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Plots to Assess Relationships between Before and After Treatment Change in Clinical Outcomes and Biomarkers with SAS SG Procedures and Graph Template Language.

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ABSTRACT

This paper describes data visualization techniques for clinical studies where before- and after-treatment outcomes, and their relationships with biological markers, are assessed. The ultimate goal is to learn whether before- and after- “good” changes in outcomes correlate with before- and after- “good” changes in biological markers. We use SAS Graph Template Language and SG procedures to visualize these associations. Results included in this paper were produced using SAS 9.3 on a Windows XP platform, using Base SAS, SAS/STAT software. SAS/GRAPH. SAS 9.2 or later is required for ODS graphics extensions.

INTRODUCTION

The data for this paper comes from a clinical research study. The depression score (Mental Fatigue) and biomarker for adiposity (VAT) are measured at baseline and 6 month post intervention. The researchers are interested to understand correlations for before-and-after change in Mental Fatigue with before-and-after change in biomarker VAT. The reduction in mental fatigue score and VAT level at 6 month post intervention is considered favorable change.

We used scatter plot, bar plot, and line plots to convey this message more effectively. The scatter plot (illustration1) and line plot (illustration 3) depict favorable and unfavorable change, its magnitude and association. The bar plot (illustration 2) shows favorable and unfavorable change by counts as bivariate variable. This paper focuses on SG procedures and GTL to create graphs. We also discuss various SG features that enabled us to enhance the graphics.

ILLUSTRATION 1

We used scatter plot procedure for this illustration. The change in mental fatigue (MentCh6MO) and VAT level (VATch6Mo) for each subject is given below.

Data

Id	MentCh6MO	VATch6mo
22	-3	-2661
23	7	-1807
27	-7	-3659
29	-4	-957
30	-1	-2728
34	0	-1469
35	-4	-2567
36	-2	-1937
58	-1	-4692
60	1	-1010
61	-1	-1561

The plot is shown in Figure 1. We use scatterplot statement in SGPlot procedure to plot MentCh6MO against VATch6Mo (step 1). This plot shows change in each subject but not intuitive to learn about the favorable change which is reduction in both variables over time. We then put reference lines at $x=0$ and $y=0$ (Step 2). Now, we can easily note that 13 subjects had reduction in both variables (both X and Y delta less than 0), 3 subjects had reduction in VAT but fatigue was increased, and for 3 subjects VAT was reduced with no change in fatigue over time. In step 3, we add reference lines at mean $\pm 1SD$ for x and y variables. With these reference lines, we can easily tell mean and SD for change over time.

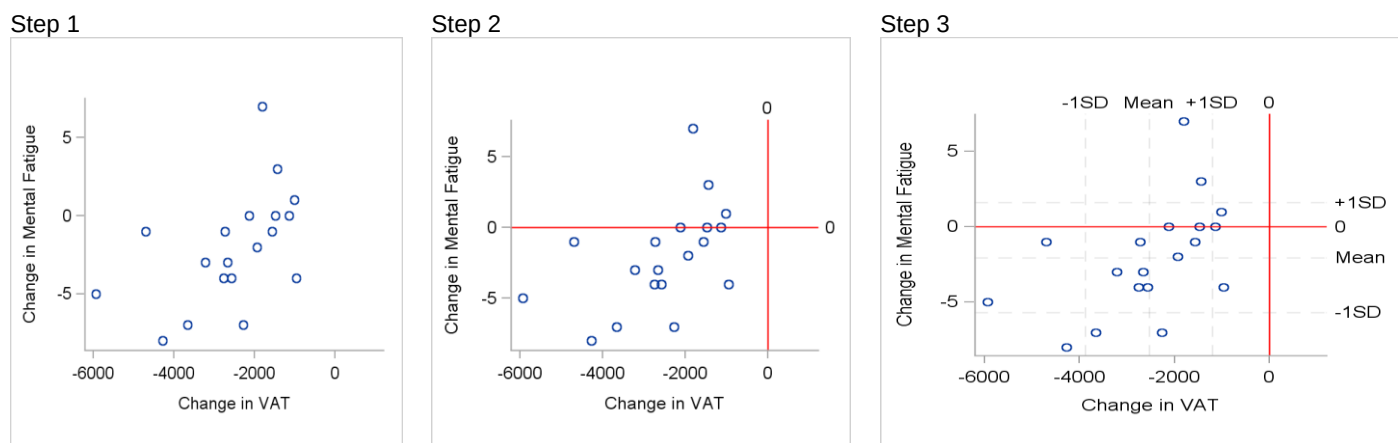


Figure 1: Scatter plot for change in depression score (Mental Fatigue) and biomarker for adiposity (VAT).

