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Inter-SUSTAIN Part 2 (researchers)

Project title: Metabolic Signatures: Coupling incretin and glucagon pathways with metabolic traits in cardiometabolic disease progression
Application number: 0114548
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Administrating institution: Aarhus Universitet

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Applicant

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Administering Institution

Administering Institution

1-1 of 1

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Proposal

Question set

Please select the relevant database from the list (up to two per research proposal).
The Fenland Study

Please select the relevant database from the list (up to two per research proposal).
The Fenland Study

Project Information

Project title
Metabolic Signatures: Coupling incretin and glucagon pathways with metabolic traits in cardiometabolic disease progression

Brief project description
Incretin hormones play a pivotal role in glucose homeostasis; modulating insulin secretion, glucagon release, gastric motility and appetite. GLP1-RA therapies have shown remarkable weight effects and are used for obesity management in people without diabetes. However, little is known about variation

in natural incretin responses (in the absence of GLP1-RA treatment) at the population level and the role it plays in defining trajectories of cardiometabolic risk deterioration and risk of progression to type 2 diabetes.

This project investigates the causal role of natural incretin and glucagon responses, aiming to identify their role as drivers of progression toward diabetes and diabetes related complications. The project will use data from the deeply phenotyped Fenland Study (UK).

The Fenland Study is a population-based cohort that combines OGTT based incretin and glucagon measurements, genotyping, proteomic and metabolomic assessments, DEXA derived adiposity measures, liver function biomarkers, and long term cardiometabolic outcomes. The study includes three phases of examination from 2005 to 2025, which allows for the assessment of individual trajectories in cardiometabolic risk. We will validate findings in the Danish ADDITION-PRO study and the UK Biobank. The project is divided into three parts. First, using traditional and novel causal inference methods, including genetically predicted and phenotypically measured traits, we aim to determine the causal relationship between incretin/glucagon responses and long term cardiometabolic outcomes and to identify mediating pathways such as liver health and inflammation. Second, we aim to decipher the impact of incretin/glucagon phenotypes in conjunction with the metabolic traits that drive long-term cardiometabolic risk. Third, we will apply machine learning methods to assess how natural incretin and glucagon responses can help to refine metabolic clusters with distinct risk profiles in addition to clinical and omics data.

Project description

This Inter-SUSTAIN Part 2 project aims to use the Fenland study to elucidate the role of natural incretin and glucagon responses to a standard 75g oral glucose tolerance test (OGTT) as drivers of heterogeneity in the long-term risk of diabetes and related complications, and to map clinical and biological traits associated with these responses, with particular emphasis on liver health, adiposity, and inflammation. In doing so, we aim to identify different (heterogeneous) patterns of metabolic dysfunction that may be linked to different risk of progression to type 2 diabetes and inform personalized treatment strategies.

The specific aims are to:

a. Phenotypically and genotypically investigate the causal role of natural incretin and glucagon responses to an oral glucose tolerance test (OGTT) in determining the risk of regression to normoglycemia, progression to type 2 diabetes, and the development of diabetes-related complications. This will be conducted using data from the Fenland study and the Danish ADDITION-PRO cohort, linked to comprehensive outcomes from the Danish National Health Registries.
b. Identify metabolites and biomarkers for liver health, adiposity and inflammation that mediate the association between phenotypically measured (Fenland study, ADDITION-PRO) and genetically predicted (Fenland study, ADDITION-PRO, UK Biobank) incretin and glucagon responses and cardiometabolic outcomes, with particular emphasis on direct and indirect markers of liver function and fat accumulation.
c. Map dimensions of metabolic traits in conjunction with incretin and glucagon responses to understand their role as drivers of deteriorating glucose metabolism and their relationship to long-term cardiometabolic health.
d. Derive and validate clustered dimensions of metabolic traits using clinical markers,

metabolites, and genes, assess the added value that natural and/or genetically predicted incretin and glucagon responses have to the definition of these clusters.

Pre-diabetes is a complex state associated with increased risk of progression to type 2 diabetes and related complications[1–3]. However, not all people with pre-diabetes progress to diabetes; many persist in the prediabetic state or regress to normoglycemia over the course of various years[2]. Remis sion to normoglycemia has been shown to reduce the risk of cardiovascular morbidity and mortality[4], however, it remains unclear to which extend if the remission is driven by lifestyle changes or by biological heterogeneity that defines a low-risk subgroup among people with pre-diabetes.

Recently the idea of metabolic heterogeneity in type 2 diabetes has been extended to pre-diabetes, and traits that distinguish individuals most likely to progress to diabetes, such as insulin-resistant fatty liver and visceral adiposity-related renal dysfunction, have been identified[1]. In recent years, incretins (Glucagon Like Peptide 1 [GLP 1] and Gastric Inhibitory Polypeptide [GIP]) and the hormone glucagon have gained increasing attention as targets in therapeutics for prevention of type 2 diabetes and diabetes-related complications[5–9]. GLP-1 and GIP enhance post-meal insulin secretion, supporting efficient nutrient handling[10]. Glucagon serves as a counter-regulatory hormone to insulin and maintains glucose balance both during fasting and following glucose intake[11]. However, in the context of heterogeneity in pre-diabetes, the role of natural incretin and glucagon responses for the progression to type 2 diabetes and diabetes-related complications remains unexplored. Prior research in the Danish ADDITION-PRO study showed that, individuals with pre-diabetes and type 2 diabetes exhibited up to 25% lower natural GLP-1 responses to oral glucose[12]. Additionally, impaired glucagon suppression and elevated fasting glucagon levels have been observed in individuals with insulin resistance and early glucose dysregulation[13], involving hepatic insulin resistance that impairs the turnover of branched-chain amino acids[14]. However, these findings have been limited investigated in relation to prospective cardiometabolic outcomes[15]. A limitation of the ADDITION-PRO cohort is the selection of individuals at high risk of diabetes based on diabetes-specific risk scores, which limits the generalizability of the findings to the broader populations.

The Fenland Study is a pioneering population-based cohort that has advanced precision in identifying individuals at high risk of type 2 diabetes[16] and elucidating causal pathways underlying cardiometabolic disease[17–20]. Leveraging extensive phenotypic and genetic data, Fenland has established causal relationships between liver function markers, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), and type 2 diabetes[17], as well as between DEXA-derived adiposity traits and metabolic dysfunction-associated liver disease[20]. Mec hanistic links between interleukin-6–mediated inflammation and type 2 diabetes have also been uncovered[21], highlighting the interplay between inflammatory and metabolic pathways. This precise characterization of adiposity, inflammation, hepatic health, and incretin–glucagon dynamics provides an unparalleled resource for investigating metabolic heterogeneity and its long-term impact on cardiometabolic health.

