Lucy Letby Murder Case: The Statistical Relationship between C-peptide and Insulin

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Executive Summary

This report examines claims regarding the relationship between insulin and C-peptide, investigating the normalcy of the corresponding measurements for babies F and L from the Lucy Letby case through statistical analysis. Using a dataset of 1,305 blood test records, we conducted hypothesis testing, rejecting a linear C-peptide/insulin relationship of factor 5.0-10.0. We then employed regression and model selection techniques which suggested the infants' C-peptide levels were unusual low, based on predictions for the high insulin levels. However, data limitations and unknown confounding factors restrict analysis, preventing definitive causal conclusions. Future research should incorporate a more representative and detailed dataset should be incorporated to explore other alternative models.

1 Introduction

Lucy Letby, a former nurse who worked at Countess of Chester Hospital's neonatal unit, was convicted of causing the deaths of multiple premature babies in 2015 and 2016. However, the case heavily relied on circumstantial medical evidence, sparking controversy. [1]

Two doctors involved in the case made the following statements regarding the blood measurements of two infants, nicknamed Child F and Child L in the case (insulin-C-peptide levels of 4,657-169 and 1,099-264 in pmol/L respectively): the ratio of C-peptide/insulin should be '5.0-10.0' and that the insulin reading of 4,657 was 'too high for a baby'. In this report, the validity of two claims will be investigated through the perspective of a statistics expert witness. [3]

2 Dataset Overview

Our dataset consists of 1,305 blood test records from the Liverpool University Hospitals NHS Foundation Trust, detailing insulin and C-peptide measurements, organized into three columns: Year (2020-2023), C-peptide (pmol/L), and insulin (pmol/L). [2]

The dataset has the following limitations, which we assume not to affect this report's statistics:

- The data comes from a hospital trust near, but not including, Lucy Letby's hospital.
- Patient and test details (e.g. age, diet, medical conditions, exogenous insulin usage) are unavailable, which may affect the data representativeness for the neonates.
- There is no information on whether the tests are done routinely and consistently on the same people or otherwise.
- Only a small number of years are covered, excluding the criminal case's occurrence years.
- Fifty rows with C-peptide "<5" or insulin "<1" were removed due to uncertainty of their value.

- Potential outliers were retained, as the neonates' blood results are potentially naturally extreme.
- Between 0.4-4% of the test results are affected by interference.

3 Results

We examine the first claim from the introduction: investigating a null hypothesis of the C-peptide/insulin ratio being 5.0-10.0, with 99% certainty. Linear regression, a method that fits linear relationships, produces Model 1:

$$\text{C-peptide} \sim \beta_1 \text{ insulin} \,, \tag{1}$$

by finding an unbiased estimate for the β constants that minimise the residual sum of squares using the data. The coefficient estimate/variance (Table 1) gives the confidence interval: 3.1133-3.5602 (Table 2), thus we reject the null hypothesis with 99% significance as there is no overlap with 5.0-10.0.

We now consider an alternative insulin-C-peptide relationship, using the following metrics to analyse the performance of fitted models and compare them:

- Adjusted r^2 finds how close the fitted model fits the data using an unbiased variance estimator, where a value closer to $+1$ (-1) indicates a stronger positive (negative) correlation.
- F-test determines whether the true model is a nested version within the supposed linear model.
- AIC quantifies the distance between the fitted model and the true data-generating model while penalizing complexity; a lower AIC suggests better predictive performance.
- Cross-validation mean-squared-error partitions the data into folds, training the model on all but one and computing the squared error on the excluded fold. This process repeats for all folds, with the final MSE being the average of these errors.

