Alterations of appetite-regulating hormones in risperidone treated children and adolescents - A posthoc analysis of the SPACe study

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Abstract

Weight gain and metabolic disruptions are common in children and adolescents treated with antipsychotics, but the underlying mechanisms are unclear, complicating prevention and treatment. This study examines the impact of risperidone on appetite-regulating hormones (insulin, leptin, bioleptin) and their relationship to body weight changes over time. In a post-hoc analysis, we evaluated the correlation of appetite-regulating hormones with BMI z-scores during treatment and at a 6-month follow-up. The sample consisted of 10 participants (80% male, median age 9.7 years). A significant increase in bioleptin ($p < 0.05$) and BMI z-scores was observed over the 6 months. Initially, HOMA-IR, insulin, leptin, and bioleptin were significantly associated with BMI z-scores, but this association diminished after 6 months of treatment. Additionally, higher risperidone exposure correlated with lower appetite-regulating hormones at the 6-month mark. These findings indicate that risperidone significantly affects appetite-regulating hormones in children and adolescents, potentially contributing to antipsychotic-induced weight gain.

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Data availability statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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Conflict of interest disclosure

The authors have no conflicts of interest.

Ethics approval statement

The study was approved by the medical ethics committee of the Erasmus Medical Center, the Netherlands (number MEC 2016-124).

Patient consent statement

All patients and/or their legal representatives provided written informed consent prior to enrolment in the study.

Clinical trial registration

This study is registered in the Netherlands Trial Register, ID 6050.

What is already known about this subject?

Although weight gain and the development of metabolic syndrome are multifactorial, disruptions in appetite-regulating hormones are likely to play a substantial role. [4] Previous studies have shown a dose- and duration-dependent effect of risperidone on weight gain and disturbance of endocrine regulation in children and adolescents. [5,6] A correlation between risperidone exposure and weight gain is suggested. However, the effects of risperidone exposure on disruptions in appetite-regulating hormones have not been explored.

What does this study add to current knowledge?

In this study, we noted increasing trends in fasting serum leptin, bioleptin, insulin levels, and HOMA-IR. These markers are correlated with BMI z-score at baseline but the association disappeared after initiation of risperidone treatment. We also observed that a higher risperidone exposure was associated with lower appetite-regulating hormones. Elevated risperidone exposure may suppress the production of leptin and bioleptin, resulting in a moderate increase in their concentrations associated with weight gain. This could indicate a disruption in the satiety mechanism within the homeostatic framework, potentially leading to excessive weight gain in children, who are more susceptible to age-inappropriate weight gain due to ongoing growth and development.

ABSTRACT

Weight gain and metabolic disruptions are common in children and adolescents treated with antipsychotics, but the underlying mechanisms are unclear, complicating prevention and treatment. This study examines the impact of risperidone on appetite-regulating hormones (insulin, leptin, bioleptin) and their relationship to body weight changes over time. In a post-hoc analysis, we evaluated the correlation of appetite-regulating hormones with BMI z-scores during treatment and at a 6-month follow-up. The sample consisted of 10 participants (80% male, median age 9.7 years). A significant increase in bioleptin ($p < 0.05$) and BMI z-scores was observed over the 6 months. Initially, HOMA-IR, insulin, leptin, and bioleptin were significantly associated with BMI z-scores, but this association diminished after 6 months of treatment. Additionally, higher risperidone exposure correlated with lower appetite-regulating hormones at the 6-month mark. These findings indicate that risperidone significantly affects appetite-regulating hormones in children and adolescents, potentially contributing to antipsychotic-induced weight gain.

KEYWORDS
Antipsychotic drugs, Risperidone, Children, Adolescents, appetite hormone

INTRODUCTION

Second-generation antipsychotic drugs play a crucial role in treating irritability and aggression in children diagnosed with ASD. Risperidone effectively reduces irritability and hyperactivity over the short and long term. [1] However, potential drawbacks of its use include metabolic consequences like excessive weight gain and cardiometabolic complications, posing especially children at higher risk than in adults. [2] Compelling evidence shows that metabolic syndrome during childhood serves as a robust indicator of future risk for type 2 diabetes and cardiovascular disease in adulthood. [3] These conditions carry significant longterm implications, including socio-occupational limitations, reduced life expectancy, and a negative effect on patient adherence and treatment outcomes.