We hypothesize that dysregulated incretin secretion and inadequate glucagon suppression (assessed during a standard 75g OGTT), together with insulin resistance, accelerate metabolic dysfunction by activating hepatic and inflammatory pathways in individuals at high risk of diabetes.

This hypothesis will be tested through three work packages:

Work Package 1: Investigate causal relationship of neutral release of incretin and glucagon and long-term cardiometabolic disease and identify mediating pathways.

Hypothesis for Work Package 1: Natural incretin and glucagon responses play a causal role as drivers of the risk of progression from pre-diabetes to type 2 diabetes and diabetes-related complications as well influence cardiometabolic trajectories. In this pathway, biomarker and metabolites related to liver health play a mediating role.

Natural incretin and glucagon reposes in epidemiological studies have been mostly investigated cross-sectionally, with a few exceptions[15]. The Fenland study includes ~12,000 individuals at baseline who underwent measurement of natural incretin and glucagon responses during a 2-point (0, 120 min) OGTT in 2005-2015, i.e. before the introduction of incretin based therapies. This unique timing provides an opportunity to prospectively analyze the associations between individuals' natural hormonal responses to glucose and progression to diabetes, regression from prediabetes to normoglycemia, and risk of diabetes-related complications. Preliminary findings from ADDITION PRO in a population with high risk of diabetes showed that higher glucagon (incidence rate ratio (IRR) per SD: 1.38 CI: 1.15 to 1.67) and GLP-1 responses (IRR: 1.34 CI: 1.05 to 1.71) at 120 minutes during the OGTT are associated with incident heart failure over an 11-year follow-up period.

Genetic variants, clinical biomarkers and metabolites serve as valuable indicators of individual predisposition for specific phenotypes and mediating pathways (metabolites and clinical biomarkers) that link phenotypes to disease outcomes. We aim to use newly developed GLP-1, GIP, and glucagon polygenic risk scores (PRS) to strengthen causal inference by applying them as instrumental variables in multi-sample Mendelian randomization studies[22]. We further aim to identify metabolic pathways that mediate the effect of genetically determined incretin/glucagon phenotypes on the incidence of diseases such as type 2 diabetes, to help us understand the biological mechanisms that link variability in these traits to disease. This understanding may in turn support the development of new targeted diagnostica approaches and interventions based on metabolic pathways.

Work Package 2: Mapping metabolic dimensions and their interaction with incretin and glucagon responses

Hypothesis: Incretin and glucagon responses may exert protective or compensatory effects under conditions of obesity, hyperglycemia, insulin resistance, and beta-cell dysfunction, with liver health and inflammation as effect modifiers.

Obesity and insulin resistance are central drivers of type 2 diabetes. Recent clustering analyses highlight liver fat as a key determinant of heterogeneity among individuals with prediabetes regarding progression risk[1]. Reduced liver function interacts with insulin resistance, glucose and glucagon responses, and is accompanied by low-grade inflammation and morphological changes, particularly MAFLD[11,14,23,24]. GLP-1 and GIP reduce hepatic inflammation[25], underscoring liver function as a central pathway modulating diabetes risk and interacting with incretin and glucagon responses.

The Fenland Study includes liver biomarkers (γ-glutamyl transferase, ALT) and ultrasound-based liver measurements[26]. Deep learning processing of ultrasound images, combined with these biomarkers, will enable calculation of a general liver health indicator. We will integrate markers of

low-grade inflammation (IL-6, adiponectin, CRP)[27] and metabolomics data (acylcarnitines, amines, sphingolipids, phospholipids) to characterize metabolic function, including liver fat accumulation[28] and tissue-specific insulin resistance[29,30].

Using phenotypes, metabolites, and genotypes, we aim to identify metabolic traits that, alongside incretin and glucagon responses, contribute to cardiometabolic risk. Machine learning–based dimensionality reduction methods will identify clusters of metabolic traits, enriched with metabolite profiles for deeper characterization. Genetic data will be incorporated through partitioned polygenic risk scores (PRS) for type 2 diabetes[31,32], combined with metabolic traits such as incretin and glucagon responses, inflammation, beta-cell function, obesity, liver fat, and insulin resistance. This approach will help decipher phenotypes driven by genetic risk and metabolic traits contributing to cardiometabolic disease.

Work Package 3: Predicting incretin and glucagon responses and metabolic dimensions using clinical and biological traits

Hypothesis for Work Package 3: Population heterogeneity of incretin and glucagon responses in conjunction with metabolic traits can be predicted to a clinically useful degree based on clinical, genetic and metabolic biomarkers, and these predictions can stratify individuals by their risk of progression to type 2 diabetes and related complications.

Given the fact that it is impractical to assess a full incretin and glucagon response in clinical practice, WP3 aims to establish a practical set of biomarkers that jointly have the capacity to characterize incretin and glucagon responses. In addition, we will predict metabolic dimensions and clusters identified in Work Package 2. Analyses in the Fenland study will be carried out across three levels: (1) traditional clinical characteristics, (2) metabolomics profiles, and (3) genomic data. The predictive utility of these traits will be evaluated in relation to cardiometabolic outcomes in large population-based cohorts that include the same biomarkers but lack incretin and glucagon measurements, such as the UK Biobank, and through available markers in Danish registries.

Study description

Table 1 displays the characteristics of the Fenland and ADDITION-PRO[33] studies, highlighting their similarities. To further validate findings and predicted characterizations we will also use data from the UK Biobank[36] as a validation cohort. UK-Biobank does not include incretin/glucagon measurements but pathway-specific polygenic risk scores (PRS) of incretin responses can be calculated. It has extensive clinical and -omic characterisation and follow-up for incident diabetes and cardiovascular events.

Causal inference analysis

To quantify the causal relationship between incretins, glucagon, and cardiometabolic disease, we will apply traditional time-to-event analysis methods (Poisson and Cox regression) within the Fenland Study, using adjustments informed by directed acyclic graphs (DAGs). We will also characterize trajectories of cardiometabolic profiles, including glucose, lipids, kidney function, adiposity markers from DEXA, liver markers, and inflammatory biomarkers, using linear mixed-effects models.

To strengthen causal inference and account for unmeasured confounding, we will conduct Mendelian

randomization analyses using pathway-specific PRS as instruments for incretins and glucagon[22], lev eraging data from the Fenland Study, ADDITION-PRO, and the UK Biobank[37].

To identify mediating pathways and key metabolites linking incretin and glucagon responses to cardiometabolic disease, we will apply a structural causal algorithm (NetCoupler)[38] to detect sequential causal pathways involving metabolites. Based on these findings, structured causal mediation analyses[39] will quantify direct and indirect effects of candidate metabolites on cardiometabolic outcomes, as illustrated in Figure 1 (Structural causal analysis framework for the association between incretin/glucagon responses and progression of cardiometabolic risk).