Starting with a larger model, we apply backward selection using AIC; by removing terms that reduce AIC the most, we refine the model iteratively (we also use F-test back selection to check for agreement). While complex models lower AIC, they overfit (driven substantially by potential outliers), particularly where insulin is 4,000–6,000 due to sparse data in this area (Figure 3). To balance performance and overfitting, we test multiple models (with the factor Year) and arrive at Model 2:

$$\text{C-peptide} \;\sim\; \beta_0 + \beta_1 \,\text{insulin}^2 + \beta_2 \,\text{insulin}^3 + \beta_3 \,\text{insulin}^{1/2} \,. \tag{2}$$

Model 2 improves on Model 1 in cross-validation MSE (from 1,239,360 to 810,313), adjusted r^2 (from 0.5417 to 0.5992), and AIC (from 21102.02 to 19962.26) (Tables 1 and 4).

To further refine the model, we analyse residuals, which should be independent, normally distributed, and have constant variance. While Model 2's residuals average around zero with one problematic leverage point, the Q-Q plot shows heavy tails, and variance increases with insulin (Figure 5). To address this, we test transforming C-peptide and find that Model 3:

$$\text{C-peptide}^{1/4} \;\sim\; \beta_0 + \beta_1 \,\text{insulin}^2 + \beta_2 \,\text{insulin}^3 + \beta_3 \,\text{insulin}^{1/2} \,, \tag{3}$$

significantly improves residual behaviour, reducing heavy tails and heteroscedasticity (Figure 7). However, it appears the heavy overfitting has returned (Figure 6), and we cannot use metrics we have discussed to directly compare transformed Model 3 to the other models.

While this potentially suggests an alternative relationship exists, the limited data opens vulnerability to confounding, and the interference raises concerns about overfitting in more complex models, so we cannot make definite statements about causality in Models 2 and 3. Replacing values "<5" and "<1" with "2.5" and "0.5" leads to the same conclusions and insignificant variation in the models.

Using Model 2, our C-peptide prediction intervals for both babies deviate significantly from their recorded values (Table 6). If not due to sparse data near their insulin levels, this suggests their

C-peptide levels should have been much higher. Additionally, assuming normally distributed insulin, we calculated the z-scores of the babies' insulin levels. These z-scores put baby L and F's insulin levels in the 0.9986th quantile, and in a quantile effectively off the charts respectively (Table 7). It is noteworthy that the dataset included one entry with insulin greater than that of both babies at 5,928 pmol/L.

4 Conclusions

Given our dataset and Model 1, the C-peptide-to-insulin ratio was found not to be 5.0-10.0 with 99% certainty. Improving our regression to Model 2, having performed best against our metrics with minimal overfitting, we compared each child's C-peptide levels to the corresponding prediction interval values, observing a significant discrepancy, strongly indicating their C-peptide levels should have been higher for their abnormally high insulin levels.

However, test interference and limited variables introduce confounding risks, restricting exploration of more complex models. Future investigation of different relationships would benefit from a more detailed, representative dataset, and clarification from Liverpool Hospital Trust regarding the entries marked as "<5" and "<1".

References

[1] Rebecca Moore Ceri Thomas Phoebe Davis. *Lucy Letby: the Expert Witness*. Accessed: 13/02/2025. Tortoise Media, Sept. 2024. URL: www.tolkienprofessor.com/audio/silmarillion_1.mp3.

[2] Liverpool University Hospitals NHS Foundation Trust. *Blood Test Records for Insulin and C-Peptide Levels*. Accessed: 13/02/2025. URL: www.whatdotheyknow.com/request/blood_test_records_for_insulin_a.

[3] Amy Wilson. *Statistical Case Studies 2024/25 Semester 2 Examining the relationship between insulin and c-peptide.* Accessed: 13/02/2025. The University of Edinburgh, Jan. 2025.

