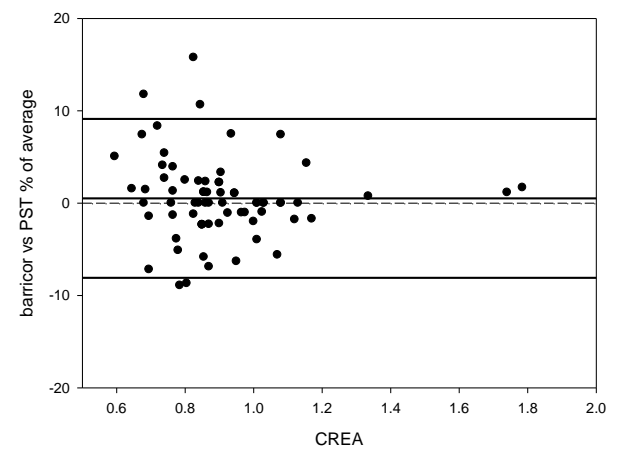
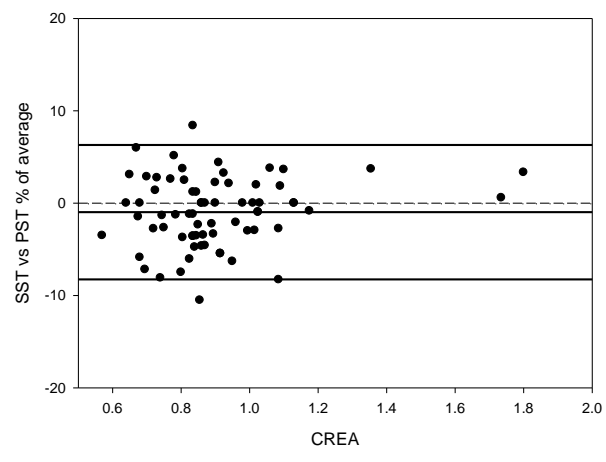
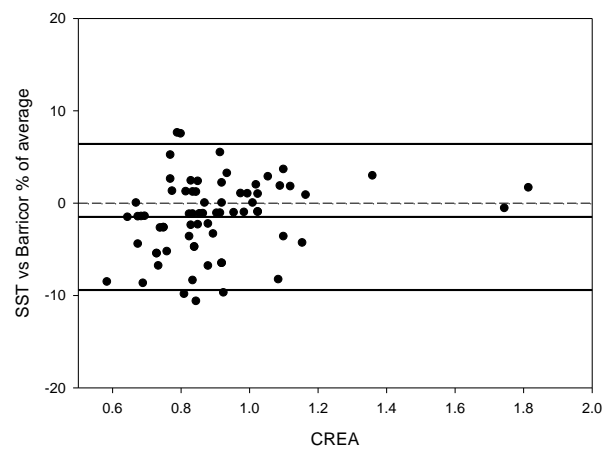
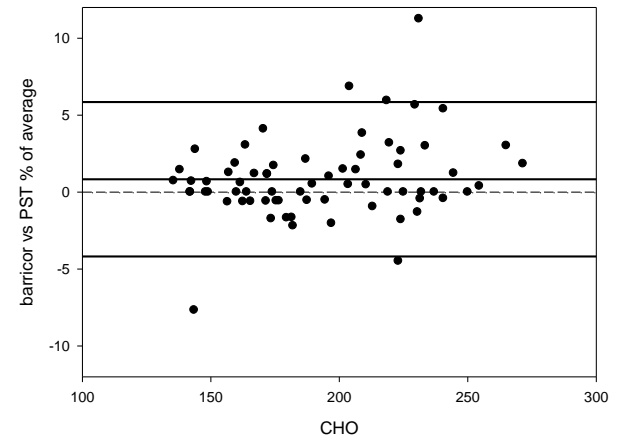
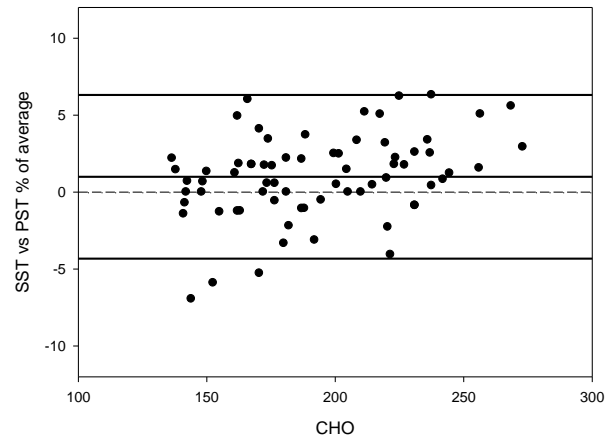
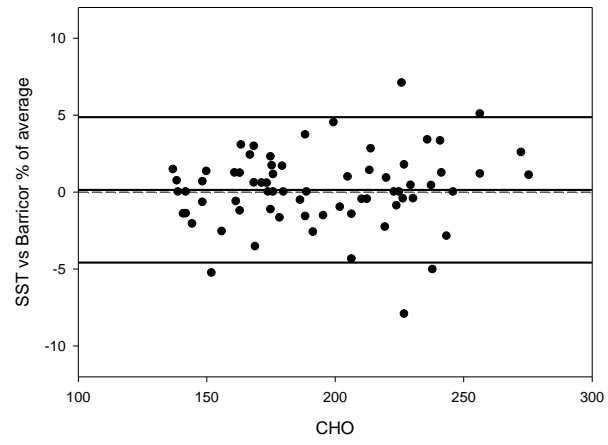




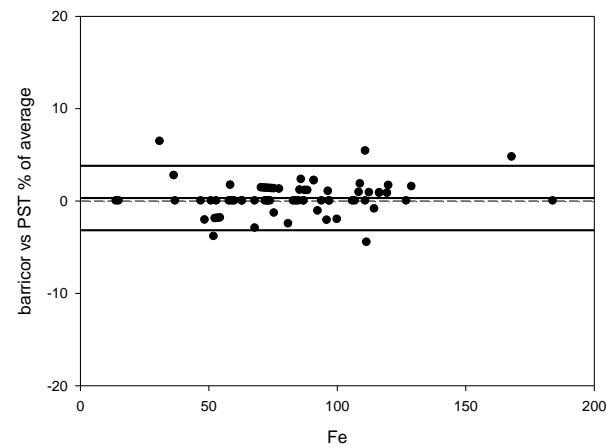
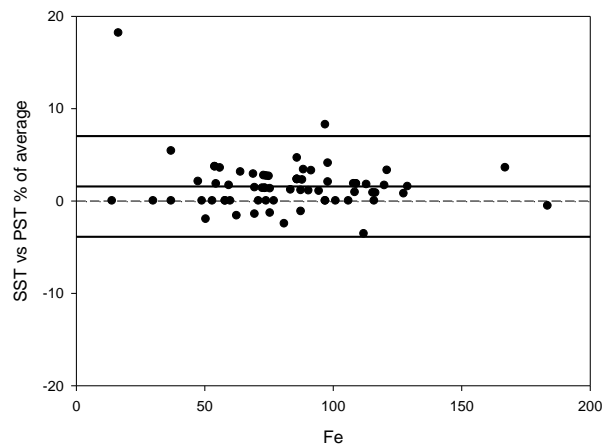
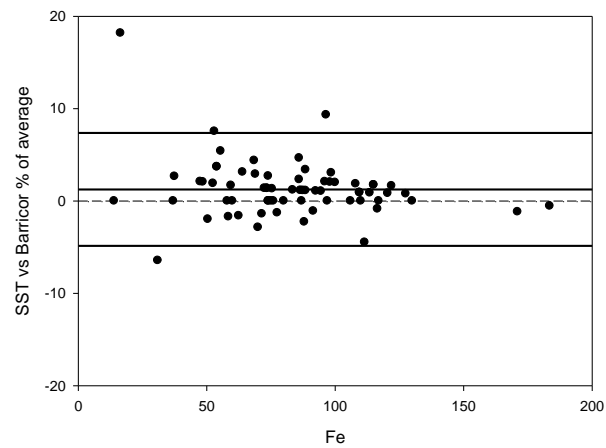
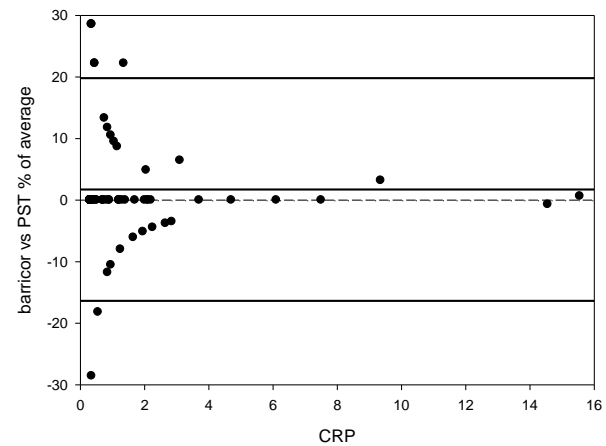
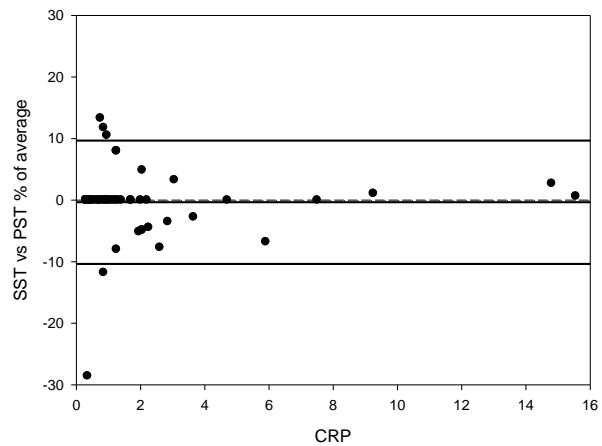
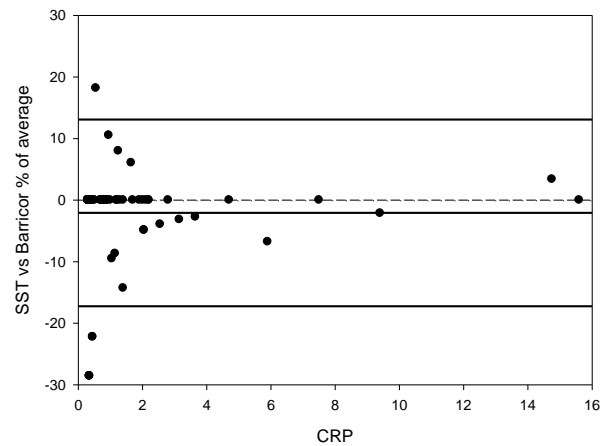


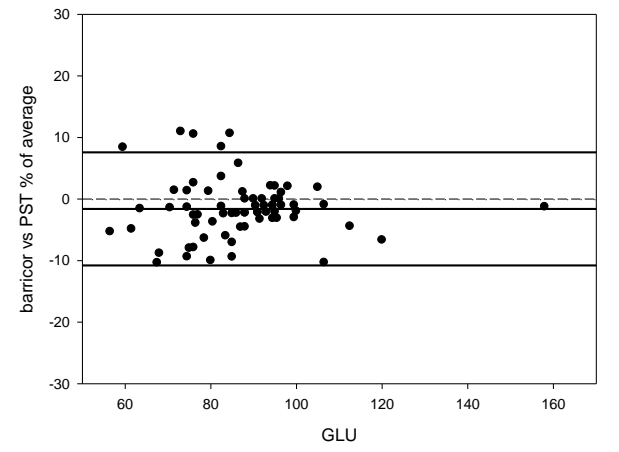
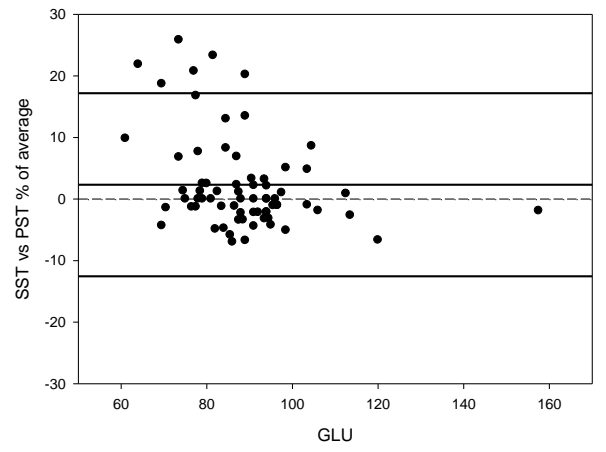
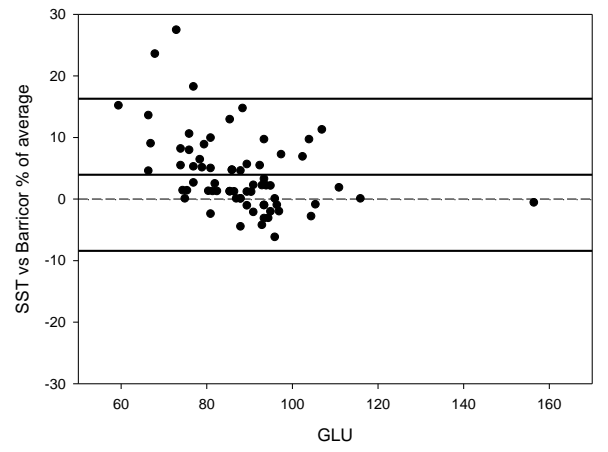
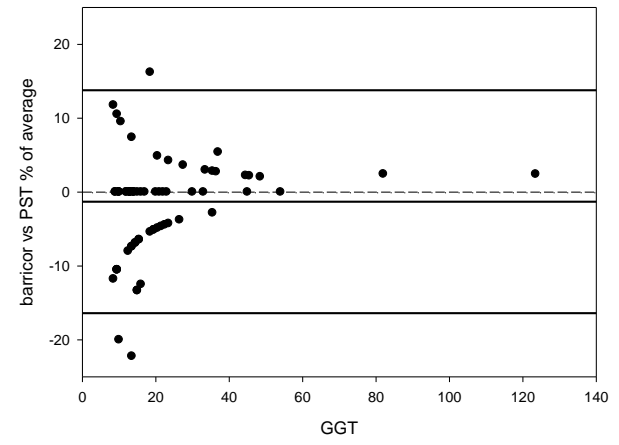
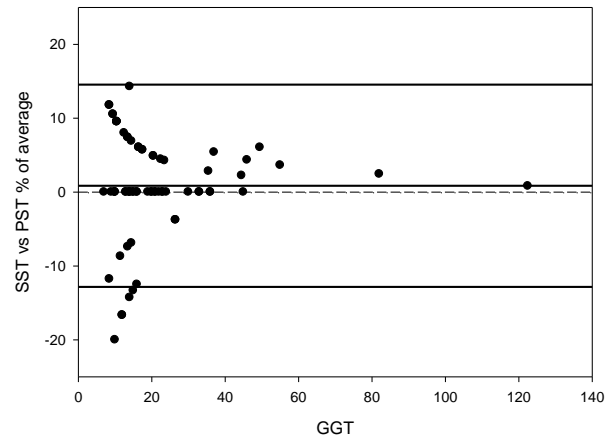
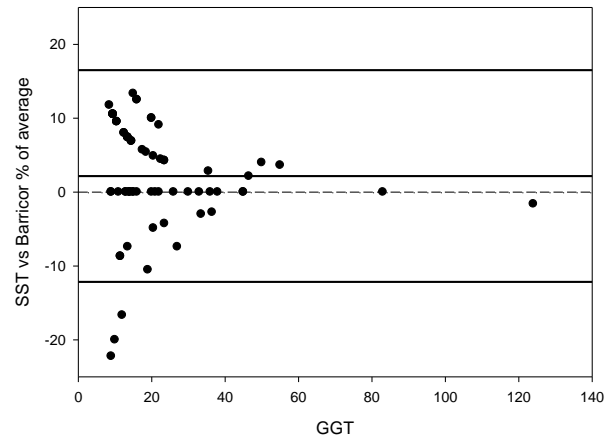


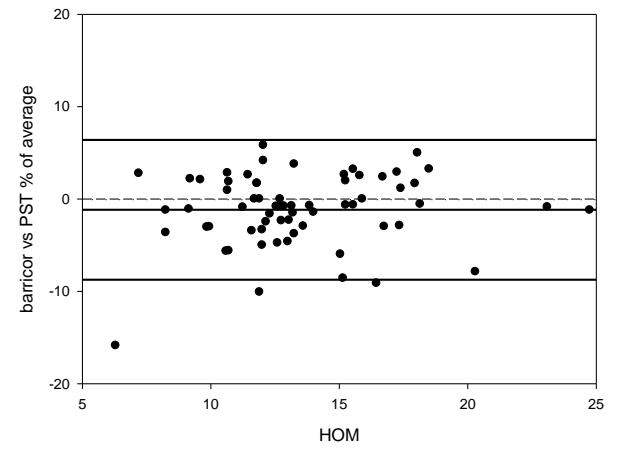
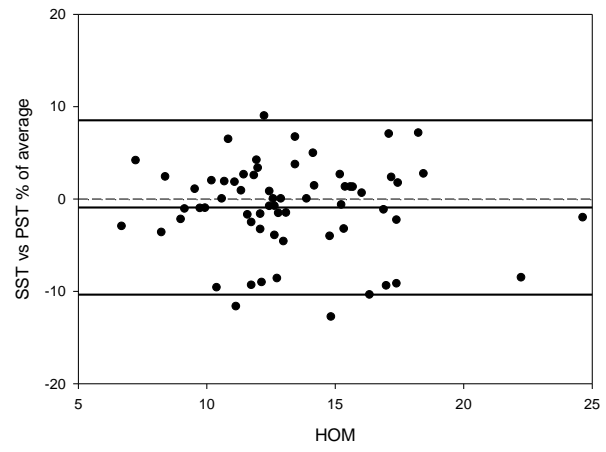
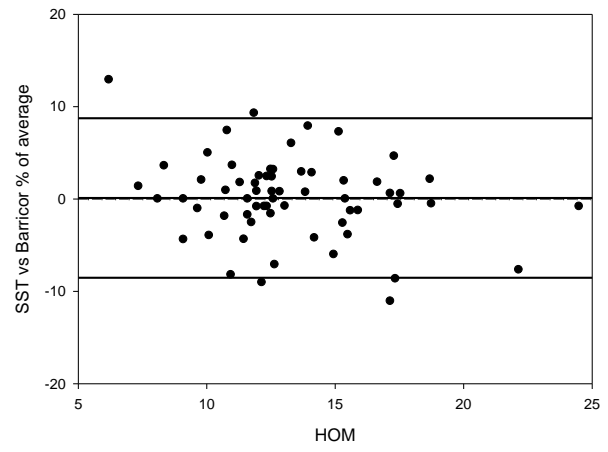
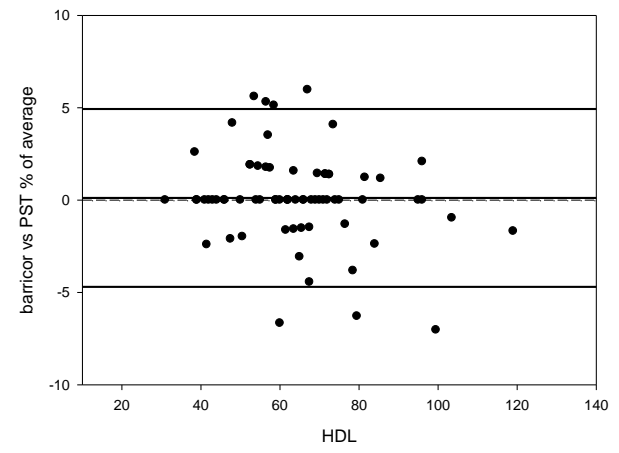
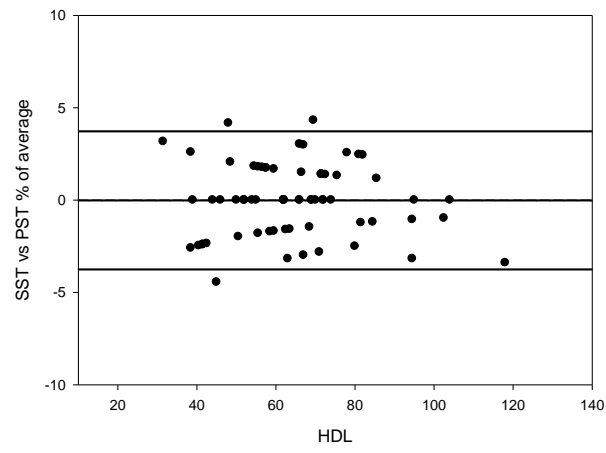
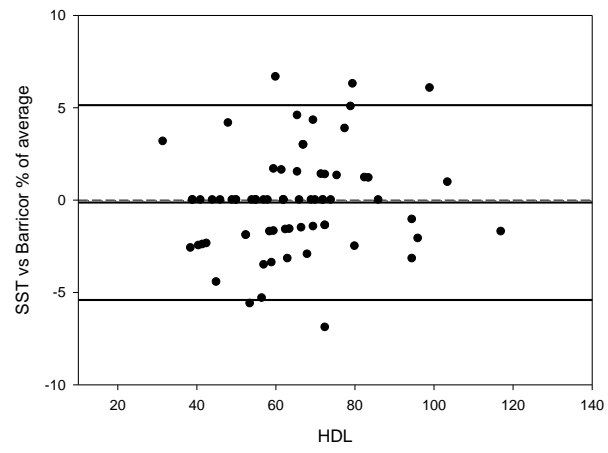


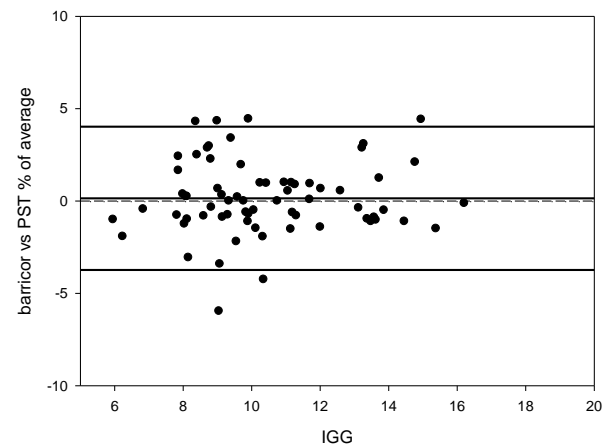
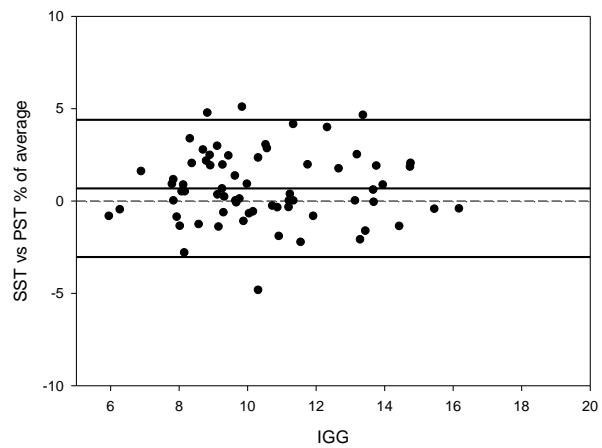
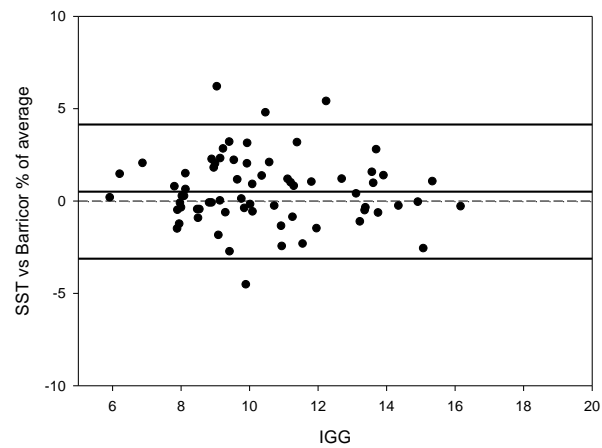
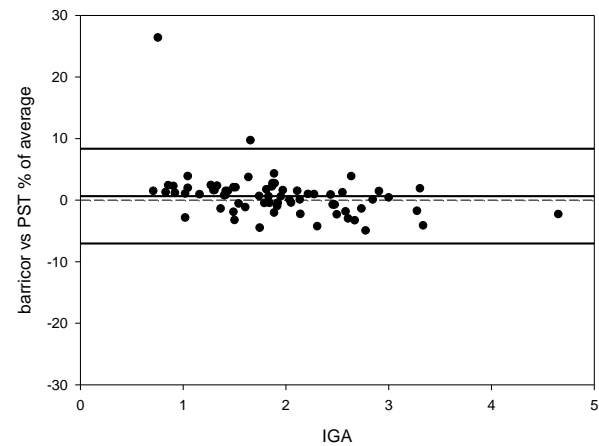
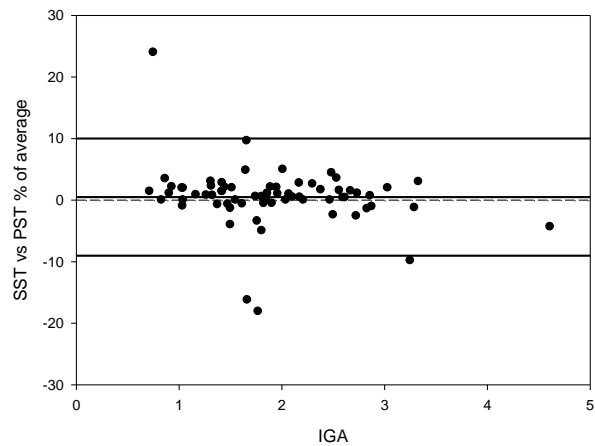
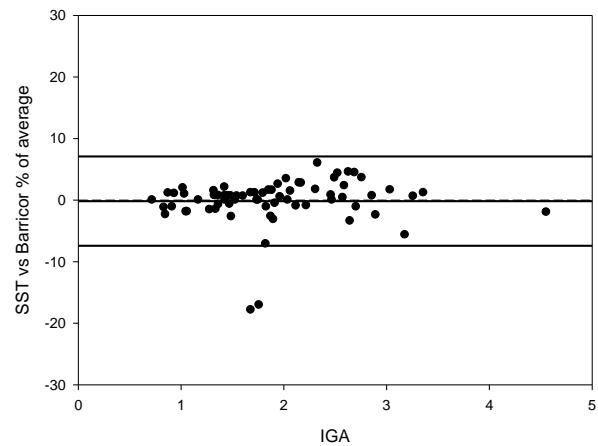


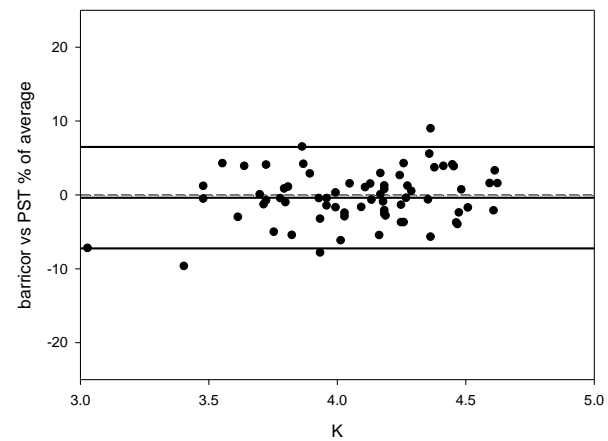
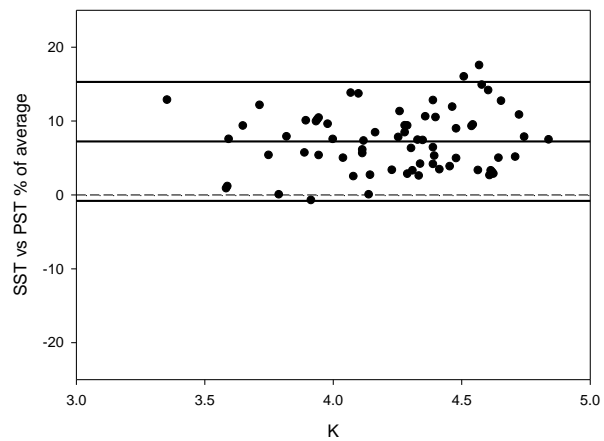
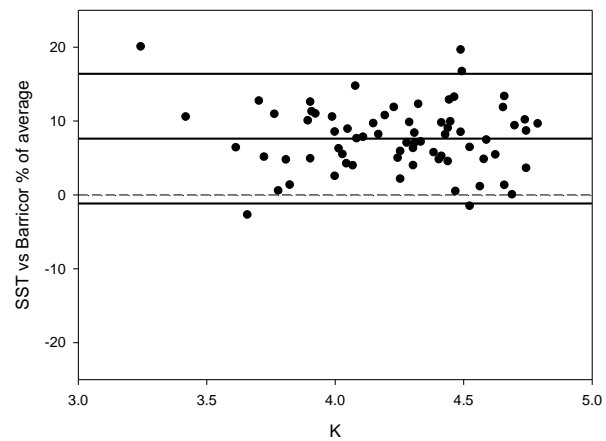
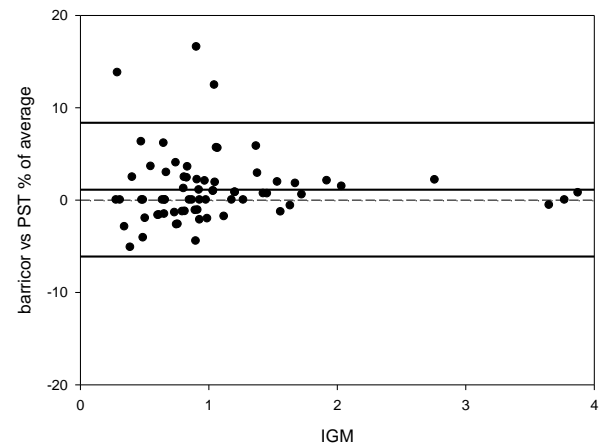
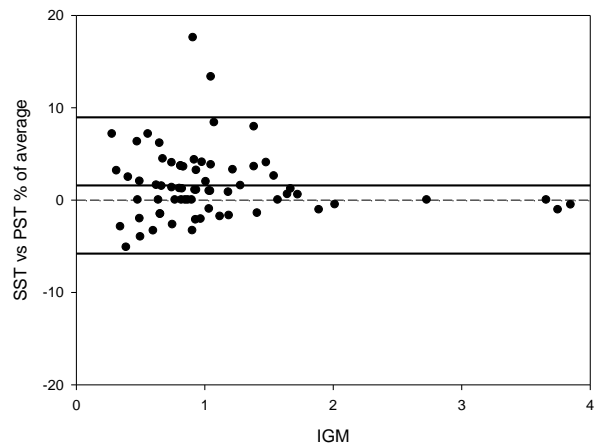
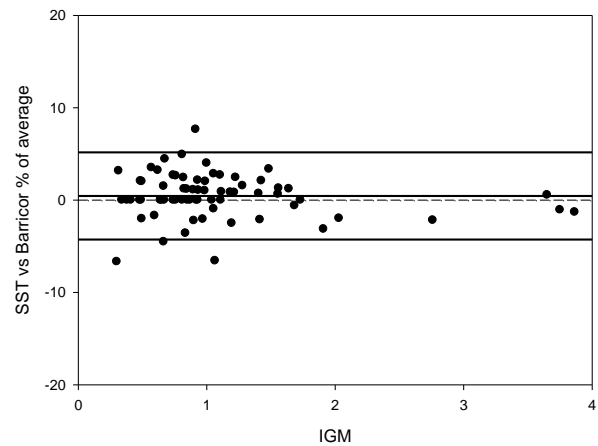


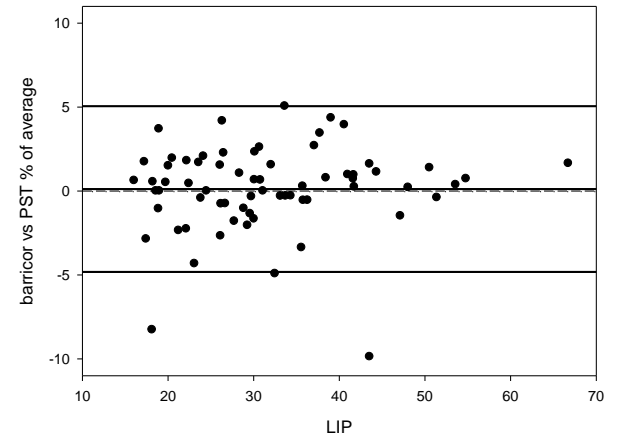
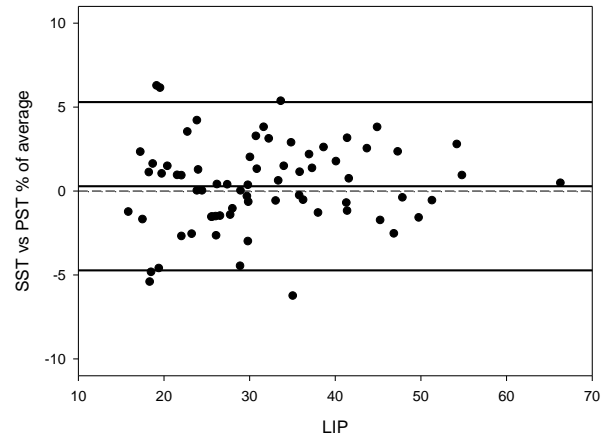
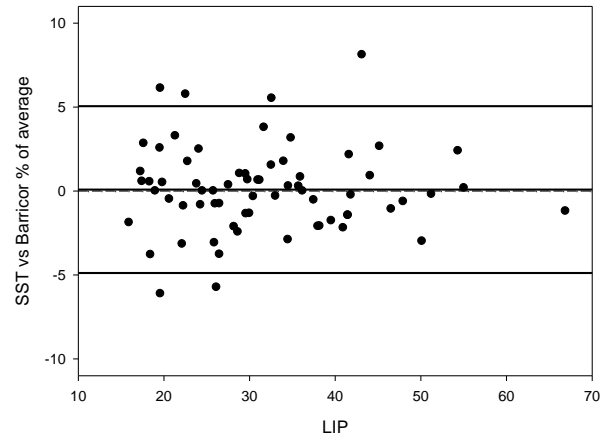
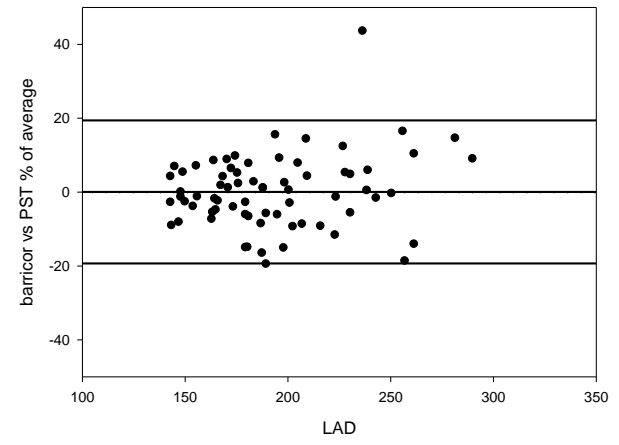
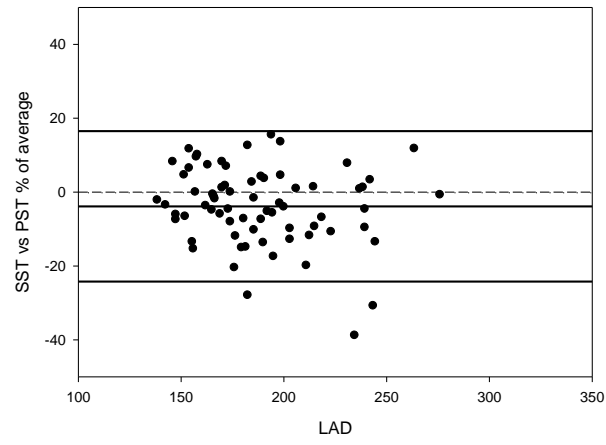
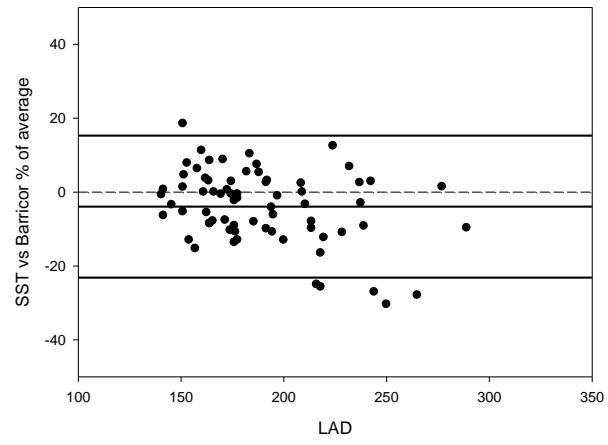


