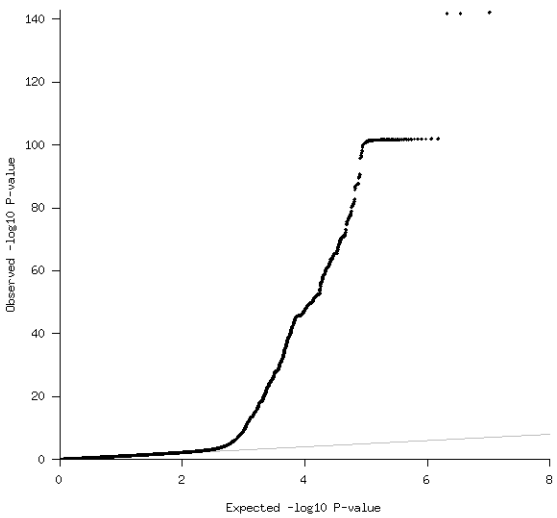
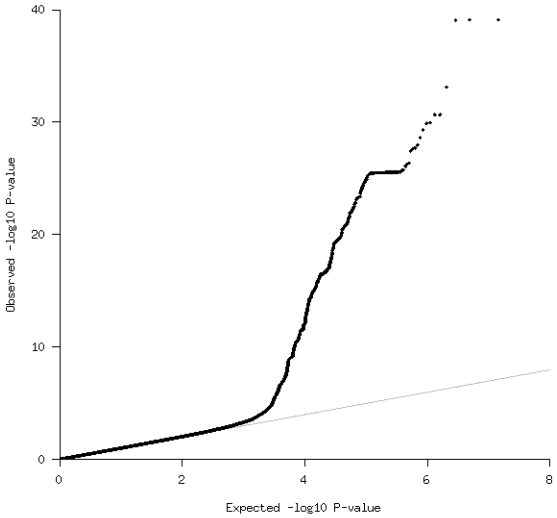
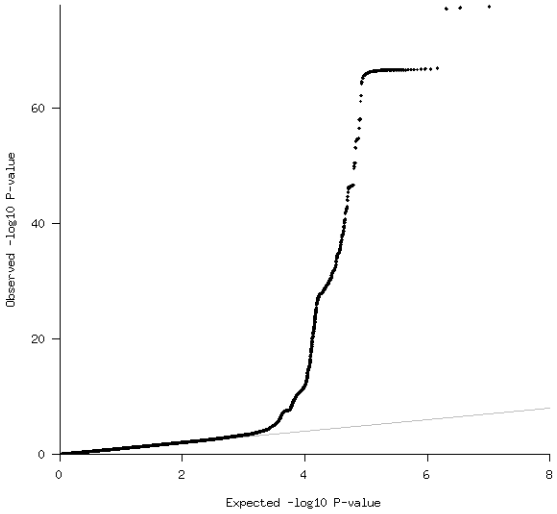
SUPPLEMENTARY DATA

Supplementary Figure 1. QQ plots for (A) LADA vs. population controls, (B) LADA vs. T1D, and (C) LADA vs. T2D