Appendix

Coefficient	Estimate	Std. Error	t value	$\Pr(>\|t\|)$
Insulin	3.33676	0.08661	38.53	$< 2e-16$
Residual Std. Error	1083 on 1254 degrees of freedom			
Multiple R-squared	0.5421			
Adjusted R-squared	0.5417			
F-statistic	1484 on 1 and 1254 DF, p-value $< 2.2e-16$			
AIC	21102.02			
Cross-Validation (MSE)	1239360			

Table 1: Regression Results for 'C-peptide $\sim$ Insulin'

Significance	Lower Bound	Upper Bound
99%	3.1133	3.5602
95%	3.1668	3.5067
90%	3.1942	3.4793

Table 2: Confidence Intervals of the Coefficient Estimate for the 'C-peptide $\sim$ Insulin' Regression

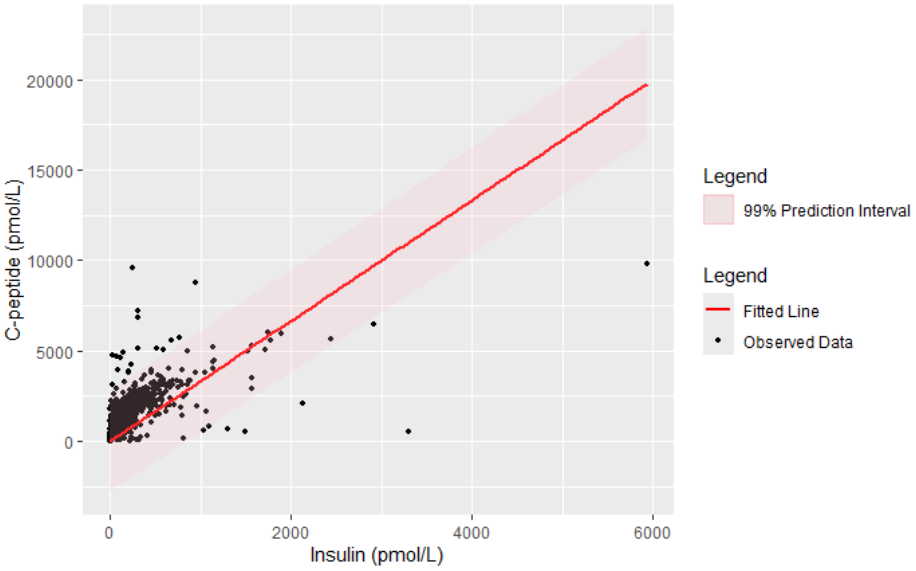

Figure 1: Fitted Regression 'C-peptide $\sim$ Insulin' with Observed Data and a 99% prediction interval

