The effect of glucose dynamics on plasma copeptin levels upon glucagon, arginine, and macimorelin stimulation in healthy adults
Data from: Glucacop, Macicop, and CARGO study

Cihan Atila[1,2], Sophie Monnerat[1,2], Sandrine Andrea Urwyler[1,2], Julie Refardt[1,2], Bettina Winzeler[1,2] & Mirjam Christ-Crain[1,2]

[1]Department of Endocrinology, Diabetology and Metabolism, University Hospital Basel, Basel, Switzerland; [2] Department of Clinical Research, University of Basel, Basel, Switzerland

1. Background

- Non-osmotic stimulation tests using glucagon, arginine, or macimorelin were recently evaluated for their ability to assess posterior pituitary function. Glucagon and arginine, but not macimorelin, stimulated copeptin secretion (a surrogate marker of vasopressin) and, therefore, provide novel tests to assess the posterior pituitary. The exact underlying mechanism behind their stimulatory effect remains elusive.
- Glucose dynamics, as observed after insulin-induced hypoglycemia, seem to trigger copeptin secretion.

2. Research questions / Hypothesis

We hypothesized that the difference in glucose dynamics might explain the differences in copeptin release between stimulating tests (arginine and glucagon) and the non-stimulating test (macimorelin).

3. Methods

Study design: pooled secondary analysis of three prospective diagnostic studies (NCT04550520, NCT01879137, NCT03844217) (1, 2, 3) conducted at the University Hospital Basel, Switzerland.

Population: healthy participants who underwent a stimulation with:
- Subcutaneous injection of 1 mg **glucagon**, (n = 22)
- Intravenous application of 0.5 g/kg **arginine**, (n=30)
- Oral intake of 0.50-0.75 mg/kg **macimorelin** (n=28)

Primary objective: To investigate glucose course upon glucagon, arginine, and macimorelin stimulation tests and its effect on plasma copeptin release.
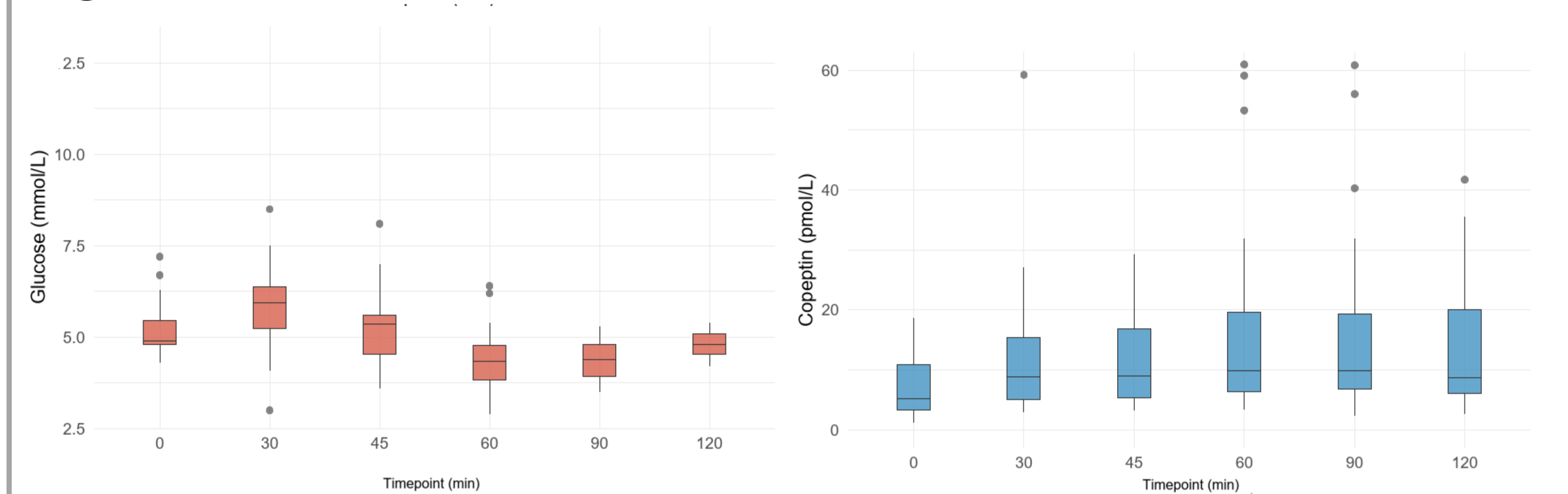
4. Results

