Department of Pharmacy
& Pharmacology

Using a primary care database to evaluate drug safety in pregnancy: possibilities & limitations

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Acknowledgements

- Julia Snowball, Rachel Charlton, John Weil, Marianne Cunnington
- Funding from GSK pharmaceuticals

Outline

- Drug safety in pregnancy research
  - Principal considerations
  - Measuring exposure, outcome, confounding
  - Possible designs (strengths & limits overview)
- Primary care databases as one of the options
  - Strengths & limitations in principle
  - Some preliminary findings using the GPRD
  - Implications

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Unique features

- Foetus is an ‘innocent bystander’
- Teratogenicity can be avoided
  - By not getting pregnant
  - Birth of a malformed infant can be prevented by a termination of pregnancy (TOP)
- Therefore, false alarms can have profound consequences (e.g. Bendectin, spray glue)
- Perceived safety of OTC medication

Investigating birth defects

- 3-4% of all live births
- Cannot be ‘lumped’: variations in
  - Gestational timing (e.g. chromosomal anomalies vs NTDs vs microcephaly)
  - Embryonic tissue of origin (e.g. cardiovascular defects, neural crest vs vasculature)
  - Mechanism of development (effect on embryonic tissue for normal development)
- Therefore malformations caused by a drug will differ by timing of intake, sensitivity of the end organ, and mechanism of teratogenesis

Implications for sample size

- Specific birth defects: 1:1000 to 1:10,000
- Follow a cohort of 100,000 pregnancies
  - Say 100 of a specific birth defect
  - If 10% exposure to a drug then 10 exposed cases
  - If 3% exposed then 3 exposed cases
- Cannot assume a class effect of drugs….

Identifying teratogens

- High risk – thalidomide, isotretinoin – overwhelm confounding issues
- Moderate risk – public health implications may be more – but need to consider confounders (e.g. ethnicity, alcohol, smoking, confounding by indication)
- Little is known about teratogenicity of prescription medication and even less of OTC medication

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Issues with measuring exposure

- Over the counter drug use (health care databases)
- Illicit drug use
- Recall bias
  - Attempts to address through choice of controls, interview techniques, quantifying the effect of recall

Issues with measuring outcome

- Need to take embryologic / teratogenic approach - not necessarily organ specific

Issues with measuring confounding

- Confounding by indication
- Reliability of smoking / alcohol / etc info
- Availability of info on e.g. ethnicity, nutrition

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Designs

- Large cohorts of pregnancies
  - + prospective data collection
  - - sample size
- Pregnancy registries
  - + prospective data collection
  - - selective loss to follow up, self-referral bias
  - - sample size (reassurance), confounding by indication
  - - data collection ends at delivery
- Case-control studies
  - + sample size, OTC, confounders
  - - recall

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Strengths

- Sample size

Strengths

- Sample size

- Depends on data quality, but could include
- Confounders (age, ethnicity, smoking, alcohol)
- Specific drug exposure data
- Pregnancy terminations
- Follow-up of child

Limitations

- Non-compliance
- OTC
- Illicit drug use
- Timing of pregnancy / exposure
- Accuracy / details of outcome recording
- Accuracy / availability of info on confounders

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GPRD

- Longitudinal data collected in UK general practice
- 5% of UK population
- Investigator is data parasite
- >100,000 Read & OXMIS codes for symptoms & diagnoses
- Utility for drug safety in pregnancy research?

Identifying pregnancies on GPRD

- Maternity files mostly paper based ☹
- Diagnoses and symptom codes relating to antenatal, neonatal and postnatal care, pregnancy, childbirth and termination of pregnancy (TOP) (e.g. ‘antenatal visit 32 weeks’, ‘forceps delivery’, ‘6-week postnatal check’).
- Each code was categorised for delivery/TOP, prematurity, postmaturity and postpartum.
- Codes were grouped into those providing sufficient evidence of pregnancy and those requiring additional evidence.
- Where appropriate, codes were assigned a gestation time.
- Linked to offspring where possible (79.7%)

Determining pregnancy episodes

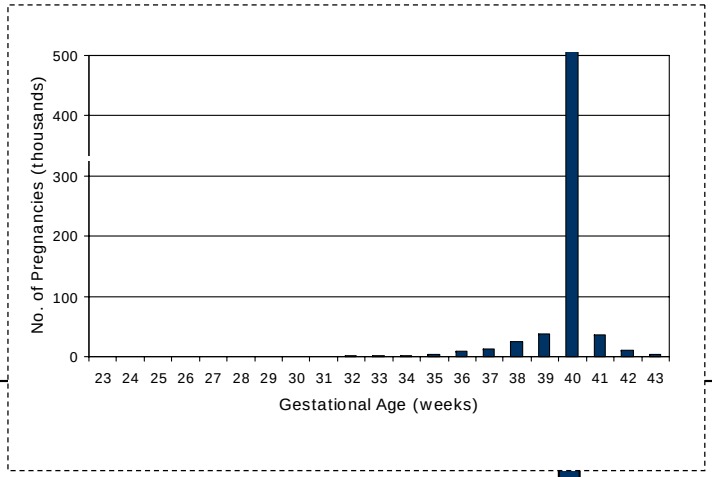
Codes for 1) Delivery 2) TOP 3) Post-partum.

