Maternal medication and chronic diseases during pregnancy and pregnancy outcomes

Drugs and pregnancy

- Finnish national database

Drugs and pregnancy –surveillance system

- Co-project of three governmental authorities:
  - the National Institute for Health and Welfare (THL),
  - the Social Insurance Institution (SII) of Finland
  - the National Agency for Medicines (FIMEA).
- Started in 2008 with the preceding pilot study conducted during 2003–2007.
- Governmental authorities are aiming the project as part of the Finnish drug safety surveillance.

High quality nationwide health register-based data

	Information from year
Register on Induced Abortions	**1950**
Malformation Register	**1963**
Hospital Discharge Register	**1967**
▪ Outpatient visits in public hospitals (1998-)	
▪ Outpatient visits in health care centres (2011-)	
Medical Birth Register	**1987**
▪ Pregnancy and delivery -related diagnoses (2004-)	
▪ Very small premature newborns (2004-)	
Drugs and pregnancy database	**1996**

Aims of the Drugs and Pregnancy surveillance system

- To give information for governmental authorities for statutory duties on pregnancy related drug use and safety
- To give information for health care, clinicians, media, citizens, pharmaceutical industry etc.
- To collaborate with internal and international scientific society
- Surveillance of drug safety; research; statistics

Database

- **National Institute for Health and Welfare (THL)**

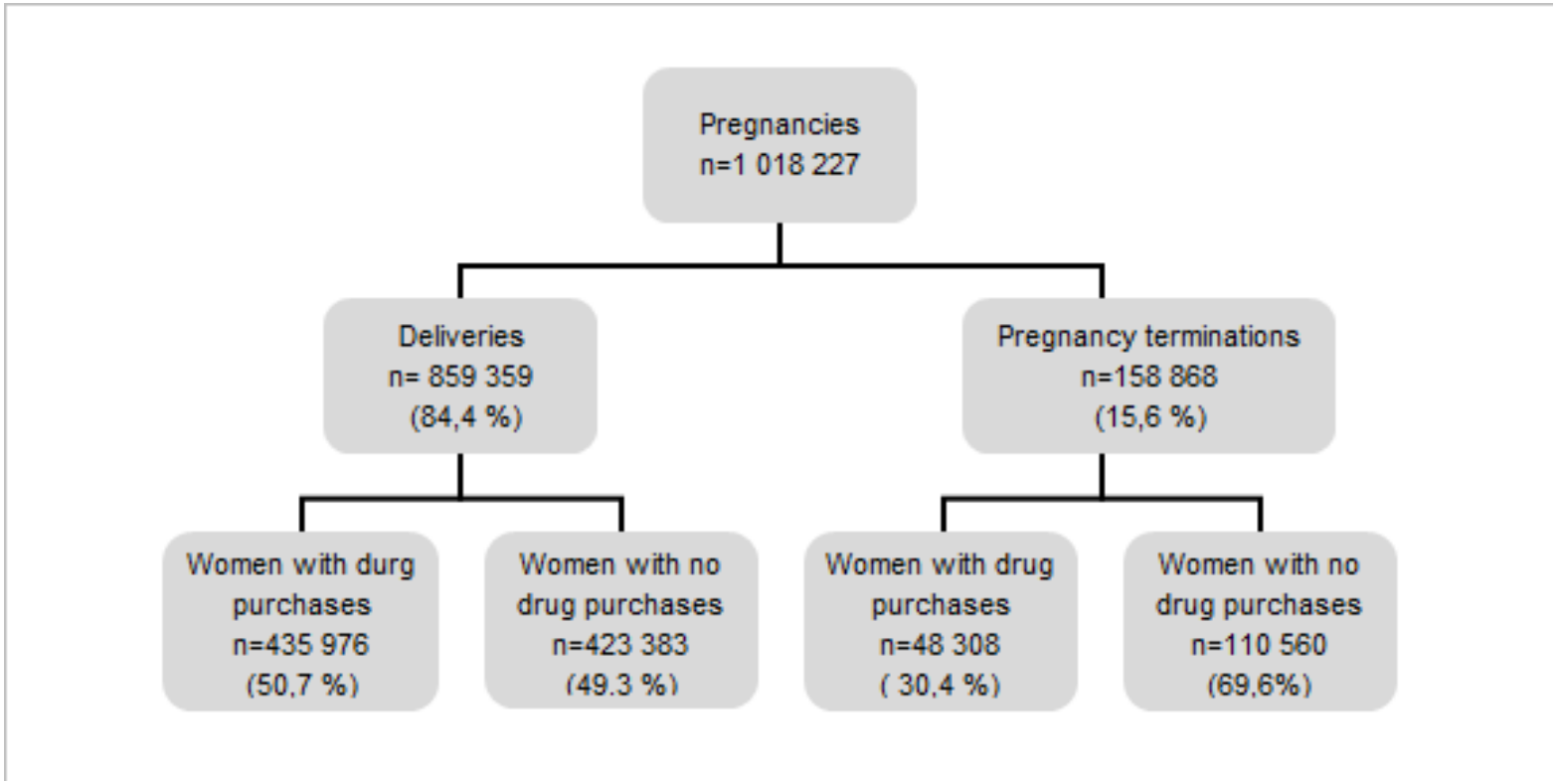
  Data on all births and terminations of pregnancy

