

# Exploring and validating different relationships among various biomarkers by using both linear and nonlinear, single variable and multiple variables regression analysis models and collected big data of a type 2 diabetes patient based on GH-Method: math-physical medicine (No. 549)

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## Abstract

In the author's previous medical research reports, he mainly applied physics theories, engineering models, mathematical equations, computer big data analytics and artificial intelligence (AI) techniques, as well as some statistical approaches to explore and interpret various biophysical phenomena. However, the majority of medical research papers he has read thus far are primarily based on statistics. As a result, for his paper no. 540 through no. 548 (except no. 545), he has selected some basic statistical tools, such as correlation, variance, *p*-values, and **regression analyses**, to study his various biomarkers using linear regression analysis model with either single variable or multiple variables. In this particular paper, he has selected 5 cases to compare their concluding findings using both linear regression and nonlinear regression. The nonlinear regression models include exponential, logarithmic, polynomial, and power. The biomarkers he selected to study are body weight for obesity, FPG & PPG for diabetes, and CVD/Stroke risk probability (chronic disease complication). The inputs or independent variables are carbohydrates & sugar intake amount, body weight, 4 medical conditions score, 6 lifestyle details score, sleep, food consumption quantity, and HbA1C to indicate the insulin resistance level. Depending on his selected case, the body weight has served as either output of dependent variable (symptom) or input independent variable (cause). By the way, since 1/1/2012, the author has collected ~3 million data thus far regarding his health, lifestyle, organs, and diseases.

His 5 selected cases are listed as below:

1. CGM sensor PPG vs. carbs/sugar
2. CGM sensor FPG vs. weight
3. CVD risk vs. disease & lifestyle
4. Weight vs. sleep & food quantity
5. Finger FPG vs. sleep, weight, A1C.

The analyses associated with these 5 selected cases utilized two different approaches. Time-domain analysis uses time as the *x*-axis and biomarker as the *y*-axis, whereas the space-domain analysis uses the independent *x* variable as the *x*-axis and the dependent *y* variable as the *y*-axis.

In this study, he will not repeat the detailed introduction of the regression analysis in the Method section because it is available in many statistics textbook. It should be noted that, in regression analysis, the correlation coefficient *R* should be  $> 0.5$  or 50% to indicate a strong inter-connectivity. The variance,  $R^2$ , should be the higher (covers more data) the better. The *p*-value should be  $< 0.05$  or 5% to be considered as statistically significant.

In summary, there are 4 specific biomedical proved conclusions as described briefly as below:

1. The fasting plasma glucose (FPG) is strongly influenced by both insulin resistance from pancreatic beta cells as indicated by HbA1C value and the body weight situation.
2. The most direct and effective way of body weight reduction and postprandial plasma glucose (PPG) reduction is

through food portion (quantity) reduction for weight concern plus carbs/sugar amount (quality) reduction for PPG concern.

3. CVD/Stroke risk probability is strongly connected with lifestyle details score, more than existing chronic disease conditions, i.e., medical conditions.
4. In conclusion, a good lifestyle intervention and management program is the best method for prevention and control of both chronic diseases and their complication.
5. The calculated variances are depending on its source data pattern which reveals certain hidden specific biomedical information. Sometime, when a variance is around 50%-80%, a nonlinear regression model could offer some extra assistance on improving the variance value from linear regression model. However, the most important task is not to study those exterior numerical values but rather to dig out and expose those hidden biomedical, biochemical and biophysical information.

The above-described explorations are not surprising findings which have been indicated by many authors of other medical research papers. The author of this article has also proven the same conclusions using his math-physical medicine methodology. However, in this paper, he has offered further numerical and quantitative proof via the traditional statistics method, such as regression analysis, similar to ~90% of existing medical publications.

Case	Title	Time Period	Observations	Time-Domain Time-domain: predict vs. measure	Predict / Measure	Accuracy	Space-Domain Space-domain variances: Linear / Nonlinear	Conclusion form Regression Variance analysis
Case 1	Sensor PPG vs. Carbs/Sugar	1/1/2020 - 10/31/2021	670 days	predicted PPG curve is narrower, pseudo-linear	121.4 / 124 mg/dL	98%	carbs: linear 0.7543 / nonlinear 0.7460 - 0.7569	lower variance of ~75% shows that PPG is controlled by carbs (60%) and exercise (40%)
Case 2	Sensor FPG vs. Weight	5/8/2018 - 11/5/2021	1278 days	predicted FPG curve is narrower, pseudo-linear	104.1 / 108 mg/dL	96%	Weight: linear 1.0 / nonlinear 0.9968 - 1.0	near 1.0 variance shows that FPG is strongly influenced by weight
Case 3	CVD risk vs. medical & lifestyle	Y2012 - Y2021	10 years	Both CVD risk based on MI and based on regression have almost identical curves due to using annual data	63% / 63% of CVD risk probability	100%	Variances: medical conditions: 0.7731 / 0.8793; Lifestyle details: 0.9889 / 0.9735-0.9920	CVD risk is less influenced by medical conditions, so the nonlinear model can improve its variance; CVD risk is mainly influenced by Lifestyle, so the linear model (~99%) is good enough for variance; CVD risk is mainly contributed by poor lifestyle (root causes), not from existing chronic diseases (symptoms)
Case 4	Weight vs. sleep & Food quantity	Y15H2 - Y21H2	13 semi-annual	Predicted weight is only slighter flatter than measured weight curve due to this semi-annual time model	Weight: predicted m1 = 1.0184 (173 lbs) / & measured m1 1.0098 (172 lbs)	99%	Variances: food quantity's linear 0.9967 / nonlinear 0.9906 - 0.9961; sleep's linear 0.6980 / 0.7287	Weight reduction through food portion reduction. Weight is mainly contributed by food quantity, so it has a high ~1.0 variance; weight is less influenced by sleep, so its ~0.7 variance can be slightly improved by nonlinear model
Case 5	Finger FPG vs. sleep, weight, HbA1C	Y15H2 - Y21H2	13 semi-annual	Predicted Finger FPG is almost identical with the measured Finger FPG curve due to this semi-annual time model	Finger FPG: both predicted and measured values are 110.7 mg/dL	100%	Variances: sleep's linear 0.5661 / nonlinear 0.5725; weight's linear 0.8354 / 0.9007; A1C's linear 0.9158 / 0.9097;	A1C (insulin resistance) is the strongest influence factor of Finger FPG (both linear & nonlinear at 0.9); weight is the second strongest influencer so nonlinear model can improve its variance; sleep is the least influencer of Finger FPG. Lifestyle intervention can indeed self-repair beta cells, but it is a slow process

## Introduction

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In this study, he will not repeat the detailed introduction of the regression analysis in the Method section because it is available in many statistics textbook. It should be noted that, in regression analysis, the correlation coefficient R should be > 0.5 or 50% to indicate a strong inter-connectivity. The variance, R<sup>2</sup>, should be the higher (covers more data) the better. The p-value should be <0.05 or 5% to be considered as statistically significant.

## Methods

### MPM Background

To learn more about the author's developed GH-Method: math-physical medicine (MPM) methodology, readers can select the following three papers from his ~500 published medical papers.

The first paper, No. 386 describes his MPM methodology in a general conceptual format. The second paper, No. 387 outlines the history of his personalized diabetes research, various application tools, and the differences between biochemical medicine (BCM) approach versus the MPM approach. The third paper, No. 397 depicts a general flow diagram containing ~10 key MPM research methods and different tools.

In particular, paper No. 453 illustrates his GH-Method: math-physical medicine in great details, "Using Topology concept of mathematics and Finite Element method of engineering to develop a mathematical model of Metabolism in medicine in order to control various chronic diseases and their complications via overall health conditions improvement".