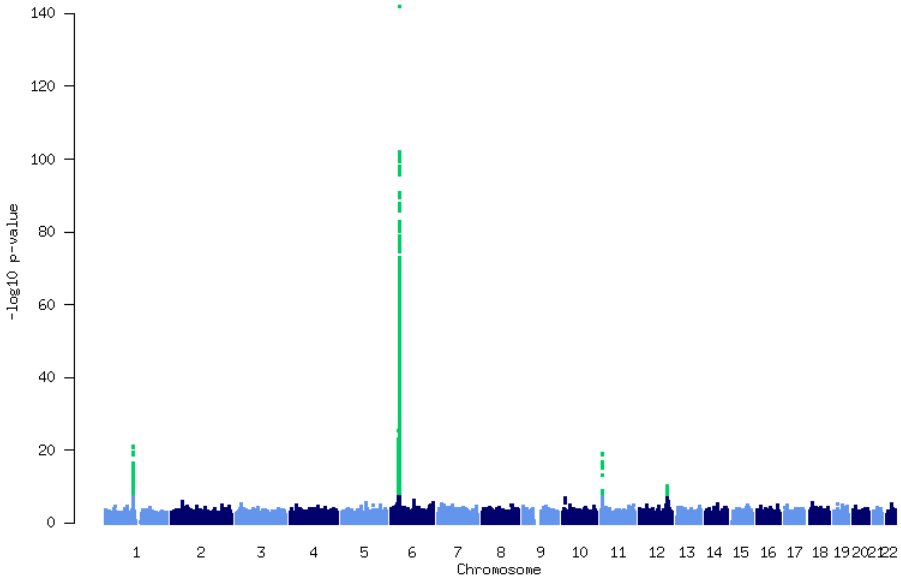


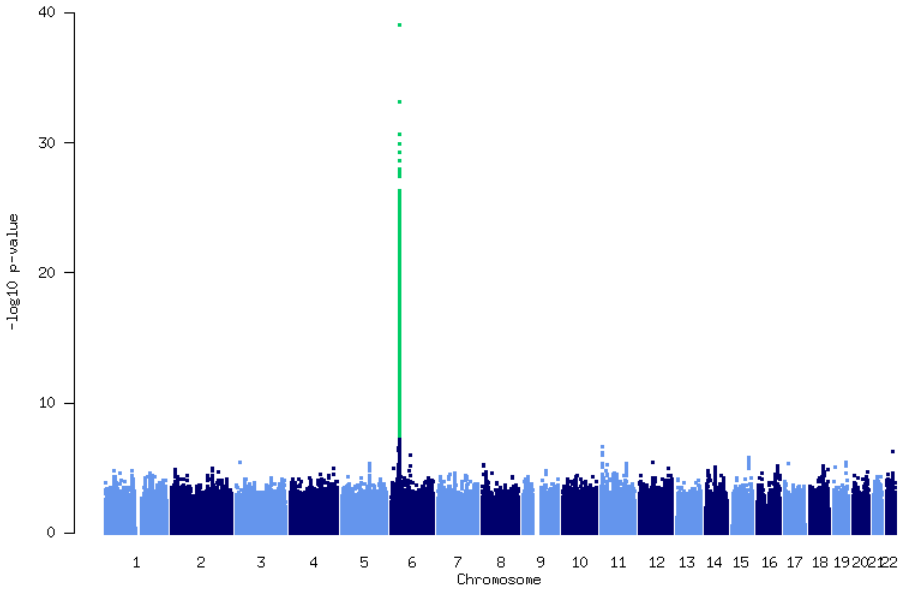




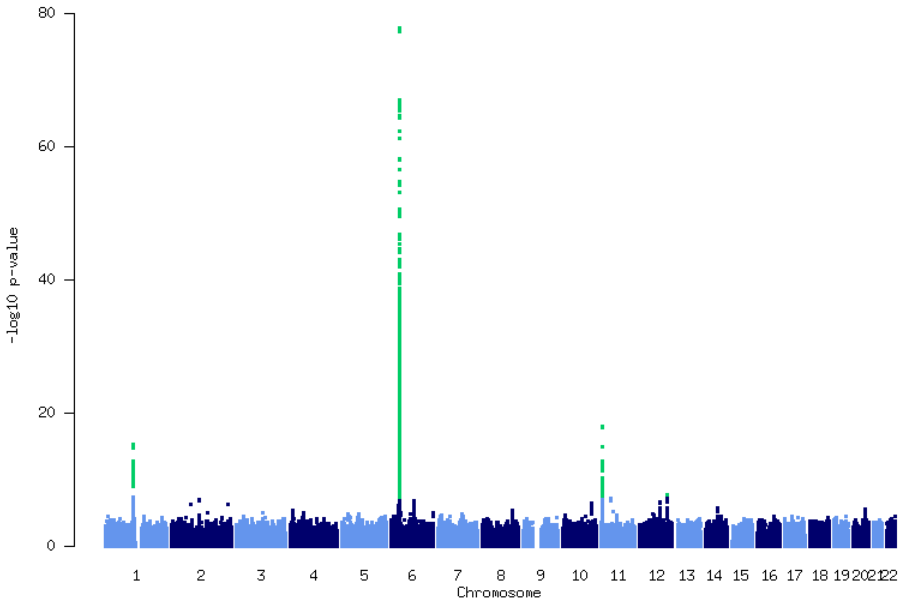
SUPPLEMENTARY DATA

Supplementary Figure 2. Manhattan plots for (A) LADA vs. population controls, (B) LADA vs. T1D, and (C) LADA vs. T2D