  - Medical Birth Register
  - Malformation Register
  - Register on Induced Abortions
- **Social Insurance Institution (SII)**

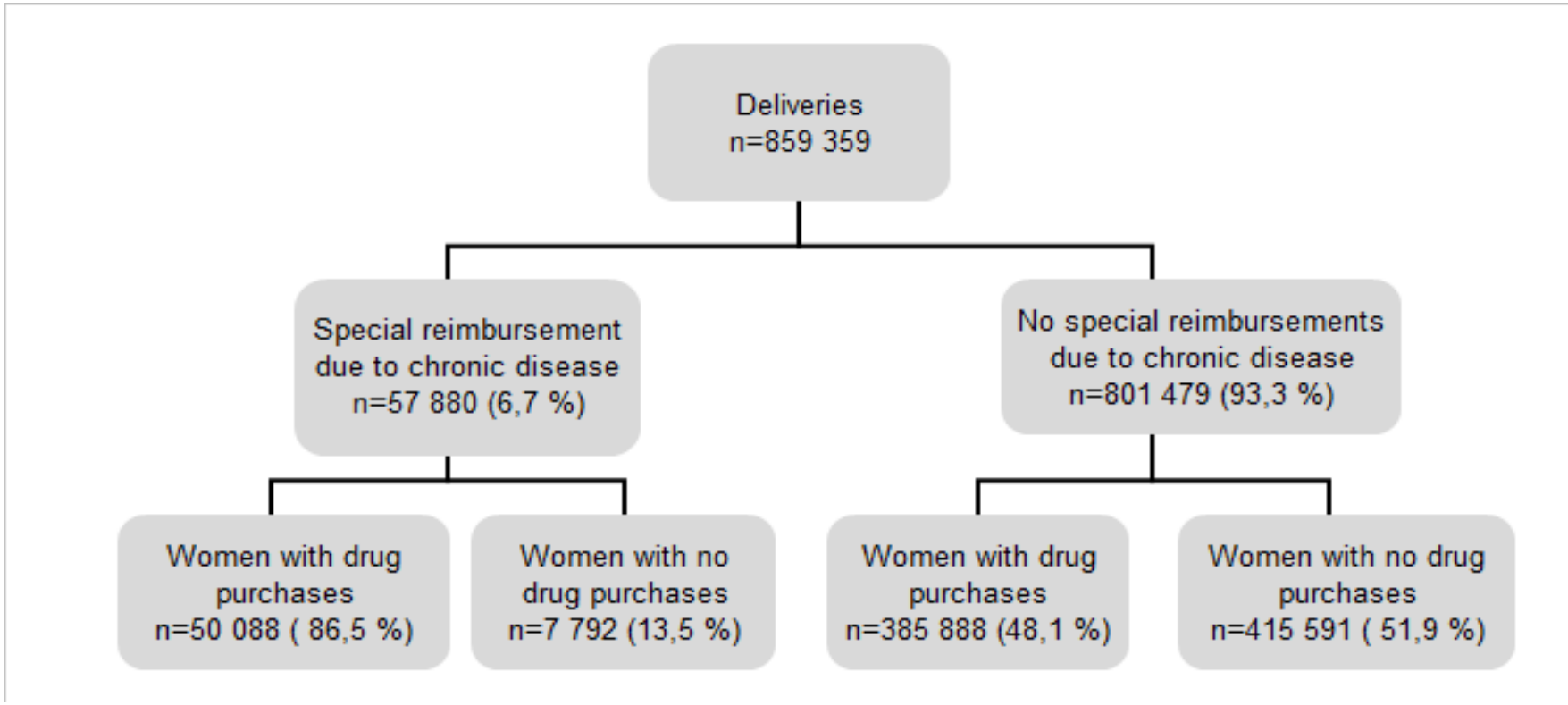
  Information on drugs and chronic diseases