#### The Author's Case of Diabetes and Complications

The author has been a severe type 2 diabetes (T2D) patient since 1996 and weighed 220 lbs. (100 kg, BMI 32.5) at that time. By 2010, he still weighed 198 lbs. (BMI 29.2) with an average daily glucose of 250 mg/dL (HbA1C of 10%). During that year, his triglycerides reached to 1161 (diabetic retinopathy or DR) and albumin-creatinine ratio (ACR) at 116 (chronic kidney disease or CKD). He also suffered five cardiac episodes within a decade. In 2010, three independent physicians warned him regarding his needs of kidney dialysis treatment and future high risk of dying from severe diabetic complications. Other than cerebrovascular disease (stroke), he has suffered most known diabetic complications, including both macro-vascular and micro-vascular complications.

In 2010, he decided to launch his self-study on endocrinology, diabetes, and food nutrition in order to save his own life. During 2015 and 2016, he developed four prediction models related to diabetes conditions: weight, PPG, fasting plasma glucose (FPG), and A1C. As a result, from using his developed mathematical metabolism index (MI) model in 2014 and the four prediction tools, by end of 2016, his weight was reduced from 220 lbs. (100 kg, BMI 32.5) to 176 lbs. (89 kg, BMI 26.0), waistline from 44 inches (112 cm, nonalcoholic fatty liver disease /NAFLD) to 33 inches (84 cm), average finger glucose reading from 250 mg/dL to 120 mg/dL, and lab-tested A1C from 10% to ~6.5%. One of his major accomplishments is that he no longer takes any diabetes medications since 12/8/2015.

In 2017, he has achieved excellent results on all fronts, especially his glucose control. However, during the pre-COVID period of 2018 and 2019, he traveled to approximately 50+ international cities to attend 65+ medical conferences and made ~120 oral presentations. This hectic schedule inflicted damage to his diabetes control, through dining out frequently, post-meal exercise disruption, jet lag, and along with the overall metabolism impact due to his irregular life patterns through a busy travel schedule; therefore, his glucose control and overall metabolism state were somewhat affected during this two-year heavy travel period.

During 2020 and 2021 with a strict COVID-19 quarantine lifestyle, not only has he written and published ~400 medical papers in 100+ journals, but he has also reached his best health conditions for the past 26 years. By the beginning of 2021, his

weight was further reduced to 165 lbs. (BMI 24.4) along with a 6.1% A1C value (daily average glucose at 105 mg/dL), without having any medication interventions or insulin injections. These good results are due to his non-traveling, low-stress, and regular daily life routines. Due to the knowledge of chronic diseases, practical lifestyle management experiences, and his developed various high-tech tools, they contributed to his excellent health status since 1/19/2020, which is the start date of being self-quarantine.

On 5/5/2018, he applied a continuous glucose monitoring (CGM) sensor device on his upper arm and checks glucose measurements every 5 minutes for a total of ~288 times each day. He has maintained the same measurement pattern to present day. In his research work, he uses the CGM sensor glucose at time-interval of 15 minutes (96 data per day). Incidentally, the difference of average sensor glucoses between 5-minute intervals and 15-minute intervals is only 0.4% (average glucose of 114.81 mg/dL for 5-minutes and average glucose of 114.35 mg/dL for 15-minutes with a correlation of 93% between these two sensor glucose curves) during the period from 2/19/20 to 8/13/21.

Therefore, over the past 11 years, he could study and analyze the collected ~3 million data regarding his health status, medical conditions, and lifestyle details. He applies his knowledge, models, and tools from mathematics, physics, engineering, and computer science to conduct his medical research work. His medical research work is based on the aims of achieving both "high precision" with "quantitative proof" in the medical findings.

The following timetable provides a rough sketch of the emphasis of his medical research during each stage:

- 2000-2013: Self-study diabetes and food nutrition, developing a data collection and analysis software.
- 2014: Develop a mathematical model of metabolism, using engineering modeling and advanced mathematics.
- 2015: Weight & FPG prediction models, using neuroscience.
- 2016: PPG & HbA1C prediction models, utilizing optical physics, AI, and neuroscience.
- 2017: Complications due to macro-vascular research such as cardiovascular disease (CVD), coronary heart disease (CHD) and stroke, using pattern analysis and segmentation analysis.
- 2018: Complications due to micro-vascular research such as CKD, bladder, foot, and eye issues such as DR.
- 2019: CGM big data analysis, using wave theory, energy theory, frequency domain analysis, quantum mechanics, and AI.
- 2020: Cancer, dementia, longevity, geriatrics, DR, hypothyroidism, diabetic foot, diabetic fungal infection, linkage between metabolism and immunity, and learning about certain infectious diseases such as COVID-19.
- 2021: Applications of LEGT and perturbation theory from quantum mechanics on medical research subjects, such as chronic diseases and their complications, cancer, and dementia. Using metabolism and immunity, it's as the



base, he expands his research into cancers, dementia, and COVID-19. In addition, he has also developed a few useful analysis methods and tools for his medical research work.

to share his findings and knowledge with patients worldwide.

## Results

Figure 1 shows a conclusion table of this particular study. It lists t selected cases for this stud which include case title, time period, observations, time-domain's predicted value versus measured value and prediction accuracy, space-domain's variances from both linear regression model and various nonlinear regression models, and observed key conclusions (see the Conclusions section).

To date, he has collected nearly 3 million data regarding his medical conditions and lifestyle details. In addition, he has written 536 medical papers and published 500+ articles in 100+ various medical journals, including 7 special editions with selected 20-25 papers for each edition. Moreover, he has given ~120 presentations at ~65 international medical conferences. He has continuously dedicated time and effort on medical research work

Case	Title	Time Period	Observations	Time-Domain			Space-Domain		Conclusion form Regression Variance analysis
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Case 4	Weight vs. sleep & Food quantity	Y15H2 - Y21H2	13 semi-annual	Predicted weight is only slighter flatterng than measured weight curve due to this semi-annual time model	Weight: predicted m1 = 1.0184 (173 lbs) / & measured m1 1.0098 (172 lbs)	99%	Variances: food quantity's linear 0.9967 / nonlinear 0.9906 - 0.9961; sleep's linear 0.6980 / 0.7287	<b>Weight reduction through food portion reduction.</b> Weight is mainly contributed by food quantity, so it has a high ~1.0 variance; weight is less influenced by sleep, so its ~0.7 variance can be slightly improved by nonlinear model	
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Figure 1: Information and data table of research findings and conclusions

Figures 2 and 3 show both time-domain and space-domain results of Case 1 of sensor PPG vs. carbs/sugar intake amount. In time-domain, his sensor PPG prediction accuracy using carbs/sugar as input is 98%; and his variances are 75% for linear model and 75%-76% for nonlinear model. **Although these varian-**

**es are high but not high enough which indicate PPG is influenced partially by carbs/sugar amount (~60% contribution) and the other partial influential factor by post-meal exercise level (~40% contribution) is not included in this study.**