SAS Code

```
Step 1:
proc sgplot data=zung_biomarkers noautolegend ;
scatter x=VATCh6MO y=MentCh6MO;
YAXIS LABEL = 'Change in Mental Fatigue' ;
XAXIS LABEL = 'Change in VAT' values=(-6000 -5000 -4000 -3000 -2000 -1000 0 1000) ;run;
```

```
Step 2:
refline 0 /axis=x lineattrs=(pattern=solid color=red) LABEL=('0') ;
refline 0 /axis=y lineattrs=(pattern=solid color=red) LABEL=('0');
```

Step 3:

```
refline -1197 -3873 -1197 /axis=x TRANSPARENCY=0.8 LABEL = ( 'Mean' '+1SD' '-1SD')
lineattrs=(pattern=dash color=grey) ;
```

```
refline 1.59 -2.05 5.69. /axis=y TRANSPARENCY=0.8 LABEL = ( 'Mean' '+1SD' '-1SD') lineattrs=(pattern=dash
color=grey) ;
```

ILLUSTRATION 2

We use bar plot procedure for this illustration. The bar plot shows frequency of subjects with favorable and unfavorable change. Data table is shown below. We create a dual category variable based on change in x and y variable (variable DeltaLabel) to indicate favorable or unfavorable change (variable Delta) and get a X axis that shows dual category variable individually. Variable group=1 if delta is favorable, otherwise group=2.

Delta	DeltaLabel	Var1	Var2	Yvar	Xvar	frequency	stat1	stat2	group
Favorable	-ve -ve	-ve	-ve	Fatigue	VAT	13	13/19	68.4%	1
NonFavorable	+ve -ve	+ve	-ve	Fatigue	VAT	3	3/19	15.8%	2
NonFavorable	No Change -ve	No Change	-ve	Fatigue	VAT	3	3/19	15.8%	2

The graph is shown in Figure 2. The graph has a bar for each possible combination of Yvar and Xvar. The x-axis label is split up to show each value of the two variables, and also the variable names on the left. We use two colors to bars to show favorable versus non-favorable change.

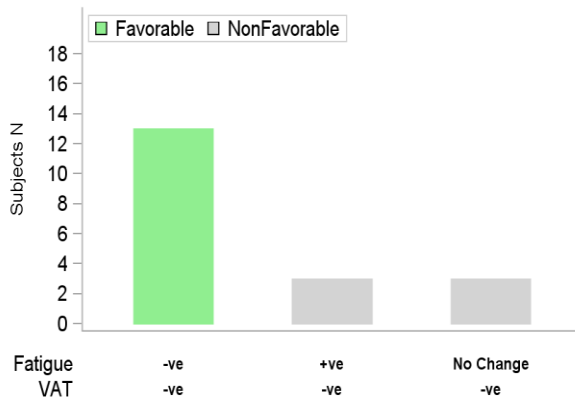
We used GTL to draw this plot (Ref Matange <http://blogs.sas.com/content/graphicallyspeaking/2012/05/25/two-variable-category-graph/>). The step 1 of GTL are as follows:

1. Use a GTL template with a Layout Lattice of two rows, upper row is 87%.
2. Add bar chart of count x delta label in the upper cell.
3. Add discrete legend to show two distinct colors to bars.
4. Add a scatter plot each of Yvar and Xvar label with marker character in lower cell.
5. Make the axes uniform and suppress the x-axes.

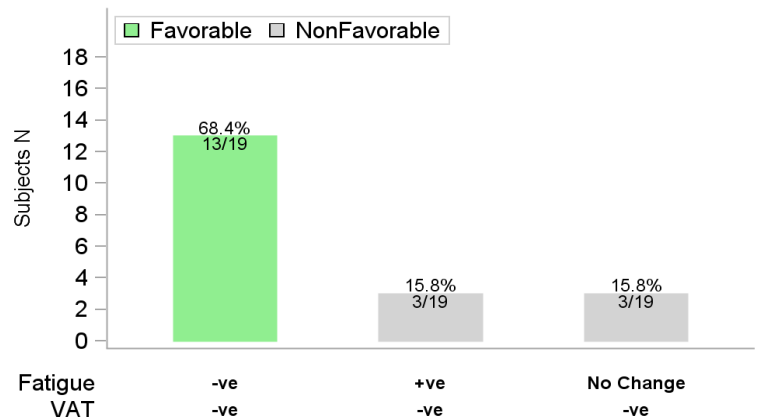
In step 2, we add frequency labels inside bar and percentage labels outside bar via a SCATTERPLOT statement and marker character option with Y-coordinates that are adjusted with an EVAL function.