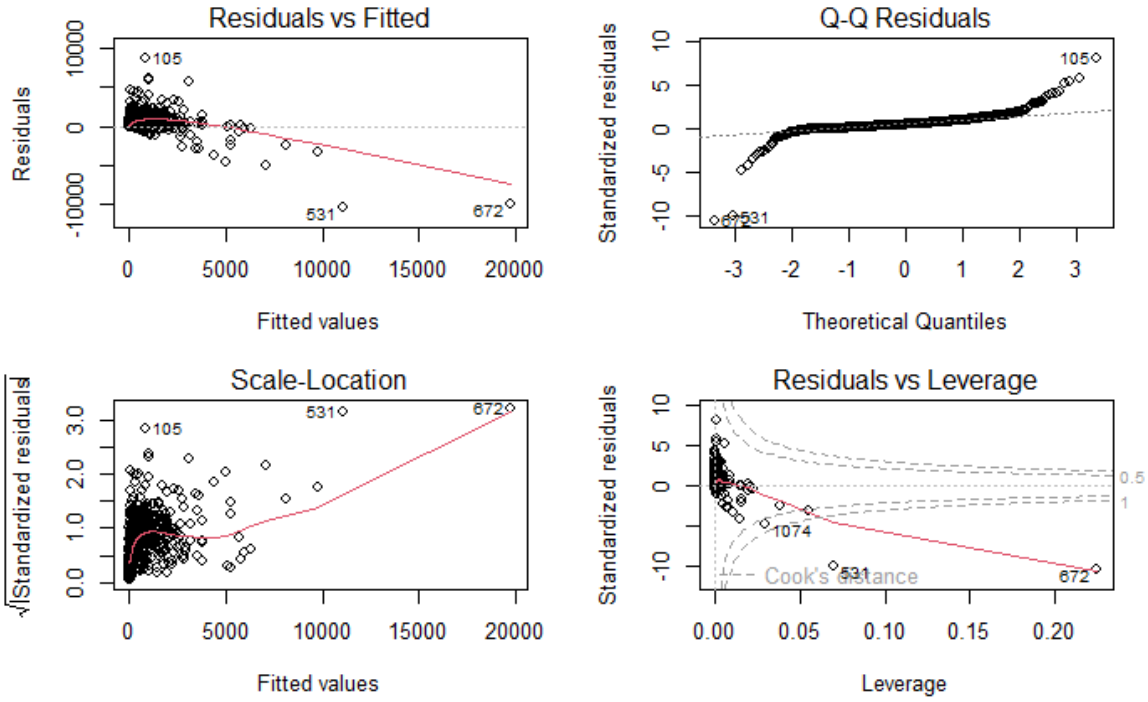

Figure 2: Residual Plots of Fitted Regression 'C-peptide ~ Insulin'

Coefficient	Estimate	Std. Error	t value	Pr(> |t|)
(Intercept)	-2038.00	703.00	-2.899	0.003807 **
Insulin	29.64	8.34	3.552	0.000397 ***
Insulin^2	-0.02230	0.00506	-4.405	1.15e-05 ***
Insulin^3	0.00001245	0.00000256	4.870	1.26e-06 ***
Insulin^4	-3.148e-09	6.065e-10	-5.191	2.44e-07 ***
Insulin^5	2.677e-13	4.960e-14	5.398	8.08e-08 ***
$\text{Insulin}^{1/2}$	-1241.00	438.80	-2.829	0.004741 **
$\text{Insulin}^{1/3}$	2756.00	925.30	2.978	0.002953 **
Residual Std. Error	677.4 on 1247 degrees of freedom			
Multiple R-squared	0.6121			
Adjusted R-squared	0.6099			
F-statistic	281.1 on 7 and 1247 DF, p-value $< 2.2e-16$			
AIC	19932.26			
Cross-Validation (MSE)	440475612			

Table 3: Regression Results for
'C-peptide $\sim \beta_0 + \beta_1$ insulin $+ \beta_2$ insulin$^2 + \beta_3$ insulin^3
$+ \beta_4$ insulin$^4 + \beta_5$ insulin$^5 + \beta_6$ insulin$^{1/2} + \beta_7$ insulin$^{1/3}$,

