Diabetic eye disease in Greenland

PhD thesis by

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LIST OF PAPERS

This thesis is based on the three following papers:

Paper I: **Low prevalence of retinopathy among Greenland Inuit** Larsen TLJ, Jørgensen ME, Pedersen ML, Lund-Andersen H, Valerius M, Juul E, Byberg S. Int J Circumpolar Health. 2021 Dec;80(1):1938420. doi: 10.1080/22423982.2021.1938420. PMID: 34134608.

Paper II: **The incidence and prevalence of diabetic retinopathy in Greenland Inuit: A register-based study** Larsen TLJ, Jørgensen ME, Pedersen ML, Lund-Andersen H, Byberg S.

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Paper III: **The use of artificial intelligence and telemedicine solution to assess diabetic eye disease in Greenland** Larsen TLJ, Petterson MB, Jensen HN, Jørgensen ME, Pedersen ML, Lund-Andersen H, Byberg, S.

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ABBREVIATIONS

AI, Artificial Intelligence;

AUC, Area Under the Curve;

BMI, Body Mass Index;

BP, Blood Pressure;

CAN, Cardiovascular Autonomic Neuropathy;

DM, Diabetes Mellitus;

ECG, Electrocardiogram;

EMR, Electronic Medical Records;

GDM, Gestational Diabetes Mellitus;

HbA1c, Hemoglobin A1c;

HDL, High Density Lipoprotein;

ICDR, International Clinical Diabetic Retinopathy severity scale;

IQR, Interquartile Range;

IRR, Incidence Rate Ratios;

LDL, Low Density Lipoprotein;

MODY, Maturity Onset Diabetes of the Young;

OCT, Optical Coherence Tomography;

OGTT, Oral Glucose Tolerance Test;

OR, Odds Ratio;

QIH, Queen Ingrid's Hospital;

ROC, Receiver Operator Characteristic;

SD, Standard Deviation;

SDCC, Steno Diabetes Center Copenhagen;

SDCG, Steno Diabetes Center Greenland;

T1D, Type 1 Diabetes;

T2D, Type 2 Diabetes;

U-ACR, Urine-Albumin Creatinine Ratio;

WHO, World Health Organization;

PREFACE

This PhD thesis marks the end of three years of work in Ilisimatusarfik, the University of Greenland, Steno Diabetes Center Copenhagen and Steno Diabetes Center Greenland.

I have always been interested in the public health of the Greenlandic population. My interest in research started, when I moved to Tromsø, Norway and worked as a registered nurse at the University Hospital. I felt the urge to increase my knowledge, with the aim to contribute my new knowledge, to the Greenlandic society and I took a Master's degree in Public Health at UiT. During my Master, I had a stay abroad, at Steno Diabetes Center Copenhagen, and I was fortunate to get acquainted with Marit Eika Jørgensen and Stine Byberg, the two persons, what I believe to be, some of the best researchers within epidemiology.

After my Masters, I became a part of the data collection team of the Greenlandic health population survey, being in charge of the late diabetes complication screenings, which motivated me to apply for this PhD, and what a nice journey it has been, surrounded by the best people I know.
A great thanks goes to Marit, my principal academic supervisor, and my co-supervisor Michael Lynge-Pedersen, thank you both for all the support, insight and help during this PhD. I also want to thank my co-supervisor Henrik Lund-Andersen, who has been working and contributing with great knowledge regarding diabetic eye disease in Greenland. I want to address a special thank you to Stine, for all your patience and all your support during these three years, you are one of coolest persons I know, and can always bring sunshine on a cloudy day. Thank you for making me a better researcher, you are one of the persons, I admire the most. Maria and Helena, thank you, very much for helping me out with developing of the AI model – it could not have been done without you!

I would like thank all you, at the group of Clinical Epidemiology at Steno, which I have known since I was a master student. You are all inspiring researchers. Thank you to all, working on the data collection team, in the population health survey. Special thanks to Else, Vive, Ingelise, Inge, Ninna, Anna, Lars and Maja-Lis, for all the good memories from working together with you. Thank you to all participants participating in the survey for contributing in the survey.
Finally, a special thanks goes to my family, David and my daughter Ava, for believing in me and always supporting me.

Trine

SUMMARY

The prevalence of diabetes in Greenland has increased during the last decades, leaving the population at risk of developing late diabetes complications such as diabetic retinopathy (DR). DR is a complex microvascular complication of diabetes, accounting for approximately 80% of vision loss in individuals with diabetes worldwide.

Previously, studies on DR in Greenland have only been conducted in Nuuk, Greenland.

Thus, this thesis sought to investigate the epidemiology of diabetic eye disease in Greenland.

In *PAPER I*, we assessed the prevalence of DR among persons with diabetes and prediabetes participating in the 2018 Population Health Survey in Greenland (B2018). We found the overall prevalence of DR was 2% (10/483) and concluded the prevalence of DR in Greenland, based on B2018, was low.

In the *PAPER II*, we assessed the incidence and prevalence of DR among the entire Greenlandic population, registered with diabetes in the national electronic medical records, and followed them over a five-year period. Finally, we investigated risk factors associated with incident and prevalent DR.

We found 10.4% (65/623) developed incident DR during follow-up, and found 13.6% (160/1175) had prevalent DR at first visit. Higher HbA_1c levels and diabetes duration were significantly associated with both incident/prevalent DR. Higher levels of LDL cholesterol and total cholesterol were associated with a lower risk of incident/prevalent DR.

In *PAPER III*, we developed an artificial intelligence (AI) model, specific for the Greenlandic population, using images from the Optos ultra wide-field fundus camera used for screening in Greenland. However, the sensitivity and specificity was too low to be applied directly at the point of screening AI in the clinic.

Together, these papers emphasize the prevalence and incidence of DR in Greenland is low, and may be explained by ethnicity or genetic protective factors. Continued focus on DR is recommended and further research on genetic traits is suggested. Finally, we created an AI model specific for the Greenlandic population, however the model must be optimized in order to be applied in a clinical setting

DANSK RESUME

Forekomsten af diabetes I Grønland er steget i løbet af de sidste årtier, og befolkningen er dermed i øget risiko for at udvikle diabetiske senkomplikationer, såsom diabetisk retinopati (DR).
DR, er en kompleks mikrovaskulær diabetes komplikation, og ansvarlig for 80% af de synstab, personer med diabetes oplever.
Tidligere undersøgelser af DR i Grønland, har kun været udført i Nuuk, Grønland.
Med denne afhandling, undersøger vi epidemiologien bag diabetisk øjensygdom i Grønland.

I *PAPER I*, undersøgte vi forekomsten af DR blandt personer med diabetes og prædiabetes, som deltog i befolkningsundersøgelsen, B2018. Vi fandt den samlede prævalens af DR var 2% (10/483) og konkluderede, på baggrund af B2018, at prævalensen af DR i Grønland var lav.

I *PAPER II*, undersøgte vi incidensen og prævalensen af DR, blandt hele den grønlandske befolkning, registreret med diabetes i de landsdækkende elektroniske patient journaler, og fulgte dem over en femårig periode.
I tillæg, undersøgte vi risikofaktorer forbundet med både incident og prævalent DR.
Vi fandt, at 10.4% (65/623) udviklede incident DR under opfølgningen, og at 13.6% (160/1175) havde prævalent DR ved første besøg. Højere HbA1c-niveauer og diabetesvarighed var signifikant associeret med både incident/prævalent DR. Højere niveauer af LDL-kolesterol og total kolesterol var associeret med en lavere risiko for incident/prevalent DR.

I *PAPER III* udviklede vi en kunstig intelligens (AI) model, specifik for den grønlandske befolkning, ved brug af billeder fra Optos ultra wide-field fundus kamera, som bruges til screening i Grønland.
Desværre var sensitiviteten og specificiteten i vores model for lav til at blive anvendt direkte til screening i klinikken.

Tilsammen understreger disse *Papers*, at incidensen og prævalensen af DR i Grønland er lav og kan muligvis forklares med etnicitet eller genetiske beskyttende faktorer. Vi anbefaler fortsat fokus på DR og yderligere forskning i genetiske egenskaber. Til sidst udviklede vi en AI-model specifik for den grønlandske befolkning, dog skal modellen optimeres for at kunne anvendes i klinikken.

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INTRODUCTION

In the mid-1960s, Sagild et al[1] , assessed the prevalence of diabetes among the Greenlandic population and concluded, diabetes was almost non-existing in Greenland. During the period Greenland underwent a rapid social transition, going from a traditional fisher and hunter lifestyle, with a marine-based diet, to a more modern sedentary lifestyle. Sagild et al, concluded, the consequences of the rapid societal and dietary transition in the future, would lead to an increase of diabetes.

Within the last past half century the total number of persons registered with diabetes in Greenland increased drastically [2–4]. The *TBC1D4* gene, which induces insulin resistance in the skeletal muscle, is common in Greenland, in which homozygous carriers of the gene have a 10-fold increased risk of developing diabetes, and finally is estimated to explain about 15% of diabetes in Greenland [5,6]. The high prevalence of diabetes, imposes a public health burden to the healthcare system, in which high quality diabetes care is needed, in order to prevent long-term complications of diabetes, as diabetic retinopathy (DR)[7].

DR, is a frequent occurring complication among individuals with diabetes, caused by prolonged hyperglycemia damaging the blood vessels in the retina, which if left untreated, can cause permanent vision loss. DR, is initially asymptomatic in its early stages, until the disease manifests with blurring or vison loss. Worldwide, it is estimated DR, accounts for 4.8% of the cases of blindness (37 million). Thus, early detection and maintenance of glycemic control, is crucial in order to prevent permanent vision loss [8–10].

In Greenland, assessment of DR is generally well organized and present in nine out of 17 towns, using Optos® ultra wide-field fundus cameras, where the images are uploaded through a server and telemedically graded by specialist ophthalmological nurses in Denmark [11].
However, the vast distances combined with a population scattered over large areas pose considerable challenges to the delivery of healthcare and DR assessment in Greenland. Persons living in settlements or towns without screening equipment, must travel to nearest screening station, in which 2-6 days must be expected in order to reach destination, depending on the weather. Further, since the screenings are telemedically assessed, at least a week can be expected, in order to receive a response of the eye examination and if any referable microvascular lesions are detected

when the images are graded, persons living far away must again travel for further diagnostics and treatment.

AIMS & OBJECTIVES

Thus, the overall aim of this thesis was to assess diabetic eye disease in Greenland and contribute with solutions in order to reduce the burden of healthcare professionals.
The specific objectives of the three studies in this PhD thesis were:

I: Estimate the prevalence of diabetic eye disease in individuals with diabetes and prediabetes, identified in the population health surveys in Greenland

II: Investigate the incidence and prevalence of diabetic retinopathy among the entire Greenlandic population registered with diabetes in the national electronic medical records, and investigate factors associated with both incident and prevalent diabetic retinopathy.

III: Develop an artificial intelligence model, to test if deep learning based automatic grading can replace manual ophthalmological grading of retina fundus photos, using Optos ultra wide-field scanning laser ophthalmoscopy, specific for the Greenlandic population.

