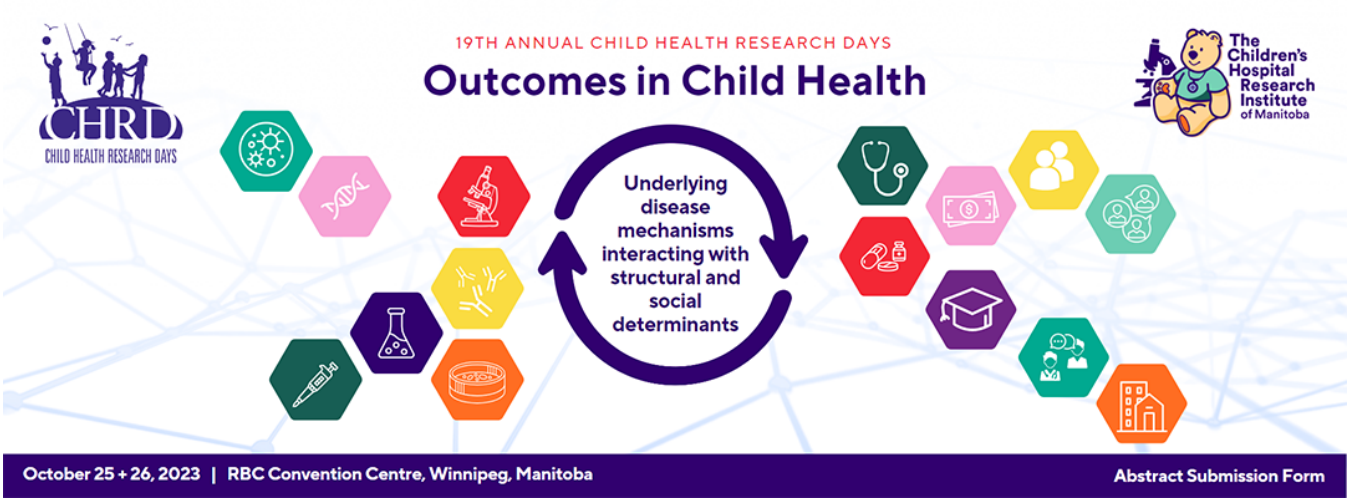


# CHRD 2023: Abstract Submission Form

**Submitter Name**
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**Presenter Name**
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**Presenter Status**
Post-Doctoral Fellows

**Research Category**
Basic Science

**Role in the project**
Design
Perform Experiments
Analyze Data
Write Abstract

**Title**
Ketone Therapy Impairs the Structure and Function of the Juvenile Heart

**Background**
Recently, there has been enhanced focus on the therapeutic potential of ketones for the management of various pediatric conditions. This is based on the observation that ketones can act as both metabolic substrates and anti-inflammatory signalling molecules. While their beneficial effects have been characterized in the adult heart, very little remains known about their safety profile in the pediatric context.

**Objective**
To determine if ketone supplementation effects the juvenile mouse heart.

**Methods**
Five-week-old male mice were administered a ketone ester (KE) drink or vehicle control, once a week for three weeks. Cardiac structure and function were assessed by in vivo echocardiography and tissues were collected for biochemical analysis. Mechanistic studies were carried out using immortalized juvenile human cardiomyocytes exposed to beta-hydroxybutyrate, the main ketone in the KE drink.

**Results**
Early-life ketone supplementation significantly impaired left ventricular (LV) ejection fraction, stroke volume, and cardiac output at 8 weeks of age (n=12). Additionally, ketone supplementation reduced heart weight and LV mass (n=12), which occurred concurrently with a significant increase in protein markers of cell death pathway activation. These markers include Bnip3, and cleaved caspase 1, which were increased

by 62.3%, and 489.6%, respectively, compared to vehicle control (n=6). Importantly, these ketone-induced cardiac alterations occurred in the absence of changes in other animal growth parameters, suggesting cardiac specificity. Mechanistic studies using immortalized juvenile cardiomyocytes demonstrated that ketone exposure inhibits HDAC1, a transcriptional repressor of Bnip3, resulting in a 201% increase in Bnip3 protein expression and an 83% increase in cardiomyocyte cell death (n=5). We further observed that silencing Bnip3 was sufficient to prevent ketone-induced cell death in juvenile cardiomyocytes (n=4).

**Conclusion**
Ketone therapy promotes Bnip3-mediated cell death in the juvenile heart, resulting in structural and functional impairments. Therefore, ketone therapy in early life may be detrimental to the young heart and should be approached with caution.

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