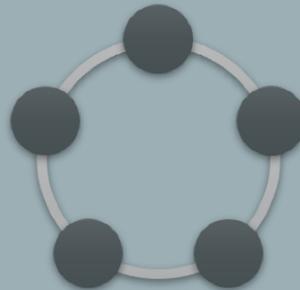
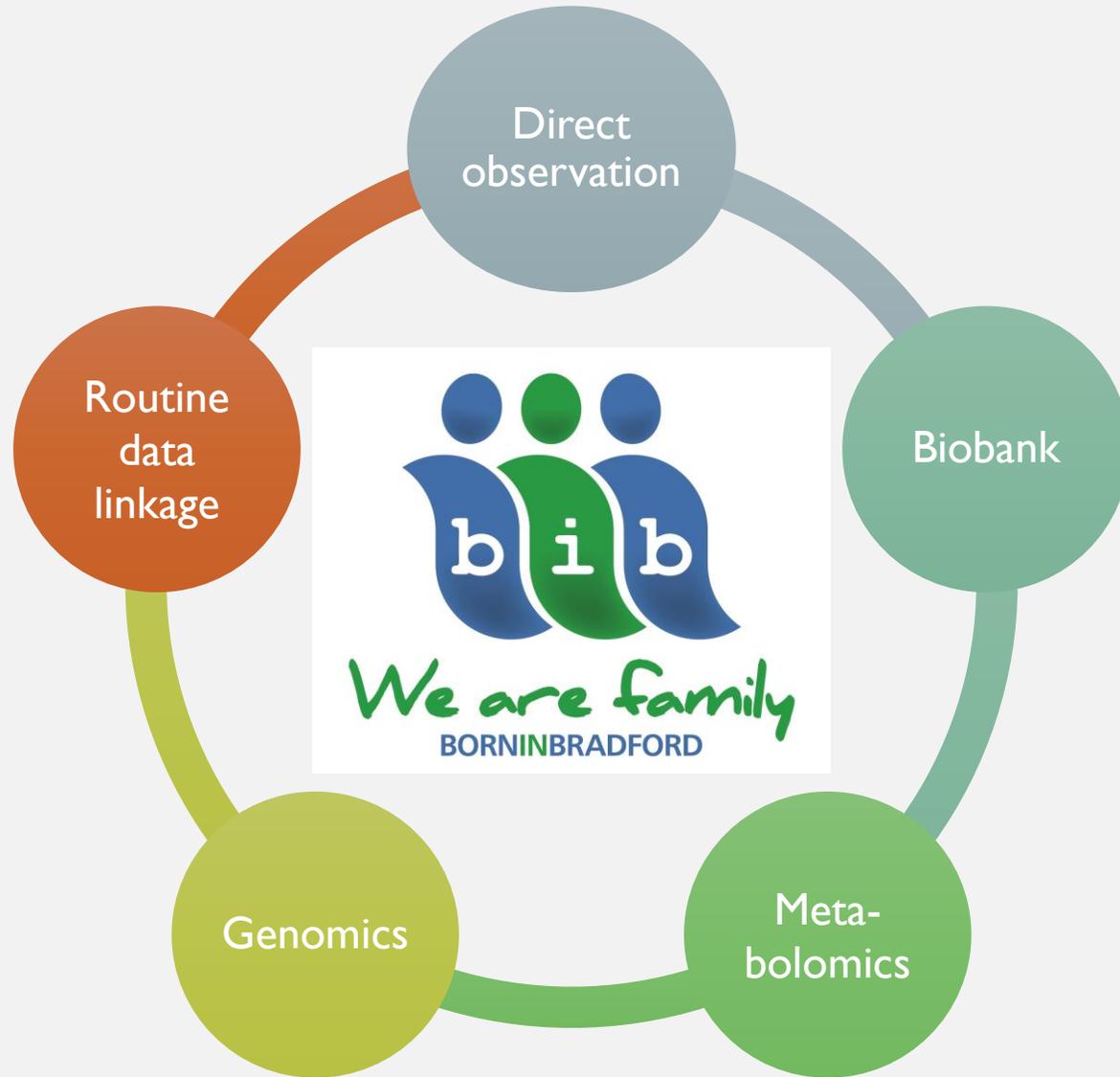




THE BORN IN BRADFORD PLATFORM

Direct Observation – Biobank – Metabolomics – Genomics – Routine Data Linkage







BACKGROUND

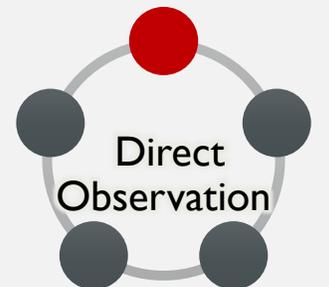
Born in Bradford is a longitudinal multi-ethnic birth cohort study aiming to examine the impact of environmental, psychological and genetic factors on maternal and child health and wellbeing.

