

Published in final edited form as:

Int J Epidemiol. 2017 June 1; 46(3): 796–796i. doi:10.1093/ije/dyw152.

Cohort Profile: Scottish Diabetes Research Network Type 1 Bioresource Study (SDRNT1BIO)

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Keywords

SDRNT1BIO; Type 1 Diabetes; Cohort Profile

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Conflict of interest:

H.M.C.: research support and honorarium and member of advisory panels and speaker's bureaus for Sanofi Aventis, Regeneron, and Eli Lilly; Advisory Panel for Novartis Pharmaceuticals; research support from Roche Pharmaceuticals, Pfizer Inc., Boehringer Ingelheim, and AstraZeneca LP; shareholder of Roche Pharmaceuticals and Bayer. R.S.L.: member of advisory panels for Novo Nordisk and Eli Lilly; research support from Novo Nordisk, Eli Lilly and GlaxoSmithKline. The other authors declare no conflict of interest.

Why was the cohort set up?

Rationale for setting up the cohort

Type 1 diabetes mellitus (T1DM) affects approximately 0.4-0.5% of the population. A 70% increase in prevalent cases of T1DM in those aged under 15 years in Europe between 2005 and 2020 is predicted.(1) T1DM continues to be associated with substantial mortality, with an estimated current period life expectancy differential of 11-13 years.(2) The main chronic complications include cardiovascular disease (CVD), nephropathy, retinopathy and neuropathy. CVD risk continues to be increased 2-3 fold relative to the general population and diabetic kidney disease remains a major determinant of early mortality in people with T1DM.(3)

As detailed in the strategic plans of the main diabetes research funders, research priorities include a better understanding of the determinants of T1DM and its complications including genetic determinants, improved methods for early detection of complications [www.diabetes.org.uk] and the development of sensitive biomarkers for complications [www.jdrf.org]. The availability of large prospective cohorts of patients, well characterised for complications, is pivotal to such research. Accordingly, we established the Scottish Diabetes Research Network Type 1 Bioresource (SDRNT1BIO) to facilitate a wide range of research including, but not limited to the following.

1 Discovery and validation of genetic determinants of type 1 diabetes

T1DM is partly genetically determined and more than 50 associated genetic loci have been identified with the human leukocyte antigen (HLA) region on chromosome 6 having the major role.(4) These discoveries yielded insights into the potential pathways causing diabetes some of which are now being targeted by novel intervention therapies. However, more than 50 known genetic loci for T1DM do not explain all the known heritability, with estimates of missing heritability varying from 20-80%.(5,6) Among several potential explanations for this “missing heritability” are the existence of rare variants with large effects and the existence of additional more common variants with effects too low to have been detected by sample sizes used so far. Existing genetic studies of T1DM have been based on around 12000 cases, which is many times lower than sample sizes in meta-analyses of genome-wide association studies (GWAS) for type 2 diabetes mellitus (T2DM).(4) Of note, almost all studies to date are in cohorts of childhood-onset T1DM, despite the fact that almost 50% of T1DM has its onset in adulthood. The largest study to date of older onset T1DM was limited to evaluation of already known loci in 1212 autoantibody-positive adults with diabetes in which subtle age of onset effects were found for some loci.(7,8) Thus, additional discovery work to detect new T1DM loci is warranted especially for those with older age of onset. We will conduct genome wide association studies using the SDRNT1BIO cohort and a background population representative control set of genotypes from Scotland.

2 Discovery and validation of genetic determinants of complications of T1DM

Many complications of diabetes are heritable (20-50% for retinopathy and nephropathy), justifying attempts to discover their genetic determinants.(9) Few unequivocal replicable genetic associations have been found, so large scale initiatives are underway although many

have greater focus on T2DM than T1DM because of the greater prevalence and larger T2DM cohorts [www.imi-summit.eu]. The GENIE Consortium has focused on nephropathy in T1DM and a JDRF funded consortium on the genetics of nephropathy in T1DM is currently underway.(10) For many other phenotypes of relevance in T1DM efforts to discover genetic determinants are sparse. For example, there is little genetic data on neuropathy,(11) propensity to hypoglycaemia, or diabetic ketoacidosis. Thus the GWAS data from the SDRNT1BIO will augment existing international efforts to understand the genetics of macro- and micro-vascular complications of diabetes and will provide novel GWAS studies of neglected traits.