Machine learning analysis

Multidimensional profiling: Dimension reduction and clustering

Evaluating the risk associated with incretin and glucagon responses to a glucose load in isolation is limited without considering concurrent insulin, glucose regulation, and other metabolic traits. To address this, we will apply principal component analysis (PCA) and uniform manifold approximation and projection (UMAP) to capture the strongest sources of variance in the combined OGTT response across all four hormones and glucose.

Building on this framework, we will leverage data from previous work in The Fenland Study and ADDITION-PRO, which include genotypes, metabolomic profiles, and markers of metabolism and inflammation[12,13,27,33–35,40]. By combining liver function biomarkers derived from imaging and blood measurements, we aim to generate a comprehensive, multidimensional indicator of liver health.

PCA and UMAP will then be used to integrate these variables and identify key metabolic dimensions that reflect the interplay between incretin and glucagon responses alongside glucose–insulin dynamics during the OGTT[41]. We will further incorporate dimensions related to obesity, insulin resistance, inflammation, and liver health markers, and examine their associations with diabetes risk [42]. Finally, metabolite-based profiles and partitioned polygenic risk scores (PRS) will be analyzed separately in relation to cardiometabolic outcomes and then integrated to enrich the multidimensional metabolic profiling. The process is illustrated in Figure 2.

Prediction of metabolic clusters

To predict incretin and glucagon responses based on clinical and metabolite data, we will apply a two-layered modeling approach in the Fenland study. Clinical and metabolic profiles will be used separately and in combination to predict responses. For variable selection in both layers, we will apply two strategies: restricting variance and using linear LASSO regression to shrink and select the most predictive variables. To support this, we will employ machine learning models to capture undefined interactions and identify important predictors based on variable importance[43]. Our approach follows established principles in machine learning and statistical modeling, adhering to standardized practices for prediction, reporting, and validation[44–47].

These PRSs will be incorporated into the aforementioned predictive layers as composite predictors of incretin and glucagon responses. PRS for other relevant traits such as obesity, insulin resistance, beta-cell function, liver function and low-grade inflammation will also be considered where relevant.

This proposal is built on strong and longstanding collaborative connections between the MRC Epidemiology Unit at the University of Cambridge, Aarhus University, and Steno Diabetes Center Aarhus. As part of the collaboration between the MRC Epidemiology Unit and the Novo Nordisk Foundation Center for Basic Metabolic Research, a research group is developing polygenic risk scores (PRS) for GLP-1, GIP, and glucagon. We will leverage and deploy these PRS within this project to strengthen causal inference and improve metabolic clustering in cardiometabolic medicine.

The MRC Epidemiology Unit, through the mentorship of experts in the Fenland Study, including Professor Nicholas Wareham and Professor Simon Griffin, will serve as primary international hosts and scientific advisors. Their role, together with their research teams, will encompass three key areas:

1. Data Provision and Oversight: Granting access to the Fenland Study (n = 12,435) and providing training to ensure a comprehensive understanding of the cohort and its data.

2. Methodological exchanges: Facilitating the exchange of methods between the MRC Epidemiology Unit and the Epidemiology group at Aarhus University, with guidance in causal inference (including Mendelian randomization and mediation analysis) and machine learning techniques.

3. Validation Expertise: Supporting the harmonization of data between the Fenland Study, ADDITION-PRO, and UK Biobank to validate identified metabolic profiles and mediating pathways, such as liver health and inflammation, across diverse geographical and demographic contexts.

The project has a 3-year duration and is structured on the work of 1 post-doctoral researcher and 1 PhD student, who will both work under the direct supervision of the PI, with regular visits to Cambridge. The synergy with the MRC Epidemiology Unit will establish an ongoing institutional bridge through PI visits, postdoctoral stays, and PhD exchanges. Regular scientific exchange will be maintained via joint virtual meetings to align analytical protocols used in the Fenland Study. This collaboration serves as a start for long-term data integration between Danish and UK cohorts, creating a permanent channel for investigating heterogeneity in risk of type 2 diabetes. By combining Danish clinical depth with the UK's extensive population-based datasets, we strive to create a powerful framework to move from observational data to causal understanding and clinical decision-making aids. The implementation plan is outlined in the Gantt chart (Figure 3).

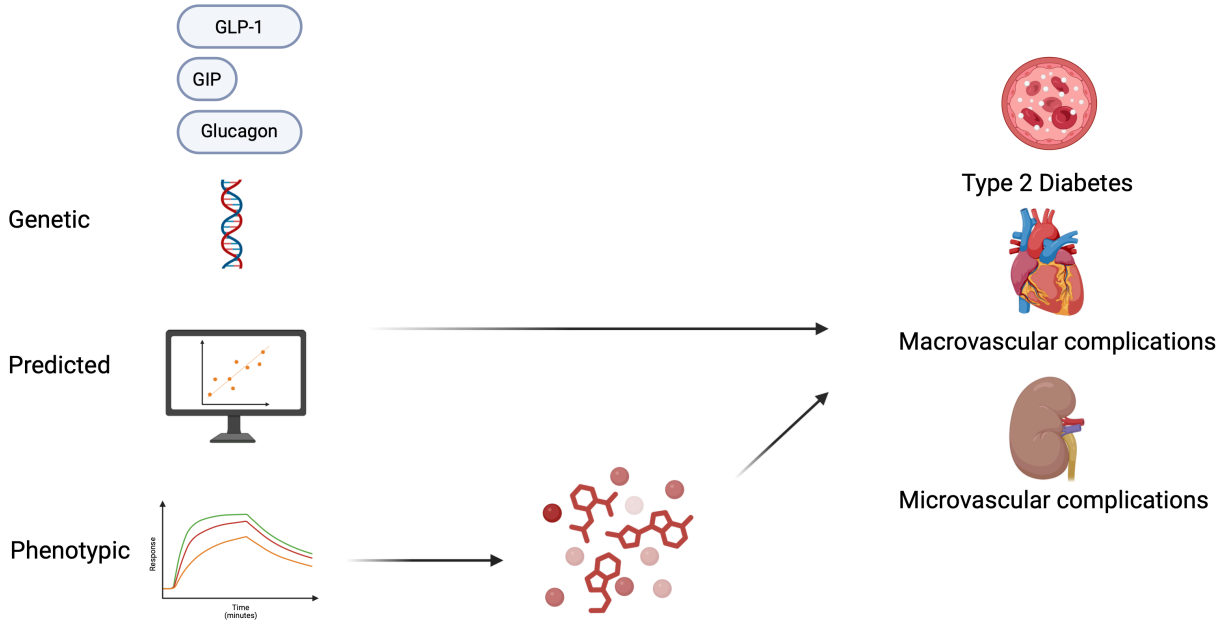
This Inter-SUSTAIN project has the ambition to advance precision diabetes prevention by elucidating the causal role of natural incretin/glucagon responses as determinants of longitudinal changes in cardiometabolic risk, and developing easily applicable models to integrate these insights in the characterization of heterogeneity in prediabetes. The broader view is ultimately to enable tailored decision-making, identifying those at greatest risk of progression to diabetes and those most likely to

