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Weight-HbA1c-Insulin-Glucose (**WHIG**) Model for long term disease progression of Type 2 Diabetes

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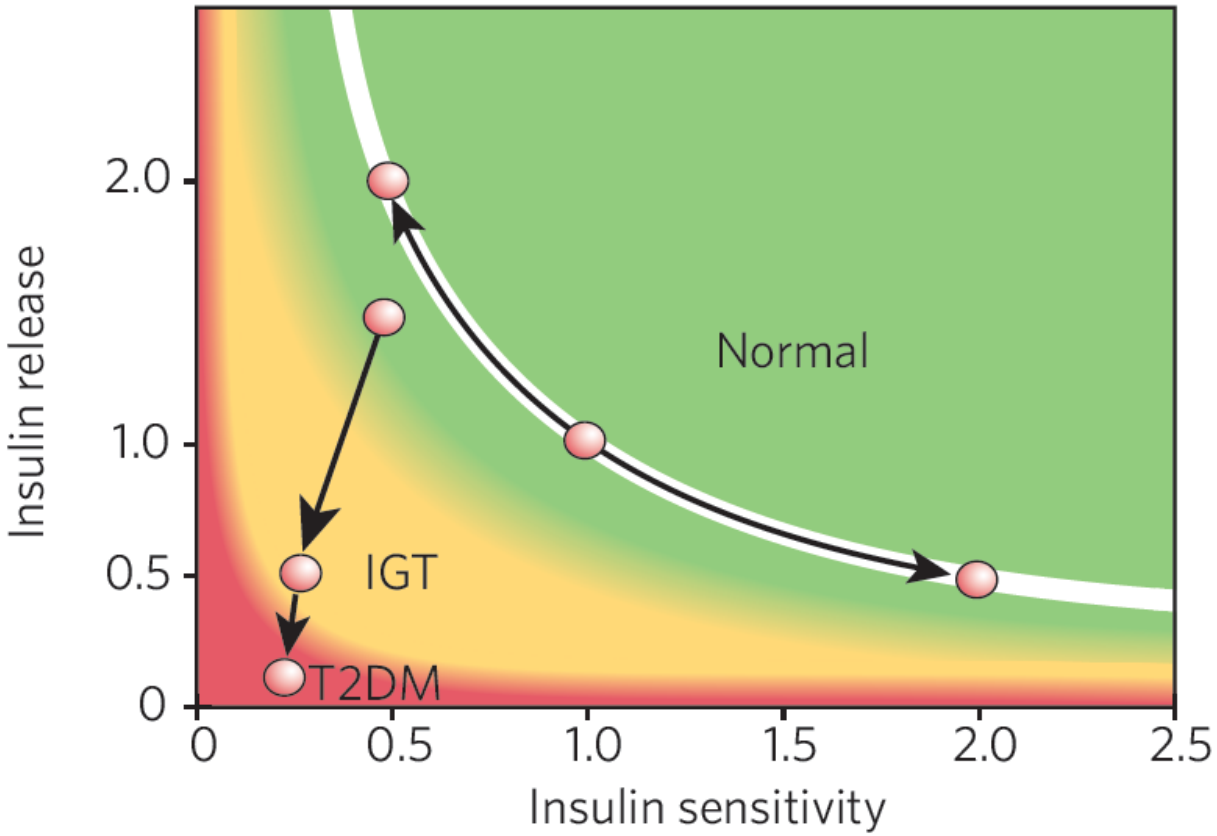
Background – T2DM

- At its simplest, T2DM is defined by a **malfunctioning of the glucose-insulin homeostasis,** caused by insulin secretion deficiency (Beta-cell dysfunction) and insulin resistance



Kahn et al. (2006). "Mechanisms linking obesity to insulin resistance and type 2 diabetes." Nature 444(7121): 840-846.

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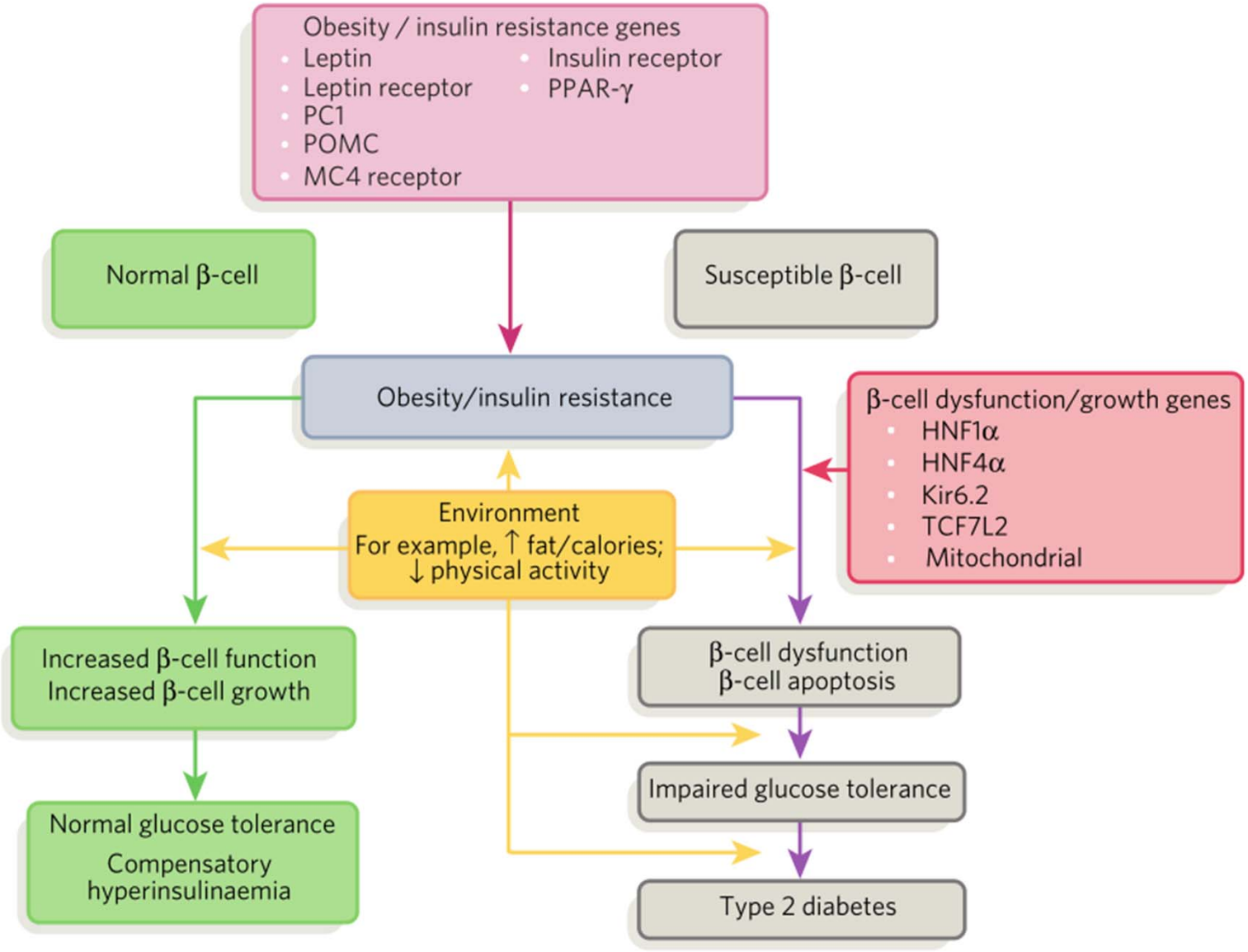
Nature & nurture



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Important biomarkers

- Insulin
  - hormone synthesized by the β-cells in pancreas
  - **F**asting **S**erum **I**nsulin (**FSI**) for long term studies
- Glucose
  - **F**asting **P**lasma **G**lucose (**FPG**) measured in the fasted state for 8+ hours
- Glycated haemoglobin A_{1c} (**HbA1c, %**)
  - Fraction of glycated haemoglobin of all haemoglobin, reflecting glucose exposure over a prolonged period of time (2-3 months)
- **Weight (kg)**
  - In long term studies, weight often varies
  - Weight change is linked to insulin sensitivity[1]

1. Goodpaster et al. Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. *Diabetes* 1999**,** 48, 839-847.

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A Mechanism-based Disease Progression Model for Comparison of Long-term Effects of Pioglitazone, Metformin and Gliclazide on Disease Processes Underlying Type 2 Diabetes Mellitus

Willem de Winter,[1] Joost DeJongh,[1,2] Teun Post,[1] Bart Ploeger,[1,2] Richard Urquhart,[3] Ian Moules,[3] David Eckland,[3] and Meindert Danhof[1,2,4]

Rece

”... There is a need to **integrate information on long-term FPG, FSI, HbA1c data into a single comprehensive, physiologically meaningful model structure”**