BACKGROUND

Setting

Greenland is the largest island in the world with a total area of 2.2 million km2, of which 80% is covered by ice. Greenland is sparsely populated by 56.000 inhabitants, living in 17 towns and 56 settlements, spread along the 44.000 km ice-free coastline.

Today, the majority (87.5%) of the population lives in towns, where Nuuk is the capital with approximately 18.800 inhabitants. A minority (12.5%) of the population lives in smaller settlements with 3-500 inhabitants[12]. Due to the vast distances in Greenland and the impenetrable ice layer, all travel between towns and settlements, must be by plane, boat or helicopter, which is expensive and depending on the weather, can be delayed.

The Healthcare system in Greenland

In 1992, Greenland took over the responsibility for the healthcare system, from Denmark and is today, a publicly financed governmental responsibility. The healthcare system in Greenland, is obligated to deliver equal care to all citizens regardless of place of residence, and all health care services, including prescribed medicine and dental care, is free of charge[13].

The healthcare system, was previously organized into 16 districts, managed by a chief district physician and a nurse. Each district comprised one town with associated settlements, coupled to a primary healthcare center, functioning as a local hospital. In Nuuk, the Queen Ingrid's Hospital (QIH), served as a national and local hospital, offering specialized and secondary health care.

In 2010, the largest healthcare reform was launched, to address several administrative, financial and health professional challenges, and the primary health care system, was divided into five regions (Fig.1). Each region consists of several towns with associated settlements and a region hospital located in the largest town, affiliated with local healthcare centers in the smaller towns and healthcare stations in the settlements (Table 1)[13,14].

The region hospitals facilitate primary care and collaborate with the local healthcare centers and healthcare stations using telemedicine. The region hospitals and local healthcare centers are employed with physicians, nurses, midwives and other healthcare professionals, depending on number of inhabitants and degree of geographical isolation. In cases, where the required examination or treatments exceeds the local capabilities, patients are referred to nearest hospital or

to QIH. Despite medical capabilities at QIH, evacuation to more advanced facility and further treatment in Denmark, may be necessary. All medical travels and stays, are covered by Greenlandic Government [15].

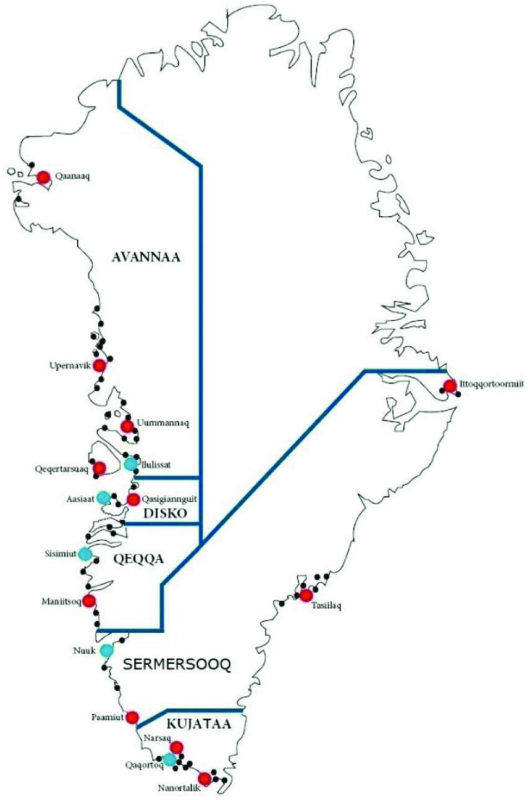

Figure 1. Overview of the five regions

In Greenland, many of the physicians working at the region hospitals and local healthcare centers, are most often specialized in general practice, surgery or obstetrics/gynaecology. Thus, medical specialists mainly from Denmark, travel for elective consultations through the country, visiting the regional hospitals, often once or twice a year. The specialist visits, reduce the transportation costs, within the Greenlandic healthcare system, as is it more cost-effective, instead of financing transportation for all patients from remote Greenlandic villages, to the centrally located specialist.

The visits, includes consultants in dermatology, ophthalmology, neurology, otolaryngology, pediatrics, psychiatry, internal medicine, cardiology, surgery, orthopedic surgery and obstetrics and gynecology. During these visits, which last around 1–2 weeks, the specialists consult, diagnose, treat and operate patients[16]

Region	Regional healthcare center	Local healthcare centers	Healthcare stations in settlements	Total number of healthcare centers and stations
Avannaa	Ilulissat	Qaanaaq, Upernavik, and Uummannaq	24	28
Disko	Aasiaat	Qasigiannguit and Qeqertarsuaq	9	12
Qeqqa	Sisimiut	Maniitsoq	6	8
Sermersooq	Nuuk*	Paamiut, Tasiilaq and Ittoqqortoormiit	8	12
Kujataa	Qaqortoq	Narsaq and Nanortalik	11	14
Total	5	11	58	74

Table 1. Overview of the Health care system in Greenland *Nuuk serves as a local and National hospital

Electronic medical records

Since the mid-1990s in Greenland, some primary health care sites have used electronically medical records (EMR). In 2007, the same EMR system, Æskulap®, was implemented in all 16 districts, along with an X-ray (Chilli web®) and laboratory system (BBC lab®).

In 2013, a new EMR system, Cosmic, was implemented, and gradually replaced Æskulap in Nuuk, during 2015. In 2016 and the first half of 2017, Cosmic, was fully implemented in all healthcare sites of Greenland, and is now the only EMR system used in the country, except in East Greenland, where limited internet capacity, limited its use and continued to use Æskulap[11].

Telemedicine

In the 1990s, telemedicine, an electronic transmission of health information, pictures, sound and/or other health related data, needed in order to make appropriate diagnosis and treatment plans, was implemented in Greenland, mainly to provide contact between Greenlandic healthcare personnel and specialists in Denmark[13,14].

In 2008 "Pipaluk", a telemedicine console with a monitoring and diagnostic equipment, with the ability to share information with other identical consoles in all parts of the healthcare system, was implemented in all hospitals and healthcare stations, with more than 50 inhabitants.

The aim with Pipaluk, was to ease the access to healthcare and medical consultations, to ensure equality in delivery of healthcare and treatment, to citizens living in rural and remote areas[17].

With Pipaluk, the rural healthcare stations, were able to consult the local and regional hospitals on daily basis. Pipaluk, enabled the nurse or healthcare worker to send electrocardiograms, clinical photographs, orthoscopic and dermatoscopic images as well as stetoscopic sound files and live video transmissions, to the local and regional hospitals for consulting.

The implementation of telemedicine significantly reduced the frequency of traveling, medical specialist consultations, and visiting psychiatrists, have mostly been replaced by tele psychiatric consultations in small towns and settlements, while visits by neurologist, completely have been replaced by tele neurological consultations[16].

Challenges within the healthcare

The vast distances in Greenland, combined with a population scattered over large areas, poses considerable challenges regarding recruitment and retention of healthcare professionals, affecting the healthcare delivery.

The majority of physicians working in Greenland, are of Danish origin and the few physicians of Greenlandic origin, mainly work at the QIH. Further, approximately half of the nurses, employed in Greenland are of Greenlandic origin[18,19].

Thus, the official language within the healthcare system in Greenland is Danish, and depends on recruiting healthcare professionals, from outside Greenland. The recruited healthcare professionals are mostly on short-term contracts, with a lack of cultural insight and language abilities, challenging the need of continuous delivering of healthcare service, within the preventive and health promotion efforts. In addition, lack of cultural insight and mutual understanding, may result in delay of adequate healthcare and/or misdiagnoses. This, is mostly among elderly people from smaller towns and settlements, who are cautious and reserved in their expression of pain and needs, growing up in a time, when this was seen as a virtue and necessity of living, in a small and isolated society. Finally, most of the availability of treatment, depends on the competences of the current staff at any given time, where the available service ranges from consulting a healthcare worker with limited formal health training in smaller settlement, to consulting a specialist at QIH[14,15,18,19].

Diabetes

Diabetes mellitus (DM), is a chronic metabolic disease characterized by elevated levels of blood glucose, caused by insufficient production of insulin, or inability to effectively use the insulin produced and is categorized in three major types. Type 1 diabetes (T1D), type 2 diabetes (T2D) and gestational diabetes (GDM). In 2017, the International Diabetes Federation estimated, approximately 8.8% (425 million) globally, had T1D or T2D[20,21].

T1D, is an autoimmune disease, in which the pancreas does not produce insulin. The risk factors for T1D, includes family history, ethnicity (white people have a higher risk compared to other racial or ethnic groups) and certain viral infections during childhood. T1D, is estimated, to globally, account for 5-10% cases of diabetes[22].

T2D, is a lifestyle related metabolic disease, occurring when the body becomes resistant to insulin or does not produce enough insulin. The risk factors for T2D, includes nonmodifiable risk factors as age, ethnicity, family history, history of gestational diabetes, and low birth weight.
The modifiable riskfactors include increased body mass index (BMI), physical inactivity, poor nutrition, hypertension, smoking, and alcohol use. Further, psychosocial factors such as depression, increased stress, lower social support, and poor mental health are also associated, with an increased risk of developing T2D. Globally, T2D, is estimated to account for 90-95% of all cases of diabetes[20,22].

GDM, occurs during pregnancy and it is estimated that GDM affects around 7–10% of all pregnancies worldwide[23]. It is estimated, that women who have had GDM, have a 20-50% increased risk of developing T2D, later in life[22].

A smaller fraction of diabetes is comprised by monogenic diabetes types which occur, as a result of a genetic defect in single genes, resulting in a disruption of the beta cell function, producing insulin. Monogenic diabetes includes neonatal diabetes with an onset before the age of six months and Maturity Onset Diabetes of the Young (MODY) before the age of 25 years. It is estimated monogenic diabetes types, globally account for approximately 1-5% cases of diabetes[20,24].

The World Health Organization (WHO), recommends four diagnostic tests to detect diabetes. Measurement of fasting plasma glucose, 2-hour post-load plasma glucose after a 75 g oral glucose tolerance test (OGTT), hemoglobin A1c (HbA1c) and a random blood glucose in the presence of sign and symptoms of diabetes. The diagnostic criteria for diabetes is:
Fasting plasma glucose ≥ 7.0 mmol/mol or 2-hour post-load plasma glucose ≥ 11.1 mmol/mol or HbA1c ≥ 48 mmol/mol (>6.5%). Prediabetes is defined as HbA1c between ≤47 mmol/mol and ≥42 mmol/mol (6.0-6.4%).
If elevated values are detected in asymptomatic people, repeat testing, preferably with the same test, is recommended as soon as practicable on a subsequent day to confirm the diagnosis[25].

Diabetes complications

Consistently high blood glucose levels, can lead to severe diabetes complications, which can occur acute and gradually.

Ketoacidosis, is a serious acute and life-threatening complication of diabetes which occurs when the body does not produce enough insulin, resulting in hyperglycemia. Hyperglycemia, induces the body to burns fat for energy, which produces ketones. When ketones are produced too quickly, they are toxic, resulting in acidosis. The symptoms of ketoacidosis are excessive thirst, nausea and confusion and can lead to dehydration, coma and, if not treated, it may lead to death[26].

