



**Department of Pharmacy  
& Pharmacology**

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

*Corinne de Vries*

# Acknowledgements

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

# Outline

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- 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

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- 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

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- 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

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- 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

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- 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

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- 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

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

# Issues with measuring confounding

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

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# Designs

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- 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

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- Sample size

# Strengths

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- 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

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- 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

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- 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

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- 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

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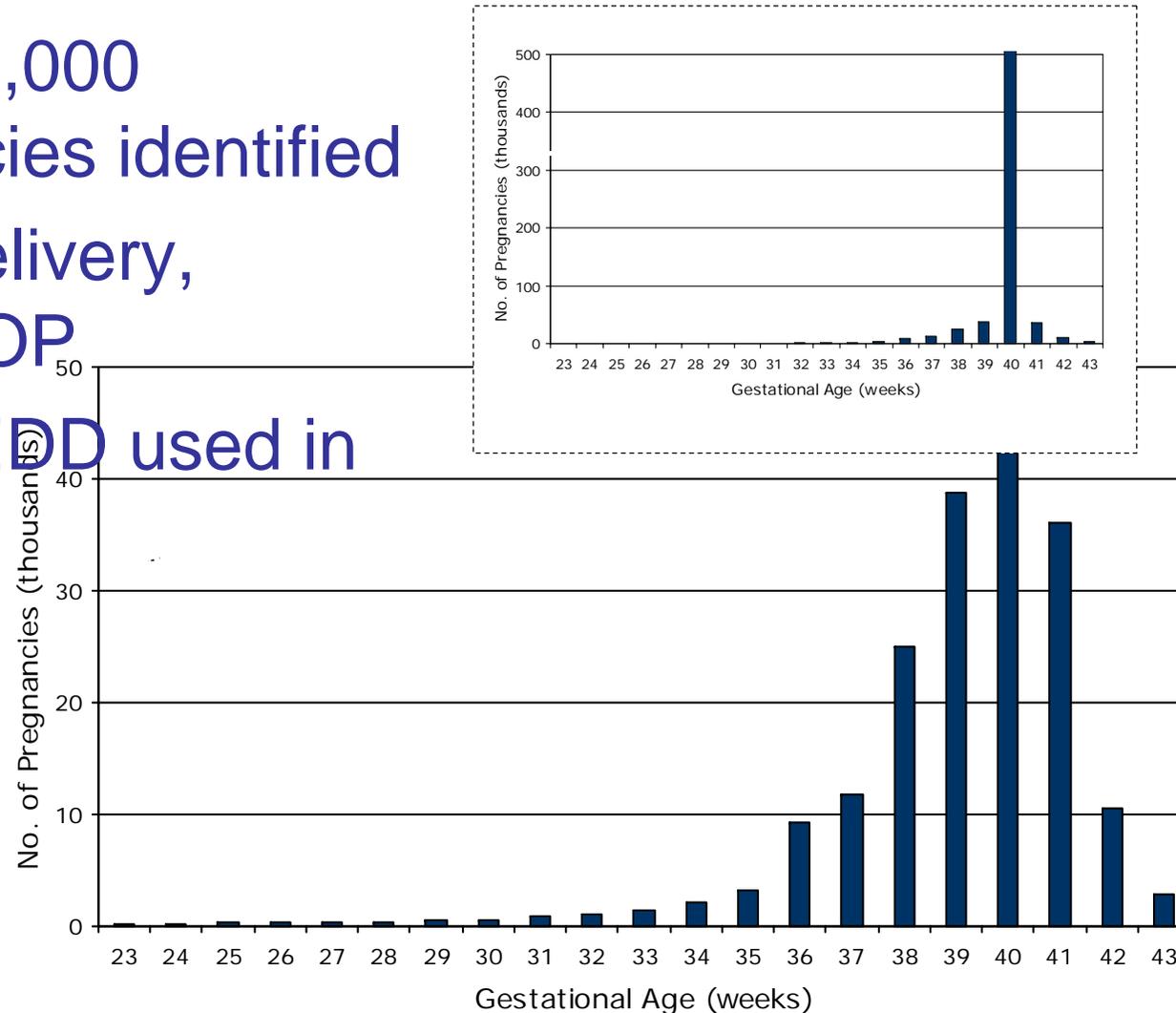
Codes for 1) Delivery 2) TOP 3) Post-partum.