Although weight gain and the development of metabolic syndrome are multifactorial, disruptions in appetite-regulating hormones are likely to play a substantial role. [4] Previous studies have shown a dose- and duration-dependent effect of risperidone on weight gain and disturbance of endocrine regulation in children and adolescents. [5,6] A correlation between risperidone exposure and weight gain is suggested. However, the effects of risperidone exposure on disruptions in appetite-regulating hormones have not been explored. This emphasize the significance of this posthoc analysis within the SPACe study, where we investigate the impact of changes in appetite-regulating hormones in children related to risperidone plasma concentrations. Despite the limited sample size, this study holds considerable importance. Our goal is a better understanding of antipsychotic-induced metabolic changes and to achieve this we analyze the changes in appetite-regulating hormones. Finally, we aim to identify which receptor signaling pathways should be targeted in the development of new antipsychotic drugs to mitigate their appetite-stimulating effects.

METHODS

Data from ten patients were collected from the 6-month SPACe study, a prospective multicenter cohort in the Netherlands. This study included patients aged 6-18 years, starting risperidone treatment for behavioral problems associated with ASD as previously described by Kloosterboer et al. [7] Risperidone and its active metabolite, 9-hydroxyrisperidone (9-OH-RIS), were assessed through sparse random sampling with venipuncture and the dried blood spot method at 6-month follow-up. Whole blood for hormone analysis was obtained by venipuncture after a minimum 9-hour overnight fast, at baseline and 6-month follow-up, followed by serum extraction and freezing at −80 °C until assayed.

Risperidone and 9-OH-RIS serum concentrations were measured using validated liquid chromatography-mass spectrometry, with dried blood spot concentrations converted to estimated serum concentrations through hematocrit correction, as previously confirmed. [8] A model-based individual pharmacokinetic prediction was used to simulate the trough concentrations of risperidone and 9-OH-RIS (i.e. sum trough concentration). The appetite-regulating hormones insulin, leptin, and bioleptin were measured by Fujirebio Lumipulse G1200 Ghent, Belgium; ELISA, E07 Mediagnost, Reutlingen, Germany; ELISA, L07 Mediagnost, Reutlingen, Germany. The HOMA-IR insulin resistance index was calculated using this formula: (fasting insulin(microU/L)× fasting glucose(nmol/L))/22.5.

To explore the impact of risperidone treatment on insulin, leptin, and bioleptin we assessed the extent of change in these hormones after risperidone treatment. The extent of the changes in insulin, HOMA IR, leptin and bioleptin between baseline and 6-month follow-up were statistically evaluated using either the Scholar-paired t-test or the two-tailed Wilcoxon signed-rank test. Depending on normal distribution of the data. Moreover, we assessed the relationship between appetite-regulating hormones and HOMA IR and BMI-z scores both before the initiation of risperidone treatment and after 6 months of use. Finally, we investigated the correlation between appetite-regulating hormones and risperidone exposure (sum trough concentration) using linear regression.

RESULTS

Patient characteristics at baseline and longitudinal changes of different parameters are detailed in Table 1. Statistical comparison of baseline, and 6-month measurements, showed a significant increase in bioleptin ($p < 0.05$) and BMI z-score. At baseline a higher BMI z-score was significantly correlated with increased concentrations of insulin, leptin, and HOMA-IR ($p<0.05$) bioleptin and a trend was seen with bioleptin (Table 2). After 6 months of risperidone treatment this correlation completely disappeared for all hormones.

After 6 months of risperidone treatment, a negative correlation between sum trough concentration, which represents the risperidone exposure, and the studied parameters was seen (fig. 1). Statistically significant negative correlations were found with leptin and bioleptin, and the relationship with insulin showed a declining trend. These correlations were not evident with both daily dosages and cumulative AUC, suggesting that measurements of risperidone concentration provide a more accurate representation of changes in appetite hormones.

