

# Pediatric Multidisciplinary Weight Management - How Can We Improve Further?

Indrajit Majumdar (✉ [imajumdar@upa.chob.edu](mailto:imajumdar@upa.chob.edu))

University at Buffalo Jacobs School of Medicine and Biomedical Sciences: University at Buffalo School of Medicine and Biomedical Sciences <https://orcid.org/0000-0003-0848-1809>

**Brittany Espino**

Children's Hospital at Montefiore

**Carroll M Harmon**

University at Buffalo Jacobs School of Medicine and Biomedical Sciences: University at Buffalo School of Medicine and Biomedical Sciences

---

## Research Article

**Keywords:** Multidisciplinary weight management, pediatric obesity, adherence, bioelectric impedance analysis

**Posted Date:** June 22nd, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-639086/v1>

**License:** © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

**Purpose:** Multidisciplinary weight management (MDM) significantly improves outcomes in youth, when compared to their routine care. However, this progress may be undermined by high follow-up attrition. We hypothesized that a pre-defined time-limited MDM clinic follow-up plan given to families from the “get-go” will improve individual clinic participation, weight, and metabolic parameters.

**Methods:** Participant follow-up rates in 7 consecutive visits in a retrospective cohort of youth followed at an urban MDM clinic between April 2017 to September 2019 after the clinic follow-up protocol was changed (Post-PC) were compared to our previously published data (Pre-PC, December 2014 to January 2017). Secondary outcomes include changes ( $\Delta$ ) in body mass index z-score (z-BMI), body composition analysis (BCA), and laboratory parameters.

**Results:** 615 records ( $12.3 \pm 3.7$  years, 46% male) were reviewed. Participants' follow up rates improved significantly starting visit 3 (Post-PC (49.2%) vs. Pre-PC (40.2%);  $p=0.03$ ). With continued MDM participation, mean z-BMI  $\Delta$  progressively improved. BCA  $\Delta$  included a mean total body fat mass (FM) decrease ( $-2.07 \pm 7.3$  kg) along with total body muscle mass (MM) increase ( $3.3 \pm 5.6$  kg). Significant improvements were noted with hemoglobin A1c %, total cholesterol (TC), triglyceride, AST, and ALT concentrations. FM  $\Delta$  correlated significantly with glucose and HOMA-IR  $\Delta$ , while MM  $\Delta$  was inversely associated with TC and LDL-cholesterol  $\Delta$ .

**Conclusion:** A protocolized MDM follow plan resulted in a small but significant improvement in the participants' follow-up along with significant improvements in weight and metabolic outcomes. Further improvements will likely require additional behavioral economic strategies.

## Introduction

Childhood obesity is a health epidemic affecting 19% of the youth in the United States [1]. Lifestyle modification remains the cornerstone of management and maximal success is seen when a family-based weight management therapy is implemented [2]. However, successes demonstrated in research settings have been difficult to replicate in general clinical practice, given the need to address the multi-factorial origins of obesity. Multidisciplinary weight management (MDM) of obesity has been very promising in both adults [3] and youth [4] since the team of specialized providers can address the multitude of underlying etiologies leading to obesity. Our group had previously demonstrated that youth followed in a pediatric urban MDM program between 2014–2017 had a reversal of the Body Mass Index z-score (z-BMI) changes with ongoing MDM participation when longitudinally compared to their pre-participation routine pediatric care. Despite successes in weight management, large attrition of participants' follow-up was noted, similar to those reported in adult MDM programs [5, 6]. Adherence to weight management programs is essential for ongoing success [5]. Further, the participants who failed to follow up possibly included non-responders who self-selected to opt-out. Therefore, follow-up attrition is a very concerning

trend and may undermine the long-term success of the weight management efforts. Strategies to improve adherence with MDM participation is needed for ultimate goal achievements.

In contrast, participation attrition rates are low in most clinical trials and research settings [2]. The commonality between clinical trials and research studies are the structured participant follow-up plan and the pre-determined duration of follow-up which are defined by the study protocols. We hypothesized that: 1) a pre-defined structured follow-up with an "end date" will improve individual participation and adherence to clinic visits while maintaining improvements in weight and metabolic parameters and 2) Body composition analyses will provide additional pieces of information that are very helpful in monitoring the outcomes of the MDM program but cannot be by measuring z-BMI changes.