Glucagon stimulation
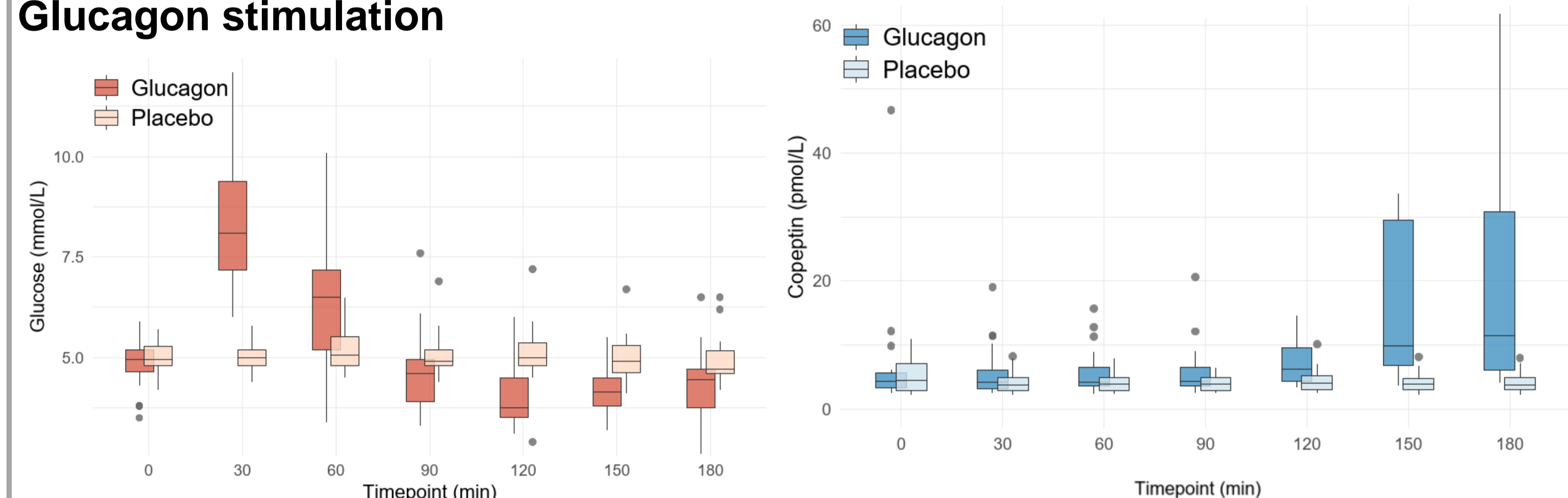
Upon glucagon stimulation, the median [IQR] glucose level at baseline was 5.0 [4.6, 5.2] mmol/l, peaked at 8.1 [7.2, 9.4] mmol/l after 30 min and