Bradford is a city in the North of England with high levels of socio-economic deprivation and ethnic diversity.

Women were recruited at the Bradford Royal Infirmary at 26-28 weeks gestation.

Researchers are looking at the links between the circumstances of a child's birth, the context in which they grow up, their health and well-being and their educational progress.

- 12453 mothers recruited across 13776 pregnancies
- 3353 fathers recruited across 3455 pregnancies
- 13858 babies (livebirths + stillbirths)
- Mean age of the mothers at study recruitment was 27 years old.
- The oldest child was born in 2007
- The youngest child was born in 2011





BASELINE DATA

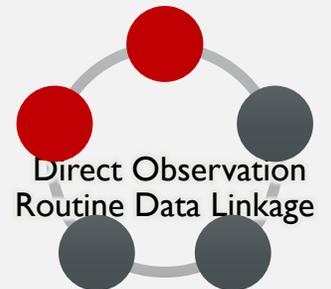
At recruitment, pregnant women were invited to complete a questionnaire, assessing detailed personal sociodemographics and family circumstances.

They were weighed and measured and many completed a glucose tolerance test (GTT).

Their partners completed a shortened version of the questionnaire and were also weighed and measured.

Linkage to maternity IT systems was completed to obtain pregnancy measures and birth outcomes.

- 10519 mothers have questionnaires across 11395 pregnancies
- 3287 fathers have questionnaires across 3387 pregnancies
- 11231 mothers have completed GTT across 12331 pregnancies
- 13361 pregnancies linked to pregnancy outcomes on maternity IT system data
- 11050 pregnancies have both questionnaire and IT system data
- 13525 babies linked to birth outcomes on maternity IT system data



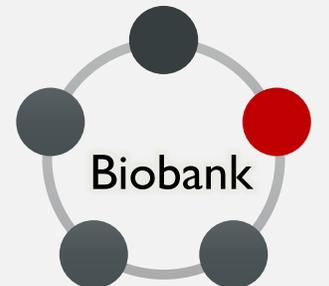


BIOBANK: MOTHER

At recruitment, consenting women provided a blood sample and urine sample for storage in a research biobank.

DNA was extracted mainly from buffy coat (hence the reduced number remaining here) but in some cases from whole blood.

- 10587 mothers have plasma across 11503 pregnancies
- 10581 mothers have RBC across 11495 pregnancies
- 10762 mothers have serum across 11715 pregnancies
- 367 mothers have buffy across 370 pregnancies
- 9619 mothers have whole blood across 10262 pregnancies
- 6662 mothers have urine across 6996 pregnancies
- 10531 mothers have DNA across 11436 pregnancies



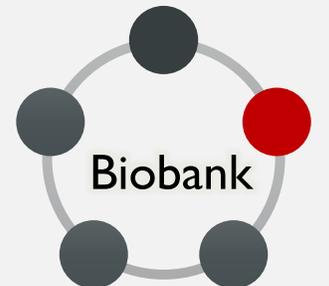


BIOBANK: BABY

At delivery of the baby, if the mother consented, a blood sample was taken from the umbilical cord for storage in a research biobank.

DNA was extracted from mainly from buffy coat but in some cases from whole blood.

- 7909 have plasma
- 7739 have RBC
- 9303 have serum
- 200 have buffy
- 6741 have whole blood
- 9158 babies have DNA

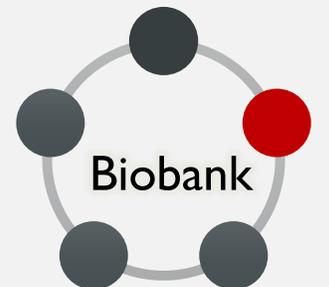




BIOBANK: FATHER

At recruitment, consenting fathers provided a saliva sample, from which DNA was extracted.