Effec ation of the c hanism- base bility to descr loss of β-cel pharma- cody tic feed- back insulin (FSI d hemo- globin A_{1c} (HbA_{1c}). This model was developed on data from two parallel one-year studies comparing the effects of pioglitazone relative to metformin or sulfonylurea treatment in 2408 treatment-naïve T2DM patients. It was found that the model provided accurate descriptions of the time-courses of FPG and HbA_{1c} for different treatment arms. It allowed the identification of the long-term effects of different treatments on loss of β-cell function and insulin-sensitivity, independently from their immediate anti-hyperglycemic effects modeled at their specific sites of action. Hence it avoided the confounding of these effects that is inherent in point estimates of β-cell function and insulin-sensitivity such as the widely used HOMA-%B and HOMA-%S. It was also found that metformin therapy did not result in a reduction in FSI levels in conjunction with reduced FPG levels, as expected for an insulin-sensitizer, whereas pioglitazone therapy did. It is concluded that, although its current implementation leaves room for further improvement, the mechanism-based approach presented here

1. de Winter *et al*. 2006 JPKPD

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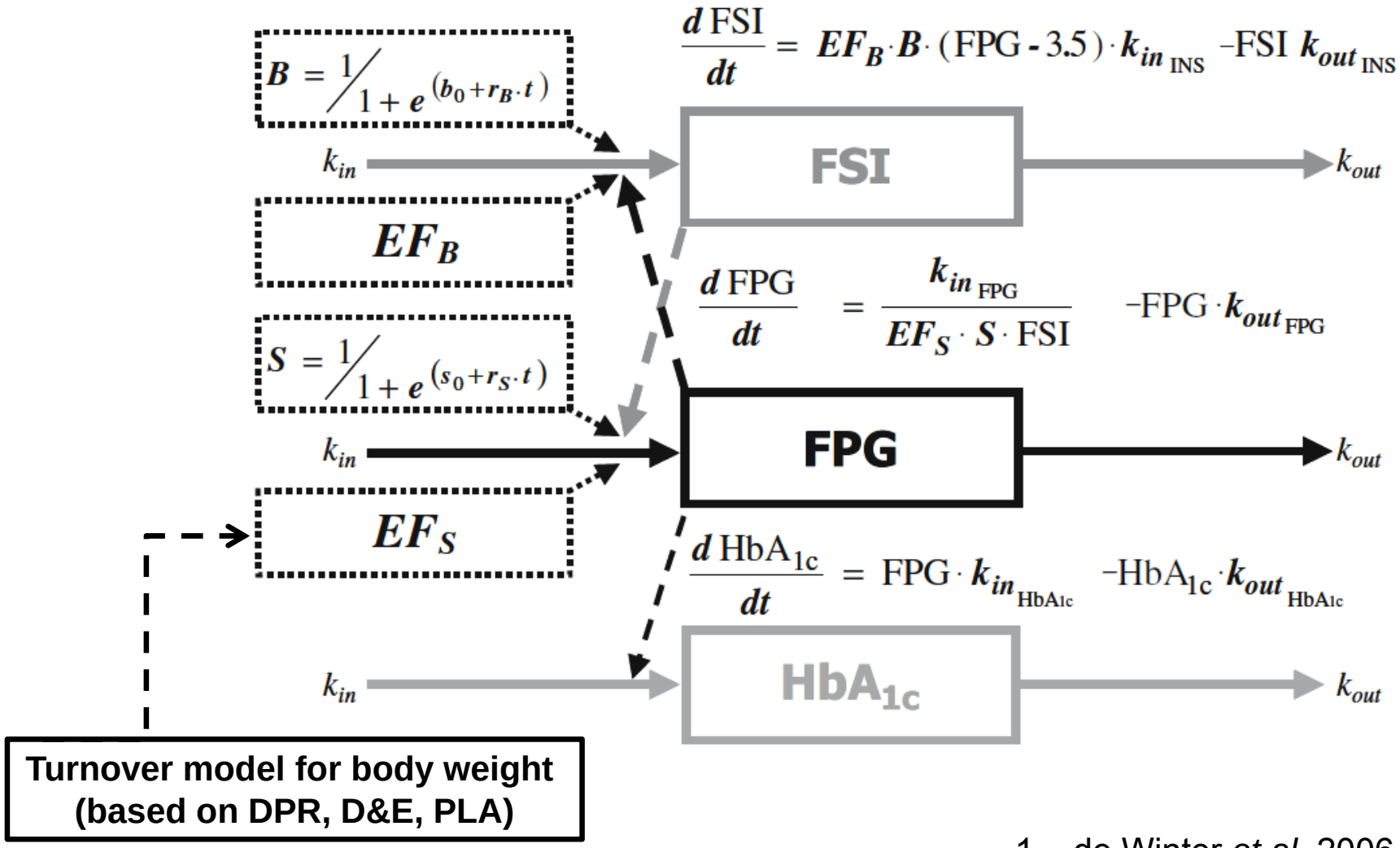
Linked turnover models



1. de Winter *et al*. 2006 JPKPD
2. de Winter *et al*. 2009 PAGE

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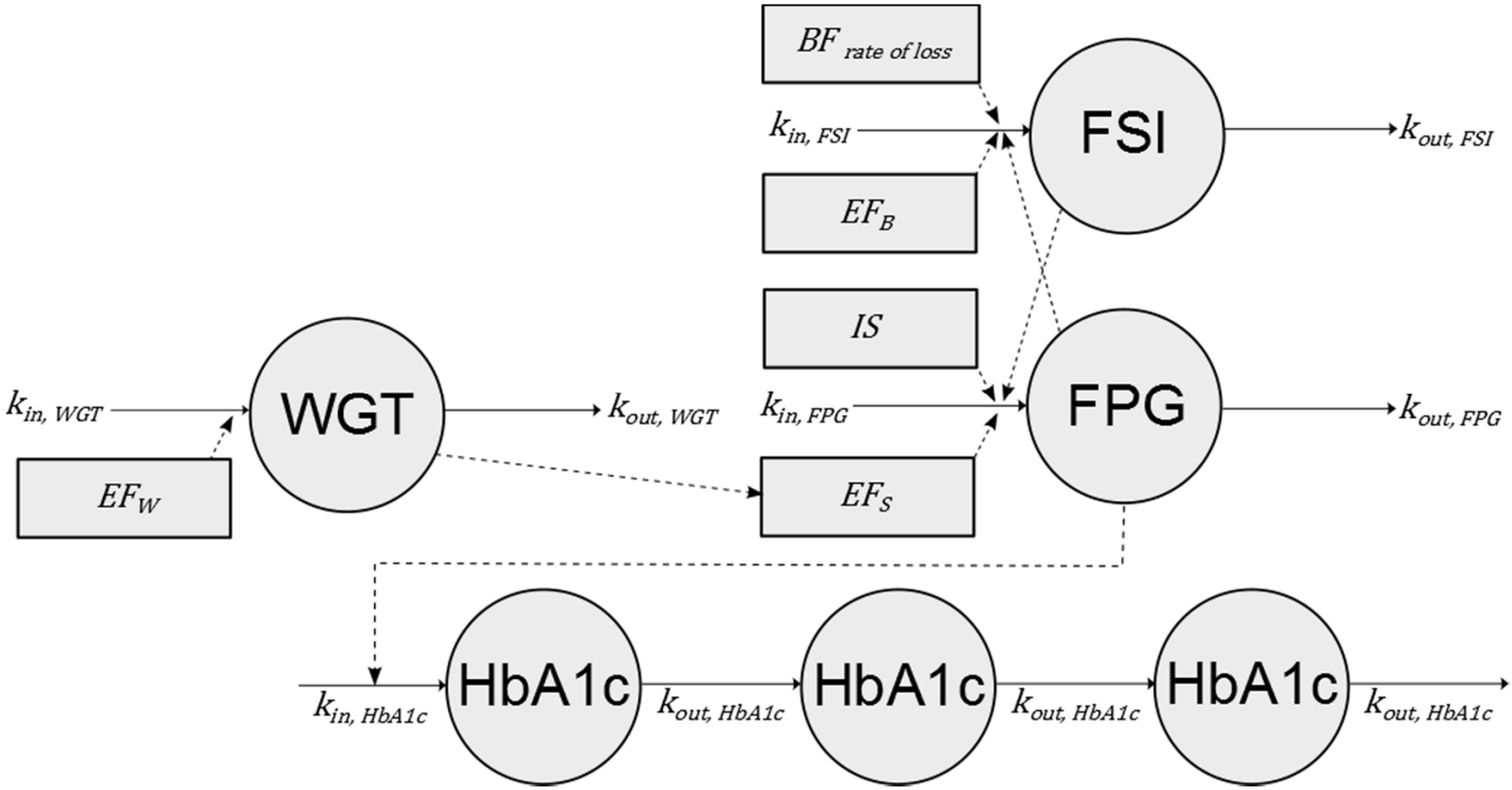
Integration of weight as a predictor for insulin sensitivity