## Materials And Methods

We retrospectively reviewed the electronic medical records (EMR) of all participants at an urban pediatric MDM program between April 2017 and September 2019, following the changes in the participant-follow-up protocol (Post-Protocol Change (PC)). The data collected included the percentage of participants returning at each clinic follow-up, measures of changes in weight outcomes, and laboratory parameters. The primary outcome was the percentage of participants returning for follow-up at each visit. The secondary outcomes included BMI z-score changes (z-BMI  $\Delta$ ), changes in various measures of body composition analyses, and changes in the laboratory parameters. These "Post-PC" data were compared to our previously published parameters which had been obtained from the clinic participants between December 2014 and January 2017. These participant data are henceforth being labeled as "Pre-PC" data [4].

The participant evaluation and management protocol at the MDM program were similar to our previously published protocol [4]. In summary, the MDM team consisting of a pediatric endocrinologist, bariatric surgeon, registered dietician, occupational therapist, physiotherapist, and clinical psychologists, evaluated all participants referred to the center, and an individualized management plan was developed per standardized clinic protocol. Following an initial evaluation, participants were advised regular follow-up with the team. Per our hypothesis, the clinic structure was changed to a time-limited program lasting a total of 12 months. Accordingly, families were given a structured clinic follow-up plan for the whole 12 months at the end of the initial clinic visit. After the initial visit, the participants were advised to follow up monthly for the next 5 months, which was subsequently spaced out to 2 monthly visits till the end of the 12 months. Participants with significant health challenges or those wishing to continue participation were encouraged to continue the MDM program beyond the 12 months.

Weight (nearest 0.1 kg) was measured using a single electronic scale, and height (nearest 0.1 cm) was measured on a wall-mounted stadiometer at each clinic visit per standard clinic protocol. BMI was calculated as kg/m<sup>2</sup> and z-BMI was calculated using software based on Center for Disease Control and Prevention (CDC) data [7]. Body composition analysis was performed using a multi-frequency segmental bioelectric impedance analysis (BIA) body composition analyzer (Tanita ® MC-780U) and measurements

were obtained at each visit per manufacturer's recommendations. Fasting blood tests were obtained at presentation and included glucose and insulin concentrations, HbA1c percentage (HbA1c%), complete metabolic panel, and lipid panel. For participants who had fasting blood tests within 3 months before referral, we obtained the laboratory results from their referring providers. These tests were repeated after 6 months of follow-up, or sooner (for individuals ending participation early), per MDM clinic protocol. Blood tests completed in our institutional laboratory were selected for comparison.

The primary outcome of the study was measured by comparing the percentage of participants returning to clinic follow-up visits after the changes in the clinic follow-up protocol (Post-PC) to those of our previously published "Pre-PC" follow-up data. The secondary outcome included 1) the measurements of the z-BMI  $\Delta$  in Post-PC participants with the MDM intervention as compared to the pre-intervention z-BMI  $\Delta$  within 3-month before participation in the MDM program, 2) the comparison of the Post-PC changes to those of our previously published "Pre-PC" data, 3) the measurements of changes in the BIA parameters at clinic follow up visits as compared to the initial assessments, 4) measurements of the changes in laboratory parameters after 3–6 month follow-up from the baseline measurements. We further analyzed the associations of the changes in zBMI, BIA parameters and the changes in laboratory metabolic markers. Consents were not obtained from participants since data was obtained from the EMR database retrospectively without any direct patient contact. The study was approved by the Institutional Review Board and was in accordance with the ethical standards of the Helsinki Declaration of 1975.

#### Data collection:

Data was collected from EMR for participants in 7 consecutive clinic visits that included the initial visit and 6 follow up visits. Data included the percentage of participants returning to clinic follow-up visits, age, gender, weight, height, BMI, and z-BMI. BIA data included total body fat mass (FM, Kgs), and total body muscle mass (MM, Kgs). We also collected results of blood tests done at baseline and after 3–6 months of follow-up as described above. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), a validated marker of insulin resistance, was calculated as follows: fasting glucose (mmol/L) x insulin concentration (micro-Units/ml) /22.5 to measure insulin resistance [8, 9].

The z-BMI  $\Delta$  was calculated in our participants as defined previously [4]. In summary, the pre-intervention z-BMI  $\Delta$  was defined as the z-BMI of the participant at the initial visit minus the z-BMI within the 3-months before the participation in the MDM care and obtained from participants' referring providers' records. Following participation in MDM, z-BMI  $\Delta$  was calculated as the difference in the z-BMI at the follow-up visit from the z-BMI at the initial visit. Similarly, we calculated the changes in the body composition parameters (FM, and MM  $\Delta$ ) as the measurements at the follow-up visits minus those measured at the initial assessments.