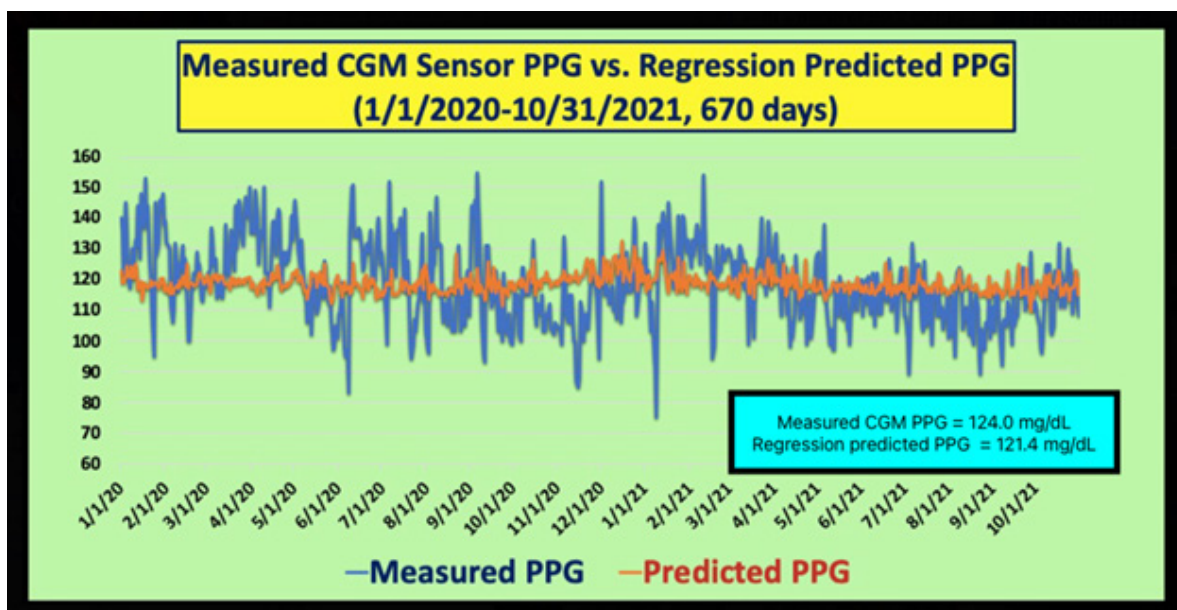


Figure 2: Time-domain analysis for Case 1 - sensor PPG vs. carbs/sugar

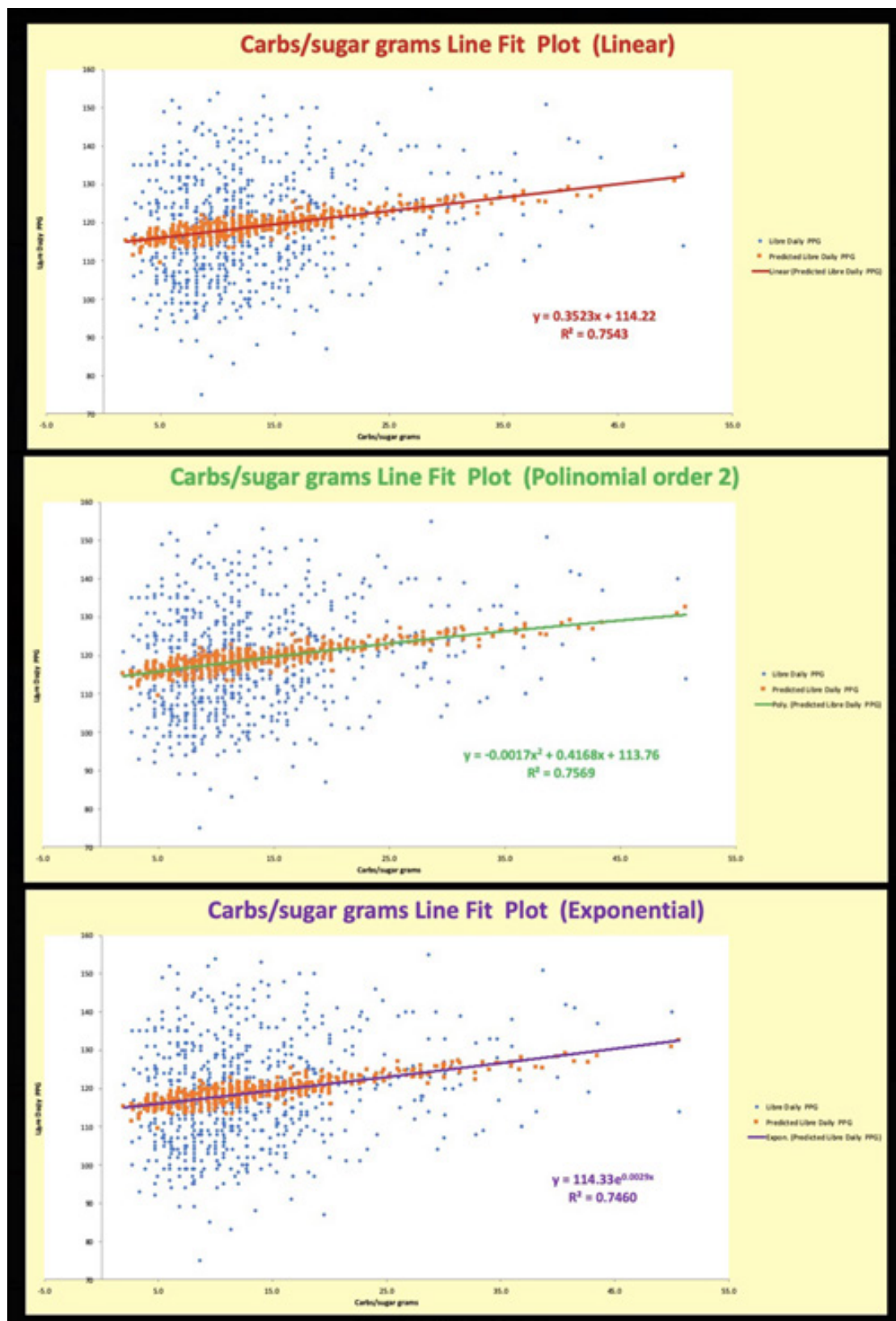


Figure 3: Space-domain analysis for Case 1 - sensor PPG vs. carbs/sugar

Figures 4 and 5 show both time-domain and space-domain results of Case 2 of sensor FPG vs. body weight. In time-domain, his sensor FPG prediction accuracy using body weight as input is 96%; and his variances for both linear model and nonlinear model are ~100%. **These extremely high variances are near ideal and perfect which indicate FPG is almost exclusively in-**

**fluenced by body weight situation and nonlinear model offers no value on variance improvement.** It should be mentioned here that, from Case 5 findings, another hidden and even stronger influential factor of FPG is insulin resistance situation of T2D patient's pancreatic beta cells health situation.

