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Assersion of comprehensive approach to dermatology

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Abstract

Study was conducted to see if comprehensive approach to dermatology is more effective than treating the skin condition alone with topicasls. Subjects were divided into the treatment and control group and 10 minute educational intervention was given to the treatment group along with topical corticosteroids and just topical corticosteroids and no intervention to the control group. Several kinds of measurement was taken before and after the intervention for the treatment group and control group of which 4 are of primary interest; phase angle, basal metabolic rate, intracellular water, and free fat mass. Result showed treatment effect in the expected direction, yet because of the small sample size result showed that treatment was not statistically significant.

1 Introduction

The objective of the study was to utilize inclusive health in a dermatologic setting to empower patients to partner in the improvement of their skin disease and overall health. The hallmark of aging cells is their inability to keep water in the intracellular compartment, secondary to damage to the cell membrane. Healthy cells are better able to fight off infection, inflammation and environmental damage. Patients with various skin diseases were given an option to be given an 10 minute educational intervention, on how to improve the health of their cells by eating a balanced diet of foods rich in antioxidants, omega 3 and essential fatty acids, lean protein, structured water as can be found in fresh fruits and vegetables, whole grains, and utilizing daily nutritional supplements, along with regular topical corticosteroids. Patients were evaluated for a chief complaint of skin disease, the ones who volunteered for educational intervention range in age from 28-79, and are interested in improving the health of their cells and by extension their skin and bodies. Therefore the treatment is not randomly assigned. But for this analysis we will assume as if the treatment assignment was random and try to see its effect. We will treat the group with the education the treatment group and the not educated group as the control group. As part of a comprehensive approach, they were also evaluated for level of stress, sleeping and eating habits. Next an assessment of the health of their cells was completed using bioelectrical impendence analysis via Quantum II RJL and Cyprus 2.7 software to capture specific data points: phase angle, Basal Metabolic Rate (BMR), Free fat mass (FFM), intracellular and extra cellular water (ICW) before and after the 10 minute educational session. The interval between before and after the treatment varied by subject with 8 days being the shortest and longest being 344 days. Any interval change in the endpoints are used to encourage the patient to continue their effort.

1.1 Outcome variables of interest

Phase Angle is an indication of how porous the cell membrane is. As a cell ages it loses its ability to keep water in the intracellular compartment because of damage to the cell membrane caused by free radical damage, inadequate nutrition, environmental damage etc. The higher this number is the better.A low phase angle is an indication of breakdown in the selective permeability of cellular membranes. A high phase angle means that the cell membrane is intact. The usual range according to via AJCN barbosa-Silva et al. 82 (1):49 (table 2) is for male (6.19-8.12) and for female (5.64-7.04). We expect the phase angle to go up after the intervention.

Basal Metabolic Rate (BMR) is the minimum caloric requirement needed to sustain life in a resting individual. It is affected by sex, height, weight, age the lower your free fat mass percent the higher your BMR. We expect BMR to increase after the intervention.

Intracellular water is the volume of water found on the inside of the cell. It is usually low in older cells or in cells with damaged cell membrane. One can increase the intracellular water by eating fruits and vegetables and eating building blocks that can restore the strength of the cell membrane such as omega thee fatty acids,lean fat, and antioxidant foods. We expect the intracellular water to increase after the intervention. It is expected that intracellular water to increase as the phase angle increases.

Free fat mass (FFM) is the amount of fat in the body. It is affected by a sedentary life style and unhealthy diet. We expect the free fat mass to decrease after the intervention. It is expected that free fat mass to decrease as the BMR increases.

2 Preliminary Analysis

Figure 1 shows the before and after treatment for each of the outcome variables. From this plot it is hard to see any trend in the data for each variable separately. However, when you look at combination of plot as in figure 5, you start to see some pattern which is an indication that it is better to model the outcomes simultaneously in a multivariate model. Also if you look closely, there is a small cluster for males displayed as red and blue, treatment and control respectively, having small cluster separate from pink and green representing treatment and control group for females. This is an indication of gender effect which we should take into account in the model.