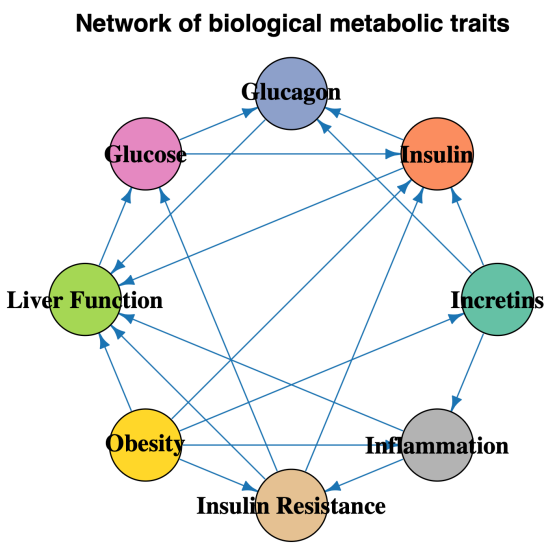
achieve remission. This work is directly connected to the objectives of the Novo Nordisk Foundation-funded Steno National Collaborative project DP-Next, which seeks to develop strategies for diabetes prevention based on better risk prediction and understanding of heterogeneity[48] (specifically Work Package 3 (Heterogeneity)).

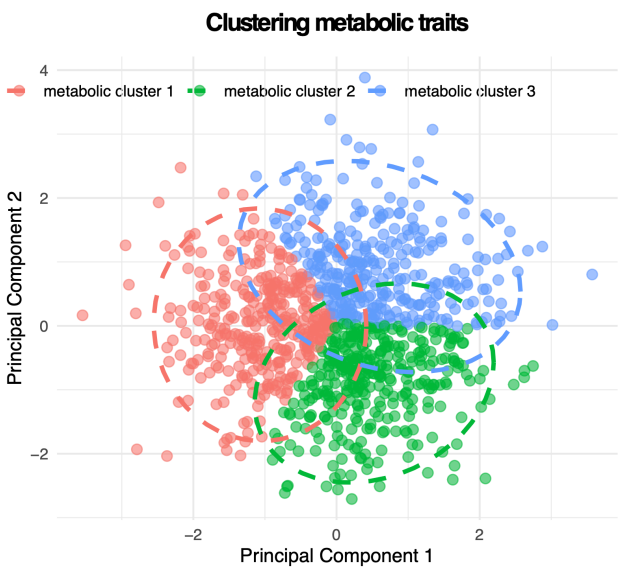
The Fenland and ADDITION-PRO studies are unique in having large-scale measurements of natural incretin/glucagon responses to an OGTT obtained before the introduction of GLP1-RA therapies. Their deep phenotyping and long-term follow-up will enable the best possible view of the contribution of incretin/glucagon physiology to long-term cardiomatabolic risk.

Metabolic Signatures: Coupling incretin and glucagon pathways with metabolic traits in cardiometabolic disease progression

Uploads




Network of biological metabolic traits
Glucagon
Glucose
Insulin
Liver Function
Incretins
Obesity
Inflammation
Insulin Resistance


Clustering metabolic traits
metabolic cluster 1
metabolic cluster 2
metabolic cluster 3
Principal Component 2
Principal Component 1
4
2
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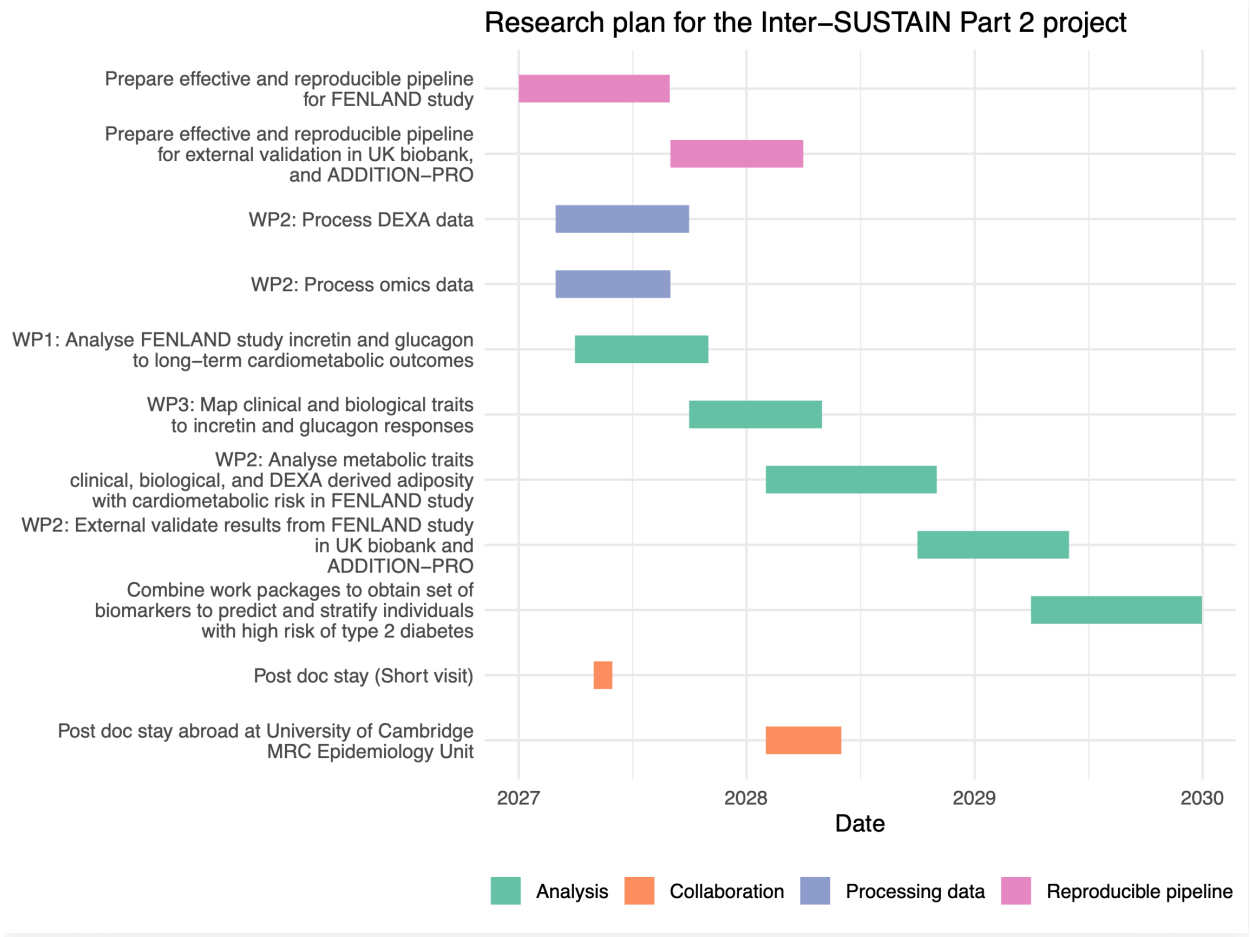
Research plan for the Inter–SUSTAIN Part 2 project
Prepare effective and reproducible pipeline for FENLAND study
Prepare effective and reproducible pipeline for external validation in UK biobank, and ADDITION–PRO
WP2: Process DEXA data
WP2: Process omics data
WP1: Analyse FENLAND study incretin and glucagon to long–term cardiometabolic outcomes
WP3: Map clinical and biological traits to incretin and glucagon responses
WP2: Analyse metabolic traits clinical, biological, and DEXA derived adiposity with cardiometabolic risk in FENLAND study
WP2: External validate results from FENLAND study in UK biobank and ADDITION–PRO
Combine work packages to obtain set of biomarkers to predict and stratify individuals with high risk of type 2 diabetes
Post doc stay (Short visit)
Post doc stay abroad at University of Cambridge MRC Epidemiology Unit
2027
2028
2029
2030
Date
Analysis
Collaboration
Processing data
Reproducible pipeline