  - Register on Reimbursement Drugs: all medicines prescribed by a doctor and reimbursed by SII
  - Special Refund Entitlement Register: specially reimbursed maternal chronic diseases and related drug purchases

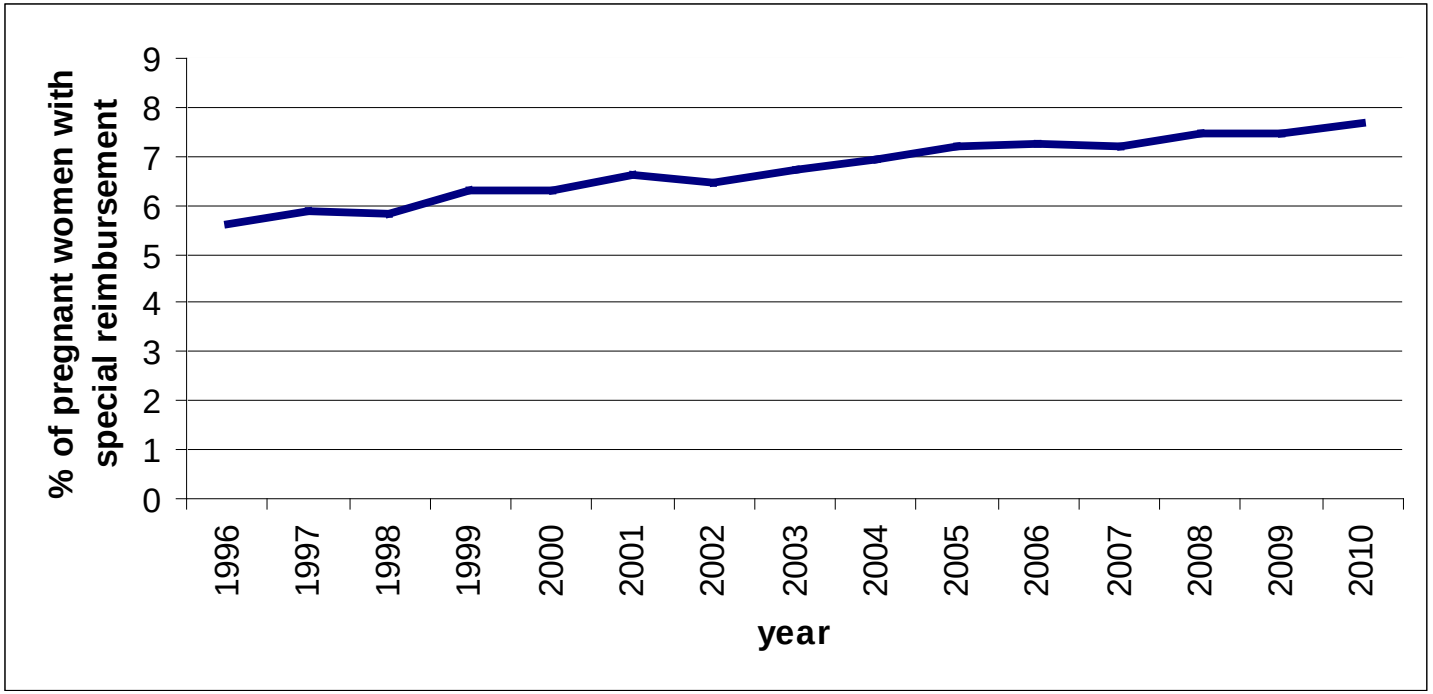
Drug purchases during pregnancy, Finland 1996–2010



Special reimbursement due certain chronic diseases and drug purchases during pregnancy, Finland 1996–2010



Proportion of women with at least one special reimbursement for drug purchases due to chronic disease during pregnancy, Finland 1996-2010