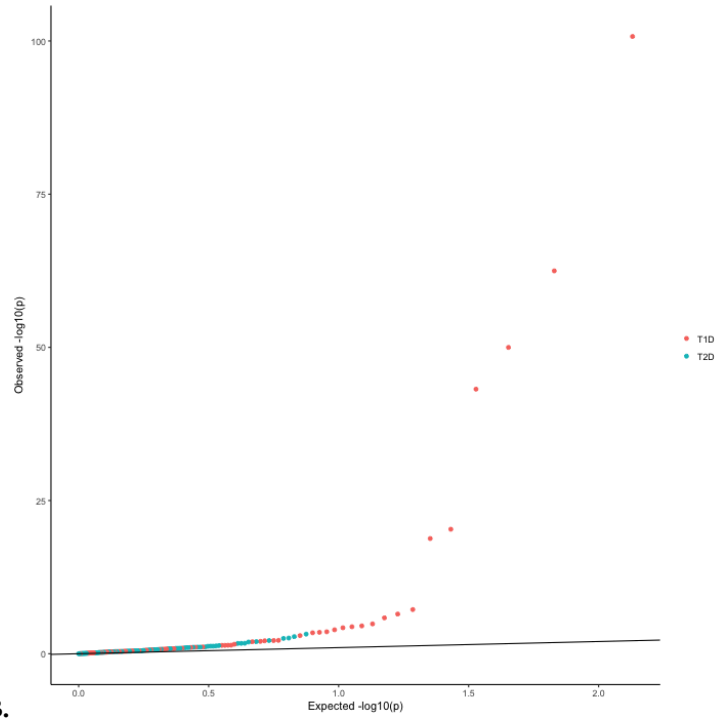
SUPPLEMENTARY DATA



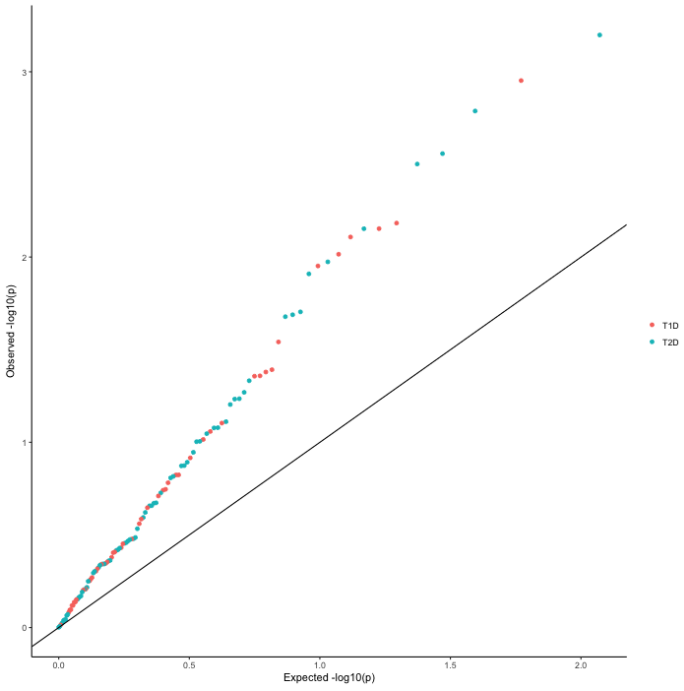
SUPPLEMENTARY DATA

Supplementary Figure 3. QQ plots showing established T1D (red) and T2D (blue) loci in LADA vs. population controls. A) All loci; B) zoomed in at $1 > P > 10^{-4}$ (excluding top T1D signals).

A.



B.