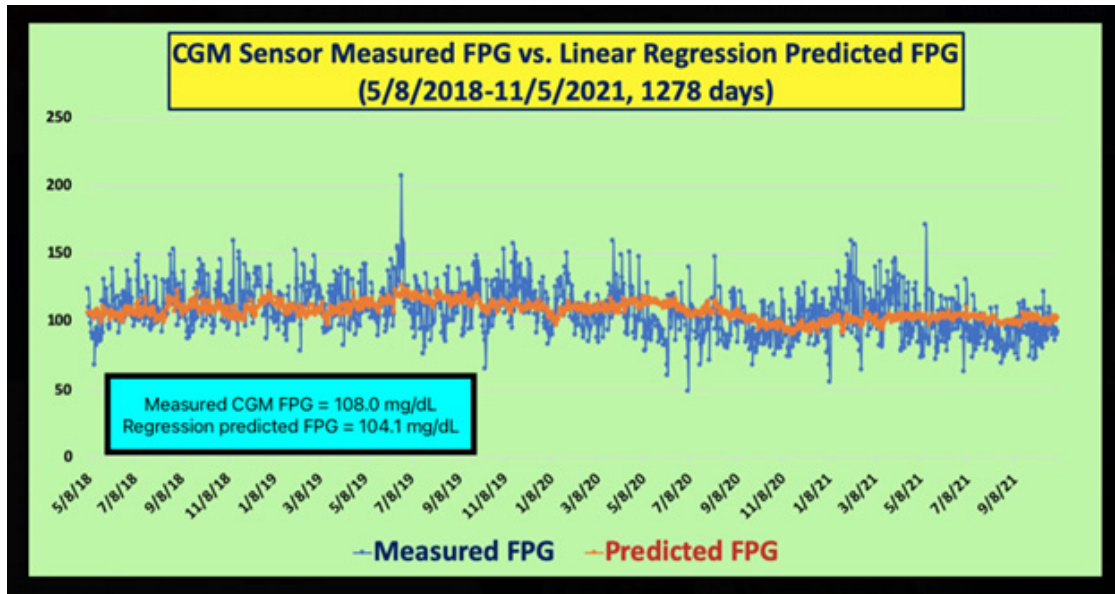


Figure 4: Time-domain analysis for Case 2 - sensor FPG vs. weight

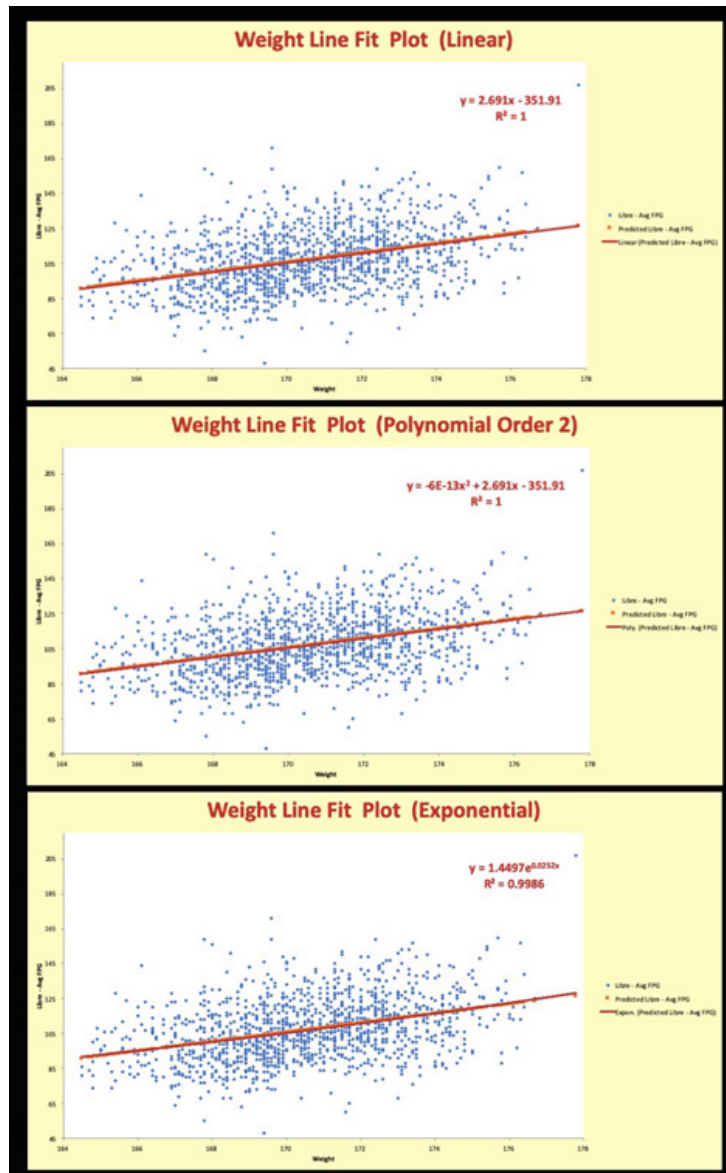


Figure 5: Space-domain analysis for Case 2 - sensor FPG vs. weight



Figures 6, 7, and 8 show both time-domain and space-domain results of Case 3, CVD risk vs. medical conditions and lifestyle details. In time-domain, his CVD risk probabilities prediction

accuracy between metabolism index (MI) based and regression analysis based using both of his medical conditions of chronic diseases and his lifestyle details as input is 100%.

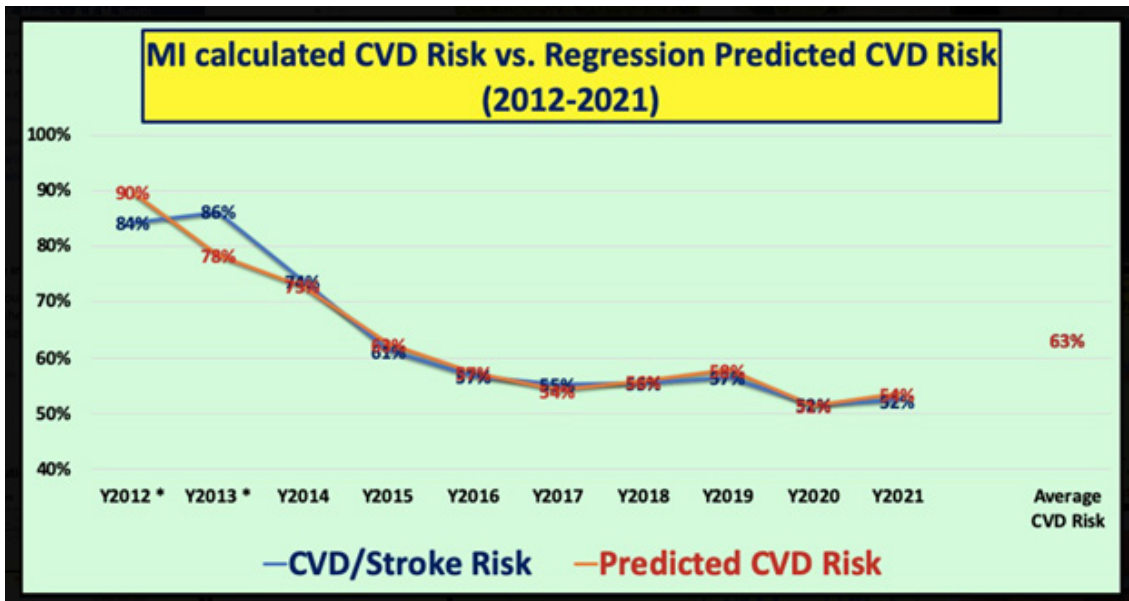


Figure 6: Time-domain analysis for Case 3 - CVD Risk vs. medical condition and lifestyle details

