Title: Reversing epigenetically programmed risk of sarcopenia with modulation of the glucocorticoid pathway

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Abstract: Early life adversity has been associated with an increased risk of a range of chronic diseases in later life including CVD, diabetes, obesity, schizophrenia, depression and sarcopenia. Sarcopenia (loss of muscle mass and strength) affects between 5-13% of 60-70 year olds and 11-50% of over 80 year olds. It leads to mobility impairment, falls and fractures and is an independent risk factor for other serious health conditions. Our research has shown that individual risk for sarcopenia is in significant part determined by adverse early life environmental exposures.

We ask if this risk is reversible by interrogating an epigenetic mechanism by which it is putatively transmitted**.** Environmental influences can be transmitted through epigenetic marks (chemical modifications to DNA or proteins that interact with DNA). These modifications impact transcription, allowing cells to respond to environmental cues. Early life environment can alter DNA methylation, a type of epigenetic modification, in a locus-specific way and modify later transcription and disease risk. However, it is unknown if this epigenetically-programmed risk is reversible.

In the Hertfordshire Cohort study, we have shown that sarcopenic phenotypes are associated with particular DNA methylation changes in muscle biopsies. Further we have found that some of these changes persist in primary myoblast cell cultures from the biopsies. Here we ask if we can reverse the epigenetic markers associated with sarcopenia in patient-derived myoblast cultures. In this proof of concept study we will use **11β-Hydroxysteroid dehydrogenase (11β-HSD**) **inhibitors**, which block the enzyme catalysing the conversion of inactive cortisone into active cortisol. High glucocorticoid exposure in early life is associated with the restricted early growth phenotypes linked with later sarcopenia and the glucocorticoid system is modulated at an epigenetic level as a result of life environment. Moreover the decrease in proliferative capacity of muscle associated with ageing is mediated in part by cortisol. Inhibition of 11β-HSD1, prevented reduction in satellite cell proliferation and muscle renewal and led to trials of 11β-HSD1 inhibitors for sarcopenia.

If we can reset the epigenetically programmed risk for sarcopenia, we open up a way to correct the increased disease risk associated with a disadvantaged early life.