

Serum 25-hydroxyvitamin D, calcium and parathyroid hormone levels in Native and European populations in Greenland

Ca homeostasis is important to human health and tightly controlled by powerful hormonal mechanisms that display ethnic variation. Ethnic variations could occur also in Arctic populations where the traditional Inuit diet is low in Ca and sun exposure is limited. We aimed to assess factors important to parathyroid hormone (PTH) and Ca in serum in Arctic populations. We included Inuit and Caucasians aged 50–69 years living in the capital city in West or in rural East Greenland. Lifestyle factors were assessed by questionnaires. The intake of Inuit diet was assessed from a FFQ. 25-Hydroxyvitamin D (25OHD2 and 25OHD3) levels were measured in serum as was albumin, Ca and PTH. The participation rate was 95 %, with 101 Caucasians and 434 Inuit. Median serum 25OHD (99.7 % was 25OHD3) in Caucasians/Inuit was 42/64 nmol/l (25, 75 percentiles 25, 54/51, 81) (P

Forfatter: Stig Andersen; Paneeraq Noahsen; Karsten Rex; I. Fleischer ; N. Albertsen ; Marit Eika Jørgensen; L.K. Schaebel ; M.B. Laursen **Type:** Article | Artikel **Årstal:** 2018 **Emner:** Parathyroid hormone; Calcium; Vitamin D; Ethnicity; Inuit; 25-hydroxyvitamin D; Parathyroid hormone **Titel på tidsskrift:** British Journal of Nutrition **Volume på tidsskrift:** 119 **Nummer på tidsskrift:** 4 **Udgiver:** Cambridge University Press **DOI nummer:** <https://doi.org/10.1017/S0007114517003944>

Genetic determinants of glycated hemoglobin levels in the Greenlandic Inuit population

We previously showed that a common genetic variant leads to a remarkably increased risk of type 2 diabetes (T2D) in the small and historically isolated Greenlandic population. Motivated by this, we aimed at discovering novel genetic determinants for glycated hemoglobin (HbA1C) and at estimating the effect of known HbA1C-associated loci in the Greenlandic population. We analyzed genotype data from 4049 Greenlanders generated using the Illumina Cardio-MetaboChip. We performed the discovery association analysis by an additive linear mixed model. To estimate the effect of known HbA1C-associated loci, we modeled the effect in the European and Inuit ancestry proportions of the Greenlandic genome (EAPGG and IAPGG, respectively). After correcting for multiple testing, we found no novel significant associations. When we investigated loci known to associate with HbA1C levels, we found that the lead variant in the GCK locus associated significantly with HbA1C levels in the IAPGG ($PIAPGG=4.8 \times 10^{-6}$, $\beta_{IAPGG}=0.13SD$). Furthermore, for 10 of 15 known HbA1C loci, the effects in IAPGG were similar to the previously reported effects. Interestingly, the ANK1 locus showed a statistically significant ancestral population differential effect, with opposing directions of effect in the two ancestral populations. In conclusion, we found only 1 of the 15 known HbA1C loci to be significantly associated with HbA1C levels in the IAPGG and that two-thirds of the loci showed similar effects in Inuit as previously found in European and East Asian populations. Our results shed light on the genetic effects across ethnicities.

Forfatter: E.V.R. Appel ; I. Moltke ; Marit Eika Jørgensen; Peter Bjerregaard; A. Linneberg ; O. Pedersen ; A. Albrechtsen ; T. Hansen ; N. Grarup **Type:** Article | Artikel **Årstal:** 2018 **Emner:** Diabetes; Inuit; Arctic; Greenland **Titel på tidsskrift:** European Journal of Human Genetics **Volume på tidsskrift:** 26

[Åben publikation](#)

Prevalence of Diabetic Neuropathy in Young Adults with Type 1 Diabetes and the Association with Insulin Pump Therapy

Aims: The aim was to investigate the prevalence of diabetic sensorimotor polyneuropathy (DSPN) and cardiovascular autonomic neuropathy (CAN) in a Danish population of young adults with type 1 diabetes (T1D) using both established and novel measuring modalities. Furthermore, to investigate the association between continuous subcutaneous insulin infusion (CSII) treatment and these complications.

Materials and Methods: CAN was assessed by cardiovascular autonomic reflex tests. DSPN was assessed not only by perception of light touch and pain, vibration perception threshold (VPT), Brief Pain Inventory (BPI), and Michigan Neuropathy Screening Instrument questionnaires but also by novel modalities: electrochemical skin conductance (ESC), sural nerve conduction velocity (SNCV), and sural nerve amplitude potential (SNAP).