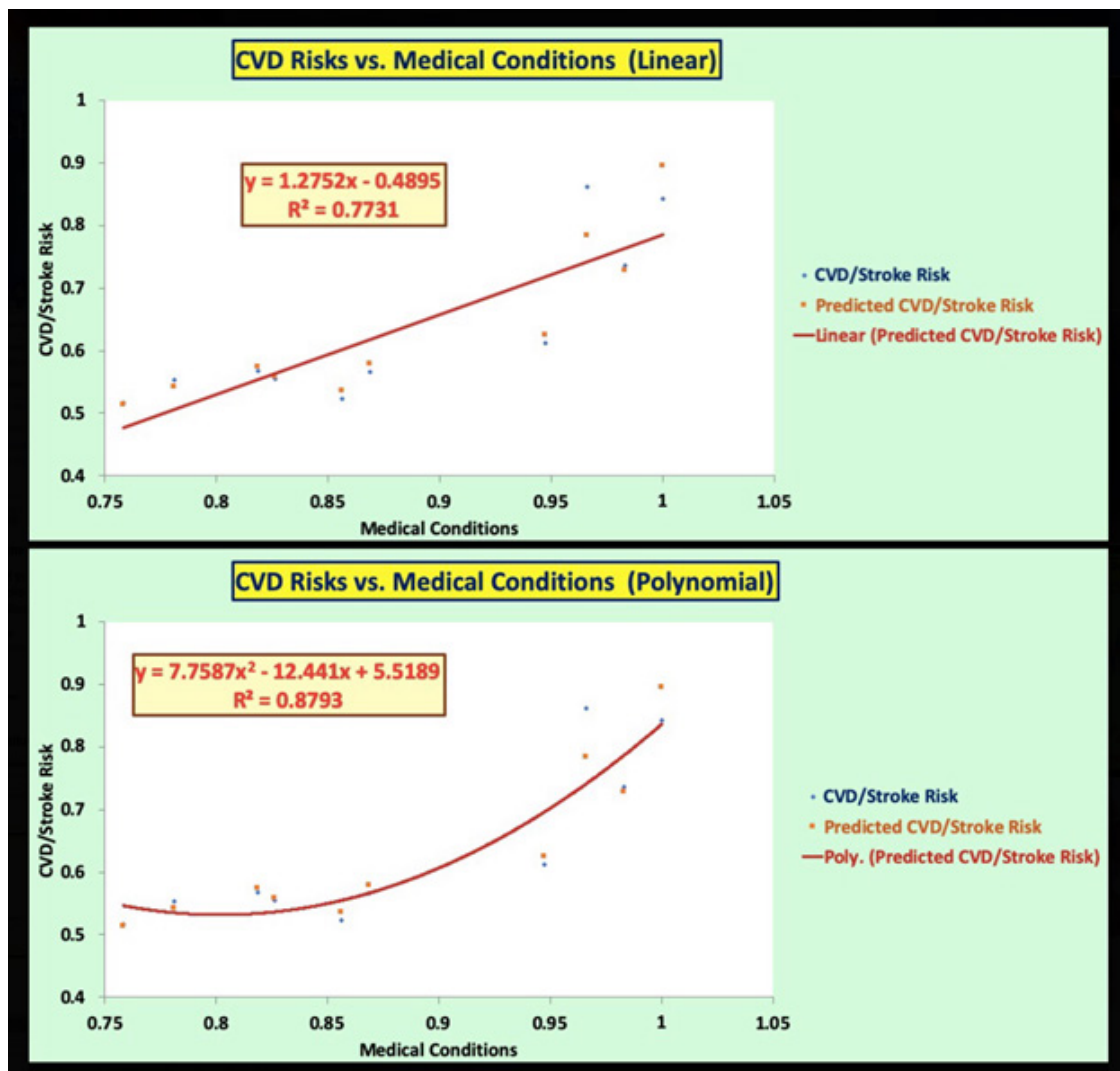


Figure 7: Space-domain analysis for Case 3 - CVD Risk vs. medical condition

## CVD risk vs. Lifestyle: 5 regression models with very similar variances

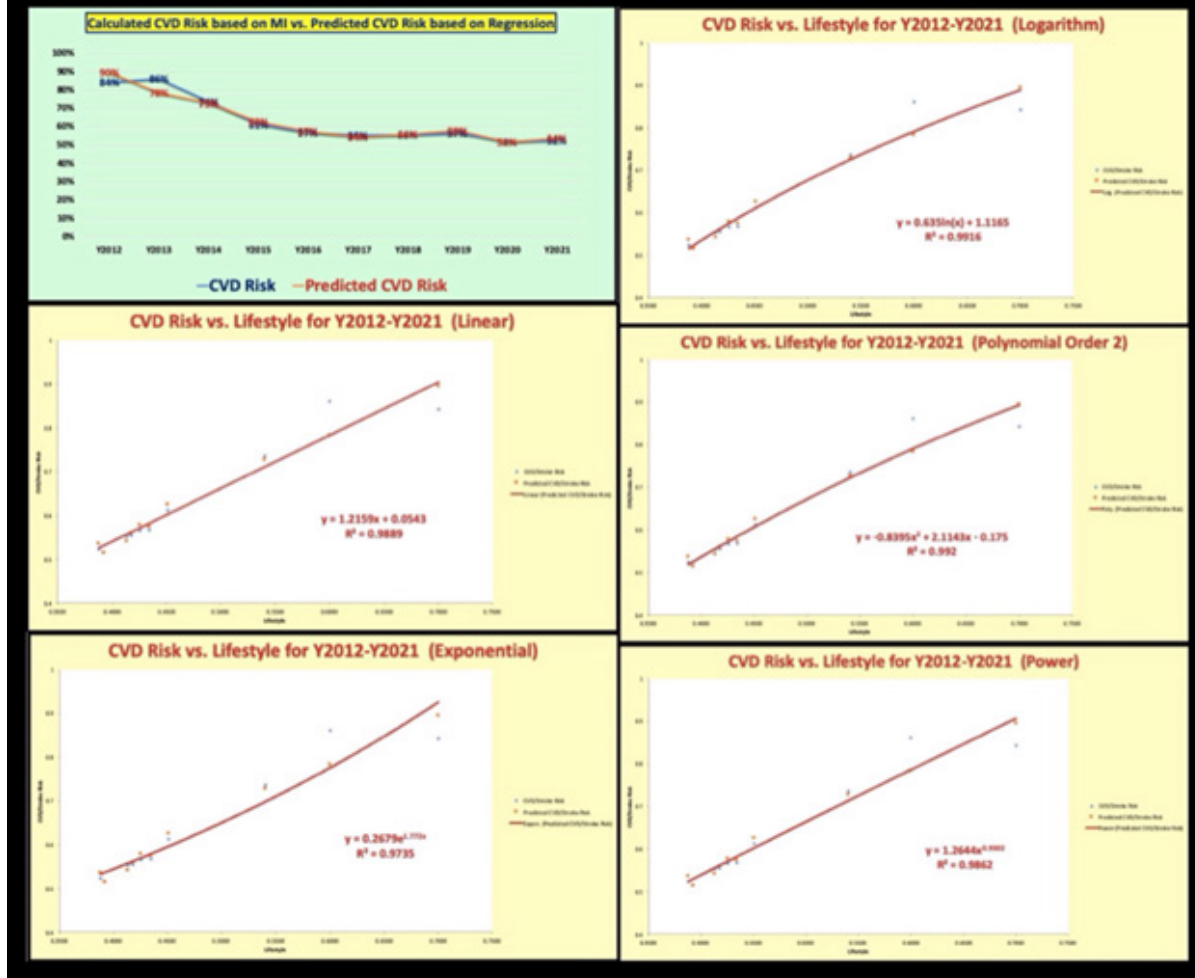


Figure 8: Space-domain analysis for Case 3 - CVD Risk vs. lifestyle details

In space-domain, his CVD risk vs. medical conditions variances for linear model is 77.3% and nonlinear model is 87.9%. This means that *his CVD risk vs. medical conditions are high but not as high as lifestyle variance and the nonlinear model indeed offers some variance improvement.*

In space-domain, his CVD risk vs. lifestyle details variances for linear model is 98.9% and nonlinear model is 97.4%-99.2%. This means that *his CVD risk vs. lifestyle is accurate enough using a linear model and any nonlinear model will not be able*

*to offer more value on variance improvement. It also indicates that his lifestyle details are more important to predict his CVD risk than his existing chronic disease conditions.*

Figures 9, 10, and 11 show both time-domain and space-domain results of Case 4, Weight vs. sleep and food quantity. In time-domain, the prediction accuracy between his measured body weight and regression predicted weight using both sleep and food quantity as input is 99%.