Pregnancy start dates estimated from:

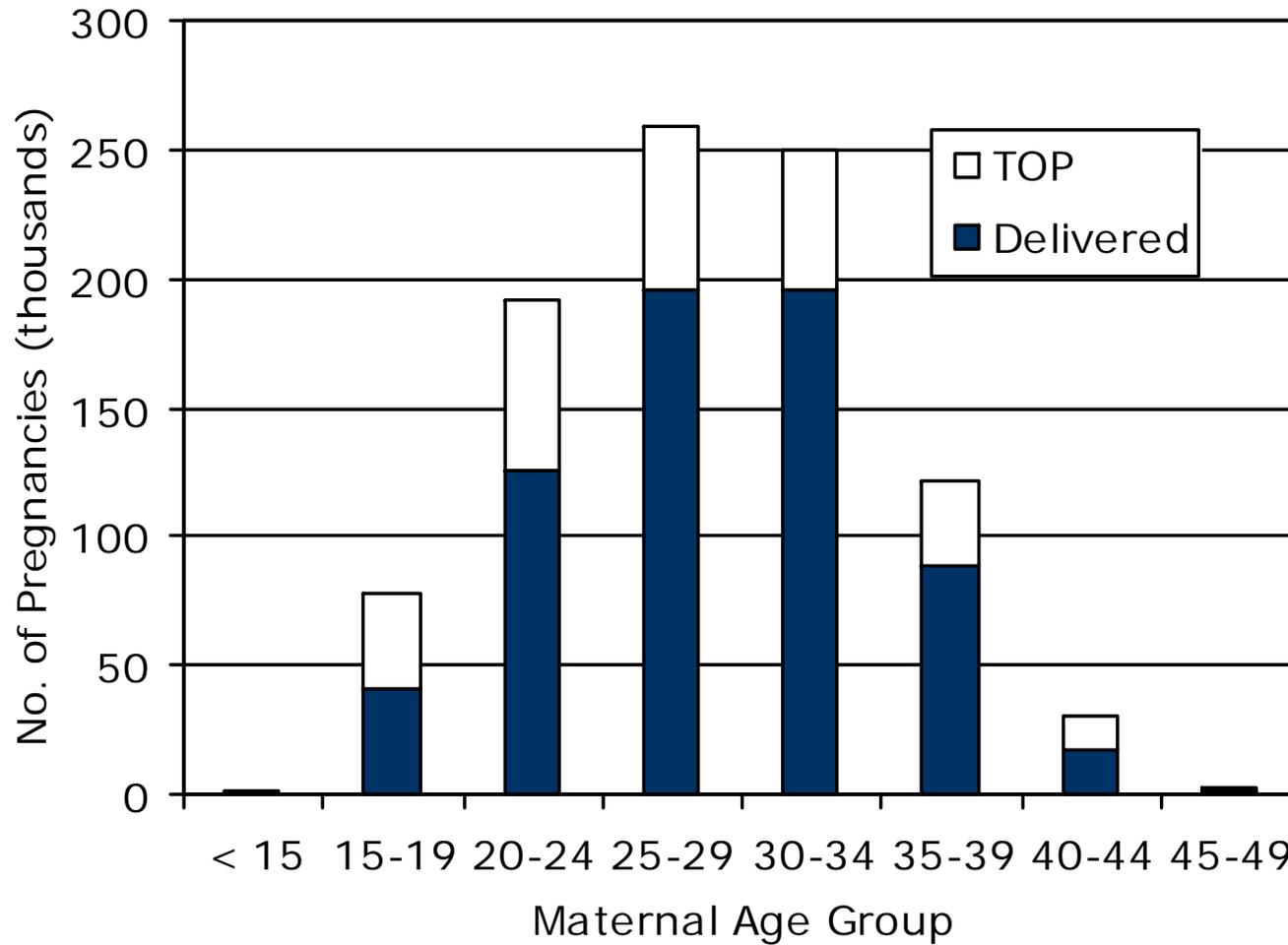
1. Expected date of delivery (EDD)
2. LMP;
3. Gestational age;
4. Default term for premature delivery (36 weeks);
5. Default pregnancy term (40 weeks for delivery, 9 weeks for TOP).

