Scottish Diabetes Research Network Type 1 Bioresource Study (SDRNT1BIO)

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Key messages

- The SDRNT1BIO is one of the largest and comprehensive collections of biomaterials from people with type 1 diabetes in existence.
- The participants of the SDRNT1BIO have been shown to be broadly representative of all type 1 diabetes adults in Scotland across a range of characteristics.
- Initial findings of note in the cohort are the low prevalence of renal complications in this contemporary cohort despite the low rate of achievement of glycaemic targets and the substantial socio-economic differentials in glucose self-management.

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 type 1 Diabetes in those aged under 15 years in Europe between 2005 and 2020 is predicted.(1) Despite advances in care, T1DM continues to be associated with substantial mortality, with an estimated current period life expectancy differential of on average 11-13 years.(2) The main chronic complications include CVD, nephropathy, retinopathy and neuropathy. Cardiovascular disease (CVD) continues to be increased 2-3 fold and diabetic kidney disease remains a major determinant of early mortality.(3)

As detailed in the strategic plans of the main diabetes specific research funders, major research priorities in T1DM include a better understanding of the determinants of type 1 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 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

Type 1 diabetes is partly genetically determined and more than 50 associated genetic loci have been identified with the HLA region on chromosome 6 having the major role.(4) These genetic discoveries in T1DM have provided valuable insights on the potential pathways causing diabetes some of which are now being targeted by novel intervention therapies. They have also yielded useful data to aid the prediction of T1DM. However, the 50+ discovered genetic loci for T1DM do not explain all of the known heritability for this disease with estimates of missing heritability varying from 20-80%.(5,6) Among several potential explanations for this "missing heritability" are the existence of very rare variants with large effects and the existence of additional more common variants but with effects too low to have been detected by sample sizes used so far. Existing studies used for discovering the genetics of T1DM have been based on up to ~12000 cases all combined which is many times lower than sample sizes in meta- analyses of GWAS data for T2DM.(4) Of note almost all studies to date are in cohorts of childhood-onset T1DM specifically, despite the fact that almost 50% of T1DM has its onset in adulthood. Indeed 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) Other studies seeking age of onset effects have had very few people with age at diagnosis >30. Thus additional discovery work to detect new T1DM loci are warranted especially for those with older age of onset. Accordingly we are genotyping the SDRNT1BIO cohort. We will conduct genome wide association studies using a background population representative control set of genotypes from Scotland and will then combine the resulting estimates of SNP associations with T1DM with the current published data to ascertain new T1DM associated loci. An important feature of the collection is that we also know the phenotypic status for other auto-immune related conditions including coeliac disease and rheumatoid arthritis.

2. Discovery and validation of genetic determinants of type 1 diabetes complications

Many complications of diabetes are also 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; many of these have much greater focus on type 2 than type 1 diabetes because larger type 2 cohorts have been available since it is more prevalent (www.imi-summit.eu). However many of these phenotypes are more heterogeneous in T2DM than T1DM making discovery less tractable. The Genie Consortium has focused on nephropathy specifically in T1DM and there is a JDRF funded wider consortium on genetics of nephropathy in T1DM that is currently underway.(10) For many other phenotypes of relevance in type 1 diabetes efforts to discover genetic determinants are sparse. So for example there is little genetic data on neuropathy,(11) propensity to hypoglycaemia or diabetic ketoacidosis or on persistent C-peptide secretion or blood pressure. Thus the GWAS data from the SDRNT1BIO will augment existing international efforts on genetics of macro-and micro-vascular complications of diabetes and will provide novel GWAS studies of neglected traits relevant in T1DM.

