All-cause and cardio-renal-metabolic mortality in people with and without type 2 diabetes: a comparative international trend study

- All-cause and CVD mortality declined in several countries (i.e., USA, Sweden), likely related to better screening and treatment of risk factors
  - *Heterogeneity: different data source, analytical plan, period investigated*
- Contemporary (standardised) trends on renal-cardio-metabolic complications in people with T2DM from other countries are unclear
- Aims:
  - *Develop a standardised protocol for data extraction and analysis*
  - *Describe trends in CRM mortality and estimate relative and absolute risk within and between countries*
- Centres involved
  - *LRWE Unit –> Clinical Practice Research Datalink (CPRD)*
  - *Canada (Ontario) –> Electronic Medical Record Administrative data Linked Database (EMRALD)*
  - *Spain (Catalonia) –> Information System for Research in Primary Care (SIDIAP)*

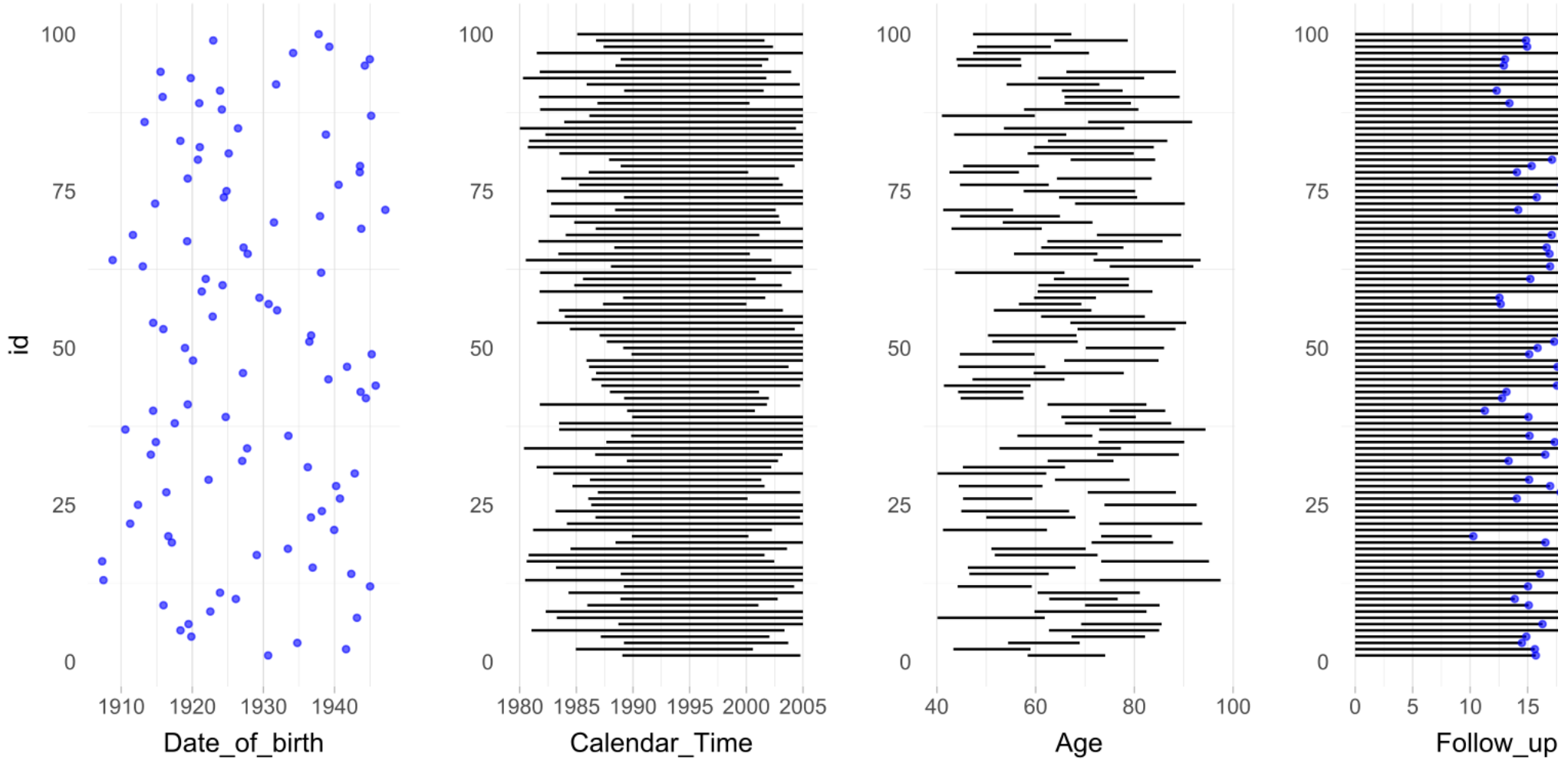
Clinical Practice Research Datalink (CPRD)