3 Pathogenesis and biomarkers of complications

Several extremely productive prospective cohort studies of T1DM have yielded much of what we know about the pathogenesis and risk factors for complications and how these differ between T1DM and T2DM. These include the EURODIAB PCS ($n=2787$) (12), the Pittsburgh EDC ($n=658$) (13), the DCCT/EDIC ($n=1300$) (14), ORPS ($n=554$) (15), WESDR (n around 1000) (16), CACTI (n around 656) (17), and FinnDiane (n around 4500). (18) However, the total sample size and number of incident cases of complications across these cohorts does not provide adequate power for discovery efforts. Larger cohort studies in T1DM such as the Swedish National Diabetes Register, use regular reporting of risk factors from clinical sites and linkage to routine data but do not currently have any sample collection.(19) To fully exploit new 'omic methods for pathway and biomarker discovery, including lipidomics, metabolomics and genomics, and to develop more precise prediction algorithms for complications that incorporate new biomarkers, further large cohorts of T1DM patients are needed to supplement these existing excellent cohorts. With SDRNT1BIO, we decided to harness Scotland's e-health care record system, and the existence of a unique health care identifier across all records in Scotland, to enable the creation of a cohort in which extensive prospective routine data are automatically captured.

4 Stratification of apparent T1DM

The gold standard biomarker of endogenous insulin production is C-peptide concentrations. Previously it was believed that those with T1DM have no residual insulin secretion. With the development of ultra-sensitive C-peptide assays, there is increasing realisation that detectable levels of C-peptide are much more common in T1DM than previously thought. (20,21,22) Exploring the genetic and immunological differences between those with and without detectable C-peptide might yield possible mechanisms for preserving beta cell function and preventing or even reversing T1DM; this is another question being addressed by the SDRNT1BIO.(23)

Another aspect of diabetes stratification is the improved detection of maturity onset diabetes of the young (MODY) among those misdiagnosed as having T1DM. Diagnosis of MODY remains difficult and at present it is estimated only around 25% of all MODY are correctly diagnosed.(24) The data collected on family history, genotype, C-peptide and auto-antibody status, along with sequencing of potential cases, will allow us to compare the yield of cases from various detection algorithms.

5 Environmental and socio-economic determinants of T1DM

The environmental determinants of T1DM remain largely unknown (putative factors include infection e.g. congenital rubella, caesarean section, older maternal age, Vitamin D deficiency).(25) Although prospective cohort studies with data pre-dating onset of diabetes are an ideal design for examining such factors they are challenging with a disease of relatively low incidence such as T1DM. Nonetheless, the SDRNT1BIO can yield useful information on the role of environment, for example by examining how the pattern of potential risk factors varies with genotype or auto-antibody phenotype. Accordingly we have collected some lifestyle, environment and pre-diagnosis data. For T1DM complications the SDRNT1BIO and linked e-health record data is being used to explore socio-economic differentials and the impact of health care activities on complications.

Where is it located and how is it funded?

The SDRNT1BIO was established with joint funding from the Scottish Chief Scientist Office and Diabetes UK. The study activities, including protocol development and recruitment of participants, were overseen by a Study Steering Committee including a patient representative, the study funders, and lead diabetes consultants from participating Scottish Health Boards. All data (baseline and prospective) are held at the co-ordinating centre at the University of Edinburgh, Scotland UK.

Who is in the cohort?

Study Design, Entry criteria and Sampling Frame

Eligibility criteria are summarised in Table 1. We aimed to recruit a representative sample of all adults aged 16 years and older with a clinical diagnosis of T1DM or with monogenic diabetes (i.e. MODY) or with a diagnosis of latent auto-immune disease of adulthood.