In step 3, we add label "Month 6 delta" using drawtext statement

Step 1



Step 2



Step 3

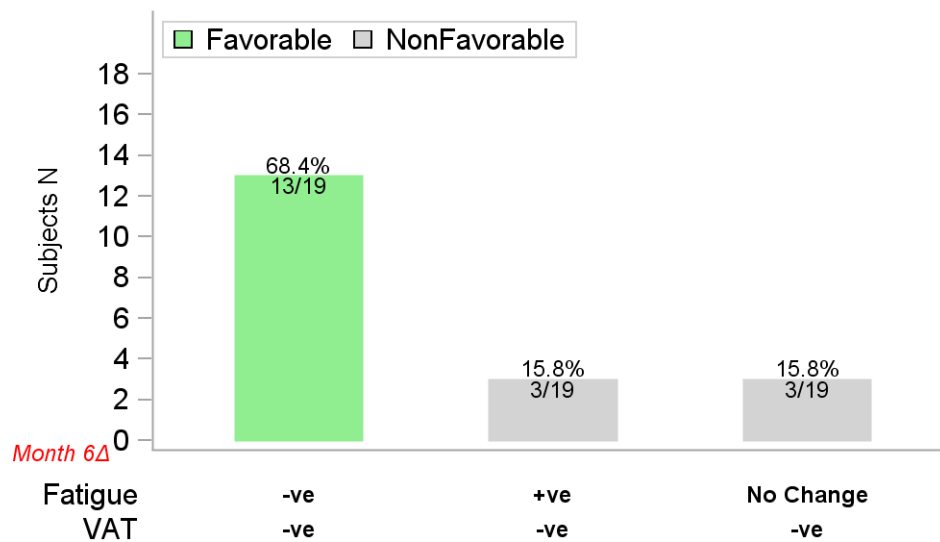


Figure 2: Frequency of subjects with favorable and unfavorable change in depression score (Mental Fatigue) and biomarker for adiposity (VAT).

STEP 1:

```
proc template;
  define statgraph two_var;
    begingraph;
      layout lattice / columndatarange=union rows=2 rowgutter=10 rowweights=(0.87 0.13);
      layout overlay / walldisplay=none xaxisopts=(display=(line))
        yaxisopts=(label="Subjects N" display=(label line ticks tickvalues))

      offsetmin=0.02 offsetmax=0.1
      linearopts=( tickvaluesequence=(start=0 end=20 increment=1) viewmin=0 viewmax=19 )) x2axisopts=(
        display=none );

      barchart x=DeltaLabel y= Frequency / group=group BarLabel=false barwidth=0.5 name="bar";
```

```

discretelegend "bar"/location=inside valign=top halign=left;

    endlayout;

layout overlay / walldisplay=none xaxisopts=(display=none)
    yaxisopts=(display=(tickvalues));

    scatterplot x= DeltaLabel y=xvar / markercharacter=var2 markercharacterattrs=(size=8pt weight=bold);
    scatterplot x= DeltaLabel y=yvar / markercharacter=var1 markercharacterattrs=(size=8pt weight=bold);
endlayout;

    endlayout;
    endgraph;
end;
run;

```

STEP 2

```

** Annotate inside frequency label. Use eval function to annotate n/N(stat1) inside edge of bar;
scatterplot y=eval(Frequency -0.5) x= DeltaLabel /markercharacterattrs=(size=8PT color=BLACK)
markercharacter= stat1;

** Annotate outside percentage label. Use eval function to annotate percentage(stat2) outside edge of bar;

scatterplot y=eval(Frequency + 0.5) x= DeltaLabel /markercharacterattrs=(size=8PT color=BLACK)
markercharacter= stat2;

```

Step 3:

```

drawtext textattrs=(size=8pt style=ITALIC color=red) "Month 6" {unicode delta_u}/ width=25 widthunit=PERCENT
xspace=WALLPERCENT yspace=DATAVALUE
x=-11.5 y=-0.6 justify=CENTER;

```

ILLUSTRATION 3

We use line plot procedure for this illustration. The line plot shows magnitude of change in x and y variables as two lines for each subject. Data table is shown below. To prepare data, we create two variables that indicate favorable (or unfavorable) change for each x and y variables (variables: yvarFav, yvarUnf, xvarFav, xvarUnf). Variable group=1 if delta is favorable, otherwise group=2.