- ISAC protocol approved (ISAC 18_296)
- Cohort definition
  - *Exposed (T2DM): First T2DM code between 1/1/1998 and 30/11/2018*
  - *Unexposed (nonDM): Excluded DM from the 'denominator file' (17M)*
  - *Both: restriction by age, sex, data quality, linkage HES/ONS (flow-chart)*
- Prevelent conditions exluded
  - *Cardio-Renal and Cancer using HES (to be consistent with other countries)*
  - *Metabolic not excluded*
- Outcomes
  - *Cardio-Renal-Metabolic fatal events (ICD-9/10, underlying cause in ONS)*
    - Cardio: HF, AF, PVD, IHD/MI, CVA
    - Renal: CKD
    - Metabolic: Hyper- & Hypo-glycaemia
  - *All-cause mortality*

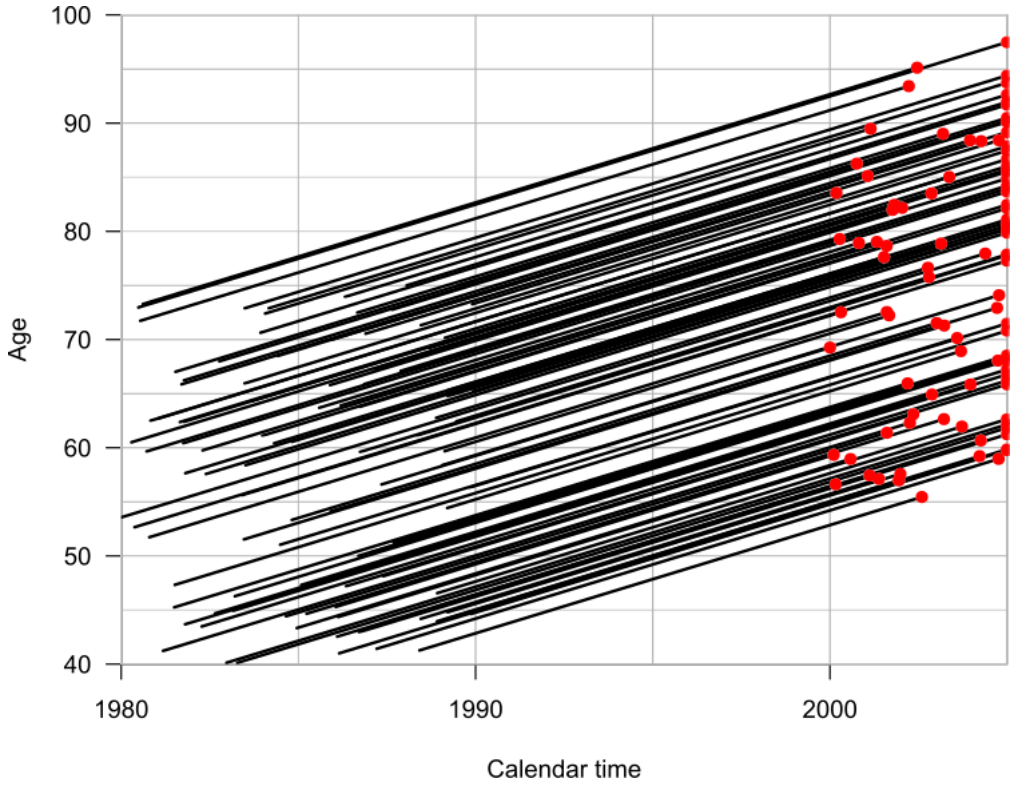
Analytical framework (1)