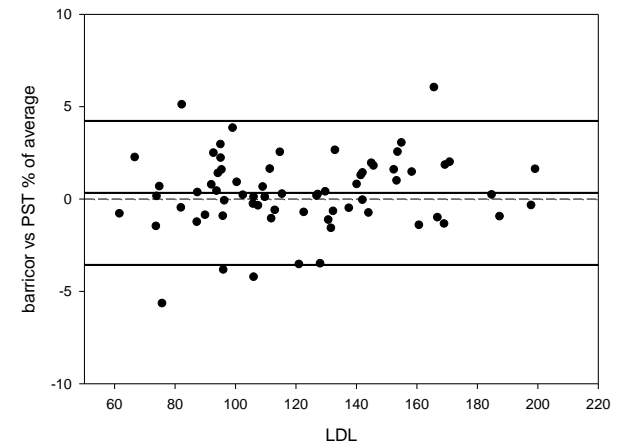
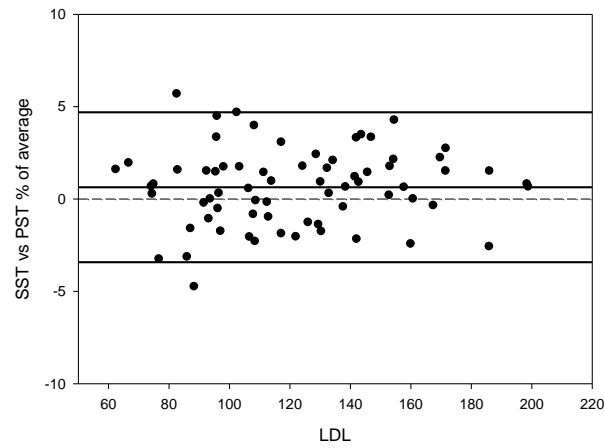
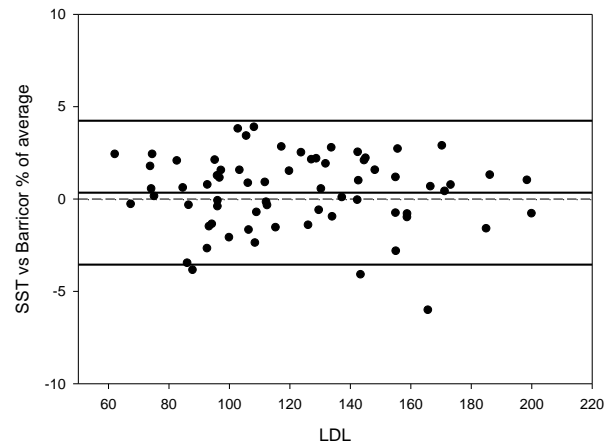
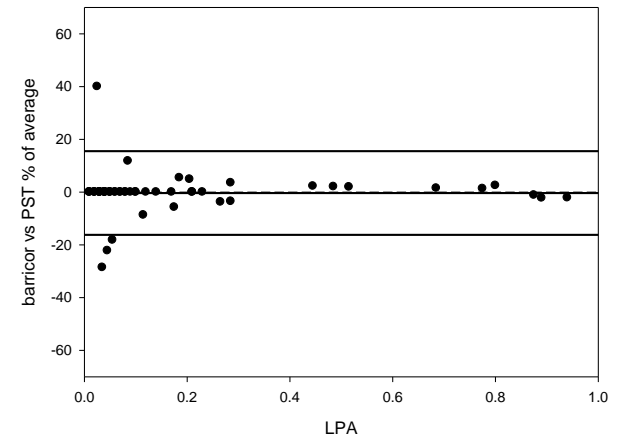
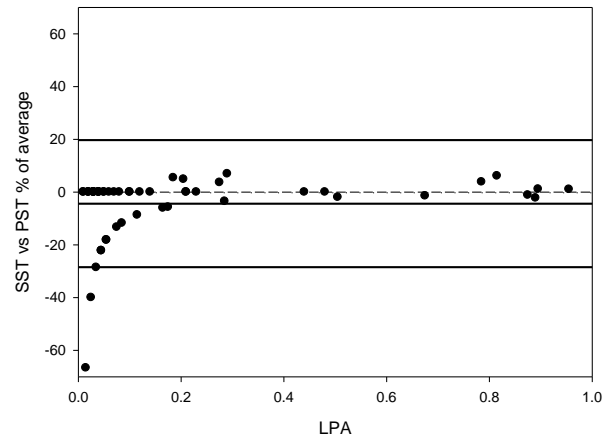
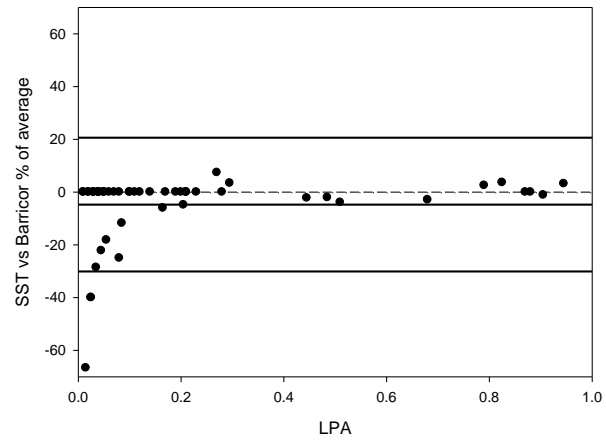


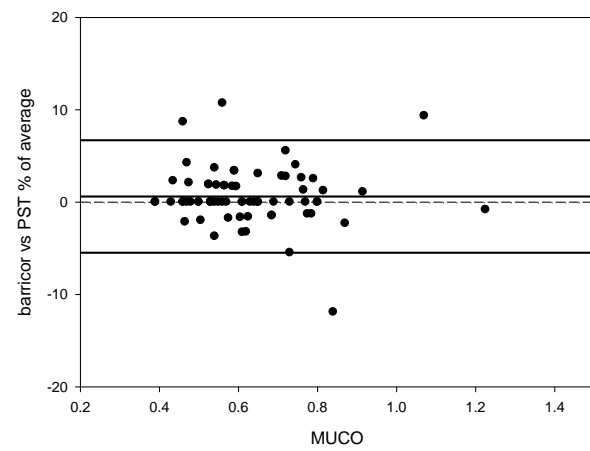
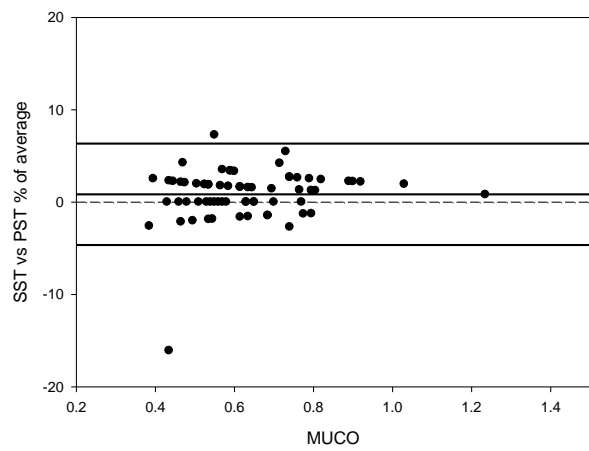
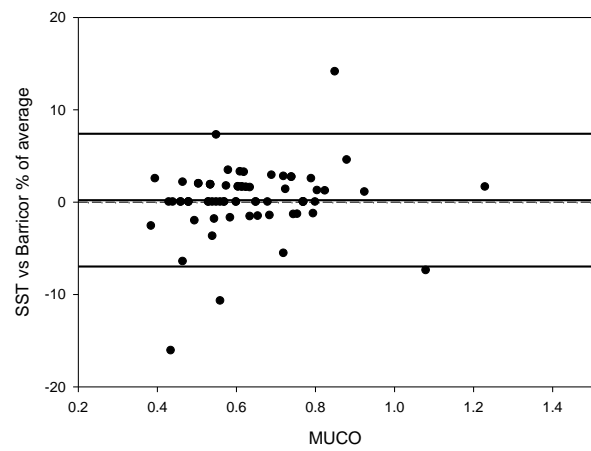
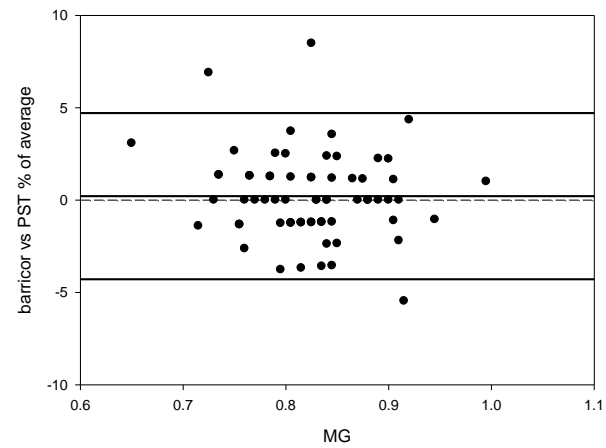
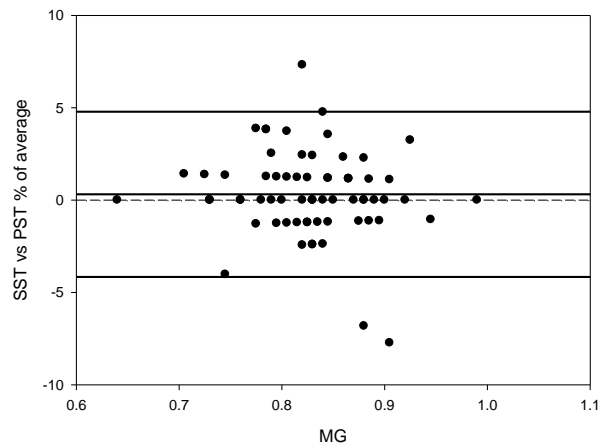
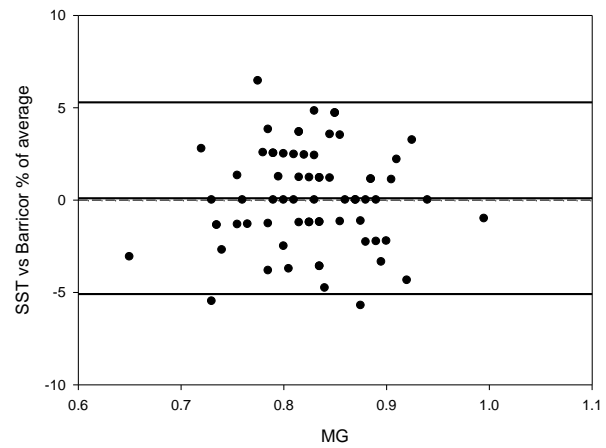




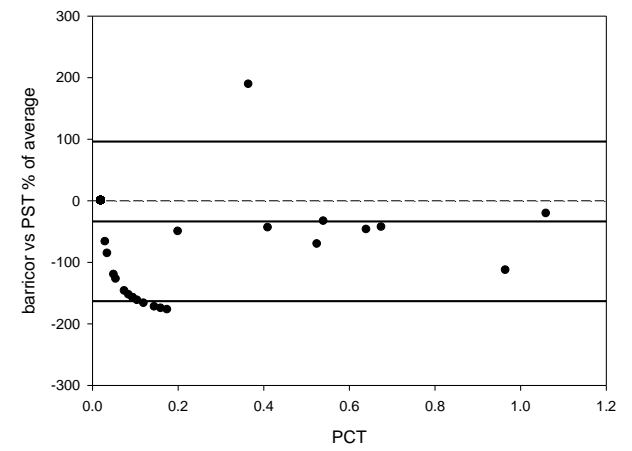
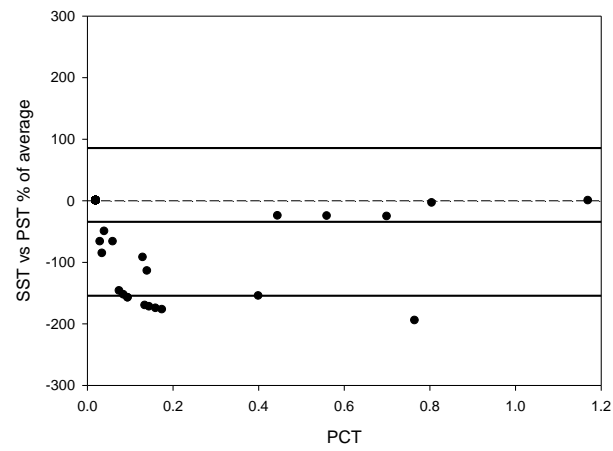
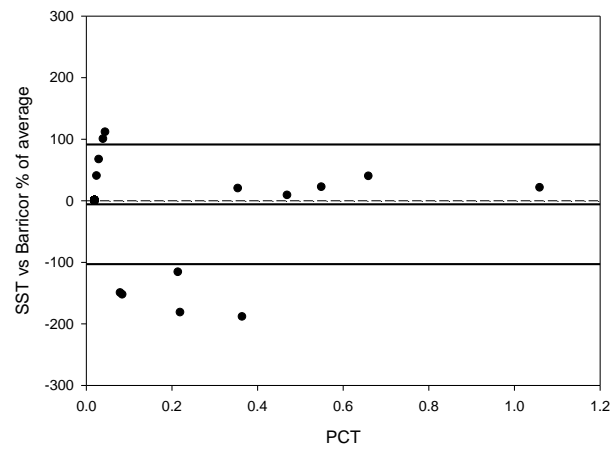
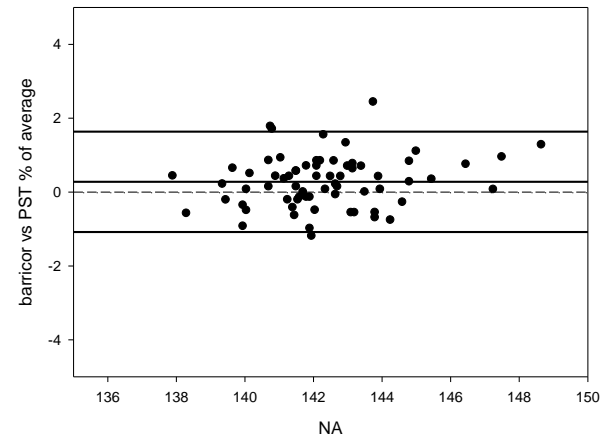
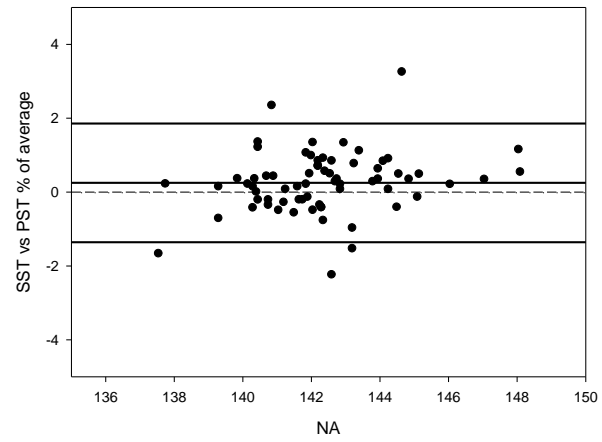
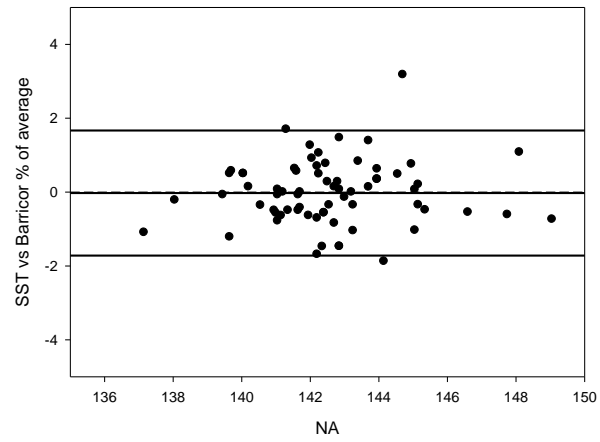


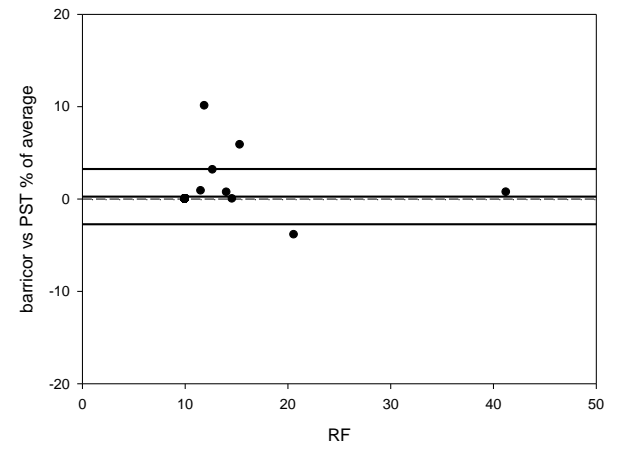
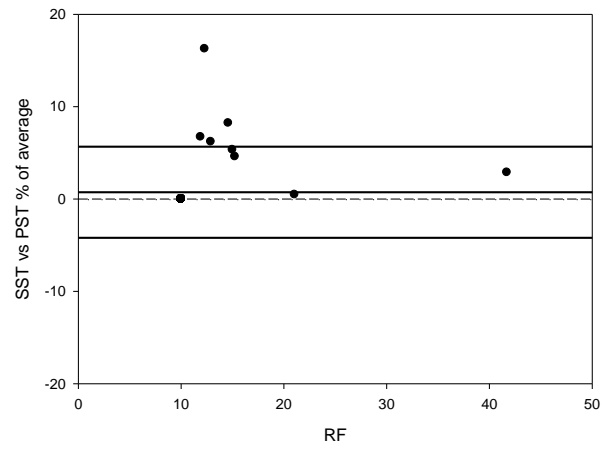
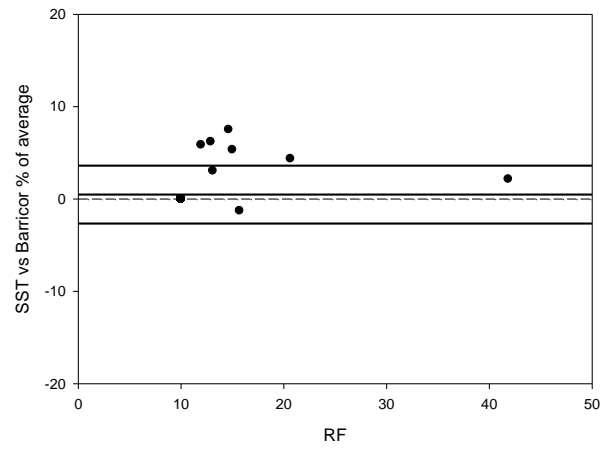
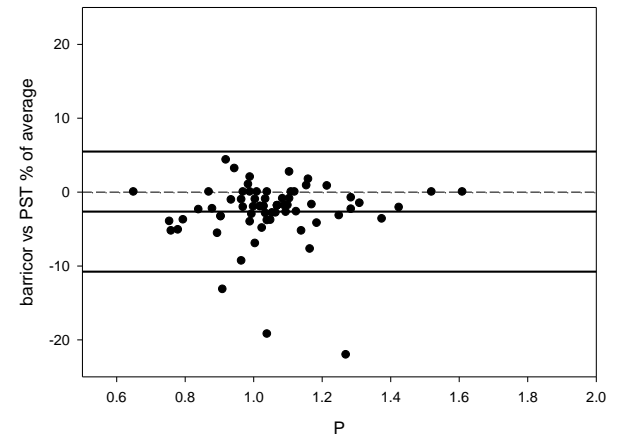
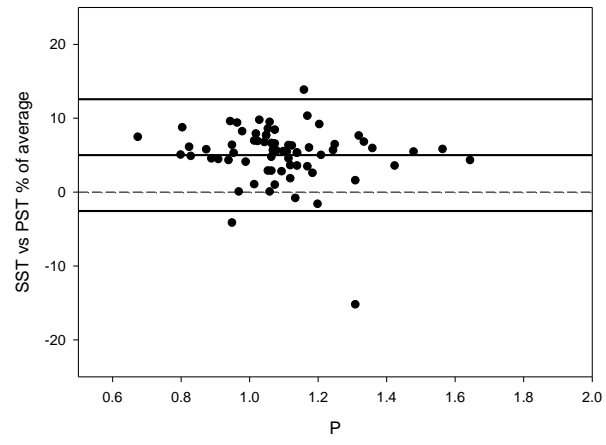
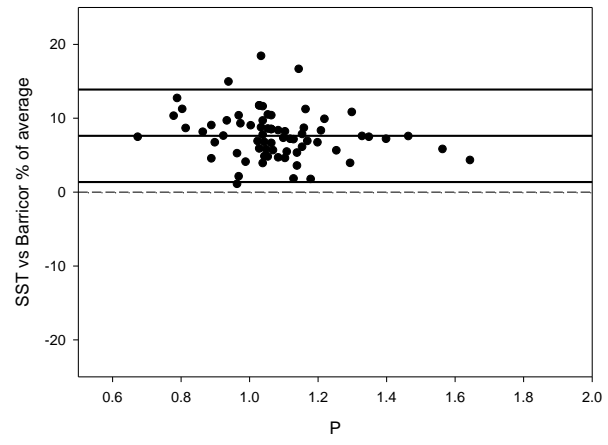


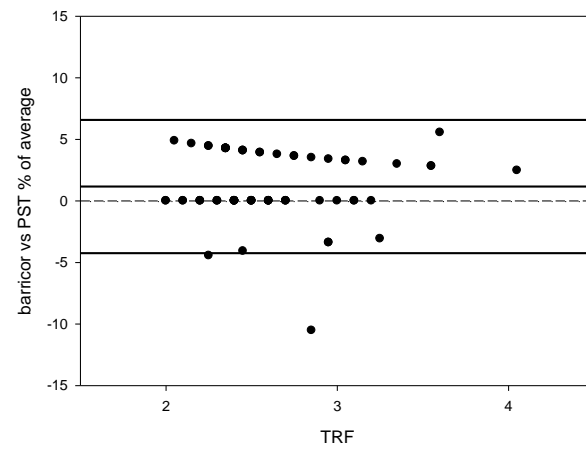
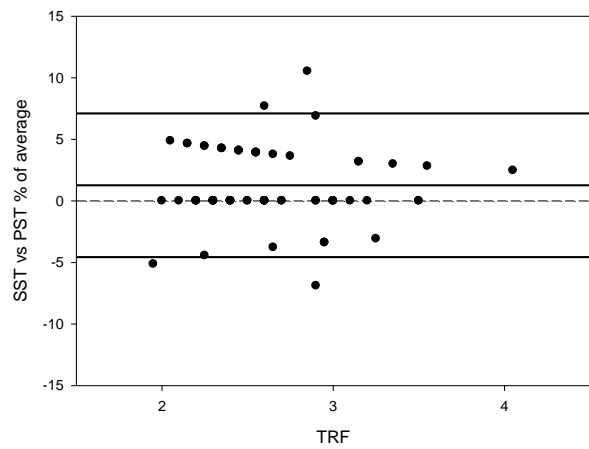
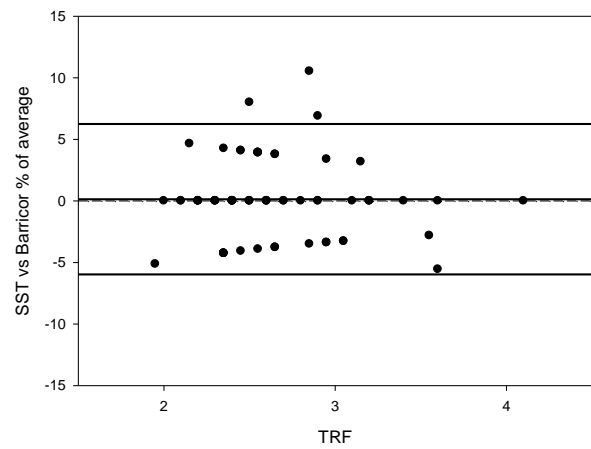
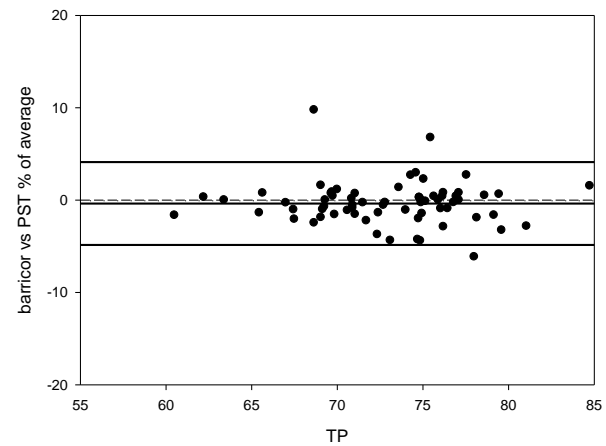
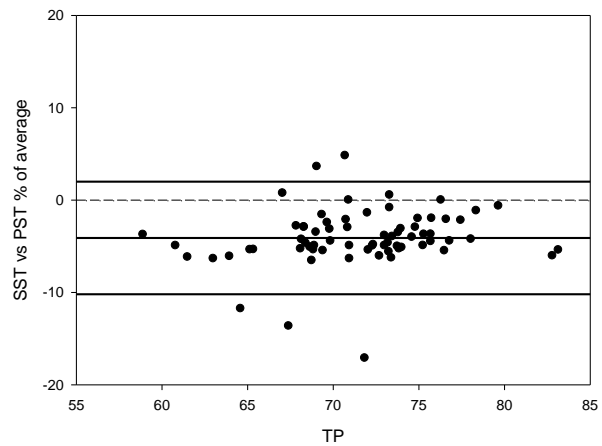
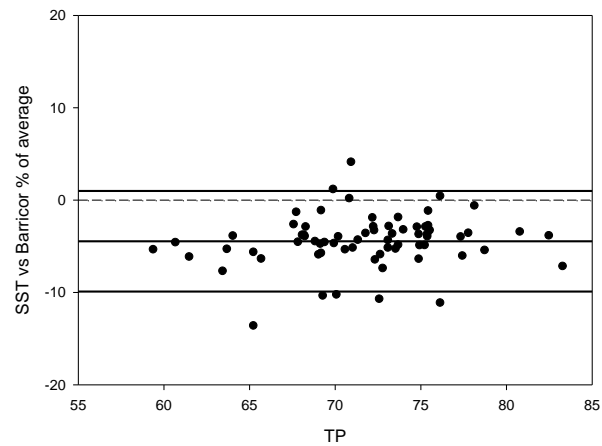


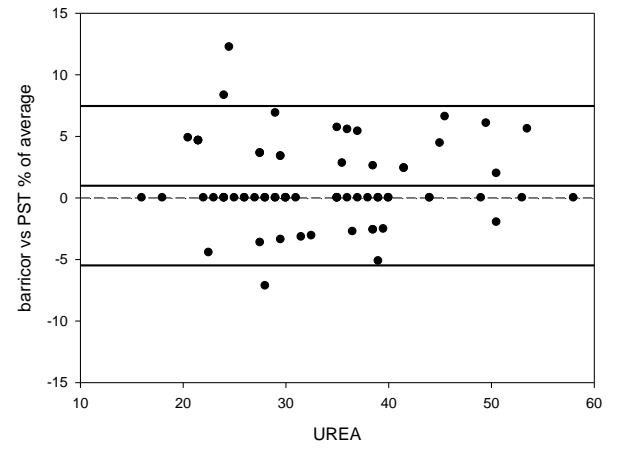
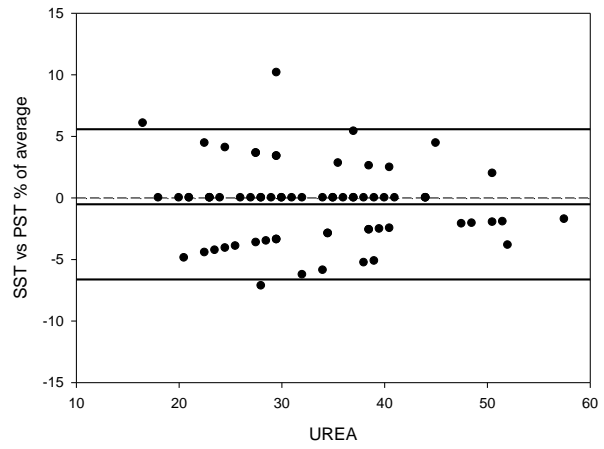
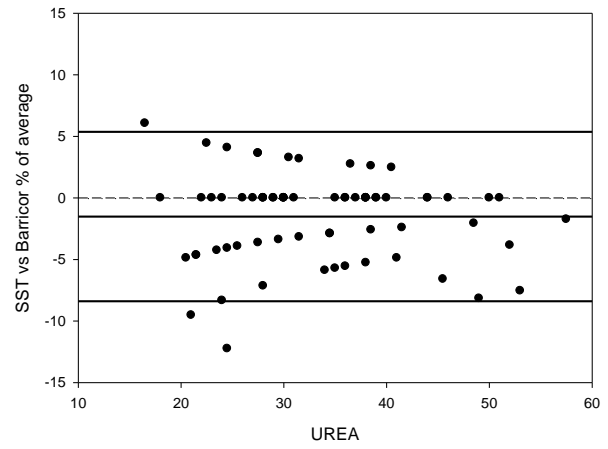
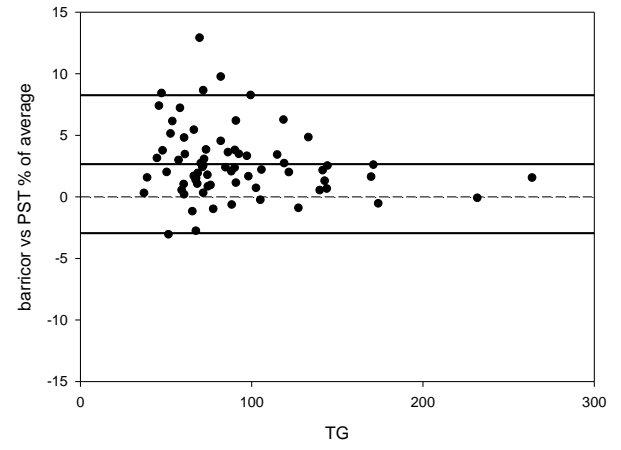
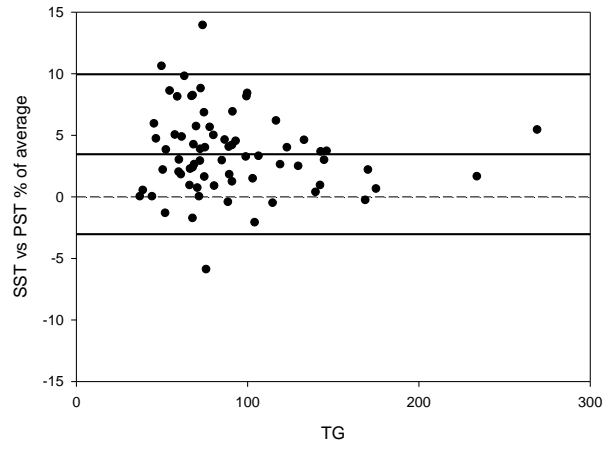
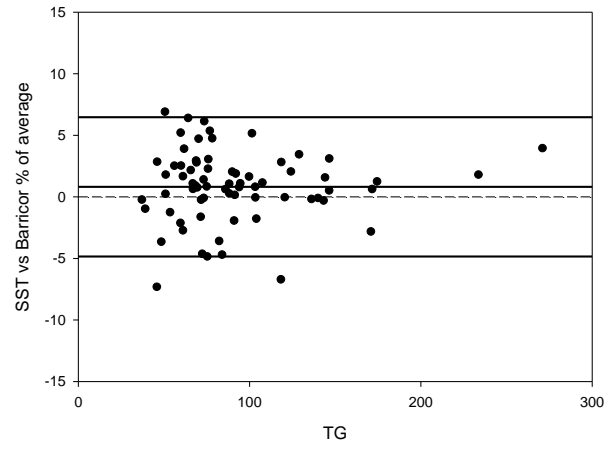