2.1 sample characteristics

The treatment and control groups where compared on figure 3 with solid red line for treatment and dashed blue line for controls. The age and gender distribution are not too different in the treatment and control groups. But for height control group has much taller patients and for weight treatment group has heavier patients. However, when before and after treatment was plotted against age, height, and weight as in figure 6, there does not seem to be special trend for extreme height nor for weight. Thus it is probably safe to assume that the effect of these imbalance will not be too large.

3 Model

To incorporate the correlation amongst the outcome variables, we modeled the 4 outcomes of interest simultaneously as multivariate normal regression with random effect. Since we expect the outcome to change relative to the current value, treatment effect was modeled as multiplicative effect. However, to model the treatment effect as an additive effect for computational convenience, all of the outcomes were converted into log scale. Also we controlled for the covariates, gender, age, height, and weight. Age, height, and weight were centered by subtracting the mean and standardized by dividing by reasonable unit, thus unit for age is 5 years, height is in 10 cm, and weight is in 10 kg. These values were chosen mostly for ease of interpretation.

For each subject i, $i = 1, \cdots, 26$, at each time point j, $j = 1, 2$, and for outcome k, $k = 1, 2, 3, 4$

$$\begin{aligned} y_{ij} &\sim N_4\left(\mu_{ij}, \Sigma\right) \\ \mu_{ijk} &= \alpha_{1k} + \alpha_{2k} Time_{ij} + \alpha_{3k} Treatment_i + \alpha_{4k} Treatment_i * Time_{ij} \\ &\quad + \alpha_{5k} Age_{ij} + \alpha_{6k} Female_i + \alpha_{7k} height_{ij} + \alpha_{8k} weight_{ij} + \beta_{ik} \\ \beta_i &\sim N_4\left(0, \Delta\right) \end{aligned}$$

The αs are coefficients of fixed effects and βs are random effects for each subject to take into account the correlation due to repeated measurements. The covariance matrix Σ models the covariance amongst the four outcomes. The multiplicative treatment effect of interest is e^{α_4}. We need to exponentiate it since α is calculated on the log scale.

4 Prior

For the prior, we basically took the objective Bayesian position and used non-informative priors. However for the treatment effect we also tried the expert prior elicitated from the expert.

4.1 Treatment effect

Prior distribution on the treatment effect was eliciteted from the researcher by a range method. Researcher estimated the effect of treatment on phase angle to be multiplicative effect of 1.15 with 95% probability that it falls between 1.05 and 1.25, on BMR to be multiplicative effect of 1.10 with 95% probability that it falls between 1.05 and 1.15, on intracellular water to be multiplicative effect of 1.15 with 95% probability that it falls between 1.05 and 1.25, and on Free Fat Mass to be multiplicative effect of 0.90 with 95% probability that it falls between 0.95 and 0.85. We converted everything onto log scale and used the point estimate as the center and upper range minus lower range divided by 2 as the standard error for the normal prior on the treatment effect. The division by 2 was chosen instead of 4 to take into account the expert's tendency to underestimate the variability. However, we will see later that since the sample size is small, the elicited standard error turns out to have strong effect on the final result. As for non-informative prior extremely vague Gaussian prior on the log scale was used.

4.2 Other fixed effects

Prior for the other fixed effects were given flat non-informative Gaussian prior on the log scale.

4.3 Covariance matrix

The covariance matrix for the random effects were modeled as unstructured with non-informative inverse-Wishart distribution.

5 Results

We used Gibbs sampling to fit the above model with WinBUGS [3]. It took roughly 25000 iterations for things to converge under the Gelman-Rubin criteria [2]. Figure 4 shows the posterior estimates of the fixed effects for each of the coefficients for each outcome. Notice that they are multiplicative effects thus our interest is relative to 1, no multiplicative effect.

5.1 Treatment effect

Treatment effect is shown in table 5.1 for the non-informative and elicited informative prior model. For the non-informative prior model, since all of the posterior intervals are wide and includes the possibility of 1, the effects are bit significantly different from 1. However FFM, BMR, and phase angle are in the direction as we expected a priori. The wide posterior interval is probably a consequence of the small sample size in the study. What is worrisome is the negative direction of treatment effect on ICW. However, with only this much information it is inconclusive. On the other hand the informative prior model although the result is what we expected a priori, has a problem, which is that the prior we used, even though we controlled for the over confidence by doubling the standard error, was still too strong relative to the data hence the resulting posterior estimate is heavily shrunk toward the prior. As you see from 2nd and 3rd blocks of table 5.1, the prior and the posterior are almost identical. Figure 7 shows this as a kernel density plot. From this result all we can infer is that the likelihood of the data does not contradict with the prior information but is weak and we need more samples to make any sorts of definite claim on the treatment effect.