#### Statistical analysis

Data are expressed as mean  $\pm$  SD for continuous variables and frequency for categorical data. The changes in z-BMI, weight, BIA, and laboratory parameters were compared using paired Student's t-test.

Spearman correlation was used to assess the associations between parameters. The changes in participants' z-BMI and the laboratory parameters between April 2017 and September 2019 (Post-PC), were further compared to those followed between December 2014 and January 2017 under the previously published protocol (Pre-PC) and assessed with independent samples Mann-Whitney U test. Analyses were performed using SPSS 27.0 (SPSS, Chicago, IL, USA). The p-value < 0.05 was considered statistically significant.

## Results

We reviewed 615 records of participants who had at least one visit to the MDM center between December 2014 and September 2019. This included the data of our previously published 316 participants between December 2014 and January 2017, which were used for comparison. Additionally, we reviewed 299 participant data between April 2017 and September 2019. Weight and z-BMI data were available from the referring providers' clinic records within the 3 months before the initial MDM visit in the majority of the participants. The average age of all the participants was  $12.3 \pm 3.7$  years, and 46% were male. The demographic data of the participants were comparable before and after the clinic follow-up protocol change (Table 1).

**Primary outcome:** Of the 299 participants at initial visit, 63.5% returned at visit 2, 49.5% at visit 3, 38.5% at visit 4, 30.1% at visit 5, 23.4% at visit 6 and 19.4% at visit 7. Participants' follow-up rates at each clinic visit following the Protocol Change (Post-PC) were compared Pre-PC participant follow-up rates over the 6 follow-up clinic visits and are shown in Fig. 1. Overall, Post-PC follow up rates significantly exceeded the Pre-PC follow-up rates starting from visit3 (visit3,  $p = 0.07$ , visit 4,  $p = 0.001$ , visit 5–7,  $p < 0.001$ ).

**Secondary outcomes:** Following MDM intervention, z-BMI  $\Delta$  in the Post-PC participants continued a negative trend as compared to their z-BMI  $\Delta$  prior to MDM participation ( $p = 0.078$ ). With continued MDM intervention, the z-BMI  $\Delta$  progressively increased at each follow-up visit (visit 3–6) and differed significantly from z-BMI  $\Delta$  before MDM participation ( $p < 0.05$ ). The z-BMI  $\Delta$  in the Post-PC participants did not differ significantly from those of our published data on the Pre-PC participants (Fig. 2).

The Post-PC data analysis included an additional assessment of the changes in BIA parameters, which indicated that the total body FM decreased ( $\Delta = -2.07 \pm 7.3$  kg) and MM increased ( $\Delta = 3.3 \pm 5.6$  kg) over the follow-up period (Fig. 3). These opposite changes in FM and MM may explain the small overall changes in weights/ z-BMI noted in the participants.

The follow-up laboratory parameters of all participants (Pre and Post-PC participant data assessed together) showed significant improvements when compared to their baseline levels. These included improvements in the hemoglobin A1C %, HOMA-IR, total cholesterol, triglyceride, AST, and ALT concentrations (Table 2). There were no significant differences in the changes in the metabolic parameters between the Pre-PC and Post-PC participants (data not shown). Correlation analyses indicated the expected associations: z-BMI  $\Delta$  was positively associated with changes in fasting glucose ( $p < 0.001$ ,  $r = 0.35$ ), Triglyceride concentrations ( $p = 0.048$ ,  $r = 0.19$ ) and was negatively associated with

changes in HDL cholesterol ( $p = 0.013$ ,  $r = -0.23$ ). Further correlation analysis of BIA parameters and markers of metabolic syndrome indicated that the initial FM  $\Delta$  (measured as FM at visit 2 minus the FM at initial visit) correlated significantly with glucose  $\Delta$  ( $p < 0.01$ ,  $r = 0.6$ ) and HOMA-IR  $\Delta$  ( $p = 0.01$ ,  $r = 0.47$ ). Additionally, the initial MM  $\Delta$  (measured as the MM at visit 2 minus the MM at initial visit) negatively correlated with Total cholesterol ( $p = 0.04$ ,  $r = -0.3$ ) and LDL-cholesterol ( $p = 0.01$ ,  $r = -0.37$ ).

## Discussion

Childhood obesity has multifactorial origins. This makes its management particularly challenging. Our group had previously demonstrated that the youth with extreme obesity participating in an urban MDM weight management program had significant improvements in weight parameters when compared to pre-participation data. This was also associated with improvements in markers of glycemic control, serum lipid concentrations, and hepatic enzyme concentrations. Despite these improvements, youth participation in MDM waned progressively [4].