Hypoglycemia, is also an acute complication of diabetes, mostly caused by low blood glucose levels. Hypoglycemia, can cause cognitive impairment, coma and seizure and is treated with either eating or drinking carbohydrates, in severe cases, hypoglycemia is treated with glucagon, to balance the blood sugar levels[27].

Long-term complications of diabetes develop gradually, caused by prolonged hyperglycemia, damaging the blood vessels. The long-term complications are categorized in macro and microvascular complications.
Macrovascular complications are primarily complications, affecting the coronary arteries, peripheral arteries and the cerebrovasculature. Early stages of macrovascular complications are usually associated with atherosclerosis, which can lead to myocardial infarction, and stroke. Further, the major cause of morbidity and mortality in patients with diabetes, is cardiovascular disease. Thus, screening for and treating hypertension and high levels of blood lipids, among persons with diabetes are important for the prevention of macrovascular complications [28,29].
Microvascular complications include nephropathy, neuropathy or DR[30,31].
Diabetic nephropathy, is a complication that affects the kidney, and is defined by an increased urinary albumin excretion (> 300 mg/day), in persons with diabetes without known kidney disease. Diabetic nephropathy, may progress to kidney failure and is prevented by maintaining a healthy lifestyle and adequate management of the diabetes and blood pressure (BP)[22].

Neuropathy, is caused by prolonged hyperglycemia, damaging the peripheral nerves, in the hands, arms and feet but also nerves supplying the digestive and cardiac system. The symptoms of peripheral neuropathy, is a gradual onset of sensory impairment, including burning and numbness in the feet. The onset is so gradual, the disease can go undetected for years, increasing the risk of foot ulceration and subsequent lower-extremity amputation[22].

Diabetic retinopathy

DR, is a frequent occurring complication among individuals with diabetes, caused by prolonged hyperglycemia damaging the blood vessels in the retina.

The blood vessels can swell, leak fluid or bleed, and in some cases, new abnormal blood vessels grow on the retina, leading to visual impairment and in worst case blindness.

The main risk factors for DR include duration of diabetes, puberty, pregnancy and ethnicity as well as hyperglycemia, hypertension, hyperlipidemia and obesity. According to WHO, it is estimated that DR, accounts for 4.8% of the cases of blindness (37 million) worldwide[22].

DR, is initially asymptomatic in its early stages, until the disease manifests with blurring or vison loss. Thus, regular screening is necessary to detect early stages of the disease, as early detection, have shown to reduce the individual risk of severe vision loss by up to 57%[32].

It is recommended that screening, is conducted using retina fundus photos using advanced retina fundus cameras with manual interpretation by specialized ophthalmologic staff[33].

The retinal fundus images are usually classified according to the International Classification of Diabetic Retinopathy disease severity scale (ICDR), where the different stages of DR are classified by the appearance of microaneurysms, haemorrhages, hard exudates and retina neuvascularization. (Fig. 2)[34].

The ICDR-scale has four severity levels:

- Level 0: No DR – No abnormalities
- Level 1: Mild non-proliferative DR – Micro aneurysm(s) only
- Level 2: Moderate non-proliferative DR – More than just micro aneurism(s) but less than severe non-proliferative DR.
- Level 3: Severe non-proliferative DR – Any of the following: > 20 intra-retinal haemorrhages in each of 4 quadrats, definite venous beading in ≥ 2 quadrants, prominent intra-retinal microvascular abnormalities in ≥ 1 quadrant, or no signs of proliferative DR.
- Level 4: Proliferative DR – One or more of the following: neovascularization and or vitreous or preretinal haemorrhages.

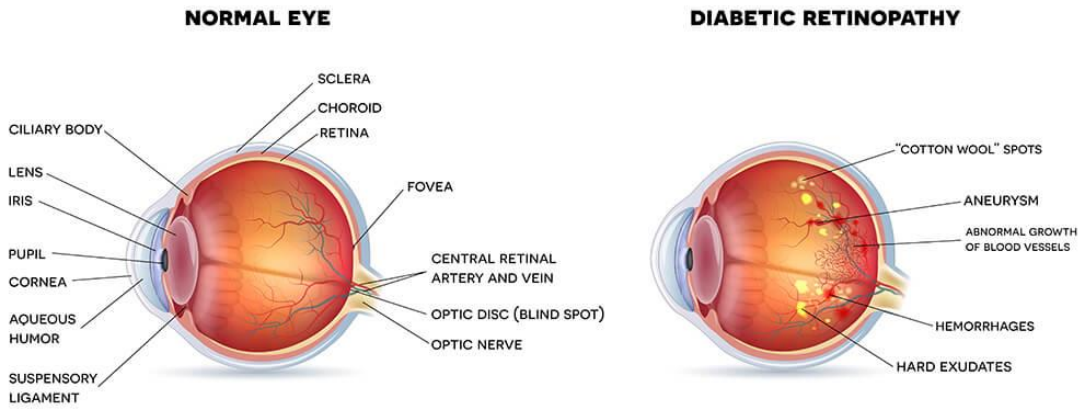

Fig.2

In addition to regular screening for DR, lifestyle counseling in the primary care, plays an important role, to ensuring adequate blood pressure and glycemic control.

The treatments of advanced DR includes laser treatment, eye injection or eye surgery.

Laser photocoagulation, can stop or slow leakage of blood and fluid in the eye.

Vascular endothelial growth factor inhibitors (anti-VEGF), can be injected into the vitreous of the eye, impairing the growth of new blood vessels and decrease fluid buildup.

Finally, a vitrectomy can be performed, in which a tiny incision in the eye, can remove the vitreous[35].

Diabetes in Greenland

Diabetes in Greenland, was previously close to non-existing, according to Alfred Berthelsen, who during 1902-1927, studied disease patterns among the Greenland Inuit[36].

In the period 1950s up until the 1970s, Kromann and Green followed a population of ~1,800 Greenlandic Inuit, over 25 years and found an incidence of diabetes of 0.05%. Corresponding to these studies, Sagild et al. found a prevalence of diabetes of 0.07% among Inuit living in three different areas of Greenland (Nuuk, Uummannaq and Angmagssalik) in 1966[1].

In the 1970s, Bang and Dyerberg, examined plasma lipid and lipoprotein patterns among Greenlandic Inuit and compared with Danish controls. The results showed low levels of cholesterol and high levels of omega-3 fatty acids, among Greenland Inuit living in Uummannaq districts, compared to Danish controls and concluded, their findings could explain the complete absence of diabetes in Greenlandic Inuit[37].

Within the last past half century, Greenland underwent a rapid social transition, going from a traditional fisher and hunter lifestyle, with a marine-based diet, to a more modern sedentary lifestyle with higher intake of carbohydrates and saturated fat, followed by a health transition resulting in an increase in obesity, hypertension and an increasing prevalence of chronic diseases, such as diabetes[38]. At the turn of the millennium, a population health survey, monitoring the disease patterns in the Greenlandic population, found 10% of adults aged 35 or older, had diabetes, and 70% of the persons with diabetes, were unaware of their condition. In addition, approximately 20% had prediabetes[2,39]. A follow up population health survey conducted in 2005-2011, confirmed the high prevalence of diabetes in Greenland (6-9%) and in addition, found the prevalence of diabetes, to be higher in settlements (8%) and smaller towns (8%) compared to larger towns (6%)[39].

The drastic increase of diabetes in Greenland, can besides the rapid social transition, be explained by genetics. Genetically, the Greenlandic population, is differentiated from other populations such as Europeans, due to the isolated and generally small population size for a long period of time, where genetic adaptation to extreme environments is believed to have been essential for survival in the Arctic region[6]. Recently, the *TBC1D4* gene variant, affecting glucose uptake, by inducing insulin resistance in the skeletal muscle, was identified as a frequent variant in Greenland, in contrast to the rest of the world. Subsequently, adaption to the traditional low carbohydrate diet of Greenlandic Inuit, may have favored a mutation in TBC1D4[6]. After the dietary transition in Greenland, homozygous carriers of the gene, have a 10-fold increased risk of developing diabetes and the gene is estimated to explain about 15% of diabetes in Greenland[5].

Diabetes complications in Greenland

Only few studies have tried to quantify the occurrence of DR in Greenland.
In 2010, a study estimated the prevalence of micro- and macrovascular complications among Greenlanders and Danes, registered with T2D in Nuuk, Greenland.
The study, consisted of 123 persons and the mean diabetes duration was 6 years.
The study found 10% had experienced at least one macrovascular complication. Further, 51% had peripheral neuropathy, 43% had microalbuminuria and 14% had DR. The study concluded the high prevalence of microvascular complications and risk factors as smoking and microalbuminuria were a matter of concern, and efforts to reduce smoking and increase physical activity were considered as primary targets for initiatives[40].

In 2015, a study further estimated and compared the proportion of microvascular complication on Greenlanders and non-Greenlanders, with T2D living in Nuuk, Greenland.
The study consisted of 393 patients, with a mean diabetes duration of 6.6 years.
The most frequent microvascular complication was neuropathy, which was observed among 49.6% of the patients. Further, 28.4% had microalbuminuria, 10.7% had DR and 7.3% had nephropathy. Comparing the results according to ethnicity, DR (21.4%) and microalbuminuria (37.5%) were observed more frequently among non-Greenlanders, compared to Greenlanders, where 7% had DR and 24.9% had microalbuminuria. The study concluded microvascular complications were frequently present among both Greenlanders and non-Greenlanders, in Nuuk. However, Greenlanders seemed to be less prone to DR compared to non-Greenlanders[41].

Diabetes care in Greenland

The confirmed high prevalence of diabetes in Greenland, by the health population surveys, emphasized the need of increased awareness of diabetes in Greenland.
In 2008, a national diabetes program was initiated, based on a large donation from Novo Nordisk A/S, to improve the detection of undiagnosed diabetes, diabetes care and promoting the awareness of diabetes. To fulfill the program, a diabetes group was established, consisting of a doctor, a registered nurse, a dietician and a registered chiropodist[11].

The diabetes group, developed diabetes profiles integrated in the EMR system and based on a statistical module, made it possible to monitor the quality of diabetes care on national level. Local key healthcare professionals, were assigned to follow diabetes patients, and further educated with annual courses on diabetes. National guidelines, inspired by Danish and Internationally accepted guidelines from the American Diabetes Association, European Association for the Study of Diabetes, European Society of Cardiology and The Danish College of General Practitioners, were developed and adapted to a Greenlandic context. Patient information in Greenlandic and Danish was developed and movies focusing on special topics like insulin treatment, were produced and distributed throughout the healthcare system. The diabetes concept, further improved the strategy, for screening of microvascular complications, and testing for microalbuminuria and nephropathy by measurements of urine-albumin creatinine ratio (U-ACR) on a spot urine were implemented, replacing the previously used method, based on a 24-hour urine sample. The affiliated chiropodist, travelled around the healthcare districts and instructed the local, key healthcare professionals in the

procedure of food examinations including use of biotensiometers and monofilaments, to increase the focus on screening of neuropathy.
Finally, all healthcare districts in Greenland, were equipped with a DCA Vantage Analyzer, to facilitate the analysis of HbA1c and the U-ACR.