	Posterior from reference prior				Posterior from expert prior				Expert Prior			
	mean	sd	2.5%	97.5%	mean	sd	2.5%	97.5%	mean	sd	2.5%	97.5%
FFM	0.94	0.15	0.69	1.26	0.90	0.05	0.81	0.99	0.90	0.05	0.80	1.00
ICW	0.99	0.18	0.70	1.39	1.09	0.05	0.99	1.19	1.10	0.05	1.00	1.20
BMR	1.17	0.18	0.85	1.54	1.11	0.05	1.02	1.20	1.10	0.05	1.00	1.20
Phase Angle	1.20	0.24	0.80	1.73	1.17	0.09	1.00	1.35	1.15	0.10	0.95	1.45

Table 1: Treatment effect for the 2 prior with the expert prior on the right.

5.2 Gender effect

As noted earlier there is significant difference for gender on FFM, ICW, and BMR. FFM is expected to be 65% less for females, ICW is expected to be 66% less for females, and BMR is expected to be 51% less for females. There was no clear indication of an effect of gender on the phase angle.

	Posterior from reference prior				Posterior from expert prior			
	mean	sd	2.5%	97.5%	mean	sd	2.5%	97.5%
FFM	0.35	0.10	0.20	0.57	0.35	0.10	0.20	0.56
ICW	0.34	0.09	0.20	0.54	0.35	0.09	0.20	0.55
BMR	0.49	0.12	0.30	0.76	0.49	0.12	0.30	0.76
phase angle	0.80	0.23	0.44	1.33	0.80	0.24	0.45	1.33

5.3 Weight effect

Coefficient for weight on FFM was estimated as 0.81, since weight is scaled by 10kg, it indicates that with every 10kg increase FFM is expected to be 19% lower. Also weight seems to have decreasing effect on ICW and increasing effect on BMR and phase angle, but the result was not as significant as FFM.

	Posterior from reference prior				Posterior from expert prior			
	mean	sd	2.5%	97.5%	mean	sd	2.5%	97.5%
FFM	0.81	0.06	0.70	0.93	0.81	0.06	0.70	0.93
ICW	0.93	0.07	0.80	1.07	0.93	0.07	0.81	1.08
BMR	1.08	0.07	0.95	1.22	1.08	0.07	0.95	1.22
phase angle	1.08	0.09	0.91	1.25	1.08	0.09	0.91	1.25

5.4 Height effect

None of the effect of height were significantly different from 1 for every 10cm increase in height, but the trend was similar as the weight effect.

	Posterior from reference prior				Posterior from expert prior			
	mean	sd	2.5%	97.5%	mean	sd	2.5%	97.5%
FFM	0.92	0.06	0.81	1.06	0.92	0.06	0.80	1.06
ICW	0.97	0.07	0.85	1.11	0.97	0.07	0.85	1.12
BMR	1.11	0.07	0.98	1.25	1.11	0.07	0.98	1.25
phase angle	1.08	0.08	0.93	1.25	1.08	0.08	0.93	1.25

5.5 Age effect

Age was scaled by 5 years thus for every 5 year increase in age, ICW, BMR and phase angle are expected to decrease by 7%, 5%, and 8% respectively. The effect of age on FFM was not significantly different from 1.

	Posterior from reference prior				Posterior from expert prior			
	mean	sd	2.5%	97.5%	mean	sd	2.5%	97.5%
FFM	0.98	0.03	0.92	1.03	0.98	0.03	0.92	1.03
ICW	0.93	0.03	0.88	0.99	0.93	0.03	0.88	0.99
BMR	0.95	0.02	0.90	1.00	0.95	0.02	0.90	1.00
phase angle	0.92	0.03	0.87	0.98	0.92	0.03	0.87	0.98

5.6 Model validation

The residual for the fixed effect was plotted against predicted value in figure 8. The residual shows no abnormality in the residuals.