# 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 <b>9170</b>	Date of Birth <b>01/01/1956</b>	Sex <b>Female</b>
Reg Date <b>31/12/1981</b>	Lcens <b>01/01/1991</b>	Practice <b>136101</b>
Transfer Date	Rcens <b>15/03/2007</b>	Death Date

Previous

First

Full History	Clinical Group	Therapy Group
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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	<b>9170</b>	Date of Birth	<b>01/01/1956</b>	Sex	<b>Female</b>
Reg Date	<b>31/12/1981</b>	Lcens	<b>01/01/1991</b>	Practice	<b>136101</b>
Transfer Date		Rcens	<b>15/03/2007</b>	Death Date	
<b>Full History</b>	<b>Clinical Group</b>	<b>Therapy Group</b>			
22/03/1994	Consultation: Repeat Issue () [38]				
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]
- 28/11/1994 CO-DYDAMOL tabs 40mg+500mg (02533001) [28]

# Terminations: why?

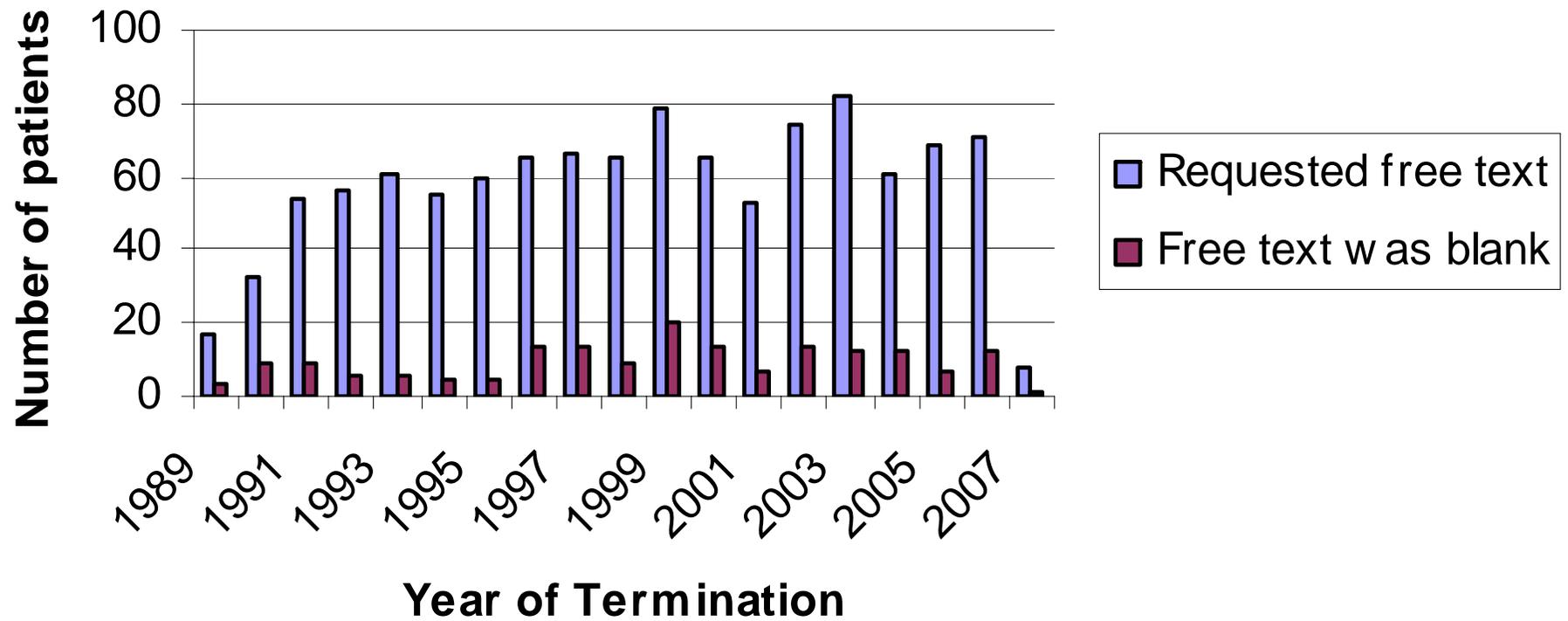
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- Algorithm devised for distinguishing between
  - Spontaneous
  - Medical reasons – ectopic / malformations
  - Other reasons
- Free text for 1132 sample TOPs
  - 33 cases with a malformation determined from the free text
  - EDD / LMP information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