In 2011, not long after the healthcare reform, the national diabetes program, was replaced by a national lifestyle initiative and in addition to diabetes care, aiming to improve the management of hypertension and chronic obstructive lung disease in Greenland. The previous diabetes group, became a lifestyle group, located in Nuuk, and lifestyle clinics were established in the region hospitals, providing consultations to patients, with lifestyle related diseases.
In 2015, the new EMR-system Cosmic, was implemented and the previously used special diabetes profiles, integrated in the provided EMR-system were replaced by a lifestyle table containing general lifestyle information as smoking, weight, height, BMI and diabetes parameters including duration of diabetes and results of screenings for neuropathy and DR[11].
In 2018, the Novo Nordisk Foundation and the Government of Greenland, entered a long-term collaboration, with the aim of strengthening the prevention and treatment of diabetes and lifestyle-related diseases in Greenland, by establishing Steno Diabetes Center Greenland (SDCG).
The overall vision of SDCG, is to improve the general health and quality of life for patient living with diabetes and lifestyle-related diseases[42].

Screening for DR in Greenland

Screening for DR in Greenland, was previously performed by travelling ophthalmologists, using direct ophthalmoscopy. In 2007, a mydriatic retinal fundus camera was installed in Nuuk. The nurse affiliated in the diabetes group, became in charge of screening patients living in Nuuk, and the grading of the images, were telemedically assessed by an ophthalmologist in Denmark. Patients living outside Nuuk, were still screened by travelling ophthalmologists, using direct ophthalmoscopy.

In 2015, a Daytona Fundus Camera from Optos®, replaced the former fundus camera in Nuuk and eight Optos fundus cameras were further installed in eight towns along the coast. The Optos fundus camera, is as of today, used for routine screenings in Greenland. Optos uses scanning laser ophthalmoscopy and permits visualization of up to 200° (82%) of the retina. In comparison,

conventional fundus cameras capture up to 90° (<20%) of the retina from 7 paired stereoscopic images (considered the gold standard). TThe Optos apparatus has fast imaging speed and does not require pupil dilation (non-mydriatic), making it easy to operate with little training required. In comparison, the conventional fundus cameras require up to 16 images per eye, good patient fixation, mydriasis and cooperation, and skilled photographers[43].

A local health care worker, trained by the Danish grading nurses and ophthalmologists from Denmark, is in charge of conducting eye examinations at each of the nine screening sites. An eye examination includes ocular pressure, autorefraction, retina imaging using Optos and an optical coherence tomography (OCT) scan. The images, are telemedically assessed by two specialist ophthalmological nurses at SDCC/ Rigshospitalet-Glostrup University Hospital in Denmark, with access to the Greenlandic health care server, and manually grade the images, according to the ICDR scale. The assessment of the images, takes approximately 7-10 workdays, and the results of the grading, are registered in the Greenlandic EMR.
Currently, all persons registered with diabetes are invited for regular DR screenings, in the town with screening facilities, closest to their home. As there are no ophthalmologists in Greenland, advanced diagnostics and treatment is done either by visiting ophthalmologists or in Denmark.

Challenges with the assessment of screening for DR in Greenland

Screening for DR in a geographically widely spread population involves several challenges;
Nine out of 17 towns, are equipped with the Optos fundus camera. Thus, persons offered DR screening living outside the nine towns, must travel from their place of residence either by boat, airplane or helicopter to the nearest eye screening station. The healthcare system covers the expenses of travel, accommodation and meals. However, travel from rural areas is expensive for the health care system, and can take days, depending on the weather. Persons attending a regular DR screening, often find it time-consuming and costly in other perspectives, as they will have to leave from their home, family and work[17].
Furthermore, the telemedical assessment of the retina fundus images is at least one week delayed relative to the time of screening. If any referable microvascular lesions are detected during image grading, persons must again travel for further diagnostics. Advanced diagnostics and treatment is done either by visiting ophthalmologists or in Denmark, as there are no ophthalmologists in Greenland. Thus, the current screening method for DR, is time consuming for the patient and expensive for the healthcare system.

Artificial intelligence solution for screening for DR in Greenland

Several artificial intelligence (AI) solutions to detect microvascular lesions in conventional retina fundus photos, have been developed, using deep learning techniques, where a neural network is trained to automatically detect DR[44–46].

The technique has proven the potential to be an important screening tool, reducing the workload of healthcare professionals and ensuring timely diagnosis[47]. In Singapore, an integrated DR screening programme using AI, has resulted in a better accuracy of the screenings (90% sensitivity and specificity), and faster response of the screening[48,49] .

In the Netherlands, algorithms for automatic grading in detection of DR, have been developed, and found to be valid for use in the primary care[50].

In Scotland, AI is already an integrated part of the DR screening program, where a three-staged grading system is used for DR screening. The algorithm initially screens all fundus images for micro aneurysms[51]. The images are initially graded in a "disease/no disease" manner, hence only images where microvascular lesions, detected by the algorithm are further graded by optometrists. In case of severe DR, the final diagnosis is given by an ophthalmologists[52].

Applying an AI grading solution, in a Greenlandic setting for automatically distinguishing images with and without microvascular lesions would mean that only patients in need of treatment and/or further diagnostics, would need their images sent to Denmark and/or to be seen by the specialist ophthalmologist nurses and doctors. Applying this method, could potentially be cost saving for the Greenlandic healthcare system, reducing the need of patient travels, thereby save resources previously used for image grading and provide immediate diagnoses to the population. From the patient perspective, this method could reduce the waiting time and possibly result in fewer travels. However, no approved AI models for DR grading of Optos images have yet been developed. Furthermore, several studies have shown that directly applying an AI algorithm developed on e.g. a Western population to other ethnic populations, may reduce the performance of the algorithm, underlining the need to train or develop a model on data representative of the population where the model is to be implemented[53,54].

METHODS

To assess diabetic eye disease in Greenland, this thesis is based on analyses of data from two different study populations in Greenland. In *Paper I*, we assessed the prevalence of DR, based on

data from the latest, 2018 Population Health Survey in Greenland (B2018). In *Paper II,* we assessed the incidence and prevalence of DR, and associated risk factors, based on data among all persons registered with diabetes in Greenland extracted from the national EMR. In paper *Paper III,* we developed an artificial intelligence model, based on retina fundus photos, extracted from EMR.

PAPER I: Prevalence of DR in B2018

In *Paper I,* we assessed the prevalence of DR among persons with diabetes and prediabetes, participating in the 2018 population health survey, conducted in Greenland during 2017-2019, who underwent a diabetes complication screening.

Population Health surveys in Greenland

Population health surveys in Greenland have been carried out, since the 1990s, monitoring the health and disease patterns of the Greenlandic population (36).

The first countrywide population health survey in Greenland, was initiated by the Department of Health in Greenland in 1993, consisting of an interview regarding health, lifestyle and living conditions.

Since 1999, 2005-2010, 2014 and 2017-19, population health surveys have been conducted and included follow-up invitation of participants who have participated in the previous population health surveys conducted. Participants included in the surveys, have been selected through a stratified random sample of adults (18+ years of age, 15+ for the latest health survey in 2017-19), from strata based on geography and community size. From each of these strata, one or more towns and 2-3 villages have been selected for the study, as being representative for the stratum with regards to living conditions. The surveys have focused on multiple health issues, including physical activity, diet, obesity and diabetes and have consisted of interviews, self-administrated questionnaires, clinical examinations and biochemical materials. The surveys have been conducted in collaboration between the Department of Health in Greenland, the National Public Health Institute in Denmark and SDCC, contributing with knowledge regarding the public health of the Greenlandic population[55].

Study population

In *paper I*, we assessed the prevalence of DR among persons participating in B2018, the latest of the countrywide health population surveys in Greenland. The survey enrolled participants from

2017-2019 and comprised 2539 Greenlandic citizens aged 15+ years. Data was collected over 11 trips with a duration of 14-28 days, from 12 towns and 8 settlements[56].

The survey included a follow-up invitation of participants, who had participated in one of the previous population health surveys as well as participants who had never participated before. Participants were invited to participate in the survey, by a personally addressed letter, with the option of accept the invitation by e-mail, letter or SMS. If no response was received, individuals selected to participate, were contacted by phone, of the person in charge of the recruitment. Participants agreeing to participate in the survey, were assigned with a date and time according to the respective town/settlement on the survey.
On the day of the survey, all participants were individually greeted by the person in charge of the recruitment and verbally informed about the objectives and the procedures of the survey, which included a clinical- and biochemical examination, an interview and a self-administered questionnaire. Participating in the survey lasted approximately 2.5 hours.

Clinical examination
Clinical examinations included measures on height, weight, waist circumference and hip circumference. Calculation of body mass index (BMI), bio impedance and body fat mass.
Finally, hand grip strength, on both hands was measured.
Participants age 35+, underwent an ECG and a pulmonary function test.

Biochemical examinations
Biochemical examinations were performed on participants aged 18+ years and included analyses of glucose, HbA1c, insulin, incretin hormones, lipids and renal function.
Participants aged 35+, without medical treatment for previously diagnosed diabetes, were instructed to fast overnight, by the person in charge of the recruitment, to perform an OGTT. Participants orally administered 75 g glucose, and had venous blood samples drawn for assessment of plasma glucose, serum insulin, and incretin hormone concentrations, drawn at 0, 30 and 120 min.
HbA_1c, was measured immediately after blood sampling, using a monoclonal antibody agglutination reaction (DCA Vantage ®, Siemens Healthineers).

Inuit genetic admixture, admixture proportions of European ancestral DNA, were estimated from blood samples for each individual, where a proportion of 1 indicates 100% Inuit ancestry and zero indicates 100% European ancestry using data generated from the Illumina MeatboChip[5].

Interview

Participants underwent an interview, by native Greenlandic speaking interviewers, trained in the study procedures, and the interview proceeded in the participant's language of choice, which most often was Greenlandic. The interview contained 252 questions regarding social and socioeconomic conditions, childhood and smoking. During the interview, participants had their BP measured and participants aged 55+, were invited to participate in a chair stand test, in which the number of times the participant was able to fully stand up was recorded by the interviewer.
The interview was estimated to last approximately one hour.

Self-administered questionnaire

The self-administered questionnaire included 91 questions regarding mental health, including substance abuse, gambling, suicides, sexual abuse and violence.

Feedback to participants

At the end of the day/survey, the person in charge of the recruitment, would verbally inform the participant about the following results: BP, BMI, percent body fat, HbA1c, pulmonary function and hand grip strength, with the ability to discuss their results.
In case of discovery of hypertension, chronic obstructive pulmonary disease or diabetes, participants were advised to seek the local healthcare service. The participants were further informed of receiving the biochemical examination results, by a letter sent to the participant.