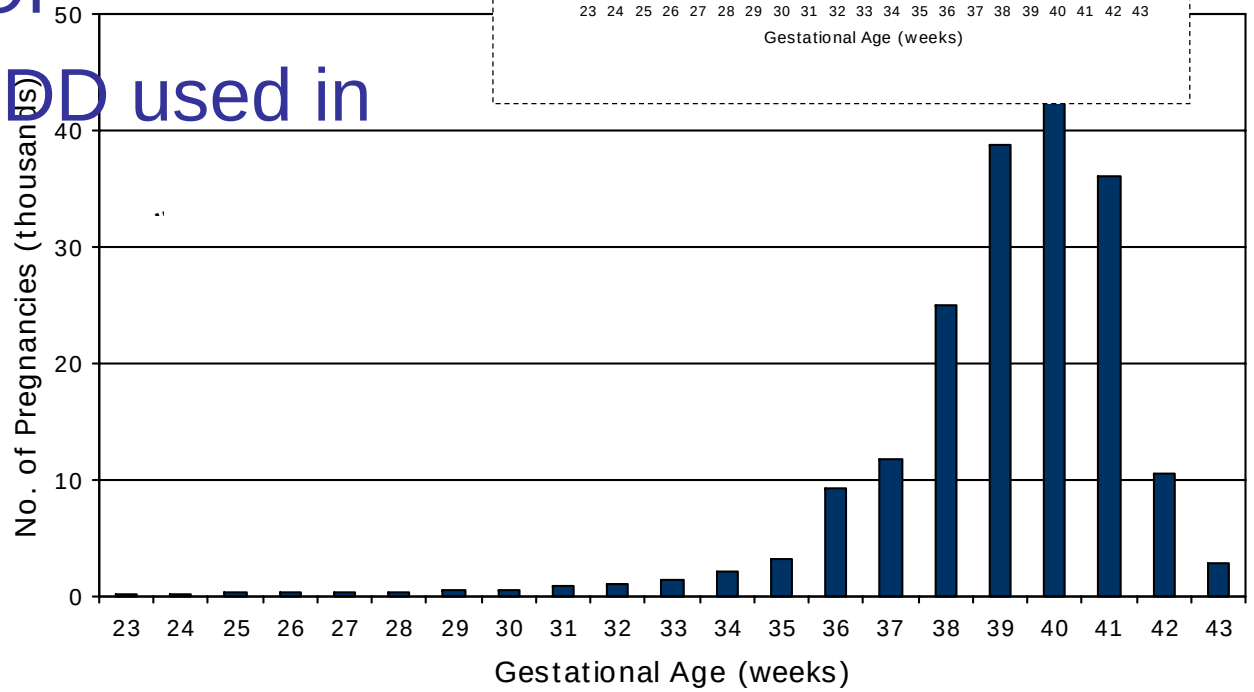
Pregnancy start dates estimated from:

1. Expected date of delivery (EDD)
2. LMP;
3. Gestational age;
4. Default term for premature delivery (36 weeks);
5. Default pregnancy term (40 weeks for delivery, 9 weeks for TOP).

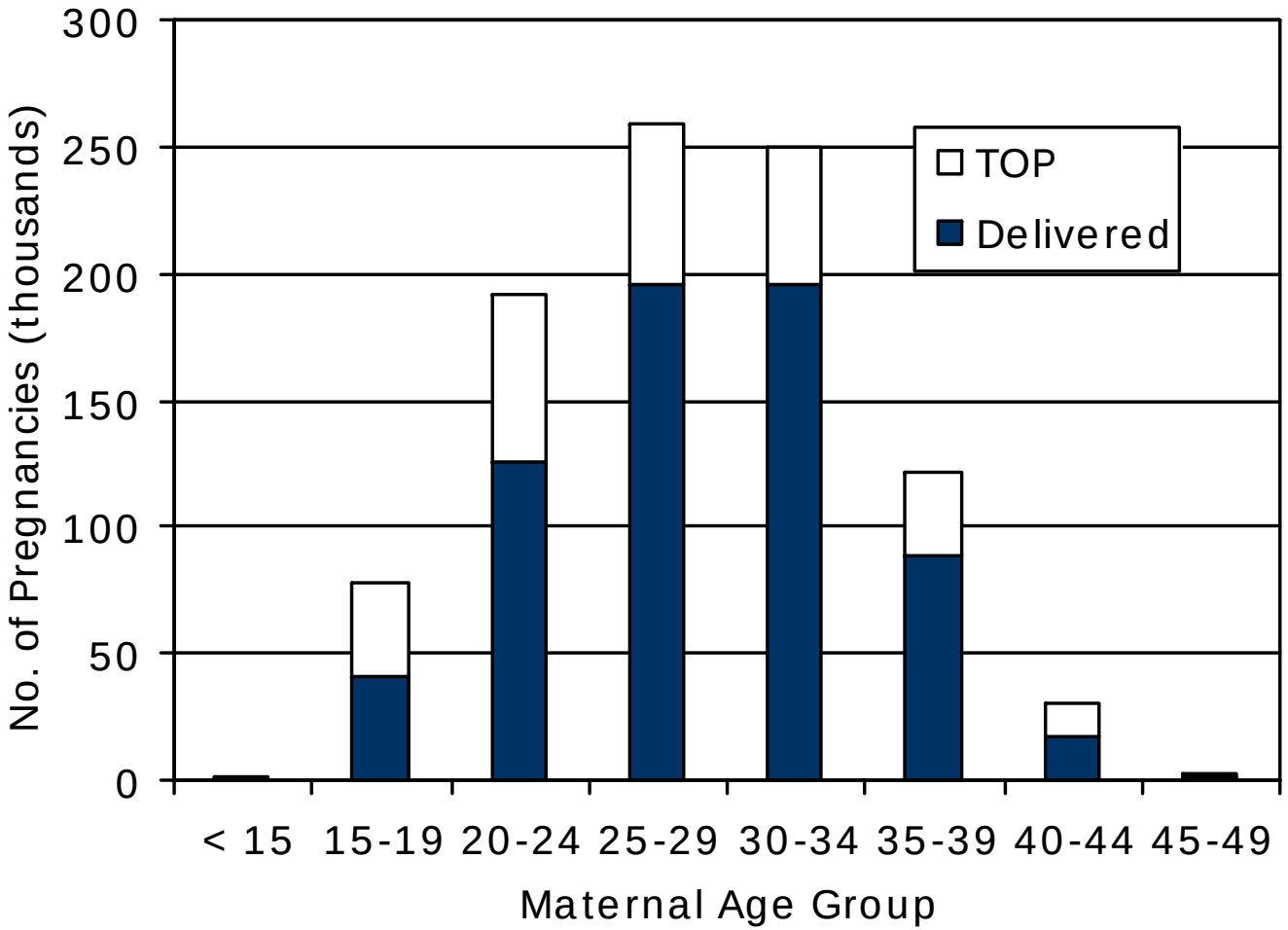
Results

- Over 900,000 pregnancies identified
- 71.2% delivery, 28.8% TOP
- LMP or EDD used in 28.4%