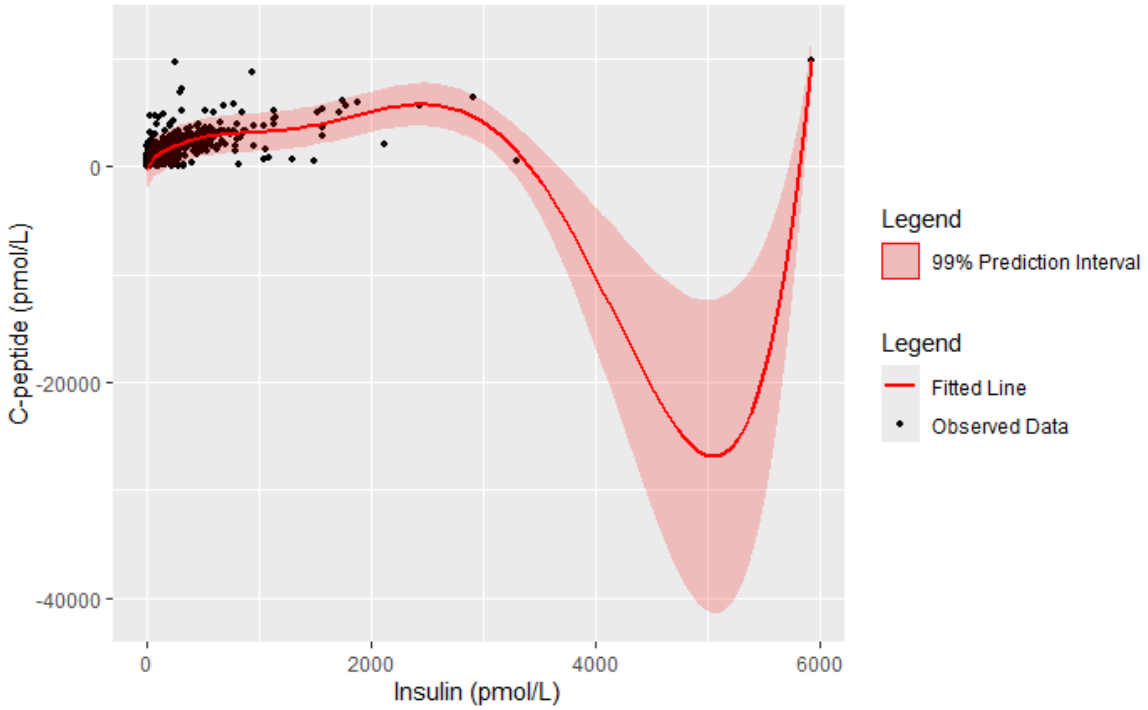

Figure 3: Fitted Regression for
'C-peptide $\sim \beta_0 + \beta_1$ insulin $+ \beta_2$ insulin$^2 + \beta_3$ insulin^3
$+ \beta_4$ insulin$^4 + \beta_5$ insulin$^5 + \beta_6$ insulin$^{1/2} + \beta_7$ insulin$^{1/3}$,
with Observed Data and a 99% prediction interval'

Coefficient	Estimate	Std. Error	t value	Pr($>|t|$)
(Intercept)	-171.7	41.31	-4.157	3.45e-05 ***
Insulin^2	-0.0006466	0.00008999	-7.185	1.15e-12 ***
Insulin^3	0.0000001073	0.0000000153	7.014	3.79e-12 ***
Insulin$^{1/2}$	131.8	3.88	33.984	$< 2e-16$ ***
Residual Std. Error	686.6 on 1251 degrees of freedom			
Multiple R-squared	0.6001			
Adjusted R-squared	0.5992			
F-statistic	625.8 on 3 and 1251 DF, p-value $< 2.2e-16$			
AIC	19962.26			
Cross-Validation (MSE)	810313			

Table 4: Regression Results for
'C-peptide $\sim \beta_0 + \beta_1$ insulin$^2 + \beta_2$ insulin$^3 + \beta_3$ insulin$^{1/2}$,