decreased to a minimum of 3.8 [3.5, 4.5] mmol/l after 120 min. The median copeptin increase upon glucagon stimulation was 7.7 [2.6, 28.0] pmol/l.
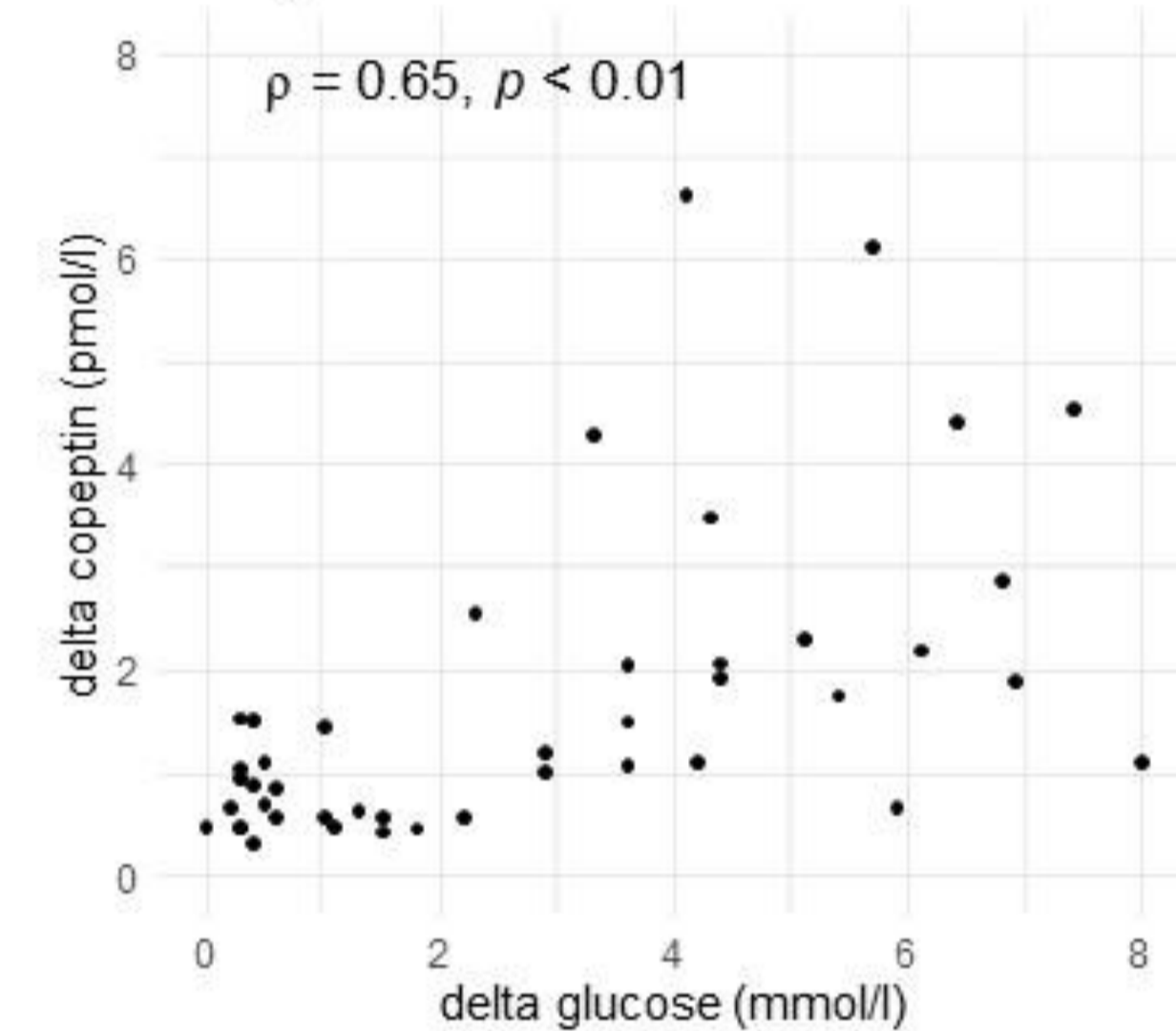
Arigine stimulation