To improve participation in MDM, we had modified our clinic follow-up protocol to mirror those of clinical trials and provided all participants with a protocolized time-limited participation plan. Our results indicate that the provision of a structured time-limited MDM clinic protocol to all participants from the “get-go” resulted in a small but significant improvement in the subsequent participants’ clinic follow-up rates. However, the overall follow-up rates remained poor and only 19.4% returned for follow-up at the 6th follow-up visit.

In line with our previously published data, our participants had significant improvements in weight parameters. The z-BMI  $\Delta$  in the participants followed a progressive negative trend with ongoing follow-up. Additionally, with continued follow-up, participants had significant improvements in their laboratory metabolic markers as compared to their baseline levels. These changes were very similar to our previously published data, indicating the changes made to the clinic follow-up protocol had no deleterious effects on patient outcomes. Our current analysis of participant weight outcomes additionally focused on the changes in the body composition analysis over the participation period. Our results indicated that the youth experienced an average reduction in their total body fat mass along with an increase in the average total body muscle mass over the follow-up duration. These improvements in body composition could not be assessed if only total body weight or even z-BMI is used for the assessment of weight parameters.

Our participants had multiple improvements in metabolic markers including markers of insulin resistance, glycemic control, cholesterol, and hepatic enzyme concentrations. The association of metabolic outcomes with the improvements in BMI and z-BMI has been demonstrated extensively in the literature. Our current study additionally demonstrated the association between the changes in BIA parameters and laboratory metabolic markers. In particular, the changes in total fat mass correlated positively with changes in glucose concentration and HOMA-IR. Similar data have been shown in adults where visceral fat was particularly assessed [11, 12]. Accurate visceral fat estimation was not available in our

population. However, further analysis of the effects of visceral fat changes on metabolic outcomes would continue to highlight the role of these metabolically active fats in the development of metabolic disorders in youth.

We additionally found significant inverse associations between muscle mass increases and changes in the total cholesterol and triglyceride concentrations. While pediatric data is limited, large adult studies have shown similar associations [13]. Our data indicate that weight increases in the form of muscle mass in youth may have metabolic health benefits in the youth and furthers the well-known benefits of regular exercise and muscle building for the overall metabolic health of youth. It is also important to remember these changes cannot be assessed by measuring the total body weight changes or even the changes in z-BMI. Unfortunately, body composition analyzers are not readily available, and families are often discouraged when they see minimal changes in weight despite their intensive efforts.

The results of our study suggests that the improvements in weight and metabolic outcomes alone may not motivate all participants to continue MDM participation despite the obvious health benefits. Additionally, it indicates that structured, pre-determined protocolized clinic follow-up may provide only limited improvements in the overall clinical follow-up rates. In contrast, most clinical trials or research studies report very low follow-up attrition. The high follow-up rates in these protocols may be the results of additional pre-screening of families and the use of the “run-in” phase of clinical trials/ studies that help choose ideal candidates. Further, ongoing participation in clinical trials and studies is often incentivized via monetary remunerations and additional perks.

Socio-economic challenges pose significant barriers to ongoing participation in medical care. Various strategies including those involving behavioral economics [14, 15] have shown promising results. The efficacy of these strategies to prevent follow-up attrition and maintain health benefits of continued care should be evaluated by larger studies in the vulnerable youth.

Our study has several limitations. Our data represent the observations of a large single-center urban tertiary MDM program. While we were able to demonstrate significant successes in weight parameters, the efficacy of our approach has not been tested in larger multi-center trials. Additionally, we have presented the outcomes of 6 follow-up visits. Changes in weight parameters, metabolic outcomes, and participant engagement on extended follow-up may differ from our data. Further, we did not assess the use of telemedicine which has become very popular in the current era of the coronavirus epidemic. Telemedicine, the judicious use of technology, and behavioral economics strategies may provide new strategies to improve patient participation and change the long-term outcome.

## Declarations

**Funding:** None

**Conflicts of interest/Competing interests:** None

**Availability of data and material:** on request

**Code availability:** Not applicable

**Authors' contributions** IM was responsible for study design, planning, data analysis, and manuscript preparation. BE was responsible for data collection, and manuscript preparation. CMH was responsible for manuscript preparation.

**Ethics approval:** The study was approved by the Institutional Review Board and was in accordance with the ethical standards of the Helsinki Declaration of 1975.

**Consent to participate:** Consents were not obtained from participants since data was obtained from the EMR database retrospectively without any direct patient contact.