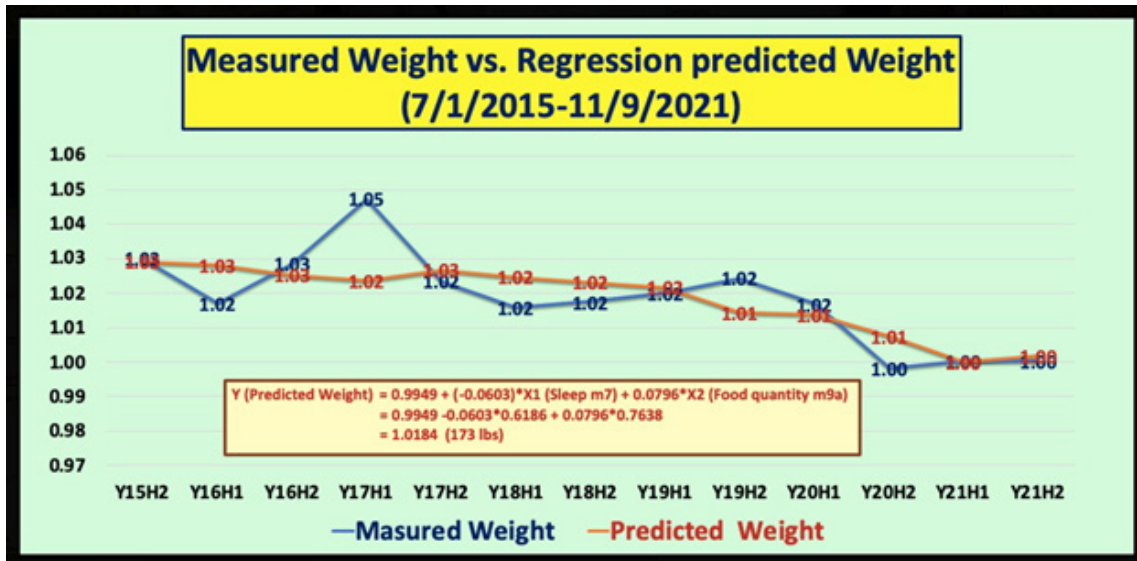


Figure 9: Time-domain analysis for Case 4 - Weight vs. sleep and food quantity

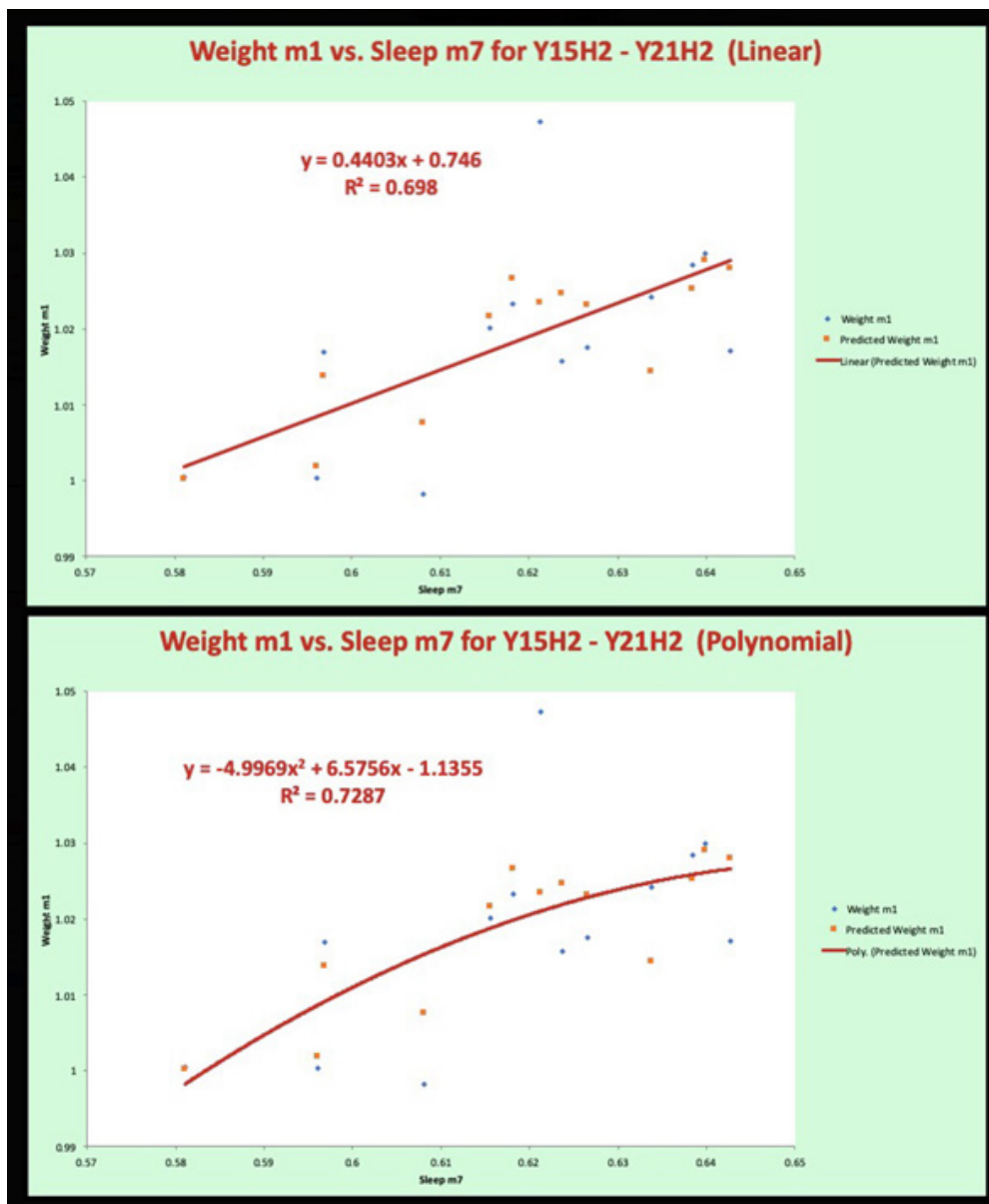


Figure 10: Space-domain analysis for Case 4 - Weight vs. sleep

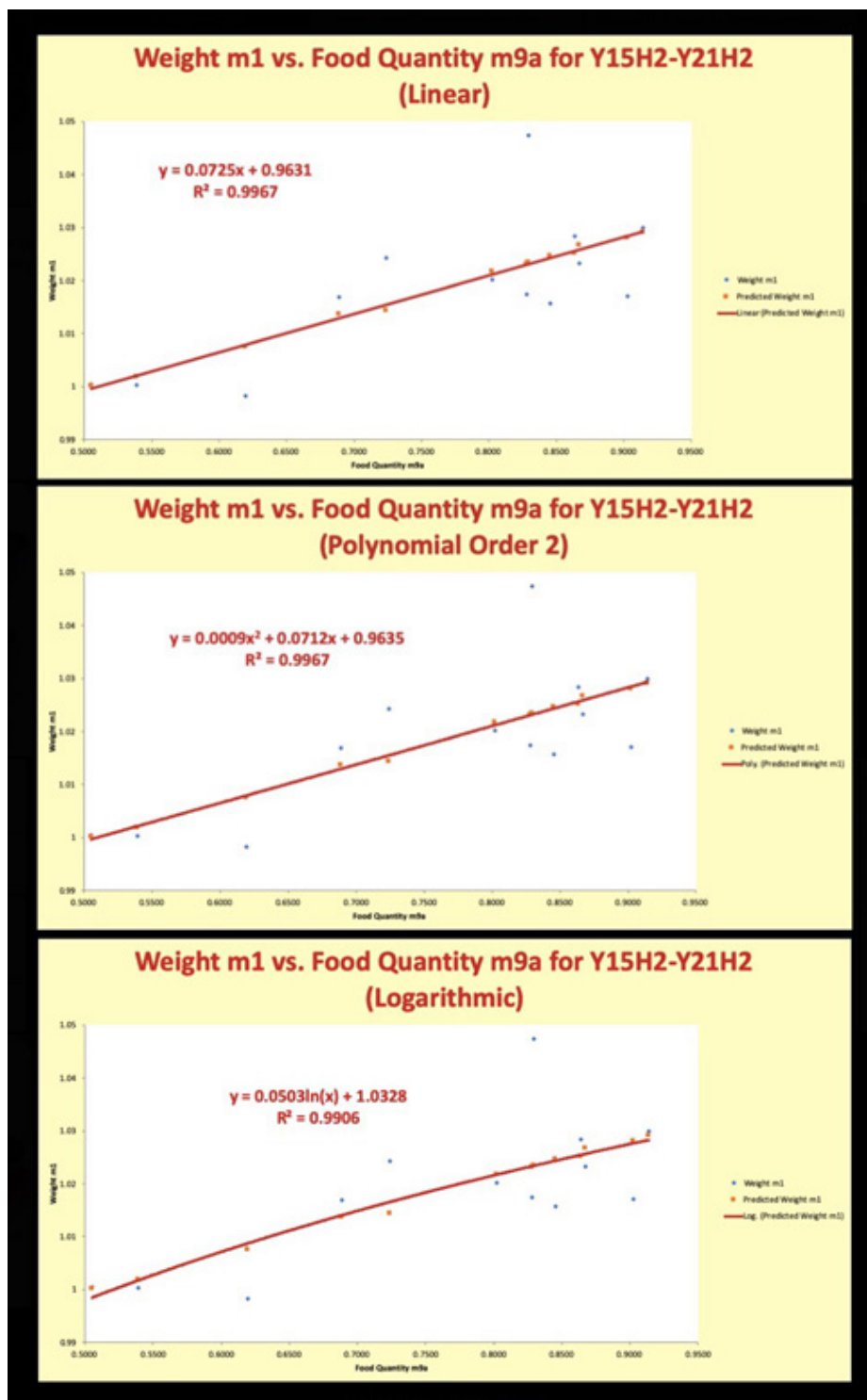


Figure 11: Space-domain analysis for Case 4 - Weight vs. food quantity

In space-domain, his weight vs. food quantity variances for linear model is 99.7% and nonlinear model is 99.1%-99.6% which is almost identical as the linear model. *This means that the weight vs. food quantity linear model is good enough for the prediction and the nonlinear model has offered no value on variance improvement.*