Finally, the person in charge of the recruitment, invited following participants to participate in a diabetes complication screening, including screening for CAN, peripheral neuropathy and DR.

- Participants identified with diabetes or prediabetes, based on an HbA1c measurement at the date of the study, defined as ≥48 mmol/mol (6.5%) or as ≤42 mmol/mol (6.0%), by the WHO[57].
- Participants with known diabetes or previously screen-detected with prediabetes in one of the previous population health surveys. (Impaired fasting glucose (6.1–6.9 mmol/mol), or

impaired glucose tolerance 120 minutes plasma glucose (7.8–11.0 mmol/mol) after OGTT) (41).

- Participants identified with diabetes in one of the previous population health surveys. (Fasting plasma glucose 7.0 mmol/mol and/or 2-h plasma glucose 11.1 mmol/mol)[25].

Diabetes complication screening

Three different persons performed the screenings; two trained nurses and one researcher.
All had been trained in the procedures by skilled personnel beforehand. The person in charge of the screening, verbally informed the volunteering participant, about the objective and the procedure of the complication screening. The screening lasted approximately 45 minutes.

CAN, was assessed from five minutes resting electrocardiogram (ECG) recordings after five minutes of initial rest. Subsequent to the five-minute ECG recording, following three standard cardiovascular autonomic reflex tests were performed: the lying-to standing test (30/15), the deep breathing test (E/I ratio) and the Valsalva manoeuvre. These three tests reflect the overall condition of the parasympathetic nerve fibres and were recorded by trained personnel using a Vagus® device (Medicus Engineering, Aarhus, Denmark). CAN was detected, if two or more tests were abnormal. If, one of the tests were abnormal, early signs of CAN would be detected[58].

Peripheral neuropathy was assessed as part of a clinical foot examination, including basic check for deformities and pulse of both feet. Sensibility check using a monofilament, three different places on each foot and finally vibration sensation was measured by biotensiometry at the distal tip of the first toe on each foot, in turn, using a BioThesiometer (Bio-medical instruments, Ohio, USA).
A reduced sensibility was achieved if two out of three touches with the monofilament, was not felt. and/ or if a measurement with the Biothesiometer of >45 volt was detected[59].

Participants were assessed for DR, using Optos Daytona ultra-widefield ophthalmoscope without pupil dilatation. Participants were verbally, instructed in the procedure and of the eye screening, and two retina fundus photos of each eye were taken[60,61]. All retina fundus photos were stored in a harddisk, and at the end of each trip, the harddisk was delivered to a medical technician at QIH, which further uploaded the images to a central server in Greenland. Through the central server in Greenland, the images were assessed and graded, by two specialist ophthalmologist nurses at

SDCC/ Rigshospitalet-Glostrup University Hospital in Denmark, according to the ICDR scale. Discrepancies between two grading's were resolved by a senior ophthalmologist.
Participants with known diabetes, who within a year had had an eye screening in the public health care system, were not imaged but gave a written consent, to look them up in the national EMR system.

At the end of the screening, participants were verbally informed about the results of the CAN and the assessment of peripheral neuropathy. They were further informed that they would receive a letter, with the results of the assessment for DR, within three months.

Statistical analysis

We assessed the prevalence of DR among persons participating in the diabetes complications screening in B2018.
We calculated the prevalence of DR, and assessed the effects of sex, diabetes and place of residence using chi square test by DR. Further, we assessed the level of Inuit genetic admixture according to DR, using t-test. As we only had few persons in the complications study with DR, we were not able to look into genetics or other relevant factors for DR.
All statistical analyses were performed, using Stata 17.

PAPER II: Incidence, prevalence and associated factors of DR

In *Paper II,* we assessed the incidence and prevalence of DR, among all persons registered with diabetes during 2016-2020 and investigated factors associated with both incident and prevalent DR. The study was conducted on extraction of data, from the national EMR systems, Æskulap and Cosmic, used in Greenland during the study period, previously described in the background.
Data comprised persons registered with T1D and T2D, attending the public lifestyle clinics in Greenland, over a five-year period, from 2016-2020.

Study population

To assess the incidence and prevalence of DR, our study population was based on pseudo-anonymized data, extracted from Cosmic, and Æskulap for East Greenland. Our data consisted of all residents of Greenland, who as of January 2016, were registered with either T89 (T1D) or T90 (T2D) in the EMR, according to the International Classification of Primary Care (2nd Edition)

system[62]. We included persons with one or more screenings for DR in our study. In order to increase the number of persons with more than one screening, we manually looked up all persons registered with diabetes in Cosmic, in the previously used EMR system, Æskulap, to assess whether any of the persons previously were registered with DR. If they had no DR in Æskulap, the last DR screening registered in Cosmic, counted as the first screening episode.

Definition of variables

We assessed the incidence and prevalence of DR, among all retina fundus photos taken with Daytona Ultra-Widefield Optos retinal fundus camera. The images were assessed by two ophthalmological nurses at SDCC, according to the ICDR scale. Any discrepancies between two grading's, were resolved by a senior ophthalmologist and the results were recorded in EMR.

We assessed the risk factors associated with both incident and prevalent DR, by including following variables all extracted from the EMR: sex, smoking status, place of residence, diabetes duration, weight, age, systolic and diastolic BP, HbA1c, U-ACR, low density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol, and type of diabetes.

For the analyses, place of residence was grouped into either town, settlement, or outside Greenland.

Information on smoking status, was based on the most recently recorded "daily use of tobacco" before entry and divided into smokers or non- smokers.

Diabetes duration was calculated from the first eye screening in Æskulap/Cosmic minus the year of the diabetes diagnosis.

Weight was measured wearing light clothes and no shoes on a weight scale.

Systolic and diastolic BP was measured in the medical office, and performed on patients after five minutes of initial rest.

HbA1c level was measured through analysis of venous blood.

LDL-HDL and total cholesterol, U-ACR were analyzed, using an Architect 8000T (Abbot Laboratories) based on an enzymatic technique.

All analyses were performed at The Central Laboratory at QIH, a member of the Danish Quality Control System for laboratories[63].

Statistical analysis

In *Paper II*, we assessed the incidence and prevalence of DR, among the entire Greenlandic population, registered with T1D and T2D in the national EMR.
Further, we investigated factors associated with both incident and prevalent DR.

We summarized baseline characteristics using descriptive statistics and tested for differences using Chi square test for categorical variables and t-test for continuous variables.
Diabetes duration, weight, age, HbA_1c, and U-ACR, were not normally distributed, thus we reported the median and interquartile range (IQR). Systolic- and diastolic BP, LDL-, HDL- and total cholesterol were normally distributed, and the mean and standard deviation (SD) was reported.

In order to assess the incidence of DR, we excluded all persons with prevalent DR at first visit in Cosmic or last visit in Æskulap (if any record in Æskulap was available).
We followed persons for incident DR from date of first eye screening in Cosmic or last eye screening in Æskulap (if no DR at last visit), until DR or their last recorded eye screening in Cosmic. Only persons with more than one screening were included in the incidence analysis.
We calculated the five-year incidence rate of DR, per 1000 person years, using Poisson regression analysis with age as the underlying time scale. We assessed risk factors associated with incident DR, by calculating the incidence rate ratios (IRR) of following variables, extracted from the EMR; T1D/T2D, diabetes duration, sex, place of residence, age, smoking, weight, BP, HDL-, LDL-, and total cholesterol, HbA_1c and U-ACR.
We assessed the effect of the risk factors, in both univariate and multivariate Poisson regression analysis.

We assessed the prevalence of DR, among all persons with at least one screening for DR, in Cosmic, and calculated the prevalence of DR
We finally, assessed the risk factors associated with prevalent DR, by calculating the Odds ratios (OR), for the same variables as above. We calculated the effects of the risk factors in both univariate and multivariate Logistic regression analyses. However, due to intercorrelation with LDL- and HDL cholesterol, total cholesterol was not included in the multivariate analyses.
All statistical analyses were performed using Stata 17.

PAPER III: Development of a Deep learning AI model

In *Paper III*, we developed an artificial intelligence (AI) deep learning model, to automatic detection of DR on retina fundus images, specific for the Greenlandic population and for the Optos® ultra wide-field scanning laser ophthalmoscope. For the development of the model, we included images, gradings and diagnoses from the routine DR screenings performed in Greenland, registered in the EMR.

Study population

In the development of our model, we extracted pseudo-anonymized data for the Greenlandic population, registered with either T1D or T2D, with screenings for DR performed between 2015 and 2020, from the EMR. We manually exported all retina fundus photos from the Greenlandic population included in this study, from a server, to a hard disk and further stored the images in an encrypted server, labeled with their corresponding ICDR grading one by one.

To have sufficient amounts of images with all DR gradings, we had to supplement our data with Optos retina fundus images, from a Danish population, as the prevalence of severe DR is rare in Greenland[64]. Thus, we extracted retina fundus images, from a Danish clinical study, OPTIMISM, (unpublished), where persons with T1D and T2D were included and imaged between 2019 and 2021. All data from the OPTIMISM study was registered in a RedCap database, with remote access[65].

Screening and grading

All retina fundus images, from the Greenlandic study population were imaged, in one of the nine screening stations placed in Greenland, using Optos® ultra wide-field scanning laser ophthalmoscope, in which images and other screening data, are uploaded through a server.

All retina fundus images, from the Danish population, were imaged at SDCC, and at an eye clinic in a small town in Northern Jutland, using Optos® ultra wide-field scanning laser ophthalmoscope.

All retina fundus images, were graded by the same two specialist ophthalmologist nurses, at SDCC/ Rigshospitalet-Glostrup University Hospital in Denmark, according to the ICDR scale, and any discrepancies between two grading's, would be resolved by a senior ophthalmologist.

Data processing

All of our data consisted of color images with a pixel range of 4000 x 4000.

The images of the different DR gradings, were divided into folders, according to their corresponding ICDR grading.
Images were excluded in the downloading process, if they were ungradable or if a laser treatment had been conducted, as laser treatments are in common with images graded of the ICDR level 4, proliferative diabetic retinopathy.
We further divided the images into four sets, in order for the model to distinguish between different ICDR level gradings.

Statistical analysis

We developed our deep learning AI model, using the ResNet50 network.
ResNet50, is a pre-trained network with over a million images from the ImageNet database, and can classify images into 1000 classes[66]. The network is 50 layer deep and consists of both convolutional layers, pooling layers and a fully connected layer, that classifies the images based on their label.
The ResNet50, uses a 224 x 224 image input layer, with three color channels.
In order to train our network, we held out 20% of our data to create a test set. Hence, we used 80% of the remaining data as a training set and 20% as validation data.

In order to develop our model, we transferred the ResNet50 network, onto our own images. Thus, we replaced the final layers of the network, and defined the new last three layers with a new fully connected layer, a softmax layer and a classification layer, based on our new images and labels.
In a preprocessing function, we extracted the green channel of the images, in which all the features we were looking for, were most prominent in the green channel [67]. We further cropped the images from 4000 x 4000 pixels, to 2473 x 2980 pixels and adjusted the brightness and contrast level to match the three color channels, in The ResNet50 net.
Finally, we used data augmentation to resize every image to the network's size, 224 x 224 pixels, and in order to create more images, by applying random rotation, reflection and sheer to the dataset.
After the preprocessing function, the model uses 48 convolutional layers, 1 max-pooling layer and 1 average pooling layer, to grade the probabilities of the images.