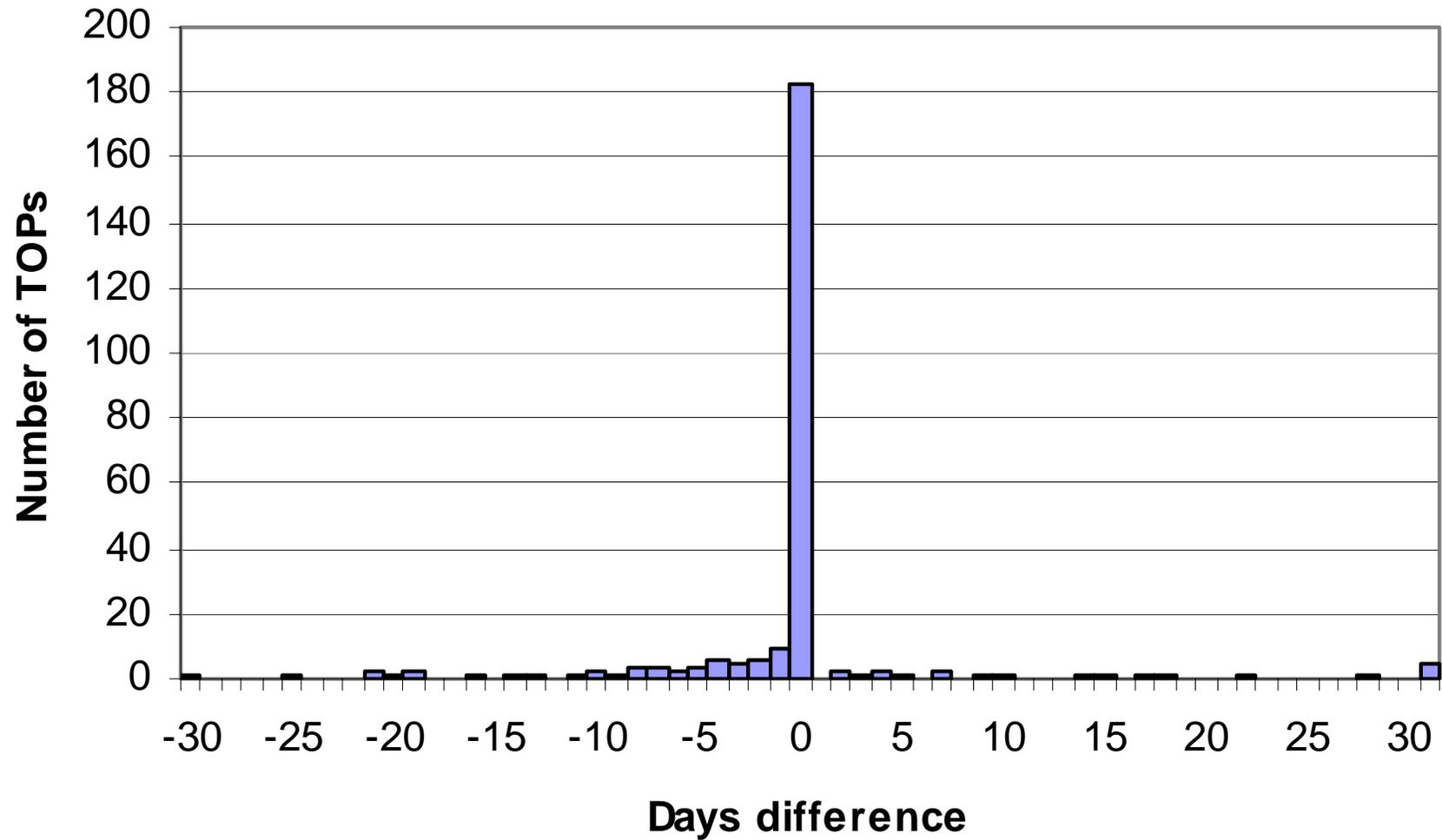
# Malformation Information

- ~~~~~ 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



### Difference in TOP date derived from algorithm and the date of TOP obtained from free text



# What about malformations?

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- 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	N° 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
<b>Total</b>	<b>177</b>	<b>73</b>	<b>18</b>	<b>86</b>

Can the GPRD replace /  
complement registries?

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Drug exposure and indication	Date range	No. of exposures in:	
