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Title of project: Understanding treatment of adolescent obesity and the underlying organ dysfunctions (UNFOLD)

ABSTRACT

At least 25% of adolescents with childhood-onset obesity are untreatable by lifestyle changes and have a very high risk of developing morbid obesity and type 2 diabetes already as young adults. Why they develop untreatable obesity is unknown and is not explained by socioeconomic factors or genetic variants. However, studies have linked obesity development to organ dysfunction of the brain (appetite sensation and eating behavior), fat (activation of brown fat and macrophage infiltration of fat) and gut (appetite hormones and microbiota). In rodents, treatment with glucagon-like peptide-1 receptor agonists (GLP-1RA) seems to directly improve these organ dysfunctions.

Thus, I hypothesize that brain, fat or gut-dependent mechanisms underlie untreatable childhood-onset obesity and that treatment with GLP-1 RA can improve dysfunction of these organs, and thereby diabetes. To investigate this I will recruit 180 adolescents with early-onset obesity from a cohort of 4.000 children who have undergone years of structured lifestyle intervention in the form of vigorous diet control, exercise and family counselling. Based on their response to the structured lifestyle changes, the adolescents will be divided into three groups: 60 poor responders (no reduction in BMI or fasting blood glucose), insufficient responders (reduction in BMI and fasting blood glucose but still severe obese and pre-diabetic) and 60 excellent responders (reduction in BMI and fasting blood glucose). I will then investigate potential brain, fat or gut-dependent organ dysfunction between the three groups, as well as their treatment response to one year randomization with GLP-1 RA or placebo.

The study has been established together with a variety of national and international experts within obesity and diabetes research; from behavioural scientists to proteomic specialists, from clinicians treating patients on an every-day basis, to industry striving to develop tomorrow's best obesity- and diabetes pharmaceuticals. This close interdisciplinary and cross-sectional collaboration enables us to unite a large variety of novel methodologies. I believe that with our combined expertise and excellence in obesity and diabetes research, this project has the potential to fundamentally change the way we approach treatment of childhood obesity and thereby diabetes.