Pregnancy outcome by maternal age group



View Patient Medical History [F024]

Patient ID	**9170**	Date of Birth	**01/01/1956**	Sex	**Female**
Reg Date	**31/12/1981**	Lcens	**01/01/1991**	Practice	**136101**
Transfer Date		Rcens	**15/03/2007**	Death Date	

List

Previous | First

Full History | Clinical Group | Therapy Group

31/12/1981 Consultation: Other () [25]
31/12/1981 Blood grouping (276562) [25]
12/06/1984 Test: Rubella Test Rubella antibody titre (258249) Value: No Data Enter Range: (-) [28]
12/06/1984 Normal delivery (213972) [28]
12/06/1984 Consultation: Surgery consultation () [28]
21/01/1986 Normal delivery (213972) [30]
21/01/1986 Consultation: Other () [30]
22/01/1986 O/E - blood pressure reading (285459) [30]
22/01/1986 Blood Pressure: Syst: 125 Dias: 80 (285459) [30]
22/01/1986 Consultation: Surgery consultation () [30]
26/09/1986 Consultation: Surgery consultation () [30]
26/09/1986 Cervical smear: negative (231117) [30]
08/04/1988 CEFALEXIN caps 500mg (06470002) [32]
08/04/1988 Consultation: Surgery consultation () [32]
01/03/1989 Consultation: Other () [33]
01/03/1989 PREGNANCY (237874) [33]
04/03/1989 Consultation: Surgery consultation () [33]
04/03/1989 Glucostix strips [BAYER] (02677005) [33]
04/03/1989 Albustix strips [BAYER] (01665005) [33]
28/03/1989 Missed abortion (271380) [33]
28/03/1989 Consultation: Other () [33]
25/10/1989 O/E - blood pressure reading (285459) [33]
25/10/1989 Cervical smear: negative (231117) [33]
25/10/1989 Cervical smear: negative (231117) [33]
25/10/1989 Smoking: N Cigarette: Cigar: OzTob: (230315) Start: Stop: Smoking [33]
25/10/1989 Consultation: Surgery consultation () [33]
25/10/1989 Current non-smoker (230315) [33]
25/10/1989 Blood Pressure: Syst: 120 Dias: 65 (285459) [33]
14/02/1990 Cervical smear: negative (231117) [34]
14/02/1990 Blood Pressure: Syst: 120 Dias: 70 (285459) [34]
14/02/1990 Consultation: Surgery consultation () [34]
14/02/1990 O/E - blood pressure reading (285459) [34]
27/12/1990 CO-TRIMOXAZOLE tabs 80mg+400mg (02799001) [34]
27/12/1990 Consultation: Surgery consultation () [34]
27/12/1990 Upper respiratory infection NOS (289163) [34]

Left Censor Dt

27/06/1991 Test: Mid-stream specimen of urine MSU - general (267647) Value: No Data Enter Range: (-) [35]

Navigation

Go To Row

Go To Patient

1122109
236756
32955

View Patient Medical History [F024]

Patient ID	**9170**	Date of Birth	**01/01/1956**	Sex	**Female**
Reg Date	**31/12/1981**	Lcens	**01/01/1991**	Practice	**136101**
Transfer Date		Rcens	**15/03/2007**	Death Date	

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26/07/1994 SUMATRIPTAN inj 6mg/syringe (05322001) [38]
26/07/1994 Consultation: Repeat Issue () [38]
14/09/1994 Consultation: Repeat Issue () [38]
14/09/1994 SUMATRIPTAN inj 6mg/syringe (05322001) [38]
25/10/1994 Last menstrual period -1st day (276157) [38]
25/10/1994 Maternity: EDD:01-AUG-1995WkGest: Last menstrual period -1st day (276157) Births: Miscar: [38]
25/10/1994 Consultation: Surgery consultation () [38]
07/12/1994 Test: Pregnancy test Urine pregnancy test (258377) Value: No Data Enter Range: (-) [38]
07/12/1994 Referral: Hospital Pathology (Out Patient) (283361) PREGNANCY TEST [38]
07/12/1994 Consultation: Surgery consultation () [38]
09/12/1994 PREGNANCY (237874) [38]
09/12/1994 Consultation: Surgery consultation () [38]
06/01/1995 Consultation: Other () [39]
06/01/1995 Referral: Hospital Obstetrics (Out Patient) (237589) REFERRAL LETTER SENT [39]
06/01/1995 REFERRAL LETTER SENT (237589) [39]
26/01/1995 SEEN IN ANTENATAL CLINIC (292542) [39]
26/01/1995 Consultation: Telephone call from a patient () [39]
05/06/1995 VULVITIS (306775) [39]
05/06/1995 Consultation: Surgery consultation () [39]
05/06/1995 AMOXICILLIN caps 250mg (02868001) [39]
05/06/1995 URTI (UPPER RESPIRATORY TRACT INFECTION) (303947) [39]
05/06/1995 GYNO-DAKTARIN crm (02737001) [39]
08/06/1995 Anaemia during pregnancy, childbirth and the puerperium (298872) [39]
08/06/1995 PREGADAY tabs (00776001) [39]
08/06/1995 Consultation: Telephone call from a patient () [39]
05/07/1995 Consultation: Telephone call from a patient () [39]
05/07/1995 Anaemia during pregnancy, childbirth and the puerperium (298872) [39]
05/07/1995 PREGADAY tabs (00776001) [39]
30/07/1995 BABY NORMAL AT BIRTH (307164) [39]
30/07/1995 Consultation: Telephone call from a patient () [39]

