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Disentangling the effect of brain insulin resistance on brain health

Submission date	Recruitment status	[X] Prospectively registered
21/10/2025	Recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
28/10/2025	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
23/10/2025	Nutritional, Metabolic, Endocrine	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
People with diabetes have a higher risk of dementia, including Alzheimer's disease and vascular dementia. They also show greater age-related brain atrophy and more cognitive difficulties compared to people without diabetes
The mechanisms behind the effects on the brain of diabetes are still unclear. New research indicates that, in some individuals with diabetes, the brain responds poorly to insulin signals. This is called brain insulin resistance (BIR). Large clinical studies on BIR are not yet available, but several small studies link BIR with declines in cognitive function
Another mechanism that may contribute to reduced brain health in people with diabetes is damage to the blood vessels in the brain. Damage to blood vessels is a well-known complication of diabetes, but how it affects the brain is not fully described
This project will examine the relationships among BIR, brain vascular dysfunction, and cognition. We will measure markers of insulin signaling and vascular health in the brain and relate them to cognitive performance and brain structure/function. The goal is to clarify how these mechanisms contribute to cognitive impairment in diabetes

Who can participate?
Patients with type 1 diabetes or type 2 diabetes and healthy controls. All participants will be aged between 50 and 80 years old

What does the study involve?
The participants will undergo four visits
Visit A: Participants will complete comprehensive cognitive testing and undergo a health examination
Visit B: Brain MRI scanning will be performed to evaluate brain volume changes and the integrity of white matter in the brain. Brain insulin resistance will be assessed using specialized MRI techniques that measure blood flow changes after participants receive insulin administered using a nasal spray
Visit C: MRI scanning will evaluate blood vessel function in the brain. This includes testing how the brain blood flow changes when participants breathe air with added CO2, and evaluating the

blood-brain barrier functioning using a contrast agent injected during MRI scanning
Visit D: Functional MRI will be used to examine how the brain detects and responds to changes in blood sugar levels from drinking water with added sugar

What are the possible benefits and risks of participating?
The study aims to investigate why people with diabetes are more likely to experience cognitive difficulties and overall declines in brain health. By characterizing potential links, such as reduced insulin signaling in the brain or impaired blood flow regulation, the study could lead to new treatments and preventative measures. The findings may also improve our understanding of how neurodegenerative diseases and dementia develop
The study is not associated with any serious risks when safety precautions are taken

Where is the study run from?
Rigshospitalet, Denmark; Steno Diabetes Center Copenhagen, Denmark; and Ulm University Hospital, Germany

When is the study starting and how long is it expected to run for?
The enrolment of participants will start beginning of November 2025 and the project will be completed January 2032

Who is funding the study?
The Novo Nordisk Foundation (Denmark)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
H-25045491

Study information

Scientific Title
Disentangling the effect of Brain Insulin Resistance on brain health (BIR-BrainHealth)

Acronym
BIR 1

Study objectives
People with diabetes exhibit an accelerated age-related cognitive decline and have a significantly heightened risk of dementia, including both Alzheimer's disease and vascular dementia. They also experience more pronounced age-related brain atrophy compared to individuals without diabetes. While it is evident that diabetes adversely affects the brain, the precise mechanisms and specific areas of pathology remain unclear. One recent proposed mechanism is brain insulin resistance (BIR), which is an emerging concept defined as the failure of brain cells to respond to insulin signalling. Another more established mechanism involves impaired cerebrovascular function caused by damages to the brain vessels. In this project, we will examine how both mechanisms contribute to cognitive decline and neurodegeneration.