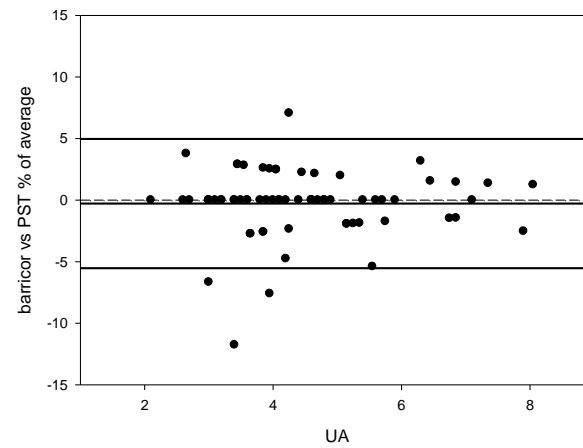
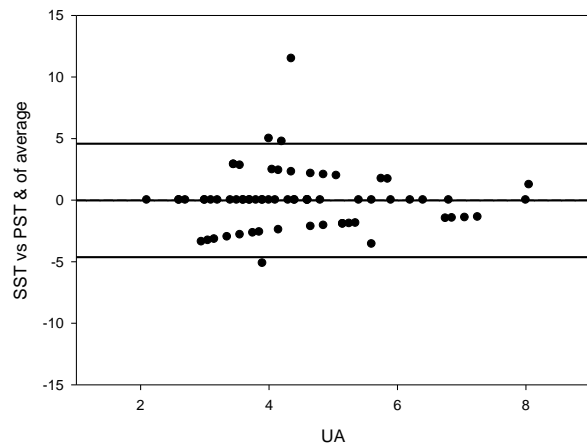
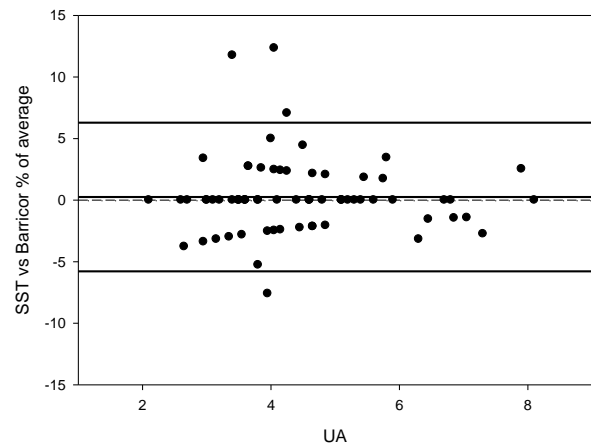




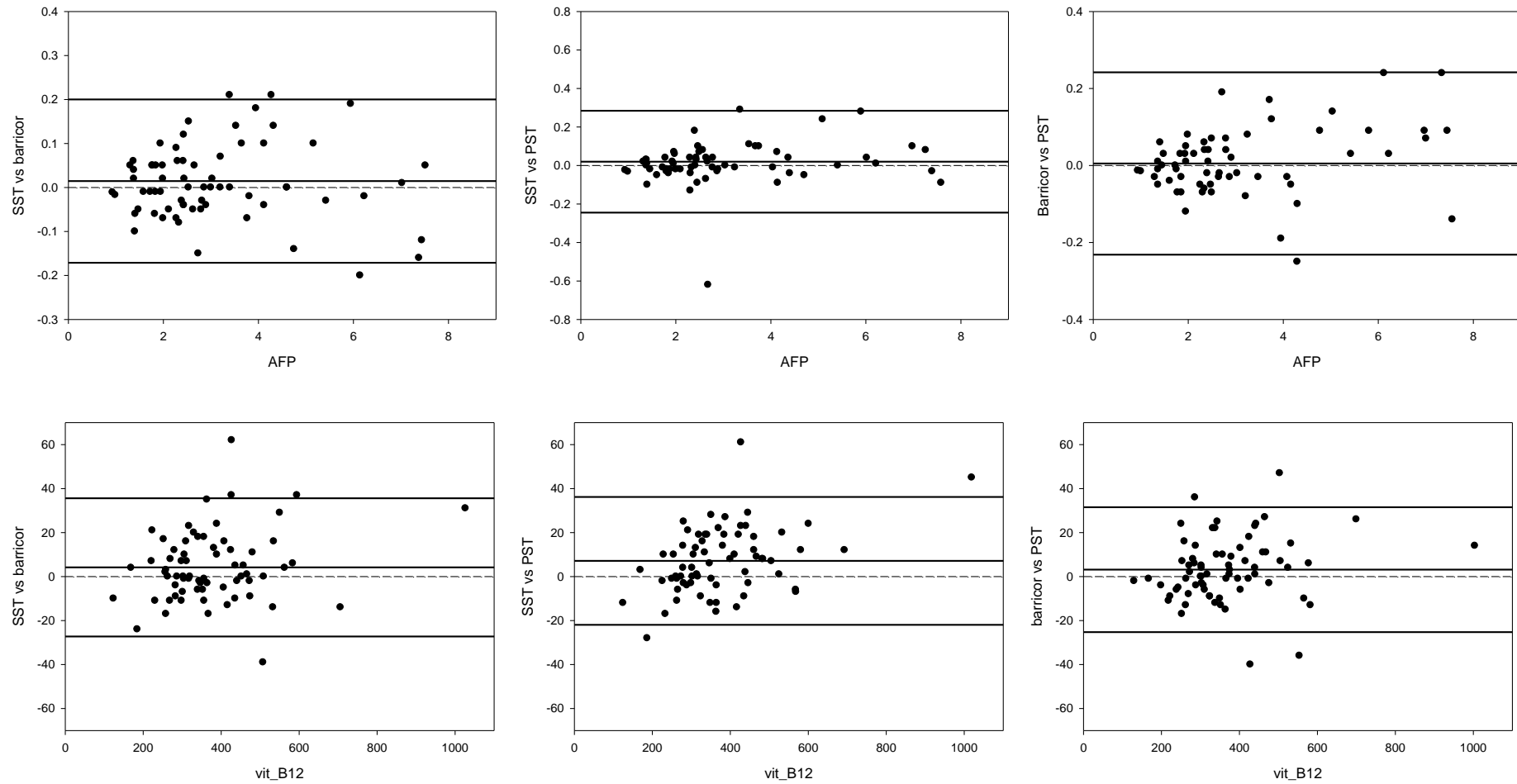


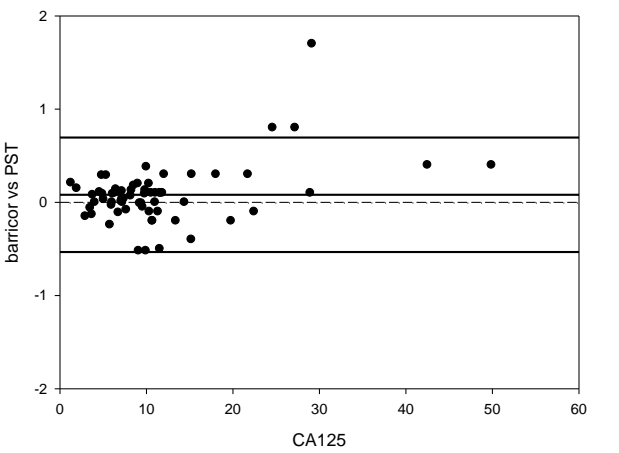
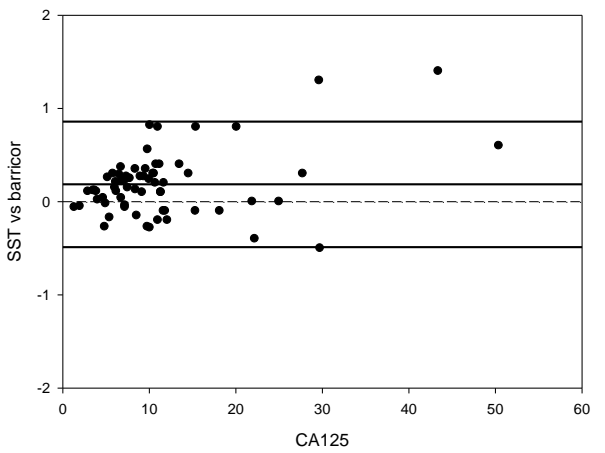
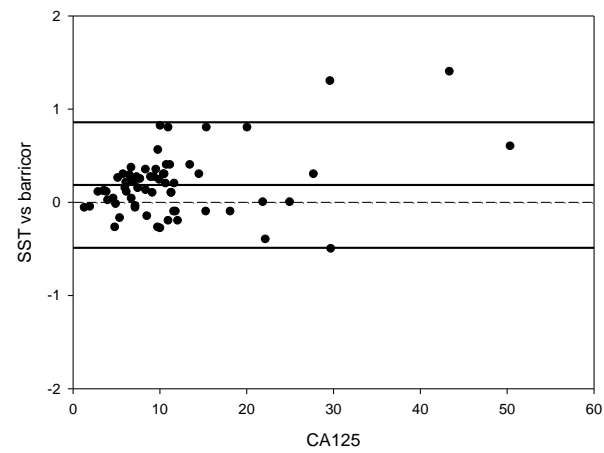
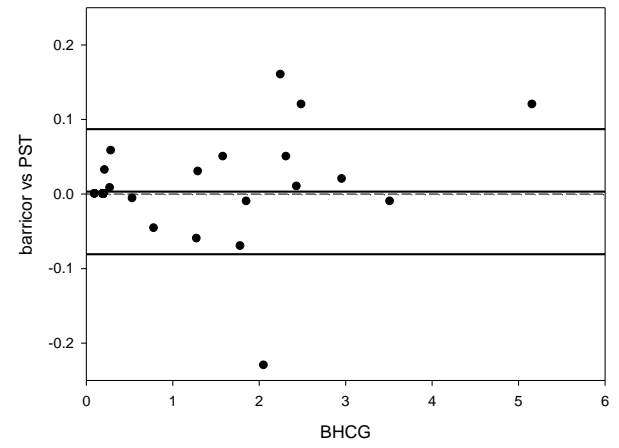
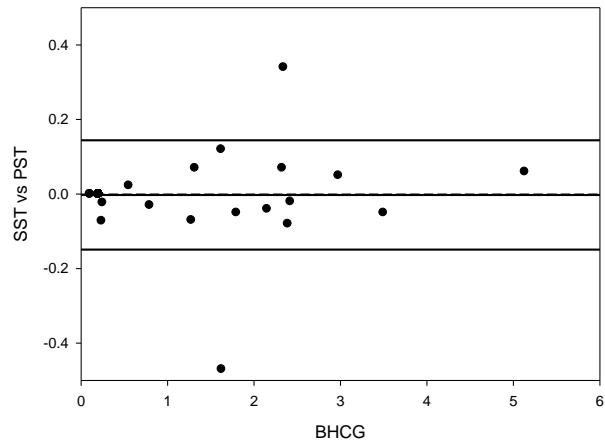
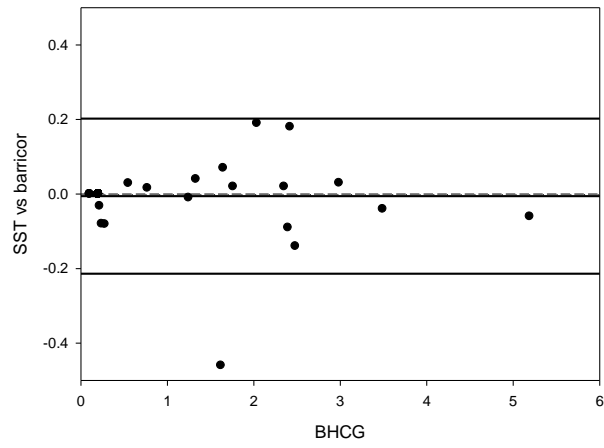


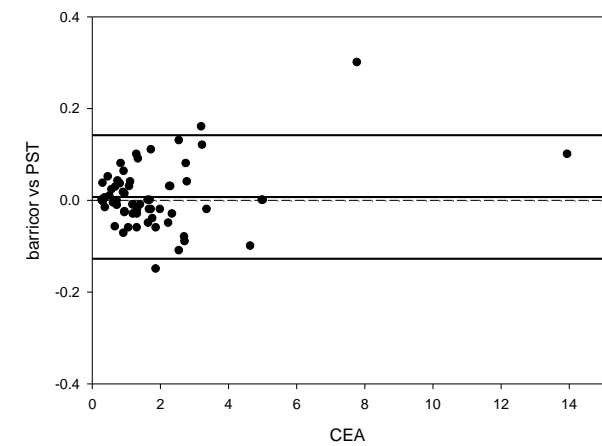
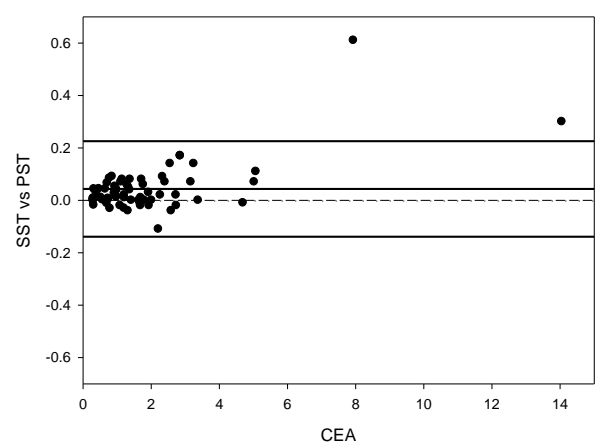
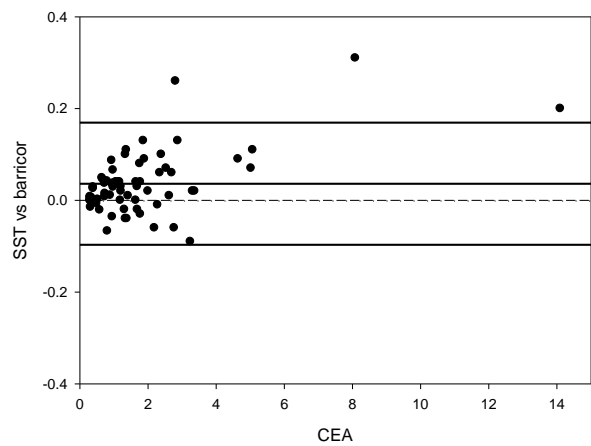
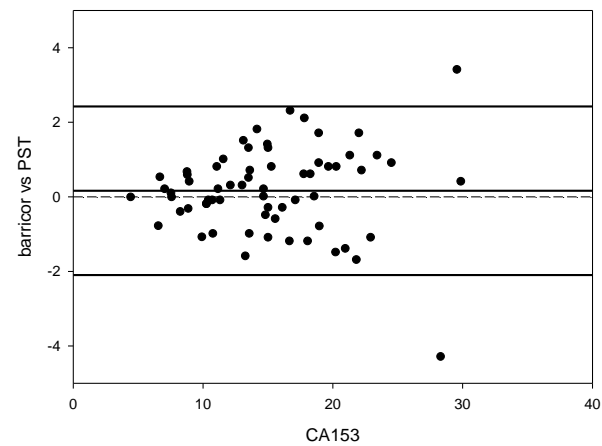
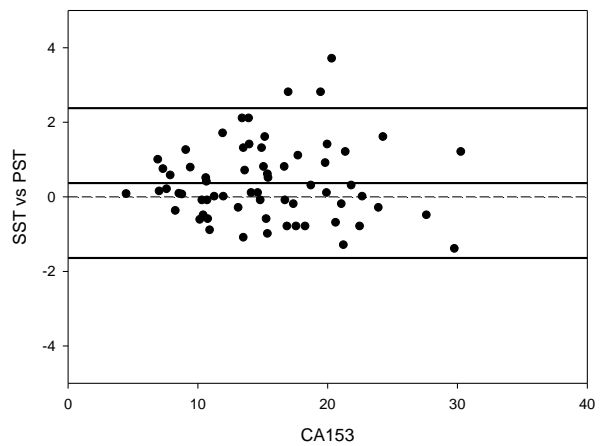
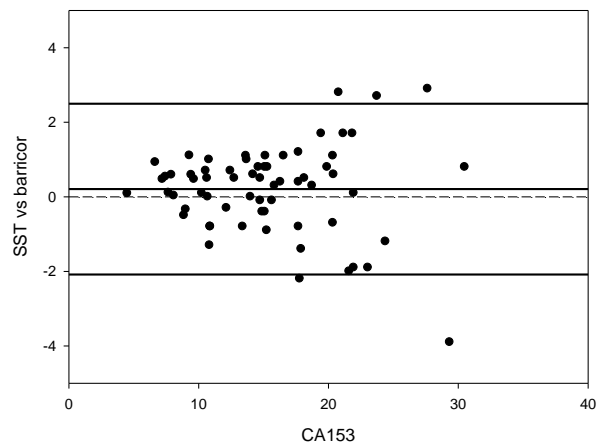




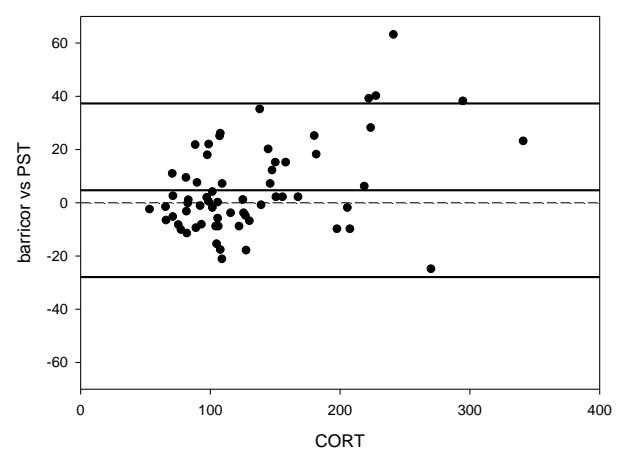
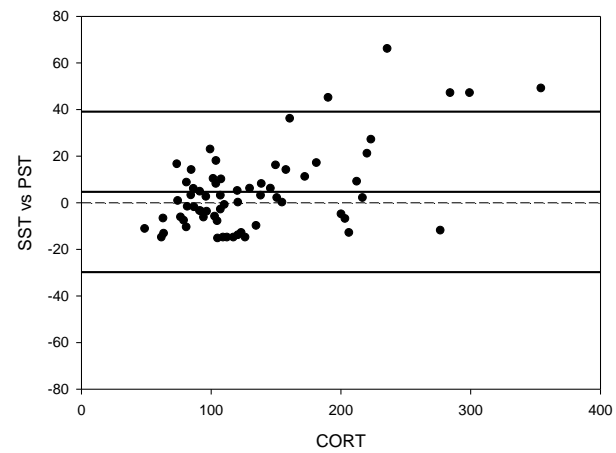
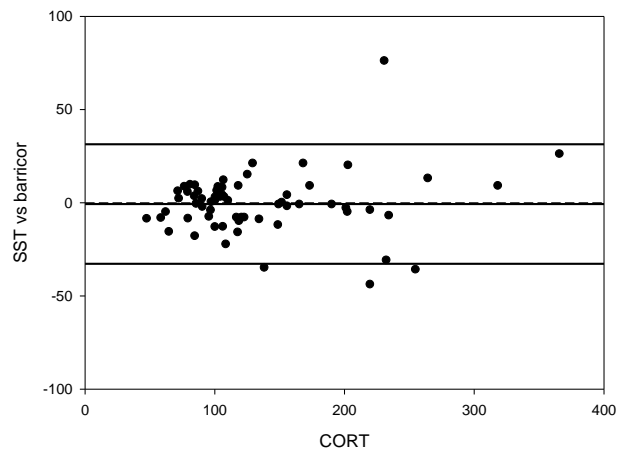
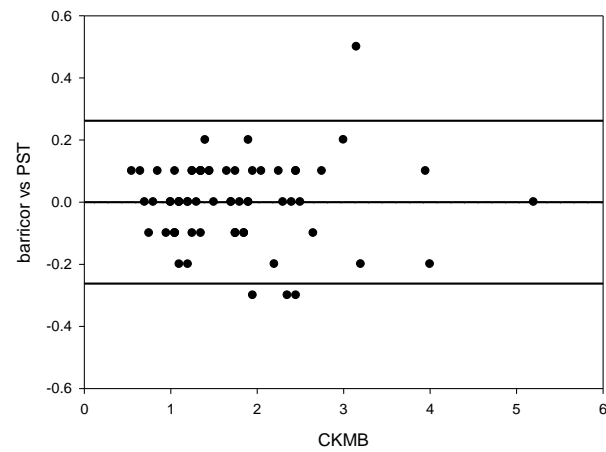
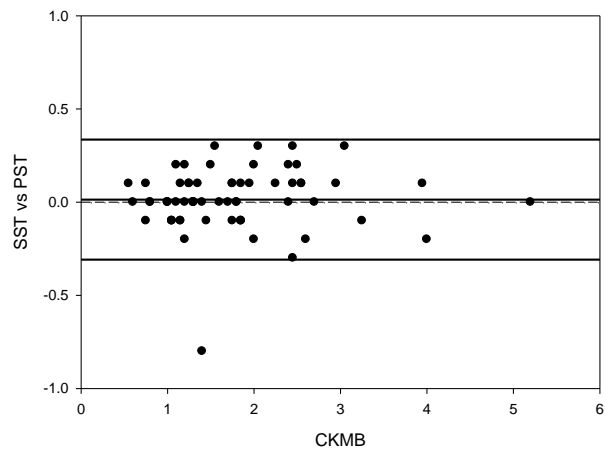
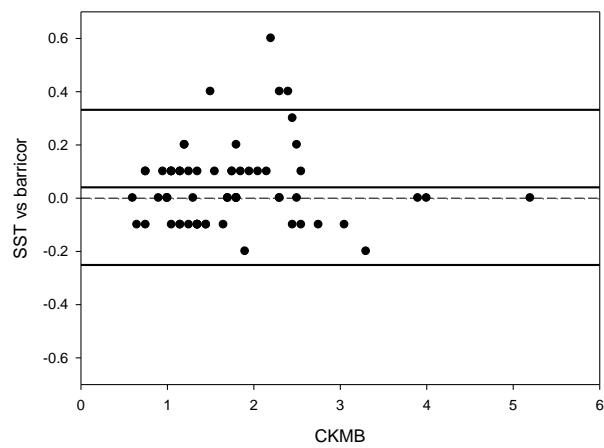
**Figure S2A.** B&A plots for immunochemical analytes: the pair value differences were expressed as real values.

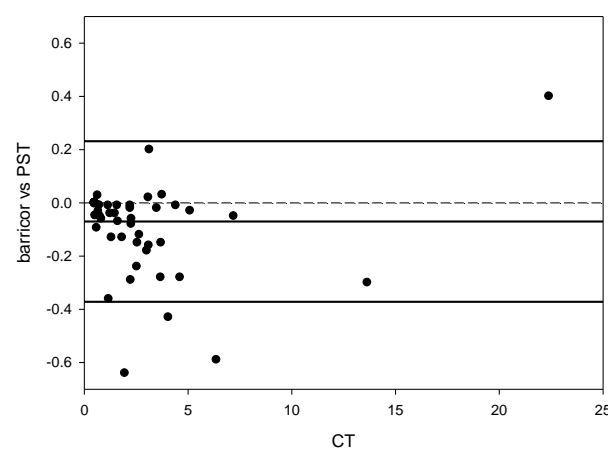
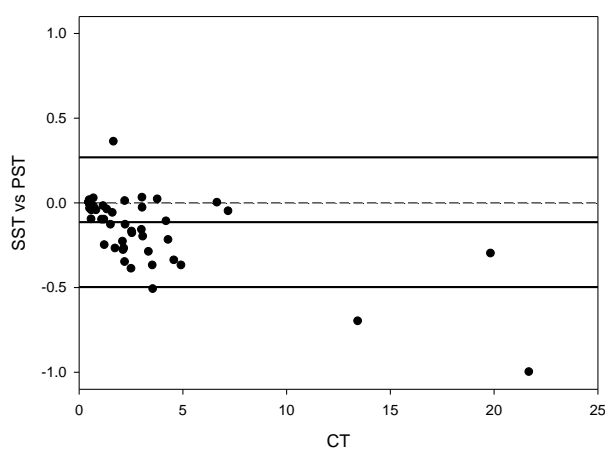
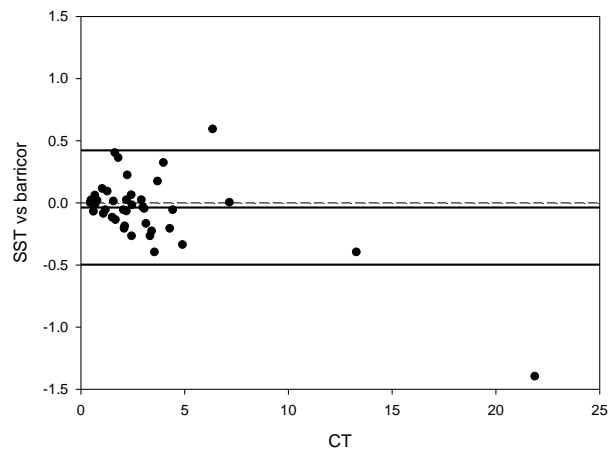
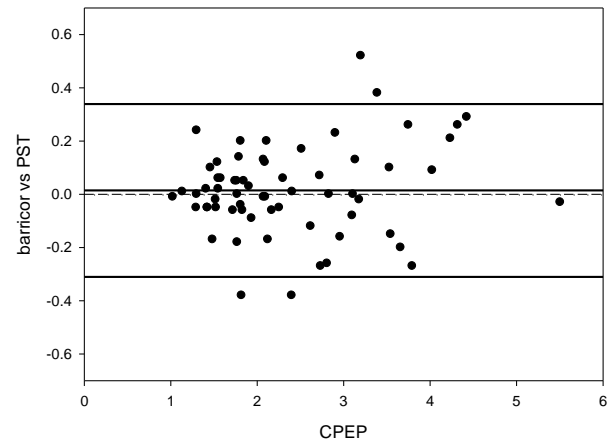
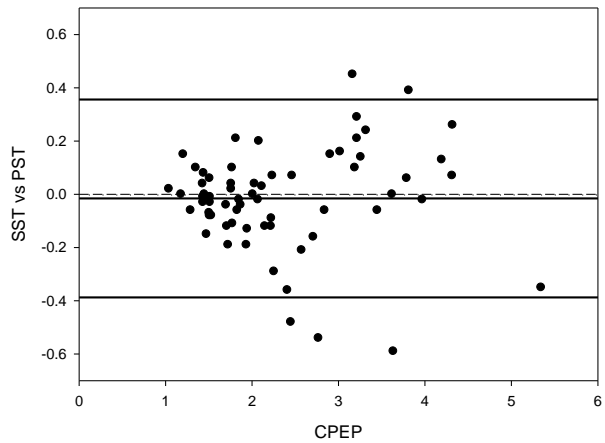
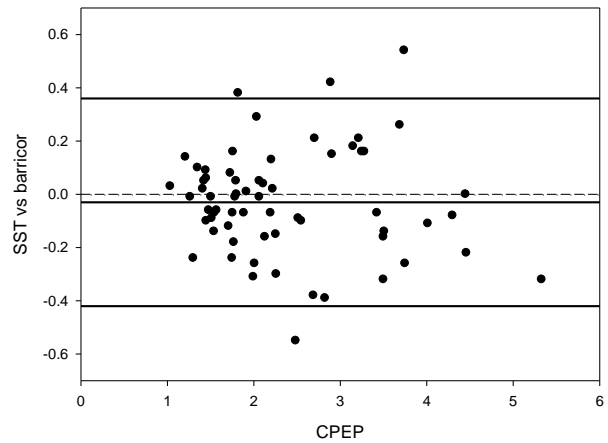


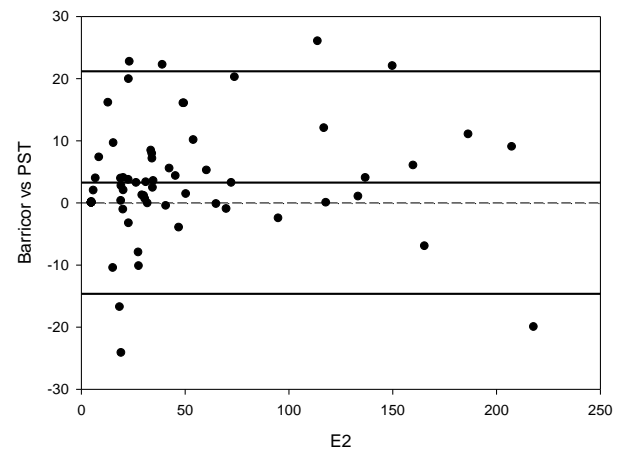
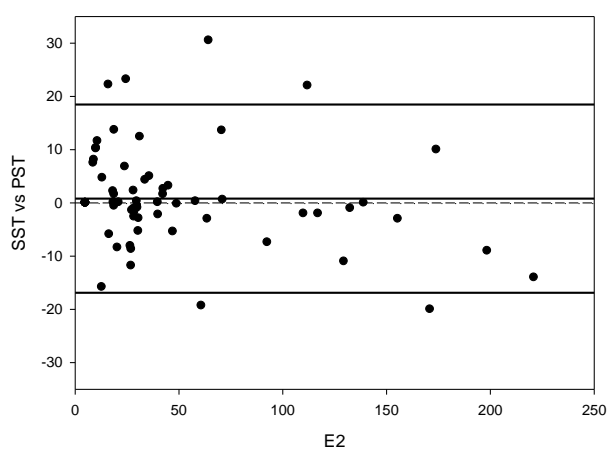
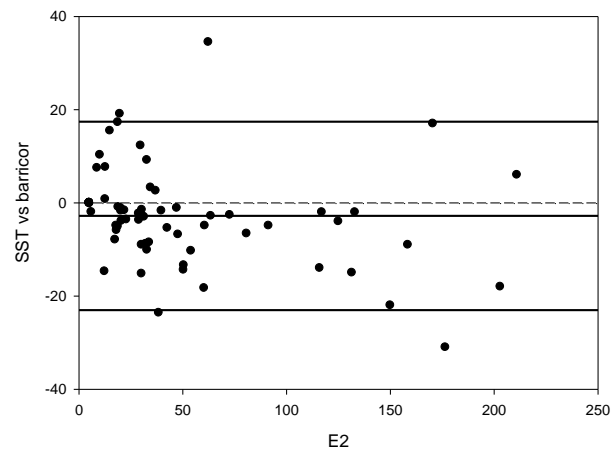
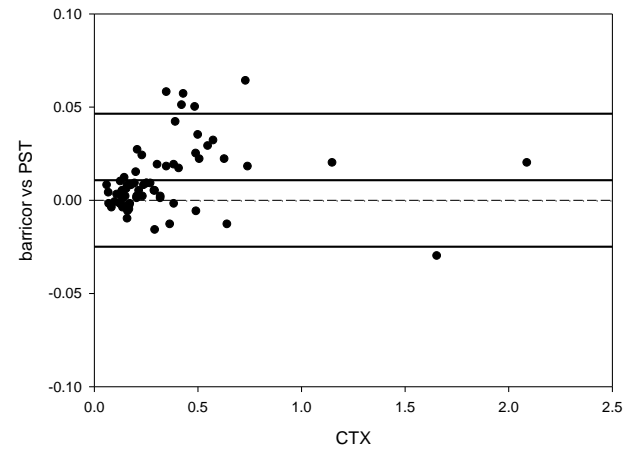
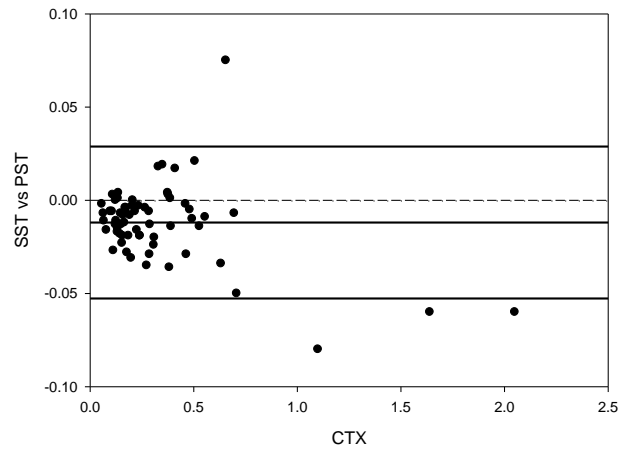
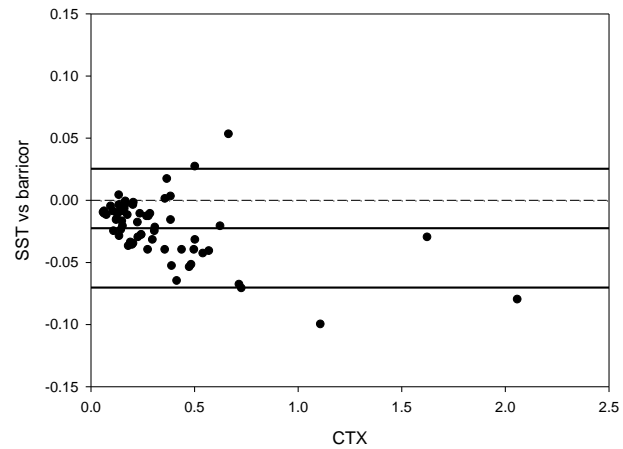