In space-domain, his weight vs. sleep variances for linear model is 69.8% and nonlinear model is 72.9%. *This means that both linear model and nonlinear model of the weight vs. sleep are not extremely high and the nonlinear model offers very little*

*value on variance improvement. These findings also indicate that sleep is probably the secondary influential factor to determine the weight in early morning.*

Figures 12, 13, 14, and 15 show both time-domain and space-domain results of Case 5, finger-piercing FPG vs. sleep, weight, and HbA1C. In time-domain, the prediction accuracy between his measured finger FPG and regression prediction finger FOG using sleep, weight, and A1C as input is 100% (both at 110.7 mg/dL).

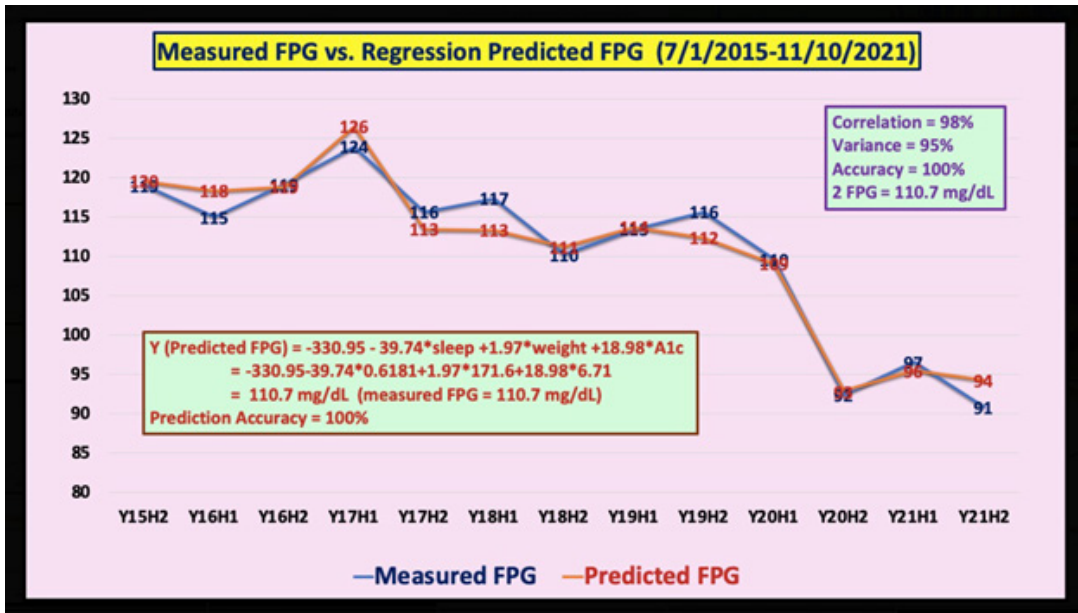


Figure 12: Time-domain analysis for Case 5 - Finger FPG vs. sleep, weight, and HbA1C