Results: The study comprised 156 young adults with a mean age of 22 years (standard deviation 1.6). The prevalence of CAN and early CAN was 9% and 28.1%, respectively. Subclinical DSPN was 55.1% and confirmed DSPN was 2.6%. Prevalence of abnormal SNAP was 23.8%, SNCV was 37.1%, ESC on the hands and feet was 4% and 8%, respectively, VPT was 1.3%, and BPI questionnaire was 1.9%. No association was found between CSII treatment and the measures of DSPN and CAN.

Conclusion: DSPN and CAN are prevalent in young adults with T1D with no association found with CSII treatment. The use of novel measuring modalities identified a higher number of subjects with DSPN compared with established measures. Screening for diabetic neuropathy in young adults may be beneficial to detect and prevent nerve damages at early stages.

Forfatter: M.M.B. Christensen ; E.E. Hommel ; Marit Eika Jørgensen; B.J. von Scholten ; J. Fleischer ; C.S. Hansen
Type: Article | Artikel **Årstal:** 2018 **Emner:** Type 1 diabetes; Cardiovascular autonomic neuropathy; Diabetic sensorimotor polyneuropathy; Young adults; Electrochemical skin conductance; Sural nerve conduction velocity; Sural nerve amplitude potential **Titel på tidsskrift:** Diabetes Technology & Therapeutics **Volume på tidsskrift:** 20 **Nummer på tidsskrift:** 12 **Udgiver:** Mary Ann Liebert, Inc.
DOI nummer: <https://doi.org/10.1089/dia.2018.0249>

Research | Forskning - peer review > Article | Artikel

Associations between vitamin D status and atherosclerosis among Inuit in Greenland

Background and aims: Low levels of vitamin D are suspected to be a risk factor for cardiovascular disease and atherosclerosis. The aim of this study was to assess the prevalence of subclinical atherosclerosis among Inuit in Greenland, and to evaluate the association with vitamin D status. We hypothesized that low vitamin D status could be associated with higher carotid intima-media thickness (IMT) as a marker of atherosclerosis.

Methods: 756 adults from the Inuit Health in Transition (IHIT) study carried out in Greenland in the period 2005–2010 were included. A blood sample donated in 1987 was available for a sub-sample of 102 individuals. Serum 25(OH)D3 from the IHIT study and the 1987 survey was used as a measure of vitamin D status. IMT measurements were conducted by ultrasound scanning. The prevalence of atherosclerosis was estimated, and the association between serum 25(OH)D3 and IMT measurements was examined by linear regression.

Results: The overall prevalence of subclinical atherosclerosis was 20.1% (n = 152). The linear regression analyses indicated a weak positive association between serum 25(OH)D3 level and IMT measurements from the IHIT study, though not statistically significant after adjustment for potential confounders ($\beta = 0.35\%$ per 10 nmol/L 25(OH)D3, $p = 0.06$). Linear regression analyses of the association between serum 25(OH)D3 level in the 1987 survey and IMT measurements also indicated a positive, though not statistically significant, association after adjustment ($\beta = 0.07\%$ per 10 nmol/L 25(OH)D3, $p = 0.86$).

Conclusions: Our findings did not support the hypothesis of an association between low vitamin D levels and risk of atherosclerosis.

Forfatter: CU Gjødesen ; Marit Eika Jørgensen; Peter Bjerregaard; IK Dahl-Petersen ; CVL Larsen ; M Noël ; M Melbye ; AS Cohen ; M Lundqvist ; DM Hougaard ; JW Helge ; NO Nielsen **Type:** Article | Artikel **Årstal:** 2018 **Emner:** Atherosclerosis; Carotid intima media thickness; Vitamin D; Inuit; Greenland **Titel på tidsskrift:** Atherosclerosis **Volume på tidsskrift:** 268 **Udgiver:** Elsevier **DOI nummer:** <https://doi.org/10.1016/j.atherosclerosis.2017.11.028>

Loss-of-function variants in ADCY3 increase risk of obesity and type 2 diabetes

We have identified a variant in ADCY3 (encoding adenylate cyclase 3) associated with markedly increased risk of obesity and type 2 diabetes in the Greenlandic population. The variant disrupts a splice acceptor site, and carriers have decreased ADCY3 RNA expression. Additionally, we observe an enrichment of rare ADCY3 loss-of-function variants among individuals with type 2 diabetes in trans-ancestry cohorts. These findings provide new information on disease etiology relevant for future treatment strategies.