Table 1. Longitudinal changes in patient characteristics, risperidone levels, and glycemic and hormonal parameters; *N* = 10

Parameter	Baseline	6-month follow-up	Baseline vs 6-month follow-up
	Median (IQR)		p-value
Patient characteristics			
Age, years	9.70 (7.57-12.03)	NA	NA
Weight, kg	32.80 (26.13-53.48)	37.22 (29.95-60.55)	< 0.001*[a]
BMI z-score	0.35 (-0.28-0.98)	0.97 (0.12-1.62)	< 0.001*[a]
Male, n (%)	8 (80%)	NA	NA
Risperidone			
Dosage, mg/day	NA	0.63 (0.5-1)	NA
Sum_trough level µg/L	NA	9.6 (6.8-12.8)	NA
Cumulative AUC mg/L.h	NA	44.05 (34.86-62.25)	NA
Glycemic parameters			
Glucose, mg/L	4.9 (4.7-5.1)	4.9 (4.6-5.4)	0.488 [a]
Insulin, U/L	47 (23-60)	59 (27-88)	0.220 [a]
HOMA-IR	1.7 (0.9-2.2)	2.3 (0.9-3.0)	0.226 [a]
Hormonal levels			
Leptin, ug/L	2.3 (0.9-4.4)	3.8 (2.8-8.4)	0.154 [b]
Bioleptin, ug/L	2.9 (1.3-5.8)	5.1 (3.3-7.3)	0.042 *[b]
Bioleptin/leptin ratio	1.29 (1.11-1.42)	1.21 (1.10-1.37)	0.945 [b]

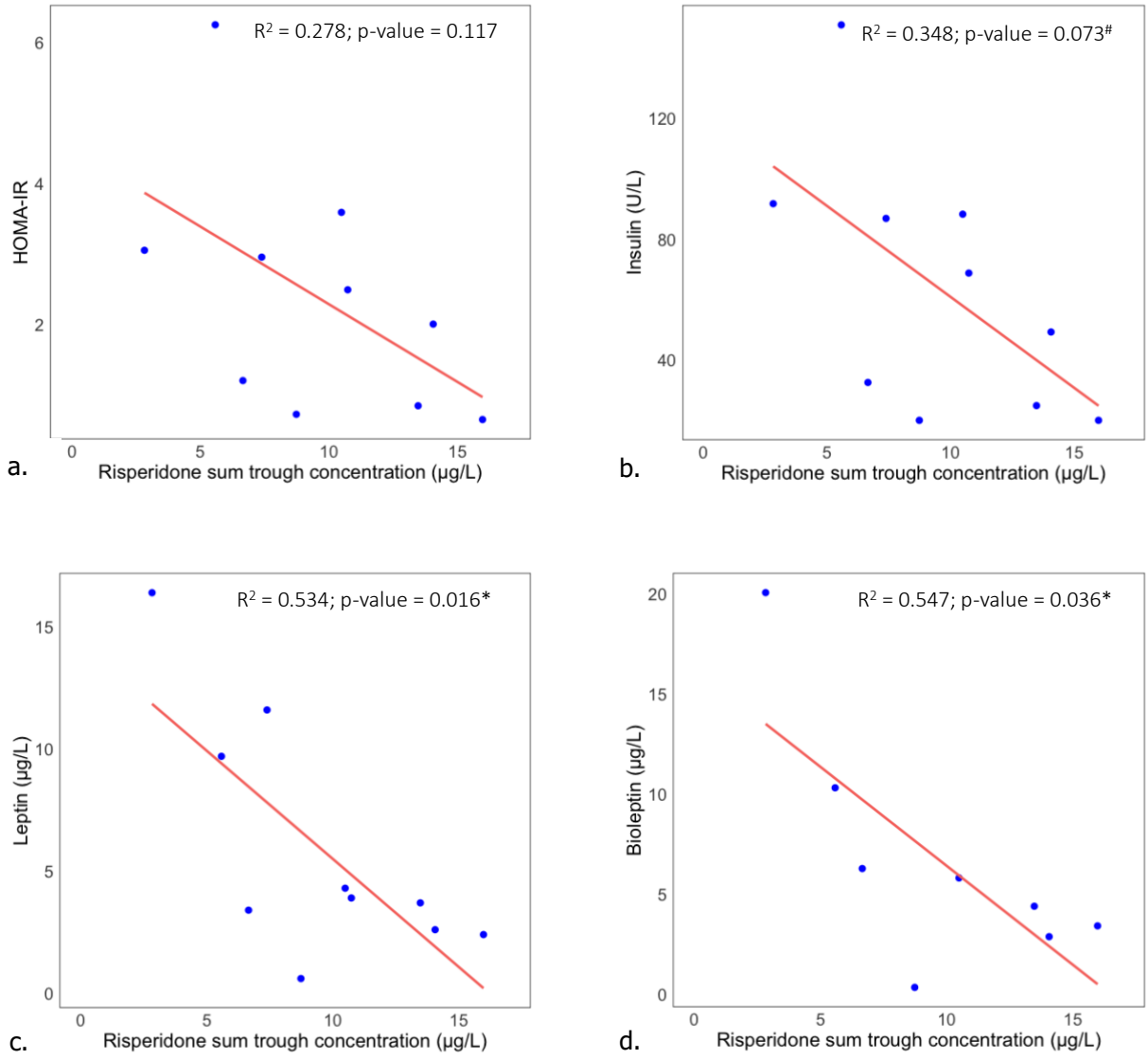
Abbreviations: BMI z-score, body mass index adjusted for age and gender; HOMA, homeostasis model assessment of insulin resistance; AUC, Area Under the Curve.
*: significance level $p < 0.05$
a: Paired t-test
b: Wilcoxon rank test