Patient ID	**9264**	Date of Birth	**01/01/1966**	Sex	**Female**
Reg Date	**01/06/1979**	Lcens	**01/01/1991**	Practice	**136101**
Transfer Date		Rcens	**15/03/2007**	Death Date	

Full History | Clinical Group | Therapy Group

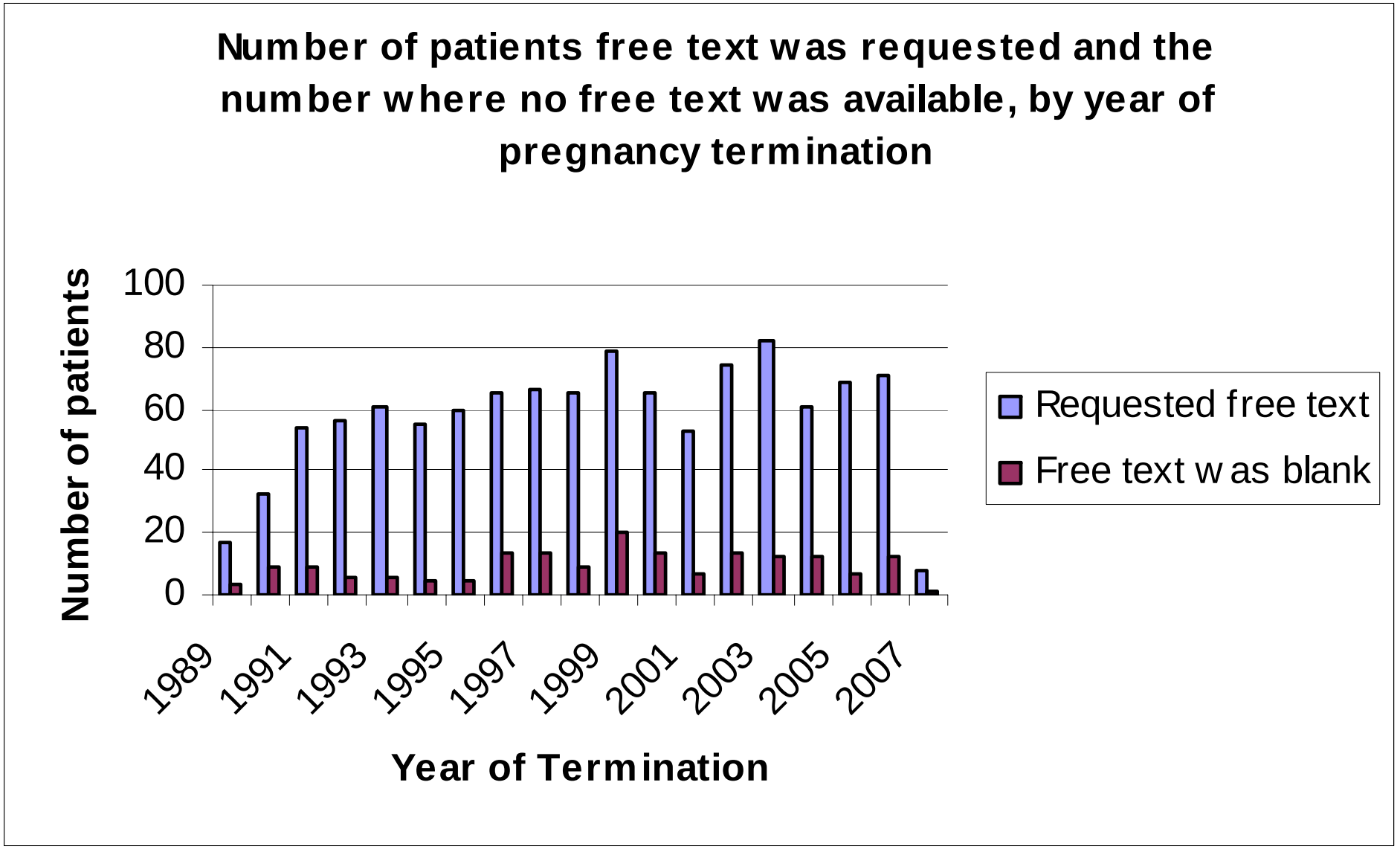
16/09/1994 Prescription dose change (268031) [28]
16/09/1994 PROPRANOLOL tabs 40mg (02876002) [28]
16/09/1994 Consultation: Surgery consultation () [28]
20/10/1994 Consultation: Surgery consultation () [28]
20/10/1994 PIROXICAM caps 20mg (04501002) [28]
20/10/1994 OSTEOCHONDRITIS (304831) [28]
07/11/1994 Consultation: Repeat Issue () [28]
07/11/1994 EUGYNON 30 tabs (02533001) [28]
08/11/1994 DYSMENORRHOEA (304439) [28]
08/11/1994 Consultation: Night visit , practice () [28]
08/11/1994 MEFENAMIC ACID tabs 500mg (04090002) [28]
17/11/1994 CO-AMOXICLAV tabs 250mg+125mg (06774001) [28]
17/11/1994 DYSMENORRHOEA (304439) [28]
17/11/1994 ALVERINE CITRATE caps 60mg (04953001) [28]
17/11/1994 Consultation: Surgery consultation () [28]
19/11/1994 Consultation: Surgery consultation () [28]
19/11/1994 PELVIC INFECTION FEMALE (304409) [28]
22/11/1994 Consultation: Surgery consultation () [28]
22/11/1994 Test: Pelvic ultra-sound U-S pelvic scan (213057) Value: No Data Enter Range: (-) [28]
22/11/1994 Referral: Hospital X-Ray (Out Patient) (301835) ULTRASOUND PELVIS [28]
23/11/1994 Consultation: Surgery consultation () [28]
23/11/1994 Ovarian cysts (289502) [28]
23/11/1994 Referral: Hospital Gynaecology (In Patient) (289502) Ovarian cysts [28]
23/11/1994 PROVERA tabs 10mg (02094002) [28]
24/11/1994 Consultation: Telephone call from a patient () [28]
24/11/1994 Ectopic pregnancy (234724) [28]
27/11/1994 Consultation: Telephone call from a patient () [28]
27/11/1994 SALPINGECTOMY (237428) [28]
28/11/1994 MEDICAL CERTIFICATE FIRST (256111) [28]
28/11/1994 Consultation: Telephone call from a patient () [28]