		pregnancy registry	GPRD (Jan 1991–Oct 2005)
<b>Epilepsy<sup>b</sup></b>		UK Epilepsy and Pregnancy Register <sup>(6)</sup>	
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
<b>Migraine</b>		Naratriptan/Sumatriptan Pregnancy Registry <sup>(9)c</sup>	
Naratriptan	1 Oct 1997–30 Apr 2006	38	78
Sumatriptan	1 Jan 1996–30 Apr 2006	372	184
<b>Depression</b>		Eli Lilly and Company Worldwide Fluoxetine Pregnancy Registry <sup>(10)</sup>	
Fluoxetine	1 Jul 1989–9 Apr 1999	796	757
<b>Antiretroviral</b>		International Antiretroviral Pregnancy Registry <sup>(8),d</sup>	
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
<b>Herpes virus infection</b>		Acyclovir and Valacyclovir Pregnancy Registry <sup>(11)</sup>	
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.

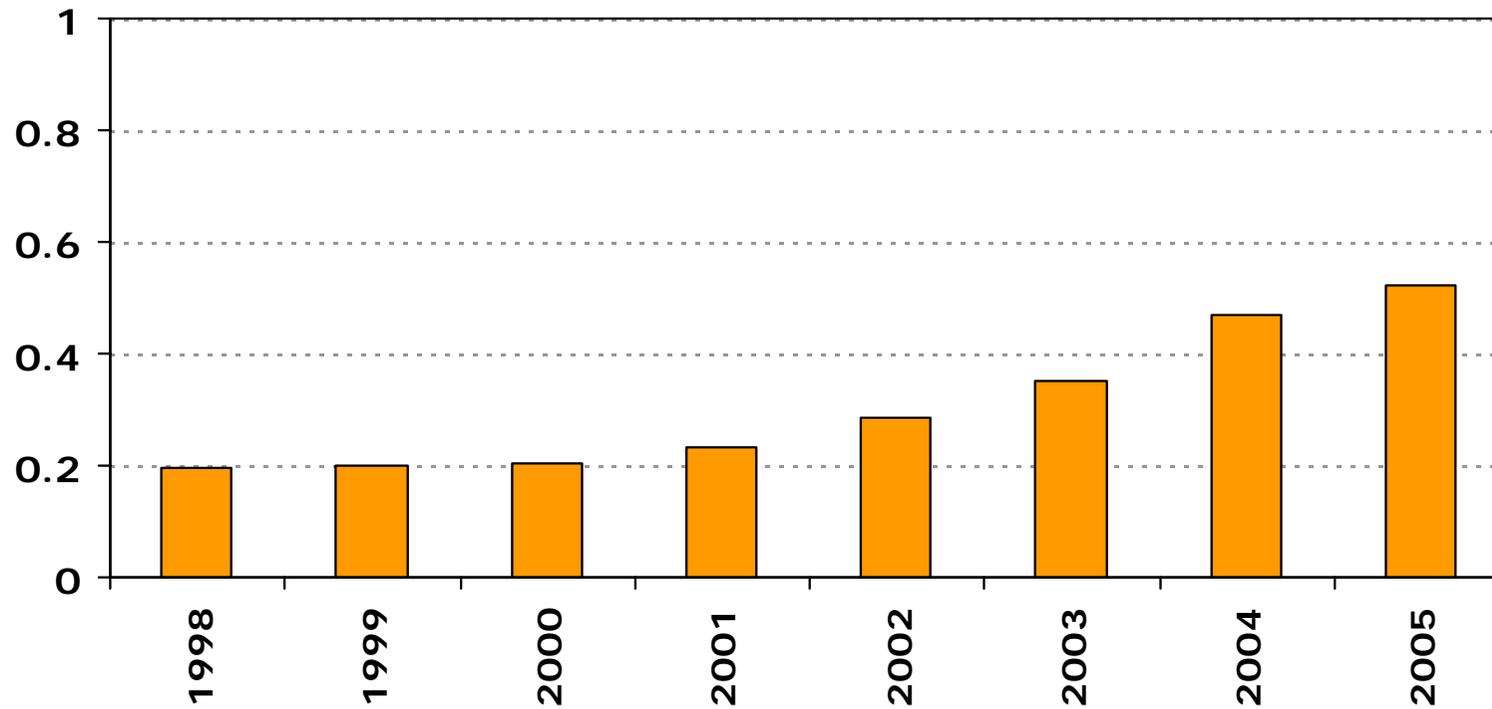
# Other information?

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- QOF in 2004

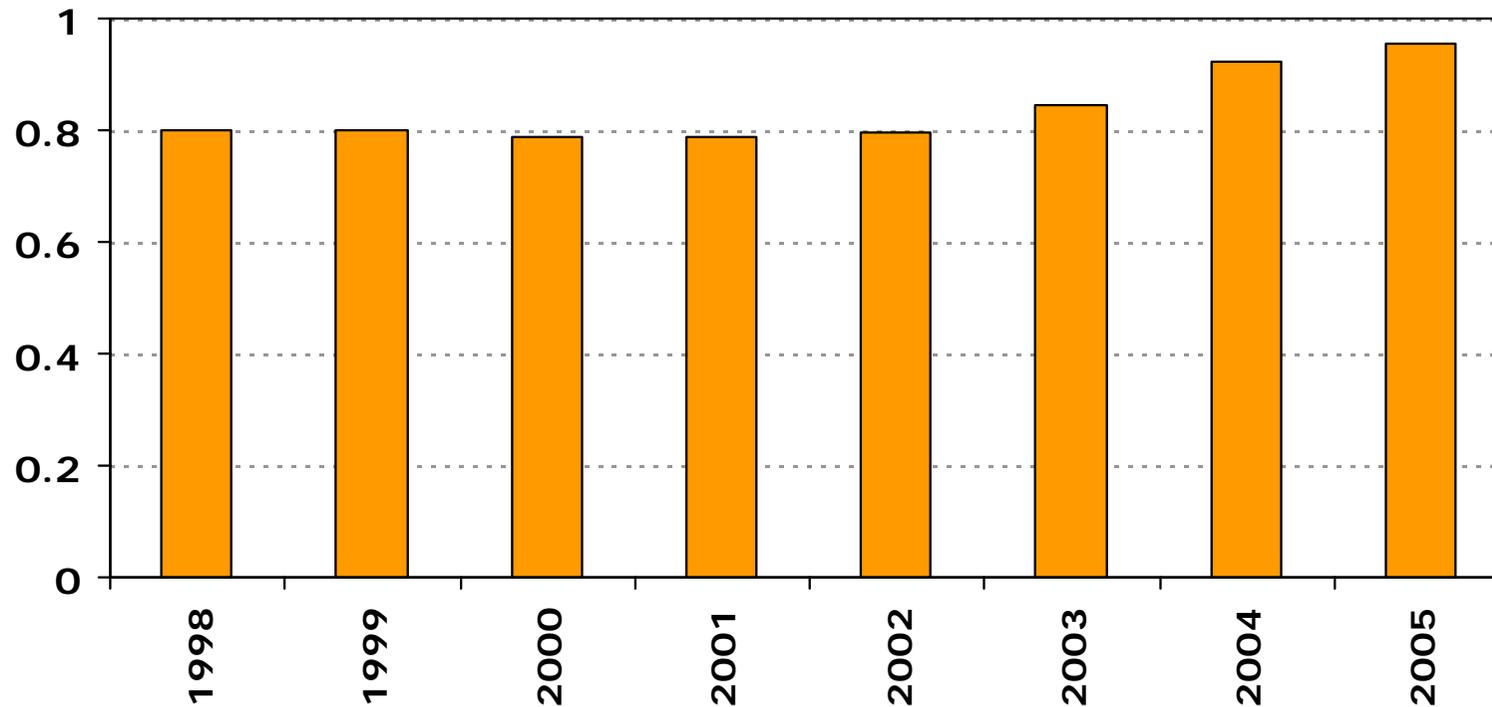
# Records of alcohol use

Proportion of study population with record of alcohol usage



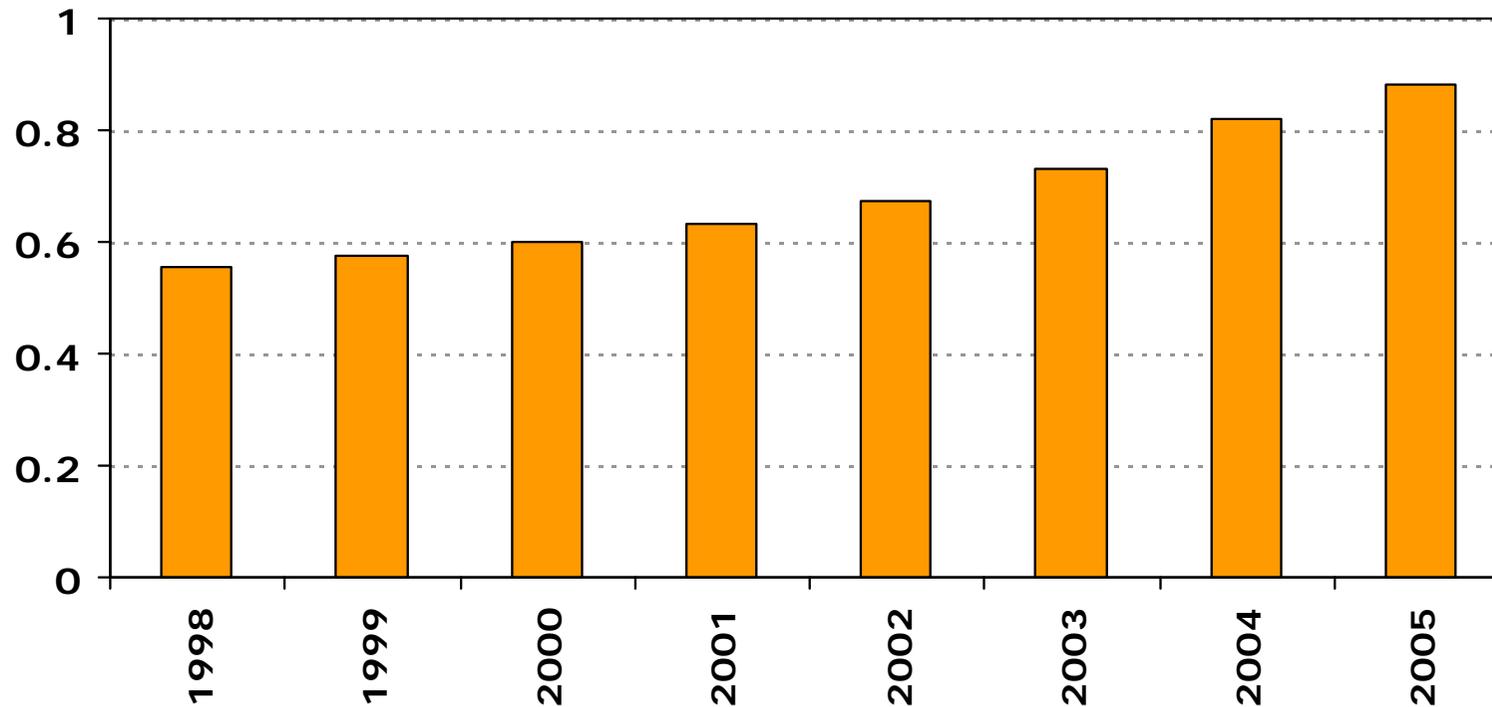
# Records of smoking status

Proportion of study population with record of smoking status



# Records of pre-pregnancy BMI

Proportion of study population with recorded BMI measurement



# Other information?

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

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DRUGS LEAD NOWHERE  
But It's The Scenic Route

# Implications

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- 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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- Primary care databases: key strength is sample size
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- 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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