We used an Adam optimizing algorithm, to develop our model, with an initial learning rate of 0.0001. We chose a mini-batch size of 16, and the Max Epochs was set to either 90 or 100, for the sake of creating a longer training time.

Measuring performance

We used a confusion matrix to visualize and describe the performance of our model.
We modelled the confusion matrix of our labels, comparing the predicted labels from the model with the actual labels.
The confusion matrix gave us multiple metrics, such as the classes true positive (TP), false positive (FP), true negative (TN) and false negative (FN).
From these values, calculated the Sensitivity: TP/(TP+FN), Specificity: TN/(FP+TN) and the Accuracy (TP+TN)/(TP+TN+FP+FN)[68].
The Accuracy is a good predictor, of how well the model predicts. The sensitivity measures how many of the positive images, classified as correct by the model. The specificity measures how many of the negative images, are correctly predicted as negative by the model.
Besides measuring the performance with a confusion matrix, we also calculated the Area Under the Curve (AUC). The AUC is calculated from the Receiver Operator Characteristic (ROC) curve, which is constructed by plotting the true positive rate against the false positive rate, and the AUC illustrates, the predictive accuracy well [69].

Ethics

The ethical review committee for Greenland approved the population health survey B2018 (KVUG 2017–10). Participants participating in the diabetes complication screening, were informed about the study objectives and procedures orally and in writing, and gave their informed consent in writing. For using EMR data, ethical approval was granted by the ethical review committee for Greenland (KVUG 2017-12) and by the Greenland Health Authorities.
For the Danish study "OPTIMISM", all participants had given their informed consent, and ethical approval was granted by the National Committee on Health Research Ethics (journal no. H19044875).

RESULTS

PAPER I: Prevalence of DR in B2018

In *paper 1,* we assessed the prevalence of DR, among persons identified with diabetes and prediabetes, in the population health surveys conducted in Greenland. The assessment of DR, was conducted among all persons, participating in a diabetes complication screening, in B2018.

A total of 499 participants, participated in the diabetes complication screening. We excluded three participants from the study population, who did not perform a screening for DR, due to blindness and difficulties in cooperating for the eye screening and further, excluded seven participants with normal glucose tolerance, as they, by mistake, were included in the diabetes complication screening. Finally, we excluded four participants, due to poor image quality and further excluded two participants due to cataract which made the images ungradable.

Thus, our final study population, with an assessment of DR, comprised 483 participants. .
The baseline characteristics and results, were stratified by DR and can be viewed in Table 2.
Our study population, consisted of 58% females (280/483) and 42% (203/483) males. The majority (79%) of the participants had prediabetes (HbA_1c<48 mmol/mol), and majority (86%), lived in towns compared to settlements.
The overall prevalence of DR in our study was 2% (10/483) and only mild or moderate DR, was detected. Comparing the prevalence of DR according to sex, DR was almost equally distributed among males (1.9%) and females (2.1%), however not statistically significant.
Among participants with diabetes, the prevalence of DR, was significantly higher (9%) compared to participants with prediabetes (<1%). According to place of residence, all participants detected with DR in our study, lived in towns, corresponding to 2.4%, however there was not significant difference according to place of residence. Finally, when we assessed the association of DR with the Inuit genetic admixture, participants with DR, had a lower level of Inuit genetic admixture, indicating a higher proportion of European ancestry, however not statistically significant.

Table 1
Baseline characteristics and results stratified by DR

Characteristics	DR *(n=10)*	No DR *(n=473)*	DR Prevalence % (2.0%)	p-value
Sex				**0.90**
- Male *(n=203)*	4	199	1.9%	
- Female *(n=280)*	6	274	2.1%	
Diabetes				**>0.001**
- $HbA_1c \geq 48$ mmol/L *(n=100)*	9	91	9.0%	
- $HbA_1c < 48$ mmol *(n=383)*	1	382	0.3%	
Place of residence				**0.20**
- Town *(n=416)*	10	396	2.4%	
- Village *(n=67)*	0	67	0,0%	
	Mean	**SD**	**95% CI**	
Inuit genetic admixture[1]				**0.89**
- DR *(n=5)*	62.6%	0.21	(0.36-0.89)	
- No DR *(n=373)*	76.2%	0.18	(0.74-0.78)	

[1] Missing (M) = 105
Table 2. Overview of results in *Paper I*

PAPER II: Incidence, prevalence and associated factors of DR

In *Paper II*, we assessed the incidence and prevalence of DR, among the entire Greenlandic population, registered with diabetes in the national EMR.

Our study population consisted, of a total of 1175 persons, registered with T1D or T2D, with one or more screenings for DR, in our study. For the incidence analysis, we included a total of 623 persons, who had more than one screening. All baseline characteristics were stratified by DR status, during follow-up (Table 3).

The median diabetes duration was significantly higher among persons with incident DR (6.8 years) compared to persons with no DR during follow-up (3.8 years). This was similar for prevalent DR In addition, HbA_1c levels, were significantly higher among persons with incident DR (72 mmol/mol) compared to persons with no DR during follow-up (55 mmol/mol). The HbA1c level was also higher, among persons with prevalent DR (68 mmol/mol) compared to persons with no DR at first visit (53 mmol/mol).

Further, we observed persons with prevalent DR, had a significantly higher level of U-ACR (3.6 mg/mmol) compared to persons with no DR at first visit (2.5 mg/mmol).

Among persons, with incident and prevalent DR, the level of LDL cholesterol was significantly lower (2.7-3.0 mmol/mol) compared to persons with no DR (3.3 mmol/mol). The same trend was seen for total cholesterol, where persons with no DR during follow-up had significantly higher levels of total cholesterol (4.9 mmol/mol) compared to persons with incident DR during follow-up (4.1 mmol/mol). The level of total cholesterol among persons with prevalent DR was higher (4.5 mmol/mol) compared to persons with incident DR, however the level was still significantly lower compared to persons with no DR at first visit in Cosmic (4.8 mmol/mol).The majority (>88%) of the persons with incident and prevalent DR had T2D, while the minority (<13%) had T1D.

Table 1. Baseline characteristics (* denotes a significant difference between the groups)

Baseline characteristic	No DR during follow-up	Incident DR during follow-up	No DR at first visit in Cosmic	Prevalent DR at first visit in Cosmic
Sex 1 missng				
-Male	48% (268)	37% (24)	47% (474)	38% (60)
-Female	52% (289)	63% (41)	53% (540)	63% (100)
Smoking status 32 missing, 81 missing				
-Yes	36% (199)	28% (18)	35% (356)	37% (59)
-No	59% (331)	66% (43)	58% (588)	57% (91)
Place of residence 1 missing, 5 missing				
-Town	89% (496)	88% (57)	87% (884)	89% (142)
-Settlement	8% (46)	6% (4)	7% (70)	6% (9)
-outside Greenland	3% (15)	6% (4)	6% (57)	5% (8)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Diabetes duration (years)* 27 missing, 21 missng	**3.8 (1.9-6.8)***	**6.8 (3.5-13.1)***	**4.2 (1.8-8.0)***	**8.8 (3.4-16.6)***
Weight (kg) 15 missing, 56 missing	83 (71-96)	88 (78-99)	86 (73-100)	85 (72-97)
Age at entry (years) 1 missing, 1 missing	61 (53-68)	61 (52-68)	61 (54-69)	61 (52-69)
Systolic blood pressure (mmHg) (mean (SD)) 40 missing, 148 missing	138 (17)	136 (17)	136 (16)	137 (18)
Diastolic blood pressure (mmHg) (mean (SD)) 40 missing, 148 missing	81 (10)	82 (11)	82 (10)	81 (11)
HbA1c (mmol/mol)* 6 missing, 18 missing	**55 (49-58)***	**72 (54-92)***	**53 (48-66)***	**68 (55-86)***
Urine albumin-creatinine ratio (per 1 unit increase) 93 missing, 192 missing	**2.5 (2.4-6.8)**	**3.3 (2.4-12.6)**	**2.5 (2.5-7.7)***	**3.6 (2.5-16.1)***
LDL cholesterol (mmol/l) (mean(SD)) 40 missing, 83 missing	**3.3 (1.3)***	**2.7 (1.3)***	**3.3 (1.3)***	**3.0 (1.2)***
HDL cholesterol (mmol/l) (mean(SD)) 38 missing, 79 missing	1.3 (0.4)	1.3 (0.5)	1.3 (0.4)	1.3 (0.4)
Total cholesterol (mmol/l) (mean(SD)) 39 missing, 80 missing	**4.9 (1.3)***	**4.1 (1.1)***	**4.8 (1.2)***	**4.5 (1.2)***
Diabetes type				
-T1DM	3% (16)	6% (4)	3% (25)	13% (20)
-T2DM	97% (541)	94% (61)	97% (989)	88% (140)

Table 3. baseline characteristics in *Paper II*

Incidence

We assessed the incidence of DR among persons with a first record in either *Æ*skulap or Cosmic, without DR. We found 10.4% (65/623) of the persons included, developed incident DR during follow-up, equivalent to an incidence rate of DR of 29.2 pr. 1000 (95%CI: 22.9-37.3) person years. According to the ICDR scale, 7.4% (46/623) developed mild non-proliferative DR (ICDR level 1), 1.4% (9/623) developed moderate non-proliferative DR (ICDR level 2), 0.6% (4 /623) developed

severe non-proliferative DR (ICDR level 3) and finally 1% (6/623) developed proliferative DR (ICDR level 4).

We assessed the risk factors for incident DR, in both univariate and multivariate analysis (Table 4). In the univariate analysis, we found diabetes duration (per five year increase) was significantly associated with incident DR. Further, HbA_1c (per five mmol/mol increase) and U-ACR significantly increased the risk of incident DR. Finally, we found higher levels of LDL cholesterol (per 1 mmol/mol increase), significantly was associated with a lower risk of incident DR. The same trend was seen for total cholesterol, in which higher levels of total cholesterol (per 1 mmol/mol increase), significantly was associated with a lower risk of incident DR in univariate analysis.
In the multivariate analysis, diabetes duration, and HbA_1c significantly increased the risk of incident DR, while higher levels of LDL cholesterol, significantly were associated with a lower risk of incident DR.

