

PROJECT PROPOSAL

2023 Academic Entry Year – Cohort 2

Supervisory Team

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Project Details

Project Summary

Title: Drug-lifestyle interactions for weight management in South Asians and white Europeans living with overweight or obesity

Summary: Pharmacological treatment for obesity combined with lifestyle intervention promotes clinically important weight loss and amelioration of obesity-related comorbidities. The glucagon-like peptide-1 receptor agonists liraglutide and semaglutide are approved for obesity treatment in the United Kingdom and induce weight loss by reducing hunger and promoting satiety via direct and indirect effects in the brain. South Asians experience a disproportionate burden of adverse obesity-related health consequences compared to other ethnicities. Strategies to optimise weight management in South Asians are essential to improve the health and wellbeing of those living with obesity. This PhD will investigate the effect of semaglutide 2.4 mg once weekly compared with placebo as an adjunct to lifestyle modification on appetite, energy balance and weight management in South Asians and white Europeans with overweight or obesity without diabetes. The project will integrate clinical assessments, brain MRI and qualitative methods to provide an evidence-based approach to improving weight management in a population predisposed to the adverse cardiometabolic health effects of obesity. The successful candidate will be based in the National Centre for Sport and Exercise Medicine (NCSEM) at Loughborough University, working within the lifestyle theme of the NIHR Leicester Biomedical Research Centre and supported by leading experts in the field.

Theme(s) the project most closely aligns to: Cardiovascular, obesity and renal; diabetes and lifestyle; experimental medicine; patient-centred methodologies.

How the PhD project and training would be appropriate for NMAHPs or GPs: This PhD will provide interdisciplinary training in patient-centred obesity treatment, experimental medicine, metabolism and neuroscience. The project will capitalise on infrastructure, facilities and methodologies at the NCSEM (Loughborough University) and the Diabetes Research Centre (University of Leicester). The successful candidate will benefit from supervision from a diverse team of early career (Dr Thackray, Dr Papamargaritis) and senior (Prof Davies, Prof Stensel, Dr Darko) researchers and clinicians with considerable combined expertise in obesity pharmacotherapy, physical activity, appetite, metabolism and EDI. Extensive training and development opportunities will be provided through Loughborough University's Doctoral College, the NIHR Leicester BRC and relevant external channels.

How the project addresses health inequalities: The adverse health effects of obesity are more severe and emerge earlier in individuals of South Asian descent compared to other ethnic groups^[1], and weight-related stigma can present barriers for accessing care and treatment^[2]. Therefore, strategies to optimise weight management in South Asians, a population under-represented in clinical trials^[3], are essential to improve the health and wellbeing of those living with obesity. This PhD research will provide critical data relating to the interactive effects of pharmacotherapy and lifestyle for the management of excess adiposity in individuals of South Asian ancestry. It will provide unique insights into the underlying weight-reducing mechanisms of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in obesity by examining homeostatic and hedonic influences on energy balance with the potential to explore ethnic-related differences. This programme of PhD work will also develop understanding of the barriers and facilitators

to weight management providing vital information for optimising the therapeutic treatment of obesity in an at-risk population. This work is imperative for reducing ethnic health inequalities in obesity and enhancing obesity treatment in South Asians through effective and culturally appropriate mechanisms.

Aim: To investigate the synergistic effects of pharmacological obesity treatment and lifestyle modification on appetite, energy balance and weight management in South Asians and white Europeans with overweight or obesity.

Background:

Obesity is a chronic, progressive, multifaceted condition associated with profound morbidity, mortality and economic consequences^[4,5]. Obesity prevalence continues to rise globally^[6], and in England, 28% of adults were classified as obese in 2019 with a further 36% classified as overweight^[7]. Lifestyle interventions targeting physical activity and diet provide the foundation of initial weight management strategies^[8], but often lead to insufficient sustained weight loss^[9]; therefore, adjunctive pharmacological obesity treatments are increasingly recommended for long-term weight management^[8,10].

Recent advances in gut hormone-based pharmacotherapy, including the GLP-1RA semaglutide, have demonstrated clinically relevant, sustained weight loss and amelioration of obesity-related comorbidities^[11-13]. Existing clinical trials are primarily composed of white populations^[14] while responses in South Asians specifically are unknown. Semaglutide-induced weight loss occurs through reduced energy intake associated with decreased appetite, reduced food cravings and altered food preferences^[15,16]. These effects are thought to arise from direct and indirect effects on appetite-related brain regions^[17], but supporting evidence for central (brain) effects is lacking in humans.

Supplementing obesity pharmacotherapies with exercise may augment weight loss maintenance and longer-term health including preserving fat free mass (FFM) and improving insulin sensitivity and cardiorespiratory fitness^[18]. The potential to gain non-pharmacological benefits from structured exercise and improved 24-h movement behaviours (limiting sitting, and increasing stepping, physical activity and sleep quality^[19]) would be favourable for South Asians who typically exhibit greater fat mass and insulin resistance, and lower FFM and cardiorespiratory fitness than white Europeans^[1].

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