Upon arginine, the glucose level at baseline was 4.9 [4.8, 5.5] mmol/l, peaked at 6.0 [5.2, 6.4] mmol/l after 30 min and decreased to a minimum of 4.3 [3.8, 4.8] mmol/l after 60 min. The median copeptin increase upon arginine stimulation was 4.5 [2.9, 7.5] pmol/l.
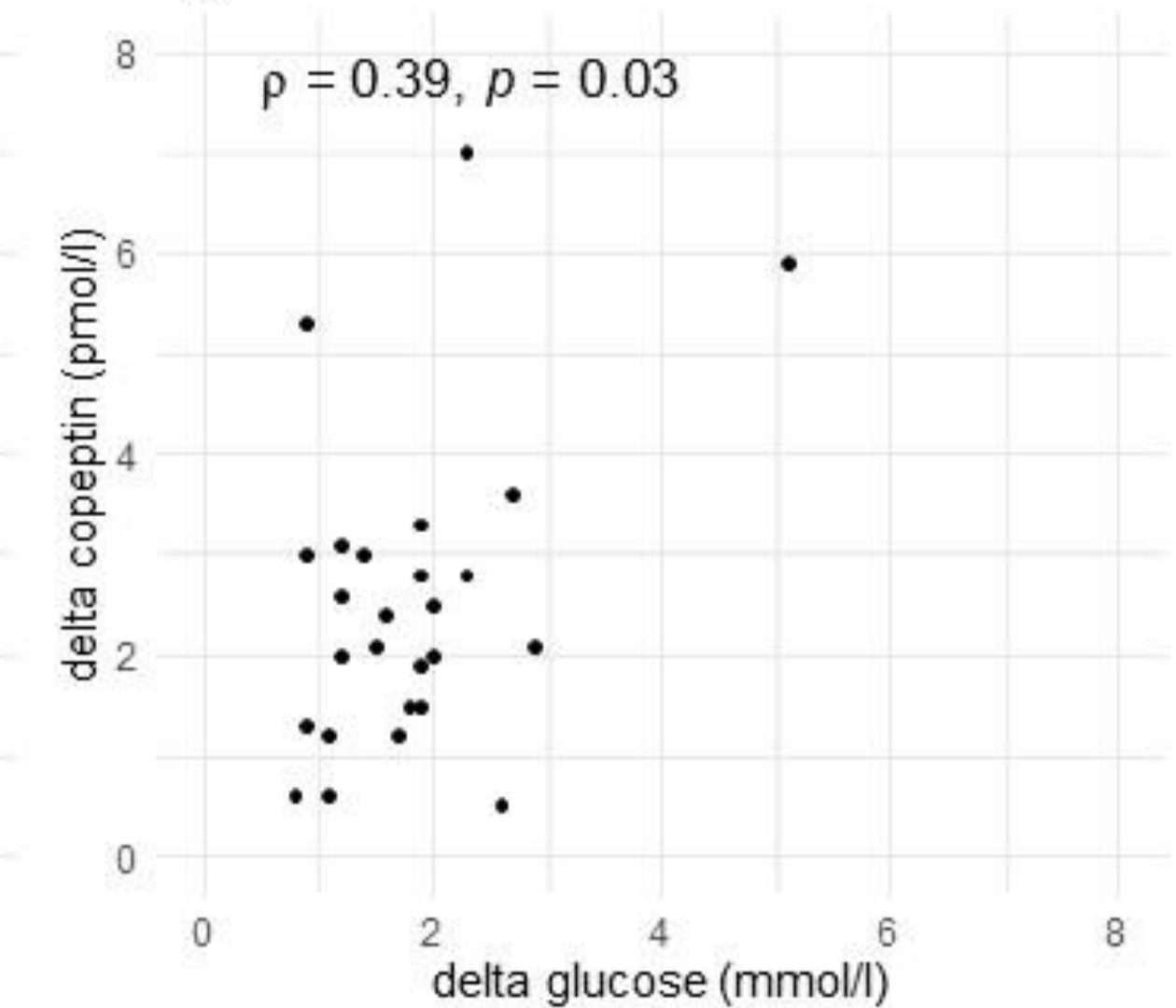
Macimorelin stimulation
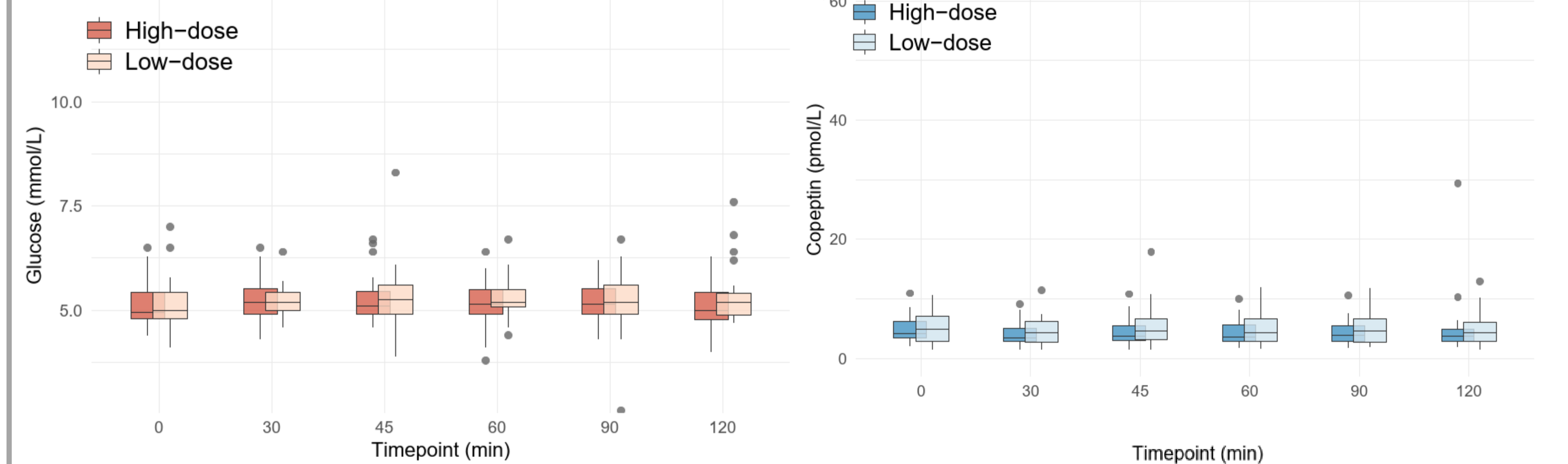
Upon macimorelin, glucose levels showed