Table 2. Linear regression between appetite regulating hormones, and HOMA-IR and BMI z-score.

Correlation	Baseline	6-month follow-up
	R^2; p-value	
Insulin vs BMI z-score	0.519; 0.019*	0.279; 0.117
HOMA-IR vs BMI z-score	0.505; 0.021*	0.290; 0.109
Leptin vs BMI z-score	0.527; 0.017*	0.117; 0.333
Bioleptin vs BMI z-score	0.382; 0.076#	0.045; 0.614

Abbreviations: BMI z-score, body mass index adjusted for age and gender; HOMA, homeostasis model assessment of insulin resistance.
*: significance level $p < 0.05$
#: trend level $p < 0.1$

Figure 1. Correlation between risperidone sum trough level (µg/L) and HOMAIR (a), insulin (b), leptin (c), and bioleptin (d) at 6-months (visit 24); $N = 10$.



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DISCUSSION

Although previous research has to some extent clarified a dose-and duration-dependent effect of risperidone on weight gain and disturbance of endocrine regulation in children and adolescents, [5,8] this study is the first to investigate changes in appetite-regulating hormones related to risperidone exposure. To comprehend drug-induced effects on appetite-regulating hormones, it is important to understand the roles of these hormones in maintaining homeostasis.

In peripheral tissues, insulin primarily facilitates glucose uptake by cells for energy and regulates blood sugar. The brain influences appetite regulation by impacting hypothalamic neural pathways governing hunger and satiation. Insulin reduces the release of the hunger-inducing hormone ghrelin, thus contributing to satiety. [4] Studies show that antipsychotic drugs elevate the risk of developing diabetes by increasing weight, impairing insulin secretion, and inducing resistance. [9] Animal and in vitro studies demonstrated that antipsychotic drugs hinder insulin secretion.
Moreover, insulin release is reduced due to D2 receptor antagonism, a characteristic exhibited by risperidone, while blocking other receptors impacts pancreatic β cells' response to glucose, and antipsychotic drugs increase β cell apoptosis. [9] HOMA-IR is a method used to quantify insulin resistance and beta-cell function from basal (fasting) glucose and insulin concentrations. A value from 1.9 onwards may indicate insulin resistance.