Study description

Feature	Fenland study	ADDITION-PRO Study
Baseline data collection period	2005-2015 (Phase 1)	2009–2011
Follow-up	2014-2020 (Phase 2) 2023-2025 (Phase 3)	Danish National Registries (up to 2024)
Included participants	UK general population aged 30-55 years	Individuals at high risk of diabetes
Number of participants	12,435	2,082
Measure from OGTT	GLP-1, GIP, glucagon, glucose and insulin (t= 0, 120 min)	GLP-1, GIP, glucagon, glucose and insulin (t= 0, 30, 120 min)[12,13,33]
Other relevant metabolic measures	**Adiposity from DEXA scan:** - Visceral and subcutaneous fat - Bone density **Liver function:** - Ultrasound liver images - GGT, ALT - glucagon – alanine index - Alkaline Phosphatase **Inflammation:** - Interleukin 6 (IL-6), high sensitivity CRP, adiponectin	**Adiposity:** - Visceral and subcutaneous fat from ultrasonography **Liver function:** - Ultrasound liver images (still B-mode images with liver protocol) - GGT, ALT - glucagon – alanine index **Inflammation:** - soluble CD163, and high sensitivity CRP, adiponectin
Assessment method of metabolites	LC electrospray ionization and flow-injection analysis tandem MS (ref), targeted metabolomics	Proton nuclear magnetic resonance spectroscopy, targeted metabolomics[34]
Sample tissue	Fasting plasma blood samples	Both fasting and during the OGTT[34,35]
Number of metabolites	175 (acylcarnitines, amines, sphingolipids and phospholipids)	231 lipid-related and 3 BCAA (fasting isoleucine, leucine and valine levels)
Genotyping	Yes	Yes

Genotyping	Yes	Yes
Follow-up period	10-15 years	13-years
Outcome	**Metabolic-related outcomes:**	**Metabolic-related outcomes:**
	- Progression to type 2 diabetes	- Progression to type 2 diabetes
	- Regression to normoglycemia	- Regression to normoglycemia
	- Glucose, lipids and kidney function, inflammation, adiposity trajectories	- Glucose, lipids and kidney function trajectories
	Macrovascular complications:	**Macrovascular complications:**
	- Ischemic cardiovascular disease	- Ischemic cardiovascular disease
	- Heart failure	- Heart failure
	Microvascular complications:	**Microvascular complications:**
	- Chronic kidney disease	- Chronic kidney disease

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Lay project description

Type 2 diabetes develops differently from person to person, and today we cannot easily identify who is most at risk. This project uses data from the large British Fenland Study to understand how two natural hormones related to the body's response to food, incretin and glucagon, influence a person's long-term risk of developing diabetes and its complications. By combining hormone measurements with information on liver health, body fat, inflammation, genes and metabolism, we aim to discover why some people progress to diabetes and related cardiometabolic diseases while others do not. The project will also create simple tools that can help identify people who may benefit from early and targeted prevention.

Type of Research
Translational Medical Research, Epidemiological Research

Research Methods / Subjects
Humans / Patients

Research Keywords
Diabetes, Disease Mechanisms, Epidemiology, Genetics, Precision Medicine

Budget

Project Overview

Requested project start date:	01/01/2027	**Requested project end date:**	31/12/2029

Budget

Requested project period in full years: 3

Budget summary

Year ->	1	2	3	Total
Salary	1.165.000 DKK	1.199.950 DKK	798.328 DKK	3.163.278 DKK
Operation	145.000 DKK	31.000 DKK	32.000 DKK	208.000 DKK
Dissemination	105.000 DKK	105.000 DKK	105.000 DKK	315.000 DKK
Project Supplement	500.000 DKK	500.000 DKK	312.500 DKK	1.312.500 DKK
Total	1.915.000 DKK	1.835.950 DKK	1.247.828 DKK	4.998.778 DKK

The detailed budget is available in NORMA.

Total requested budget: 4.998.778
Total project cost: 4.998.778

Supplementary information
Budget Justification
The total requested funding for the project period 2027–2029 is DKK 4,998,778. The budget has been prepared in accordance with the NNF Inter-SUSTAIN guidelines and the joint agreement between Universities Denmark and the Novo Nordisk Foundation regarding project supplements for Danish universities.
1. Personnel (FTE)
The research team consists of 2.0 Full-Time Equivalents (FTEs) annually, ensuring dedicated scientific focus on the project objectives:
Postdoctoral Researcher (1.0 FTE for 3 years): Responsible for the primary data analysis, coordination with the selected database custodian, and manuscript preparation. Salary is based on Aarhus University's standard scales, including a 3% annual inflation/COLA adjustment.
PhD Student (1.0 FTE for 2 years, 0.25 FTE in the 3rd year): Will focus on sub-aims 1 and 2 of the project. A PhD Tuition Fee of DKK 60,000 per year is included (total DKK 180,000). In the 3rd project year the remaining 0.75 FTE will be obtained through application for co-funding from Aarhus University, Department of Public Health.
2. Operating Expenses
Smaller Equipment (DKK 115,000 in the first year): This allocation covers the purchase of high-performance computing (HPC) workstations required for handling large-scale datasets and specialized software licenses for epidemiological modeling.
Software/Data licenses: (DKK 93,000 over 3 years): will cover fees for data access (UK Biobank) and software licenses.