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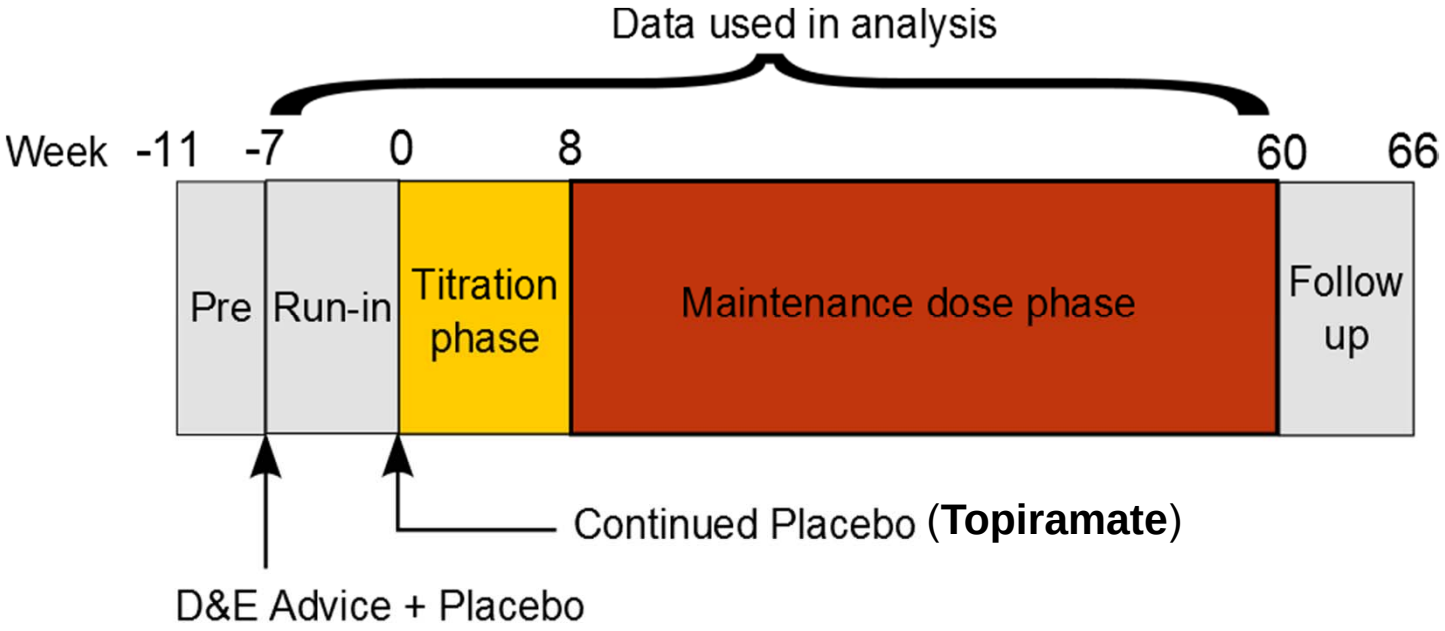
Study design

181 newly diagnosed T2DM Swedish obese patients (mean 104kg) with controlled diet, treatment naive

72 week study:

- 5+6 weeks pre-enrollment and run-in
- 8 weeks titration phase + 52 weeks maintenance dose phase
- 2 weeks down titration and 4 weeks off treatment then final visit



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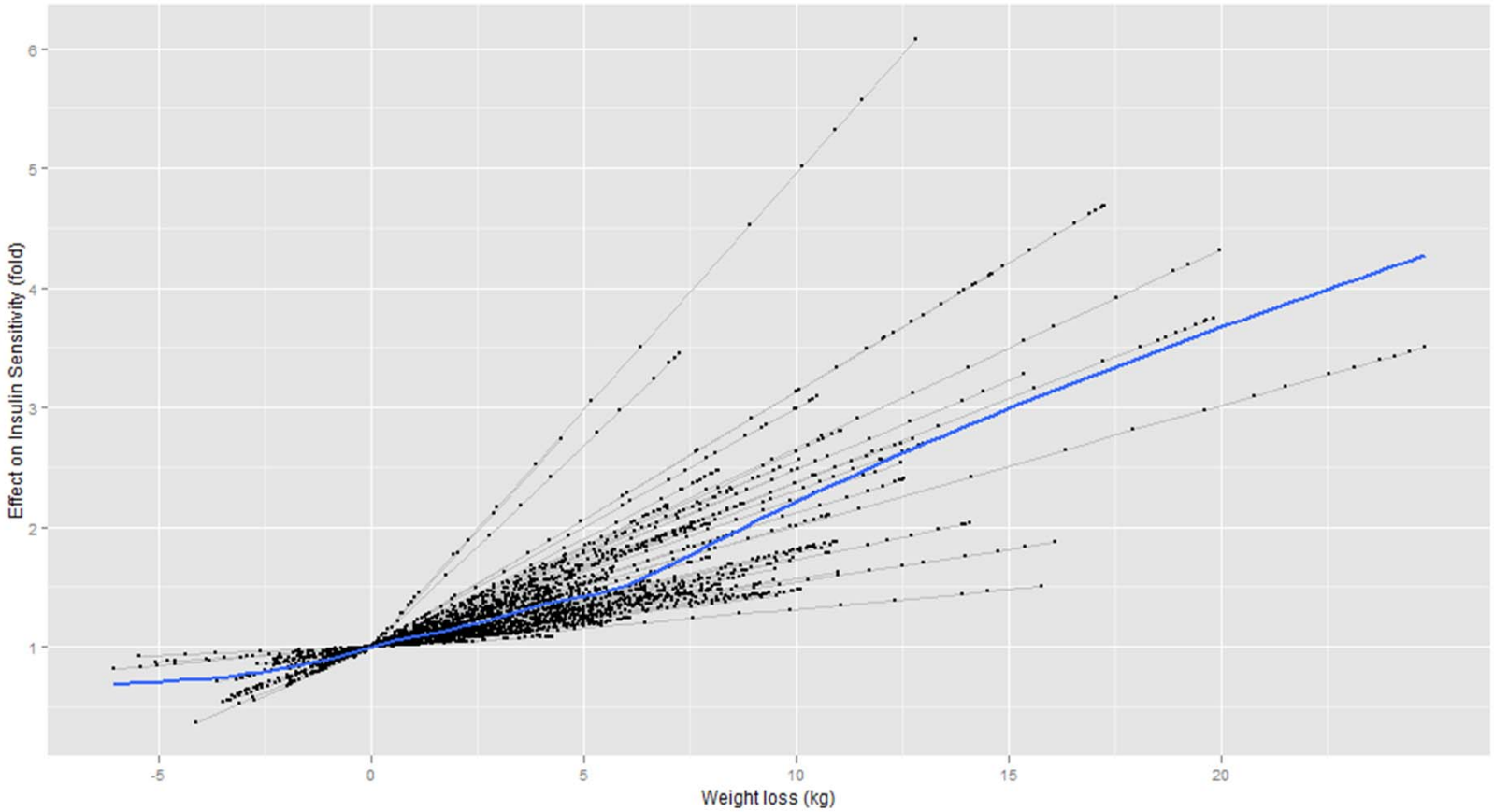
Results – effect of weight change (dWT) on insulin sensitivity (IS)



- The estimated baseline values for beta-cell function (BF) and insulin sensitivity (IS) was 32.1% and 7.5% of normal, respectively
- At the end of the study, the mean gain in IS due to dWT (mean -4.1kg decrease) was estimated to be 45%