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 type 1 and type 2 DM. These include the EURODIAB PCS n=2787 (12), the Pittsburgh EDC n=658 (13), the DCCT/EDIC n=1300 (14), ORPS n=554 (15), and WESDR n=~1000 (16), CACTI n~656 (17), and FinnDiane n~4500 (18). However, the total sample size and number of incident cases of complications across these cohorts does not provide optimal power for discovery efforts. Other large 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) It is clear that to fully exploit new 'omic methods for pathway and biomarker discovery, including lipidomics, metabolomics and genetics and to develop more precise prediction algorithms for complications that incorporate new biomarkers, further large cohorts of T1DM patients need to be laid down now in addition to the continued support of these existing excellent cohorts. The creation of larger cohorts has been hampered by the logistical difficulties in obtaining repeated long term direct patient follow up in the many centres needed to create a large T1DM cohort. Thus, 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 are serum C-peptide concentrations. Previously it was believed that all 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) with up to 75% of those with diabetes duration >5 years showing detectable levels and at least 8% having levels associated with reduced complications (>200pmol/L).(21,22) This is of critical importance since it shows that the paradigm that T1DM is inevitably accompanied by complete beta-cell destruction is incorrect. Specifically 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 so this is another question being addressed by the SDRNT1BIO. Also of interest is the role of residual insulin secretion in resistance to acute and chronic T1DM complications.(23)

Another aspect of diabetes stratification is the improved detection of monogenic diabetes among those misdiagnosed as having T1DM. Differentiating monogenic diabetes (hereafter MODY) from type 1 diabetes has important clinical consequences for patients with all with glucokinase gene mutations and most with HNF1A and HNF4A mutations able to come off insulin.(24) However diagnosis of MODY remains difficult and at present it is estimated that only ~25 % of all MODY is diagnosed as such.(25) Many potential MODY cases are never referred for sequencing. Even when they are, the results of sequencing are not always interpretable unless a mutation that has been previously characterised as pathogenic or a new mutation of obvious functional effect is detected (a problem that will remain even when whole genome sequencing becomes widely used). Several algorithms for improving detection have been proposed utilising clinical and family history, C-peptide status, auto-antibody status, and sometimes other biomarkers such as C-reactive protein and glycan signatures so as to select those warranting sequencing at known MODY loci.(25) Yet detection rates remain low. About 2.9% of those diagnosed as T1DM under age 30 years will actually have MODY. About half of misdiagnosed cases are initially diagnosed as T1DM. Only about 1% of MODY cases have de novo mutations. Most affected individuals will therefore have relatives in the population who bear the same mutation on a haplotype inherited from a common ancestor. Clinical course, family history data and known MODY status were collected in the SDRNT1BIO. These data items will soon be augmented by genome wide SNP data, C-peptide and auto-antibody status. Importantly the coverage fraction of the total population with apparent type 1 diabetes is 1/3 and we anticipate that 1/6 of all misdiagnosed MODY in Scotland (n~125-150) cases are likely to have been sampled into the bioresource. Together these data allow us to explore various strategies for improved detection of unidentified MODY cases.

5. Environmental determinants of TIDM and complications including socio-economic determinants

The environmental determinants of type 1 diabetes remain largely unknown (putative factors include infection e.g. congenital rubella, caesarean section, older maternal age, Vitamin D deficiency etc.).(26) 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. Accordingly the approach used most

commonly has been the prospective study of first degree relatives of known cases of T1DM. Nonetheless with respect to T1DM aetiology the SDRNT1BIO can yield useful information on the role of environment in T1DM aetiology, especially by examining how the pattern of potential risk factors may vary with genotype or auto-antibody phenotype for example yielding insights into pathways. Accordingly we have collected some lifestyle, environment and pre-diagnosis data by questionnaire. For T1DM complications the SDRNT1BIO combined with the extensive 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 Chief Scientist Office and Diabetes UK. The study activities including protocol development and recruitment of participants were overseen by a Study Steering Committee comprising representation from a patient representative, the study funders, and the lead diabetes consultants from ten participating Scottish Health Boards. All data (baseline and prospective) are held at the co-ordinating centre, University of Dundee, 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 upwards with a clinical diagnosis of type 1 diabetes or with monogenic diabetes (i.e. a diagnosis of Maturity Onset Diabetes of the Young –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 Health Board possible regions in Scotland. The boards not targeted were due to the envisaged high cost per participant given the geographic location and low population density (i.e. the Shetland Orkney and Western Islands and Borders). As shown in Table 2 compared to the national T1DM population the Type 1 Bioresource follows a broadly similar pattern with most recruits coming from the more populated boards but with somewhat fewer patients from Greater Glasgow & Clyde and Lanarkshire.