Travel (DKK 15,000/year including conference fees): Funds are requested for the Postdoc and PhD student to present research findings at major international conferences (e.g., EASD or ADA) and for project coordination meetings with international collaborators at MRC Epidemiology unit at Cambridge University. This is within the DKK 25,000 annual cap.
Publication (DKK 30,000/year): To ensure maximum visibility and impact, we aim to publish in high-impact, open-access journals. These funds cover Article Processing Charges (APCs).
3. Project Supplement (Danish Universities Only)
As the project is anchored at Aarhus University, a project supplement for research grants is included. This follows the standardized model which replaces traditional overhead, bench fees, and administrative support.
Rate: DKK 250,000 per scientific FTE (Postdoc and PhD) per year.
Total: DKK 500,000 annually. This supplement covers indirect costs including office space, IT infrastructure, and administrative support (HR, finance, and legal) provided by the host institution.

Additional Contributions for the Project

Received from the administering institution:
Received from other sources:
Applied for from other funding sources:

Information for additional contributions
We will apply for co-funding for the PhD student salaries from Aarhus University Graduate School of Health and from the Department of Public Health. Based on previous experience we expect 9 months of PhD student salary to be co-funded in the third year of the project (DKK437620). We have not yet applied for this funding, but will do so as soon as the PhD candidate has been selected and submits their PhD protocol.

Appendices

Inter-Sustain Evaluation Committee,
Novo Nordisk Foundation, Copenhagen

9th February 2026

Dear Colleagues,

RE: Letter of Support; Daniel Witte et al entitled "Metabolic Signatures: Coupling incretin and glucagon pathways with metabolic traits in cardiometabolic disease progression"

As Head of the MRC Epidemiology Unit, University of Cambridge, I write to confirm our strong support for Daniel Witte's application as it aligns well with our strategic aim of advancing precision prevention strategies for type 2 diabetes and related cardiometabolic complications.

We are happy to commit to:
Data Access and Collaboration. We will provide access to the Fenland Study data (n = 12,435 participants) and support harmonization of data between the Fenland Study, ADDITION-PRO, and UK Biobank for validation purposes.
Methodological Mentorship. We will offer guidance in advanced epidemiological methods to PhD students and Postdocs working in the analysis team on techniques including causal inference and Mendelian randomization, to strengthen the project's analytical framework.
Scientific Exchange and Infrastructure. We will facilitate regular scientific exchange through joint meetings and provide expertise in integrating genetic, metabolomic and phenotypic data for precision epidemiology.

We look forward to collaborating on this project and contributing to its success. Please do not hesitate to contact us for further information.

Yours sincerely,

Professor Nick Wareham FMedSci FRCP FFPHM
PI- Fenland Study
Director, Medical Research Council Epidemiology Unit and Co-Director, Institute of Metabolic Science
T: +44 (0)1223 330315
E: nick.wareham@mrc-epid.cam.ac.uk

Medical Research Council Epidemiology Unit
University of Cambridge School of Clinical Medicine, Box 285, Institute of Metabolic Science,
Cambridge Biomedical Campus, Cambridge CB2 0QQ

Hosting Confirmation for Use of the Fenland Study in the Novo Nordisk Foundation INTER-SUSTAIN Part 2: Research Projects

To Whom It May Concern,
I hereby confirm that Department of Public Health, Aarhus Univeristy will host the above-mentioned project led by Daniel R. Witte as part of the Inter-SUSTAIN initiative. The institution agrees to the following:

1. Project Hosting and Infrastructure
   The project will be hosted at the Department of Public Health, which will provide the necessary infrastructure, including office space and administrative support for the management of Fenland study data and the grant.

2. Budget Agreement and Grant Administration
   The institution has reviewed and agreed to the submitted budget and will manage any potential grant in accordance with this budget and institutional financial policies.

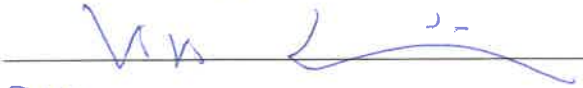
3. Terms of Employment
   The main applicant's employment at Department of Public Health is secured for the duration of the project. Funding for the main applicant's salary is guaranteed under existing institutional arrangements.

We look forward to supporting this important research, which aims to elucidate the role of natural incretin and glucagon responses in the progression of pre-diabetes and related cardiometabolic complications, leveraging data from the Fenland Study, with validation in the Aarhus University–accessible ADDITION-PRO cohort and UK Biobank.

Should you require any further information, please do not hesitate to contact us.

Sincerely,
Vice Deputy for Research Vivi Schlünssen, on behalf of Head of Department
Department of Public Health, Aarhus University

Name: Vivi Schlünssen

Signature: 

Date: 9/2-2026

Department of Public Health

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Bartholins Allé 2, 8000 Aarhus C
Danmark

Date: 9 February 2026

Inter-Sustain Evaluation Committee,
Novo Nordisk Foundation,
Copenhagen

9th February 2026

Dear Colleagues,

RE: Letter of commitment; the Fenland Study for the grant by Daniel Witte et al entitled "Metabolic Signatures: Coupling incretin and glucagon pathways with metabolic traits in cardiometabolic disease progression"

As Chief PI of the Fenland Study I write to provide confirmation that we gladly support this application to the Inter-SUSTAIN Part 2: Research Projects call.

Confirmation of Suitability, Feasibility, and Appropriateness of the Fenland Study Data
I confirm that the data requested in the proposal from the Fenland Study (listed at the end of this letter) are available, suitable, feasible to access and appropriate for the scientific aims of the project. We also confirm that these data align with the needs of the proposed analytical framework ie. to investigate causal inference, longitudinal trajectories, mediation, clustering, and prediction models. No new participant-level data will be collected and all work will comply with existing ethical approvals.

Commitment to No-Payment Access
If the project is funded under the Inter-SUSTAIN Part 2 call, we commit to providing no-payment access to the above-listed data types, in accordance with our governance and data-sharing policies. I can confirm the feasibility of data access within standard timelines. These limitations are standard for the cohort and do not affect the ability to carry out the analyses proposed.

Added value to the Fenland Study
I can confirm that the proposed study will provide added value to the Fenland study, most notably through the use of reproducible methods for causal inference models including pathway-specific mediation and machine-learning-based prediction models. The work will enable harmonization between the Fenland study, ADDITION-PRO, and UK Biobank and all workflow code (including data processing, analysis, and validation) will be published on GitHub for sharing reproducible workflow. These outputs will enrich the utility of the Fenland data and contribute to future precision-prevention research by creating data on metabolic trait clusters, giving improved characterisation of metabolic heterogeneity across indivduals in

the Fenland study. The study will also enable the identification of causal genotypes, metabolites, and phenotypes that influence cardiometabolic disease risk.