6 Summary

It has been shown that the effect of educational intervention seems to have positive effect on BMR and phase angle and negative effect on FFM, however, the result is inconclusive with small same size we have. If "statistical significance" is called for, using the sample size calculation sort of argument, assuming the effect is indeed as assumed apriori and data is a random sample of the same nature, standard error needs to be decreased by factor of 3, which means we need at least 9 times more data.

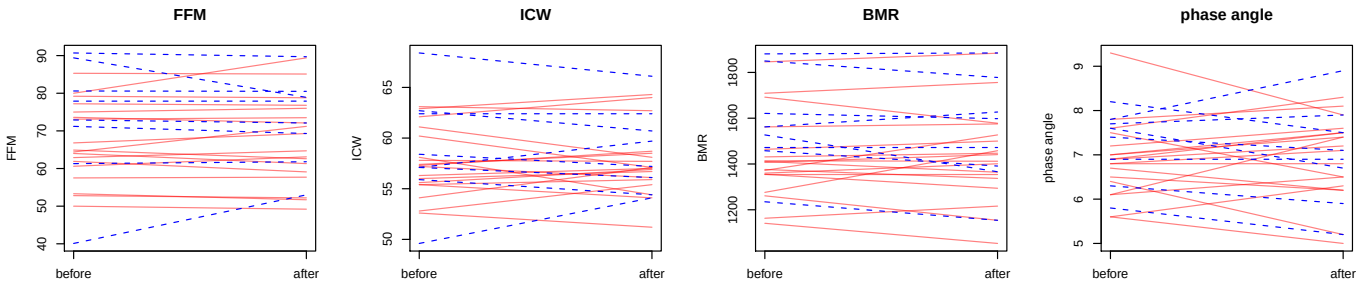

Figure 1: Change in each of the measurement before and after the intervention. The red solid lines are for the treatment group and blue dotted lines are for the control group. There does not seem to be clear sign of the effect of treatment

As for the elicited expert prior, the information turned out to be too strong, making it useless in the real analysis. Although, the fact that the result from non-informative prior model did not contradict with the informative prior model do suggest that it might be worth while to do more experiment to see if indeed this is the case.

There is one concern about the model which I was not able to include which is to model the effect of time as continuous variable. In the treatment and control group, there was large difference in the times between the first and the second measurement as you can see in figure 2. Although I did not see strong effect do to this difference in the period, this is indeed something that may require consideration in future study.

7 References

References

[1] Gelman, A., Carlin, J.B., Stern, H.S., Rubin, D.B. (2003):Bayesian Data Analysis, 2nd edition, CRC Press.

[2] Gelman, A., and D. B. Rubin. 1992. Inferences from iterative simulation using multiple sequences (with discussion). Statistical Science 7: 457 - 511.

[3] Sturtz, S., Ligges, U., Gelman, A. (2005): R2WinBUGS: A Package for Running WinBUGS from R. Journal of Statistical Software 12(3), 1-16.

8 Appendix

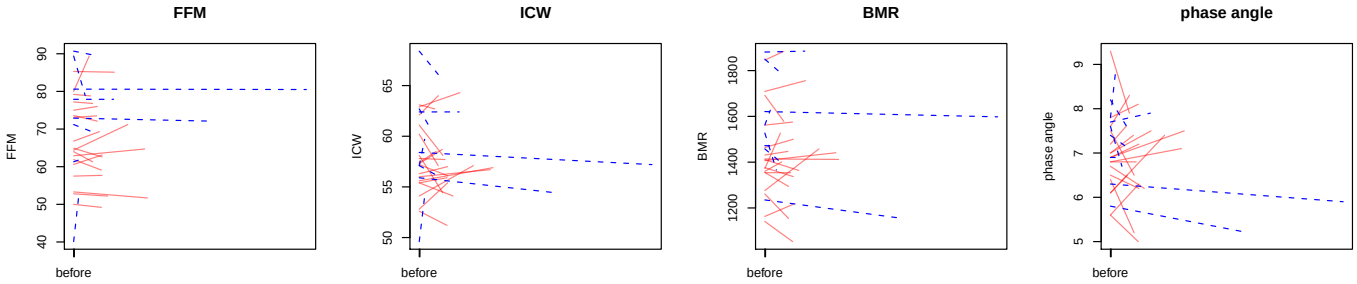

Figure 2: Change in each of the measurement before and after the intervention with interval scaled by date. The red solid lines are for the treatment group and blue dotted lines are for the control group.