SUPPLEMENTARY DATA

Supplementary Note: Cohort Information

Cohort name: Action Lada

Cohort type: LADA cases

Inclusion/exclusion criteria: Patients were designated with diabetes according to standard criteria, and LADA was defined as follows: patients 1) aged 30–70 years, 2) with diabetes associated autoantibodies, and 3) who did not require insulin treatment for at least 6 months post diagnosis. Type 1 autoimmune diabetic patients were defined as case subjects with diabetes and with diabetes-associated autoantibodies where insulin was started at diagnosis or within 1 month of diagnosis. Inclusion criteria for all patients were that patients have diabetes (with at least two recorded fasting blood glucose measurements >7 mmol/L), that time from diagnosis was 5 years for all patients, and that patients were aged 30–70 years at the time of recruitment. Exclusion criteria were insufficient dataset, current pregnancy, renal disease with raised creatinine or proteinuria, or acute illness at the time of testing.

Number of study subjects: 1098

Acknowledgements: We would like to acknowledge the Action Lada consortium.

Funding: This study was partially funded by the 5th Framework Programme of the European Union.

Cohort reference: REC Reference P/02/240

Conflicts of interest: No potential conflicts of interest relevant to this work.

Cohort name: Action Lada 'Plus'

Cohort type: LADA cases

Inclusion/exclusion criteria: Patients were designated with diabetes according to standard criteria, and LADA was defined as follows: patients 1) aged 30–70 years, 2) with diabetes associated autoantibodies, and 3) who did not require insulin treatment for at least 6 months post diagnosis. Type 1 autoimmune diabetic patients were defined as case subjects with diabetes and with diabetes-associated autoantibodies where insulin was started at diagnosis or within 1 month of diagnosis. Inclusion criteria for all patients were that patients have diabetes (with at least two recorded fasting blood glucose measurements >7 mmol/L), that time from diagnosis was 5 years for all patients, and that patients were aged 30–70 years at the time of recruitment. Exclusion criteria were insufficient dataset, current pregnancy, renal disease with raised creatinine or proteinuria, or acute illness at the time of testing.

Number of study subjects: 441

Acknowledgements:

Funding:

SUPPLEMENTARY DATA

Cohort reference:

Conflicts of interest:

Cohort name: All New Diabetics In Scania (ANDIS)

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): LADA cases

Inclusion/exclusion criteria:

GAD

ELISA: Negative:< 5 kE/L, Positive:=> 10 kE/L

RIA: Negative:0-34 U/ml, Positive:> 50 U/ml

LADA

Age at onset ≥ 35 years

GAD (ELISA) > 10 kE/L

GAD (RIA) >50 U/ml

Non-Scandinavian individuals excluded

Number of study subjects: 440

Acknowledgements: We thank all the patients and the health care providers across Scania and Ostrobothnia for their support and their willingness to participate. We would also like to thank Johan Hultman, Jasmina Kravic, Maria Fälemark, Christina Rosborn, Gabriella Gremsperger, Maria Sterner, Malin Neptin, Lisa Sundman, Paula Kokko, and Ulrika Blom-Nilsson for excellent technical and administrative support. Finally we would like to thank Rita Jedlert and Region Skåne (Scania County) as well as the ANDIS steering committee for their support.

Funding: Supported by grants from the Swedish Research Council (including project grants Dnr.521-2010-3490 and infrastructure grants Dnr. 2010-5983 and Dnr 2012-5538 to LG), Linnéus grant 349-2006-237, a strategic research grant (Exodiab Dnr 2009-1039), an ERC Advanced Research grant (GA 269045) and Academy of Finland (grants no. 263401 and 267882) to LG.

Cohort reference: http://andis.ludc.med.lu.se/

Conflicts of interest: None

Cohort name: Bone Mineral Density in Childhood Study (BMDCS)

SUPPLEMENTARY DATA

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): population controls

Cohort description: The Bone Mineral Density in Childhood Study is a multicenter, longitudinal study of bone accrual in healthy children.
Inclusion/exclusion criteria: Only individuals of European ancestry were included.

Number of study subjects: 1056

Acknowledgements: We appreciate the dedication of the study participants and their families, and the support of Dr. Karen Winer, Scientific Director of the Bone Mineral Density in Childhood Study.