Table 2. Risk factors for incident DR (* denotes a significant risk factor)

	Univariate analyses	Multivariate analyses
	Incidence rate ratio (95%CI)	Incidence rate ratio (95%CI)
Sex		
-Male	1.00 (ref)	1.00 (ref)
-Female	1.36 (0.82-2.25)	0.76 (0.40-1.43)
Smoking status		
-Yes	1.00 (ref)	1.00 (ref)
-No	1.34 (0.77-2.31)	1.21 (0.61-2.41)
Place of screening		
-Town	1.00 (ref)	1.00 (ref)
-Settlement	0.95 (0.34-2.61)	0.86 (0.26-2.88)
-outside Greenland	1.44 (0.52-3.96)	1.51 (0.51-4.44)
Diabetes duration (per 5 year increase)	**1.05 (1.02-1.08)***	**1.04 (1.00-1.08)***
Weight (per 5 kg increase)	1.04 (0.98-1.01)	1.07 (0.99-1.15)
Age at entry (per 5 year increase)	1.04 (0.93-1.15)	1.13 (0.95-1.36)
Systolic blood pressure (per 5 mmHg increase)	0.99 (0.92-1.06)	0.96 (0.92-1.08)
Diastolic blood pressure (per 5 mmHg increase)	1.04 (0.93-1.17)	1.11 (0.91-1.36)
HbA1c (per 5 mmol/mol increase)	**1.09 (1.04-1.15)***	**1.13 (1.06-1.22)***
Urine albumin-creatinine ratio (per 1 unit increase)	**1.01 (1.00-1.03)***	1.00 (0.98-1.02)
LDL (per 1 mmol/l increase)	**0.77 (0.62-0.96)***	**0.67 (0.52-0.87)***
HDL (per 1 mmol/l increase)	0.85 (0.49-1.51)	1.48 (0.74-2.95)
Total cholesterol (per 1 mmol/l increase)	**0.62 (0.49-0.79)***	
Diabetes type		
-T1DM	1.58 (0.58-4.35)	1.31 (0.34-5.05)
-T2DM	1.00 (ref)	1.00 (ref)

Table. 4. Risk factors for incident DR in, *Paper II*,

Prevalence

During the five-year study period from 2016-2020, we found an overall prevalence of DR of 13.6% (160/1175). According to the ICDR scale, 8.7% (102/1175) had DR equivalent to ICDR level 1, 2.5% (29/1175) had ICDR level 2, 0.4% (5/1175) had ICDR level 3 and finally, 2% (24/1175) had severity level 4.

We assessed the risk factors for prevalent DR in both univariate and multi variate analysis (Table 5). In the univariate analysis, females had a significantly higher risk of prevalent DR, compared with males. Further, diabetes duration, HbA_1c and U-ACR were also significantly associated with

prevalent DR. Persons registered with T1D had a significantly higher risk of prevalent DR, while higher levels of LDL cholesterol and higher levels of total cholesterol significantly, were associated with a lower risk of prevalent DR. In the multivariate analyses, longer diabetes duration was significantly associated with an increased risk of prevalent DR. The same was seen for HbA_1c and U-ACR. Finally, higher levels of LDL cholesterol, were significantly associated with a lower risk of prevalent DR. The association seen with T1D in the univariate analyses, were attenuated after adjustments and no longer significant.

Table 3 – Risk factors for prevalent DR (* denotes a significant risk factor)

	Univariate analyses	Multivariate analyses
	Odd ratio (95%CI)	Odds ratio (95%CI)
Sex		
-Male	1.00 (ref)	1.00 (ref)
-Female	**1.46 (1.04-2.06)***	1.48 (0.90-2.45)
Smoking status		
-Yes	1.00 (ref)	1.00 (ref)
-No	0.93 (0.66-1.33)	0.78 (0.49-1.24)
Place of screening		
-Town	1.00 (ref)	1.00 (ref)
-Settlement	0.80 (0.39-1.64)	0.66 (0.24-1.72)
-outside Greenland	0.87 (0.41-1.87)	0.87 (0.31-2.39)
Diabetes duration (per 5 year increase)	**1.59 (1.31-1.93)***	**1.27 (1.02-1.58)***
Weight (per 5 kg increase)	0.98 (0.95-1.02)	1.00 (0.95-1.06)
Age at entry (per 5 year increase)	0.98 (0.91-1.05)	0.93 (0.82-1.05)
Systolic blood pressure (per 5 mmHg increase)	1.03 (0.97-1.09)	1.08 (0.99-1.18)
Diastolic blood pressure (per 5 mmHg increase)	0.97 (0.89-1.06)	0.88 (0.75-1.03)
HbA1c (per 5 mmol/mol increase)	**1.15 (1.11-1.19)***	**1.14 (1.08-1.20)***
Urine albumin-creatinine ratio (per 1 unit increase)	**1.01 (1.00-1.01)***	**1.01 (1.00-1.01)***
LDL (per 1 mmol/l increase)	**0.85 (0.74-0.98)***	**0.82 (0.68-0.98)***
HDL (per 1 mmol/l increase)	0.94 (0.63-1.40)	1.31 (0.75-2.28)
Total cholesterol (per 1 mmol/l increase)	**0.80 (0.68-0.93)***	
Diabetes type		
-T1DM	**5.65 (3.06-10.4)***	1.94 (0.73-5.12)
-T2DM	1.00 (ref)	1.00 (ref)

Table. 5. Risk factor for prevalent DR, in *Paper II,*

Paper III: Development of a Deep learning AI model

We developed an AI model, to automatically detect DR on retina fundus photos, specific for the Greenlandic population, conducted on Optos® ultra wide-field scanning laser ophthalmoscope, using the ResNet50 network.

We manually extracted a total of 1700 images, from the Greenlandic health server, to a hard disk, and stored the images in an encrypted server. We excluded images, which were not ”single color images”, and, in order to attempt, to achieve balanced data including all ICDR gradings, we excluded several images with no DR. Thus, we included a total of 248 images from the Greenlandic population.

From the Danish population, a total of 5000 images, were available from the OPTIMISM study. In line with the Greenlandic images, we excluded images, which were not ”single color images” , ungradable images and several images with no DR, in order to achieve balanced data. Thus, we included a total of 551 images, from the OPTIMISM study.

Hence, our final dataset, consisted of a total of 799 retina fundus images, from a Greenlandic and Danish study population, assessed according to ICDR. (Table 6).

	Danish	Greenlandic	Total
0 (No DR)	124	83	207
1 (Mild NPDR)	78	63	141
2 (Moderate NPDR)	130	54	184
3 (Severe NPDR)	95	29	124
4 (PDR)	124	19	143
Total	551	248	799

Table 6. Overview of the final study population, in *Paper III*,

We compared the model’s ability of distinguishing between different images of ICDR severity levels (table 7); firstly, we compared images graded 4, with images graded 0. We found a good model performance with an accuracy of 0.9655, AUC of 0.9905, sensitivity and specificity of 96.6%. Secondly, we compared images graded 3-4 with images graded 0. The model performance was modest with an accuracy of 0.8171, an AUC of 0.8543, a sensitivity at 78% and a specificity at 87.8%. Thirdly, we compared images graded 0, 1 and 2, with images graded 3 and 4. The

performance was similar to the comparisons above with an accuracy of 0.8077 and an AUC of 0.8728. The sensitivity was higher than above (84.6%) however, the specificity was correspondingly lower (78.8%). Fourthly, we assessed the performance of the model in distinguishing between images grade 0 versus images graded 1 and 2 versus images graded 3 and 4. The models ability to distinguish these three gradings from each other, was lower than in the other comparisons, with an accuracy of 0.6583, an AUC of 0.8063, a sensitivity of 60% and a specificity of 74.6%.

ICDR Severity level	Accuracy/ Performance	AUC	Sensitivity	Specificity
0 vs. 4	0.9655	0.9905	96.6%	96.6%
0 vs. 3+4	0.8171	0.8543	78.0%	87.8%
0+1+2 vs. 3+4	0.8077	0.8728	84.6%	78.8%
0 vs. 1+2 vs. 3+4	0.6583	0.8063	60.0%	74.6%

Tabel 7. Performance of the model for different images gradings

DISCUSSION

We assessed the prevalence and incidence of DR among the Greenlandic population participating in B2018, and among persons registered with diabetes in the National EMR.

We found a low prevalence and incidence of DR, and a low prevalence of severe DR.

Higher HbA_1c levels and diabetes duration were significantly associated with prevalent/incident DR, while higher levels of both LDL and total cholesterol were associated with a lower risk of both incident and prevalent DR.

Finally, we developed an AI model, to automatically detect DR on Optos retina fundus images, however, the sensitivity and specificity was too low to be applied directly at the point of screening AI in the clinic.

PAPER I: Prevalence of DR in B2018

In *Paper I*, we found a low prevalence of DR, and only mild or moderate DR, was detected.

The prevalence of DR, was significantly higher among persons with diabetes compared to participants with prediabetes, and all persons with DR, lived in towns compared to settlements. According to sex, we found no significant differences. Finally, participants with DR, had a lower level of Inuit genetic admixture, indicating a higher proportion of European ancestry, however not statistically significant.

In our study, we found the prevalence of DR was <1% (1/10), among persons with prediabetes. However, a previous study, found that DR and other complications of diabetes, can be present even at the prediabetic stage[70].
A recent study conducted in India, assessed the prevalence of DR among 192 Asian Indians, with prediabetes. In contrast to our study, the study found 6.3% (12/192) had DR.

Previous studies, assessing diabetes in Greenland, have found a higher prevalence of diabetes in settlements, compared to towns[39]
All participants detected with DR in our study however, lived in towns. Studies regarding dietary patterns in Greenland, have found the consumption of the traditional diet, which is high in Omega-3 fatty acids, is higher in settlements[4,71,72]. A review found that Omega-3 fatty acids might have a potential to prevent the progression of DR, as a results of their wide range of neurovascular protective properties[73]. Thus, it is possible the consumption of traditional diet, may protect the participants against DR and explain why DR was only found among people living in towns. However, as we only found few cases of DR, we were not able to assess any association between dietary patterns and DR.

In our study, we assessed the association between the Inuit genetic admixture and DR, as ethnicity, previously has been found to be a complex, independent risk factor for DR[74].
We found the level of Inuit genetic admixture among participants with DR, was lower, compared to participants with no DR, indicating a higher proportion of European ancestry among persons with DR, however it was not statistically significant most likely due to few cases. However, previous studies assessing diabetes complications in Nuuk, Greenland, found that persons with Greenlandic ethnicity had a lower risk of DR, supporting our findings of a potential genetic gradient in the development of DR [40,41].

Strengths
This was the first study to assess the general prevalence of DR, in a representative sample of the Greenlandic population, based on Health Population Surveys, including both participants with diabetes and prediabetes and persons living in remote areas.

Limitations
As a result of few cases of DR, we were not able to conduct further analysis, of which the original purpose, was to assess the effect of the genetic variant TBC1D4.

Finally, a notable limitation, is the number of persons with missing information regarding Inuit genetic admixture.

PAPER II: Incidence, prevalence and associated factors of DR

In *Paper II*¸ we found a low incidence and prevalence of DR, among the entire Greenlandic population, registered with diabetes. Further, we found, that higher HbA_1c levels and longer diabetes duration significantly were associated with both incident and prevalent DR.
Higher levels of LDL cholesterol were significantly associated with a lower risk of incident DR.