**Consent for publication:** Granted

## References

1. Fryar CD, Carroll MD, J, A.: Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2–19 years: United States, 1963–1965 through 2017–2018. NCHS Health E-Stats. (2020).
2. Epstein, L.H., Paluch, R.A., Roemmich, J.N., Beecher, M.D.: Family-based obesity treatment, then and now: twenty-five years of pediatric obesity treatment. *Health Psychol* 26(4), 381-391 (2007). doi:10.1037/0278-6133.26.4.381
3. Kovac Blaz, M., Svab, I.: A Multidisciplinary Approach to Treating Obesity in a Community Health Centre. *Zdr Varst* 54(4), 252-258 (2015). doi:10.1515/sjph-2015-0033
4. Majumdar, I., Espino, B., Bianco, K., Epstein, J., Mamilly, L., Harmon, C.M.: Multi-disciplinary weight management compared to routine care in youth with obesity: what else should be monitored? *Endocrine* 65(2), 263-269 (2019). doi:10.1007/s12020-019-01988-9
5. Dalle Grave, R., Melchionda, N., Calugi, S., Centis, E., Tufano, A., Fatati, G., Fusco, M.A., Marchesini, G.: Continuous care in the treatment of obesity: an observational multicentre study. *J Intern Med* 258(3), 265-273 (2005). doi:10.1111/j.1365-2796.2005.01524.x
6. Gill, R.S., Karmali, S., Hadi, G., Al-Adra, D.P., Shi, X., Birch, D.W.: Predictors of attrition in a multidisciplinary adult weight management clinic. *Can J Surg* 55(4), 239-243 (2012). doi:10.1503/cjs.035710
7. Kuczmarski, R.J., Ogden, C.L., Guo, S.S., Grummer-Strawn, L.M., Flegal, K.M., Mei, Z., Wei, R., Curtin, L.R., Roche, A.F., Johnson, C.L.: 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat* 11(246), 1-190 (2002).
8. Kurtoglu, S., Hatipoglu, N., Mazicioglu, M., Kendirici, M., Keskin, M., Kondolot, M.: Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods. *J Clin Res Pediatr Endocrinol* 2(3), 100-106 (2010). doi:10.4274/jcrpe.v2i3.100

9. Lee, J.M., Okumura, M.J., Davis, M.M., Herman, W.H., Gurney, J.G.: Prevalence and determinants of insulin resistance among U.S. adolescents: a population-based study. *Diabetes Care* 29(11), 2427-2432 (2006). doi:10.2337/dc06-0709
10. Flack, J.M., Calhoun, D., Schiffrin, E.L.: The New ACC/AHA Hypertension Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *Am J Hypertens* 31(2), 133-135 (2018). doi:10.1093/ajh/hpx207
11. Szymanska, E., Bouwman, J., Strassburg, K., Vervoort, J., Kangas, A.J., Soininen, P., Ala-Korpela, M., Westerhuis, J., van Duynhoven, J.P., Mela, D.J., Macdonald, I.A., Vreeken, R.J., Smilde, A.K., Jacobs, D.M.: Gender-dependent associations of metabolite profiles and body fat distribution in a healthy population with central obesity: towards metabolomics diagnostics. *OMICS* 16(12), 652-667 (2012). doi:10.1089/omi.2012.0062
12. Graner, M., Siren, R., Nyman, K., Lundbom, J., Hakkarainen, A., Pentikainen, M.O., Lauerma, K., Lundbom, N., Adiels, M., Nieminen, M.S., Taskinen, M.R.: Cardiac steatosis associates with visceral obesity in nondiabetic obese men. *J Clin Endocrinol Metab* 98(3), 1189-1197 (2013). doi:10.1210/jc.2012-3190
13. Oh, Y.H., Choi, S., Lee, G., Son, J.S., Kim, K.H., Park, S.M.: Changes in Body Composition Are Associated with Metabolic Changes and the Risk of Metabolic Syndrome. *J Clin Med* 10(4) (2021). doi:10.3390/jcm10040745
14. Vlaev, I., King, D., Darzi, A., Dolan, P.: Changing health behaviors using financial incentives: a review from behavioral economics. *BMC Public Health* 19(1), 1059 (2019). doi:10.1186/s12889-019-7407-8
15. Wilfley, D.E., Hayes, J.F., Balantekin, K.N., Van Buren, D.J., Epstein, L.H.: Behavioral interventions for obesity in children and adults: Evidence base, novel approaches, and translation into practice. *Am Psychol* 73(8), 981-993 (2018). doi:10.1037/amp0000293