- 2938 fathers have DNA across 3022 pregnancies



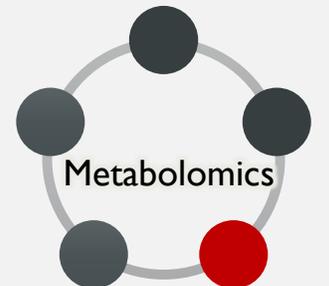


PREGNANCY BIOMARKERS

Insulin, cholesterol, LDL, HDL, triglycerides

Subcohort vitamin D sample: albumin, calcium,
phthalates, 25(OH) Vit D2, 25(OH) Vit D3

- 10685 mothers at 11625 pregnancies have blood biomarkers data
- 1498 mothers have vitamin D data (at one pregnancy)

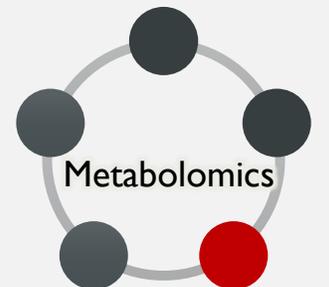




BABY BIOMARKERS

From cord blood sample. Adiponectin, cholesterol, HDL, LDL, insulin, leptin, triglyceride.

- 7910 babies have blood biomarkers data





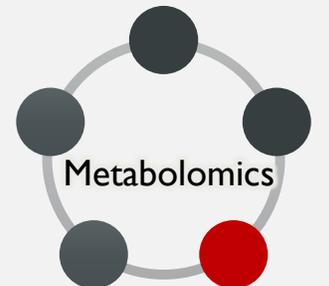
METABOLITE PROFILES

High throughput NMR metabolomics platform to derive quantitative molecular information on ~150 metabolites. The platform focuses primarily on lipids and fatty acids, and also includes glucose, lactose, some amino acids and ketone bodies.

Selected all women with fasting pregnancy serum or EDTA plasma sample

The MS metabolomics platform provides quantified data on ~1000 metabolites, including several that reflect diet, vitamins, all essential amino acids, carbon metabolism biomarkers, a much more detailed lipid profile and fatty acids

- 10574 mothers at 11479 pregnancies have NMR metabolomics
- Also expected in 2018:
 - 1000 mother-child pairs (2000 samples) to have metabolomics profiles using MS metabolomics platform
 - Selection criteria for the 1000 pairs:
 - Completed GTT
 - 50% Pakistani, 50% white British
 - Singleton birth
 - Existing methylation data





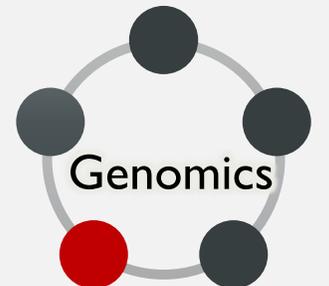
GENOMICS: GENOTYPING MICROARRAYS

Genotyping completed using Illumina
HumanCoreExome microarrays.

Currently available: complete mother-offspring
pairs, and many unpaired samples with good
phenotypic characterisation e.g. complete
GTT, complete pregnancy height/weight data.

All samples will be completed soon and will
become available in 2018.

- 8610 mothers at 9099 pregnancies have microarray genotype data
- This means there are 489 mother-level replicates
- 7157 children have microarray genotype data
- 6256 of these children have paired mother with genotype data, and 6131 of these pairs are from the same pregnancy
- The above data are available now.
- To complete the cohort, the following samples are currently running and will become available in Q2 2017:
 - 2237 mother samples
 - 2991 father samples
 - 2005 child samples





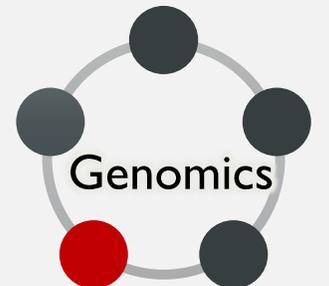
GENOMICS: EXOME SEQUENCING

Exome sequencing completed on Illumina HiSeq 2000 platform.

Variant calls stored for further linkage and analysis in VCF format.

Raw BAM files are available via the European Genome-Phenome Archive.