The SDRNT1BIO cohort was established using a cross-sectional design for the study fieldwork with recruitment primarily focused on 10 of 14 NHS Board regions in Scotland (Table 2). The Boards not targeted were excluded because of the envisaged high cost per participant recruited given the remote geographic location and low population density (i.e. the Shetland Orkney and Western Islands and Scottish Borders).

The sampling frame used was the comprehensive SCI-Diabetes electronic health care record in which > 99% of patients with diagnosed diabetes are estimated to be registered. This estimate is based on the fact that 99.5% of general practices nationally are electronically queried nightly for all records with diagnostic codes for diabetes. Diagnostic coding levels are very high for adults because they are required before practices can receive payments under the general practice United Kingdom pay-for-performance program. Validation against other datasets such as hospital admissions with diabetes codes are consistent with this > 99% estimate of coverage.(26) Recruitment was primarily undertaken at diabetes outpatient clinics with some additional recruitment in renal units since end stage renal disease patients have lower attendance at diabetes clinics. GP-based clinics were included at a few sites of high population density, though at present very few people with T1DM in Scotland are managed solely in primary care. At participating clinics we systematically

evaluated each clinic list for the subsequent week and as many eligible patients, that could be seen on the day, were invited to take part on the day or at a subsequent clinic visit. There was sufficient research nurse time for 78% (7593/9731) of all attending eligible patients to be invited and of these 80.7% (6127/7593) participated. No financial incentive for participation was offered with the exception of travel expenses if a visit outside a routine clinic visit was needed.

Representativeness

Tables 3A and 3B show the distribution of some key characteristics among the SDRNT1BIO recruits compared to the national population from SCI-Diabetes. As shown, the participants are similar to the national population in almost all characteristics. With regard to socio-economic status, 16% of SDRNT1BIO participants are resident in areas with the most deprived quintile of Scottish Index of Multiple Deprivation (SIMD) scores (a residential area based measure of deprivation) compared to 20% of the total national T1DM population (Table 3B).(27) As shown in Table 3B, although we sampled from renal clinics to ensure capture of those with end stage renal disease the prevalence of dialysis was 1.2% versus 1.5% nationally and slightly fewer were albuminuric (11%) compared to the national prevalence (19%).

What has been measured?

Baseline data collection took place between 1 December 2010 and 29 November 2013 inclusive, and comprised a single study visit of approximately 30 minutes. Informed consent was documented for all participants. Participants were asked to complete a self-report questionnaire, and had clinical measures and a blood sample taken. Additionally patients were asked to provide a urine sample at the study visit and were provided a sample tube to post back a second urine sample later. Table 4 summarises the items collected.

Established validated questionnaire instruments were used where these were available. We included the physical activity questions from the International Physical Activity Questionnaire (IPAQ) (28), the Hospital Anxiety and Depression Scale (29), and the widely used Michigan Neuropathy Scale.(30) Acute crises were captured based on reports of diabetic ketoacidosis and hypoglycaemic events in the past 12 months and included a measure of hypoglycaemic awareness.(31)

For physical examination we captured two blood pressure readings after five minutes of sitting quietly, using the OMRON digital BP monitor or equivalent which was validated by the British Hypertension Society. Weight and height were measured using the existing scales and stadiometers of each clinic. Bioimpedance measurements were obtained using the Tanita Body Composition Analyser BC-420MA or BC-418MA. Waist and hip measurements were taken using a protocol based on guidance published by the Scottish Diabetes Research Network.(32)

Blood samples obtained from participants were processed at the end of each clinic, aliquoted and then frozen. The time elapsed between sampling and freezing at -80°C was recorded and the median and interquartile range was 2 h 15 min (1 h 30 min to 3h 10 min). Samples were

periodically shipped on dry ice to the central laboratory where DNA was extracted and samples banked.

How often have they been followed up?