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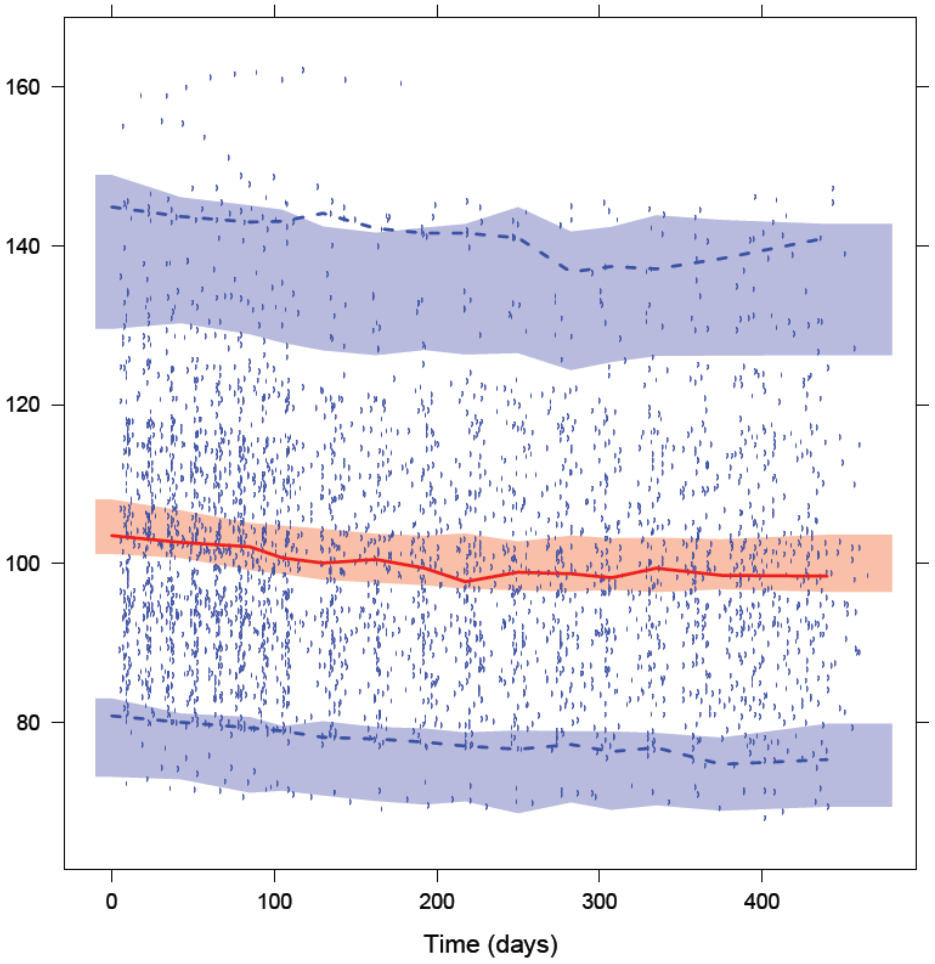
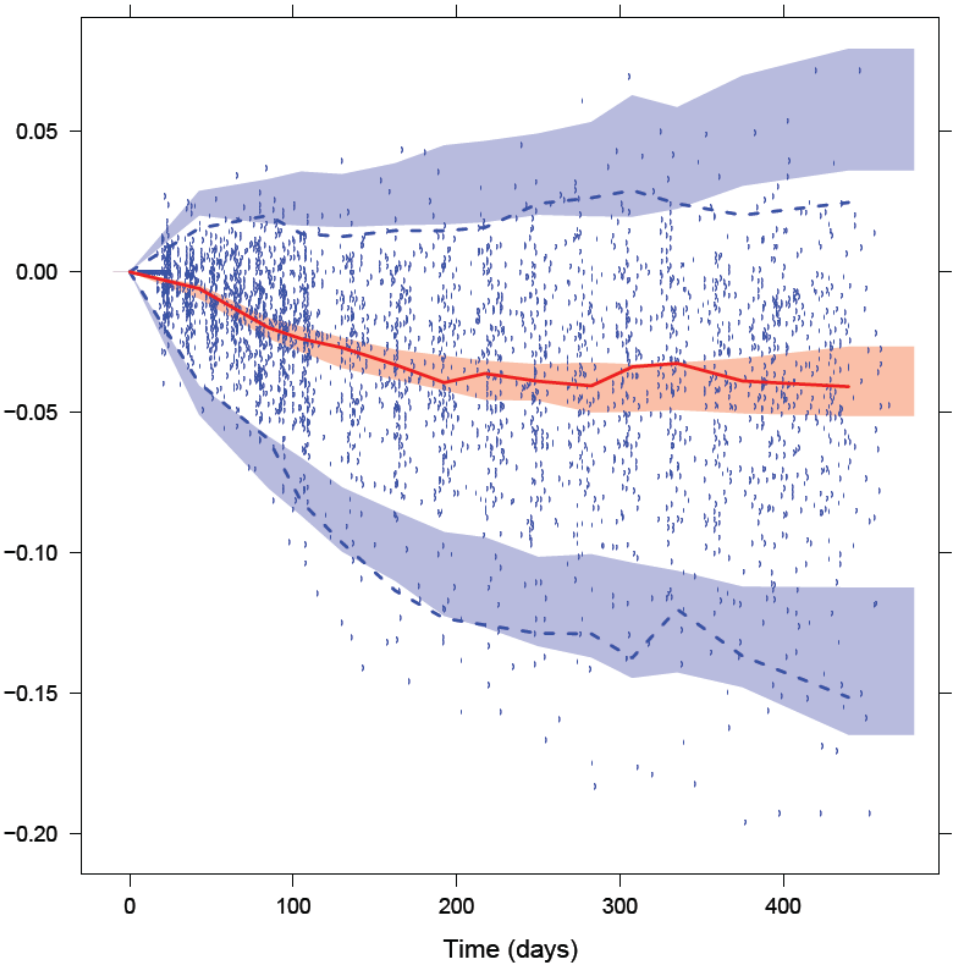
Results – VPC: WGT

Weight (kg)



Fractional change from baseline (CFB)



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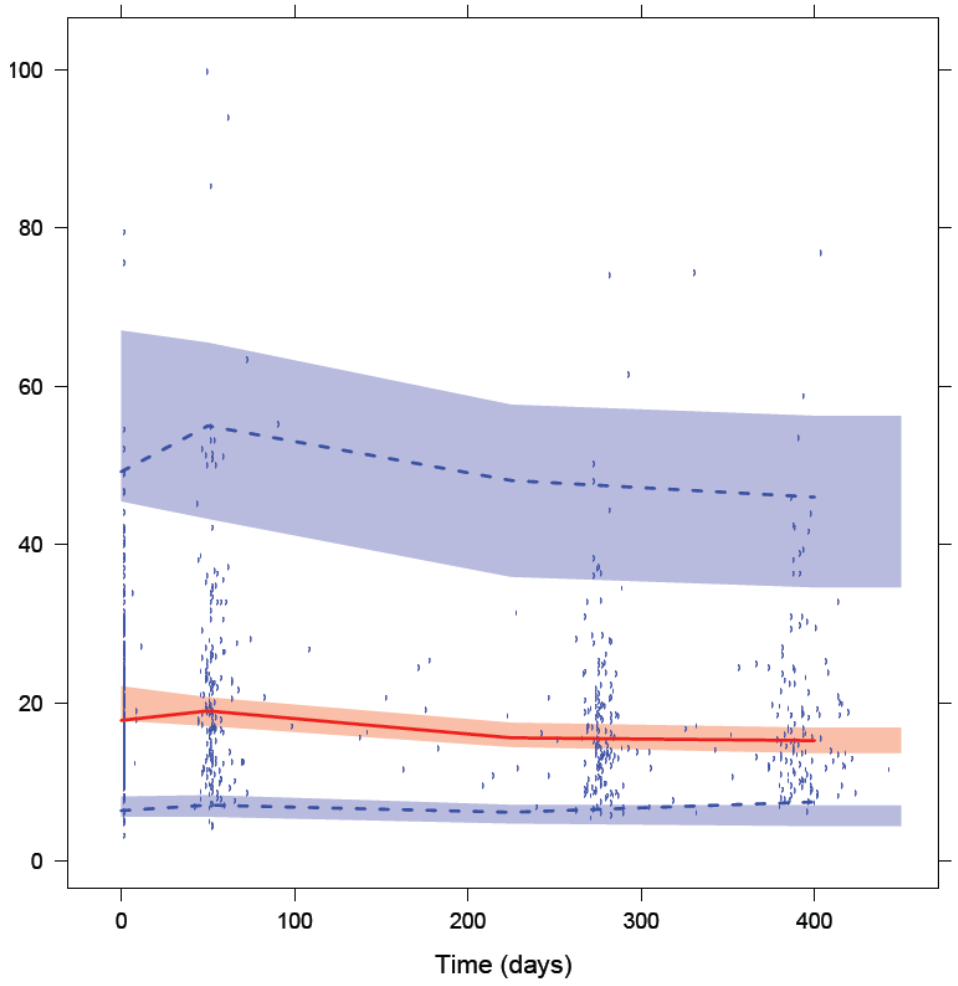
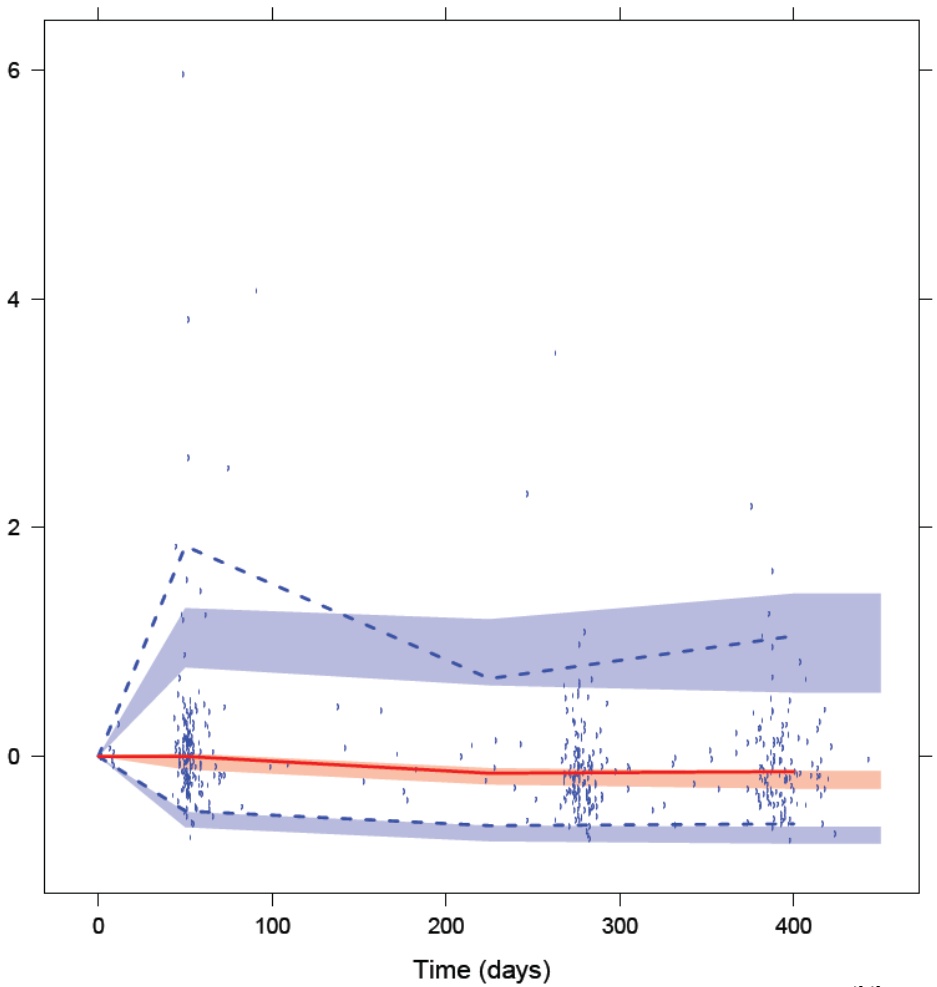
Results – VPC: FSI