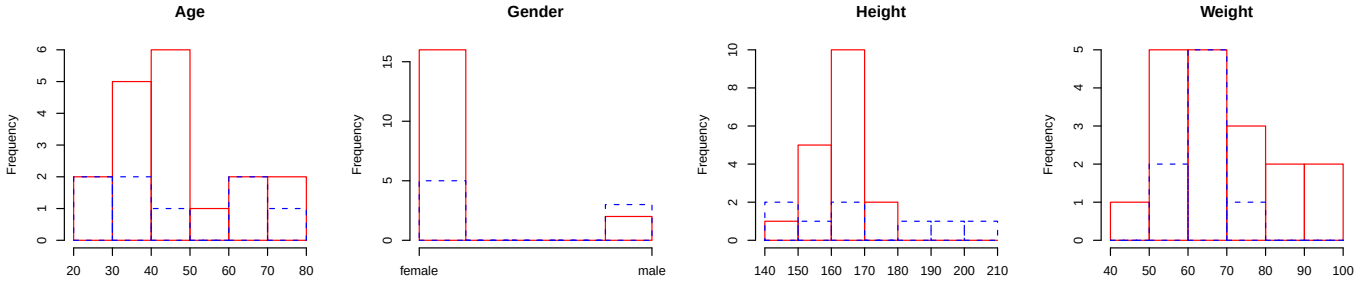

Figure 3: Characteristics of treatment group in red solid line and control group in blue dashed line.

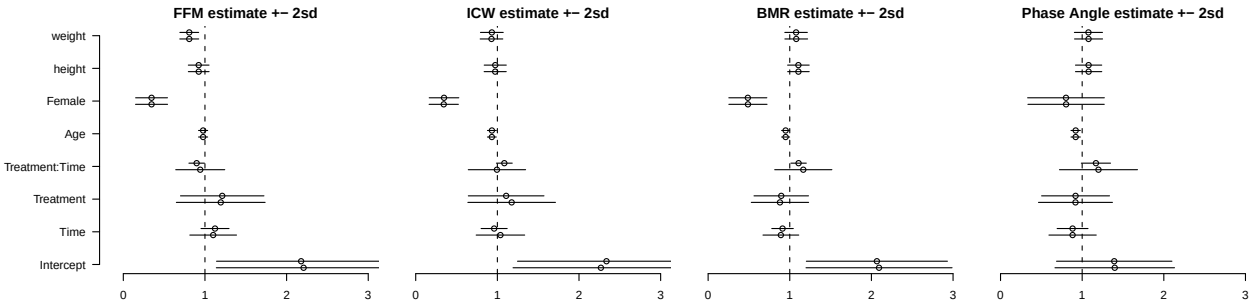

Figure 4: Estimated coefficients $\pm$ 2 standard deviation to indicate 95% confidence interval. For each estimate, one on the top is the estimate from the expert prior and one on the bottom is the reference flat prior.