At present very few people with T1DM in Scotland are managed solely in primary care. Therefore the sampling frame used was the comprehensive SCI-Diabetes electronic health care record in which >99% of patients are registered. Recruitment was primarily carried out at diabetes outpatient clinics in participating boards with some additional recruitment in renal units as some end stage renal disease patients have lower attendance at diabetes clinics. In addition GP based clinics were carried out at a few sites of high population density. At participating clinics we systematically evaluated each clinic list for the subsequent week for eligibility and as many attending eligible patients as 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 eligibles 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

Table 3 shows the distribution of some key characteristics among the SDRNT1BIO recruits compared to the total distribution in the national registry from SCI-Diabetes. As shown the participants are very representative of the national population in almost all characteristics. With regard to socio-economic status 16% of cohort participants are from areas with the most deprived Scottish Index of Multiple Deprivation compared to 20% of the total national T1DM population.

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 which took place at a hospital or primary care diabetes clinic. Informed consent was documented for all participants and all samples. 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 clinic visit and were provided a sample tube to post back a second urine sample later. Table 4 summarises the items collected. The current residential location of the participant was geocoded at the datazone level and its area Scottish Index of Multiple deprivation recorded.

For the questionnaire items we attempted to use established validated instruments where these were available. Accordingly we include the physical activity questions from the International Physical Activity Questionnaire (IPAQ).(27) We used the established questions from the Michigan Neuropathy Scale that has been widely used.(28). Acute crises were captured based on report of diabetic ketoacidosis and hypoglycaemic events in the past 12 months and included a measure of hypoglycaemic awareness.(29) The Hospital Anxiety and Depression Scale questionnaire was used.(30)

For physical examination we captured two sitting blood pressure readings after five minutes of sitting quietly using the OMRON digital BP monitor or equivalent that has been 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.(31)

Blood samples obtained from participants were processed at the end of each clinic and aliquoted then frozen. The time elapsed between sampling and freezing at -80^{o}C was recorded. The median and interquartile range for time to freezer was 2 hrs 15 mins (1 hr 30 mins – 3hrs 10 mins). Samples were then periodically shipped on dry ice to the central laboratory where DNA was extracted and samples banked.

Frequency of follow 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 all health care records are 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 (all health care is free at the point of delivery so almost all residents register with a general practitioner). Such linkage can capture both retrospective and prospective data. In the SDRNT1BIO all participants consented to such linkage. Study day data have therefore been linked to extensive records specifically:

1) SCI-Diabetes which captures 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. National coverage was obtained 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 that captures data on all those in receipt of renal replacement therapy since 1960
3) Routine Data from Information Services Division (ISD) Scotland:
    a) Outpatient attendance (from 1997)
    b) Hospital Admissions & Discharges (from 1981)
    c) Birth outcomes including infant mortality and stillbirths (from 1997)
    d) Scottish Cancer Registry (from 1958)
    e) Deaths (from study day participation onwards)

To date, linkages have been performed at baseline in 2013 and refreshed to include data up to end of 2014. The prospective data linkages are ongoing with annual linkages planned for the foreseeable future. By the end of 2014 it was possible to determine that 118 (1.2%) participants were already deceased. The % of participants on whom linkage data have been obtained is sought is 100%. Participants are considered to have become unobservable (through emigration or death) if at least 1 year has elapsed without any HbA1c or prescription records or if they have been de-registered at their general practice without re-registration. To date there are 59 such persons (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. In addition, participants were 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 a spare blood capture for the participants in two of the health board areas and plan to roll out nationally as part of the GoSHARE Spare Blood Project (http://www.goshare.org.uk/). To date there are 224 patients for whom we now hold follow-up EDTA plasma.

Initial findings of interest

We intend this cohort description to be the first publication from the cohort. Here we include some initial observations on glycaemia that have policy relevance.

Glycaemic management by sex and social class

Management of type 1 diabetes has changed in recent years with moves towards more frequent bolus in basal bolus insulin regimes, use of pumps, more frequent blood glucose self-testing and carbohydrate counting. Current data on the uptake of these more intensive self-management practices is lacking. 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 Scottish Index of Multiple Deprivation (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 (BG) testing : <4 or ≥ 4 tests a day
- Carbohydrate Counting or exchanges (CC) : yes/no.