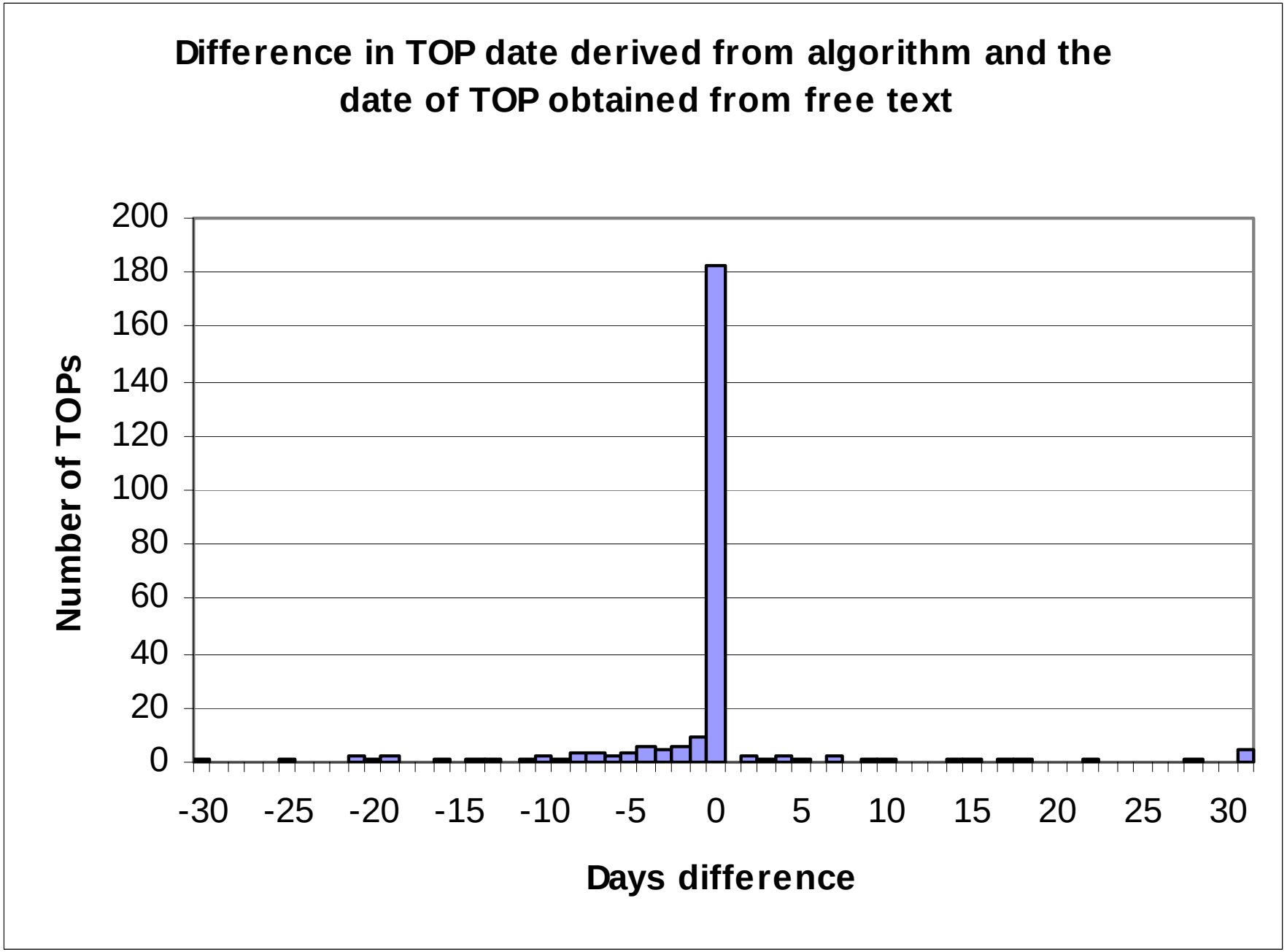
Terminations: why?