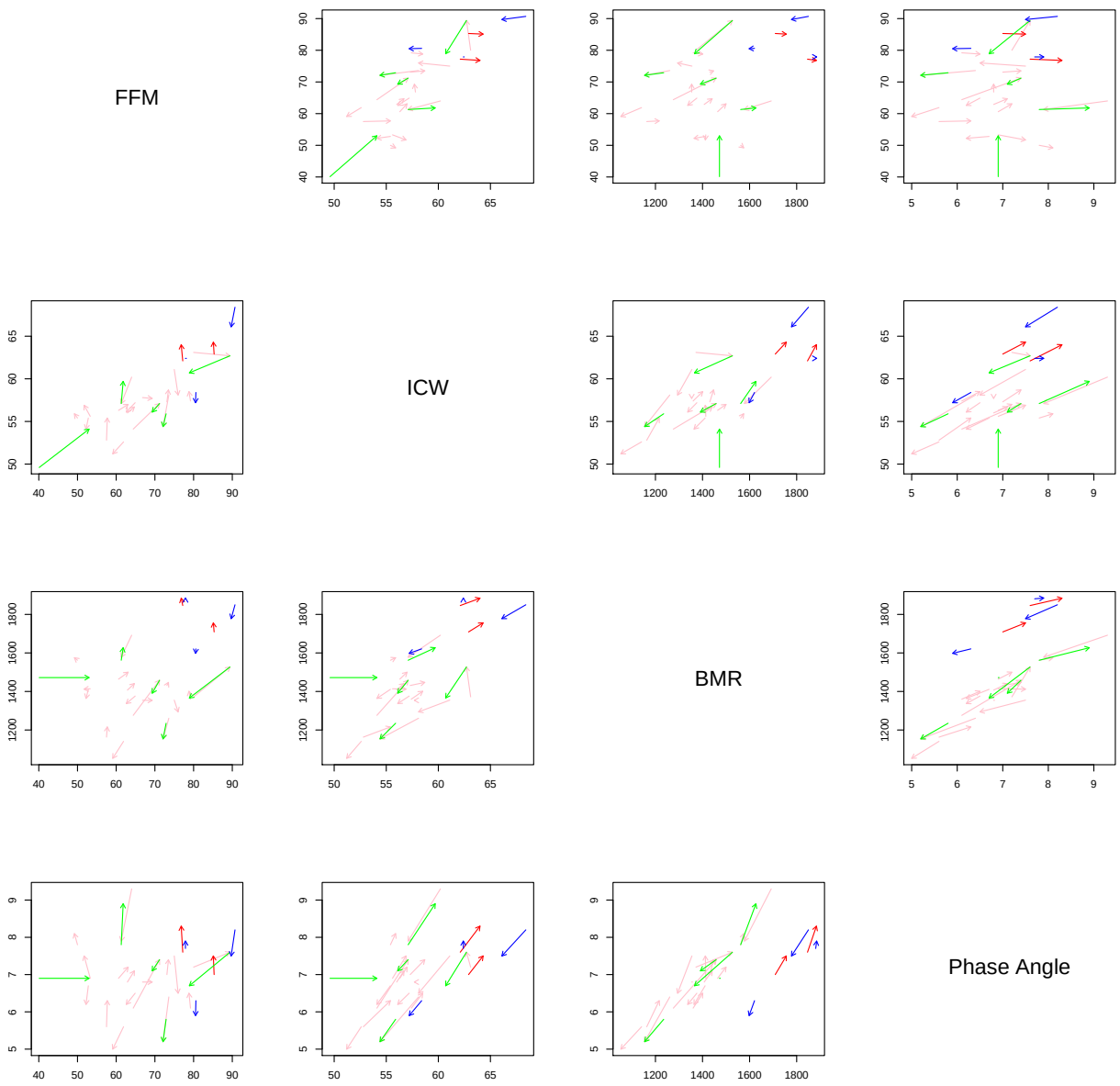

Figure 5: Bivariate scatter plot of before and after measurement for treatment in red and control in blue for males and treatment in pink and control in green for females. Again the pattern is hard to see but there is diagonal trend indicating correlation amongst the variables.

