

**Project title: Early-onset type 2 diabetes, nationwide investigation of etiology and prognosis.**

Background

T2D is increasing rapidly in younger people (age <40) which is alarming since there is evidence to suggest that they develop a more aggressive form of T2D, with far worse prognosis than both T1D and T2D with onset at later ages<sup>1</sup>. There is a need for targeted interventions to halt this development and mitigate the adverse consequences of those affected<sup>2</sup>. Research on factors influencing the risk of early-onset T2D, as well as factors contributing to poor prognosis is limited and the few available studies are based on selected samples. Studies on early-onset T2D in Sweden and other Nordic countries is almost non-existent.

Objectives

The overall aim is to contribute with new knowledge on the causes and consequences of early-onset T2D. The specific aims are to:

- **Evaluate potential causes** of early onset T2D (heritability, perinatal factors, adverse socioeconomic/demographic background, environmental factors, disorders diagnosed during childhood/young adulthood and lifestyle).
- **Determine consequences** of early-onset T2D (mortality, micro- and macrovascular disease) and the prognostic role of lifestyle, sociodemographic, cardiometabolic and genetic factors, glucose control, insulin resistance and beta-cell function.
- **Build models to predict** a) who will develop early-onset T2D and 2) who will have the worst prognosis.

Methodology

We have created a cohort consisting of the entire Swedish population, identified relatives within the cohort and retrieved information from many nationwide, high-quality registers covering more than a 30-year time span. This makes it possible to combine traditional cohort designs with family-based designs to minimize confounding and for familial aggregation studies and for quantification of heritability using previously described methods<sup>3</sup>. We can also study a range of exposures across the life course. We can also follow all early-onset T2D patients in Sweden from diagnosis and assess the risk of micro- and macrovascular disease comparing them to those without diabetes, late-onset T2D and adult-onset type 1 diabetes, seeking to clarify to what extent suboptimal treatment, comorbidity, metabolic risk factors, lifestyle and sociodemographic factors contributes to poor outcomes. To get detailed genetic and phenotype data (e.g. insulin resistance/secretion) unavailable in registers, we will also use data from the ANDIS (All New Diabetics In Scania) biobank<sup>5</sup>. This is a regionally representative subsample of Swedish diabetes patients. In addition to traditional epidemiological/statistical modelling, we will use machine learning, i.e. Random Forest models<sup>6</sup> to predict early-onset T2D based on all available information retrieved during early life, childhood, adolescence and young adulthood, including lifestyle behaviors, environmental exposures, socio-demographic traits, family history of diabetes and medical history. We will use the same models to predict adverse vascular events and these models will, in addition, include information on clinical variables and treatment from the National Prescribed Drug and Diabetes Registers.

Work plan (including description of the work the postdoc fellow will perform)

The post doc will join the research group of the mentor and work together with the mentor and seven colleagues (including a senior biostatistician) in the diabetes epidemiology group at IMM. It is a collaborative project conducted together with Professor and senior consultant in endocrinology, Tiinamaija Tuomi at Helsinki University Hospital, Professor Thomas Nyström at KI, and senior lecturer Emma Ahlqvist at Lund University (PI of ANDIS) and the post doc will have access to their expertise and networks. The task of the post doc includes formulating hypothesis, drafting protocols, data management and analysis, writing papers and presenting the findings at international conferences. This is a highly suitable post doc project since: 1) it is novel and internationally unique; 2) feasibility is excellent as most of the data is already available, the necessary expertise is available and the Nordic team has a long-standing collaboration; 3) the post doc may play a key role in its realization and choose the path that aligns with his/her interests, which allows for independent growth as a researcher and 4) it fills a major knowledge gap and can be expected to generate a number of important publications.

Relevance of project for diabetes

A rise in T2D among adolescents and younger adults has raised concerns due to its aggressive nature and poor prognosis. International research on early-onset T2D is limited, with Swedish research almost non-existent. We will address critical knowledge gaps regarding the causes and consequences of early-onset T2D in Sweden. To our knowledge, this is the most comprehensive research effort on early-onset T2D to date. The ultimate goal is to be able to identify high risk individuals and key factors contributing to poor prognosis in order to improve primary and secondary prevention.

References:

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- 4 Wei Y, Liu S, Andersson T, Feychting M, Kuja-Halkola R, Carlsson S. Familial aggregation and heritability of childhood-onset and adult-onset type 1 diabetes: a Swedish register-based cohort study. *Lancet Diabetes Endocrinol.* 2024 Mar 28:S2213-8587(24)00068-8.
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