Fasting Serum Insulin (uU/mL)



Fractional change from baseline (CFB)



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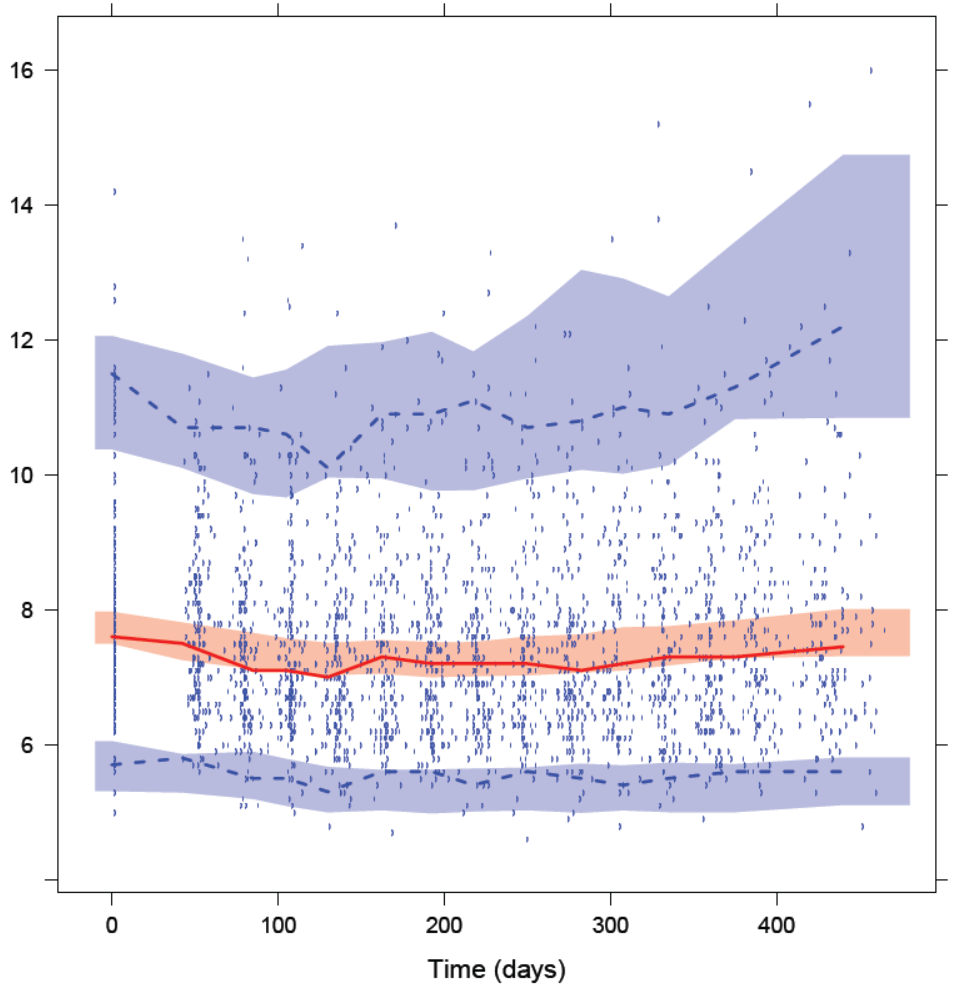
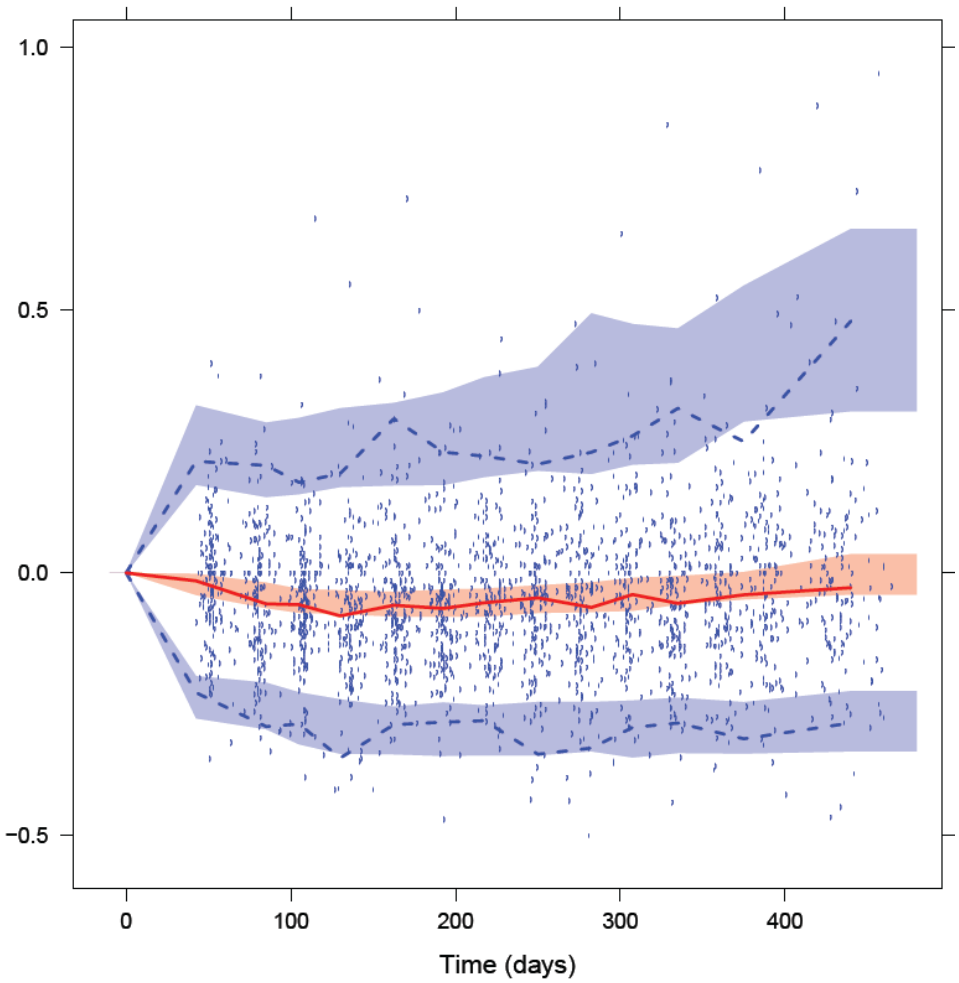
Results – VPC: FPG

Fasting Plasma Glucose (mmol/L)



Fractional change from baseline (CFB)