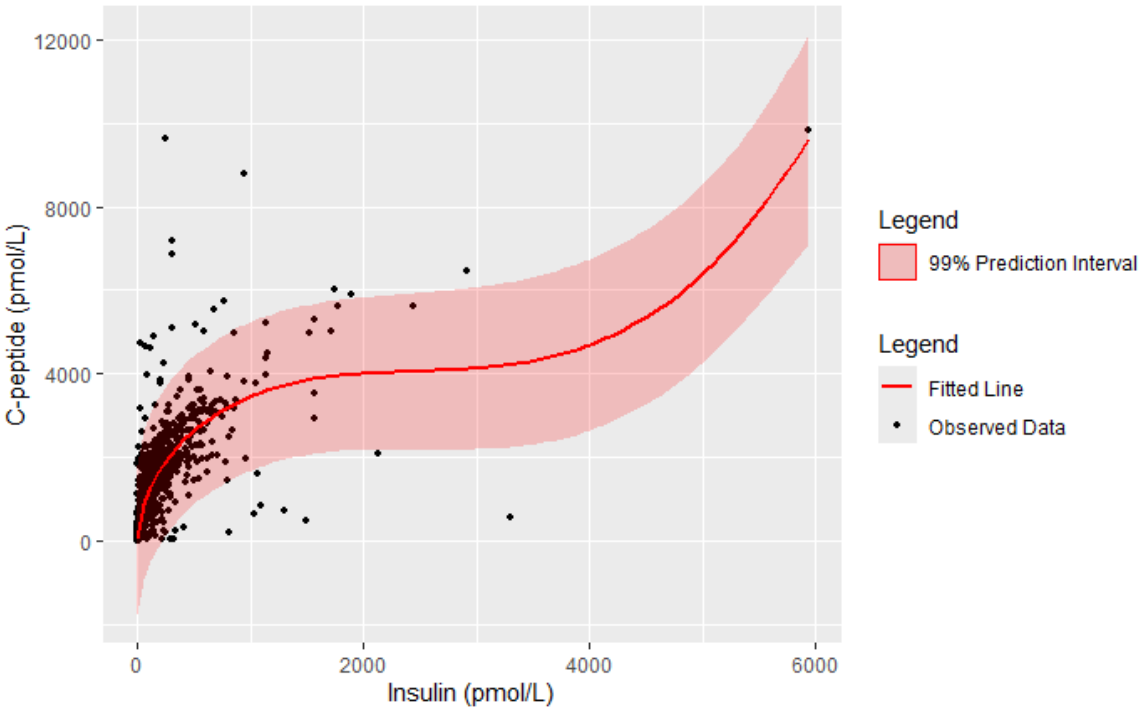

Figure 4: Fitted regression for
'C-peptide $\sim \beta_0 + \beta_1$ insulin$^2 + \beta_2$ insulin$^3 + \beta_3$ insulin$^{1/2}$,
with observed data and a 99% prediction interval