A key aim in setting up the cohort was to harness the potential of data linkage to routine electronic health care records as a means of follow up of participants. Such linkage is feasible in Scotland because the health care records of all patients have a unique health care identifier, the Community Health Index (CHI) number. This is assigned at birth or, for those immigrating into Scotland, on registration with a general practitioner (health care is free at the point of delivery so almost all residents register with a general practitioner). All SDRNT1BIO participants were consented for such linkage and their study day data have been linked to capture both retrospective and prospective data specifically:

- 1) SCI-Diabetes which captures data on over 99% of patients with diabetes in Scotland and contains key clinical encounters for diabetes related care including primary care, retinopathy screening, foot screening and issued prescriptions from 2004. Blood and urine test results are also captured, being fed from SCI-Store, a Scotland wide federated database from NHS laboratories;
- 2) The Scottish Renal Registry which captures data on all those in receipt of renal replacement therapy in Scotland since 1960;
- 3) Routine data from Information Services Division (ISD) Scotland:
 - a) Outpatient attendance (from 1997)
 - b) Hospital Inpatient and Day Case Discharges (from 1981)
 - c) Birth outcomes including infant mortality and stillbirths (from 1975)
 - d) Scottish Cancer Registry data (from 1980)
 - e) Deaths (from study day participation onwards).

To date, two linkages have been performed with data coverage up to the end of 2014 for the SCI-Diabetes, deaths and cancer linkages and to end 2013 for the others with a further linkage pending. The prospective data linkages are ongoing with annual linkages planned for the foreseeable future. Participants are considered to have become unobservable if at least 1 year has elapsed without any HbA1c measurement or prescription records, or if they have been de-registered at their general practice without re-registration there or elsewhere in Scotland. By the end of 2014 it was possible to determine that 118 (1.2%) participants were already deceased and of those not deceased 59 persons had no follow up data, presumably because of emigration (0.96%).

At recruitment, participants were invited to give consent for future face-to-face follow up, to which 93% agreed; as yet we have not taken up this opportunity. Participants were also invited to give consent for having spare blood captured and stored from any future clinical encounters, to which 94% of participants agreed. We have established a mechanism for such spare blood capture for the participants in two of the Health Boards and plan to roll out this collection nationally as part of the GoSHARE Spare Blood Project [<http://>

www.goshare.org.uk/]. To date we hold follow-up EDTA plasma for 300 SDRNT1BIO participants.

What has it found? Initial findings of interest

The initial studies using the biosamples of the bioresource are now underway but here we describe one useful set of information from the questionnaire data. Management of T1DM has changed in recent years with moves towards more frequent use of basal bolus insulin regimens, pumps, more frequent blood glucose self-testing and carbohydrate counting. Here we describe the patterns of insulin management and glucose management among the SDRNT1BIO participants and examine associations with gender and socio-economic status. Socio-economic status was assessed using the SIMD based on address at time of interview divided into quintiles. Three measures of self-reported insulin and glucose management were analysed:

- Insulin Frequency (IF) : < 4 or 4 injections a day or using pump;
- Blood Glucose Monitoring (BGM) testing : < 4 or 4 tests a day;
- and carbohydrate counting or exchanges (CC) : yes/no.

Overall 73% (4316) were injecting at least four times daily (IF 4) but just 4.6% (269) were using a pump (Table 5). Overall 52% (3055) were testing blood glucose at least four times daily (BGM 4) and 61% (3552) were using carbohydrate counting or exchange (CC). Men had lower rates than women of IF 4 (71% vs. 76%), pump use (2.7% vs 6.9%), BGM 4 (48% vs 57%), and CC (56% vs 68%). All measures varied widely by SIMD. Age-sex adjusted odds ratios (OR) (95% CI) per unit increase in SIMD quintile were 1.15 (1.10-1.20) for IF 4, 1.32 (1.20-1.45) for pump use, 1.11 (1.07-1.16) for BGM 4, 1.22 (1.17-1.27) and for CC, ($P=0.001$ for all) (Table 6). All three measures (IF, BGM and CC) were associated with lower mean HbA1c (Table 7). HbA1c was lower in those in the more affluent areas (beta regression coefficient per SIMD quintile -0.17 (95% CI -0.20,-0.14), $P=0.0001$ adjusted for age and sex, beta -0.14 (95% CI -0.17,-0.11) on adjustment for glucose management). We conclude that structured patient education programmes aimed at improving self-management, as recommended in our national diabetes strategy, need to explicitly tackle inequalities by sex and deprivation.