The aims of the BIR-BrainHealth project are to:
1. Examine the degree and severity of brain insulin resistance (BIR) in different types and subgroups of diabetes
2. Assess the clinical impact of BIR in relation to cognitive performance, structural changes in the brain (brain atrophy, white matter lesions, and white matter integrity), cerebrovascular function, and systemic metabolism including decline/worsening of these measures
3. Disentangle which part of the declining brain health is due to cerebrovascular damage and which part occurs because of BIR
4. Find biomarkers related to BIR, cognitive dysfunction, and poor brain health status using a multiomics
approach

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 09/10/2025, Health Ethics Committee of Copenhagen (Borgervænget 3, st., Copenhagen, 2100, Denmark; +45 38666395; vek@regionh.dk), ref: H-25045491

Study design
Multicenter case-control study

Primary study design
Observational

Study type(s)
Prevention, Quality of life, Treatment

Health condition(s) or problem(s) studied
Diabetes type 1 and diabetes type 2

Interventions
All participants will undergo a comprehensive clinical evaluation to characterize diabetes duration, severity, and systemic comorbidities.
The cognitive performance of the participants will be assessed using a neuropsychological test battery of standardized tests. Tests will be grouped by cognitive domains, and each domain score is calculated as the mean of the individual component z-scores. A cognitive composite (global score) will be derived from the mean of the domains: learning and memory, executive function and working memory, processing speed, and attention.
Blood, urine and stool will be collected for biomarker development and characterization of

patients with BIR. A multi-omics approach will be applied to identify reliable biomarkers of BIR, incorporating lipidomics, metabolomics, proteomics, and transcriptomics.
Magnetic resonance imaging (MRI) will be performed to assess BIR and structural brain changes, including atrophy. All MRS-scans will be performed on a research-optimized 3 Tesla MRI scanner. BIR will be evaluated by measuring changes in cerebral perfusion from administration of intranasal insulin delivered via nasal spray.
A subset of participants will undergo additional advanced MRI-scanning for assessments of cerebrovascular function. Brain perfusion, blood–brain barrier integrity, and capillary perfusion distribution will be measured using dynamic contrast-enhanced MRI. Cerebrovascular reactivity will be measured by perfusion-weighted MRI during inhalation of air enriched with 5% CO_2, a potent cerebral vasodilator. Cerebral blood flow responses to neuronal activation induced by visual stimulation will be assessed using perfusion-weighted MRI. Lastly, in a subset of participants the brain glucose sensing will be assessed using functional MRI (fMRI). fMRI will be measured prior to, during and following oral ingestion of water containing 75 grams of glucose. The glucose drink is given through a long straw while the participants are lying in the scanner and will be consumed over a period of 5 minutes. Blood samples will be collected throughout the scan for measurements of blood glucose.

Intervention Type
Mixed

Primary outcome(s)
1. Brain insulin response is measured using changes in cerebral blood flow assessed by arterial spin labelling (ASL) MRI following intranasal insulin administration at baseline
2. Cerebrovascular reactivity is measured using changes in cerebral blood flow responses to inhalation of hypercapnic air assessed by blood-oxygen-level-dependent (BOLD) MRI, arterial spin labelling (ASL) MRI, and phase contrast mapping (PCM) MRI at baseline
3. Verbal learning is measured using the Rey Auditory Verbal Learning Test (RAVLT) at baseline
4. Processing speed and executive function are measured using the Trail Making Test (TMT) part A and B at baseline
5. Attention and processing speed are measured using the Symbol Digit Modalities Test (SDMT) at baseline
6. Working memory is measured using the RBANS Digit Span forward (Version A) at baseline
7. Working memory and sequencing ability are measured using the Wechsler Adult Intelligence Scale III Letter-Number Sequencing test (WAIS-LNS) at baseline
8. Verbal fluency is measured using the Verbal Fluency test (phonetic and semantic) at baseline
9. Sustained attention is measured using the Rapid Visual Processing (RVP) test from the Cambridge Neuropsychological Test Automated Battery (CANTAB), using A' (RVP-A) and mean latency for correct responses at baseline
10. Motor function is measured using the Grooved Pegboard test at baseline
11. Global cognitive function is measured using the Montreal Cognitive Assessment (MoCA) at baseline

Key secondary outcome(s))
1. Blood-brain-barrier permeability is measured using dynamic contrast enhanced MRI at baseline
2. Neurovascular coupling is measured using cerebral blood flow responses to visual stimulation assessed by ASL MRI at baseline
3. Hypothalamic glucose sensing is measured using cerebral blood flow response in the hypothalamus to glucose ingestion assessed by combined BOLD and ASL MRI at baseline
4. Brain insulin response is measured using changes in cerebral blood flow following intranasal insulin administration assessed by ASL MRI at baseline