- Algorithm devised for distinguishing between
  - Spontaneous
  - Medical reasons – ectopic / malformations
  - Other reasons
- Free text for 1132 sample TOPs
  - 33 cases with a malformation determined from the free text
  - EDD / LMP information for 36.4%
  - Algorithm picked up half of the BDs

Malformation Information

- ~~~~~~~ Foetal renal abnormalities. Medical ToP
- secondary scan at ~~~ showed severe facial abnormalities thought to be incompatible with life
- is having termination at 20 weeks, baby has transposition of great arteries
- spina bifida @23 weeks
- anencephalic foetus


Number of patients free text was requested and the number where no free text was available, by year of pregnancy termination
Number of patients
100
80
60
40
20
0
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007
Year of Termination
Requested free text
Free text was blank


Difference in TOP date derived from algorithm and the date of TOP obtained from free text
Number of TOPs
200
180
160
140
120
100
80
60
40
20
0
-30
-25
-20
-15
-10
-5
0
5
10
15
20
25
30
Days difference

What about malformations?

- An evaluation of rates on the GPRD is needed *(e.g. Devine et al in PDS 2008)*
- TOPs and BDs will need to be considered
- Quality of BD recording?

Table 1. Malformations diagnosed at any age for infants registered at 1 year

Malformation class	Nº of cases	Verified via photocopied records		Pending verification from free text