Our findings show a significant correlation between both insulin level and HOMA-IR, with BMI z-score at baseline. The correlation has ceased after 6 months of risperidone treatment. This may indicate dysfunction in insulin secretion, and an altered sensitivity induced by risperidone.

Leptin, and its bioactive form bioleptin are satiety hormones. The serum levels are positively correlated with total body fat, and tightly coupled with energy status. Moreover, an elevation in leptin levels can indicate leptin resistance. [4]

As expected, in our cohort, leptin and bioleptin, are tightly correlated to the BMI z-score at baseline. However, this association disappears at six months of risperidone treatment. In addition, a negative correlation between risperidone exposure and leptin and bioleptin was observed, despite a significant increase in weight with risperidone treatment, which may indicate that risperidone exposure suppresses the production of leptin, thereby disrupting the satiety mechanism. This may lead to excessive weight gain.

Our results are contextually limited due to a naturalistic design and small sample size, and should therefore be interpreted with caution. The substantial interindividual variability in hormone levels adds complexity. These findings warrant larger follow-up future studies for confirmation. Moreover, incorporating postprandial hormone levels and exploring satiety hormones like GLP-1, CCK, and PYY in future studies would provide valuable insights.

In this study, we described increasing trends in serum leptin, bioleptin, insulin levels, and HOMA-IR among children with ASD during treatment with risperidone. Moreover, relations of these indices to BMI-z are present at baseline but ceased after initiation of risperidone treatment. Significant inverse correlations between leptin, and bioleptin and risperidone exposure were observed warranting further investigation. The upcoming SPACe2: STAR follow-up study will explore these associations in a larger cohort.

References

1. Maneeton N, Maneeton B, Putthisri S, Woottiluk P, Narkpongphun A, Srisurapanont M. Risperidone for children and adolescents with autism spectrum disorder: a systematic review. *Neuropsychiatr Dis Treat*. 2018;14:1811-1820. doi:10.2147/NDT.S151802
2. Martinez-Ortega JM, Funes-Godoy S, Diaz-Atienza F, Gutierrez-Rojas L, Perez-Costillas L, Gurpegui M. Weight gain and increase of body mass index among children and adolescents treated with antipsychotics: a critical review. *Eur Child Adolesc Psychiatry*. Aug 2013;22(8):457-479. doi:10.1007/s00787-013-0399-5
3. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. Jan 30 2007;49(4):403-14. doi:10.1016/j.jacc.2006.09.032
4. Kuckuck S, van der Valk ES, Scheurink AJW, et al. Glucocorticoids, stress and eating: The mediating role of appetite-regulating hormones. *Obes Rev*. Mar 2023;24(3):e13539. doi:10.1111/obr.13539
5. Piras M, Dubath C, Gholam M, et al. Daily Dose Effects of Risperidone on Weight and Other Metabolic Parameters: A Prospective Cohort Study. *J Clin Psychiatry*. May 9 2022;83(4)doi:10.4088/JCP.21m14110
6. Srisawasdi P, Vanwong N, Hongkaew Y, et al. Impact of risperidone on leptin and insulin in children and adolescents with autistic spectrum disorders. Article. *Clin Biochem*. 2017;50(12):678-685. doi:10.1016/j.clinbiochem.2017.02.003
7. Kloosterboer SM, de Winter BCM, Reichart CG, et al. Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with autism spectrum disorder. *Br J Clin Pharmacol*. Mar 2021;87(3):1069-1081. doi:10.1111/bcp.14465
8. Tron C, Kloosterboer SM, van der Nagel BCH, et al. Dried Blood Spots Combined With Ultra-High-Performance Liquid Chromatography-Mass Spectrometry for the Quantification of the Antipsychotics Risperidone, Aripiprazole, Pipamperone, and Their Major Metabolites. *Ther Drug Monit*. Aug 2017;39(4):429-440. doi:10.1097/FTD.0000000000000411
9. Holt RIG. Association Between Antipsychotic Medication Use and Diabetes. *Curr Diab Rep*. Sep 2 2019;19(10):96. doi:10.1007/s11892-019-1220-8