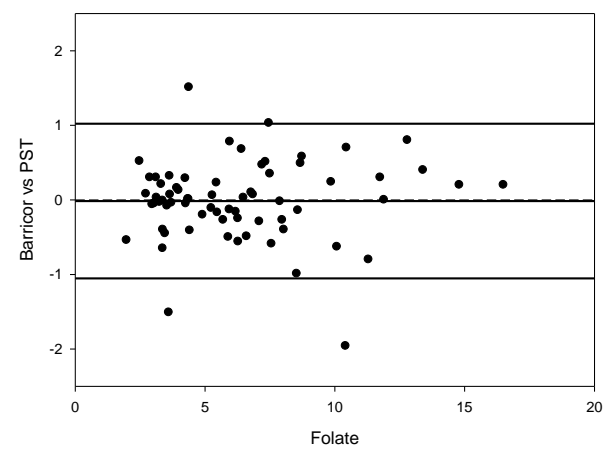
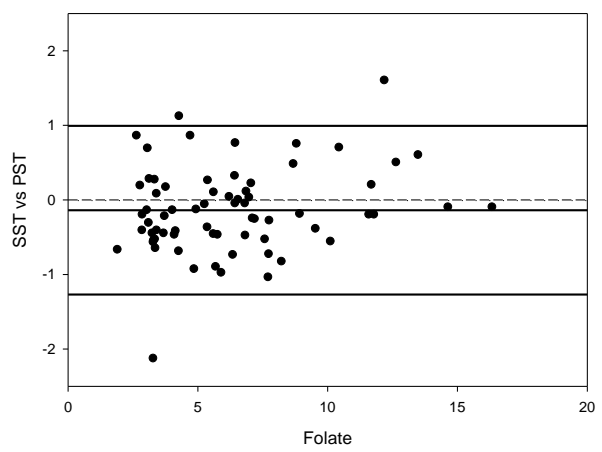
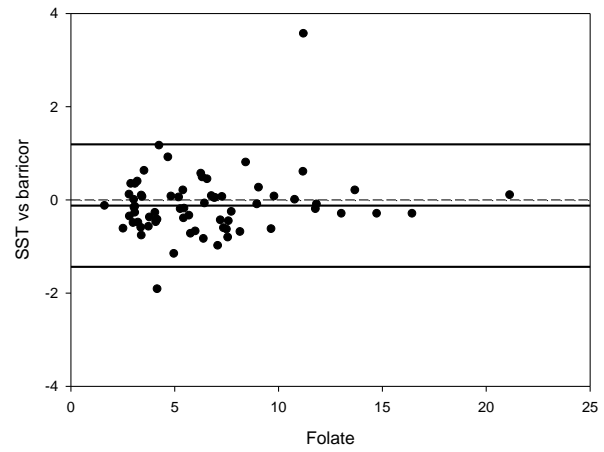
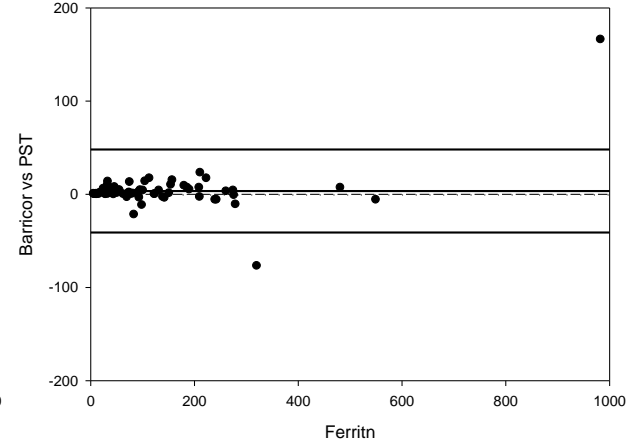
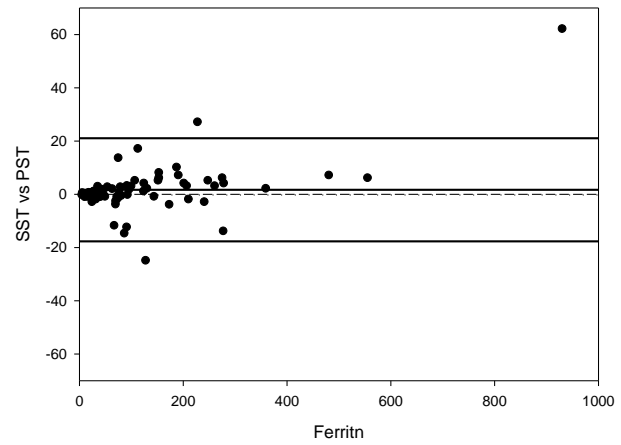
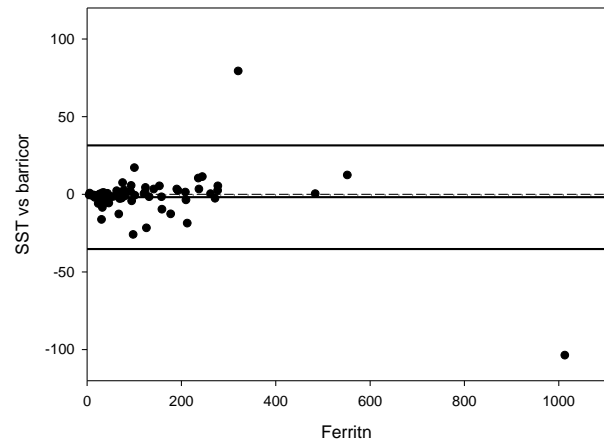


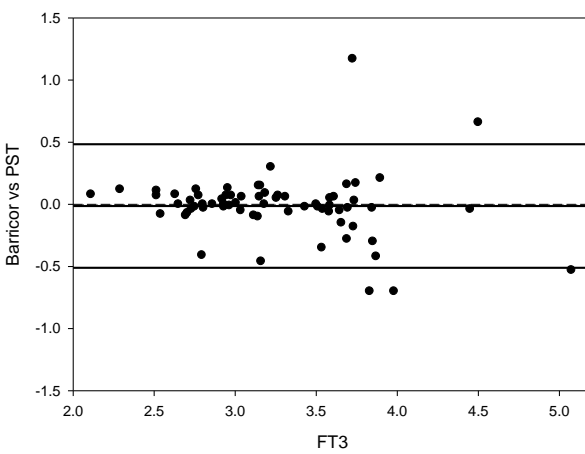
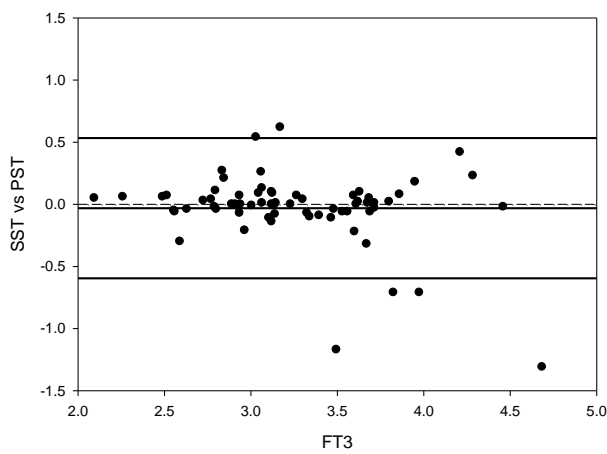
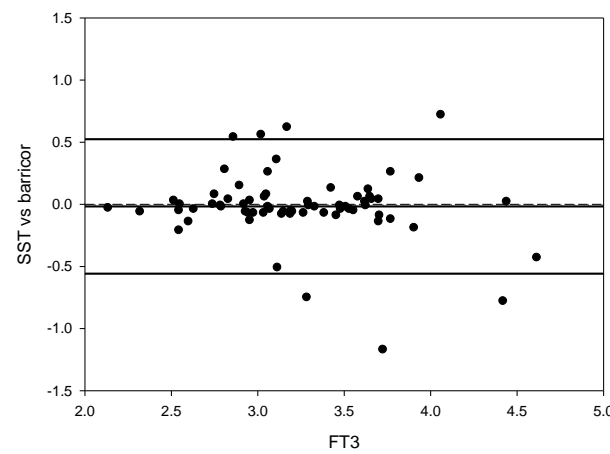
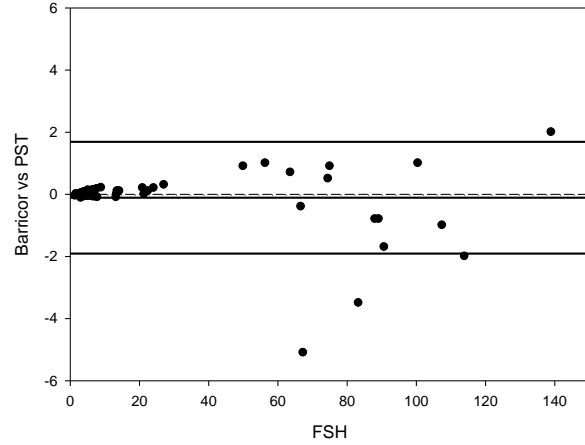
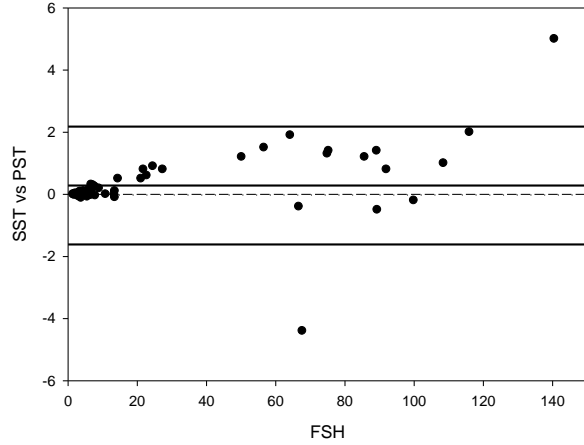
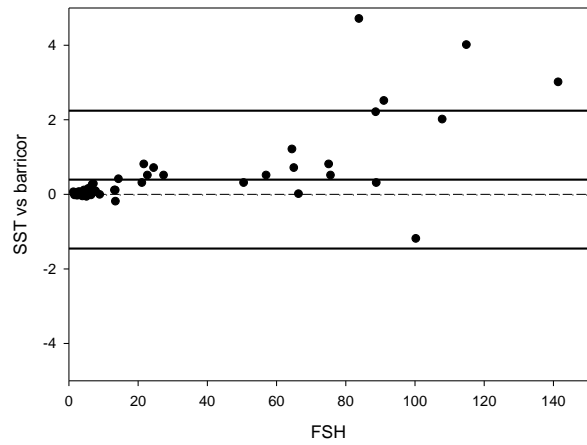


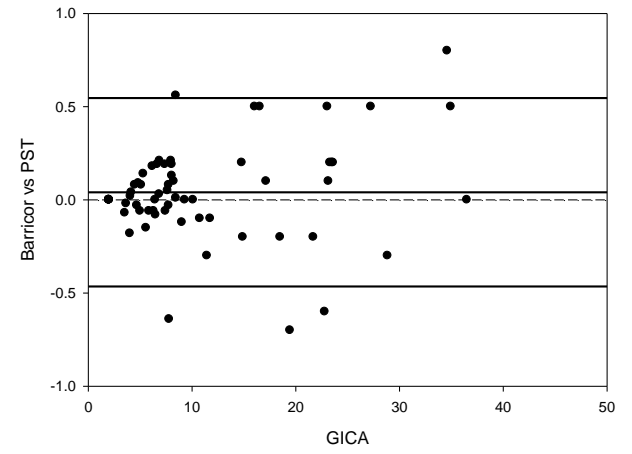
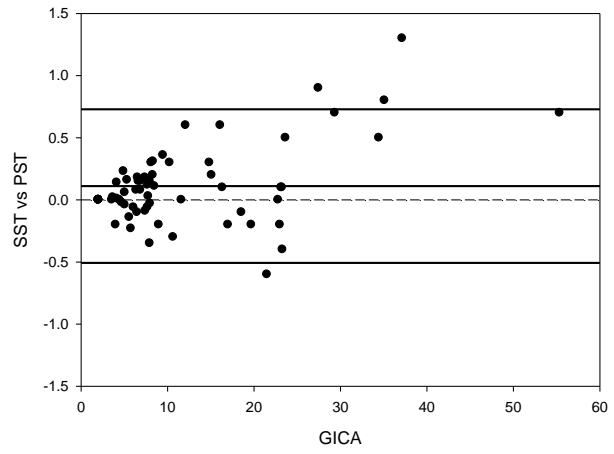
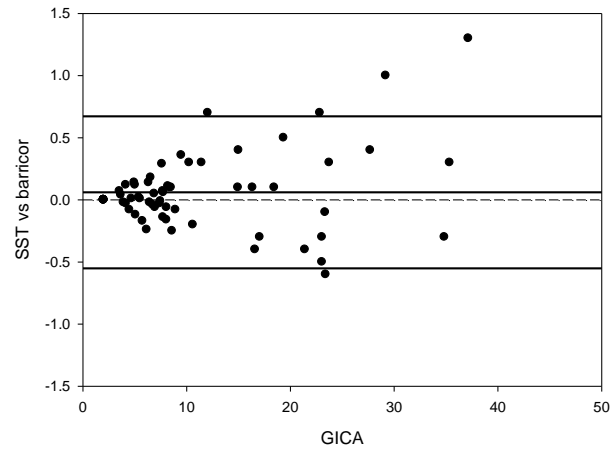
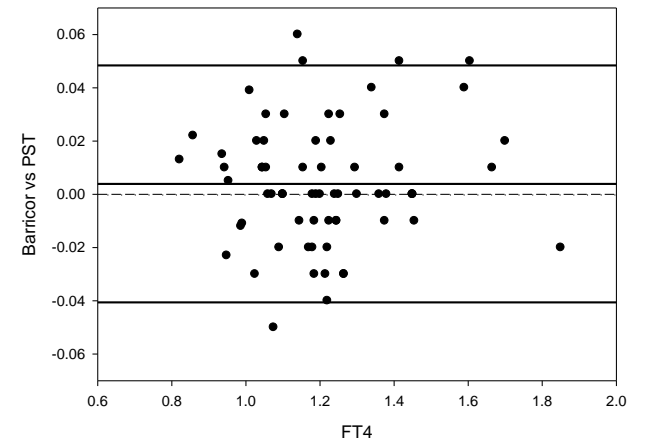
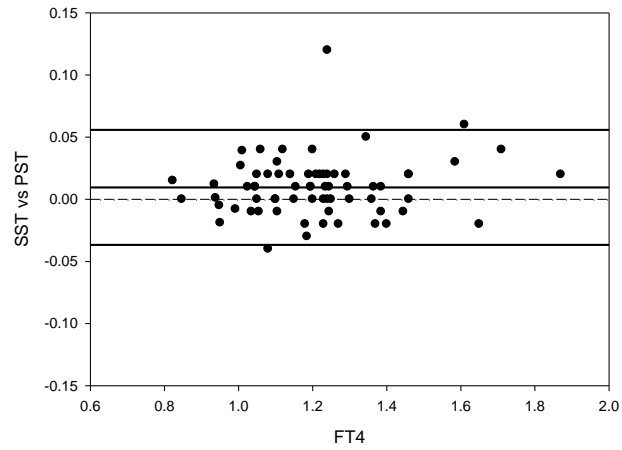
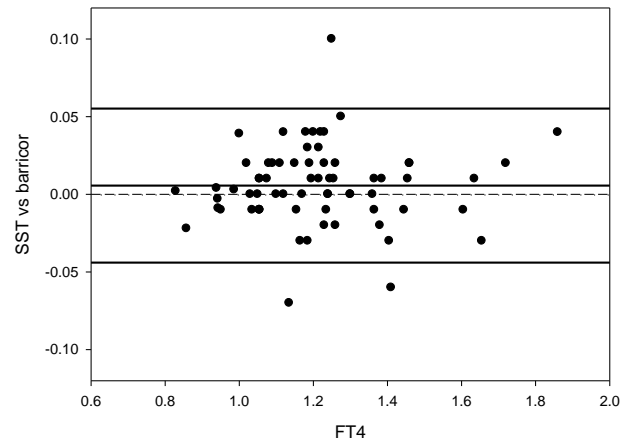


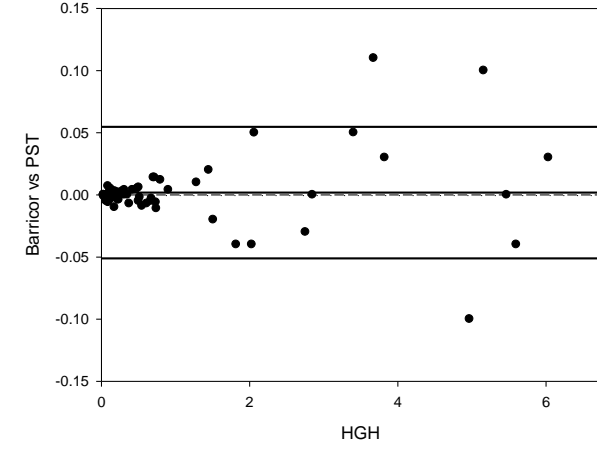
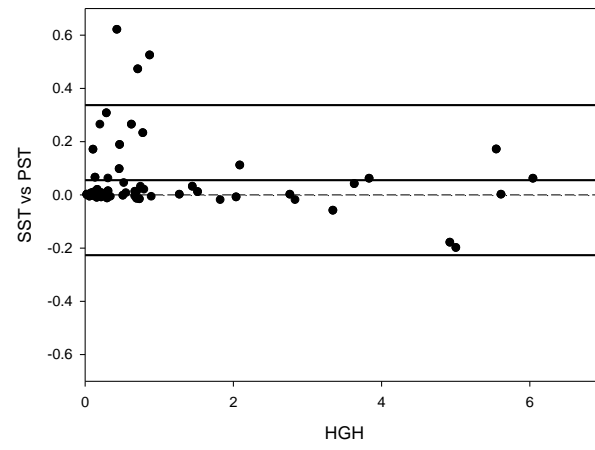
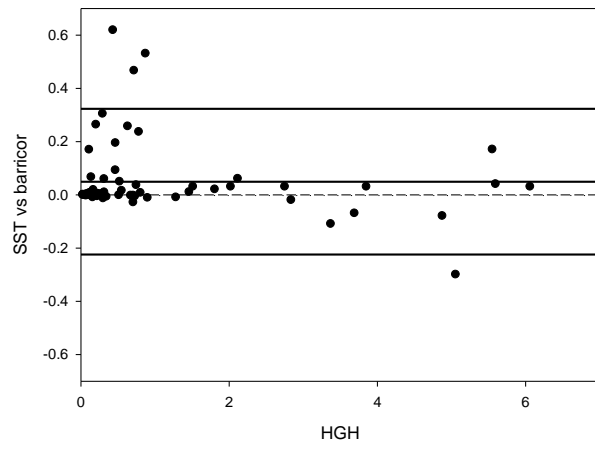
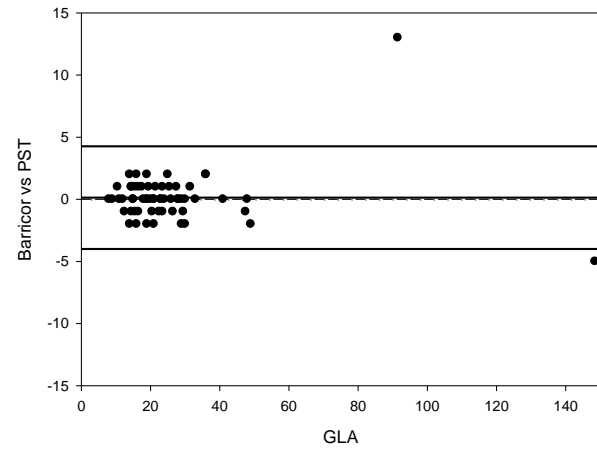
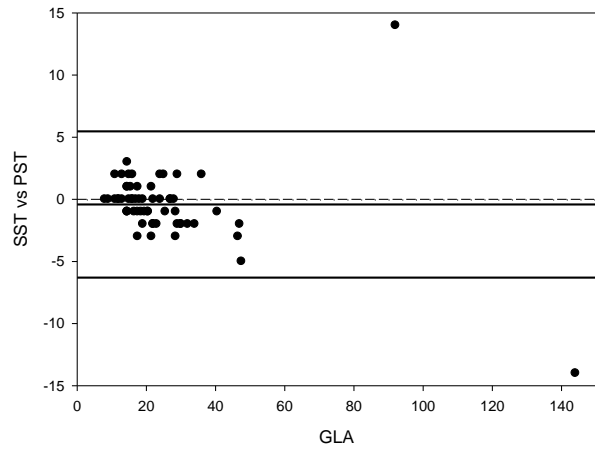
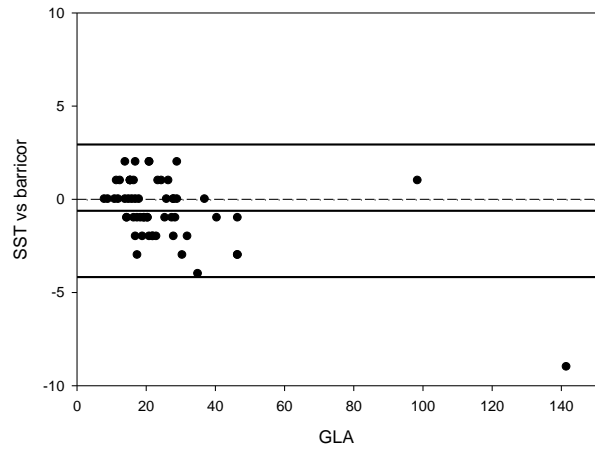


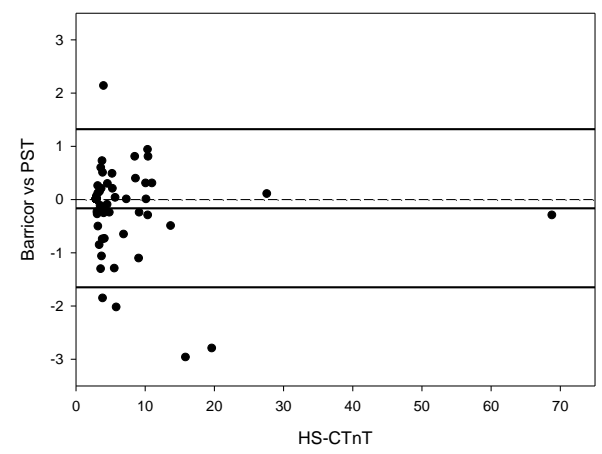
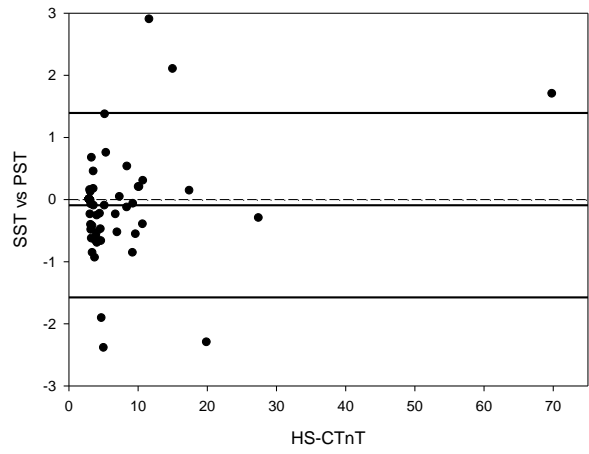
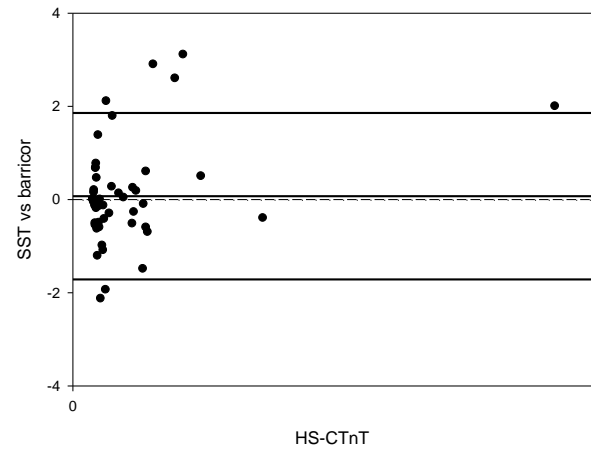
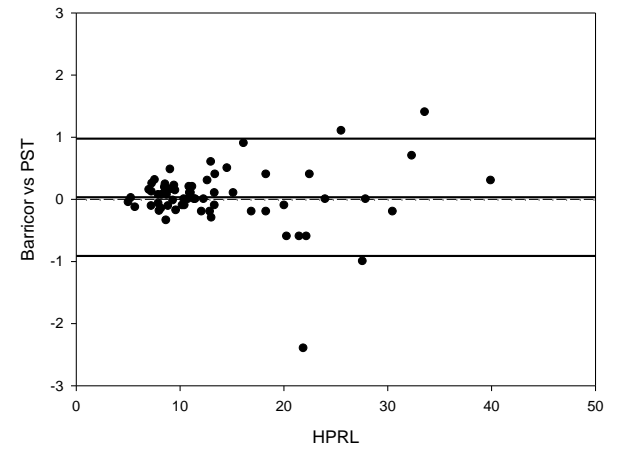
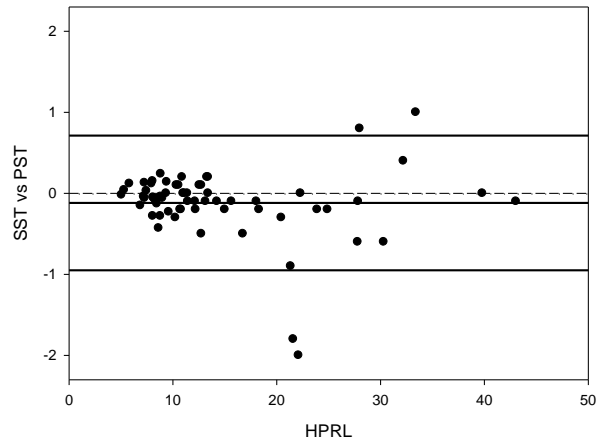
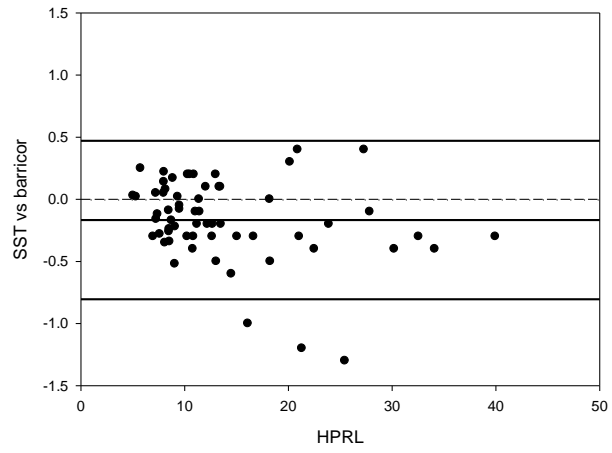




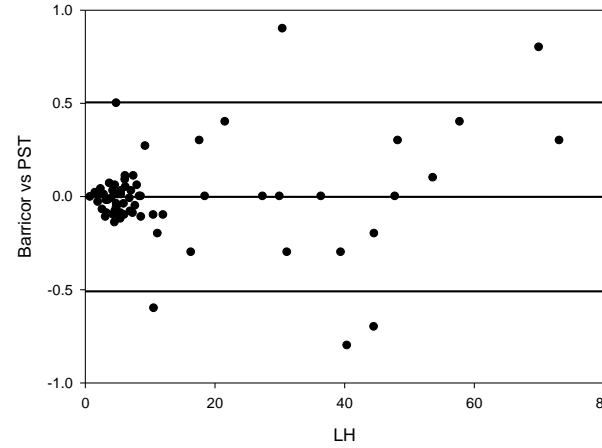
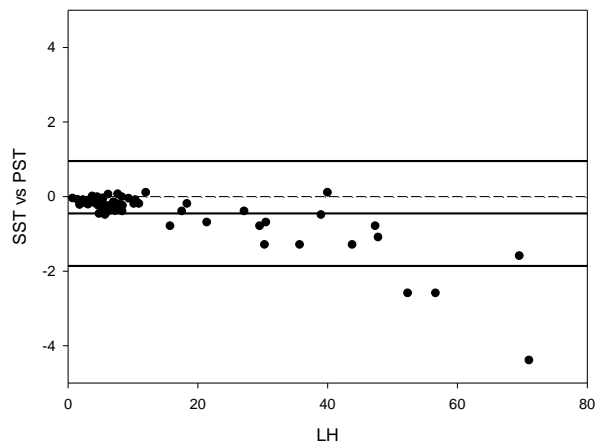
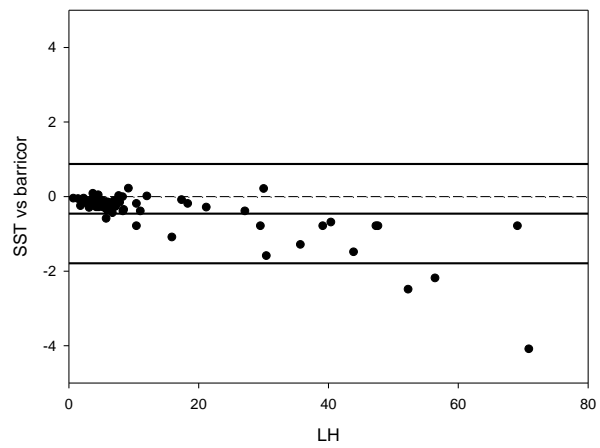
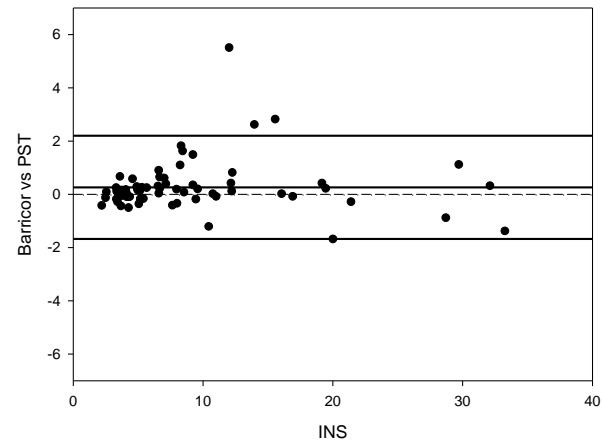
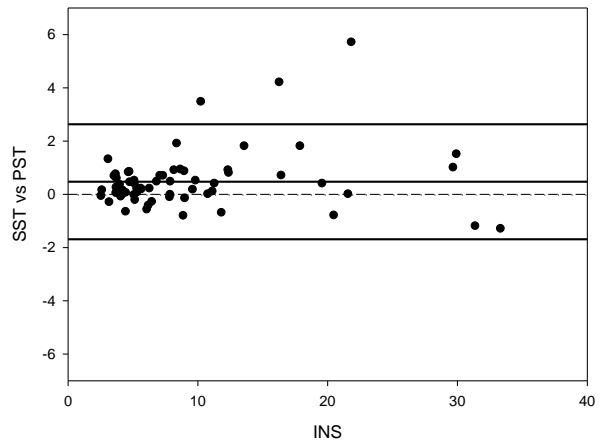
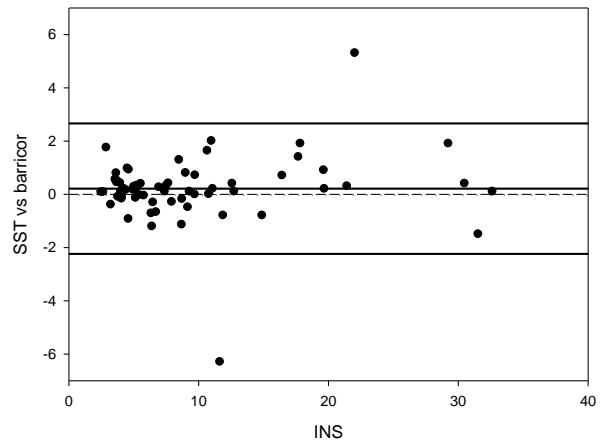


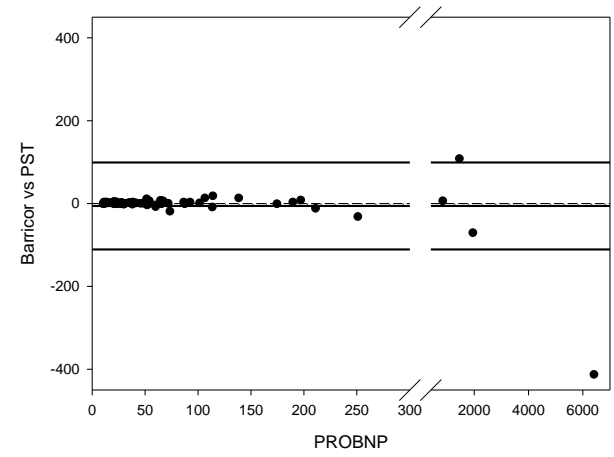
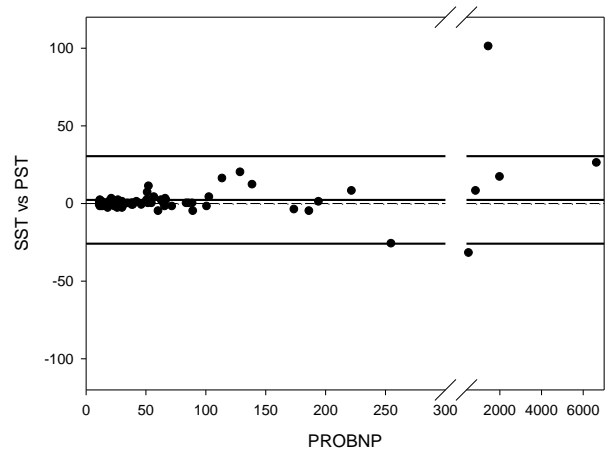
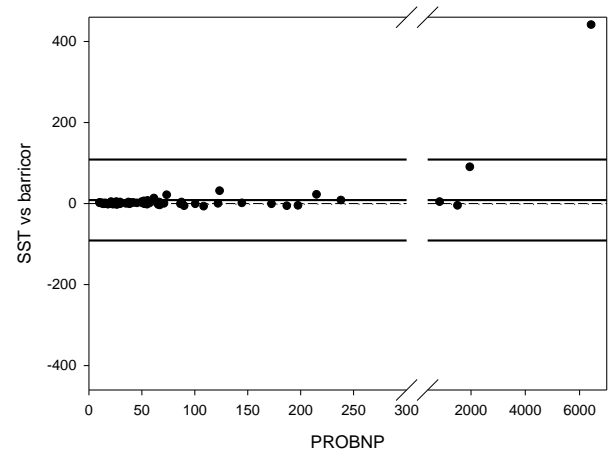
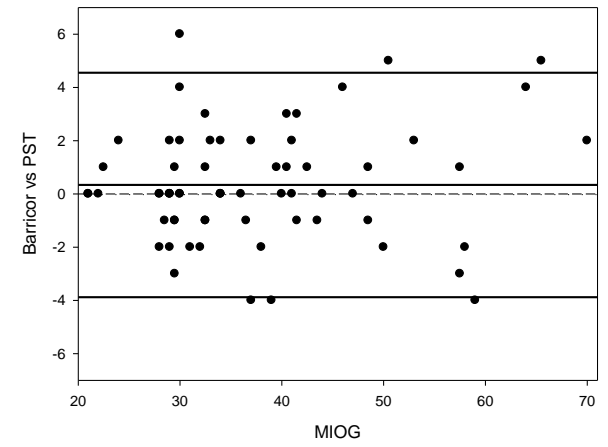
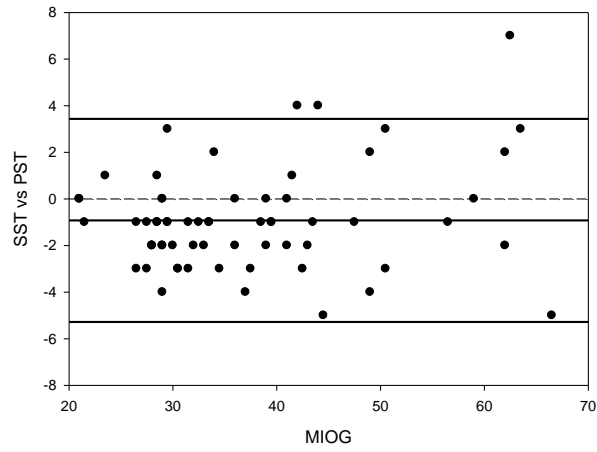
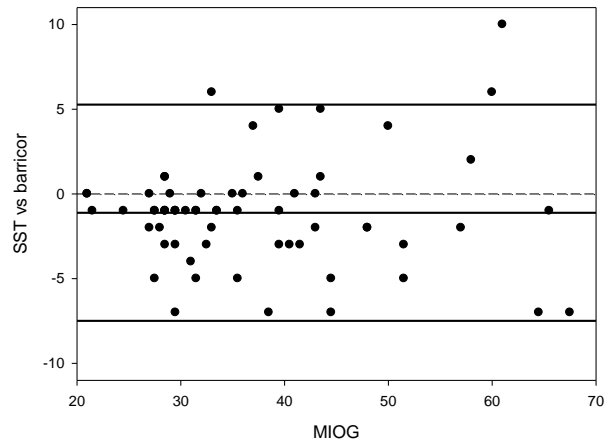