The graph is shown in Figure 3. The x-axis shows individual subject (n=19). Each subject has two lines to show fatigue and VAT change. Y axis is used for change in fatigue and Y2 axis is used for change in VAT. X-axis intersects Y-axis and Y2-axis at zero. The scale of Y-axis and y2axis must be spaced evenly at zero. The favorable change is shown by green line and nonfavorable change by red line. We show line tip as either B or D to show variable. We used SGPLOT procedure to draw this plot. The steps are as follows:

1. Use needle statements to show favorable change in fatigue and VAT with lineattrs(color=green).
2. Use needle statements to show nonfavorable change in fatigue and VAT with lineattrs(color=red).
3. Use scatter statement to render tip using markerchar = option.
4. Add symmetric scale for Y2axis and Yaxis.
5. Use INSET statement to label "Favorable change..." on left corner with textattrs=(color=green).
6. Use INSET statement to label "Nonfavorable change.." on right corner with textattrs=(color=red).
7. Add keylegend statement.
8. Add two vector statements to show green and red arrows on top.
9. First 13 subjects showed favorable change. A vertical line at x=13.5 is added.

The entire SGPLOT code is given below.

Data

Id1	Id2	group	Yvar	Xvar	Yvar Fav	Yvar UnF	Xvar Fav	Xvar UnF	Vector XO	Vector X	Vector Y	bio	dep
1	1.3	1	-5	-5929	-5	.	-5929	.	16.5	13.5	7.8	B	D
2	2.3	1	-1	-4692	-1	.	-4692	.	16.5	13.5	7.8	B	D
14	14.3	2	0	-2117	.	0	-2117	.	16.5	13.5	7.8	B	D
15	15.3	2	7	-1807	.	7	-1807	.	16.5	13.5	7.8	B	D
16	16.3	2	0	-1469	.	0	-1469	.	16.5	13.5	7.8	B	D
17	17.3	2	3	-1432	.	3	-1432	.	16.5	13.5	7.8	B	D
18	18.3	2	0	-1139	.	0	-1139	.	16.5	13.5	7.8	B	D
19	19.3	2	1	-1010	.	1	-1010	.	16.5	13.5	7.8	B	D