What are the main strengths and weaknesses?

The main strengths of the SDRNT1BIO cohort are: (i) its large size; (ii) the comprehensive retrospective and prospective capture of a wide range of health data; (iii) the large set of biosamples obtained; (iv) that the cohort is being comprehensively genotyped; (v) its broad representativeness of the national adult population with T1DM; (vi) the high rate of consent to future follow up; (vii) the high rate of consent to spare blood capture; and (viii) the low cost of the work given the amount of data collected. Weaknesses are that: (i) only a subset have follow-up biosamples as yet; (ii) lack of funding to date for re-examination; and (iii) need to improve discoverability and infrastructure support for collaborative use.

Can I get hold of the data? Where can I find out more?

The study was carried out in accordance with the ethical principles in the Declaration of Helsinki and was approved by the Tayside Research Ethics Committee (Reference 10/S1402/43). Biosamples are held under the governance of the Tayside Tissue Bank. Data linkages are approved by the National Caldicott Guardians (References: 2013/009; 2013/0014), Public Benefit and Privacy Panel for Health and Social Care (Reference 15/13), NHS Central Register (NHSCR), and the Scottish Renal Registry.

The SDRNT1BIO was established to support collaborative research use. We aim to achieve the appropriate balance between fostering use and maintaining the data governance and security of linked data. All data are held in an anonymised form with the file linking study identifier to identifiable patient details held separately and unavailable to researchers. Data are held on a secure server accessible only to approved researchers. Analysis takes place on the server with access via end-to-end encrypted secure shell tunneling. Analysts must have undertaken an approved data security course. A data access committee oversees applications for collaboration. Criteria for approval include having a scientifically justified question, the feasibility and power to address the question in the dataset, whether the question is already being examined using the data, whether the application is a *bone fide* researcher in a research institution and whether exhaustible material is being requested. Samples are not issued externally but application can be made to have specified funded measures made if these are scientifically valid and if the question exploits the unique characteristics of the cohort (i.e. cannot be examined in a less extensive resource). In-person follow-up studies cannot be initiated by external collaborators for privacy reasons but can be proposed as collaborations.

To date biosamples have been used for DNA extraction and genome wide genotyping. Serum samples have been used for the measurement of C-peptide, serum creatinine, auto-antibodies (GAD, ZnT8, IA2) and for N-glycome analysis.(33) The results of these are awaited. Urine samples have been used for measurement of albumin:creatinine ratio. These studies represent collaborations with researchers in the United States, Croatia, Finland, Scotland, and the rest of the United Kingdom. Interested collaborators should contact the study coordinator in the first place for access forms [Helen.Colhoun@igmm.ed.ac.uk].

Profile in a nutshell

- The SDRNT1BIO is one of the largest and most comprehensive collections of biomaterials from people with type 1 diabetes (T1DM) in existence, and has been shown to be representative of the national adult population with T1DM.
- 6,127 adults, aged 16 years or older, with T1DM were recruited from across Scotland between 01/12/2010 and 29/11/2013 with a high rate of consent to future follow-up.
- Biosamples include baseline collections of serum, plasma, whole blood and urine alongside follow-up capture of plasma where patients consented to spare blood capture.

- Baseline data includes sociodemographics, details of diabetes diagnosis and treatment, history of complications and lifestyle assessment e.g. physical activity, smoking and alcohol aspects, alongside results from physical measures e.g. anthropometry, bioimpedance, and blood pressure.
- Data linkage to routine electronic health care records has allowed retrospective and prospective data capture across a number of health outcomes including diabetes-related care in primary care, renal replacement therapy, outpatient attendance, hospitalizations, cancers and deaths. The SDRNT1BIO has also been comprehensively genotyped.
- SDRNT1BIO was established to support collaborative research use; access forms are available from the study coordinator [Helen.Colhoun@igmm.ed.ac.uk].