## Tables

**Table 1** Comparison of participants

	All Participants (n= 615)	Pre-PC (n= 316)	Post-PC (n= 299)
Age (years)	12.7 ± 3.5	12.9 ± 3.5	12.6 + 3.4
Male %	40.6	41.2	40.4
Weight (kg)	96.1 ± 35.3	99.7 ± 37.2	92.2 ± 32.7
BMI	37.4 ± 8.7	36.5 ± 8.7	36.5 ± 7.9
z-BMI	2.5 ± 0.4	2.59 ± 0.4	2.51 ± 0.4
BMI percentile	>99	>99	>99
Fat Mass (kg)	37.5 ± 19.2 (n= 257)	Insufficient data	37.5 ± 19.2 (n= 257)
Muscle Mass (kg)	52.0 ± 14.4 (n= 251)	Insufficient data	52.0 ± 14.4 (n= 251)

The data are expressed as Mean ± SD or percentage.

*z-BMI* BMI-Z-score, *Pre-PC* Participants followed between December2014- January2017 (Pre-Protocol change)

*Post-PC* Participants followed between April2017- September2017 (Post- Protocol change)

**Table 2** Changes in laboratory parameters in all participants

	Initial	Follow up	p-value
HbA1c (%)	5.5 + 0.5	5.4 + 0.6	0.02
Serum glucose (mg/dl)	90.6 + 13.2	90.1 + 15.5	0.74
HOMA-IR	2.3 + 3.6	1.2 + 2.96	<0.01
Total cholesterol (mg/dl)	170.7 + 34.9	167.0 + 33.9	0.045
Triglycerides (mg/dl)	132.8 + 69.9	121.3 + 56.2	0.017
HDL (mg/dL)	40.7 + 9.1	40.7 + 9.2	0.97
LDL (mg/dL)	104.5 + 29.8	102.7 + 29.0	0.23
AST (units/L)	23.4 + 9.4	21.3 + 7.5	<0.01
ALT (units/L)	26.1 + 17.4	23.6 + 13.9	0.013

*HOMA- IR* Homeostatic Model Assessment for Insulin Resistance= fasting glucose (mmol/L)\* insulin concentration (micro-Units/ml) /22.5

Conversion: HbA1c (mmol/mol, IFCC) = 10.93\*HbA1c (%) - 23.5;

Glucose (mmol/L) = 0.0555\*mg/dl;

Cholesterol (mmol/L) = 0.0259\*mg/dl;