Funding: The BMDCS was funded by the National Institutes of Health [grant number R01 HD58886 to B.Z. and S.G.]; the Eunice Kennedy Shriver National Institute of Child Health and Human Development [grant numbers N01-HD-1-3228, -3329, -3330, -3331, -3332, -3333]; the Clinical and Translational Science Awards Program [grant number 8 UL1 TR000077]; American Diabetes Association Grant 1-17-PDF-077 [to D.C.]; and the Institute for Translational Medicine and Theraputics (ITMAT) Transdisciplinary Program in Translational Medicine and Therapeutics (to D.C., B.V., and S.G.). The project described was supported by the National Center for Research Resources [grant number UL1RR024134], and is now at the National Center for Advancing Translational Sciences [grant number UL1TR000003]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of interest: None

Study cohort: Copenhagen Controls

The Copenhagen Control sample is collected from two cohorts (The 1936 birth cohort and ADDITION-PRO), and comprises 1974 non-diabetic adults. The control subjects had a mean age of 64.42 (range, 34.44), and 49.9% were male.

Cohort name: The 1936 birth cohort

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): Population controls

Cohort description/inclusion/exclusion criteria: The cohort consists of all subjects born in 1936, who, on 2 April 1976, were resident in one of four municipalities nearby Glostrup Hospital, Denmark (n=695). The cohort was collected to assess the age-specific prevalence of diabetes mellitus and impaired glucose tolerance in 60-year-old individuals in 1996/97.

Number of study subjects: 624 non-diabetic individuals (502 NGTs, 122 IFG/IGTs)

Acknowledgements: The authors are grateful to the staff at the Centre of Preventive Medicine, and to MD, general practitioner, Professor Hanne Hollnagel Dr Med. Sci., who initiated the study of the 1936 cohort.

SUPPLEMENTARY DATA

Funding: The collection of the cohort was financially supported by The Danish Heart Foundation and The Danish Medical Research Council.

Cohort reference: Drivsholm T. Increasing prevalence of diabetes mellitus and impaired glucose tolerance among 60-year-old Danes. *Diabet Med* 2001.

Conflicts of interest: NA

Cohort name: ADDITION-PRO

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): Controls

Cohort description/inclusion/exclusion criteria: ADDITION-PRO is a longitudinal cohort study of 2082 adults (>45 years) collected to have IGT, IFG, or NGT either with high or low risk of developing type 2 diabetes (based on information about age, sex, gestational diabetes, family history of diabetes, hypertension, BMI, and level of physical activity).

The samples were collected in 2009–2011from four Danish research centres (Steno Diabetes Center, Aarhus University Hospital, Holstebro Hospital, and Hospital of South West Jutland, Esbjerg).

Number of study subjects: 1350 non-diabetic individuals (812 NGTs, 538 IFG/IGTs)

Acknowledgements: The ADDITION-PRO study is managed by the ADDITION-DK steering committee (Torsten Lauritzen, Knut Borch-Johnsen, Annelli Sandbæk, Marit E. Jørgensen, and Daniel Witte).

Funding: The ADDITION-PRO study was funded by an unrestricted grant from the European Foundation for the Study of Diabetes/Pfizer for Research into Cardiovascular Disease Risk Reduction in Patients with Diabetes (74550801), the Danish Council for Strategic Research, internal research and equipment funds from Steno Diabetes Center and supported by research grants from the Novo Nordisk Foundation.

Cohort reference: Johansen et al. Protocol for ADDITION-PRO: a longitudinal cohort study of the cardiovascular experience of individuals at high risk for diabetes recruited from Danish primary care. *BMC Public Health* 2012.

Conflicts of interest: NA

Study cohort: Copenhagen LADA

The Copenhagen LADA sample (n=539) is collected from six cohorts (DD2, Vejle Biobank, OUH, CIMT, Inter99, and SDC). The LADA patients had a mean age of 58.32 (range, 67.31), and 56.2% were male.

The following inclusion criteria for LADA have been applied in all sub-cohorts: GADA positive, ≥20 years at the time of diagnosis, and treated without insulin for the first year after diagnosis or having fasting serum C-peptide ≥300 pmol/L at the time of investigation.