Acknowledgements

We would like to thank the fieldworkers, supervisors, and collaborators from the NHS Health Boards across Scotland for facilitating this research study in their facilities. We would also like to thank the participants who took the time to participate in the study.

Funding

This work was supported by the Chief Scientist Office [ETM/47] and Diabetes UK [10/0004010] and received in-kind contribution from Scottish Diabetes Research Network to facilitate recruitment.

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Table 1

Inclusion and exclusion criteria for participation in SDRNT1BIO cohort

Inclusion criteria main study

- (1) Male or female
- (2) 16 years of age or over
- (3) Not currently pregnant
- (4) Able to give informed consent
- (5) A label of type 1 diabetes (T1DM), MODY or LADA on SCI-DC database or in clinical record
- (6) Interval between diagnosis and starting insulin <1 year for patients with diagnosis of T1DM
- (7) Current use of insulin if diagnosed with T1DM

Exclusion criteria for main study and MODY sub-study

- (1) Known secondary basis for diabetes e.g. haemochromatosis, pancreatitis, pancreatectomy
-

MODY, maturity onset diabetes of the young; LADA, latent autoimmune diabetes in adults

Table 2

Health Boards in order of contribution to Scottish-wide population with T1DM

	Type 1 Bioresource participants (N=6127) N, percent (SE)	National T1DM population (N= 24552) N, percent (SE)
Greater Glasgow & Clyde	949, 15.50 (0.014)	5327, 21.70 (0.003)
Lothian	1592, 26.00 (0.012)	3900, 15.89 (0.003)
Lanarkshire	407, 6.65 (0.015)	2816, 11.47 (0.004)
Grampian	749, 12.23 (0.014)	2679, 10.91 (0.004)
Ayrshire & Arran	113, 1.85 (0.016)	1782, 7.26 (0.004)
Fife	699, 11.41 (0.014)	1759, 7.16 (0.004)
Tayside	937, 15.30 (0.014)	1716, 6.99 (0.004)
Highlands	176, 2.87 (0.016)	1481, 6.03 (0.004)
Forth Valley	243, 3.97 (0.016)	1453, 5.92 (0.004)
Dumfries & Galloway	231, 3.77 (0.016)	737, 3.00 (0.004)
Borders	18, 0.29 (0.016)	512, 2.09 (0.004)
Western Isles, Orkney and Shetland	12, 0.20 (0.001)	390, 1.59 (0.001)

SE, standard error.

Table 3A
A Comparison of SDRNTIBIO participants with national Scottish population with Type 1 Diabetes (continuous variables)

Characteristic	Type 1 Bioresource participants (N=6127)			National T1DM population (N=24552)		
	N, mean (SD)	Median (25th,75th percentile)	N, mean (SD)	Median (25th,75th percentile)	N, mean (SD)	Median (25th,75th percentile)
Age at entry, y	6127, 44.8 (14.8)	45.1 (33.1,55.5)	24552, 43.3 (15.6)	42.9 (30.9,53.9)		
Diabetes duration, y	6127, 21.5 (13.5)	20.2 (10.8, 31.0)	24552, 20.7 (13.1)	18.9 (10.4,29.8)		
Age at diagnosis, y	6127, 23.3 (14.1)	22.3 (12.0,32.0)	24552, 22.6 (13.3)	21.0 (12.1,31.0)		
HbA1c, mmol/mol	6103, 71.4 (16.9)	69.0 (60.0,80.0)	22318, 73.1 (19.2)	70.3 (60.7,83.0)		
MDRD eGFR, ml/min/1.73m ²	5752, 89.2 (24.5)	88.7 (74.2,103.5)	20909, 89.1 (26.5)	88.3 (73.4,104.2)		
Systolic blood pressure, mmHg	6094, 130.1 (16.9)	129 (119,140)	22515, 129.3 (17.1)	129 (118,140)		
Diastolic blood pressure, mmHg	6094, 75.0 (10.2)	75 (68, 82)	22513, 74.6 (10.1)	75 (68,80)		
BMI, kg/m ²	5637, 26.9 (4.6)	26.3 (23.7, 29.5)	21674, 27.1 (5.5)	26.4 (23.4,30.0)		