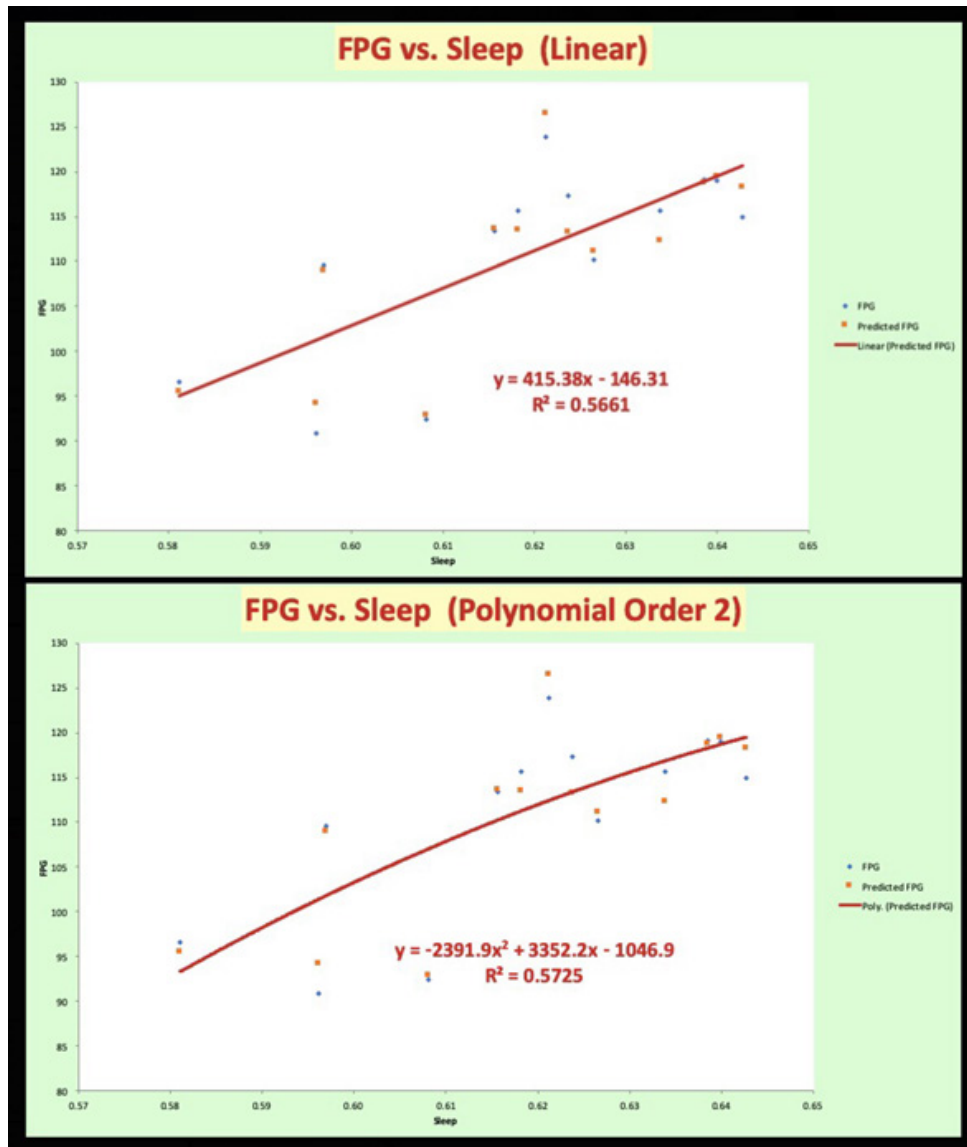


Figure 13: Space-domain analysis for Case 5 - Finger FPG vs. sleep



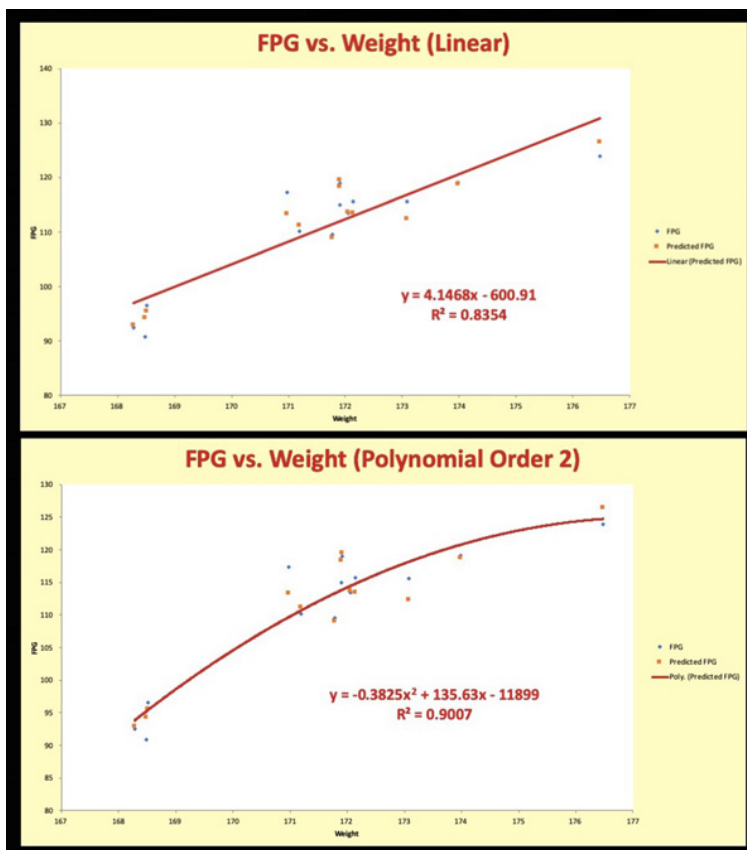


Figure 14: Space-domain analysis for Case 5 - Finger FPG vs. weight

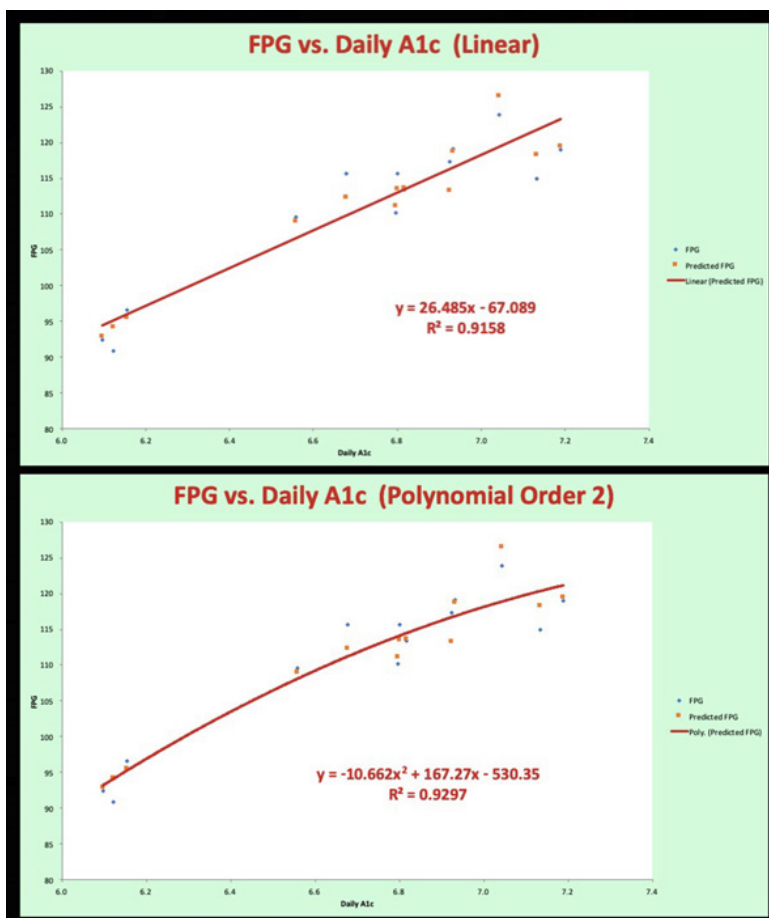


Figure 15: Space-domain analysis for Case 5 - Finger FPG vs. HbA1C

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In space-domain, his finger FPG vs. sleep variances for linear model is 56.6% and nonlinear model is 57.3% which means *sleep is a secondary influential factor and nonlinear model offers not much value on variance improvement.*

In space-domain, his finger FPG vs. weight variances for linear model is 83.5% and nonlinear model is 90.1%. *This means that weight is a strong influential factor to weight and, furthermore, from high variances of both linear model and nonlinear model, the nonlinear model indeed offer some visible variance improvement, but not significant though.*

In space-domain, his finger FPG vs. HbA1C variances for linear model is 91.6% and nonlinear model is 91%. *This means that HbA1C, the carrier of information of insulin resistance, is a very strong influential factor to finger FPG and, furthermore, from such a high variances of both linear model and nonlinear model, the nonlinear model offers no extra value at all on variance improvement.*

### Conclusions

In summary, there are 4 specific biomedical proved conclusions as described briefly as below:

1. The fasting plasma glucose (FPG) is strongly influenced by both insulin resistance from pancreatic beta cells as indicated by HbA1C value and the body weight situation.
2. The most direct and effective way of body weight reduction and postprandial plasma glucose (PPG) reduction is through food portion (quantity) reduction for weight concern plus carbs/sugar amount (quality) reduction for PPG concern.
3. CVD/Stroke risk probability is strongly connected with lifestyle details score, more than existing chronic disease conditions, i.e., medical conditions.

4. In conclusion, a good lifestyle intervention and management program is the best method for prevention and control of both chronic diseases and their complication.
5. The calculated variances are depending on its source data pattern which reveals certain hidden specific biomedical information. Sometime, when a variance is around 50%-80%, a nonlinear regression model could offer some extra assistance on improving the variance value from linear regression model. However, the most important task is not to study those exterior numerical values but rather to dig out and expose those hidden biomedical, biochemical and biophysical information.

The above-described explorations are not surprising findings which have been indicated by many authors of other medical research papers. The author of this article has also proven the same conclusions using his math-physical medicine methodology. But, in this paper, he has offered further numerical and quantitative proof via the traditional statistics method, such as regression analysis, similar to ~90% of existing medical publications.

### References

For editing purposes, majority of the references in this paper, which are self-references, have been removed for this article. Only references from other authors' published sources remain. The bibliography of the author's original self-references can be viewed at [www.eclairemd.com](http://www.eclairemd.com).

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