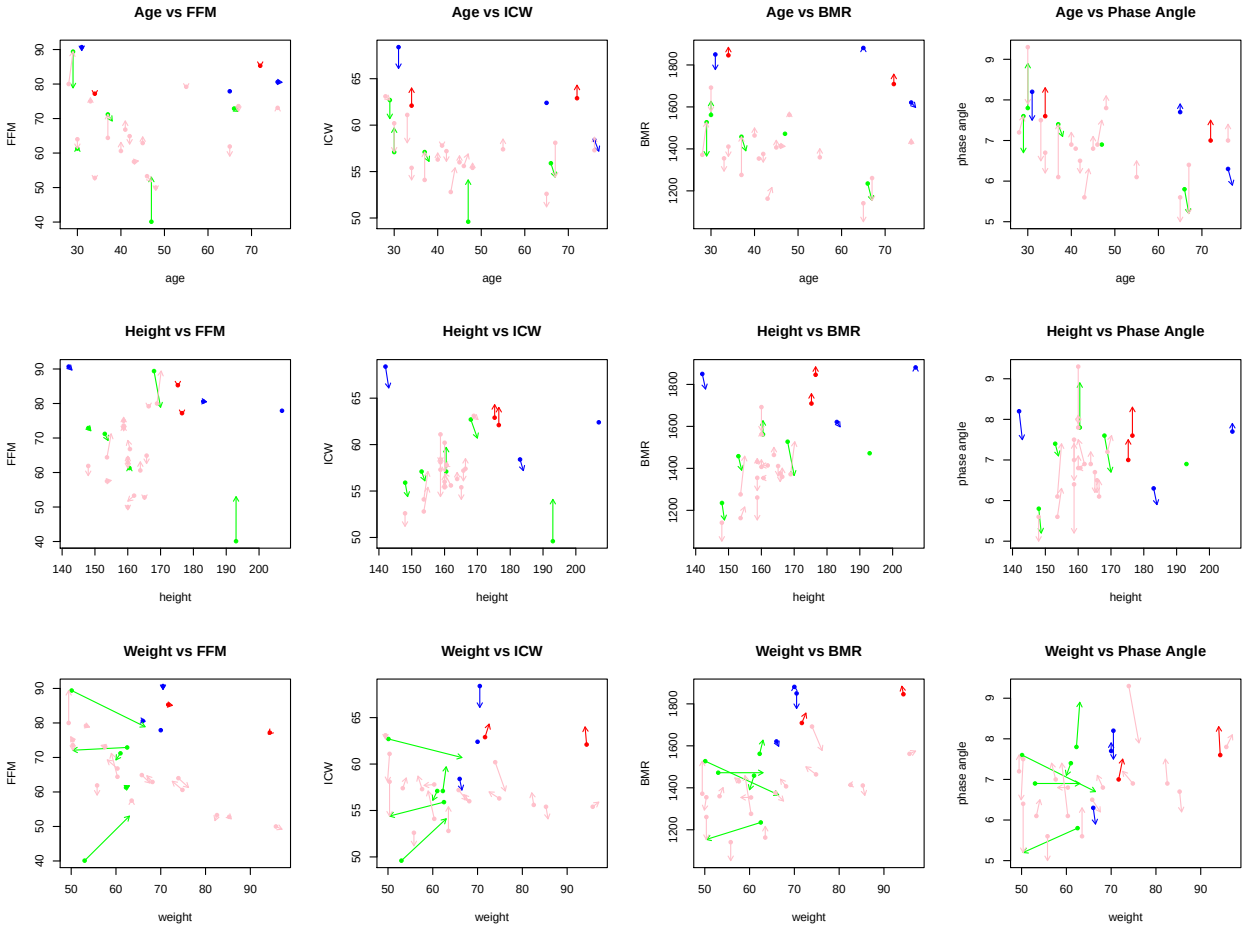

Figure 6: Directional scatter plot with treatment in red and control in blue for males and treatment in pink and control in green for females. The direction of the arrow points from before the treatment to after the treatment. There is no clear indication of trend of treatment effect.

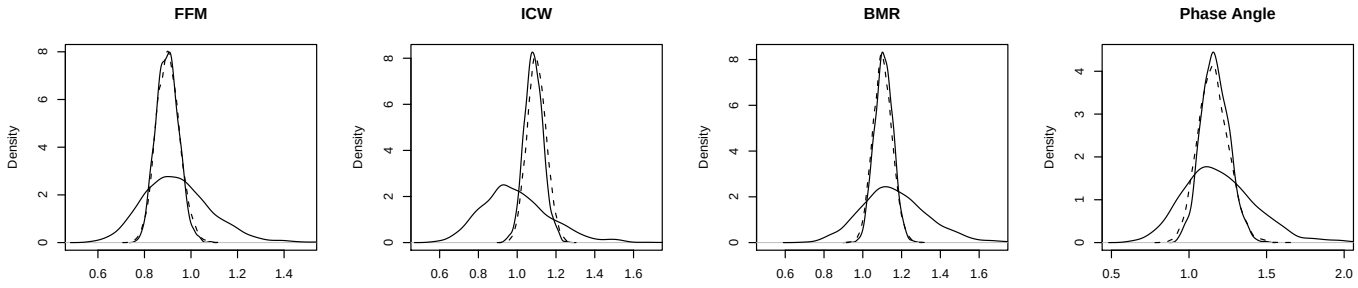

Figure 7: Two posteriors for the multiplicative treatment effect in solid line with expert prior in dotted line. The wide posterior is the result of non-informative prior, where as the narrow one is from the expert prior. Expert prior clearly dominates the posterior for the informative prior model. This indicates that there was very small information in the likelihood.