S, standard deviation; y, years; MDRD, Modification of Diet in Renal Disease, eGFR = $186 \times (\text{creatinine in mmol/l}/88.4)^{-1.154} \times 0.742$ (if female) \times (1.210 if black),

Table 3B

Comparison of SDRNT1BIO participants with national Scottish population with Type 1 Diabetes (categorical variables)

Characteristic	Type 1 Bioresource participants (N=6127) N, percent (SE)	National T1DM population (N=24552) N, percent (SE)
Female sex	2696, 44.0 (0.009)	10718, 43.7 (0.002)
Diabetes duration 5 y	5440, 88.8 (0.002)	21793, 88.8 (0.000)
Diabetes diagnosed at age 50 y	308, 5.03 (0.016)	892, 3.6 (0.004)
Known MODY	29, 0.47 (0.016)	N/A
Known LADA	4, 0.07 (0.016)	N/A
SIMD quintile		
1 (most deprived)	956, 15.8 (0.014)	4750, 20.0 (0.003)
2	1021, 16.8 (0.014)	4807, 20.3 (0.003)
3	1158, 19.1 (0.013)	4932, 20.8 (0.003)
4	1369, 22.6 (0.013)	4723, 19.9 (0.003)
5 (least deprived)	1562, 25.8 (0.012)	4515, 19.0 (0.003)
History of diabetes related complications		
Any retinopathy ever	4681, 77.4 (0.004)	17862, 77.1 (0.001)
Retinopathy at most recent screening	3832, 63.4 (0.006)	12777, 55.1 (0.002)
Cardiovascular disease admission	473, 7.7 (0.015)	2212, 9.0 (0.004)
Ever received dialysis	73, 1.2 (0.016)	363, 1.5 (0.004)
Albuminuric status		
Normoalbuminuric	4605, 88.6 (0.002)	17578, 81.4 (0.001)
Microalbuminuric	449, 8.6 (0.018)	3196, 14.8 (0.004)
Macroalbuminuric	141, 2.7 (0.019)	823, 3.8 (0.004)
Albuminuric status based on SDRNT1BIO samples (1 ACR reading)	5839, 95.3 (0.00)	

SE, standard error of mean; ACR, urine albumin to creatinine ratio; y, years; N/A, not applicable.

Table 4

Summary of SDRNT1BIO baseline measures (2011-13)

Measure	Variables
Self-report questionnaire	Demographic characteristics
	• Date of birth
	• Sex
	• Ethnicity
	• Location when diabetes diagnosed
	Family History of diabetes Diabetes & Clinical History
	• Date of diagnosis
	• Other health conditions including specific questions on coeliac, rheumatoid and other auto-immune conditions
	Glucose and Insulin management
	• Start of insulin therapy and current regime
	• Date insulin injections started
	• Current insulin dose
	• Carbohydrate counting/exchange
	• Glucose self-monitoring
	Diabetes acute crises
	• Ketoacidosis
	• Hypoglycaemia
History of diabetes complications	
• Kidney dialysis/transplant	
• Laser therapy to back of the eye	
• Amputation	
• Complications affecting legs and/or feet	
• Diabetic neuropathy diagnosis	
• Michigan neuropathy scale	
• Hospital Anxiety and Depression Scale (HADS) – 14 items	
Lifestyle	
Alcohol units per week	
Smoking habits (cigarettes/cigars/pipes)	
• Current smoker, ex-smoker, non-smoker	
• Frequency/number times a day smoked	
• Age started to smoke	
Physical activity	
• Intensity over previous week: vigorous, moderate, walking, sitting	
• Duration of activity over previous 7 days	
• Typical daily duration (hours and minutes)	