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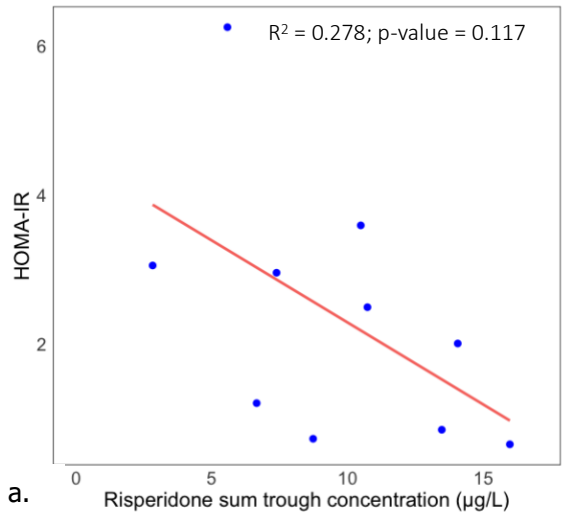

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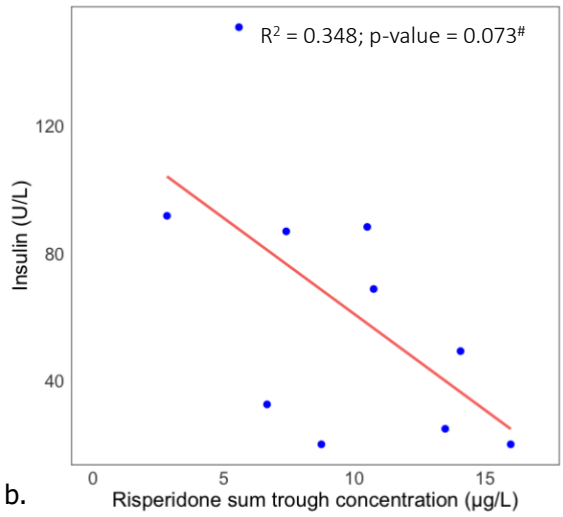

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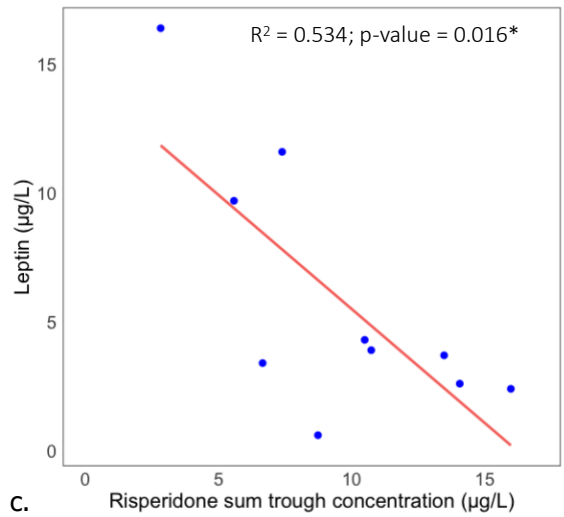

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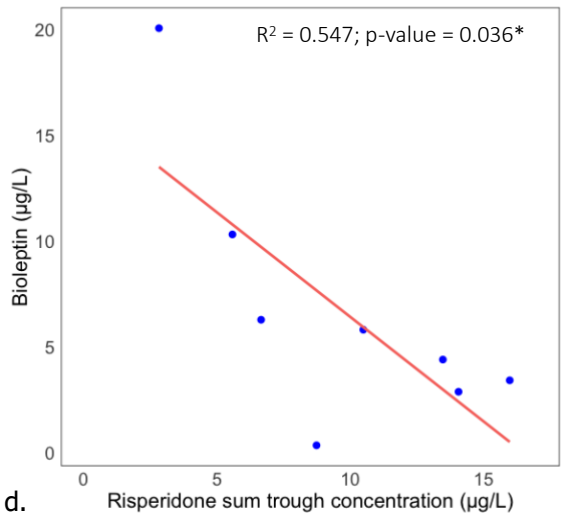

d.

*: significance level p < 0.05
#: trend level p < 0.1