5. Cerebrovascular reactivity is measured using changes in cerebral blood flow in response to inhalation of hypercapnic air assessed by BOLD MRI, ASL MRI, and phase contrast mapping (PCM) MRI at baseline
6. Brain atrophy is measured using T1-weighted structural MRI at baseline
7. White matter lesion load is measured using Fluid-Attenuated Inversion Recovery (FLAIR) MRI at baseline
8. Cerebral microbleeds are measured using susceptibility-weighted MRI at baseline
9. Structural connectivity is measured using diffusion tensor imaging (DTI) MRI at baseline
10. White matter diffusion integrity is measured using DTI MRI at baseline
11. White matter diffusion is measured using DTI MRI at baseline
12. Resting cerebral blood flow is measured using ASL MRI and PCM MRI at baseline
13. Cerebral metabolic rate of oxygen is measured using PCM MRI and susceptibility-based oximetry (SBO) MRI at baseline
14. Regional brain glucose sensing is measured using cerebral blood flow response to glucose ingestion assessed by combined BOLD and ASL MRI at baseline
15. Cerebral blood flow response in the hypothalamus to glucose ingestion is measured using combined BOLD and ASL MRI at baseline
16. Brain insulin sensing biomarkers are measured using a multiomics approach integrating lipidomics, metabolomics, proteomics, transcriptomics, and genotyping at baseline
17. Brain insulin response is measured using changes in cerebral blood flow following intranasal insulin administration assessed by ASL MRI at baseline
18. Neuronal damage, neuroinflammation, and brain insulin resistance biomarkers are measured using a multiomics approach integrating lipidomics, metabolomics, proteomics, transcriptomics, and genotyping at baseline
19. Blood-brain-barrier permeability is measured using dynamic contrast enhanced MRI at baseline
20. Vascular function and blood-brain barrier integrity biomarkers are measured using a multiomics approach integrating lipidomics, metabolomics, proteomics, transcriptomics, and genotyping at baseline
21. Cognitive biomarkers are measured using a multiomics approach integrating lipidomics, metabolomics, proteomics, transcriptomics, and genotyping at baseline

Completion date
31/01/2032

Eligibility

Key inclusion criteria
1. Type 1 diabetes with a duration of ≥10 years
2. Type 2 diabetes with a duration of ≥5 years
3. Healthy controls

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
50 years

Upper age limit
80 years

Sex
All

Key exclusion criteria
1. HbA1c >100 mmol/mol
2. Other type of diabetes
3. Weight >140 Kg
4. Treatment with drugs that cannot be paused for 12 hours
5. Diagnosis of dementia
6. Active and recent (1year) malignant disease
7. History of major stroke
8. Major depression and/or treatment with antipsychotics
9. History of traumatic brain injury
10. Other medical condition or disorder (e.g., epilepsy, recent concussion) that in the opinion of the investigator precludes compliance with the protocol, evaluation of the results or represent an unacceptable risk for the participant's safety.
11. Inability to perform neuropsychological tests (e.g., severe vision and hearing impairment that cannot be improved with aids such as glasses and hearing aids, or language barrier.)
12. Severe claustrophobia
13. Foreign bodies of metal in the body which prohibits brain MRI scans (e.g. pacemaker or screws/plates from surgery in the head or neck region)
14. Participants who do not wish to be informed about accidental findings by MRI
15. eGFR measurement <45 within 3 months of study visit

Date of first enrolment
01/11/2025

Date of final enrolment
31/10/2031

Locations

Countries of recruitment
Denmark

Germany

Study participating centre
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Sponsor information

Organisation
Rigshospitalet

ROR
https://ror.org/03mchdq19

Funder(s)

Funder type
Industry

Funder Name
Novo Nordisk Fonden

Alternative Name(s)
Novo Nordisk Foundation, Novo Nordic Foundation, NNF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Denmark

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date