Measure	Variables
Clinical measures	Sitting Blood pressure Height Weight Waist-hip ratio Bioimpedence
Biosamples stored	Blood – non-fasting ($n=6005$ persons with a sample) <ul style="list-style-type: none"> • Serum, Plasma, whole blood in EDTA, whole blood in Paxgene tubes Single urine sample ($n=5839$ persons with a sample) Two urine samples ($n=4902$ persons with two or more samples)

Table 5

Glucose management measures by age (years) and sex

	Males 16-24	25-49	50-74	75	All ages
<i>n</i>	344	1809	1214	64	3431
HbA1c, mmol/mol	77.3 (1.2)	71.94 (0.4)	68.4 (0.4)	66.8 (1.7)	71.1 (0.3)
Insulin Frequency 4 injections/day	254 (78.9)	1330 (76.3)	743 (63.7)	21 (35.0)	2348 (71.3)
Insulin pump use	11 (3.4)	42 (2.4)	37 (3.2)	0 (0)	90 (2.7)
Blood glucose Monitoring 4 tests/day	124 (38.6)	832 (47.9)	589 (50.5)	27 (44.3)	1572 (47.9)
Carbohydrate counting	181 (56.4)	983 (56.8)	616 (54.1)	30 (50.0)	1810 (55.7)
	Females 16-24	25-49	50-74	75	All ages
<i>N</i>	302	1413	919	62	2696
HbA1c, mmol/mol	82.4 (1.3)	72.8 (0.5)	71.0 (0.5)	69.9 (1.9)	73.2 (0.4)
Insulin Frequency 4 injections/day	233 (79.3)	1078 (79.0)	624 (71.4)	33 (54.1)	1968 (75.9)
Insulin pump use	18 (6.1)	115 (8.4)	46 (5.3)	0	179 (6.9)
Blood glucose Monitoring 4 tests/day	151 (51.2)	775 (56.9)	519 (59.7)	38 (62.3)	1483 (57.3)
Carbohydrate counting	189 (64.3)	964 (70.7)	568 (66.5)	21 (36.2)	1742 (67.8)

Data shown are mean and standard error for HbA1c, and numerator (%) for the other measures.

Table 6

Odds of glucose management measures according to the Scottish Index of Multiple Deprivation

Indicator	Quintile of Scottish Index of Multiple Deprivation					Least versus most deprived OR (95% CI)
	1 (most deprived)	2	3	4	5 (least deprived)	
Insulin frequency 4 injections/day	612 (67.8)	681 (70.3)	808 (73.1)	1012 (76.3)	1156 (75.9)	1.48 (1.26,1.72)
Insulin pump use	13 (1.4)	30 (3.1)	53 (4.8)	87 (6.6)	81 (5.3)	4.08 (2.33, 7.73)
Blood glucose Monitoring 4 tests/day	408 (45.6)	464 (48.0)	572 (51.9)	715 (54.0)	864 (56.6)	1.53 (1.29,1.81)
Carbohydrate counting	422 (47.2)	543 (56.9)	687 (63.1)	866 (65.8)	997 (66.1)	2.31 (1.94,2.74)

Data are numerator (%) unless otherwise indicated; odds ratio adjusted for age and sex, $P < 0.001$ for all indicators.

Table 7

HbA1c in mmol/mol by glucose management measures

Indicator	Yes Mean (SE)	No Mean (SE)	Age-sex adjusted P-value
Insulin frequency 4 injections/day	71.8 (0.1)	72.1 (0.2)	<0.001
Insulin pump use	64.8 (0.8)	72.2 (0.3)	<0.001
Blood glucose Monitoring 4 tests/day	69.3 (0.3)	74.6 (0.4)	<0.001
Carbohydrate counting	70.8 (0.3)	73.4 (0.4)	<0.001

SE= standard error.