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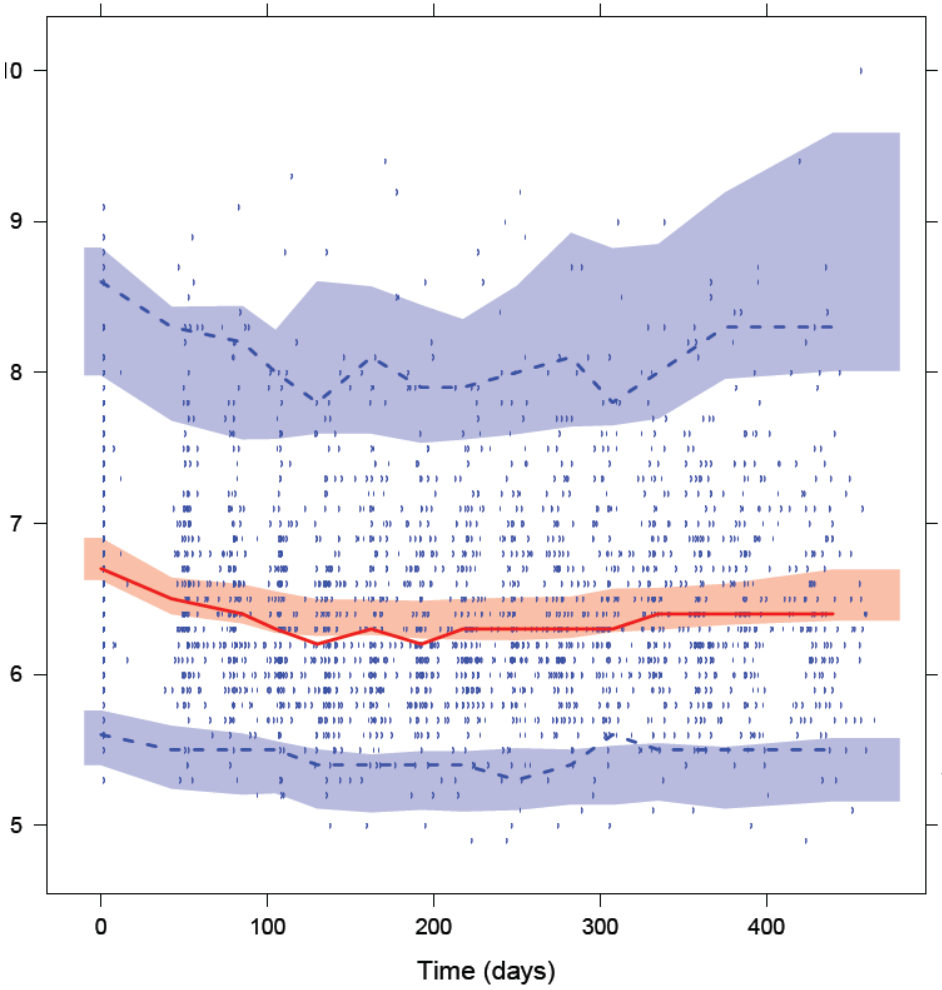
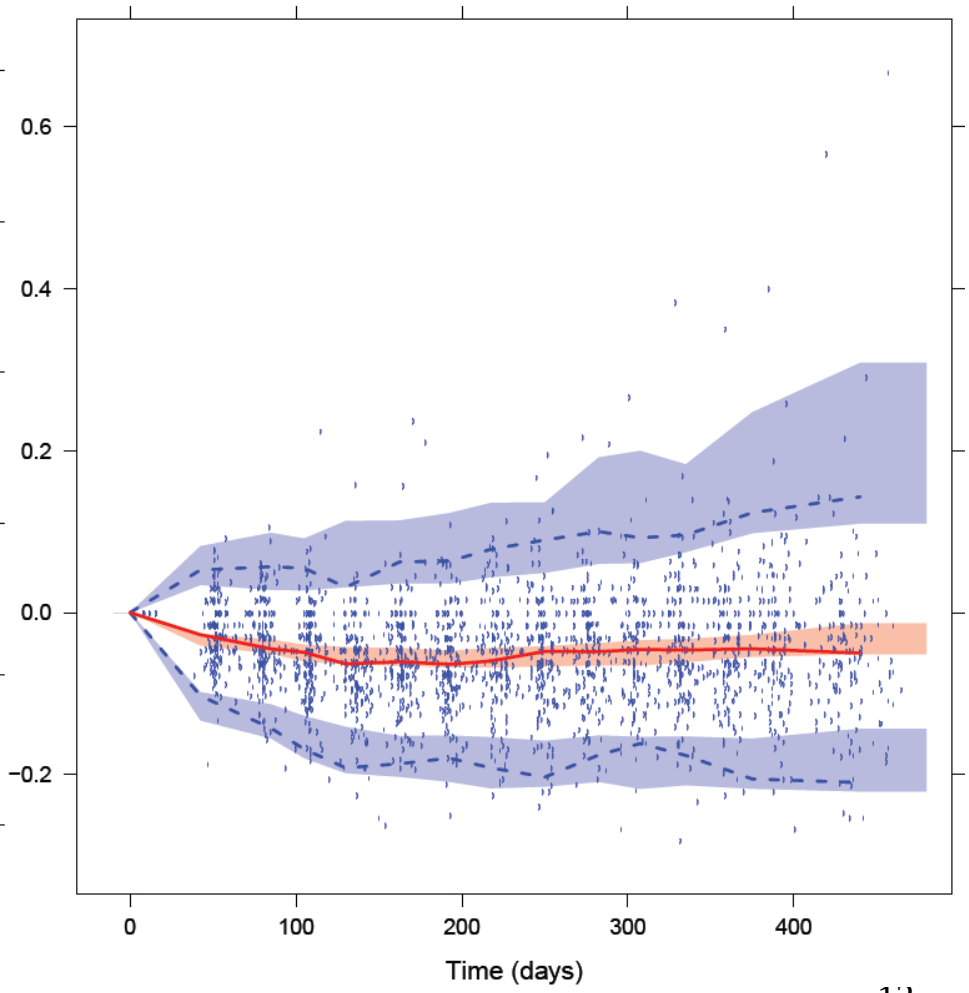
Results – VPC: HbA1c

Glycated haemoglobin (%)



Fractional change from baseline (CFB)



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Conclusions

- Weight change as an effector for insulin sensitivity has been successfully integrated on the semi-mechanistic disease progression model for T2DM
- Weight loss resulting from D&E has a positive effect on regaining IS, leading to decreased FPG and HbA1c
- Adequate prediction of the elevation for FPG and HbA1c levels at the end of the study validates the WHIG model's ability to model disease progression of T2DM

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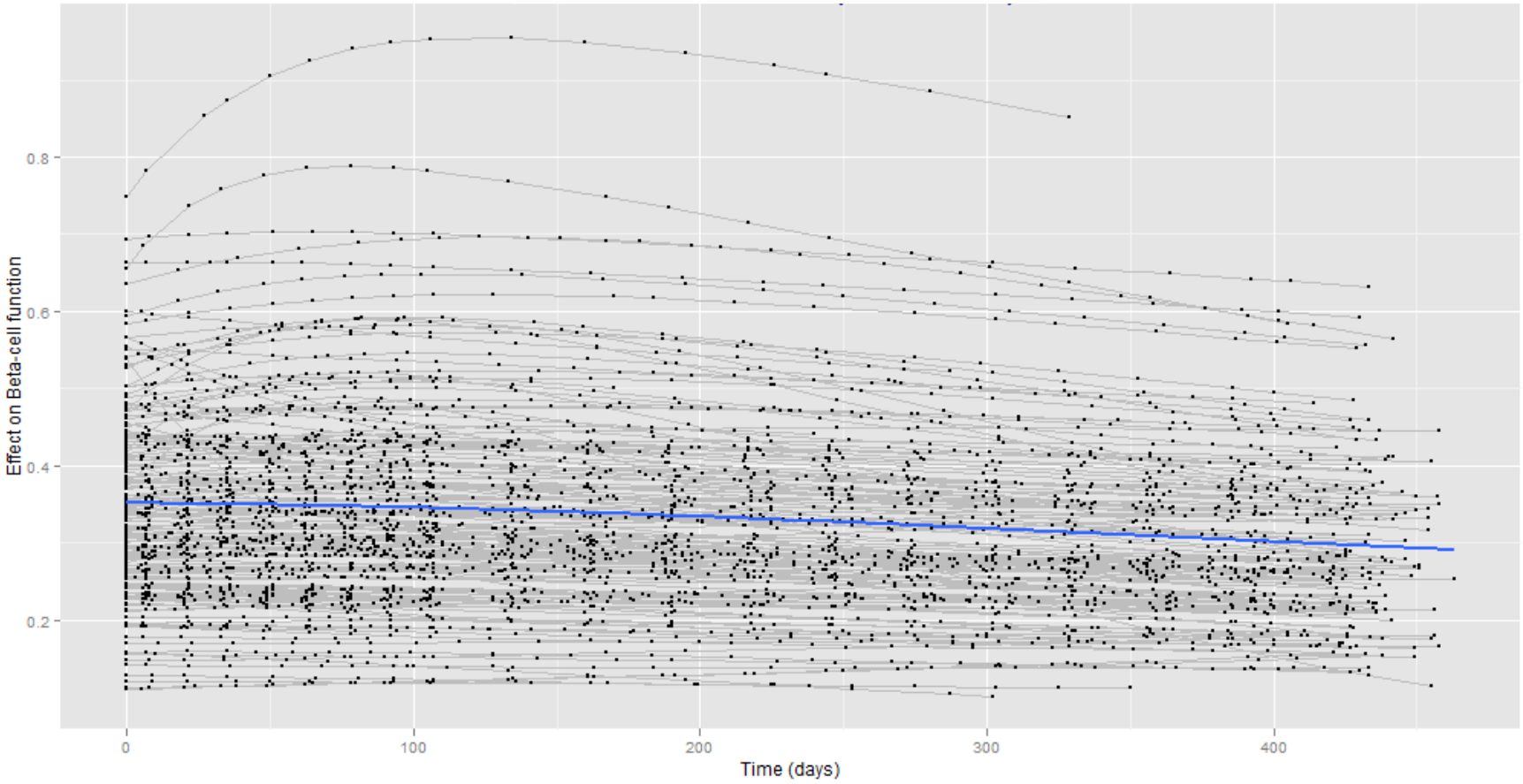
Beta-cell function decreases over time



- Beta-cell function is modeled as an empirical function that first rises and then decreases with time

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Future direction

- Implement more mechanistic components into the model based on known physiology, e.g. Replace empirical beta-cell function as a function of time

- Test the model on different demographics:
  - Non-obese
  - Chronic diabetics
  - Healthy volunteers

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Acknowledgements

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- Mats Karlsson
- Willem de Winter
- Colleagues from Uppsala University
- Janssen Pharmaceutica

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Thank you for listening!