In our study, we found a lower prevalence and incidence of DR, compared to studies from other similar populations, as Denmark, England and Canada[75–77].
We found the majority (>85%) of persons with incident and prevalent DR, had no DR and less than 2.5% had severe-none proliferative DR or proliferative DR.
In contrast, a study from Canada, assessed the prevalence of DR among native Canadians and non-native Canadians, and found higher rates, and more severe changes of DR, among native Canadians compared to non-native Canadians. They concluded that ethnicity played a significant role in the development and severity of diabetic retinopathy[78].
Thus, as previously described above, ethnicity may play a role in the development of DR. However, native Canadians, may have different dietary patterns and different screening programmes to detect DR, compared to Greenland.

Our study, found higher levels of HbA_1c and longer diabetes duration, significantly were associated with both incident and prevalent DR. Although high levels of HbA1c and long diabetes duration are considered to be well established risk factors for developing DR, some studies have found that the major risk factors, only account for approximately 10% of the risk of developing DR, and that genetics may play a bigger role in the development and progression of DR[79].

The Greenlandic population, is genetically differentiated from other populations such as Europeans, because of its isolated and generally small population size for a long period of time, where genetic adaptation to extreme environments is believed to have been essential for survival in the Arctic region[80]. It is estimated, that more than 20% of cases of diabetes in Greenland have a monogenic diabetes etiology, primarily explained by the recessive *TBC1D4* variant, and *MODY* diabetes.

The *TBC1D4* variant causes severe muscular insulin resistance with postprandial hyperglycemia[5]. Homozygous carriers make up 10-15% of all diabetes found in the population surveys in Greenland. However, *TBC1D4*-diabetes seems to reflect a rather healthy phenotype with low BMI, low fasting glycemia and a low risk of cardiovascular disease[81] and low incidence of diabetic kidney disease (yet unpublished data). If the *TBC1D4* variant makes up a large proportion of the population with diagnosed diabetes in Greenland, this may explain the observed lower prevalence and incidence of DR.

For *MODY* diabetes, a recent study has identified a novel *HNF1A* variant with an allele frequency of 1·9% in the total Greenlandic Inuit population and absent elsewhere. As for the *TBC1D4* variant, the novel *HNF1A* variant together with *HNF4A- (MODY1), GCK- (MODY2), and HNF1B-(MODY5)* diabetes explain 10-15% of all diabetes in Greenland[82]. Similar numbers for monogenic diabetes are 1-3% in large admixed populations. Particularly *MODY2* and *MODY3* diabetes may associate with a lower risk of microvascular complications, however, this has not been studied in Greenland yet.

Interestingly, we found higher levels of LDL cholesterol and higher levels of total cholesterol, were associated with a significantly lower risk of both incident and prevalent DR. However, our findings may be a result of confounding by statin-indication, reflecting a higher use of statins in high risk groups of micro- and macrovascular complications. Unfortunately, information on medication was not available in the study at hand.

Finally, in our study, we observed no significant differences of DR, according to sex and place of residence in our study. Considering the challenges within the healthcare and the challenges of screening for DR in Greenland, described in the background, one could imagine that persons living in settlements and small towns, are less aware of diabetes complications, as DR, generally is asymptomatic in the initial stages or that persons living in settlements are reluctant to seek healthcare. People living in small towns and villages nearby where DR screening with fundus photo is not available are typically examined by consulting ophtalmologists using an ophtalmoscope with markedly lower sensitivity for mild and thereby risk of under-detection[83].

A recent study found 50%, of persons registered with diabetes in Greenland, were aware of symptoms and complications to diabetes, and , and emphasized, room for improvement of diabetes awareness in the settlements[84].
Nonetheless, a recent study only found minor differences in the quality of diabetes care in settlements compared to towns and approximately 80% of diabetes patients in all regions of Greenland, had had an eye screening for DR within a two-year period, while approximately 78% of diabetes patients living in settlements, received a screening within the two-year period[85].

Strengths
This was the first study to assess the overall prevalence and incidence of DR in Greenland over a five-year period. A major strength of the study, was the study, comprised all persons diagnosed with diabetes, registered in the national EMR.

Limitations
A limitation in our study could be an under detection of DR, as a high proportion of persons in Greenland have unknown diabetes, and thus do not appear in the national EMR. Furthermore, the population with diabetes in Greenland is characterized by young age and short diabetes duration, and the relatively short follow up of 5 years may not show the full landscape of DR in Greenland. Finally, information on genetics as well as information on medication could have had an explanatory impact on our results.

PAPER III: Development of a Deep learning AI model
In, *Paper III, w*e developed an AI model to automatically recognize DR on Optos images from Greenland. We achieved a very good performance and specificity, when we compared images of ICDR level 0 to images of ICDR level 4. However, the performance was suboptimal when comparing no/mild vs. severe DR with sensitivity and specificity for the models of around 80%.

In 1995, a consensus view was put forward, by clinicians at a meeting of the British Diabetic Association in Exeter, that screening for DR should have a minimum sensitivity of 80% and a specificity of 95%[86,87].

In correlation, to the corresponding recommendations above, we achieved a very good performance and specificity, when we compared images of ICDR level 0 to images of ICDR level 4. However, as

early detection of advanced DR is crucial for adequate treatment outcomes, it would be too risky to directly implement a model only capable of recognizing very severe forms of DR, for autonomous grading in Greenland [88]. However, one application of the model could be as a decision tool, to immediately identify proliferative changes at the screening station and thus, avoid delays in referral and treatment considering that advanced diagnostics and treatment must be done telemedically or in Denmark.

Recently, a semi-automated deep learning algorithm-assisted approach, was developed to detect vision-threatening referable DR, among a Chinese population. The approach combined both AI and human grading procedures.
The model detected vision-threatening referable DR, of which the high-risk cases, detected by the model, were manually graded by a senior ophthalmologist. Applying the model, in a clinical setting, presented advantages in time and economic savings for grading the images, enabling accurate and efficient diagnoses[89].

In line with the study above, we managed to develop a model, with the potential to use in the clinic, when we compared images graded 0, 1 and 2, with images graded 3 and 4.
The model had an accuracy of 0.8077 and an AUC of 0.8728, with a sensitivity 84.6% and a specificity of 78.8%. In order to develop an AI model, that could function more or less autonomous in a clinical setting, we would need a model with high specificity and sensitivity as well as overall good performance, to distinguish referable from non-referable images autonomously, as the imaging healthcare professionals in Greenland are not trained in image grading. For safety reasons, sensitivity should though to be prioritized over specificity, to ensure a true detection of DR.

In order for our model to be used as an autonomous AI model in Greenland, we would have to optimize our model by development of a large training and evaluation dataset[90]. According to the assessment of grading the images, which is manually conducted by two ophthalmological nurses, each grading a separate batch of images, consequently our model could be learning from the same error. Optimizing the assessment of the images with more ophthalmological nurses grading the same images, could reduce the potential human errors and increase the quality of the training data[91]. Finally, our model would have to be strictly validated in pre-registered studies for safety, efficacy and equity, involving real-work workflow[92].

This could be done by testing the model in Nuuk, and at the same time get the ophthalmological nurses at SDCC, to give their assessment of the same image and we could hereby get an indication of what the model does not recognize.

Strengths

This is the first study, to develop an AI model, which automatically can detect DR on retina images, specific for the Greenlandic population on images conducted on the Optos® ultra wide-field scanning laser ophthalmoscope.

The same two specialist ophthalmological nurses at SDCC/Rigshospitalet Glostrup in Denmark, manually graded all retina fundus photos from the Greenlandic and Danish study population, included in this study.

Limitations

Our model was only developed to detect DR, thus other ocular disease are missed when using the model. Currently, the ophthalmological nurses assess the images and supplementary information for signs of other ocular diseases and refer persons to ophthalmologists if deemed necessary.

Due to the low prevalence of severe DR in Greenland, found in *Paper II*, we had to include images from a Danish population in order to achieve an acceptable performance. However, during recent centuries, the Greenlandic population have intermixed with Europeans, leading to a relatively high proportion of genetic European ancestry in modern Greenlanders, where the average estimated degree of European ancestry admixture in present day Inuit in Greenland is 25%, varying with the degree of geographical isolation[6]. Thus, many of the people screened for DR in Greenland today will anyways share many common features with an ethnic Danish population, suggesting that the model might perform well in Greenland despite its training on partially Danish data.

We excluded images in the downloading process, if they were ungradable or if a laser treatment had been conducted, however blurry or partial images could disturb the accuracy of the model. Pre-processing the images and splitting the images of their respective grading, according to quality, and train the model with high quality images first and during the training add blurry or partial images of less quality, could further improve the model[93].

CONCLUSIONS

We found a low prevalence and incidence of DR in the Greenlandic population, and that the prevalence of severe DR, was rare in Greenland.
In agreement with previous studies on risk factors for DR, we found that higher HbA_1c levels and diabetes duration significantly were associated with prevalent/incident DR, while higher levels of both LDL and total cholesterol were associated with a lower risk of both incident and prevalent DR.
Finally, we managed to develop an AI model using Greenlandic data, to automatically detect DR on Optos retina fundus images, however, the sensitivity and specificity was too low to be applied directly at the point of screening AI in the clinic.

FUTURE PERSPECTIVES

In this PhD-thesis, the overall aim was to assess diabetic eye disease in Greenland and contribute with solutions, to reduce the burden of patients and healthcare professionals.

In this PhD-thesis, the overall aim was to assess diabetic eye disease in Greenland and contribute with solutions, to reduce the burden for healthcare professionals.

With this thesis, I have thoroughly investigated DR in Greenland; the prevalence and incidence of DR is low, however many of the well known risk factors for DR were also found in Greenland. The low occurrence of DR is enticing hopefully more research on ethnicity, genetics and epigenetic traits will elucidate whether monogenetic types of diabetes can be associated with a possibly a protective effect, and if so, which mechanisms could account for the protective effects.
The Greenlandic Inuit have a very distinct traditional diet mainly high in protein and fat and the effect of diet, especially the traditional diet, could also pose as an explanation of the lower DR prevalence and incidence.
A potential future study, could include a matched case-control study, on persons registered with diabetes in Greenland, match them to a Danish population, on the risk factors identified in this study; HbA1c levels and diabetes duration, and further observe if there would be any differences between the two populations, regarding the prevalence and severity of DR.

In relation to the AI model, optimizing the model to be applied in a clinical setting, should be prioritized, so that DR screening could be conducted almost exclusively in Greenland. As only few

people have severe DR, only few people would need an evaluation by a specialist from Denmark if a successful AI model could conduct the DR gradings in screening visits.
Although a successful AI model for DR grading intuitively seems cost-effective in a Greenlandic setting, it is important to assess the feasibility of implementing such a model in a Greenlandic setting, and compare the costs and effects to other potential scenarios.
In addition, qualitative studies, should be undertaken to assess the attitudes and uptake of an AI model for DR screening, both among patients and healthcare professionals

Concluding remarks

I have contributed to studies of DR in Greenland – findings of interest not only in Greenland but also in the Arctic area and outside western countries. Particularly studies exploring methods to improve access to DR screening and diagnosis under difficult geographical, organizational- and socio-economic conditions are of interest in low- and middle income countries.

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APPENDENCIES

PAPERS I,II,III