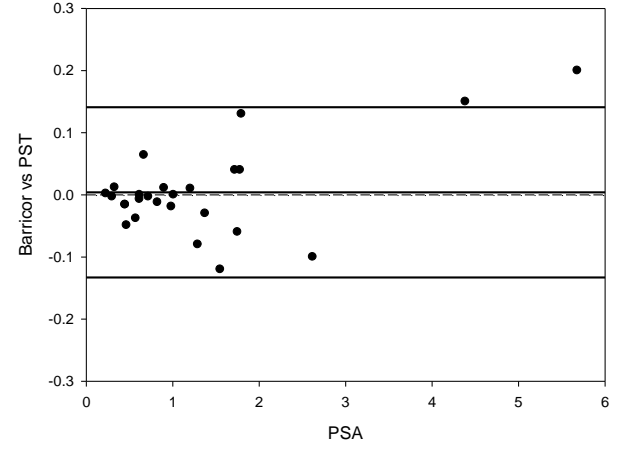
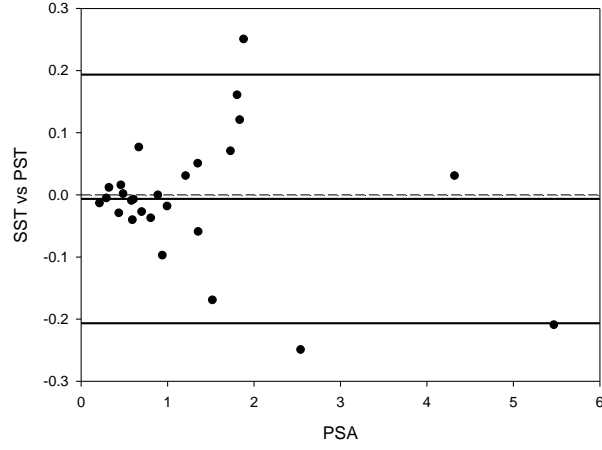
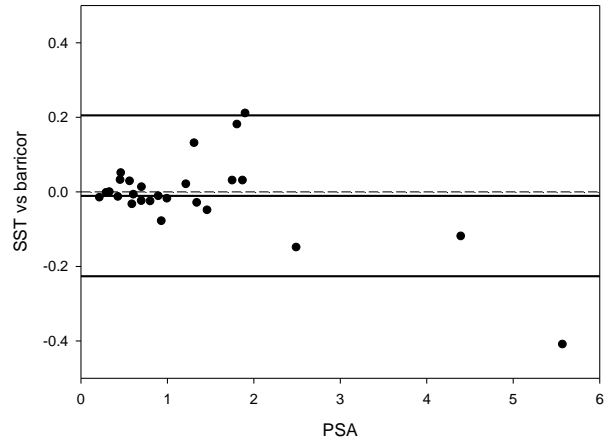
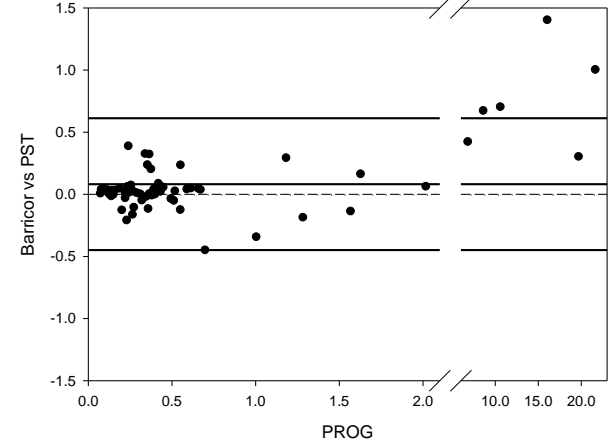
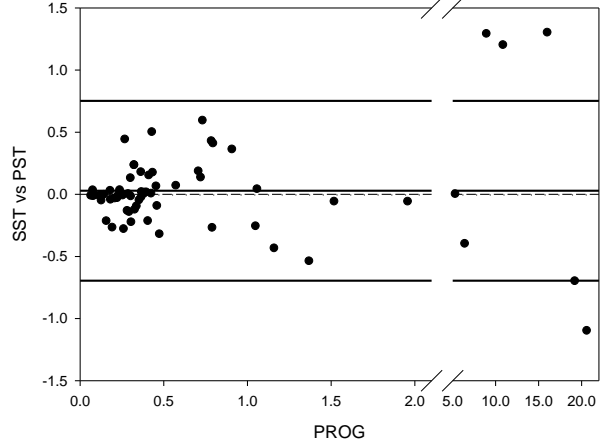
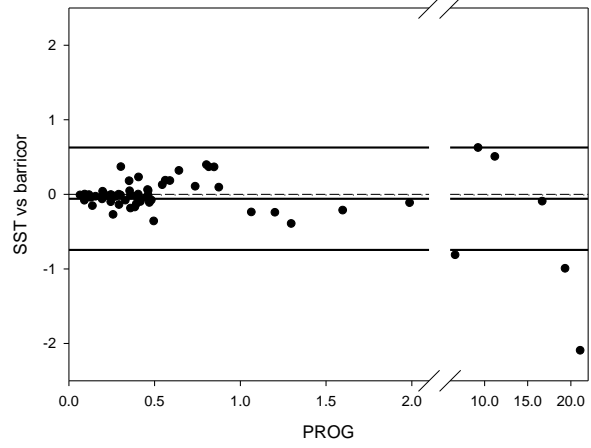


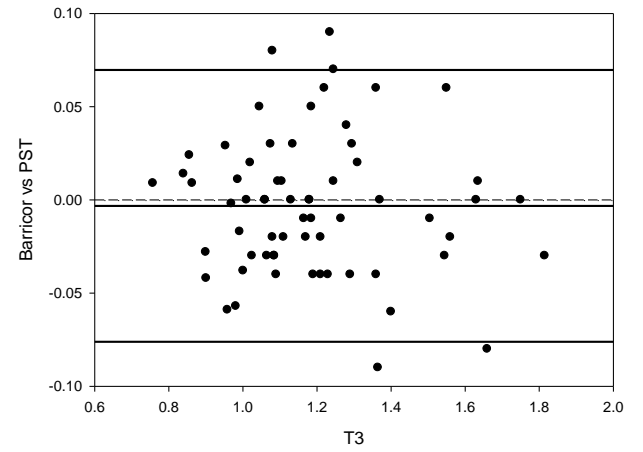
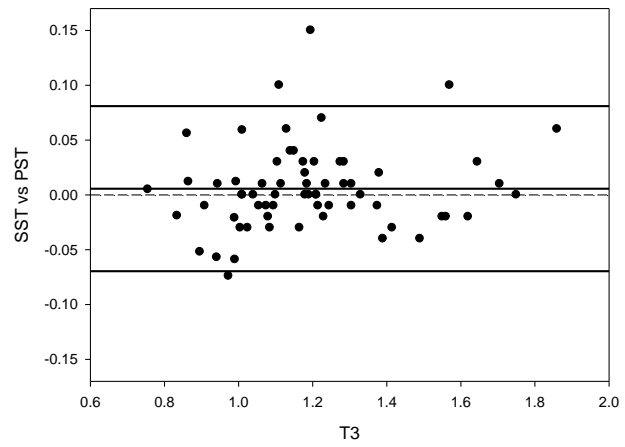
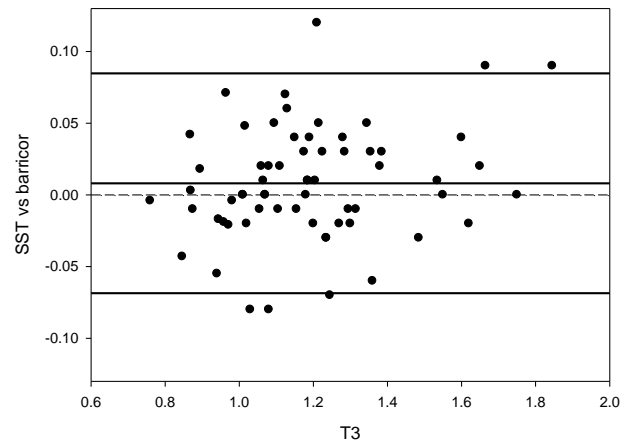
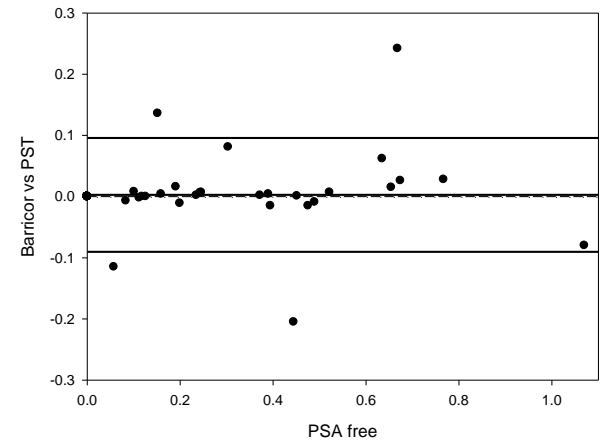
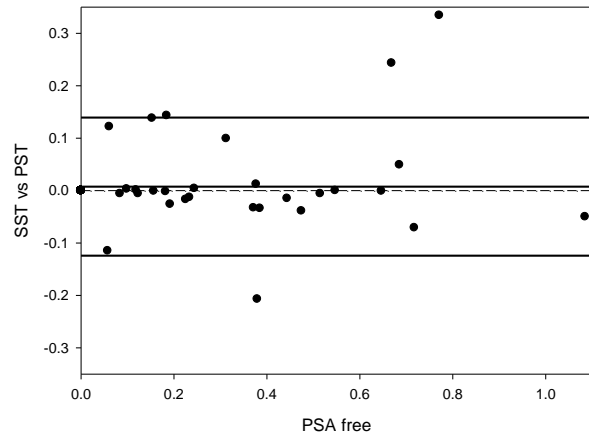
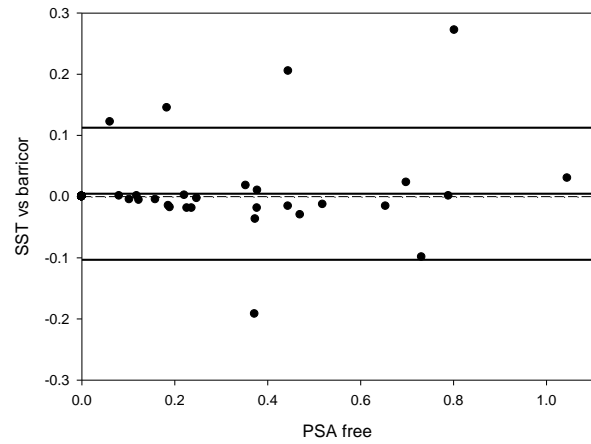


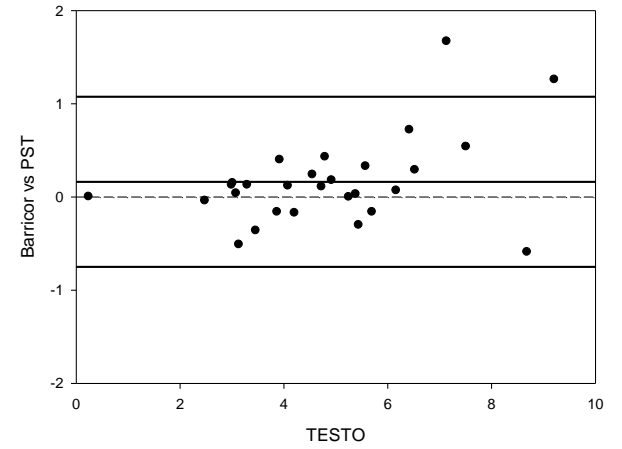
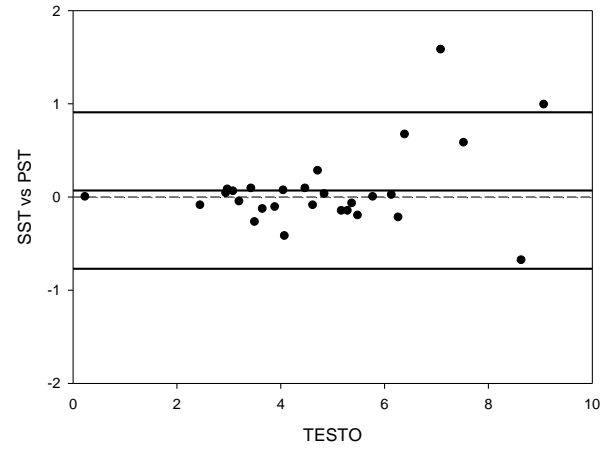
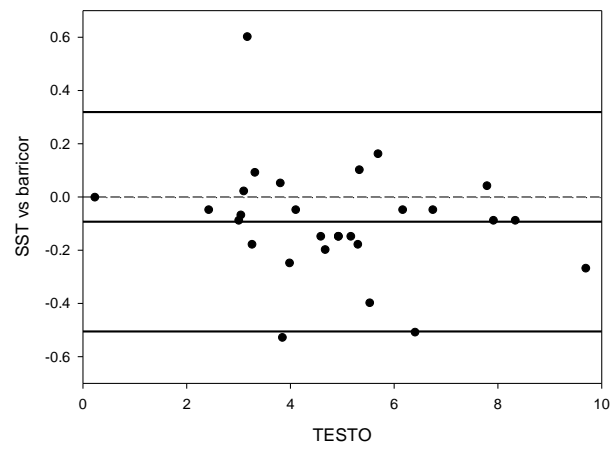
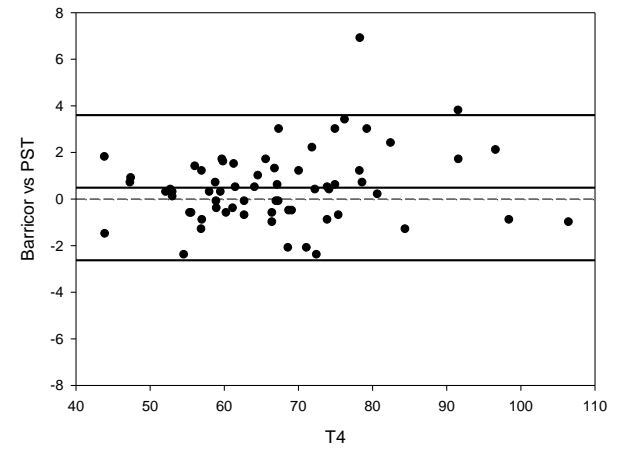
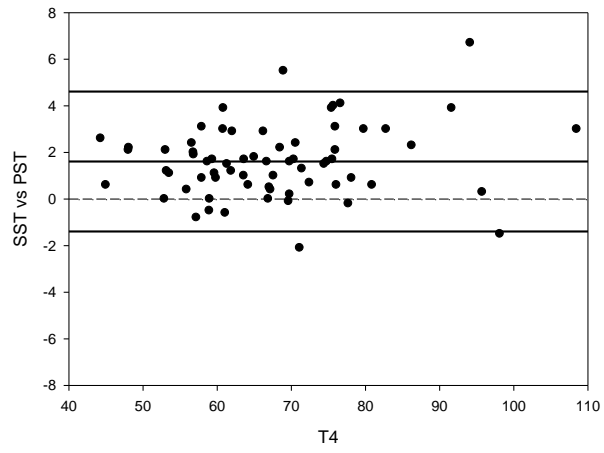
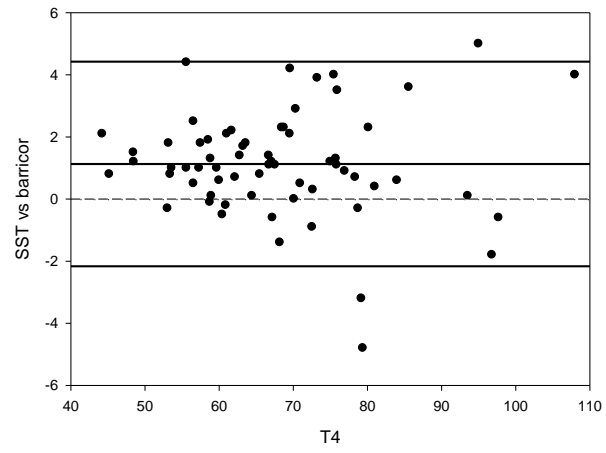


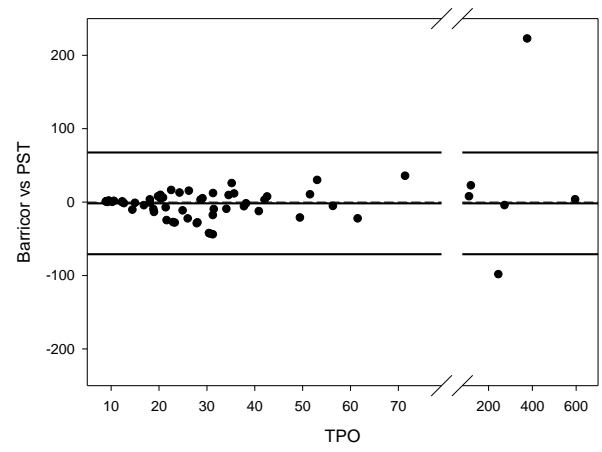
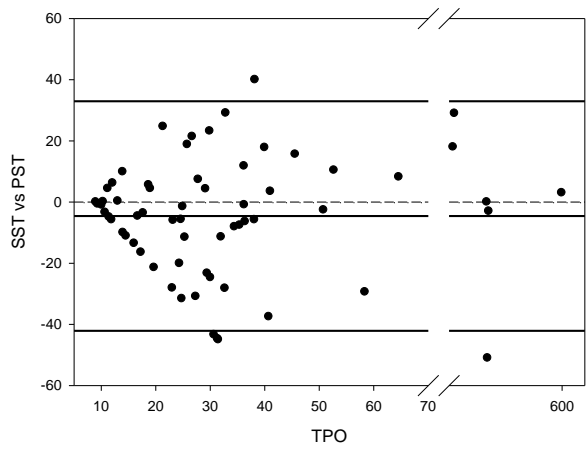
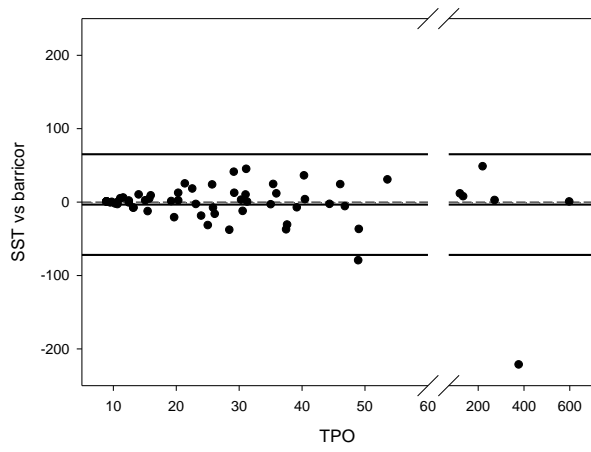
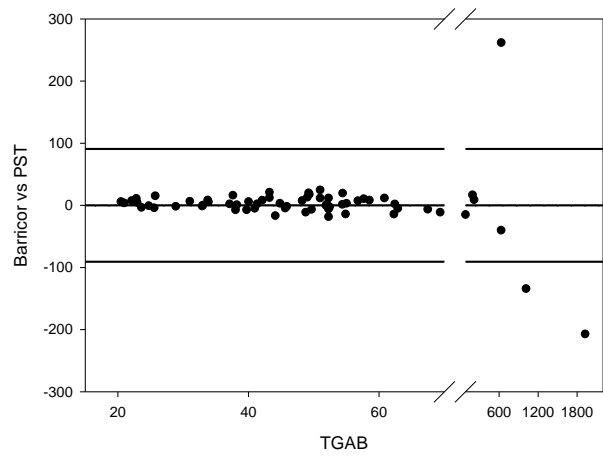
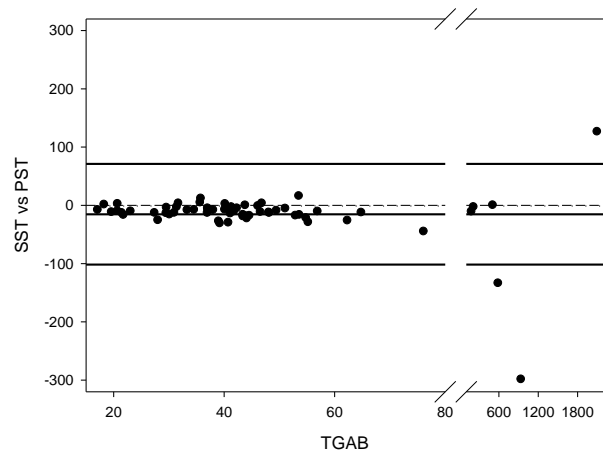
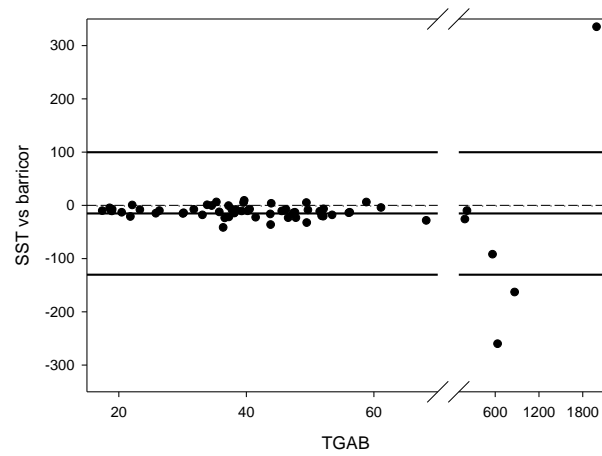


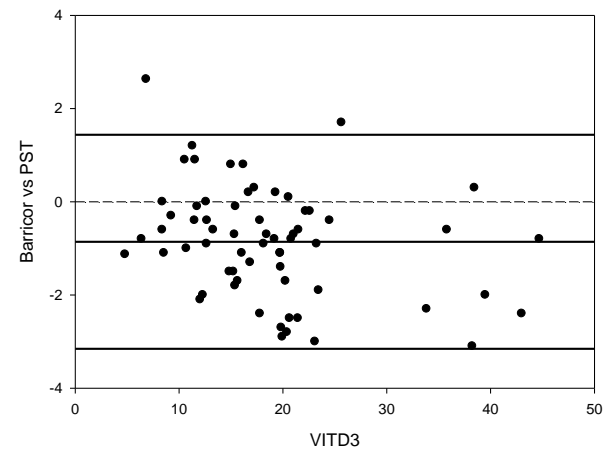
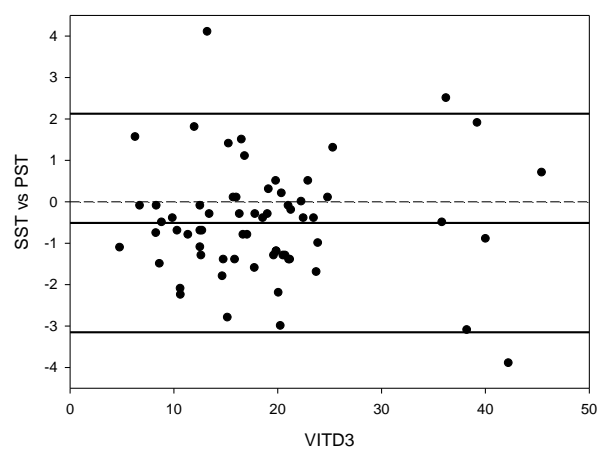
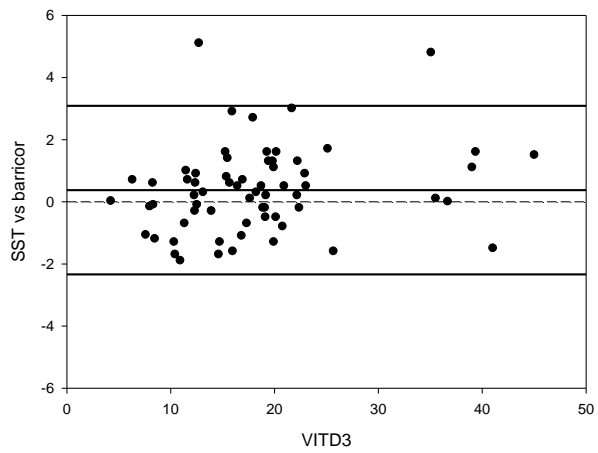
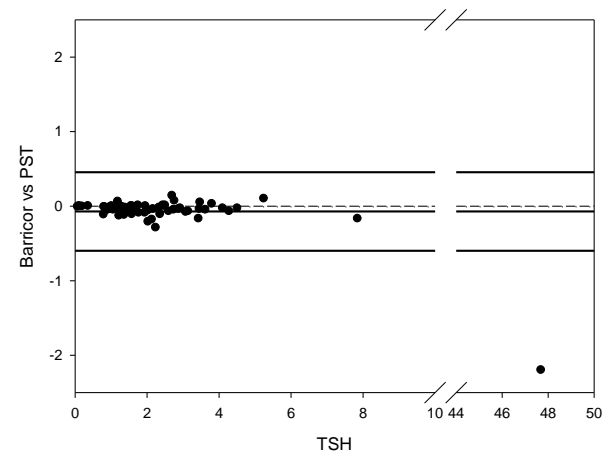
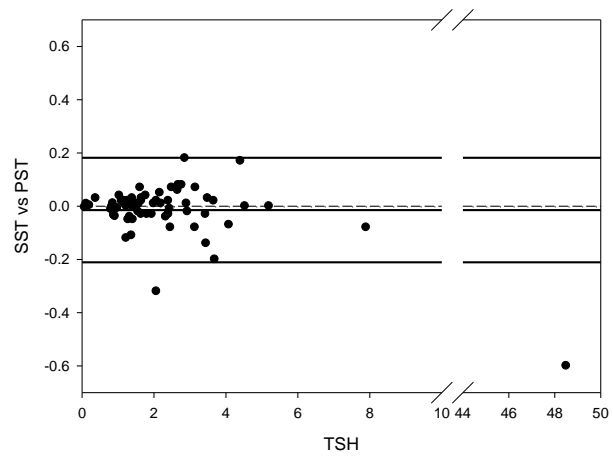
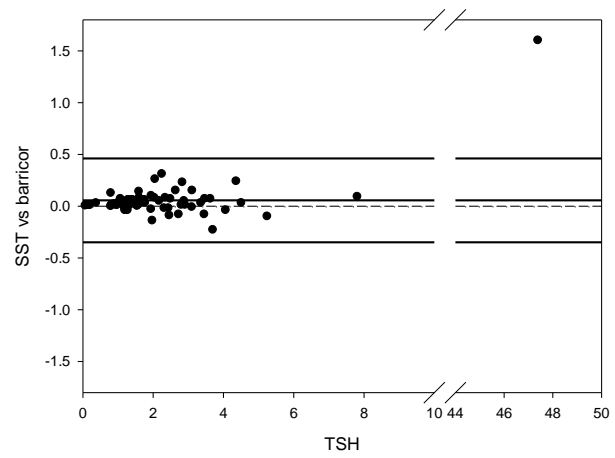




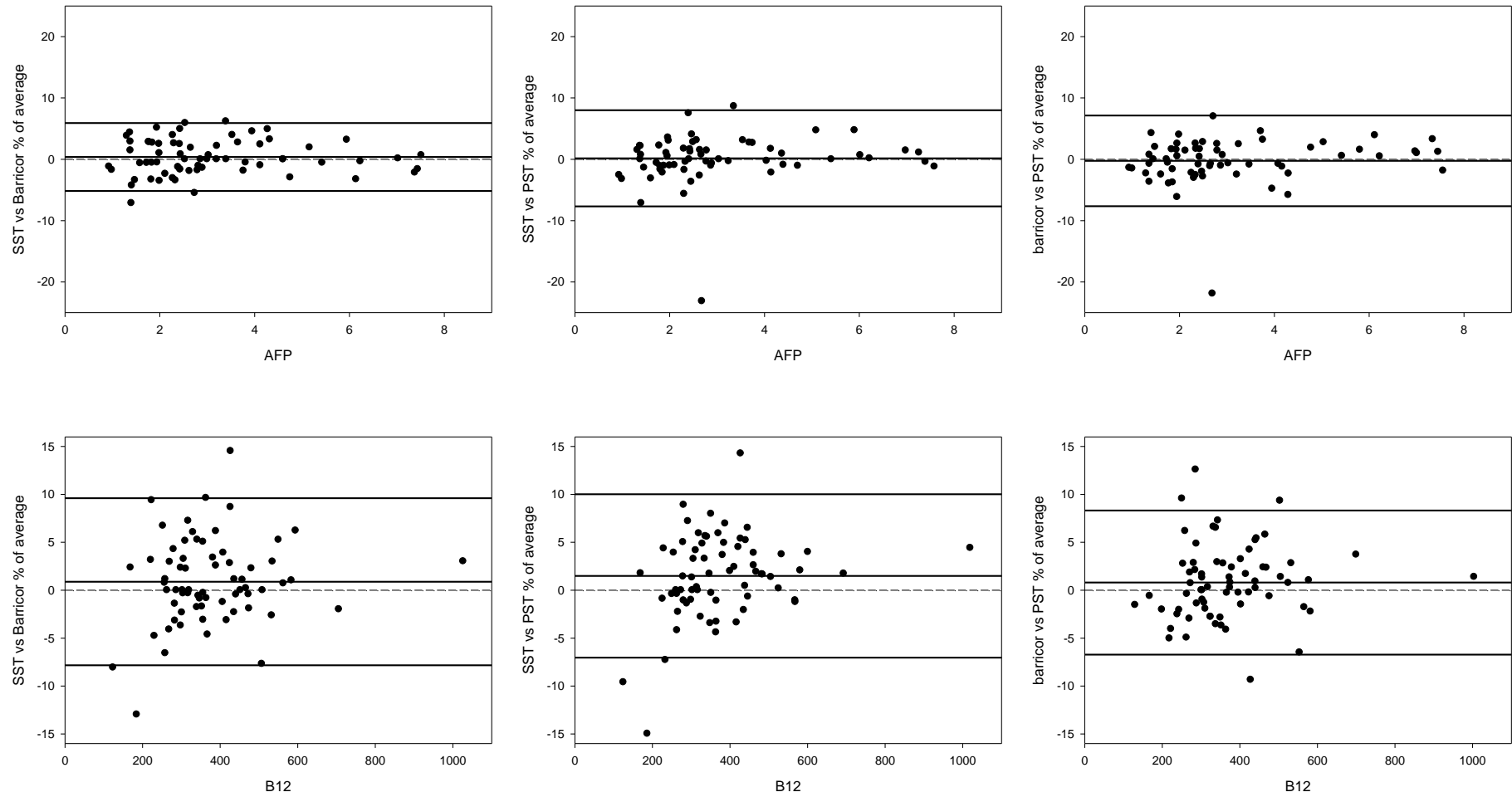




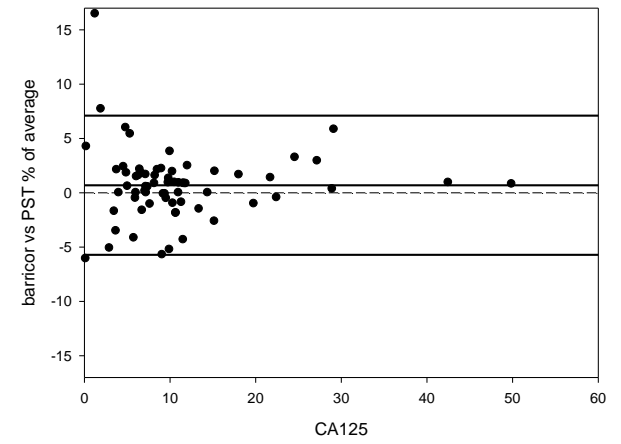
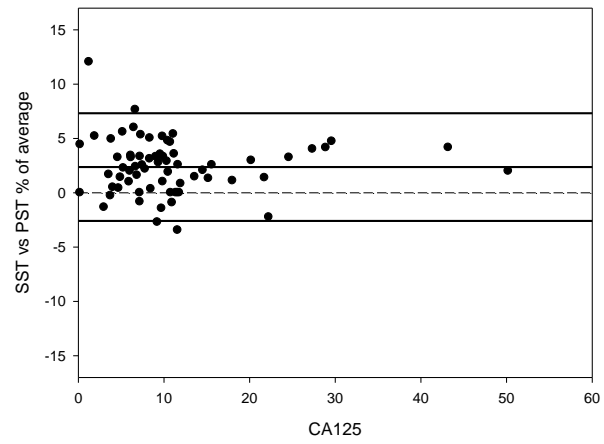
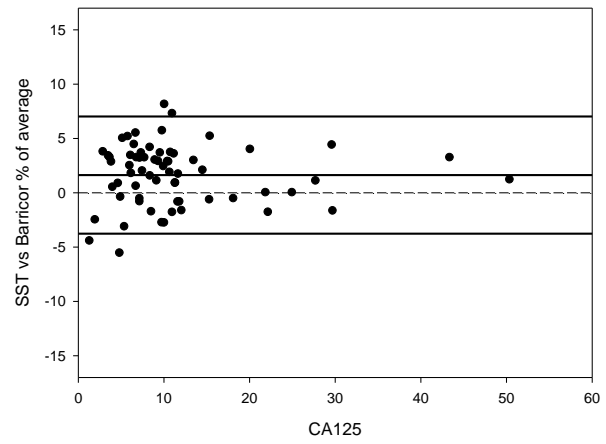
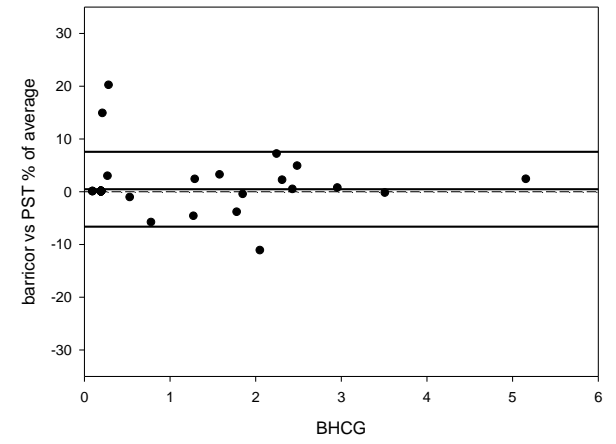
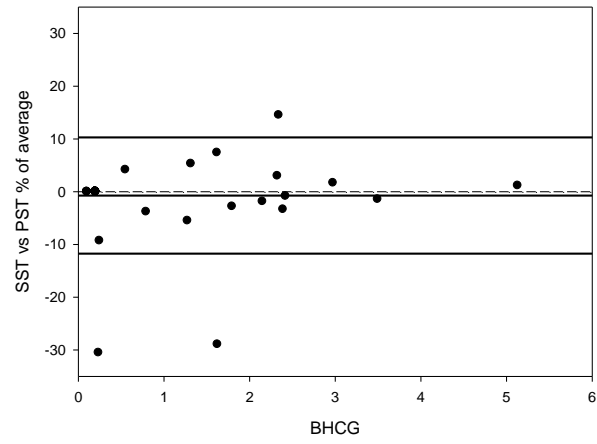
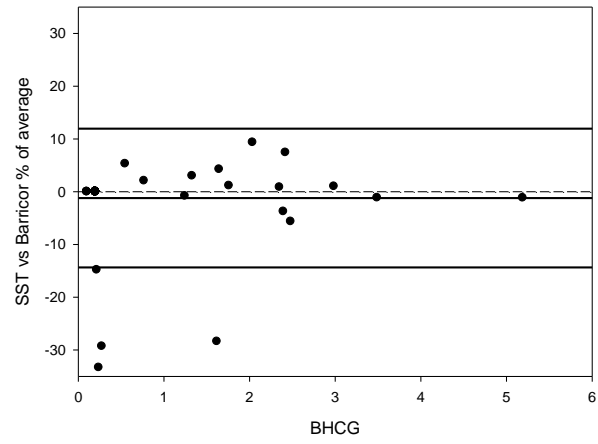