SUPPLEMENTARY DATA

Cohort name: Danish Centre for strategic Research in Type 2 Diabetes (DD2)

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): LADA cases

Cohort description/inclusion/exclusion criteria: DD2 is nationwide cohort, enrolling patients with newly diagnosed type 2 diabetes from general practitioners and hospital specialist outpatient clinics since 2010. GADA was measured in 5966 patients, with an AESKULISA assay.

Number of study subjects: 158 LADA cases

Acknowledgements: The DD2-project partners are listed on the website ww.DD2.nu.

Funding: The DD2 study is supported by the Danish Agency for Science (grant no. 09-067009 and 09-075724), the Danish Health and Medicines Authority, the Danish Diabetes Association, and an unrestricted donation from Novo Nordisk A/S.

Cohort reference: Thomsen et al. The Danish Centre for Strategic Research in Type 2 Diabetes (DD2): Organization of diabetes care in Denmark and supplementary data sources for data collection among DD2 study participants. *Clin Epidemiol* 2012.

Conflicts of interest: NA

Cohort name: Vejle Biobank

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): LADA cases

Cohort description/inclusion/exclusion criteria: The Vejle Diabetes Biobank was established as a regional Bio bank and comprises individuals with diabetes and a gender- and age-matched control population. All participants were aged between 25 and 75 years (both ages included) and residing in the former County of Vejle area on December 31, 2006. Altogether, 3320 patients with type 2 diabetes or type 1 diabetes were recruited from the central database at Vejle Hospital Laboratory Center. GADA were measured in all 3320 patients, with an AESKULISA assay.

Number of study subjects: 124 LADA cases

Acknowledgements: The laboratory technologists Britta Kristensen, Lene Juul Hansen, Annette Kaaris, Jan Johannsen, Merete Willumsen, Birgitte Henriksen, Camilla Davidsen, and Sara Egsgaard are acknowledged for their continued engagement and dedicated work.

Funding: The Vejle Biobank project was funded by the Danish Council for Independent Research/Medical Sciences, the Research Council of Vejle Hospital, the Department of Internal Medicine, Vejle Hospital, Vejle County, the Danish Research Fund, the Lions Club International Denmark, and anonymous donations.

SUPPLEMENTARY DATA

Cohort reference: Petersen et al. Vejle Diabetes Biobank – a resource for studies of the etiologies of diabetes and its comorbidities. *Clin Epidemiol*. 2016.

Conflicts of interest: NA

Cohort name: OUH

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): LADA cases

Cohort description/inclusion/exclusion criteria: The OUH LADA cohort is collected from a database of patients with diabetes newly referred to Odense University Hospital (OUH), Denmark, between 1997 and 2011. GAD autoantibodies were measured in 5,671 patients with diabetes, applying an RSR RIA assay, 279 were GADA positive, above 30 years of age, and had fasting C-peptide above 300 pmol/l. Of these DNA was available for 66.

Number of study subjects: 66 LADA cases

Acknowledgements: Department of Endocrinology, Odense University Hospital, Denmark, is acknowledged for their collection of the OUH cohort.

Funding: NA

Cohort reference: NA

Conflicts of interest: NA

Cohort name: CIMT

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): LADA cases

Cohort description/inclusion/exclusion criteria: The CIMT trial is a multicenter randomized placebo controlled superiority trail conducted from 2008 to 2012 at eight hospitals in the capital region of Denmark. Inclusion criteria included diagnosis of type 2 diabetes, >30 years at diagnosis, BMI >25 kg/m^2, HbA_{1c}>7.5%, treatment with oral anti-diabetic drugs for ≥1 year, and/or insulin treatment for ≥3 months. Exclusion criteria included: major cardiovascular disease within the past 3 months, carotid artery stenosis >70%, heart failure, recent cancer, renal or liver disease, alcohol or drug abuse, unstable retinopathy, pregnancy, breastfeeding, fertile women not using anticonception, or allergy towards trial medication. Altogether, 412 type 2 diabetes patients were included in the trial and were screened for the presence of GADA with an RSR ELISA kit.

Number of study subjects: 31 LADA cases

Acknowledgements: The CIMT trial group is acknowledged for their effort in collecting and characterizing the cohort.