- Sample selection criteria:
 - All women who indicated their parents were related other than by marriage
 - Children with clinician-diagnosed congenital anomalies
- 2333 mothers at 2489 pregnancies have exome sequence data
- This means there are 156 mother-level replicates
- 262 children have exome sequence data
- A further 672 mothers have been sequenced, and data will be loaded and linked early 2018.
 - The additional 672 were identified consanguineous from microarray genotype profiles



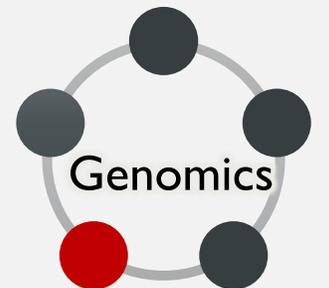


GENOMICS: DNA METHYLATION

Illumina MethylationEPIC (850k) chip

Expected 2018

- 1000 mother-offspring pairs (2000 samples)
- Selection criteria:
 - Mother completed GTT
 - 50% Pakistani, 50% white British
 - Singleton birth
 - Existing good quality GWAS data for both in the pair



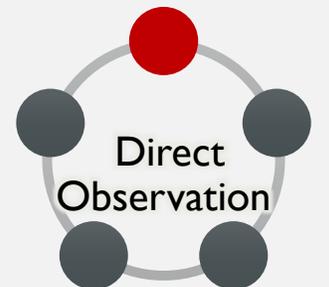


CHILD FOLLOW-UPS

Primary research follow-ups of the children from 0-7 years were conducted through a series of subcohort.

A broad range of sociodemographic, developmental and clinical measures were taken. Separate data dictionaries are available.

- 1763 children recruited to BiB 1000 (6m, 12m, 18m, 24m, 36m follow-ups)
- 2553 children in ALL IN 12m follow-up
- 2067 children in ALL IN 18m follow-up
- 2594 children in MeDALL 48m follow-up
- 2269 children in MeDALL have skinprick data
- 233 children in HELIX 7y follow-up





STARTING SCHOOL

Cognitive development follow-up subcohort
focused on two full academic years in Bradford
schools.

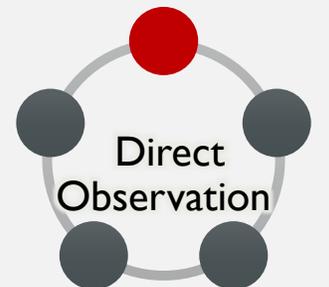
CKAT measures sensorimotor control

SDQ measures emotional development

BPVS measures receptive vocabulary

Letter ID measures letter identification

- 3444 children in the Starting School Reception year follow-up study
- 3253 children have Reception year CKAT
- 2340 children have Reception year SDQ
- 3297 children have Reception year BPVS/Letter ID



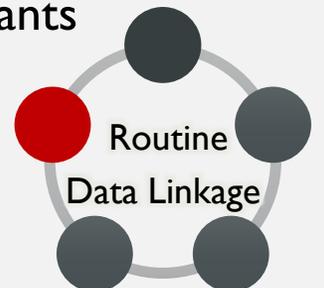


MATERNITY HEALTHCARE RECORD

All pregnancy ultrasound scans were obtained via data linkage with maternity hospital records, including reason for scan and measurements.

Blood pressures, maternity hospital admissions and other information from the written maternity notes were manually entered by clinical researchers into electronic data capture systems.

- 13248 pregnancies have ultrasound scans
- 10939 pregnancies have had information abstracted from patient notes, leading to:
- 10895 pregnancies with pregnancy blood pressures
- 8523 pregnancies with blood pressure during labour
- 10024 pregnancies with postpartum blood pressures
- 855 pregnancies with maternity-related hospital admissions information
- 5611 mothers with information abstracted about pre-BiB pregnancies and infants



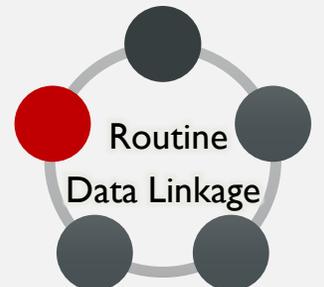


ROUTINE HEALTHCARE: GP RECORD

All GP practices in Bradford use an electronic patient record called SystemOne to record clinical codes and prescriptions.

We extract complete GP data records from SystemOne where we find an exact match on NHS number, surname, date of birth and gender.