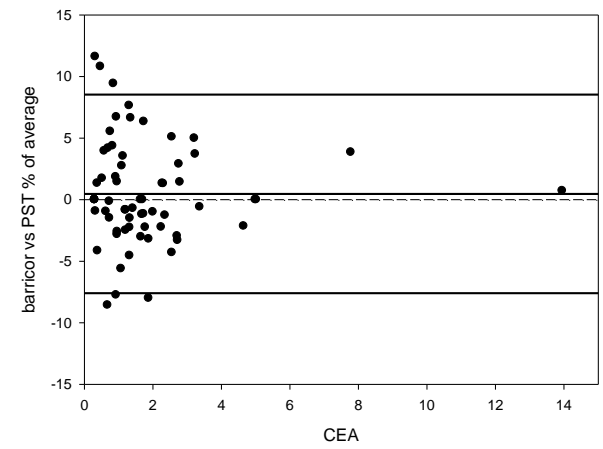
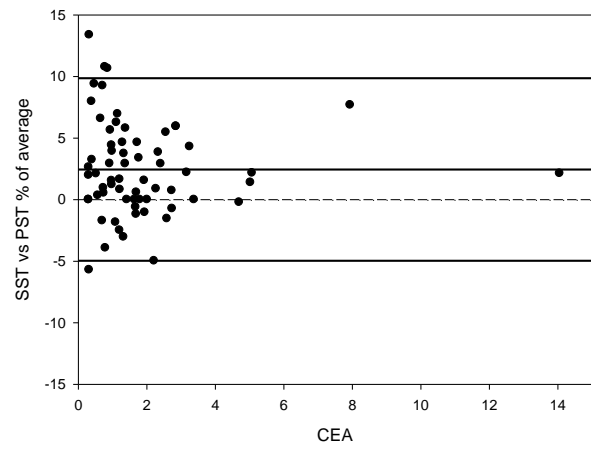
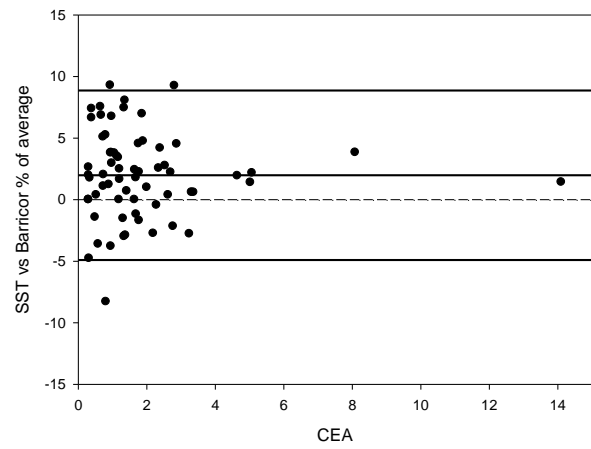
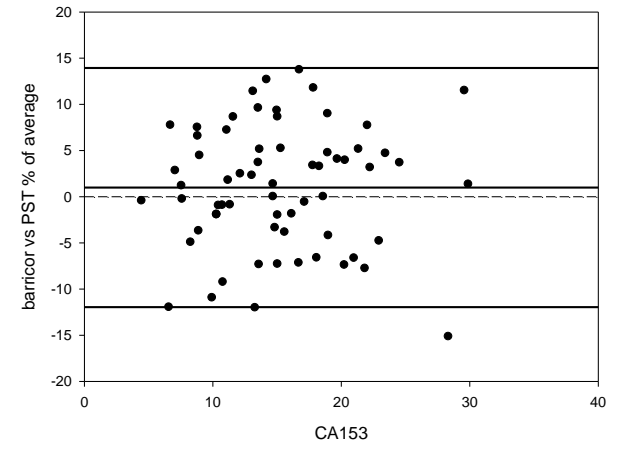
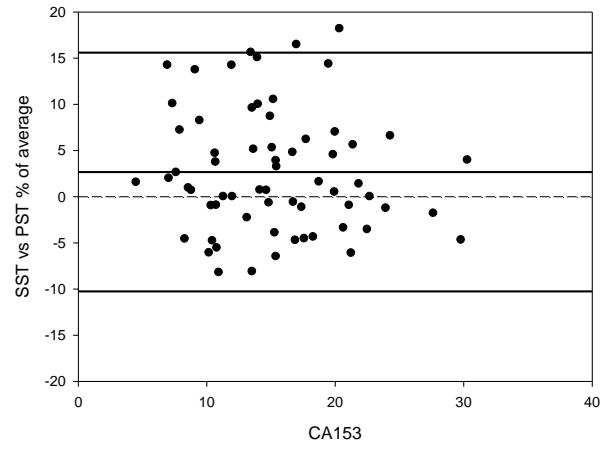
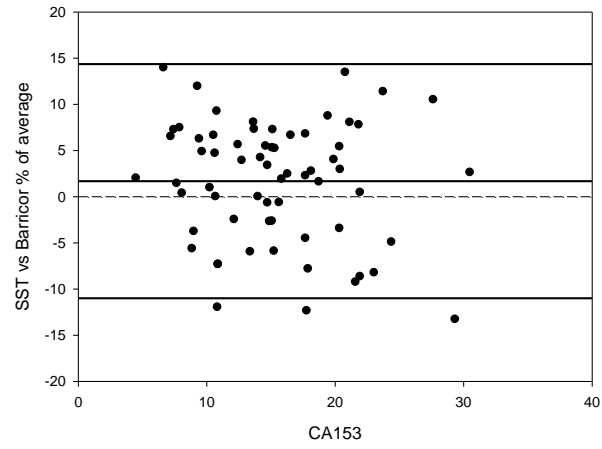


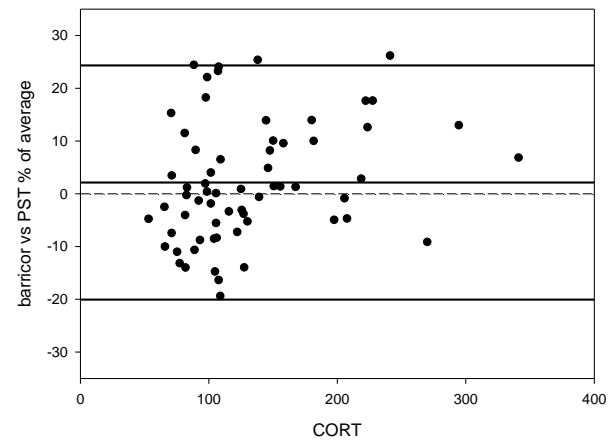
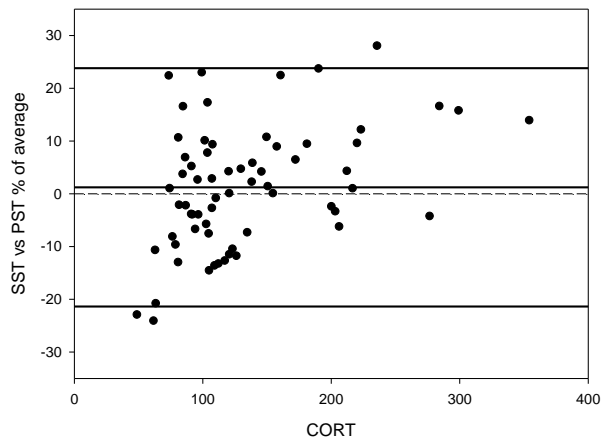
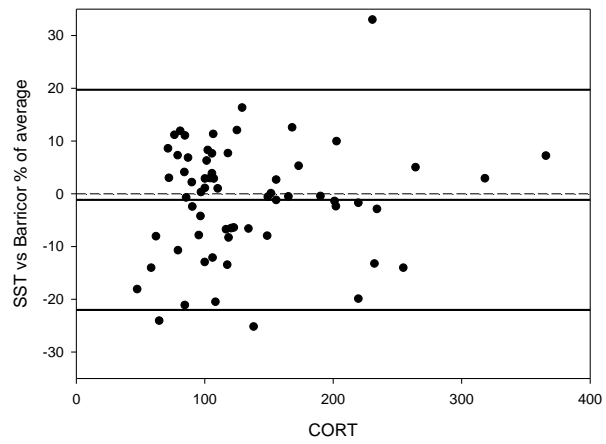
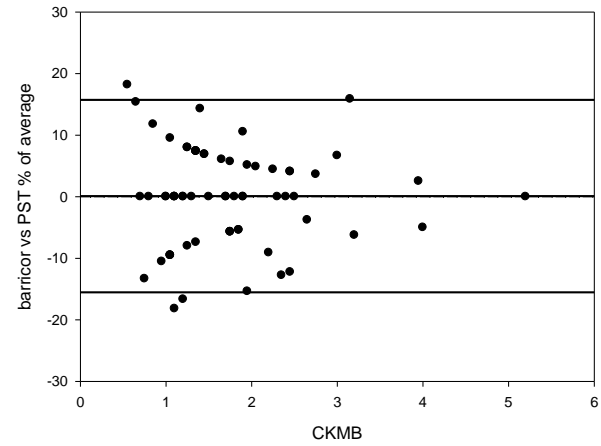
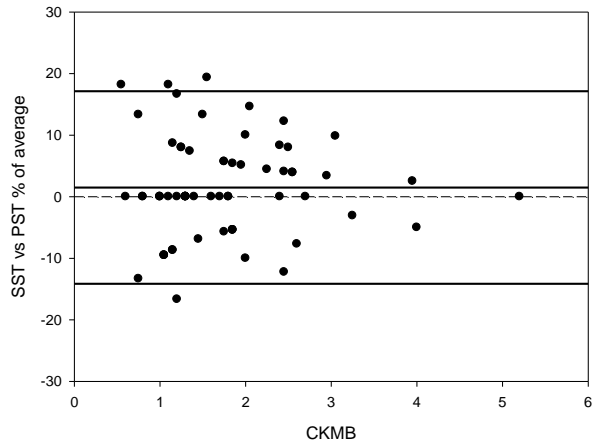
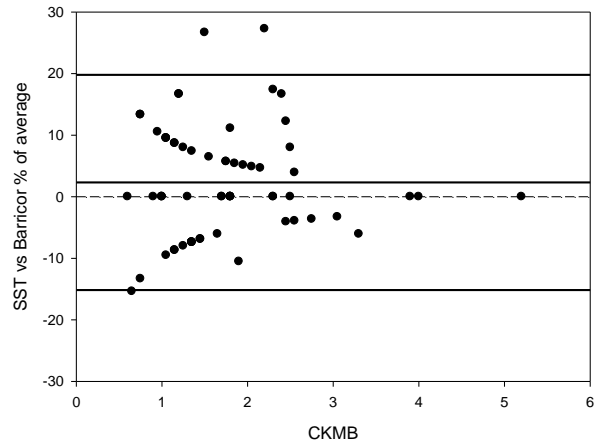
**Figure S2B:** B&A plots for immunochemical analytes: the pair value differences were expressed as percentage.

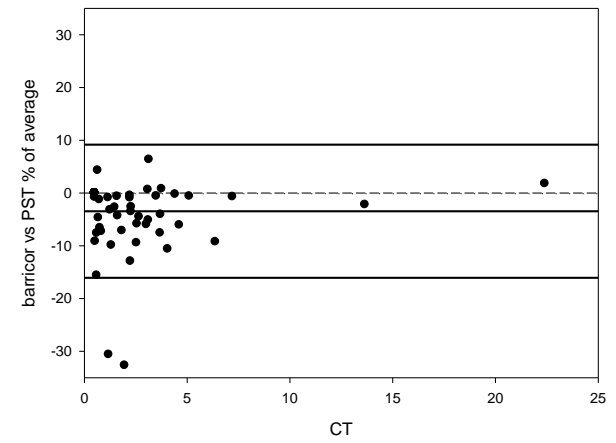
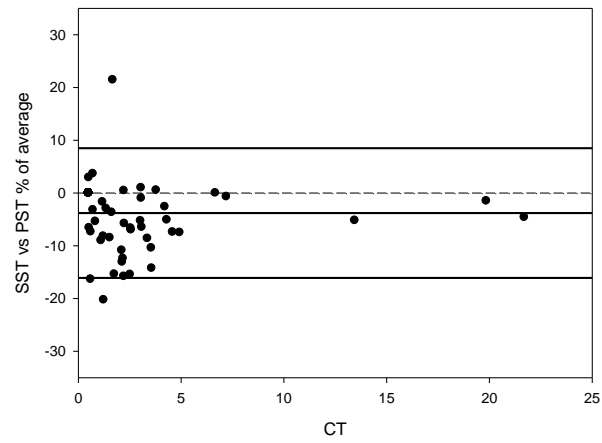
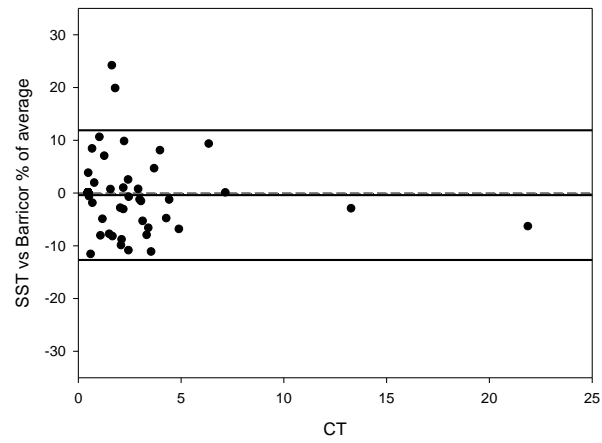
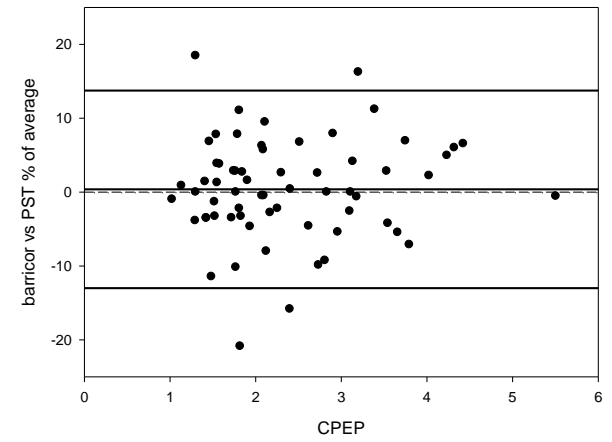
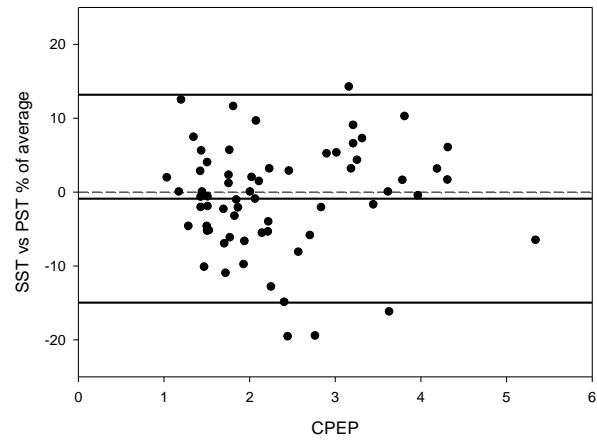
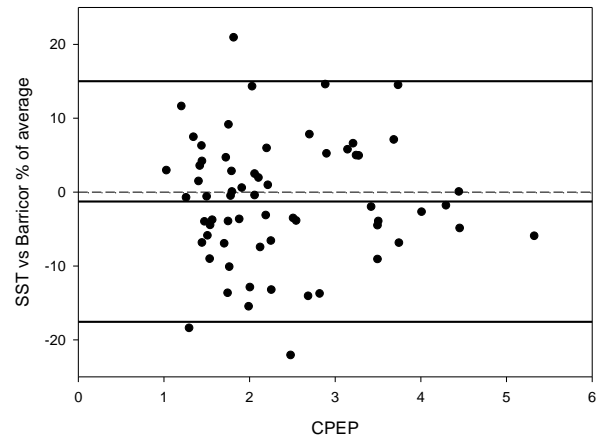


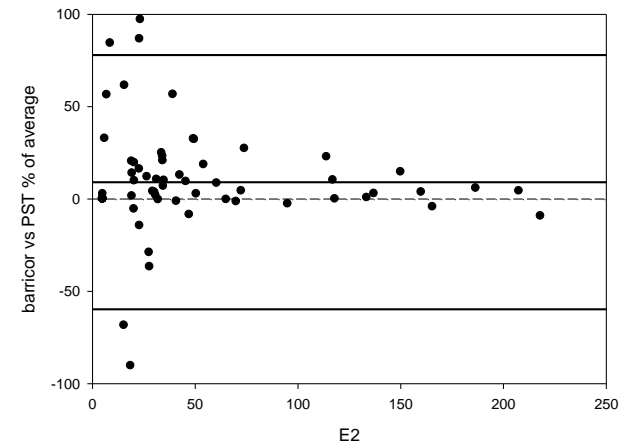
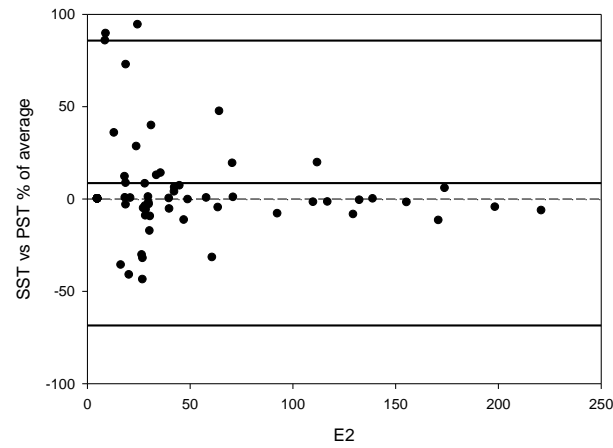
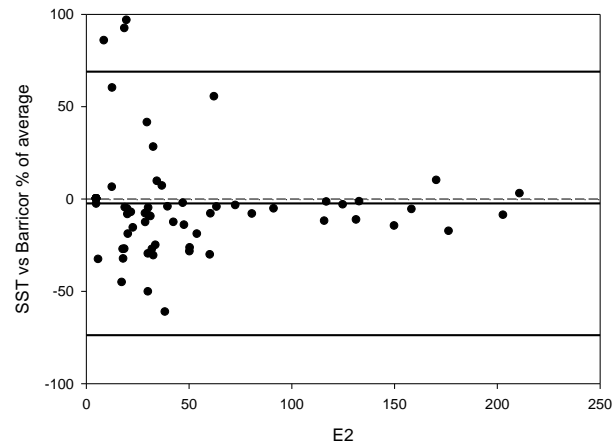
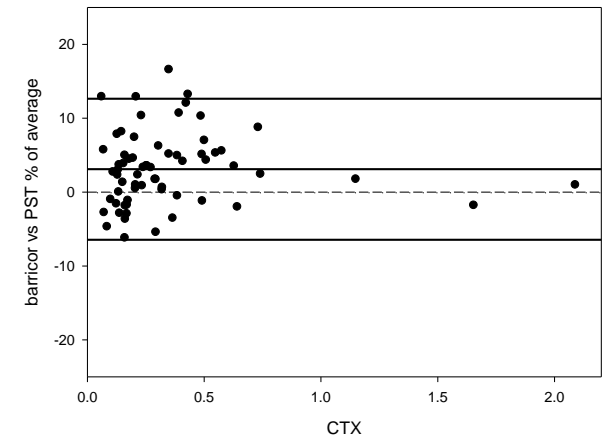
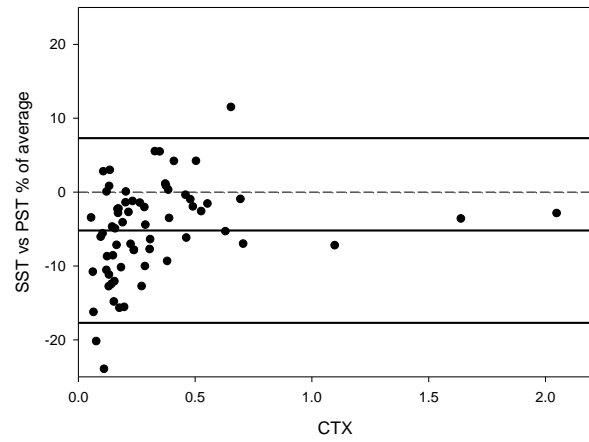
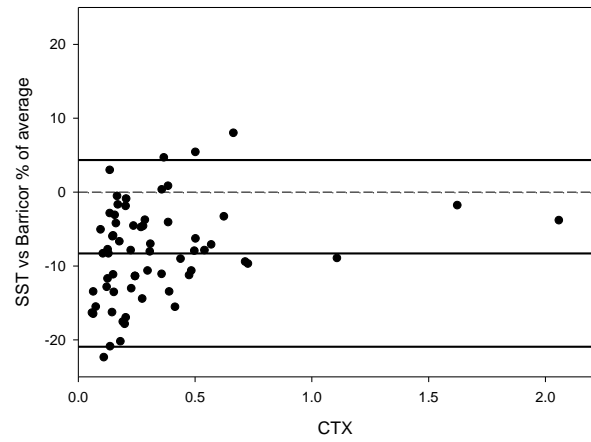


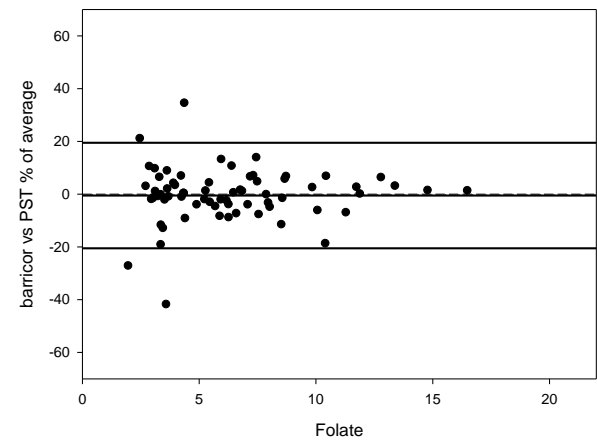
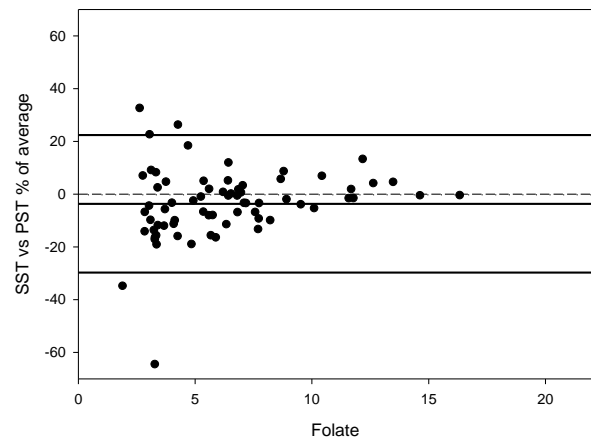
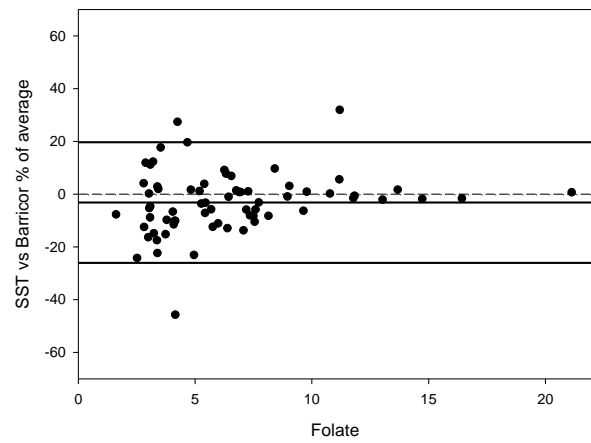
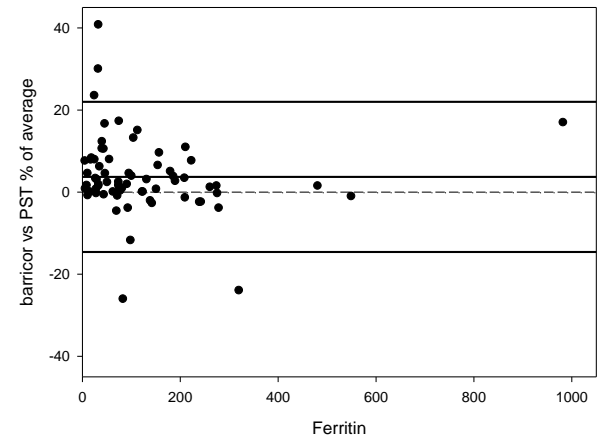
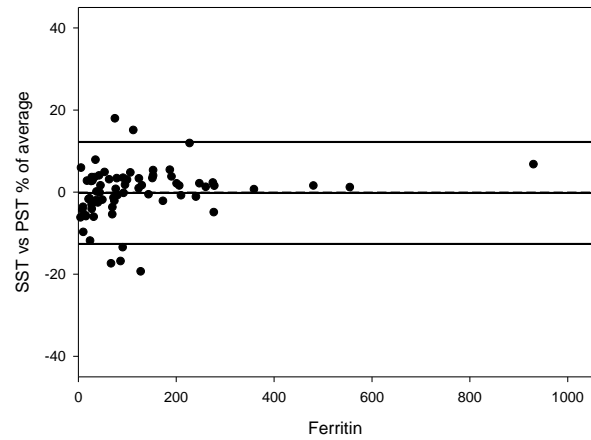
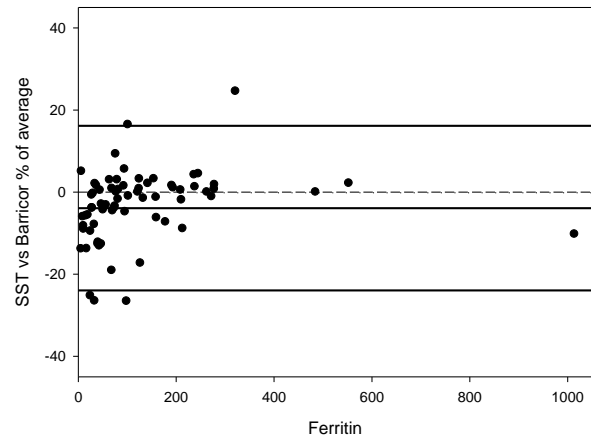


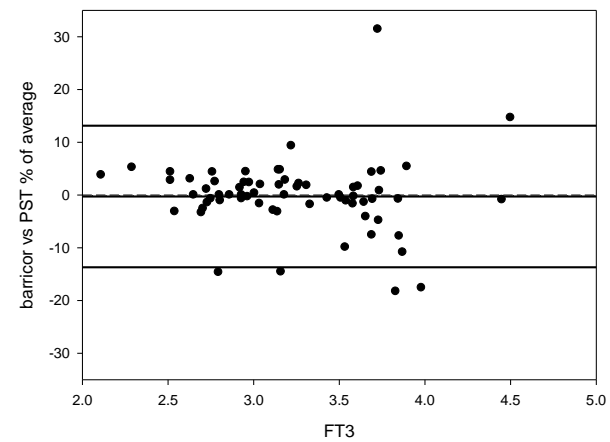
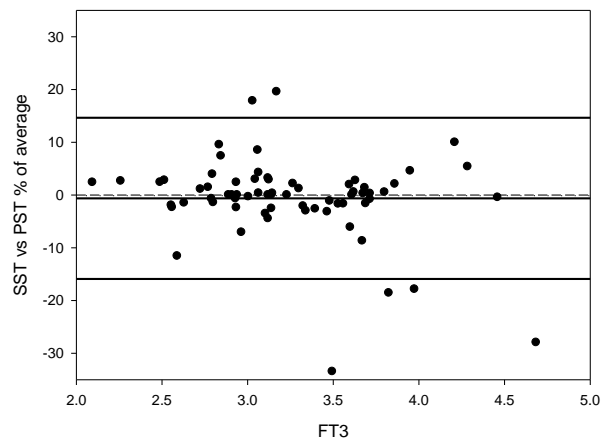
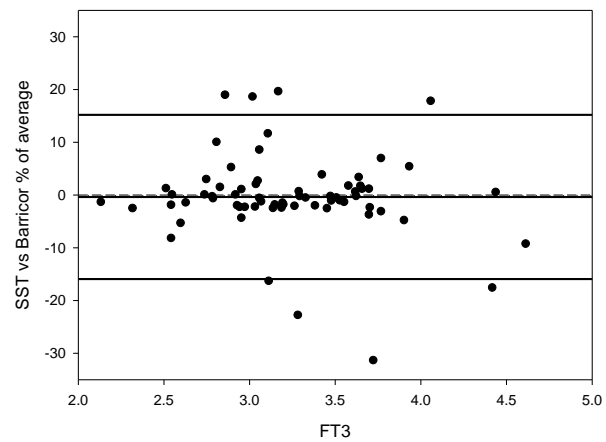
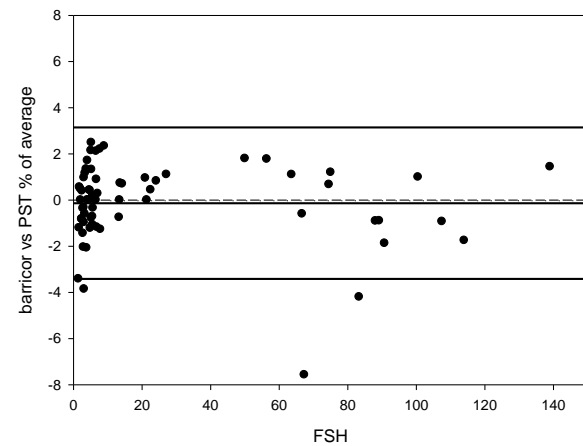
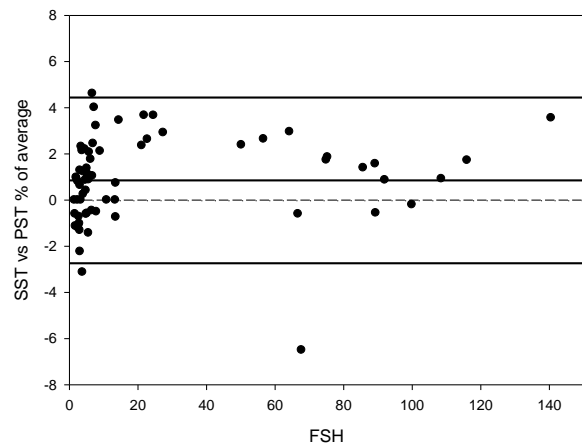
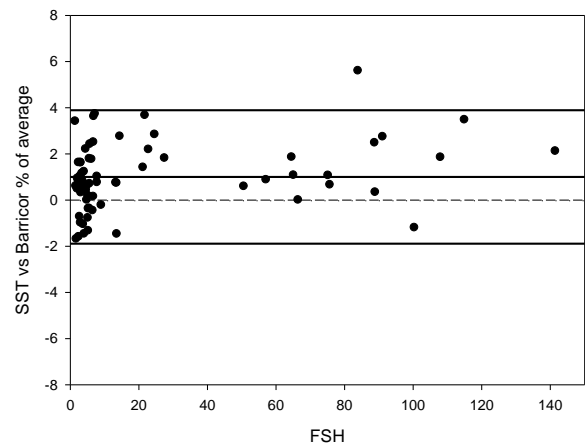