SUPPLEMENTARY DATA

Funding: The CIMT study was funded by an unrestricted grant from Novo Nordisk A/S.

Cohort reference: Lundby et al. Study rationale and design of the CIMT trial: the Copenhagen Insulin and Metformin Therapy trial. *Diabetes Obes Metab* 2009.

Conflicts of interest: NA

Cohort name: Inter99

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): LADA cases

Cohort description/inclusion/exclusion criteria: Inter99 is a population based intervention cohort, comprising individuals from the Copenhagen area. Altogether 6784 individuals participated in the baseline examination. GADA were measured in 2531 individuals, with an RSR ELISA kit.

Number of study subjects: 19 LADA cases

Acknowledgements: The staff from Research Centre for Prevention and Health, The capital region, Glostrup, Denmark is acknowledged their effort in making the Inter99 study possible.

Funding: The Inter99 study is funded by The Danish Medical Research Council, The Danish Centre for Evaluation and Health Technology Assessment, Novo Nordisk, Copenhagen County, The Danish Heart Foundation, The Danish Pharmaceutical Association, Augustinus foundation, Ib Henriksen foundation and Becket foundation.

Cohort reference: Jørgensen et al. A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: baseline results Inter99. *Eur J Cardiovasc Prev Rehabil*. 2003.

Conflicts of interest: NA

Cohort name: SDC

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): LADA cases

Cohort description/inclusion/exclusion criteria: The SDC cohort comprises patients >18 years with type 2 diabetes (n=1676) recruited from the outpatient clinic at Steno Diabetes Center, Gentofte, Denmark. Individuals in pregnancy, having another cause of diabetes or being of another ethnicity than Danish were excluded. GADA were measured in 1595 individuals. Of the 141 LADA patients, GADA were measured with RSR ELISA in 52 patients, and with AESKULISA in 89 patients.

Number of study subjects: 141 LADA cases

Acknowledgements: NA

SUPPLEMENTARY DATA

Funding: NA

Cohort reference: NA

Conflicts of interest: NA

Copenhagen general acknowledgements: Novo Nordisk Foundation Center for Basic Metabolic Research is an independent research center at the University of Copenhagen and is partly funded by an unrestricted donation from the Novo Nordisk Foundation. This work was supported by a research grant from the Danish Diabetes Academy supported by the Novo Nordisk Foundation, and grants from The Danish Council for Independent Research - Medical Sciences.

Cohort name: Diabetes Registry Vasa (DIREVA)

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): LADA cases/ T1D cases/ T2D cases

Inclusion/exclusion criteria: LADA

Age at onset ≥ 35 years
C-peptide (KLU) > 0.2 nmol/L
GAD65a (EIA) ≥ 10 U/ml

T1D
Age at onset < 35 years
C-peptide (KLU) < 0.2 nmol/L

T2D
Age at onset ≥ 35 years
C-peptide (KLU) ≥ 0.2 nmol/L
GAD65a (EIA) <10 U/ml

Number of study subjects: 3290

Acknowledgements: Same as for ANDIS

Funding: DIREVA was supported by the Vasa Hospital district.

+funding overlapping with ANDIS

Cohort reference: NA

Conflicts of interest: None

Cohort name: GoDARTS

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):

- population controls (replication study only) 969
- LADA cases 206
- T2D cases 4413

Inclusion/exclusion criteria:

- Age diagnosis <35
- No insulin within 1 year diagnosis
- GADA positive

Number of study subjects: (see above)

Acknowledgements: The Wellcome Trust United Kingdom Type 2 Diabetes Case Control Collection (GoDARTS) cohort collection was funded by The Wellcome Trust and informatics support is provided by the Chief Scientist Office, Scotland. E.R.P. holds a Wellcome Trust New Investigator Award (102820/Z/13/Z).

Funding: NA

Cohort reference: Diabetes Care. 2014;37(3):718-24. (PMID: 24186880)

Conflicts of interest: NA

Cohort name: HUNT

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): LADA and T2D cases and non-diabetic population controls

Inclusion/exclusion criteria: LADA: Self-reported yes to having diabetes, positive for GAD antibodies, initial age at diagnosis >30 years old and no insulin treatment within one year of diagnosis.