- Time-to-event analysis
- Descriptive first (trends) and aetiological then (relative risk)
- Central difference aetiological (Cox) vs descriptive/prognostic (parametric models)
  - *Former: just interested in the relative (multiplicative) risk*
  - *Latter: interested in both relative and absolute risk (i.e., absolute rates)*
  - *Benedix Carstensen: "Who needs the Cox model anyway?" http://bendixcarstensen.com/WntCma.pdf*"
- Descriptive (demographical) epidemiology tools
  - *Jointpoint regression (https://surveillance.cancer.gov/joinpoint/download)*
  - *Age-period-cohort model (https://analysistools.nci.nih.gov/apc/help.html)*
  - *Ready-to-use; more flexibility using R packages (sometimes Stata)*

Analytical framework (2): Lexis



Analytical framework (3): Lexis, plotting time scales

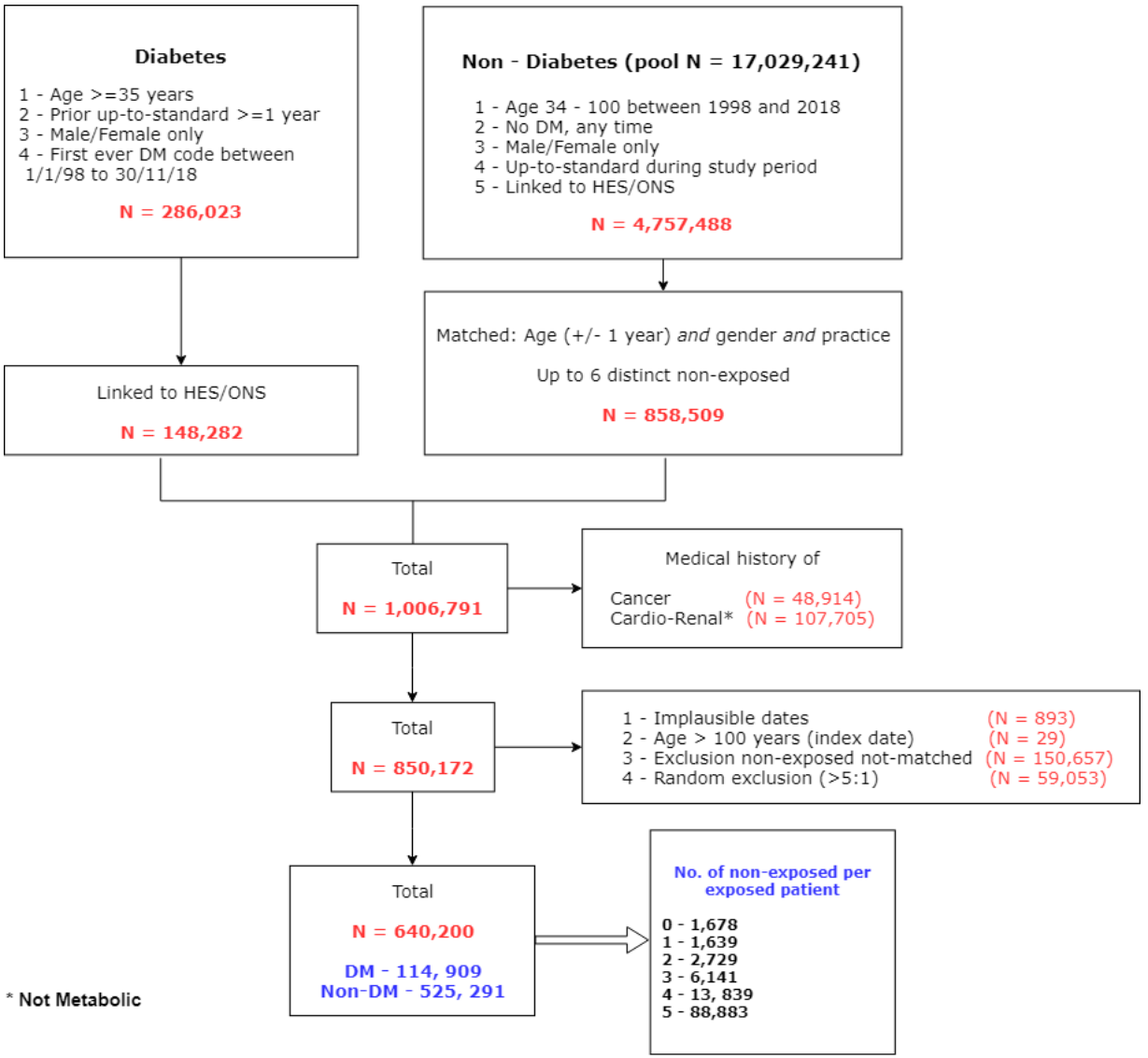


- Split by calendar time/Age
- Parametric model: *glm(event ~ axis1 + axis2 + … + covs, offset, family = poisson)*

Analytical framework (4): Poisson regression

```
db1  <-Lexis(entry = list(period  = yearin,
                          age   = agein),
             exit = list(period  = outm),
       exit.status = crm,
                id = patid,
             data = subset(db, DM == 1))

dbs1 <-splitMulti(db1, age = seq(30,100,1), period= seq(1998,2018,1))

a.kn <- with(subset(dbs1, lex.Xst==1), quantile(age+lex.dur,(1:5-0.5)/5))