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Backup slides

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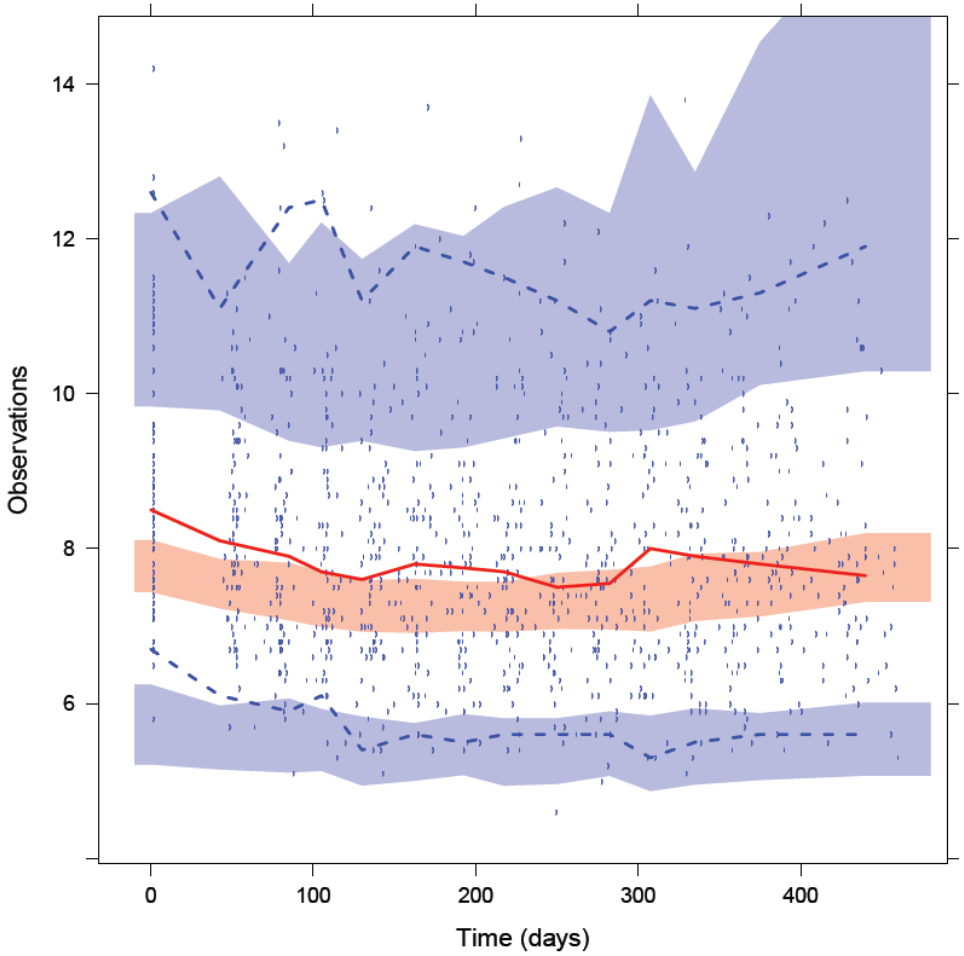
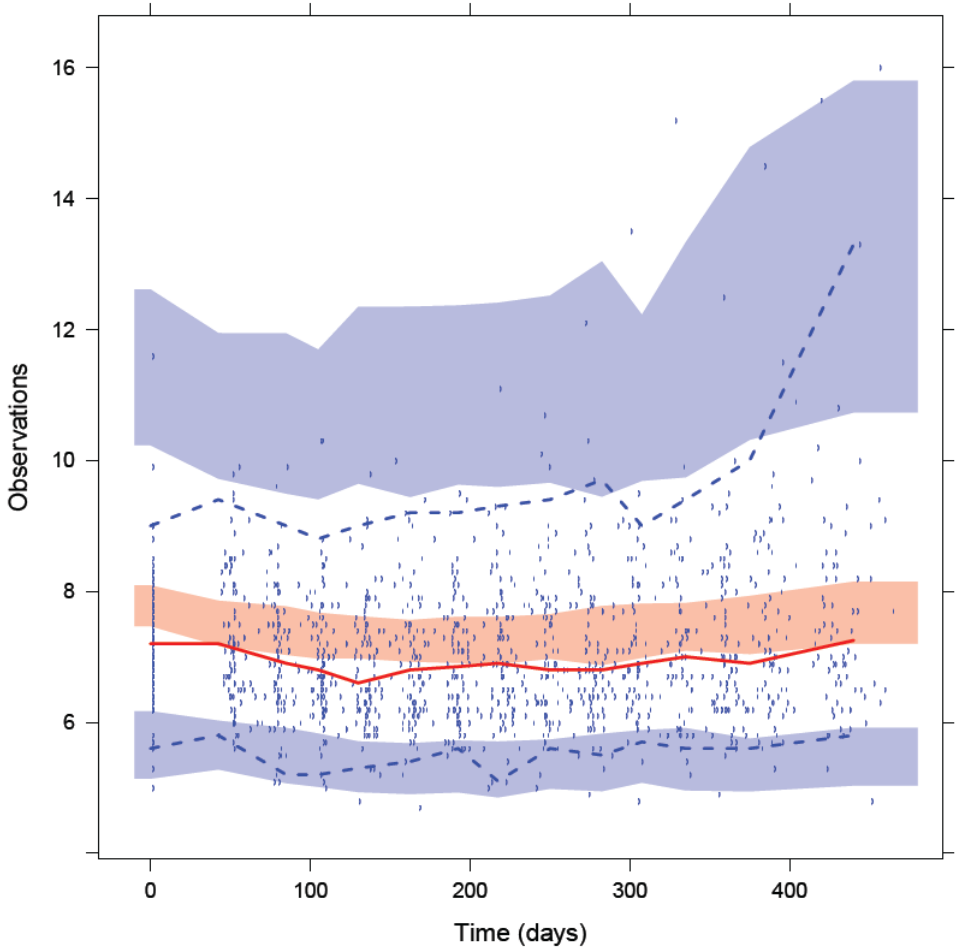
Stratify into High/Low groups FPG

run262 (FPG – Higher HbA1c baseline than median)



run262 (FPG – Low)



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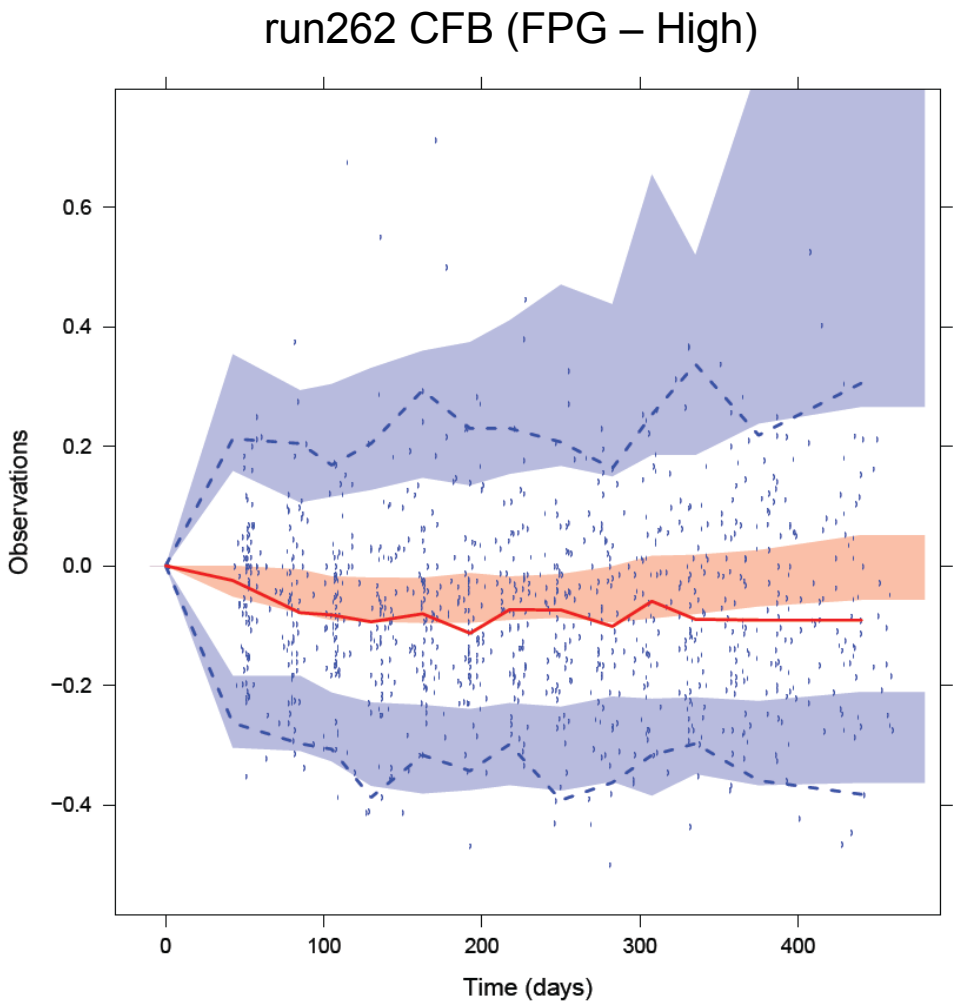
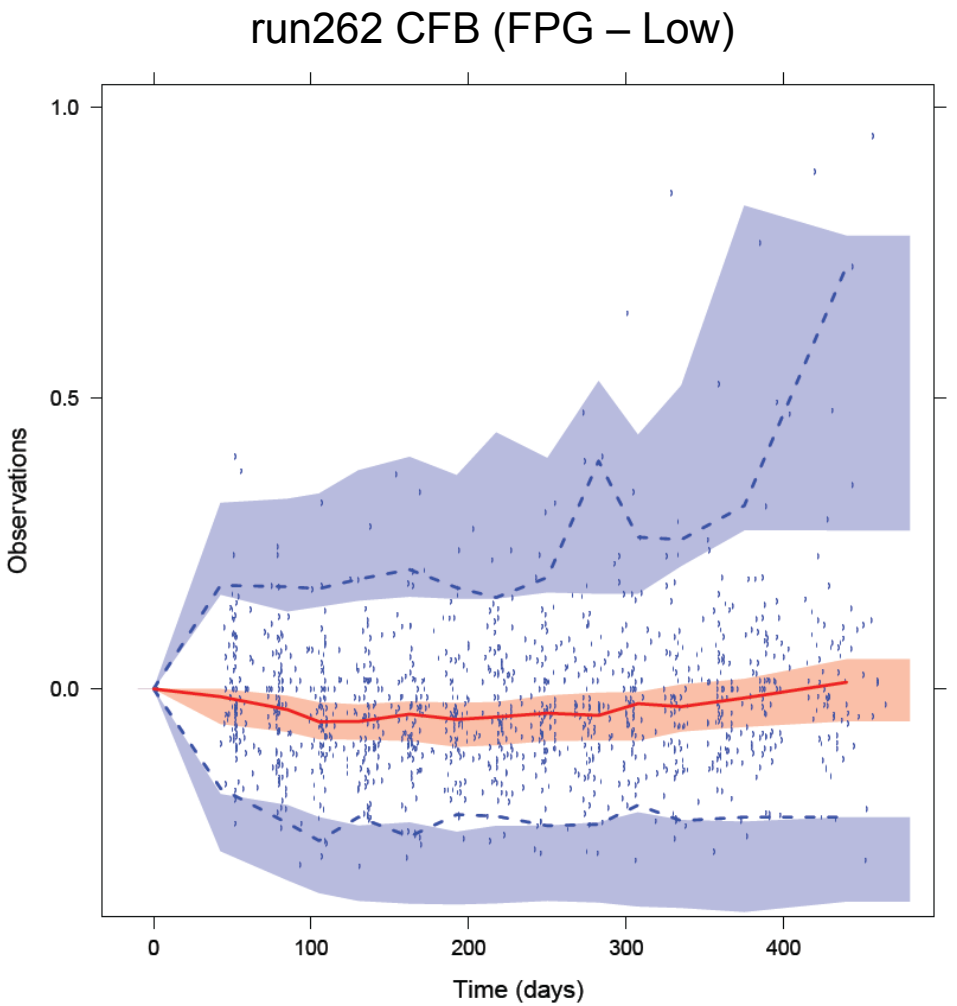
Stratify into High/Low groups FPG