We found that overall 73% (n=4316) were injecting at least four times daily (IF ≥4) but just 4.6% (n=269) were using a pump (Table 5). Overall 52% (n=3055) were testing blood glucose at least four times daily (BG ≥4) and 61% (n=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%), BG ≥4 (48% vs 57%), and CC (56% vs 68%), age adjusted p-values all <0.001. All measures varied widely by SIMD. Age-sex adjusted Odds Ratio (OR) 95% CI per unit increase in SIMD quintile was 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 BG ≥4, 1.22 (1.17-1.27) for CC, (p<0.001 for all) (Table 6). All three measures (IF, BG and CC) measures were associated with lower mean HbA1c (Table 7). HbA1c was significantly lower in those in the more affluent areas (beta regression coefficient per SIMD quintile -0.16, p<0.0001 adjusted for age and sex, beta -0.13 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 demonstrable representativeness of the national adult population with type 1 diabetes vi) the high rate of consent to future follow up vii) the high rate of consent to spare blood capture viii) the low cost of the work given the amount of data collected. Weaknesses are i) only a subset have follow up biosamples as yet ii) lack of funding to date for re-examination and improving 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) and the biosamples are held under the governance of the Tayside Tissue

Bank. The data linkages are approved by the National Caldicott Guardians (References: 2013/009; 2013/0014), Privacy Advisory Committee (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 linker file linking study identifier to identifiable 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 application for collaboration.

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.(32) 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 (via h.colhoun@dundee.ac.uk).

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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.

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.

• 6127 adults, aged 16 years or older, with T1DM, were recruited from across Scotland between 1 December 2010 and 29 November 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].

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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, 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 type 1 diabetes
(7) Current use of insulin if diagnosed with Type 1 diabetes

Exclusion criteria for main study and MODY sub-study

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

Table 2. Health boards in order of contribution to Scottish wide population with T1DM

	Type 1 Bioresource participants (N=6127)	**National T1DM population (N= 24552)**
	N, percent (SE)	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)

Table 3a Comparison of SDRNT1BIO participants with national Scottish population with Type 1 Diabetes (continuous variables)

	Type 1 Bioresource participants (N=6127)		National T1DM population (N=24552)	
Characteristic	N, Mean (SD)	Median (25^{th},75^{th} percentile)	N, Mean (SD)	Median (25^{th},75^{th} 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)

Table 3b. Comparison of SDRNT1BIO participants with national Scottish population with Type 1 Diabetes (categorical variables)

	Type 1 Bioresource participants (N=6127)	**National T1DM population (N=24552)**
Characteristic	N, Percent (SE)	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	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

Table 4. Summary of measures collected during baseline for SDRNT1BIO study population (2011-2013)

	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 • History of 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)
Clinical measures	Sitting Blood pressure Height Weight Waist Hip Ratio Bioimpedence
Biosamples stored	Blood – non-fasting (n=6005 persons with a sample) • 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 2 or more samples)

Table 5. Glucose management measures by age (years) and sex

	Males				
	16-24	25-49	50-74	≥75	All ages
n	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 ≥4 tests/day	124 (38.6)	832 (47.9)	589 (50.5)	27 (44.3)	1572 (47.0)
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
n	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 (1.3)	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 (0)	179 (6.9)
Blood Glucose ≥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 is N (%)

Table 6. Odds of Glucose Management Measures according to the Scottish Index of Multiple Deprivation

	Quintile of Scottish Index of Multiple Deprivation					Least versus most deprived
Indicator	1 (most deprived)	2	3	4	5 (least deprived)	OR (95% CI)
Insulin Frequency ≥4 injections/day	625 (69.3)	711 (73.3)	861 (77.8)	1099 (82.8)	1237 (81.2)	2.29 (1.88,2.79)
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 ≥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 is N (%) unless otherwise indicated; OR=odds ratio adjusted for age and sex, P<0.001 for all indicators

Table 7. HbA1c by Glucose Management Measures adjusted for age and sex

	Yes	**No**	
Indicator	Mean (SE)	Mean (SE)	**P-value**
Insulin Frequency ≥4 injections/day	8.66 (0.02)	8.69 (0.004)	<0.001
Insulin pump use	8.04 (0.07)	8.70 (0.02)	<0.001
Blood Glucose ≥4 tests/day	8.38 (0.03)	8.97 (0.03)	<0.001
Carbohydrate Counting	8.55 (0.02)	8.84 (0.03)	<0.001