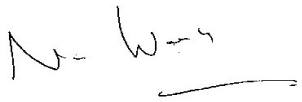
Status of Applicant and Collaborators as Users of the Database

The Principal Investigator Daniel R. Witte and his collaborating Danish partners are new users of the Fenland Study and we are delighted that they see the value in working with this detailed metabolic quantitative trait study.

Statement of Support

I am, therefore, pleased, as the Fenland Study PI to confirm our full support for this project and its ambitious scientific aims.

Yours sincerely,



Professor Nick Wareham FMedSci FRCP FFPHM
PI- Fenland Study
Director, Medical Research Council Epidemiology Unit and Co-Director, Institute of Metabolic Science

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Medical Research Council Epidemiology Unit
University of Cambridge School of Clinical Medicine, Box 285, Institute of Metabolic Science,
Cambridge Biomedical Campus, Cambridge CB2 0QQ

Requested available and accessible data types in the Fenland Study

Category	Requested Data
OGTT hormonal & metabolic measurements	Glucose, Insulin, GLP 1, GIP, Glucagon (0, 120 min)
Clinical phenotyping and biomarkers	Anthropometrics Blood pressure Lipids (fasting) Liver markers ALT, AST, GGT, ALP, glucagon–alanine index Inflammation markers IL 6, hsCRP, adiponectin
Imaging and body composition data	DEXA body composition (visceral & subcutaneous fat) Liver ultrasound imaging
Metabolomics	Targeted metabolomics (175 acylcarnitines, amines, sphingolipids, phospholipids)
Genetic data	Genome wide genotyping
Long term follow up outcomes	Incident type 2 diabetes Mortality Repeated phenotypic data from Phase 2 & Phase 3 Planned collection of outcomes in 2026 Macrovascular events (IHD, heart failure) Microvascular complications (CKD)

novo nordisk fonden

Applicant Details - Daniel Witte
Inter-SUSTAIN Part 2 (researchers) (#0114548)

Applicant Details Type: Applicant

Inter-SUSTAIN Part 2 (researchers) (#0114548) ~ Daniel Witte

Personal Details

Full Name:	Daniel Witte	**Email:**	daniel.witte@ph.au.dk
Gender:	Male	**Nationality:**	Dutch
Date of Birth:	1973-01-14	**Country of Residence:**	Netherlands
Phone:	+31628423150	**ORCID:**	0000-0002-0769-2922
Most Recent Degree:	Ph.D.	**Date of Degree:**	23/05/2003

Current Institution

Institution:	Aarhus Universitet	**Phone Number:**	+31634390007
Department:	Public Health	**City:**	Aarhus
Position:	Professor	**Country:**	Denmark

Experience

CV

Education:

2000-2003	PhD in Clinical Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands
2000-2002	MSc in Clinical Epidemiology, Netherlands Institute for Health Sciences, Erasmus University, Rotterdam, The Netherlands
1991-2000	Medical degree, Faculty of Medicine, University of Utrecht, Utrecht, The Netherlands

Current academic affiliations:

2019-present	Steno Diabetes Center Aarhus, Aarhus, Denmark
2015-present	Professor of Diabetes Epidemiology, Aarhus University, Aarhus, Denmark
2015-present	Member of the Danish Diabetes Academy, Odense, Denmark

Positions held:

2019-present	Research Group Leader, Diabetes Epidemiology Group, Steno Diabetes Center Aarhus, Aarhus, Denmark
2015-present	Professor of Diabetes Epidemiology, Aarhus University, Aarhus, Denmark
2012-2014	Principal Investigator for the Luxembourg Cohort, Luxembourg Institute of Health, Strassen, Luxembourg
2008-2012	Research Group Leader, Epidemiology research group, Steno Diabetes Center Copenhagen, Gentofte, Denmark
2009-2012	Honorary Senior Research Fellow, Department of Epidemiology and Public Health, University College London, London, UK
2003-2008	Clinical Research Fellow, Department of Epidemiology and Public Health, University College London, London, UK
2000-2003	PhD-fellow, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands
2000-2003	Duty Physician, Clinical Pharmacology Unit, Kendle International, Utrecht, The Netherlands

Teaching

2022-2024	Instructor for the elective course ‘Diet and the major chronic conditions’ (BSc Medicine, 5th semester, Aarhus University)
2020-2024	Course coordinator and main instructor for the ‘Masterclass in Public Health’ (BSc Public Health 5th semester, Aarhus University)
2024	Faculty member for the Cambridge International Diabetes Epidemiology Course, Cambridge University, UK
2016-2022	Course coordination and teaching on different Diabetes Epidemiology and Advanced Epidemiology PhD courses (Danish Diabetes Academy, Aarhus University)
2019-2021	Teaching on ‘Reproducible Research in R’ courses (Danish Diabetes Academy)
2017&2024	Faculty member for the Latin American Diabetes Epidemiology Course (GLED)

Supervision:

2006-present Main supervisor for 9 PhD students, co-supervisor for 8 PhD students and main supervisor for 10 MSc students

Awards:

2017 Harry Keen Memorial Award from the International Diabetes Epidemiology Group (IDEG) for outstanding contributions to the areas of diabetes epidemiology and public health

2006 New Investigator Award, Medical Research Council (UK)

Other Activities:

2025-present Member of the EASD programme committee

2025-present Principal Investigator and chair of the steering committee of the DP-Next Study

2017-2019 Chairman of the programme subcommittee of the International Diabetes Epidemiology Group

2016-present Member of the Steering Committee of the ADDITION-Europe study

2010-present Member of the Steering Committee of the ADDITION-Denmark study

2010-2012 Member of the Steering Committee of the Lundbeck Foundation Centre for Applied Medical Genomics in Personalised Disease Prediction, Prevention and Care (LuCAMP)

2010 & 2012 Programme organiser for the Steno Diabetes Center Symposium 'Frontiers in Diabetes'

2008-2013 Secretary and Member of the Steering Committee of the European Diabetes Epidemiology Group (EDEG)

2009-present Peer reviewer for competitive research fund applications for the EU and in several European countries (Germany, France, Denmark, UK)

2003-present Reviewer for Diabetologia, Diabetes Care, International Journal of Epidemiology, European Journal of Epidemiology, Diabetic Medicine, PLoS One, PLoS Medicine, BMJ, JAMA, BMC Medicine, Diabetes & Metabolism, Journal of Epidemiology and Community Health, Hormone & Metabolic Research

Publications: 264 publications in peer-reviewed journals, H-index: 73 (Scopus)

Publications (up to 10 most relevant)

1. Schaarup JR, Bjerg L, Hansen CS, Grove EL, Andersen ST, Vistisen D, Brage S, Sandbæk A, **Witte DR**. Cardiovascular autonomic dysfunction precedes cardiovascular disease and all-cause mortality: 11-year follow-up in the ADDITION-PRO study. Diabetes Obes Metab. 2025 Sep;27(9):5147-5159. doi: 10.1111/dom.16566.