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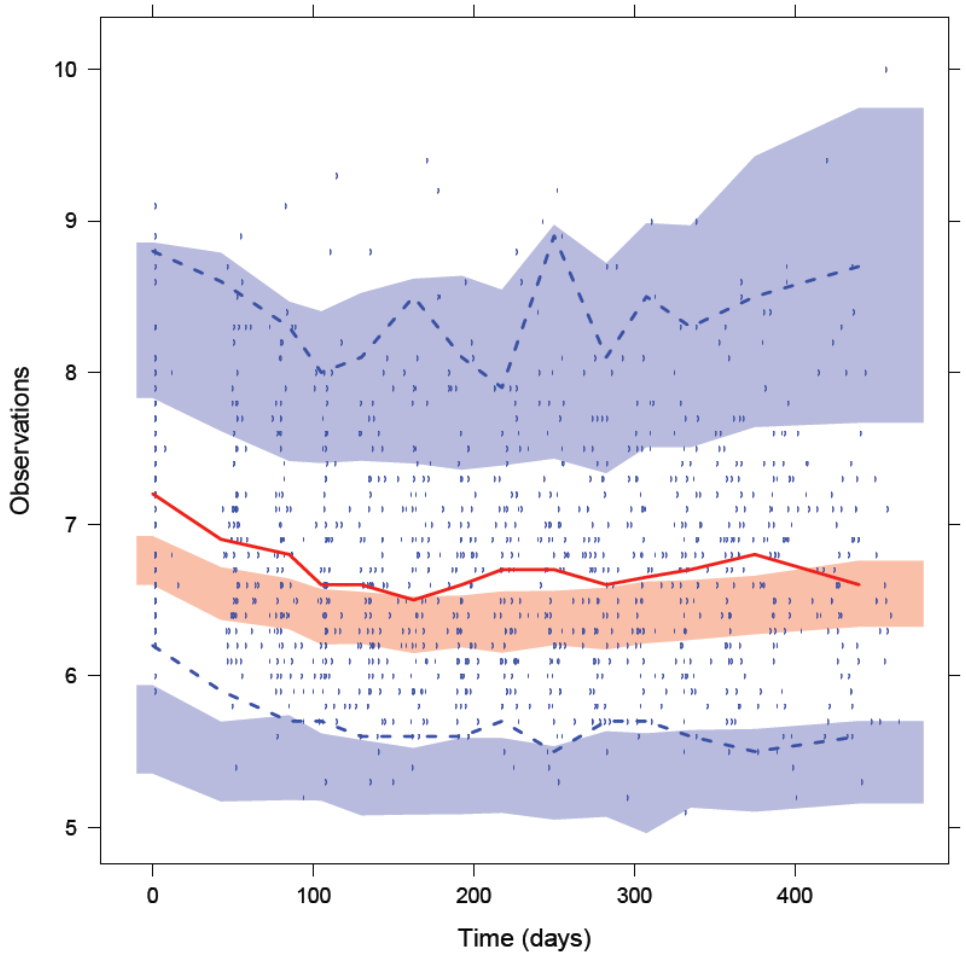
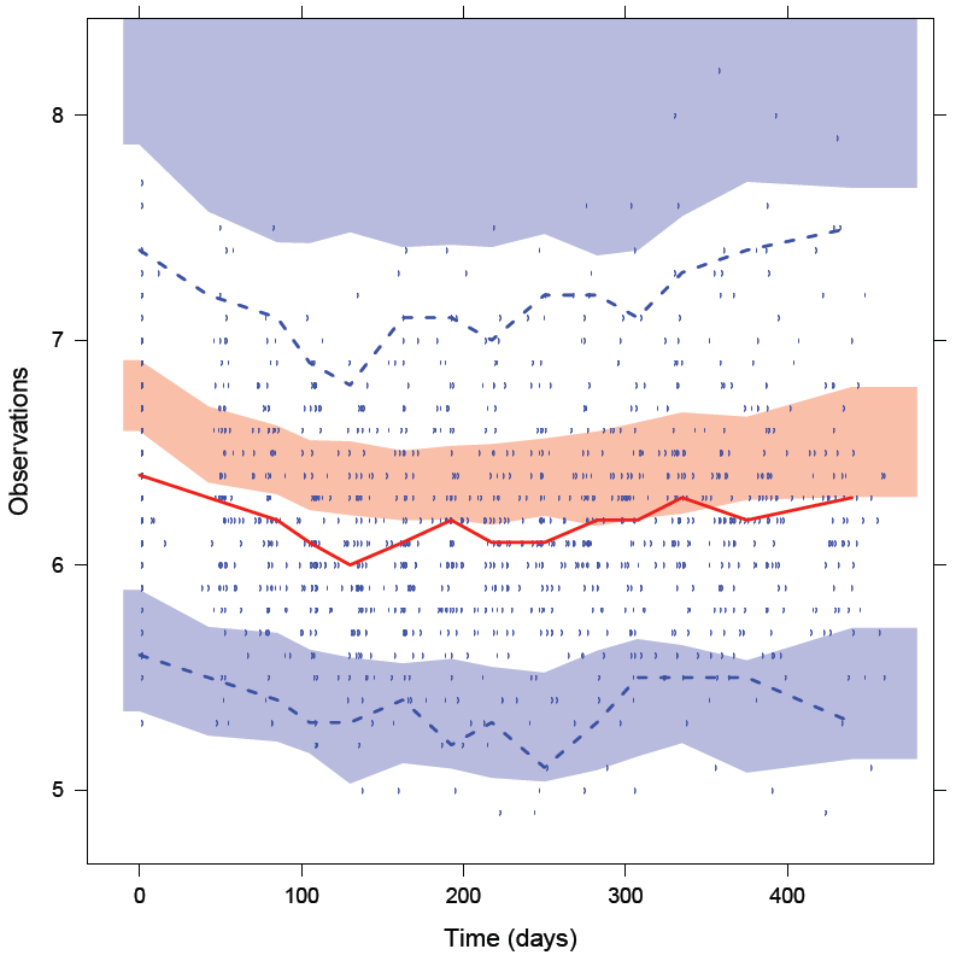
Stratify into High/Low groups HbA1c

run262 (HbA1c – Higher FPG baseline than median)



run262 (HbA1c – Low)



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Stratify into High/Low groups HbA1c