Triglycerides (mmol/L) = 0.0113\*mg/dl

## Figures

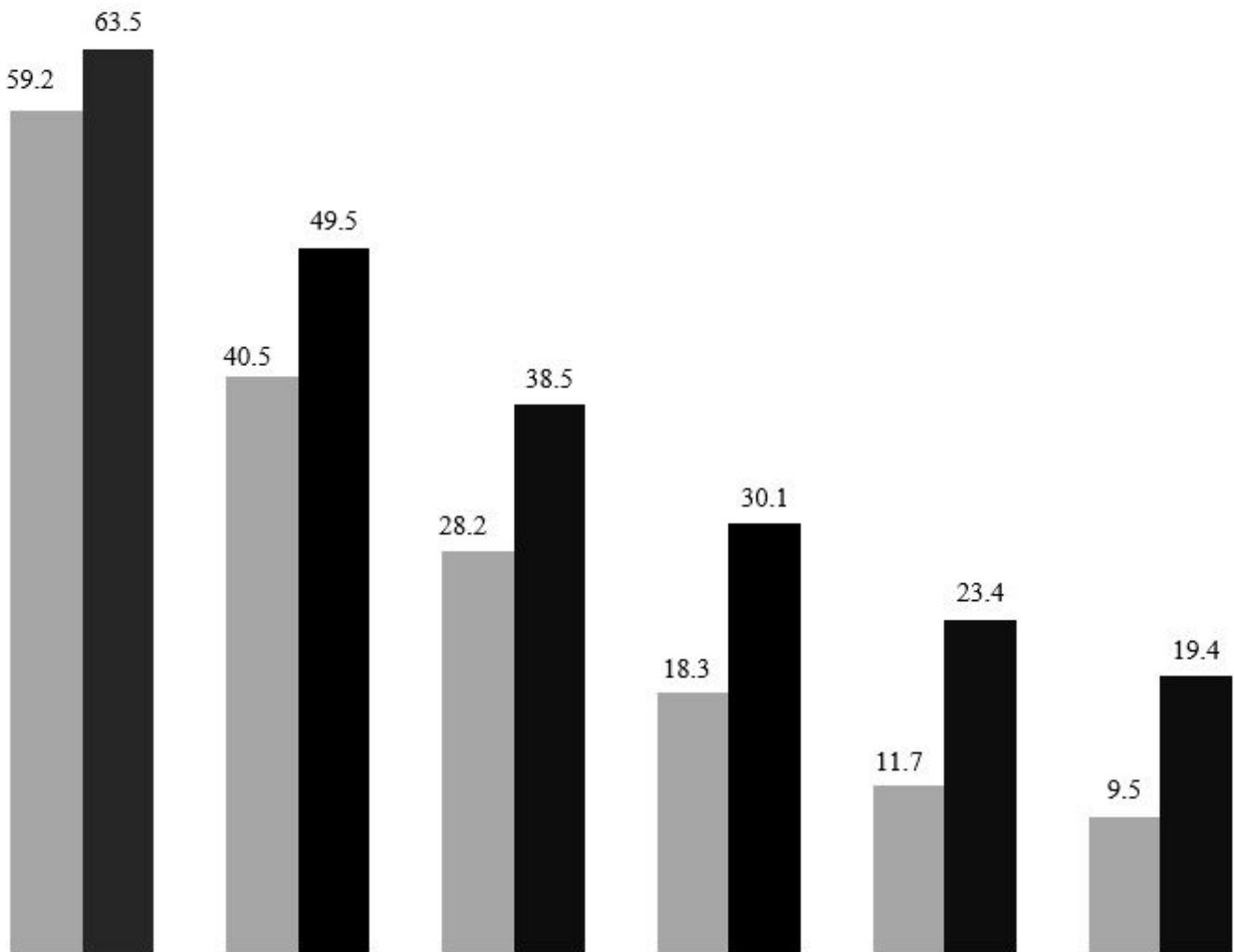
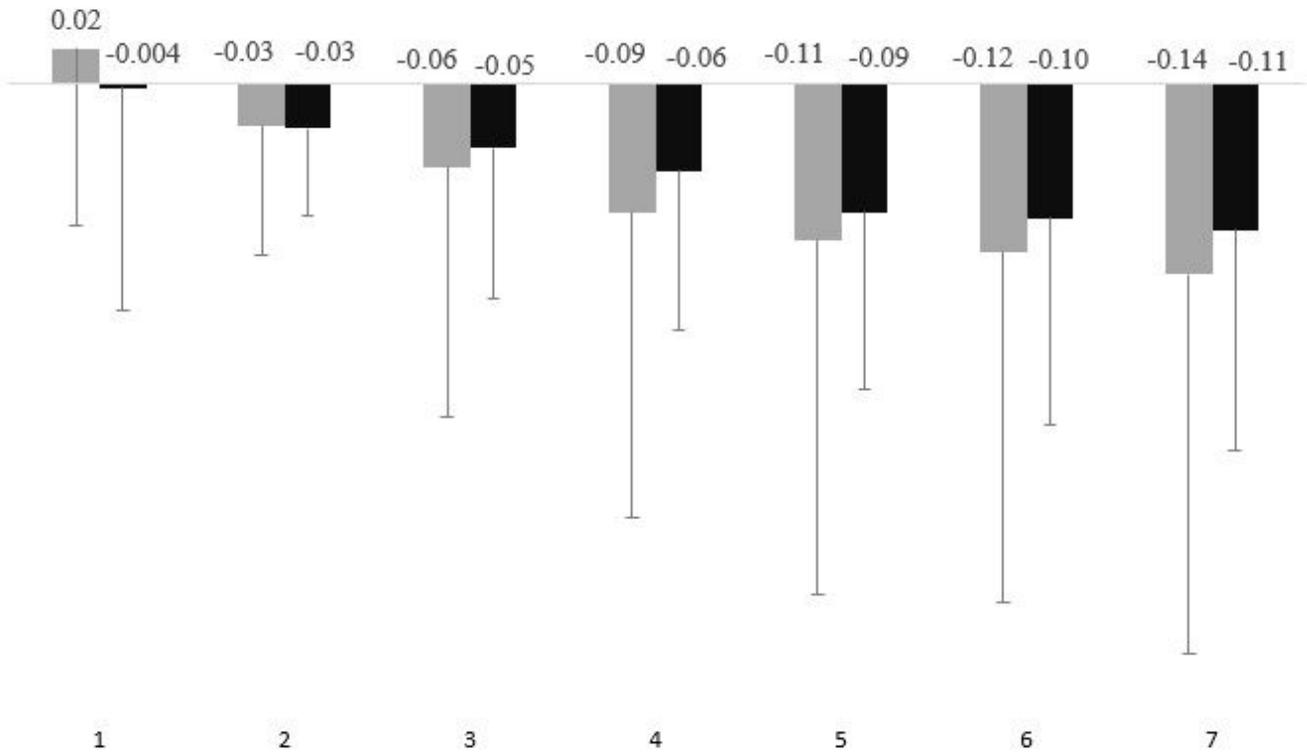