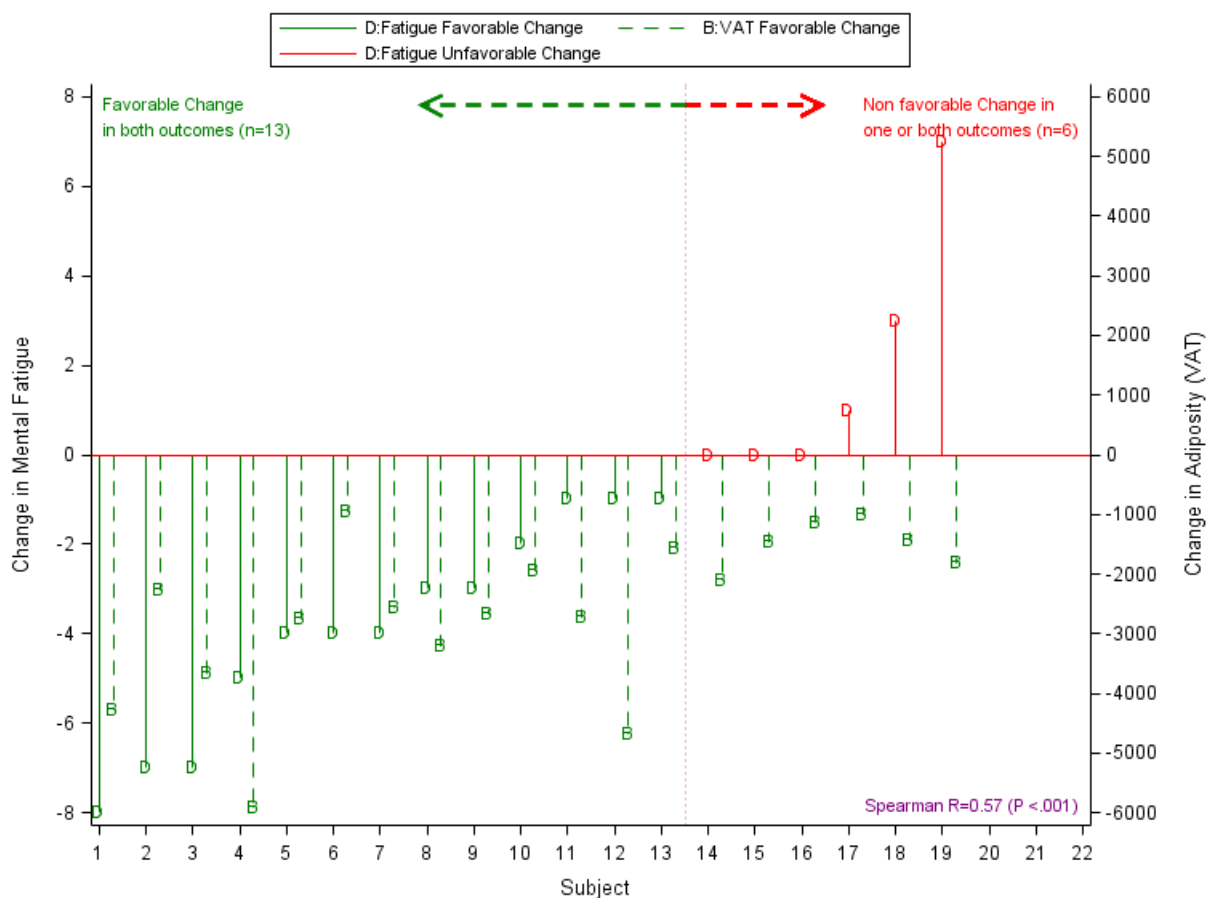


Figure 3: Before and After Change in depression score (Mental Fatigue) and biomarker for adiposity (VAT).

SAS Code

```

ODS GRAPHICS /reset height=6in WIDTH=8.0IN noborder noscale;
proc sgplot data=fatiguevat2 noborder;
*** plot favorable ( green line) and unfavorable change (red line) for each subject;
needle y=YvarFav x=id / lineattrs=(color=green pattern=solid) name="a1" legendlabel="D:Fatigue
Favorable Change" ;
needle y=XvarFav x=id2/y2axis lineattrs=(color=green pattern=dash) name="b1" legendlabel="B:VAT
Favorable Change";;

needle y=YvarUnf x=id / lineattrs=(color=red pattern=solid) name="a2" legendlabel="D:Fatigue
Unfavorable Change" ;
needle y=XvarUnf x=id2/y2axis lineattrs=(color=red pattern=dash) name="b2" legendlabel="F:VAT
Unfavorable Change" ;;

*** add markertips for each subject;
scatter y=YvarFav x=id / markerchar=dep markercharattrs=(color=green size=8pt );
scatter y=XvarFav x=id2/y2axis markerchar=bio markercharattrs=(color=green size=8pt );

scatter y=YvarUnf x=id / markerchar=dep markercharattrs=(color=red size=8pt );
scatter y=XvarUnf x=id2/y2axis markerchar=bio markercharattrs=(color=red size=8pt );

*** Refline;
refline 13.5/axis=x TRANSPARENCY=0.5 lineattrs=(pattern=dot color=purple) ;

*** Vectors;
vector x=vectorXO y=vectorY / xorigin=vectorX yorigin=vectorY TRANSPARENCY=0.2
ARROWDIRECTION= OUT
lineattrs=(color=red pattern=dash thickness=2) ;

vector x=vectorY y=vectorY / xorigin=vectorX yorigin=vectorY TRANSPARENCY=0.8
ARROWDIRECTION= out
lineattrs=(color=green pattern=dash thickness=2);

*** insets ;
INSET "Favorable Change" "in both outcomes (n=13)" / POSITION = TOPleft NOBORDER
textattrs=(color=green size=8pt);

INSET "Non favorable Change in " "one or both outcomes (n=6)" / POSITION = TOPRight NOBORDER
textattrs=(color=red size=8pt);

INSET "Spearman R=0.57 (P <.001)" / POSITION = bottomright NOBORDER textattrs=(color=purple
size=8pt);

*** The scale of Y and y2axis must be spaced evenly at zero ;
Y2AXIS LABEL = 'Change in Adiposity (VAT)' values=(-6000 to 6000 by 1000);
YAXIS LABEL = 'Change in Mental Fatigue' values=( -8 to 8 by 2 ) ;
XAXIS LABEL = 'Subject' values=(1 to 22 by 1) ;
X2AXIS display=none;

keylegend "a1" "b1" "a2" "b2"/location=outside position=top across=2 valueattrs=(size=8pt);
run;

```

CONCLUSION

This paper shows examples to demonstrate relationships of clinical outcomes. These plots can be used to assess before and after treatment change in two or more outcomes and learn associations between them. We used SAS PROC SGPLOT and GTL together with available plotting options to refine these simple plots so that the investigators can easily capture associations between outcomes.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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