Forfatter: N Grarup ; I Moltke ; MK Andersen ; M Dalby ; K Vitting-Seerup ; T Kern ; Y Mahendran ; E Jørsboe ; CVL Larsen ; IK Dahl-Petersen ; A Gilly ; D Suveges ; G Dedoussis ; E Zeggini ; O Pedersen ; R Andersson ; Peter Bjerregaard ; Marit Eika Jørgensen ; A Albrechtsen ; T Hansen **Type:** Article | Artikel **Årstal:** 2018 **Emner:** ADCY3; Diabetes; Greenland **Titel på tidsskrift:** Nature Genetics **Volume på tidsskrift:** 50 **DOI nummer:** doi: 10.1038/s41588-017-0022-7

Identification of novel high-impact recessively inherited type 2 diabetes risk variants in the Greenlandic population

Aims/hypothesis: In a recent study using a standard additive genetic model, we identified a TBC1D4 loss-of-function variant with a large recessive impact on risk of type 2 diabetes in Greenlanders. The aim of the current study was to identify additional genetic variation underlying type 2 diabetes using a recessive genetic model, thereby increasing the power to detect variants with recessive effects.

Methods: We investigated three cohorts of Greenlanders (B99, n = 1401; IHIT, n = 3115; and BBH, n = 547), which were genotyped using Illumina MetaboChip. Of the 4674 genotyped individuals passing quality control, 4648 had phenotype data available, and type 2 diabetes association analyses were performed for 317 individuals with type 2 diabetes and 2631 participants with normal glucose tolerance. Statistical association analyses were performed using a linear mixed model.

Results: Using a recessive genetic model, we identified two novel loci associated with type 2 diabetes in Greenlanders, namely rs870992 in ITGA1 on chromosome 5 (OR 2.79, $p = 1.8 \times 10^{-8}$), and rs16993330 upstream of LARGE1 on chromosome 22 (OR 3.52, $p = 1.3 \times 10^{-7}$). The LARGE1 variant did not reach the conventional threshold for genome-wide significance ($p 5 \times 10^{-8}$) but did withstand a study-wide Bonferroni-corrected significance threshold. Both variants were common in Greenlanders, with minor allele frequencies of 23% and 16%, respectively, and were estimated to have large recessive effects on risk of type 2 diabetes in Greenlanders, compared with additively inherited variants previously observed in European populations.

Conclusions/interpretation: We demonstrate the value of using a recessive genetic model in a historically small and isolated population to identify genetic risk variants. Our findings give new insights into the genetic architecture of type 2 diabetes, and further support the existence of high-effect genetic risk factors of potential clinical relevance, particularly in isolated populations.

Forfatter: N Grarup ; I Moltke ; MK Andersen ; Peter Bjerregaard ; CVL Larsen ; IK Dahl-Petersen ; E Jørsboe ; HK Tiwari ; SE Hopkins ; HW Wiener ; BB Boyer ; A Linneberg ; O Pedersen ; Marit Eika Jørgensen ; A Albrechtsen ; T Hansen **Type:** Article | Artikel **Årstal:** 2018 **Emner:** Genetic association; Genome-wide association study; Greenlanders; Inuit; ITGA1; LARGE1; Recessive genetic model; Type 2 diabetes **Titel på tidsskrift:** Diabetologia **Volume på tidsskrift:** 61 **Nummer på tidsskrift:** 9 **Udgiver:** Springer **DOI nummer:** doi: 10.1007/s00125-018-4659-2.

Whole blood mercury and the risk of cardiovascular disease among the Greenlandic population

Background: Studies have found mercury to be associated with cardiovascular disease (CVD), however, primarily in populations with low exposure. The highest levels, and variations in the levels, of whole blood mercury (WBM) worldwide have been found in Greenland. We prospectively assessed the association between WBM and the risk of developing CVD in the Greenlandic population.

Methods: We assessed the effects of WBM levels on incident CVD among 3083 Greenlandic Inuit, participating in a population-based cohort study conducted from 2005 to 2010. WBM was measured at baseline. Participants were followed in the National Patient Registries for Denmark and Greenland and in the causes of death register for CVD events from inclusion in the study until CVD event, emigration, death or end of follow-up (30/9–2013). Using Cox regression analyses, we calculated the incidence rates and the hazard ratio of CVD events according to WBM levels. Potential interactions with sex were also investigated.

Results: The highest levels of WBM were found in men, who had a significantly higher median level (19 µg/L (IQR:1–44)), compared with women (15 µg/L (IQR: 1–32), (p 0.001)). The crude hazard ratio (HR) for incident CVD was 1.00 (95% CI 1.00–1.00) for 5 µg/l increase in WBM. After adjusting for several potential confounders, there was still no association between WBM and incident CVD (HR 0.99; 95%CI:0.99–1.00). We found no interactions with sex.