- 12311 (98.9%) mothers matched
- 13776 (99.4%) children matched
- 3296 (98.3%) fathers matched
- Clinical events are coded using a standardised terminology called CTV3 Read. This will soon migrate to SNOMED-CT
- Prescription events are coded using the British National Formulary
- 1.1m prescription events and 5.8m clinical codes from mothers
- 490,000 prescription events and 2.3m clinical codes from children
- 200,000 prescription events and 790,000 clinical codes from fathers





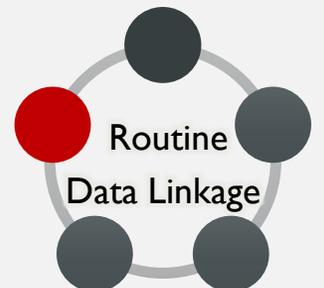
ROUTINE HEALTHCARE: HOSPITAL ADMISSIONS

We matched participants to Bradford Royal Infirmary hospital records on the basis of NHS number and extracted up to 10 years of information on admissions, including diagnostic and procedure codes.

The denominator is unknown since we cannot estimate the likelihood of a hospital admission taking place at another hospital. So, we only count events.

We do, however, know that the match rate was high, given the number of participants with detected events.

- 12342 (99.1%) mothers have at least one event recorded, the youngest at 10 years old, the oldest at 51 years old. There are 72112 events spanning a total of 3801 days.
- 12469 (90.0%) children have at least one event recorded, the youngest at birth, the oldest at 7 years old. There are 22299 events spanning a total of 2972 days.
- This is a healthy cohort and most of these admissions are maternity and birth related.





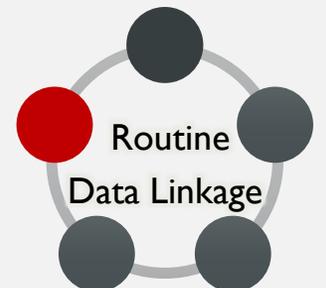
ROUTINE HEALTHCARE: ACCIDENT & EMERGENCY

We matched participants to Bradford Royal Infirmary hospital records on the basis of NHS number and extracted information A&E visits.

The denominator is unknown since we cannot estimate the likelihood of an A&E visit taking place at another hospital. So, we only count events here.

The match rate is known to be high from the hospital admissions events matching (previous slide).

- 7054 (56.6%) mothers have at least one event recorded, the youngest at 14 years old, the oldest at 54 years old. There are 19671 events spanning a total of 2097 days.
- 9686 (69.9%) children have at least one event recorded, the youngest at birth, the oldest at 7 years old. There are 28072 events spanning a total of 2097 days.
- Currently only a limited slice of data is available, from September 2009 to May 2015.





EDUCATION RECORD

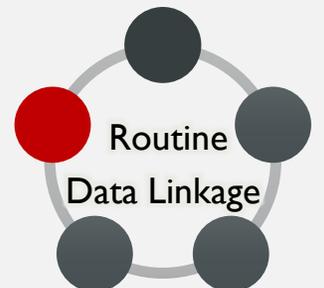
EYFSP: Standard teacher-led assessment that occurs towards the end of the child's Reception year at school. It changed from the start of the 2012/13 academic year.

Y1 Phonics: Teacher-led assessment to determine whether the child has met the required phonics standard by the end of Year 1.

KSI Assessment: Standard teacher-led assessment that occurs towards the end of the child's Year 2 at school.

Education Contextual: obtained from schools by the Local Authority. Contains child level indicators of English as an additional language, child ethnic origin, free school meals, gifted and talented, looked after child and special educational needs.

- 84% record match rate
- A total of 11258 children with complete EYFSP data, from two different test versions:
 - 705 EYFSP pre-2012
 - 10553 EYFSP post-2012
- 11027 Y1 Phonics Assessment
- A total of 9347 children with complete Key Stage 1 Assessment data
 - NB: Complete up to 2016/2017 academic year assessments. Expecting a further ~1600 by end of 2018
- 11667 children with Education Contextual data





RESIDENTIAL GRID REFERENCE FOR GIS

Residential address was provided by the mother at recruitment and updated when the baby was born if necessary.

Following that, data linkage via NHS number to the NHS Personal Demographic Service has provided monthly updates to residential address information.

Linkage to the Local Land Property Gazetteer provides a data cleaning function and grid reference data for GIS analyses.

- Baseline registration maternal address, updated at delivery of child if necessary.
- Monthly name and address searches via PDS for all mothers and children since 2010
- Addresses linked to Local Land Property Gazetteer to get grid reference for GIS analysis.