no notable dynamics over the 120 min, and no major change in copeptin was observed.
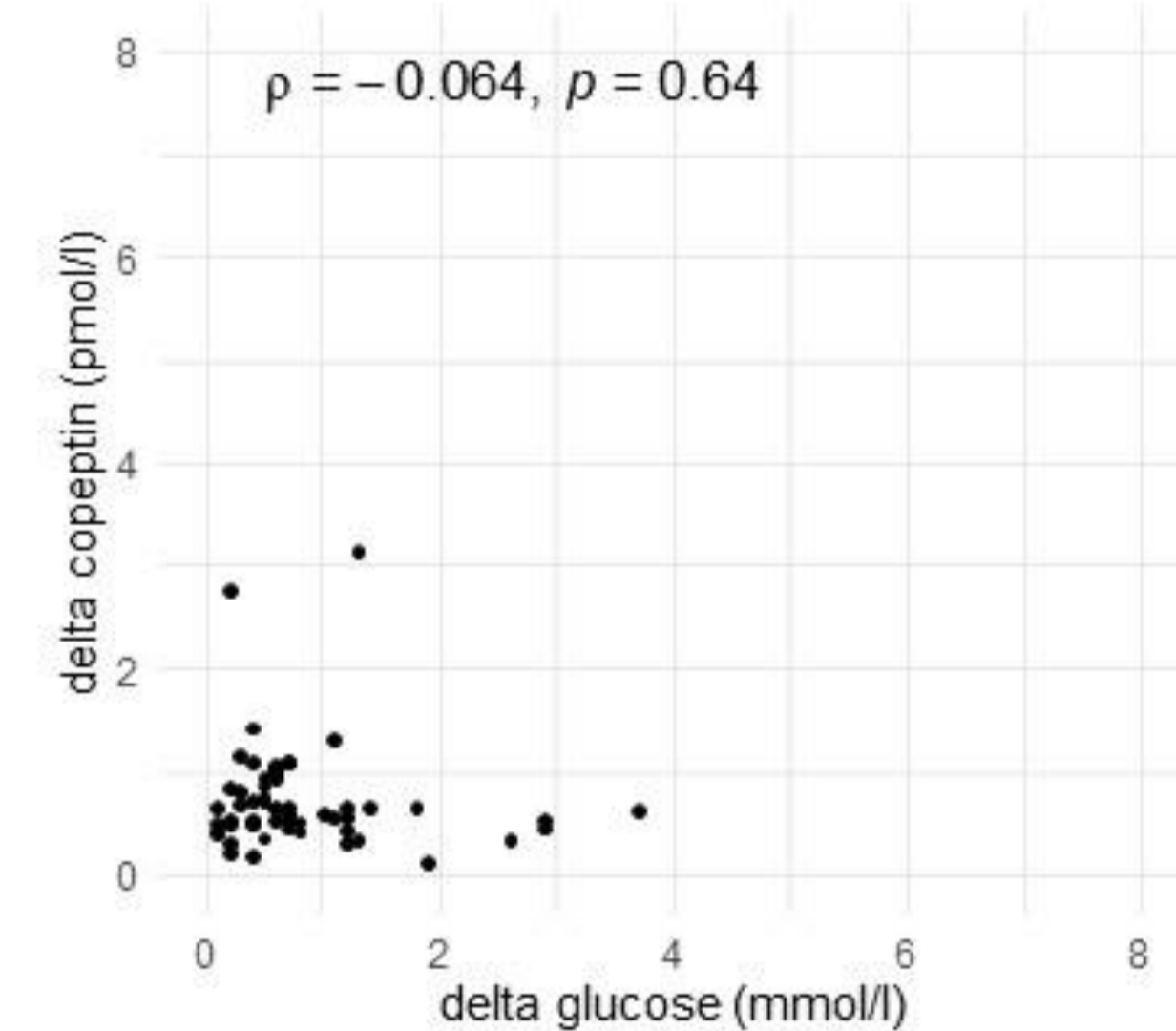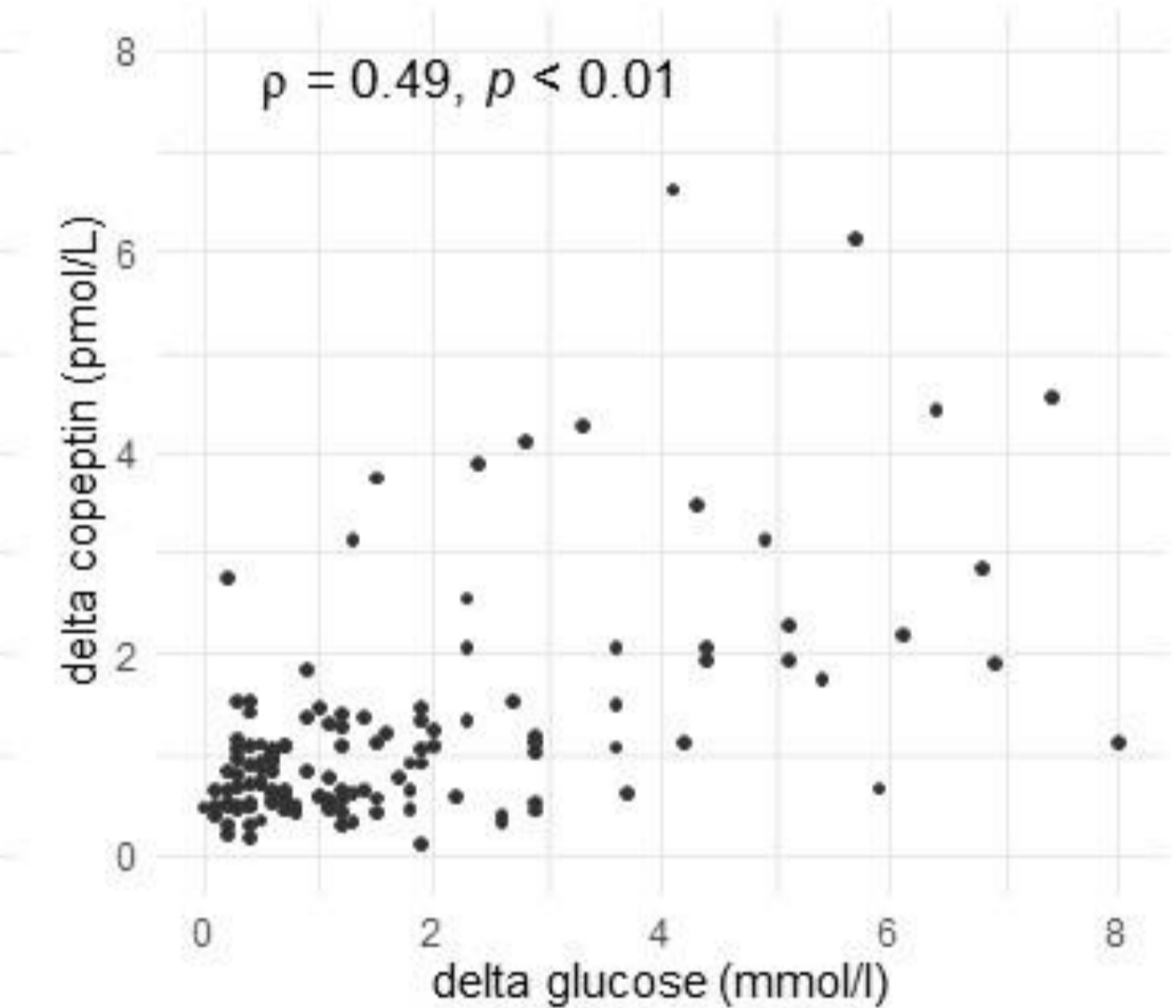
A   Glucagon $\rho = 0.65$, $p < 0.01$