T2D: Self-reported yes to having diabetes, GAD antibodies negative, initial age at diagnosis >30 years old and no insulin treatment within one year of diagnosis. Age and gender matched to the LADA cases.

Non-diabetic controls: Self-reported no to ever having diabetes and had non-fasting serum glucose <7.0 mmol/l. Age and gender matched to the LADA cases.

Number of study subjects: 139 LADA, 695 T2D and 695 non-diabetic controls

SUPPLEMENTARY DATA

Acknowledgements: The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

Funding: The K.G. Jebsen Center for Genetic Epidemiology is financed by Stiftelsen Kristian Gerhard Jebsen; Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology; the Liaison Committee between the Central Norway Regional Health Authority and NTNU; and the Liaison Committee between St. Olavs Hospital and the Faculty of Medicine and Health Sciences at NTNU.

The genotyping was financed by the National Institute of Health (NIH), University of Michigan, The Norwegian Research Council, the Liaison Committee between the Central Norway Regional Health Authority and NTNU, and the Liaison Committee between St. Olavs Hospital and the Faculty of Medicine and Health Sciences at NTNU.

Cohort references:

Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen TL, Bratberg GH, Vatten L, Lund-Larsen PG. *The Nord-Trøndelag Health Study 1995–97 (HUNT2): objectives. contents. methods and participation.* Norsk Epidemiologi 2003. **13**(1): p. 19-32.

Krokstad S, et al. *Cohort Profile: the HUNT Study. Norway.* Int J Epidemiol. 2013. **42**(4): p. 968-77.

Nielsen JB et al (2018) Genome-wide Study of Atrial Fibrillation Identifies Seven Risk Loci and Highlights Biological Pathways and Regulatory Elements Involved in Cardiac Development. Am J Hum Genet. 102(1):103-115 [29290336].

Conflicts of interest: There are no disclosures to report.

Cohort name: Malmö Diet and Cancer study

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): Non-diabetic controls

Inclusion/exclusion criteria:

Diabetes

Number of study subjects: 3126

Acknowledgements: NA

Funding: NA

SUPPLEMENTARY DATA

Cohort reference: Berglund G, Nilsson P, Eriksson KF, Nilsson JA, Hedblad B, Kristenson H, et al. Long-term outcome of the Malmo preventive project: mortality and cardiovascular morbidity. J Intern Med. 2000;247(1):19-29. Epub 2000/02/15.

Conflicts of interest: None

Cohort name: Scania Diabetes Registry (SDR)

Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases): LADA cases/ T1D cases/ T2D cases

Inclusion/exclusion criteria:

SDR

GAD (Wallenberg lab (AU ref < 5.0)

GAD (Wallenberg lab (IU/ml ref <32)

C-peptide (Klin kem (RIA) ref 0.25-0.75)

C-peptide (Klin kem ref 0.3-1.3)

C-peptide (Lund (ref 0.25-0.75)

LADA

Age at onset ≥ 35

GAD ≥ 10 AU

GAD ≥ 50 IU/ml

T1D

Age at onset < 35

GAD ≥ 20 AU

GAD ≥ 100 IU/ml

C-peptide ≥ 0.25 (Klin kem (RIA))

C-peptide ≥ 0.3 (Klin kem)

C-peptide ≥ 0.25 (Lund)

T2D

BMI > 25

GAD < 5 AU

GAD ≤ 34 IU/ml

C-peptide (Klin kem (RIA)) ≥ 0.75

C-peptide (Klin kem) ≥ 1.3

C-peptide (Lund) ≥ 0.75

For patients that did not fulfill the criteria for any of the above, the diagnosis given by their physician was used

SUPPLEMENTARY DATA

Non-Scandinavian individuals excluded

Number of study subjects: 3567

Acknowledgements: NA

Funding: NA

Cohort reference: Lindholm E, Agardh E, Tuomi T, Groop L, Agardh CD. Classifying diabetes according to the new WHO clinical stages. Eur J Epidemiol. 2001;17(11):983-9. Epub 2002/10/17.

Conflicts of interest: None

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