		Included	Excluded	
Central nervous system	5	3		2
Congenital heart disease	43	28	2	13
Orofacial cleft	7	4		3
Eye	3			3
Digestive system	4	1		3
Internal urogenital system	23	12	4	7
Hypospadias	26	6	6	14
Talipes	17	4	1	12
Hip dislocation/dysplasia	17	4	2	11
Poly/Syndactyly	9	1	2	6
Limb reduction	7	6		1
Musculoskeletal	1		1	
Chromosomal	1	1		
Fetal valproate syndrome	4	2		2
Other	10	1		9
Total	**177**	**73**	**18**	**86**

Can the GPRD replace / complement registries?

Drug exposure and indication	Date range	No. of exposures in:	
		pregnancy registry	GPRD (Jan 1991–Oct 2005
Epilepsy[b]		UK Epilepsy and Pregnancy Register[6]	
Valproate	1 Dec 1996–31 Mar 2005	715	270
Lamotrigine	1 Dec 1996–31 Mar 2005	647	82
Carbamazepine	1 Dec 1996–31 Mar 2005	900	431
Gabapentin	1 Dec 1996–31 Mar 2005	31	13
Levetiracetam	1 Nov 2000–31 Mar 2005	22	0
Topiramate	1 Dec 1996–31 Mar 2005	28	4
Phenytoin	1 Dec 1996–31 Mar 2005	82	62
Migraine		Naratriptan/Sumatriptan Pregnancy Registry[9][c]	
Naratriptan	1 Oct 1997–30 Apr 2006	38	78
Sumatriptan	1 Jan 1996–30 Apr 2006	372	184
Depression		Eli Lilly and Company Worldwide Fluoxetine Pregnancy Registry[10]	
Fluoxetine	1 Jul 1989–9 Apr 1999	796	757
Antiretroviral		International Antiretroviral Pregnancy Registry[8][c,d]	
Abacavir	1 Jan 1999–31 Jan 2006	345	0
Lamivudine	1 Nov 1995–31 Jan 2006	1663	1
Zidovudine	1 Jan 1989–31 Jan 2006	1459	1