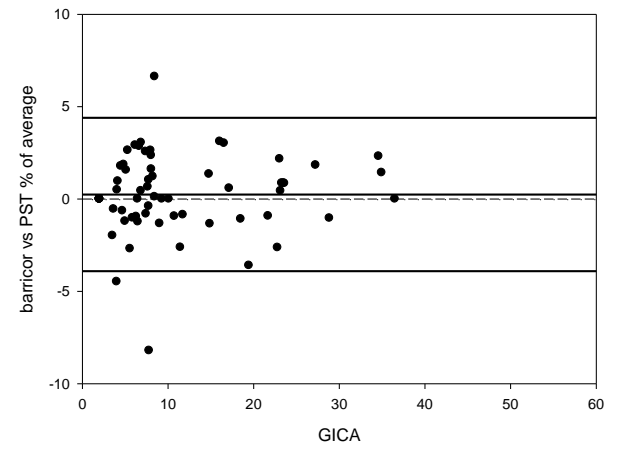
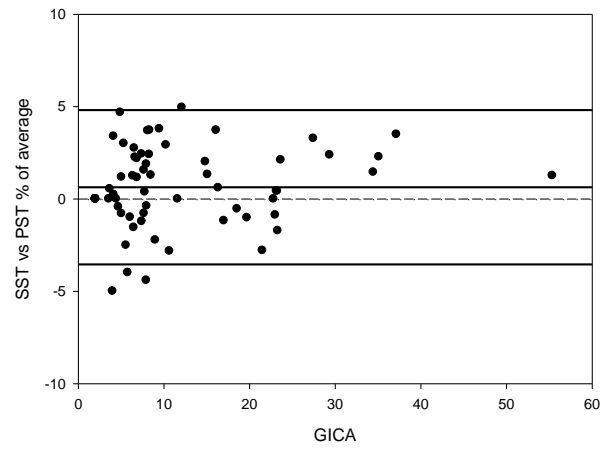
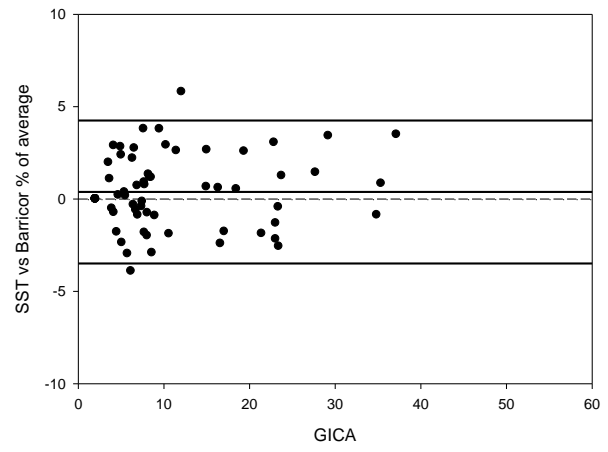
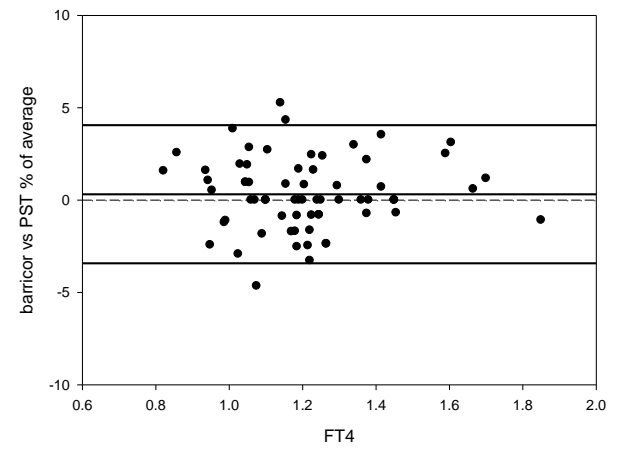
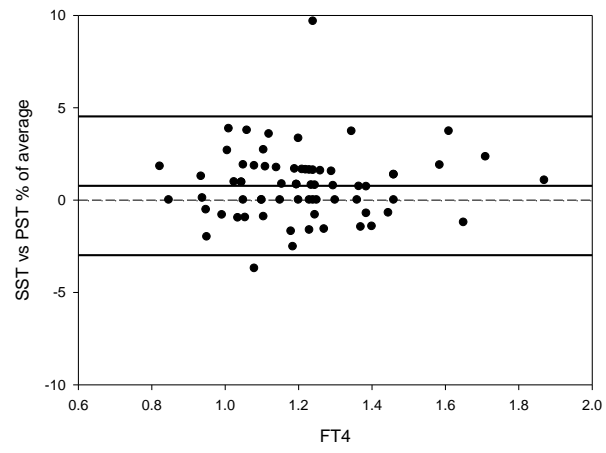
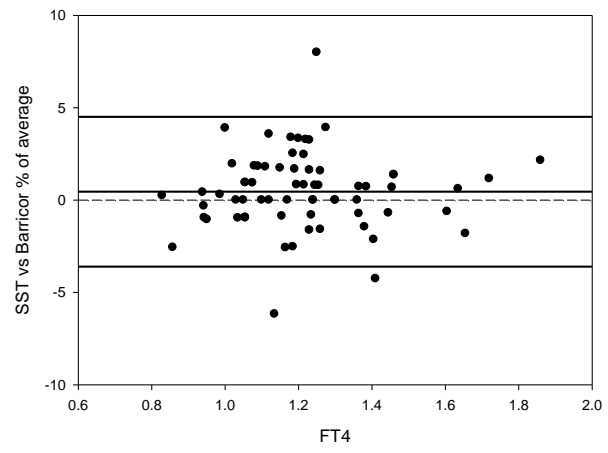




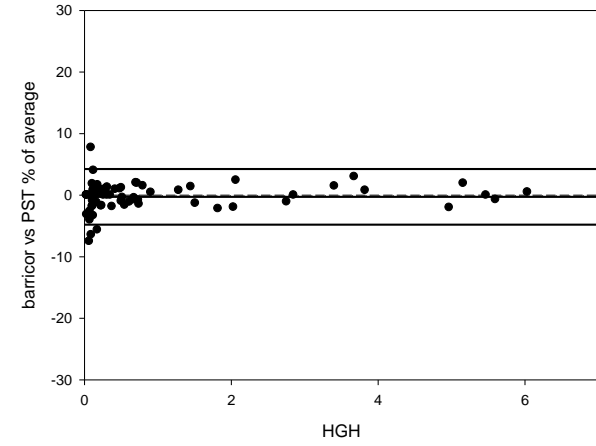
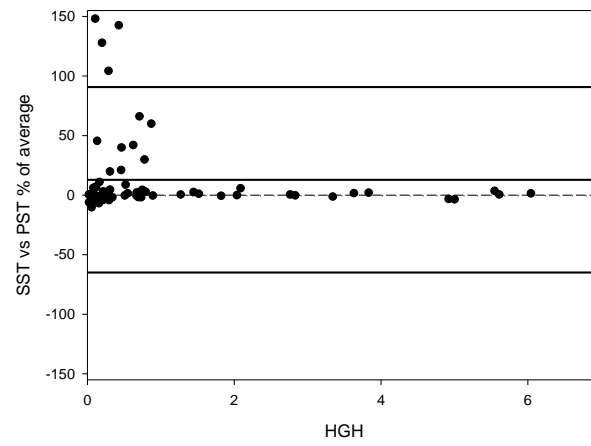
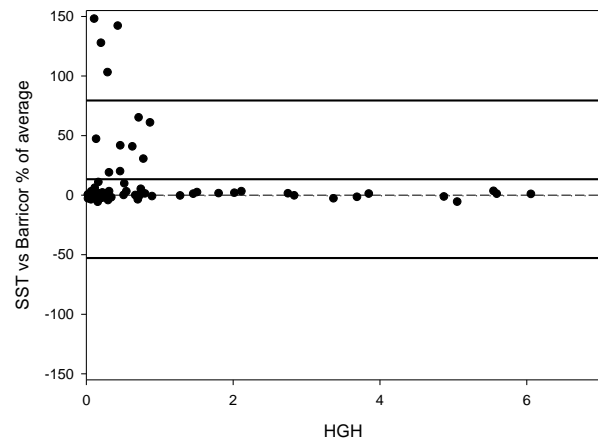
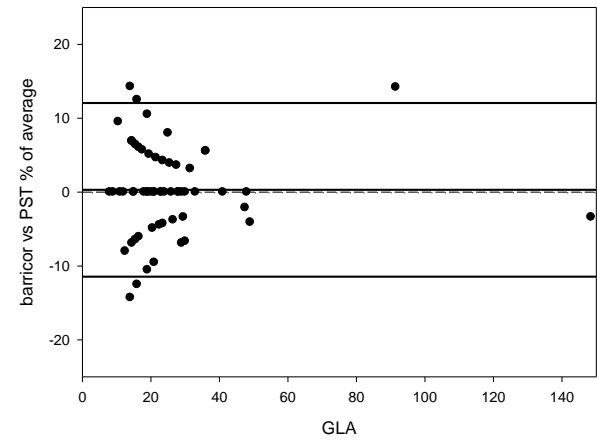
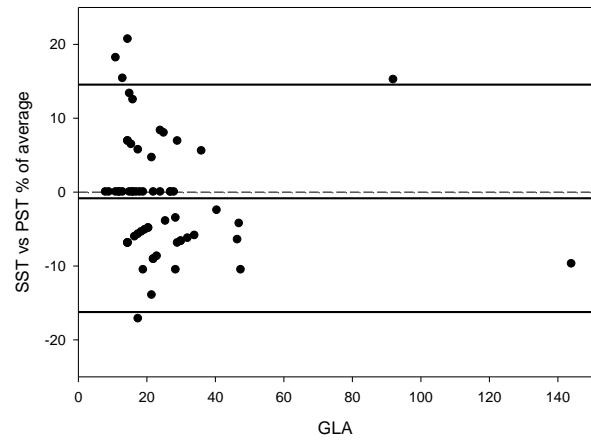
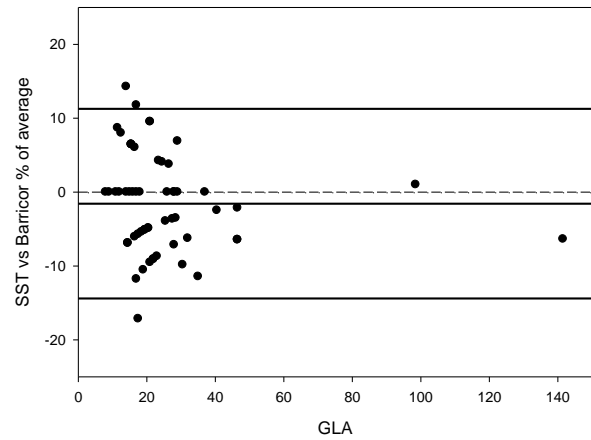


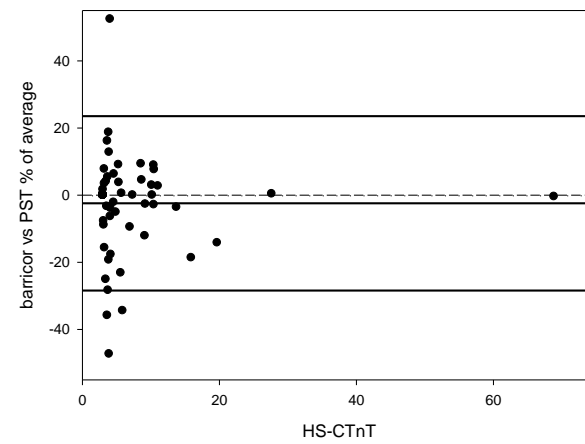
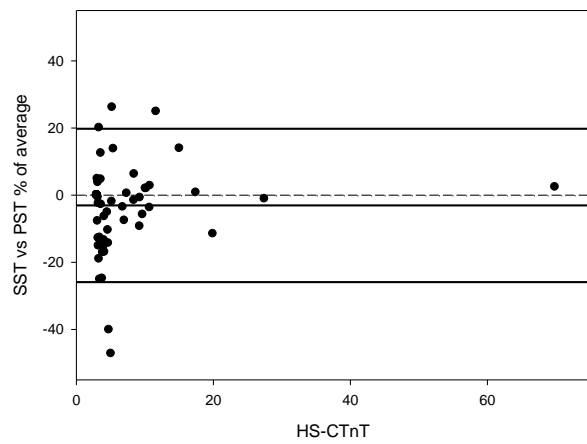
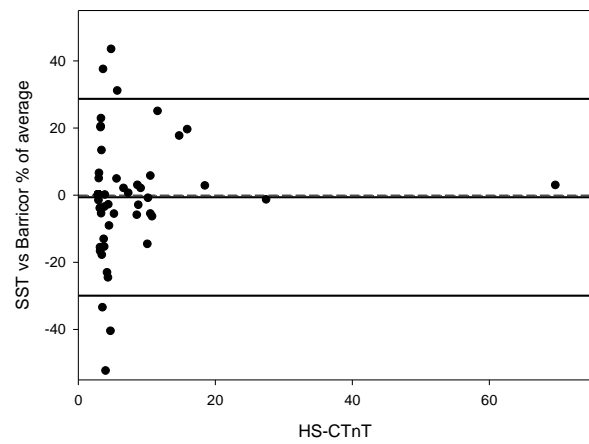
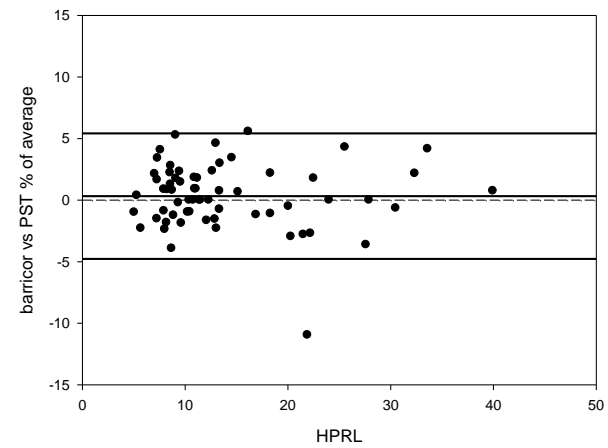
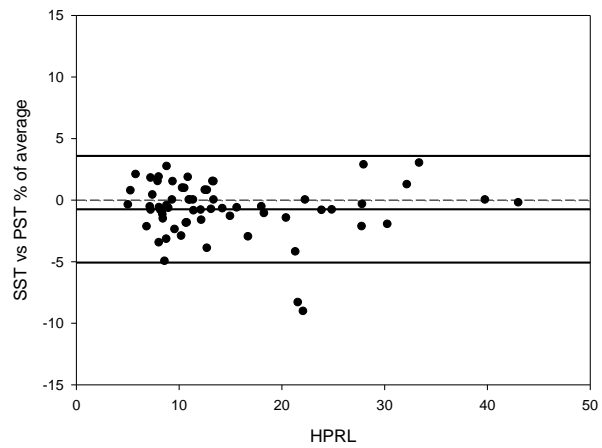
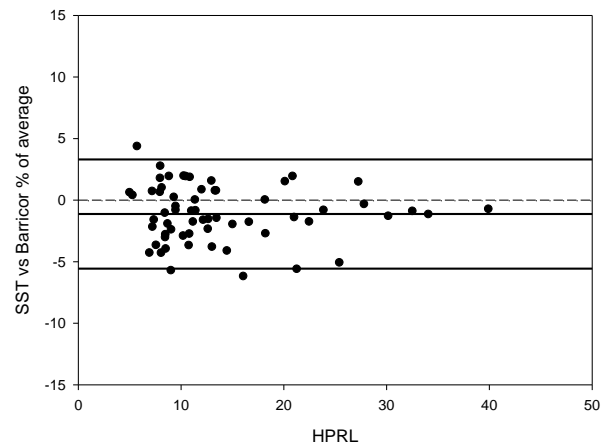


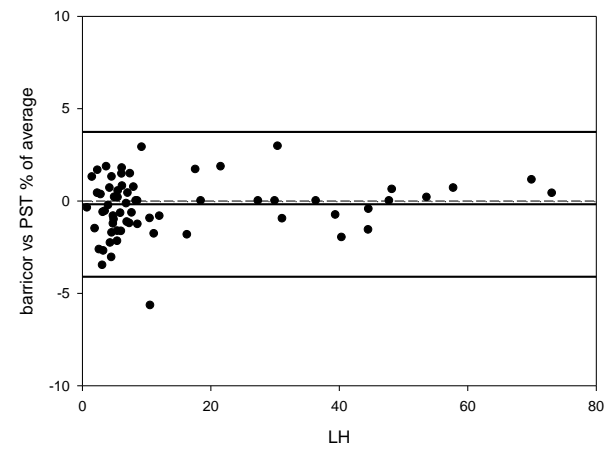
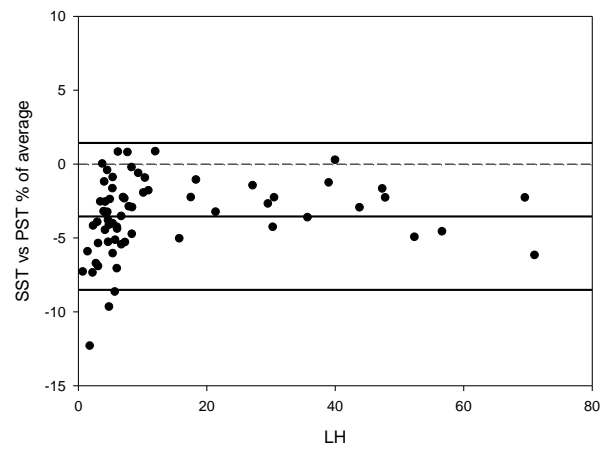
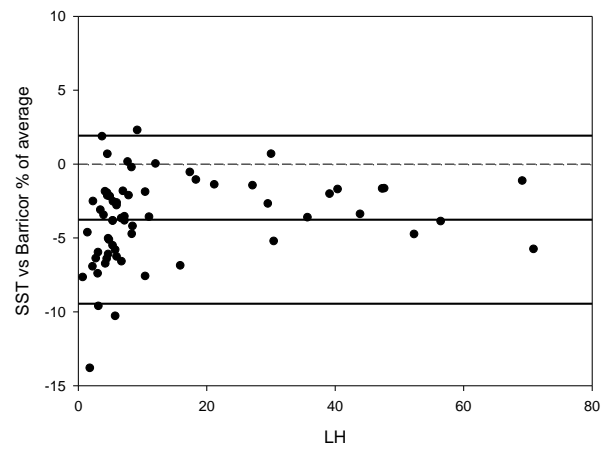
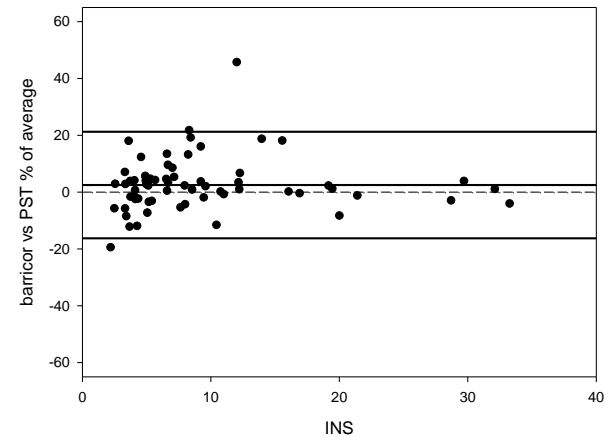
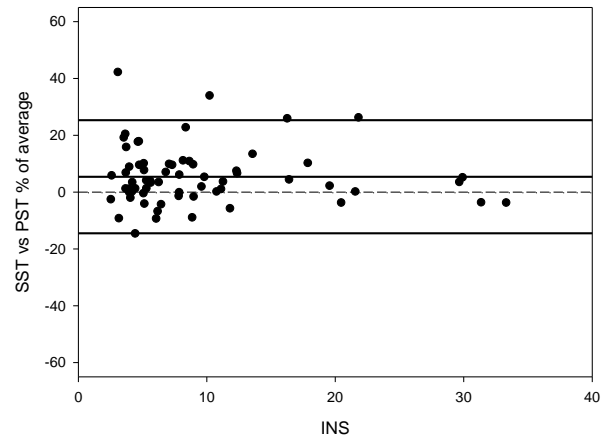
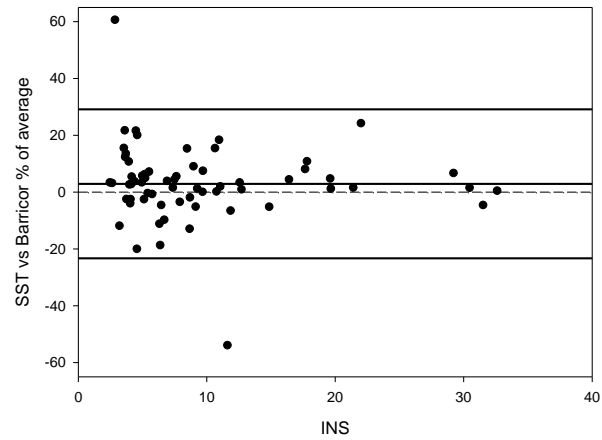


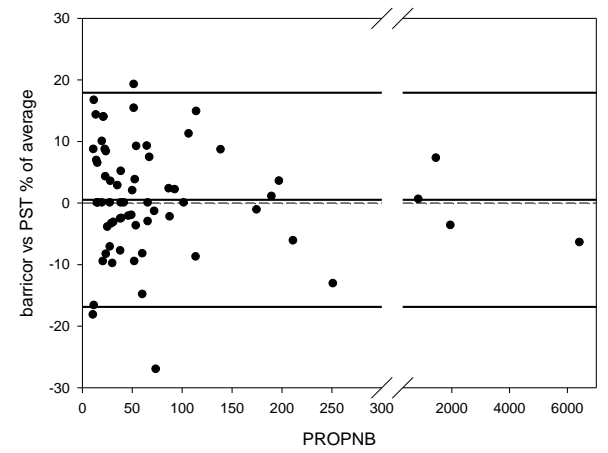
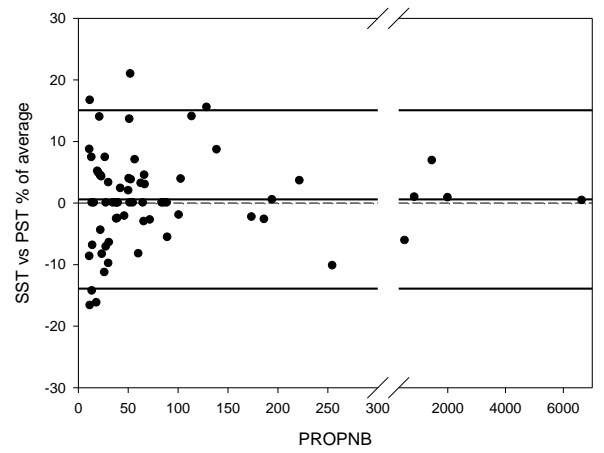
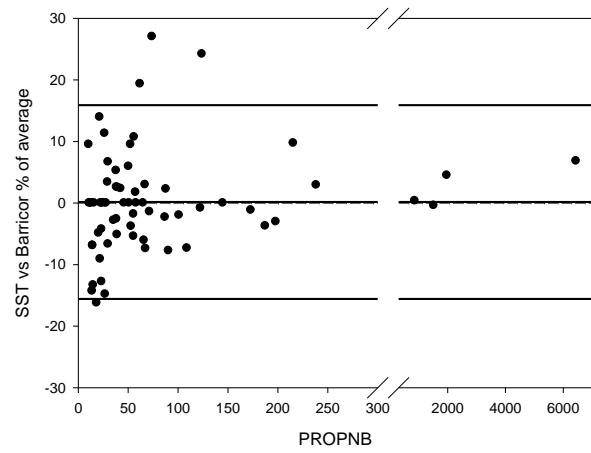
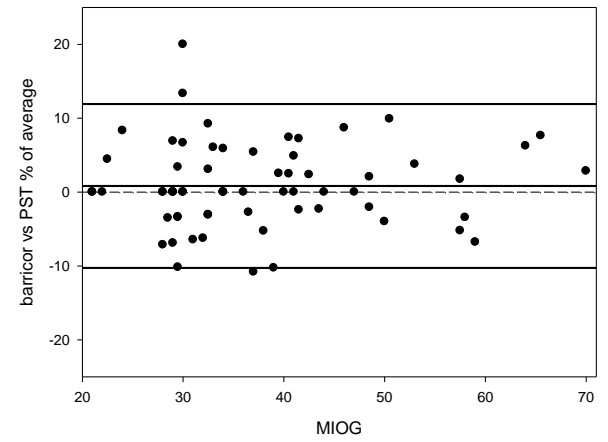
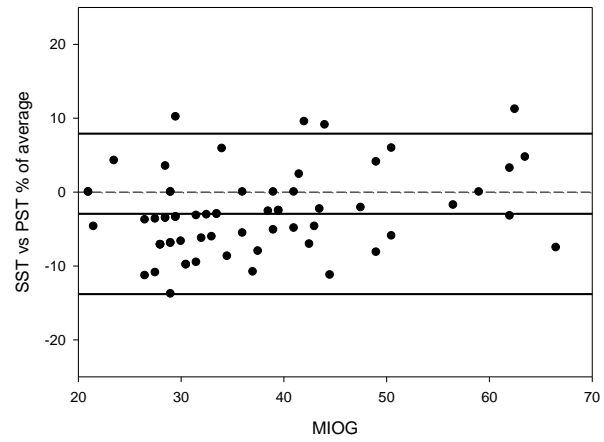
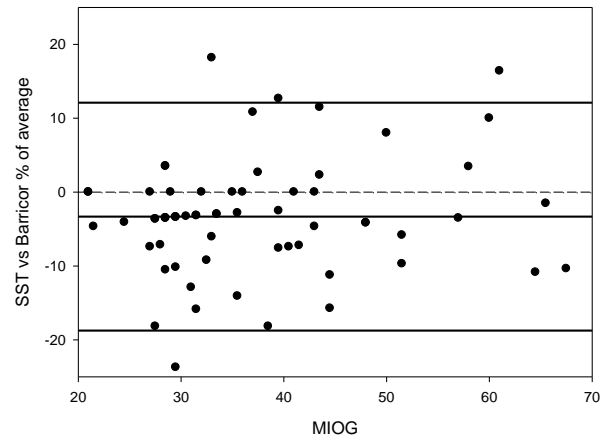


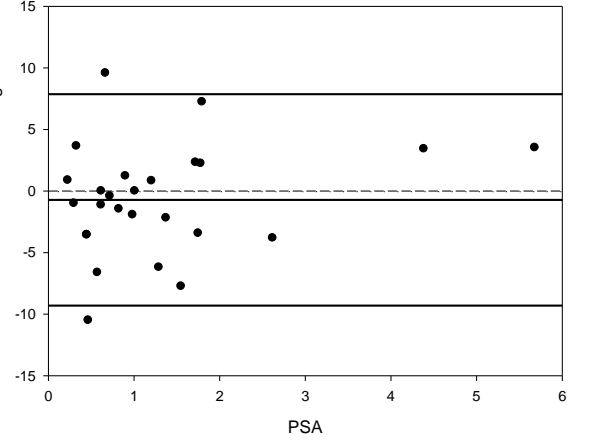
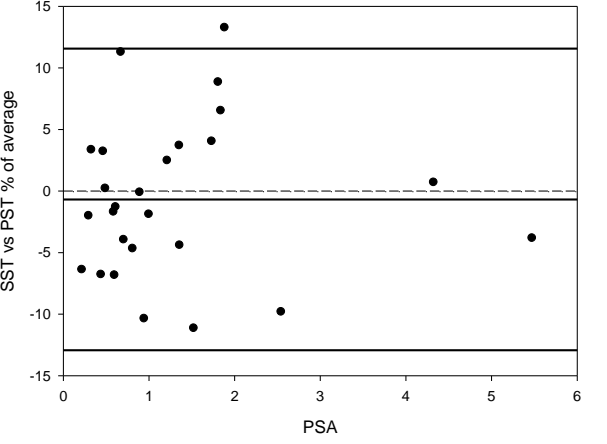
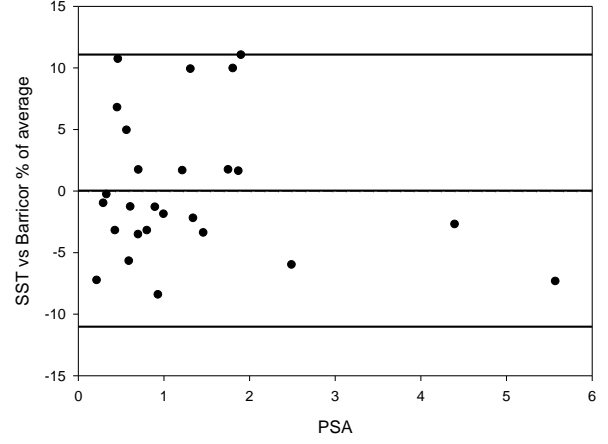
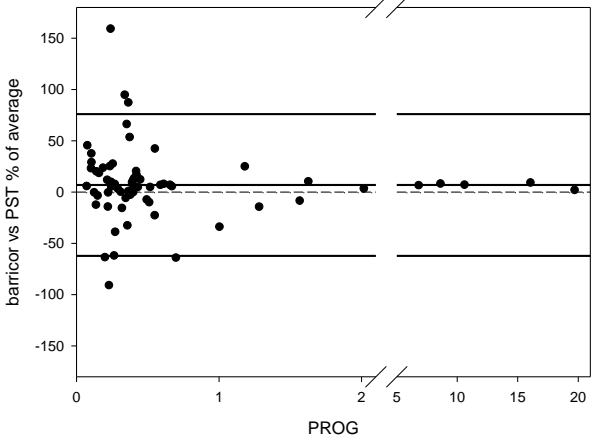
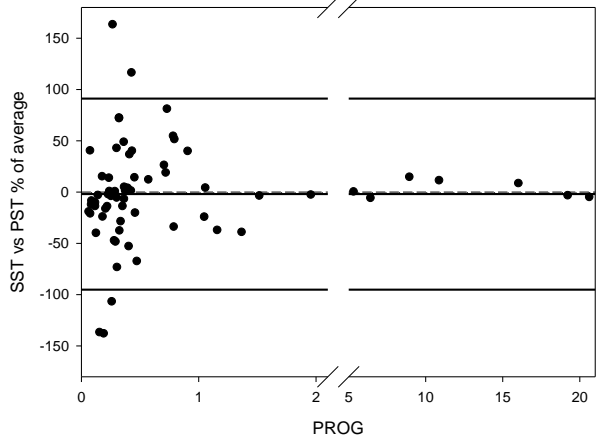
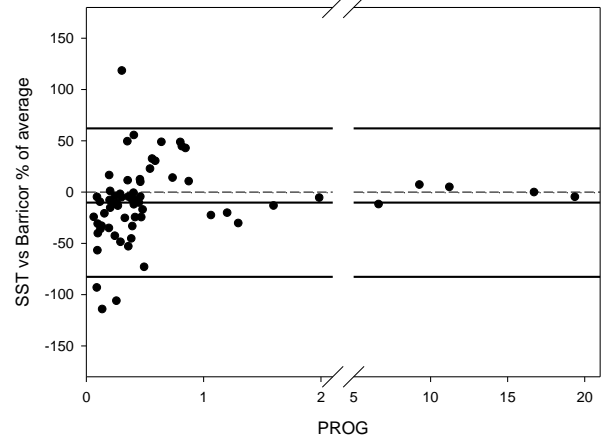


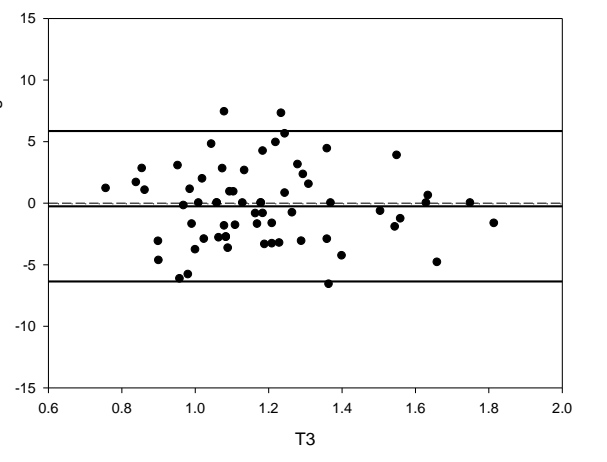
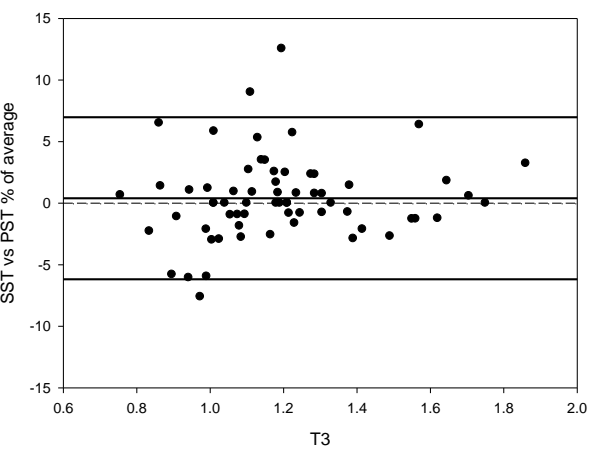
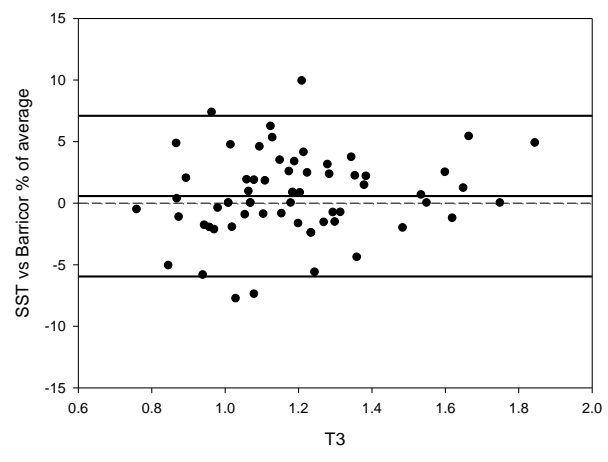
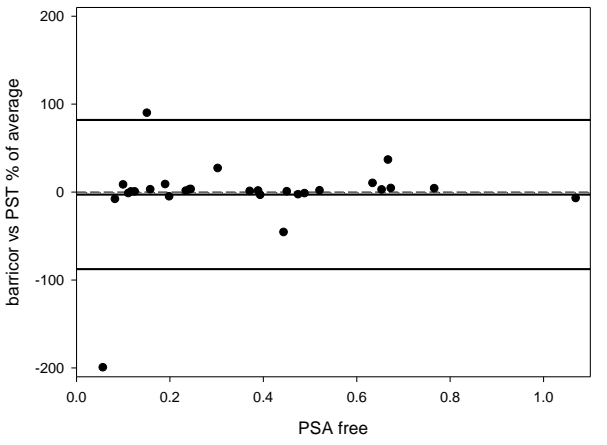
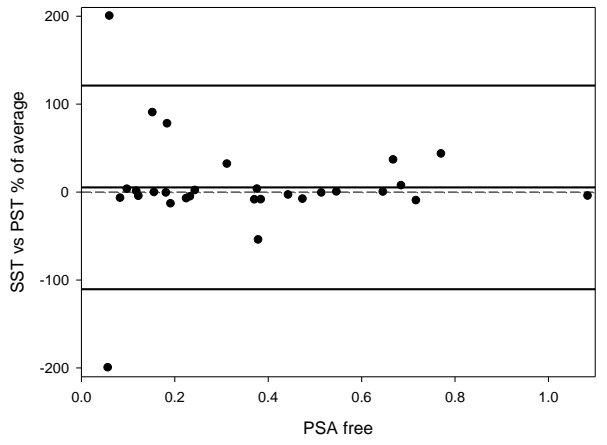
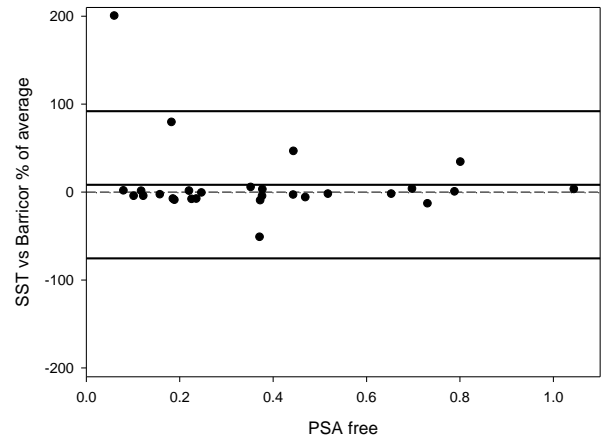