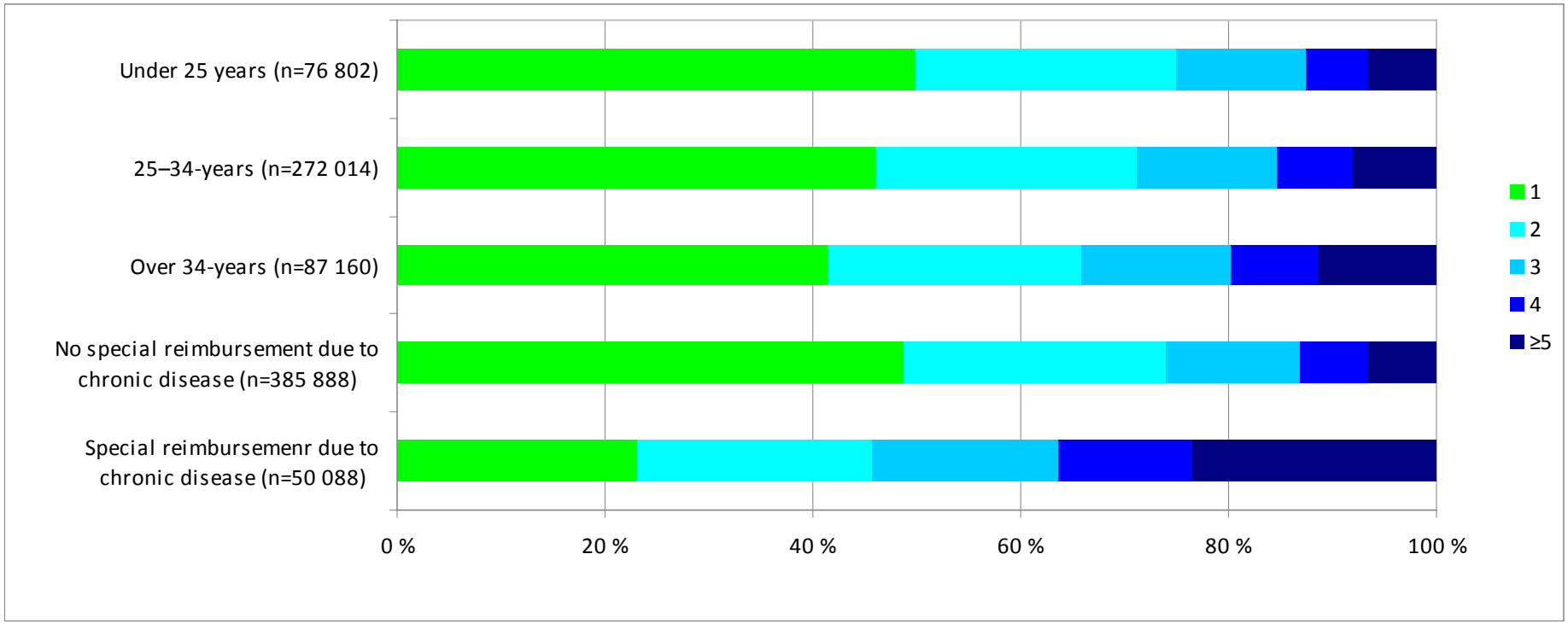
Drug purchases related to most frequent chronic diseases during pregnancy, %

Chronic disease	Women with special reimbursement for drug purchases due to chronic disease			Drug purchases due to special reimbursement	
	n	% [1]	% [2]	n	% [2]
Asthma	23 803	2,8	41,1	15 751	66,2
Hypothyreosis	7 058	0,8	12,2	6 582	93,3
Epilepsy	6 866	0,8	11,9	3 950	57,5
Rheumatoid arthritis	5 204	0,6	9,0	2 148	41,3
Diabetes	4 440	0,5	7,7	4 289	96,6
Crohn´s disease	4 303	0,5	7,4	3 180	73,9
Chronic hypertension	3 250	0,4	5,6	2 323	71,5
Psychosis	3 001	0,3	5,2	1 618	53,9

[1] Of women with delivery

[2] Of women with special reimbursement

Proprotions of number of drug purchases among pregnant women according to age and chronic disease, Finland 1996-2010