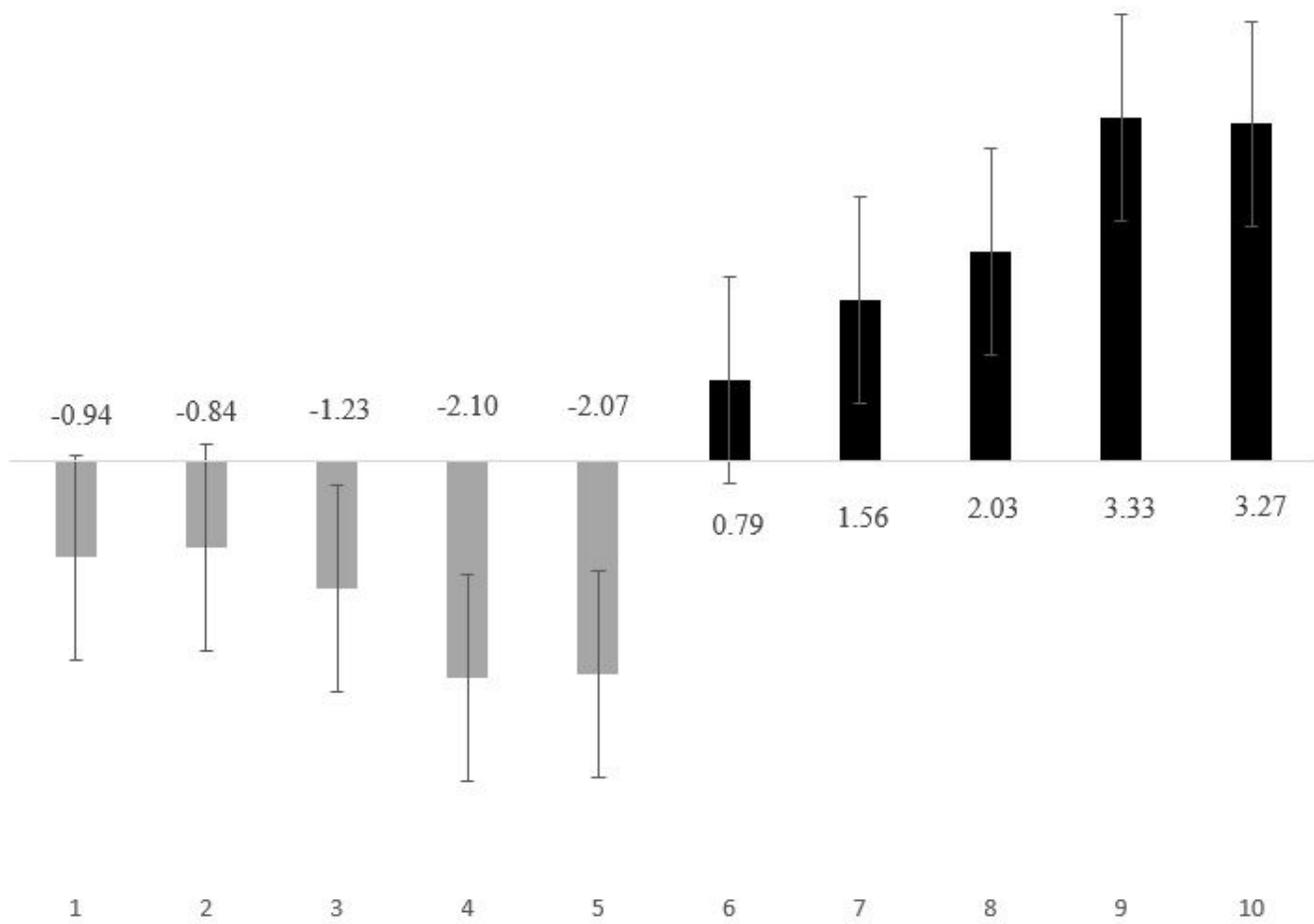
Figure 1

Please see the Manuscript file for the complete figure caption.



**Figure 2**

Please see the Manuscript file for the complete figure caption.



**Figure 3**

Please see the Manuscript file for the complete figure caption.