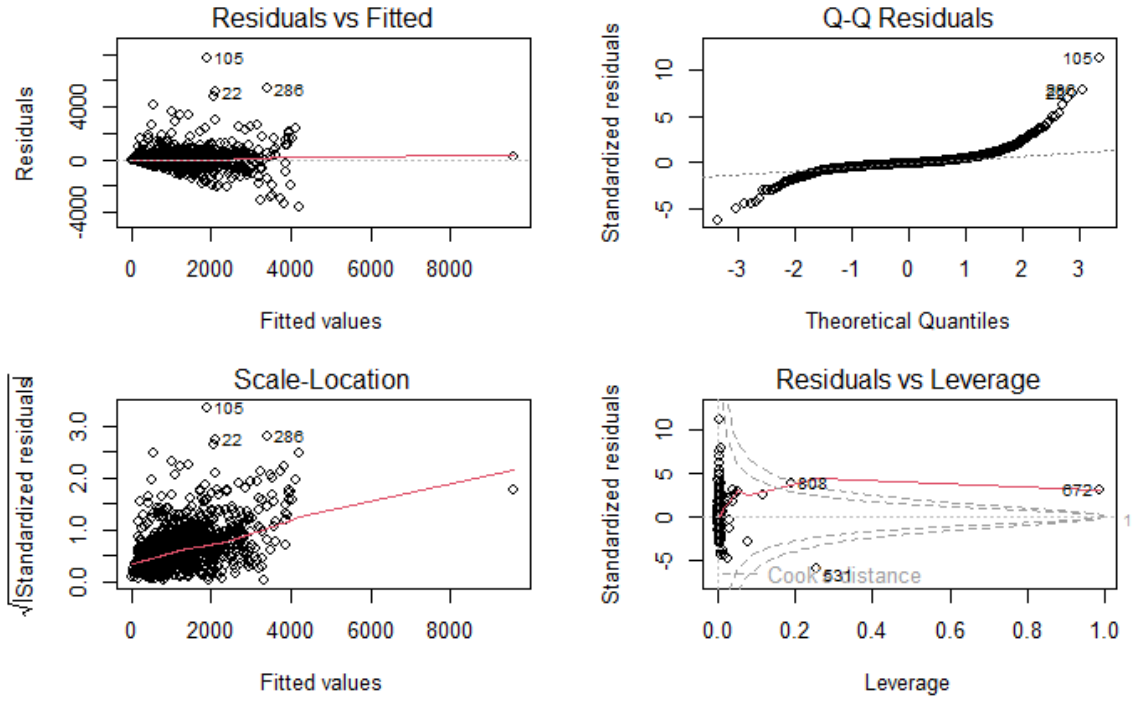

Figure 5: Residual Plots of Fitted Regression for
'C-peptide $\sim \beta_0 + \beta_1$ insulin$^2 + \beta_2$ insulin$^3 + \beta_3$ insulin$^{1/2}$,

Coefficient	Estimate	Std. Error	t value	$\Pr(>\|t\|)$
(Intercept)	3.594	0.04928	72.94	$< 2e-16$
Insulin^2	-1.609e-06	1.073e-07	-14.99	$< 2e-16$
Insulin^3	2.354e-10	1.825e-11	12.89	$< 2e-16$
$\text{Insulin}^{1/2}$	0.1856	0.004628	40.10	$< 2e-16$
Residual Std. Error	0.8191 on 1251 degrees of freedom			
Multiple R-squared	0.6104			
Adjusted R-squared	0.6095			
F-statistic	653.3 on 3 and 1251 DF, p-value $< 2.2e-16$			

Table 5: Regression Results for
'C-peptide$^{1/4}$ $\sim$ $\beta_0 + \beta_1$ insulin^2 $+ \beta_2$ insulin^3 $+ \beta_3$ insulin$^{1/2}$,

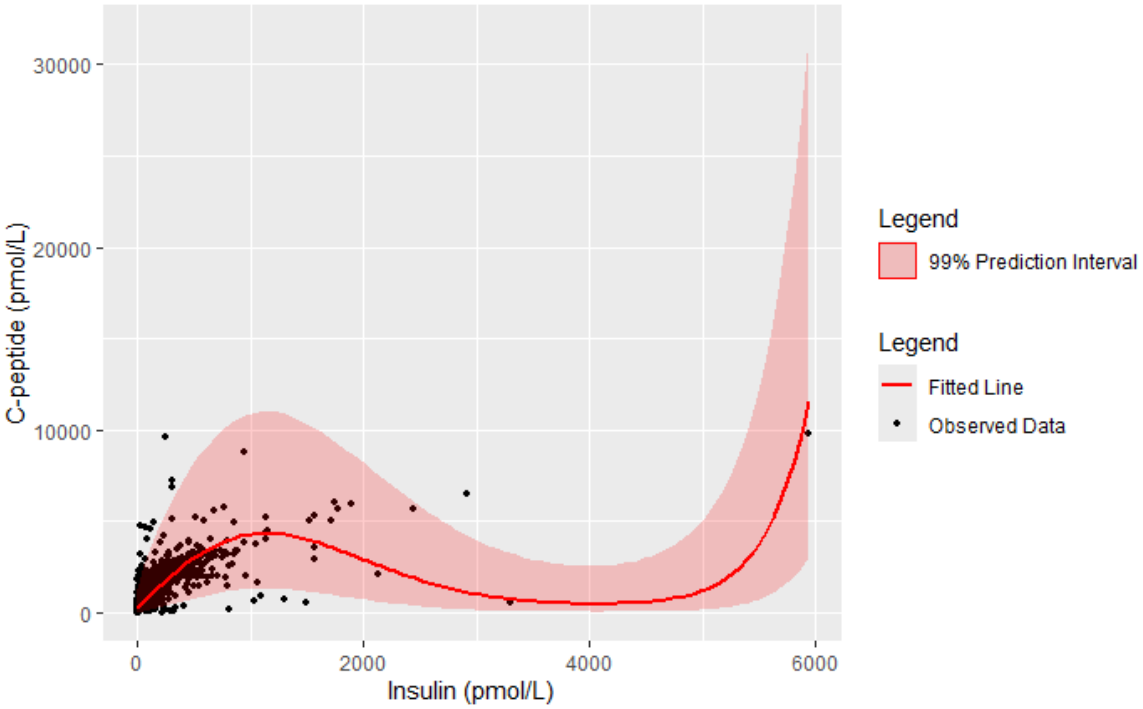

Figure 6: Plot of fitted regression for
'C-peptide$^{1/4} \sim \beta_0 + \beta_1$ insulin^2 $+ \beta_2$ insulin^3 $+ \beta_3$ insulin$^{1/2}$,
with observed data and a 99% prediction interval