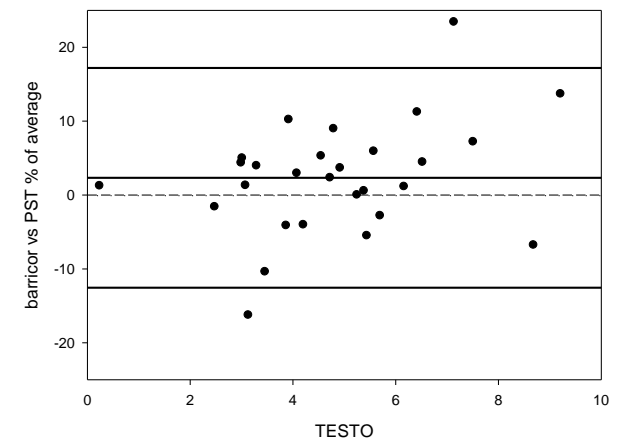
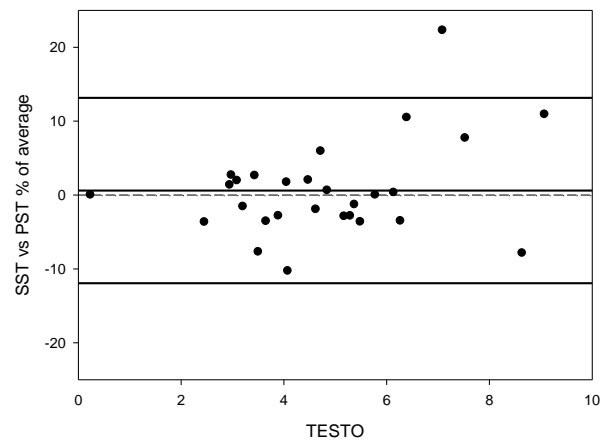
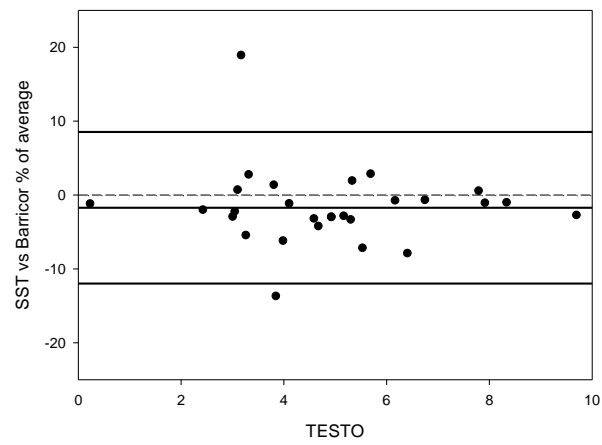
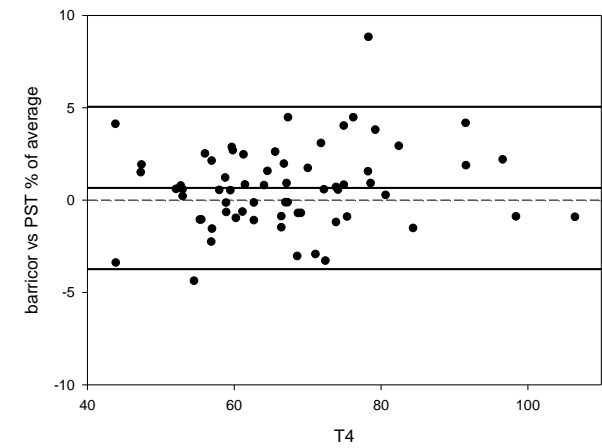
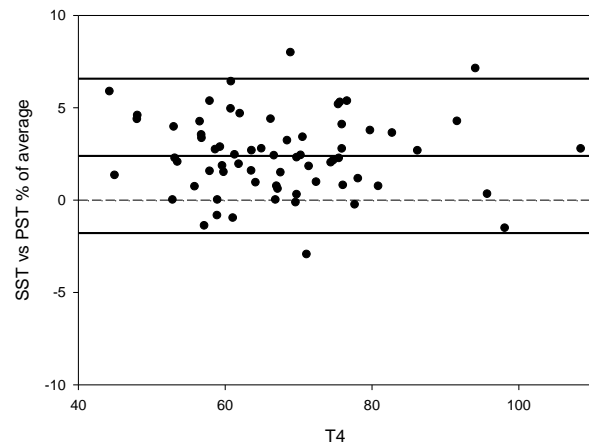
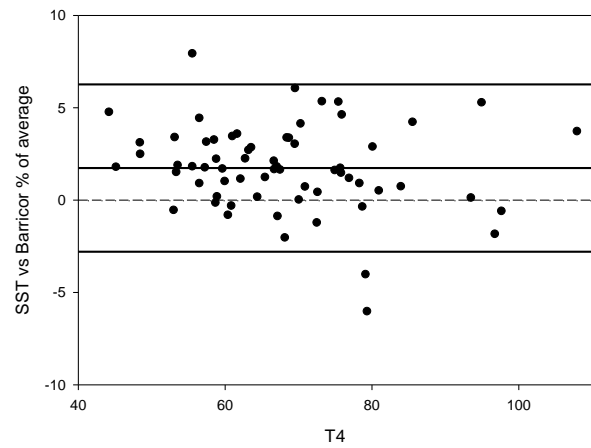


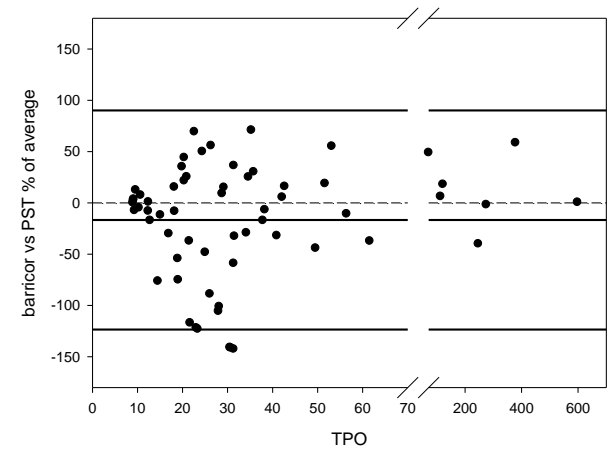
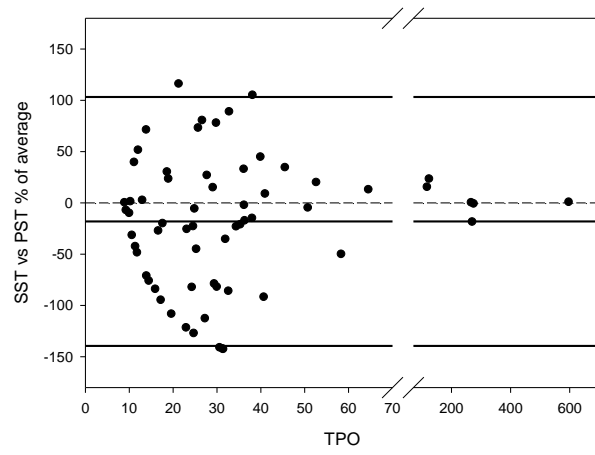
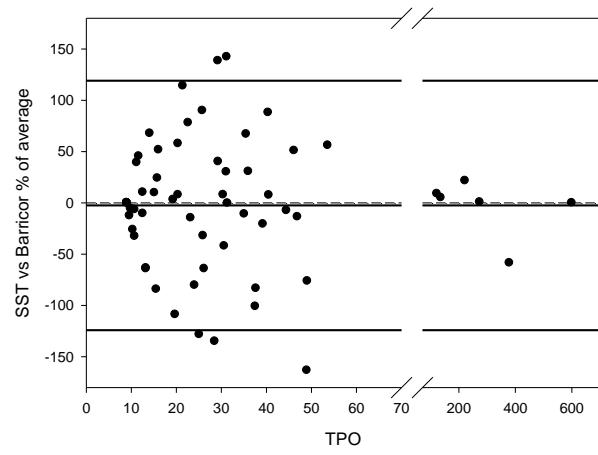
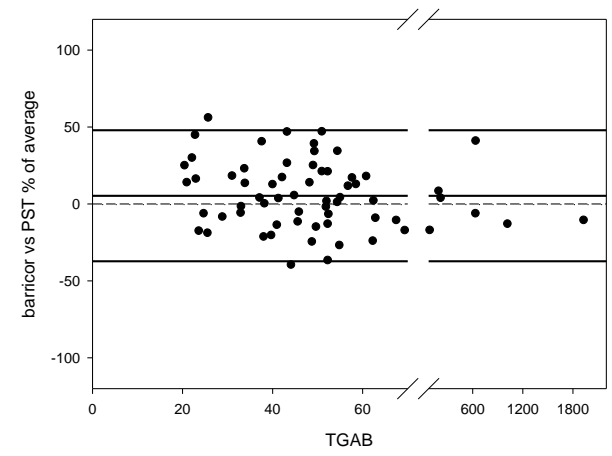
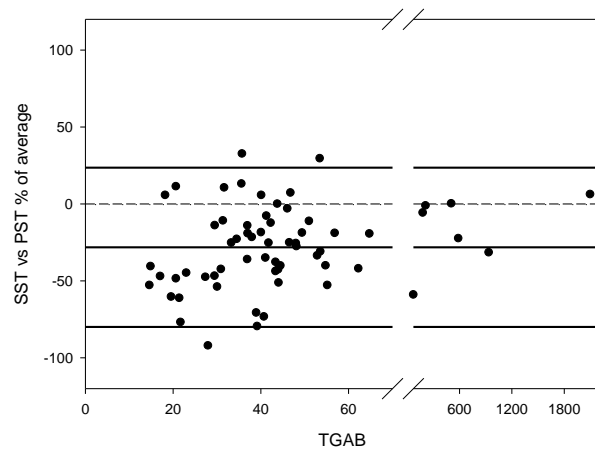
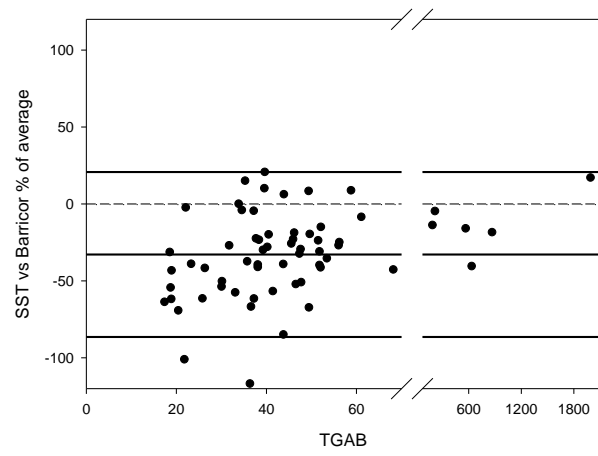




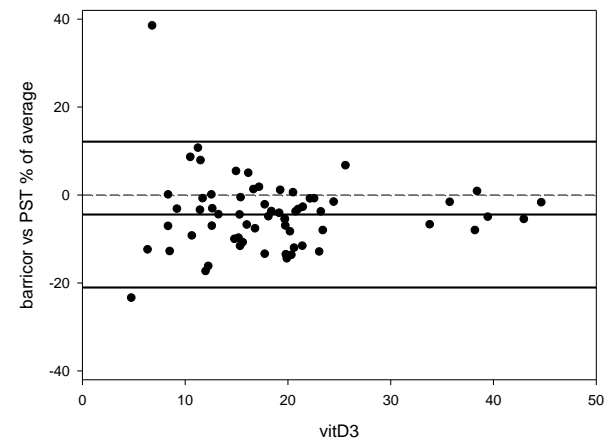
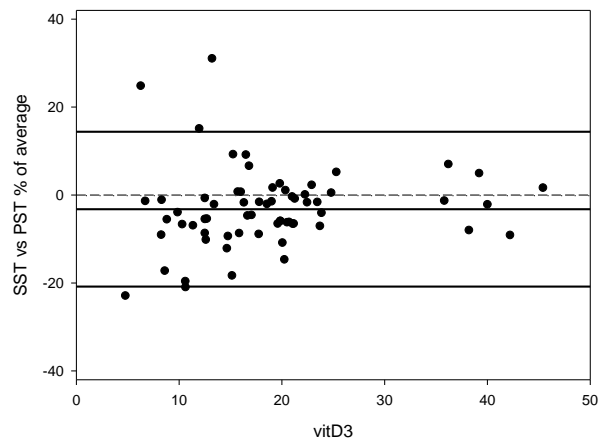
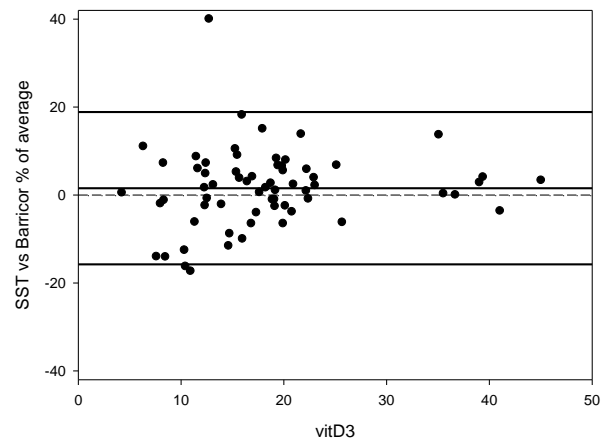
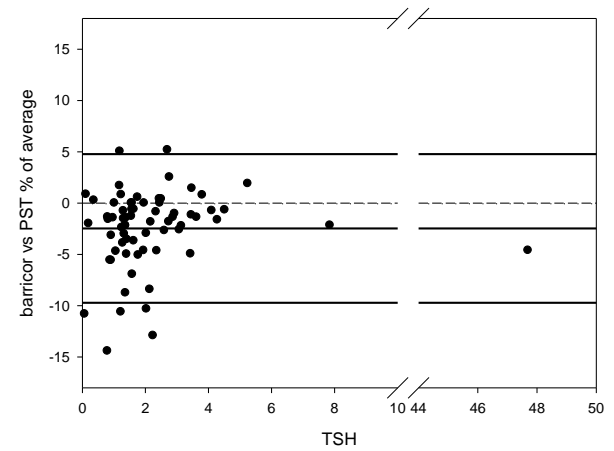
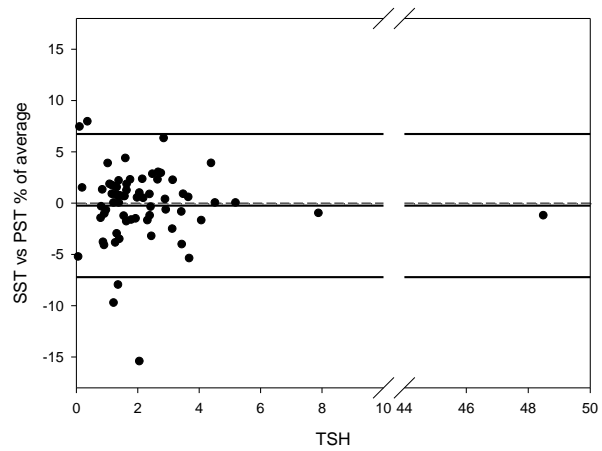
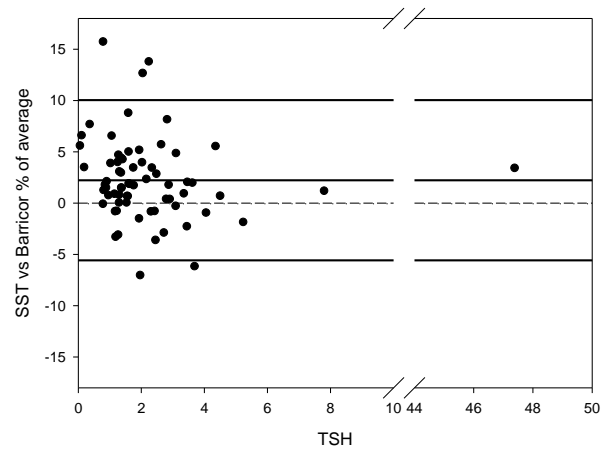




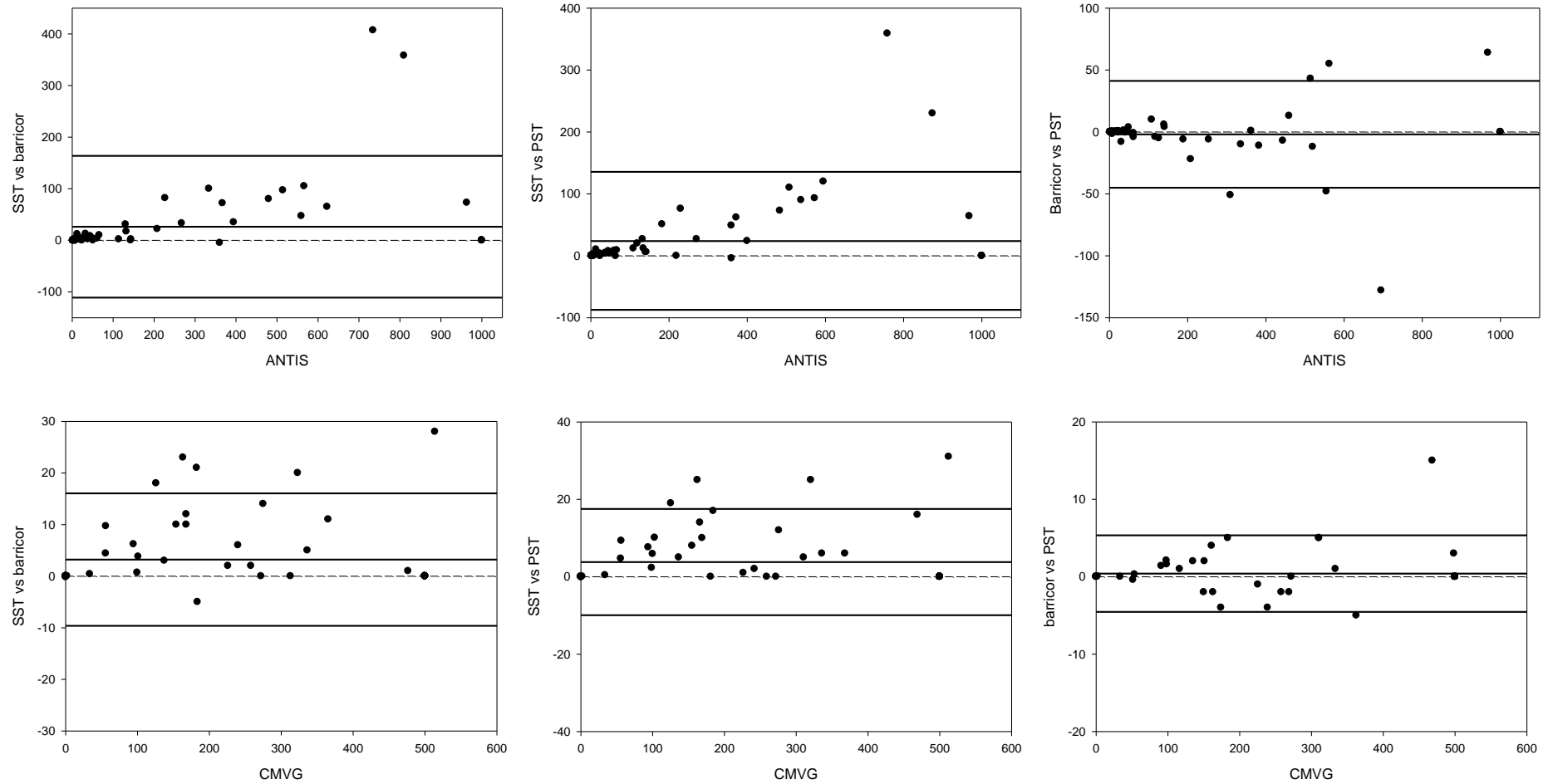


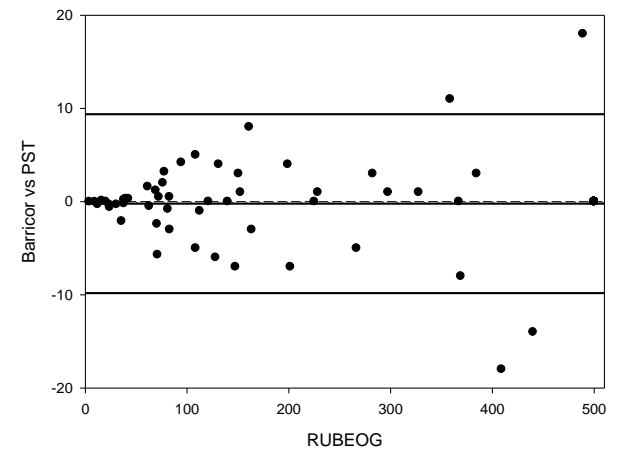
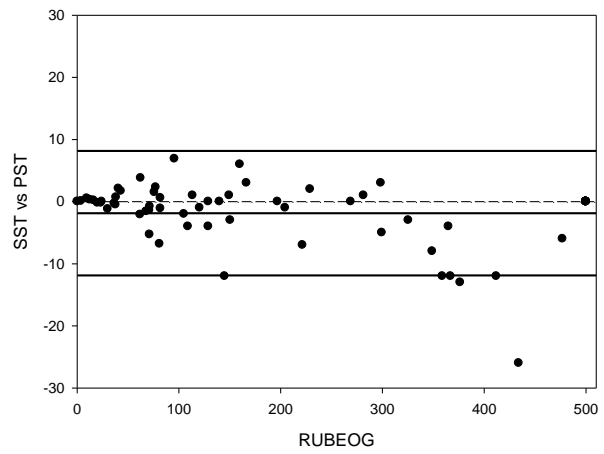
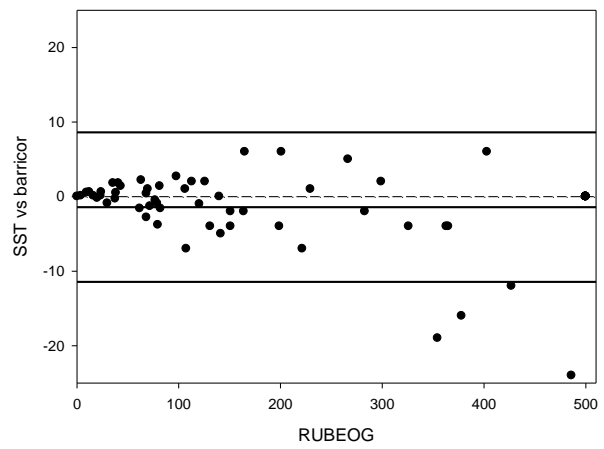
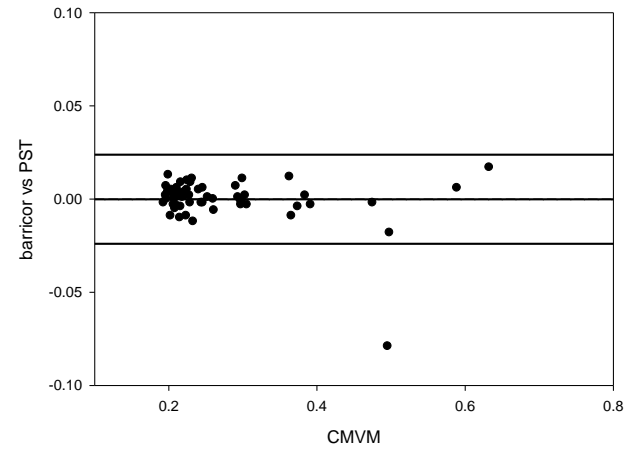
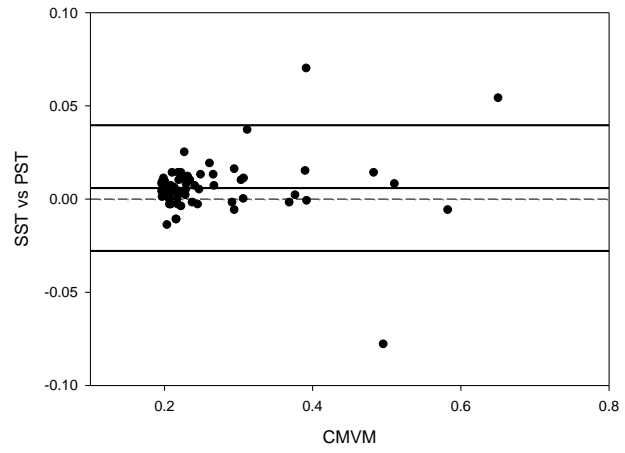
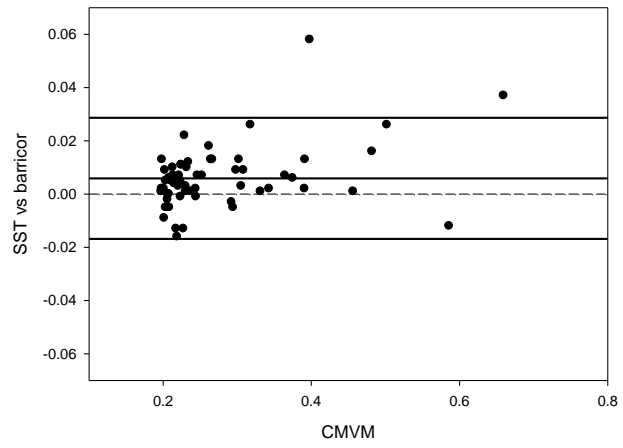


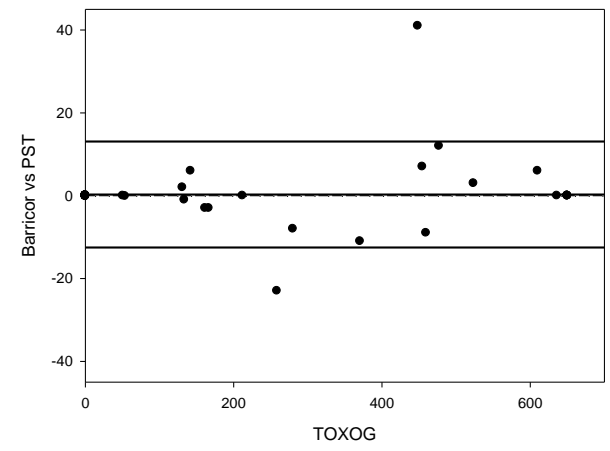
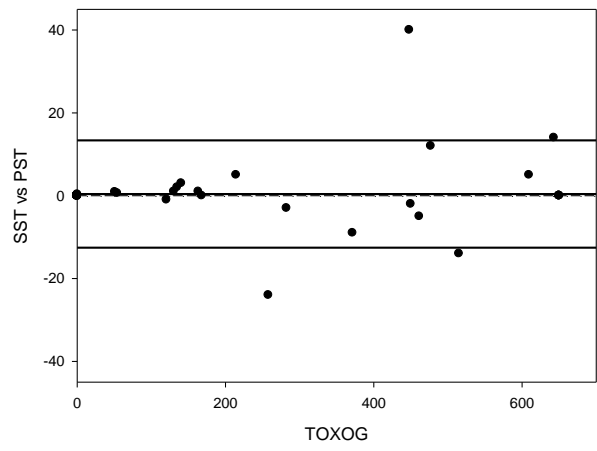
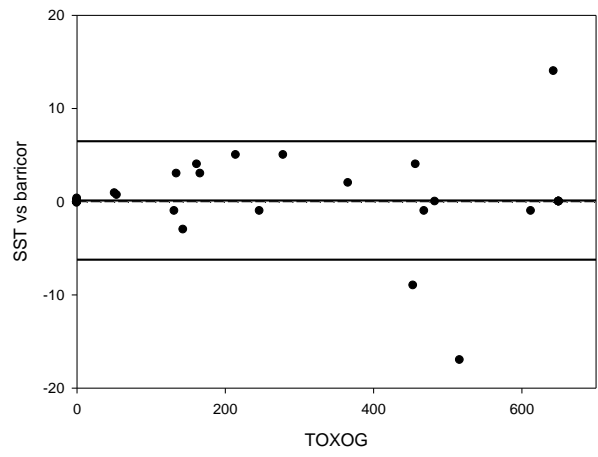
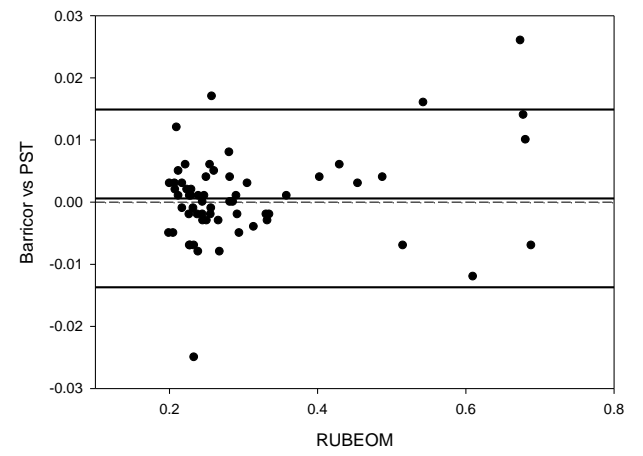
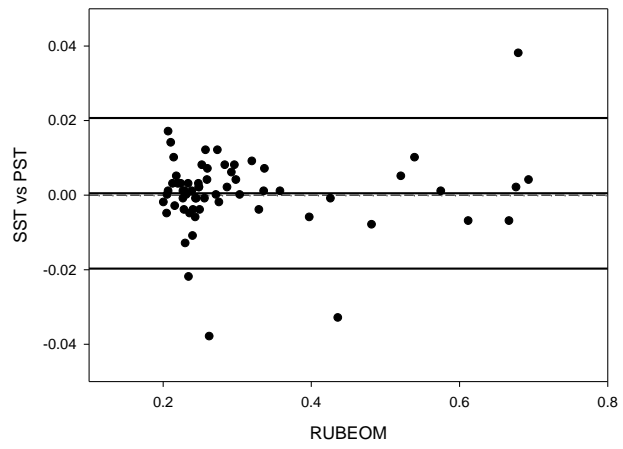
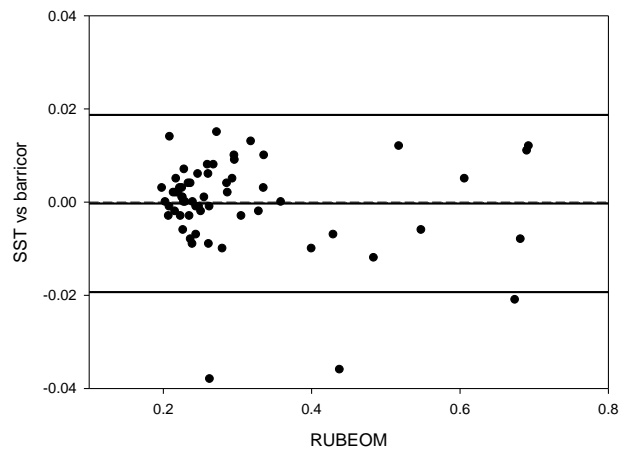


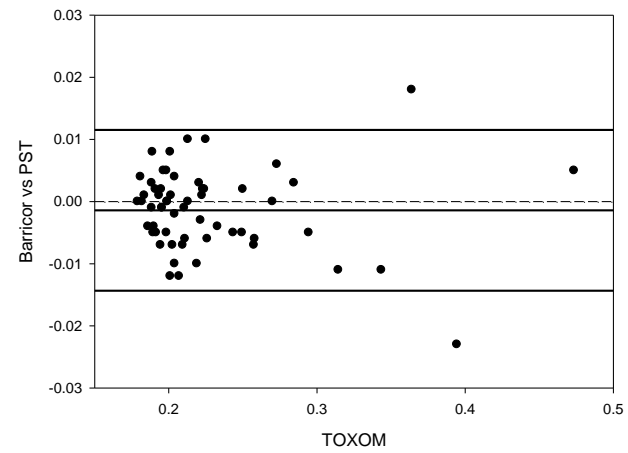
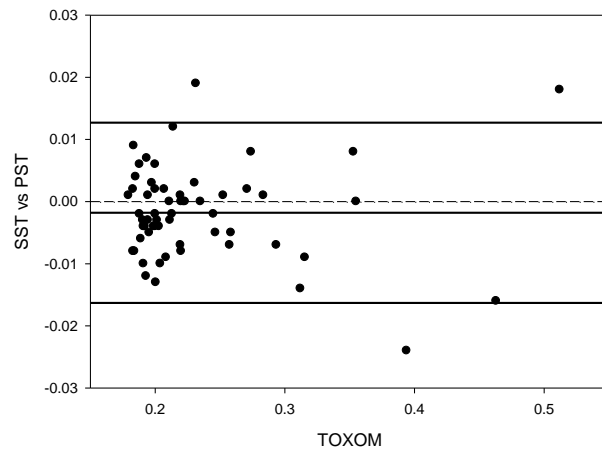
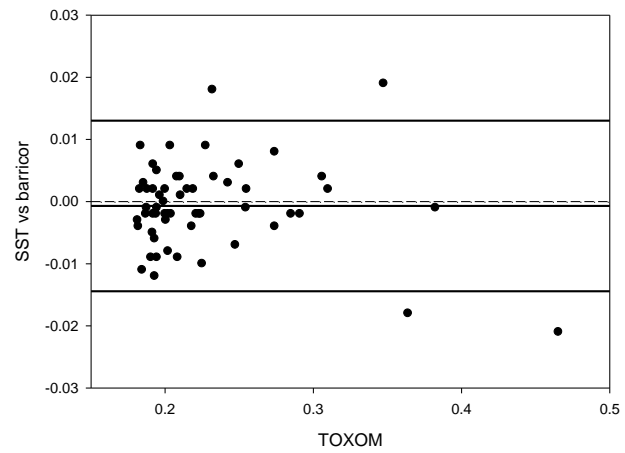


**Figure S3A.** B&A plots for serology analytes: the pair value differences were expressed as real values.









**Figure S3B.** B&A plots for serology analytes: the pair value differences were expressed as percentage.