p.kn <- with(subset(dbs1, lex.Xst==1), quantile(period+lex.dur,(1:5-0.5)/5))

r1   <- glm((lex.Xst==1) ~ Ns(age, knots = a.kn)*Ns(period, knots = p.kn)*gender,
        family = poisson,
        offset = log(lex.dur),
        data   = dbs1)

age          <- c(40:80)
period       <- seq(1998,2018,0.1)
gender       <- c(1:2)
nd           <- expand.grid(age, period, gender)
colnames(nd) <- c("age","period","gender")
nd           <- cbind(nd, lex.dur=1000)

p1           <- ci.pred(r1, newdata = nd)
```

Results (1): Participant flow



Results (2): Baseline characteristics and events

Variable	Level	DM = 0	T2DM = 1	p-value
N		525291	114909	
Sex	Men	281335 (53.6%)	62477 (54.4%)	<0.001
	Women	243956 (46.4%)	52432 (45.6%)	
Ethnicity	White	396668 (93.9%)	92678 (89.6%)	<0.001
	South Asian	7441 (1.8%)	4344 (4.2%)	
	Black	7831 (1.9%)	2588 (2.5%)	
	Other	10639 (2.5%)	3811 (3.7%)	
Cardio-renal-metabolic mortality	No	502678 (95.7%)	107705 (93.7%)	<0.001
	Yes	22613 (4.3%)	7204 (6.3%)	
All-cause mortality	No	421529 (80.2%)	86772 (75.5%)	<0.001
	Yes	103762 (19.8%)	28137 (24.5%)	
Deprivation (IMD)	1	120383 (22.9%)	22284 (19.4%)	<0.001
	2	122187 (23.3%)	25538 (22.2%)	
	3	107109 (20.4%)	23409 (20.4%)	
	4	97361 (18.6%)	23505 (20.5%)	
Lowest	5	77625 (14.8%)	20080 (17.5%)	

Results (3): Cardio-Renal-Metabolic rates, by sex