Baby	C-peptide	Lower Bound	Estimate	Upper Bound
F	169	4086.302	5123.86	6161.418
L	264	3469.729	3647.07	3824.410

Table 6: 95% prediction interval for C-peptide levels (in pmol/L) of babies F and L

Baby	Insulin	Z-score	Quantile
F	4657	14.42033	1.00000
L	1099	2.99569	0.99863

Table 7: Insulin z-scores and quantiles of babies F and L (5 d.p.)

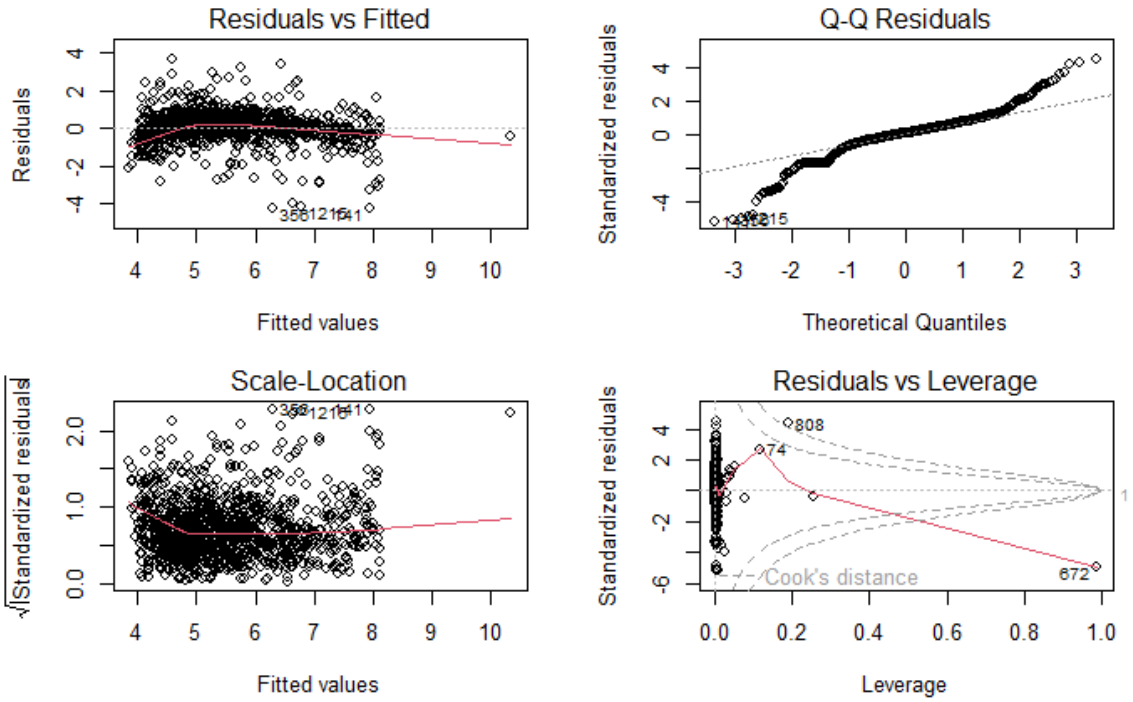

Figure 7: Residual Plots of Fitted Regression for
'C-peptide$^{1/4} \sim \beta_0 + \beta_1$ insulin$^2 + \beta_2$ insulin$^3 + \beta_3$ insulin$^{1/2}$,