Title

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# ABSTRACT

# INTRODUCTION

# METHODS

## Animal Husbandry

Wild-type mice are defined as homozygous floxed *Tsc1*, absent the *Ckmm*-Cre transgene, while Muscle *Tsc1* knockout mice are defined as homozygous floxed *Tsc1*, with one copy of the *Ckmm*-Cre transgene.

## BHB Tolerance Test

# RESULTS

## KD Improves KB Disposal

## KD Increases Muscle MTOR activity

## Activation of MTOR promotes Ketone Disposal

To test whether activation of mTORC1 in muscle tissue alters disposal of ketone bodies, we performed a BHB tolerance test in *Tsc1* knockout mice. The *Ckmm*-Cre induced ablation of *Tsc1* causes activation of mTORC1 in muscle tissues. As shown in Figure 3A, both male and female knockout mice cleared the injected beta-hydroxybutyrate much more rapidly than their wild-type littermates. Using mixed-linear models and using sex as a covariate, and the animal as a random intercept, we found a significant reduction in BHB levels after the challenge (p=0.004). Similarly, when calculating the area under the curve from 0 to 60 minutes, there was a reduction in the knockouts, after adjusting for sex (25%; p=0.016). When stratifying by sex, knockouts had 41% lower AUC in males and 11% lower in females though sex differences did not reach statistical significance (p=0.20).

## MTORC regulates expression of Ketolysis genes

# DISCUSSION