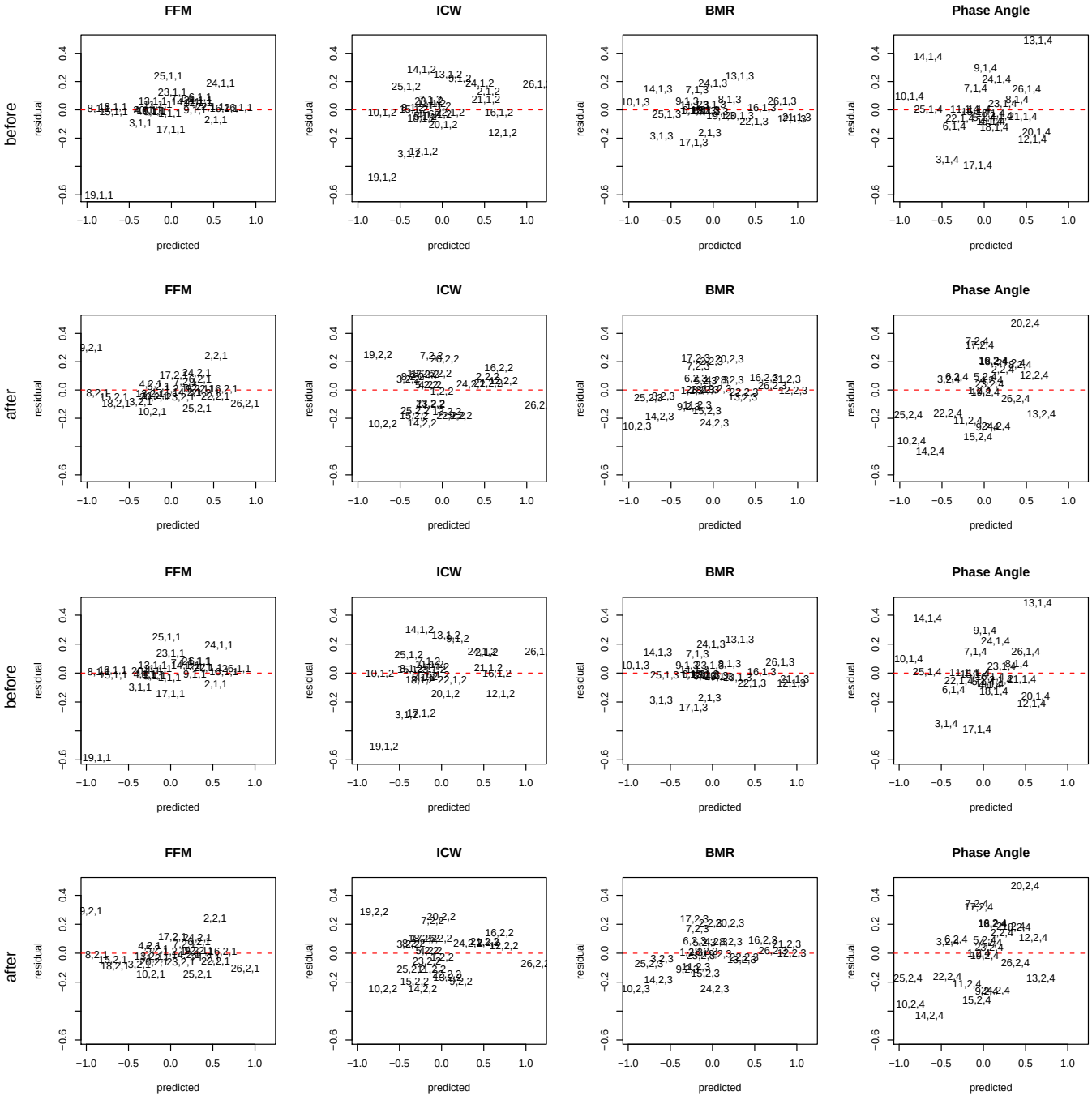

Figure 8: Residuals from 2 models plotted against the predicted value for each outcome and time points. There is no trend in the residual which indicates the model is a good fit.