Nevirapine	1 Jun 1996–31 Jan 2006	479	1
Herpes virus infection		Acyclovir and Valacyclovir Pregnancy Registry[11]	
Acyclovir	1 Jun 1984–30 Apr 1999	597	1798
Valacyclovir	1 Jan 1995–30 Apr 1999	22	8

a For those where the drug became marketed after the start date of data collection, the mean numbers of exposure first marketed.

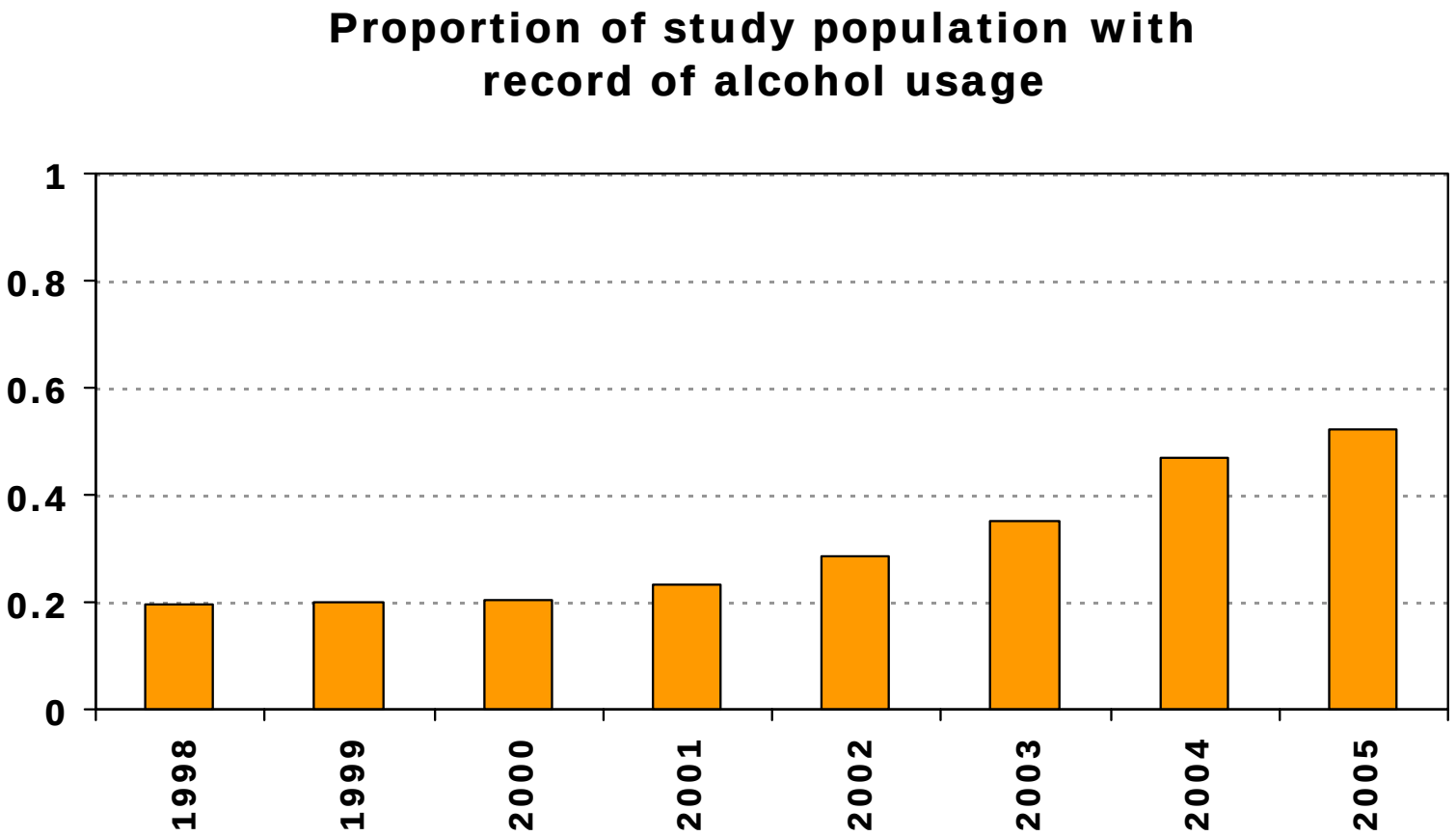
b In monotherapy.

c Sponsored by GlaxoSmithKline and contracted out to an independent research organization.

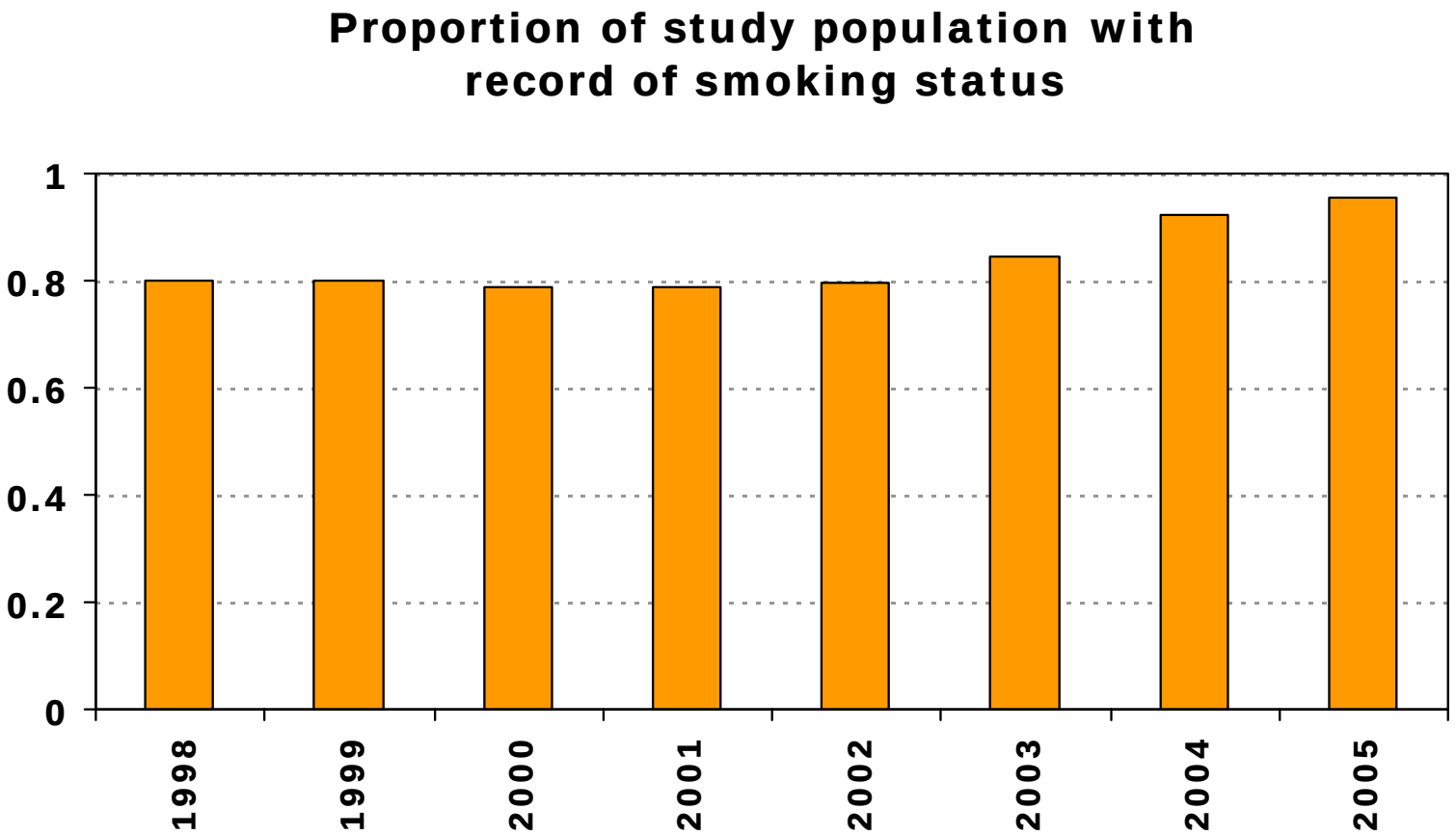
Other information?

- QOF in 2004

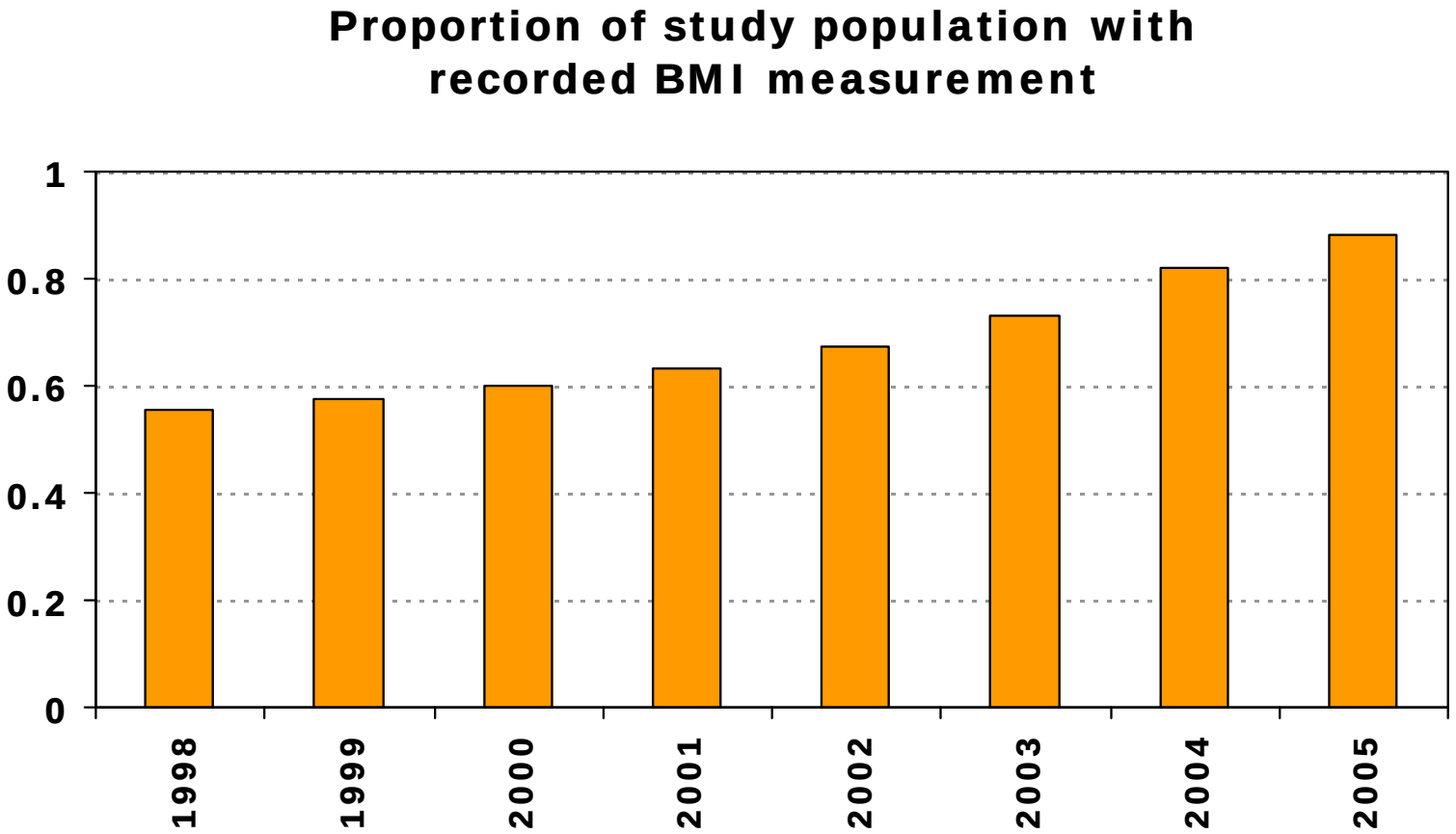
Records of alcohol use



Records of smoking status



Records of pre-pregnancy BMI



Other information?

- QOF in 2004
- OTC use
- Non-compliance
- Ethnicity

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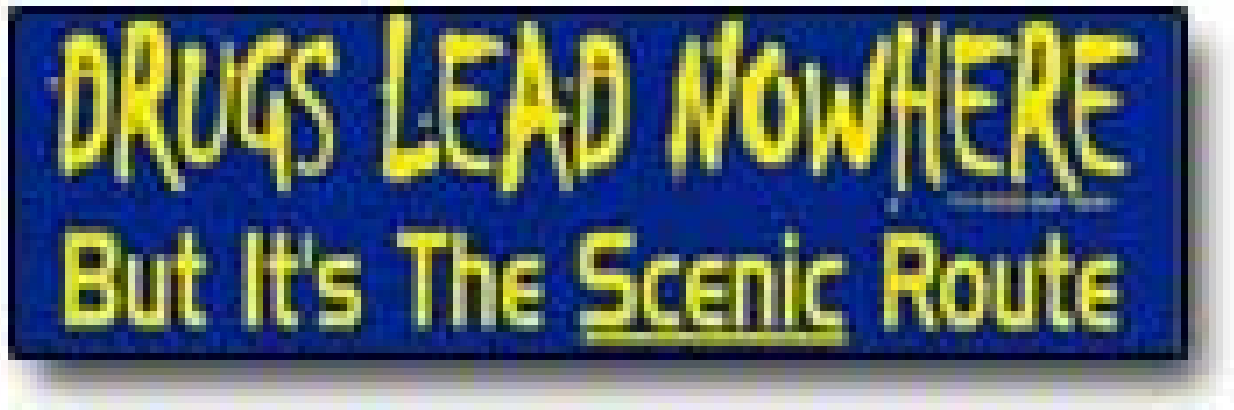
DRUGS LEAD NOWHERE
But It's The Scenic Route

Implications

- Primary care databases: key strength is sample size
- High risk teratogens +
- Moderate risk: +/-
- No system is perfect
- GPRD might be one of the few options to provide reassurance about risk

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- Moderate risk: +/-
- No system is perfect
- GPRD might be one of the few options to provide reassurance about risk
- Equally, GPRD might give false alarms…

Thank you

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