2. Madsen AL, Bonàs-Guarch S, Gheibi S, Prasad R, Vangipurapu J, Ahuja V, Cataldo LR, Dwivedi O, Hatem G, Atla G, Guindo-Martínez M, Jørgensen AM, Jonsson AE, Miguel-Escalada I, Hassan S, Linneberg A, Ahluwalia TS, Drivsholm T, Pedersen O, Sørensen TIA, Astrup A, **Witte D**, Damm P, Clausen TD, Mathiesen E, Pers TH, Loos RJF, Hakaste L, Fex M, Grarup N, Tuomi T, Laakso M, Mulder H, Ferrer J, Hansen T. Genetic architecture of oral glucose-stimulated insulin release provides biological insights into type 2 diabetes aetiology. Nat Metab. 2024 Oct;6(10):1897-1912. doi: 10.1038/s42255-024-01140-6.

3. Bjerg L, Laugesen E, Andersen ST, Rosborg JF, Charles M, Vistisen D, **Witte DR**. Long-term effects of intensive multifactorial treatment on aortic stiffness and central hemodynamics after 13 years with screen-detected type 2 diabetes: the ADDITION-Denmark trial. Diabetol Metab Syndr. 2022 Aug 17;14(1):116.

4. Jonsson A, Stinson SE, Torekov SS, Clausen TD, Færch K, Kelstrup L, Grarup N, Mathiesen ER, Damm P, **Witte DR**, Jørgensen ME, Pedersen O, Holst JJ, Hansen T. Genome-wide association study of circulating levels of glucagon during an oral glucose tolerance test. BMC Med Genomics. 2021 Jan 6;14(1):3. doi: 10.1186/s12920-020-00841-7. PMID: 33407418.

5. Clemmensen KK, Quist JS, Vistisen D, **Witte DR**, Jonsson A, Pedersen O, Hansen T, Holst JJ, Lauritzen T, Jørgensen ME, Torekov S, Færch K. Role of fasting duration and weekday in incretin and glucose regulation. Endocr Connect. 2020 Mar 1;9(4):279–88. doi: 10.1530/EC-20-0009.

6. Janus C, Vistisen D, Amadid H, **Witte DR**, Lauritzen T, Brage S, Bjerregaard AL, Hansen T, Holst JJ, Jørgensen ME, Pedersen O, Færch K, Torekov SS. Habitual physical activity is associated with lower fasting and greater glucose-induced GLP-1 response in men. Endocr Connect. 2019 Dec;8(12):1607-1617.

7. Griffin SJ, Rutten GEHM, Khunti K, **Witte DR**, Lauritzen T, Sharp SJ, Dalsgaard EM, Davies MJ, Irving GJ, Vos RC, Webb DR, Wareham NJ, Sandbæk A. Long-term effects of intensive multifactorial therapy in individuals with screen-detected type 2 diabetes in primary care: 10-year follow-up of the ADDITION-Europe cluster-randomised trial. Lancet Diabetes Endocrinol. 2019 Dec;7(12):925-937.

8. Lundgren JR, Færch K, **Witte DR**, Jonsson AE, Pedersen O, Hansen T, Lauritzen T, Holst JJ, Vistisen D, Jørgensen ME, Torekov SS, Johansen NB. Greater glucagon-like peptide-1 responses to oral glucose are associated with lower central and peripheral blood pressures. Cardiovasc Diabetol. 2019 Oct 5;18(1):130.

9. Vistisen D, Kivimäki M, Perreault L, Hulman A, **Witte DR**, Brunner EJ, Tabák A, Jørgensen ME, Færch K. Reversion from prediabetes to normoglycaemia and risk of cardiovascular disease and mortality: the Whitehall II cohort study. Diabetologia. 2019 Aug;62(8):1385-1390.

10. Hansen CS, Færch K, Jørgensen ME, Malik M, **Witte DR**, Brunner EJ, Tabák AG, Kivimäki M, Vistisen D. Heart Rate, Autonomic Function, and Future Changes in Glucose Metabolism in Individuals Without Diabetes: The Whitehall II Cohort Study. Diabetes Care. 2019 May;42(5):867-874.

Summary of own research

My research career, spanning over 2 decades, has focused mainly on the pathophysiological mechanisms that drive the transition from normal glucose control, to pre-diabetes and diabetes at the population level. Additional work includes early stages of diabetic complications, their management, and long-term consequences. I have a special focus on longitudinal trajectory analyses and clustering of diabetic complications and risk factors, particularly in families/social networks. My work is based on several large longitudinal studies, including the Inter99 and ADDITION trials, the ADDITION-PRO, Whitehall II and Maastricht cohorts, as well as medical and population registers in Denmark, Sweden and the UK.

I studied medicine and completed a PhD in clinical epidemiology at Utrecht University, the Netherlands, followed by 5 years as an MRC Clinical Research Fellow in the Department of Epidemiology and Public Health, University College London. Between 2008 and 2012 I led the Diabetes Epidemiology research group at Steno Diabetes Center Copenhagen. Between 2012 and 2014 I worked at the Luxembourg Institute of Health. In January 2025 I was appointed Professor of Diabetes Epidemiology at Aarhus University, based initially on a grant from the Danish Diabetes Academy and since 2020 through a joint appointment with Steno Diabetes Center Aarhus. In 2017 I received the Harry Keen Memorial Award from the International Diabetes Epidemiology Group (IDEG) "for outstanding contributions to the areas of diabetes epidemiology and public health".

I currently lead the diabetes epidemiology research group at Steno Diabetes Center Aarhus, consisting of 20 PhD students, post-doctoral and senior researchers. The group has a wide focus including register-based research, Artificial Intelligence / Machine Learning, clinical, genetic and life-course epidemiology. The group has a solid commitment to open and reproducible scientific practices.

Supplementary information

In 2025 I led the successful application for a 5-year Steno National Collaborative project from the Novo Nordisk Foundation, and I am now the Principal Investigator for the DP-Next study, which aims to develop new approaches for diabetes prevention, by developing a register-focused population-wide risk prediction model, examining heterogeneity in pre-diabetes through a new deep-phenotyping cohort of 1000 individuals and developing components for sustainable diabetes prevention strategies through a participatory system dynamics approach.

Application History

Call Name	Application Ref	Project Title	Main Applicant	Granted Amt	Status	Relevance
Steno National Collaborative Grant 2024	0089168	Sustainable Type 2 Diabetes Prevention for the 21st Century (DP-Next)	Daniel Witte	24988813	Grant In Progress	