Conclusions: In a population with high levels of WBM, we found no association between WBM and the risk of developing CVD in Greenland.

Forfatter: TJ Larsen ; Marit Eika Jørgensen; CVL Larsen ; IK Dahl-Petersen ; PF Rønn ; Peter Bjerregaard; S Byberg **Type:** Article | Artikel **Årstal:** 2018 **Emner:** Whole blood mercury; Cardiovascular disease; Inuit; Greenland **Titel på tidsskrift:** Environmental Research **Volume på tidsskrift:** 146 **Udgiver:** Elsevier **DOI nummer:** <https://doi.org/10.1016/j.envres.2018.03.003>

Research | Forskning - peer review > Article | Artikel

Gestational diabetes and macrosomia among Greenlanders. Time to change diagnostic strategy?

Gestational diabetes mellitus (GDM) is a serious condition associated to both maternal and offspring complications. Yet, no globally accepted consensus exists on how to test and diagnose GDM. In Greenland, the clinical criteria for testing and diagnosing GDM are adapted from Danish guidelines. The aim of this study was to estimate the prevalence of GDM among Greenlanders using both the current clinical GDM criteria and the recent WHO 2013 criteria and, further, to study the association between GDM, pre-pregnant overweight or obesity and macrosomia. A cross-sectional study of all 450 Greenlandic women who gave birth to a singleton in Nuuk within 1 year was performed. Based on an oral glucose tolerance test measuring capillary whole blood glucose, 119 women were categorised as having clinical GDM, WHO 2013 GDM or not GDM. Macrosomia defined as birth weight above 4,000 g was used as outcome variable. The prevalence of clinical GDM and WHO 2013 GDM was 0.4% (95% CI; 0–1.1) and 6.9% (95% CI; 4.5–9.2). WHO 2013 GDM, fasting blood glucose, pre-pregnant maternal overweight and obesity were associated with macrosomia. WHO 2013 GDM criteria were superior to clinical criteria in predicting macrosomia indicating that it may be time to consider the diagnostic strategy used in Greenland. Pre-pregnant overweight may also need more intensified lifestyle-intervention.

Forfatter: Michael Lyng Pedersen; O Lind ; T Abelsen ; J Olesen ; Marit Eika Jørgensen **Type:** Article | Artikel **Årstal:** 2018 **Emner:** Gestational diabetes; Diagnostic; Prevalence; Macrosomia; Overweight; Inuit; Greenland **Titel på tidsskrift:** Journal of Circumpolar Health **Volume på tidsskrift:** 77 **Udgiver:** Taylor & Francis **DOI nummer:** <https://doi.org/10.1080/22423982.2018.1528126>

Research | Forskning - peer review > Article | Artikel

Validation of cardiovascular diagnoses in the Greenlandic Hospital Discharge Register for epidemiological use

Cardiovascular disease (CVD) is one of the leading causes of death worldwide. In Greenland, valid estimates of prevalence and incidence of CVD do not exist and can only be calculated if diagnoses of CVD in the Greenlandic Hospital Discharge Register (GHDR) are correct. Diagnoses of CVD in GHDR have not previously been validated specifically. The objective of the study was to validate diagnoses of CVD in GHDR. The study was conducted as a validation study with primary investigator comparing information in GHDR with information in medical records. Diagnoses in GHDR were considered correct and thus valid if they matched the diagnoses or the medical information in the medical records. A total of 432 online accessible medical records with a cardiovascular diagnosis according to GHDR from Queen Ingrid's Hospital from 2001 to 2013 (n=291) and from local health care centres from 2007 to 2013 (n=141) were reviewed. Ninety-nine and ninety-two percent of discharge diagnosis in GHDR from Queen Ingrid's Hospital and local health care centres were correct in comparison with diagnoses in the medical record indicating valid registration practice. The correctness of cardiovascular diagnoses in GHDR was considered high in terms of acceptable agreement between medical records and diagnoses in GHDR. Cardiovascular diagnoses are valid for epidemiological use.

Forfatter: M Tvermosegaard ; PF Rønn ; Michael Lynge Pedersen; Peter Bjerregaard; IK Dahl Pedersen ; CVL Larsen ; Marit Eika Jørgensen **Type:** Article | Artikel **Årstal:** 2018 **Emner:** Cardiovascular disease; Diagnoses; Inuit; Greenland; Register **Titel på tidsskrift:** International Journal of Circumpolar Health **Volume på tidsskrift:** 77 **Udgiver:** Taylor & Francis **DOI nummer:** <https://doi.org/10.1080/22423982.2017.1422668>