B   Arginine $\rho = 0.39$, $p = 0.03$

C   Macimorelin $\rho = -0.064$, $p = 0.64$

D   Overall $\rho = 0.49$, $p < 0.01$

In the pooled dataset (D), a decrease in glucose levels was significantly correlated with copeptin increase ($\rho = 0.53$, $p < 0.01$). For each test separately, we observed:

A) a strong correlation for the glucagon stimulation ($\rho = 0.65$, $p < 0.01$)

B) a moderate correlation for the arginine stimulation ($\rho = 0.45$, $p = 0.01$)

C) no correlation for the macimorelin stimulation ($\rho = -0.064$, $p = 0.64$)

5. Conclusion

These findings suggest that a drop in glucose levels might be a possible explanation for the increase in copeptin levels in both glucagon and arginine stimulation tests. Whether the drop in glucose levels itself leads to copeptin secretion, or whether it mirrors other stimuli such as hypoglycemia-induced stress should be further investigated.

6. References

1) Urwyler SA et al (2021) Effects of oral macimorelin on copeptin and anterior pituitary hormones in healthy volunteers. Pituitary 24(4):555–563
2) Winzeler B et al (2019) Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study. Lancet 394(10198):587–595
3) Atila C et al (2022) Glucagon-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a double-blind randomized placebo-controlled study. Eur J Endocrinol. https://doi.org/10.1530/endoabs.81.P150

Sophie Monnerat*
Department of Endocrinology, Diabetology and Metabolism
University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland
*sophie.monnerat@usb.ch

Universitätsspital Basel