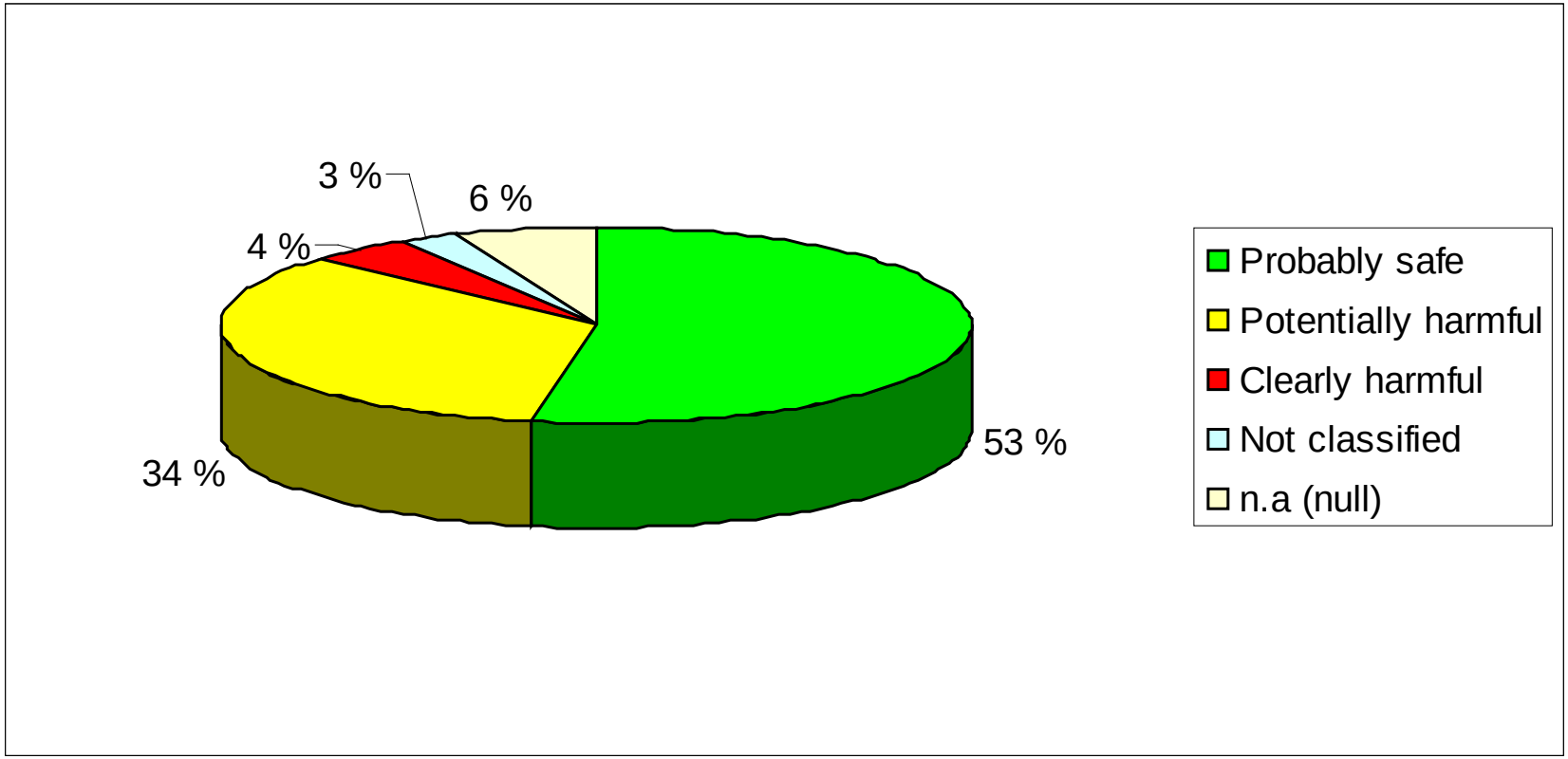


Pregnant women with drug purchases during pregnancy and the mean number of drug purchases according to exposure period of pregnancy, Finland 1996–2010

	Parturients with drug purchases					Drug purchases per parturient	
	Overall		Due to a chronic disease				
exposure period	**n**	**%**	**n**	**%**	**% [1]**	**n**	**mean**
one month prior to pregnancy	122 622	14,3	11 931	1,4	20,6	209 752	1,7
one month prior to pregnancy and/or 1st trimester	266 857	31,1	30 810	3,6	53,2	623 112	2,3
1st trimester	206 565	24,0	26 131	3,0	45,1	411 708	2,0
2nd trimester	206 691	24,1	28 932	3,4	50,0	382 256	1,8
3rd trimester	206 150	24,0	28 794	3,4	49,7	384 191	1,9
pregnancy (1.-3. trimesters)	403 081	46,9	38 353	4,5	66,3	1 179 695	2,9
one month prior to pregnancy and/or during pregnancy	435 976	50,7	39 371	4,6	68,0	1 391 099	3,2
3 months after pregnancy	294 990	34,3	24 880	2,9	43,0	558 671	1,9

[1] Of women with special reimbursement

Drug purchases during pregnancy according to the Swedish FASS safety classification, Finland 1996-2012



Latest publications and submitted papers using data from the Drugs and Pregnancy database

- Malm H, Artama M, Brown AS, Gissler M, Gyllenberg D, Hinkka-Yli-Salomaki S et al. Infant and Childhood Neurodevelopmental Outcomes Following Prenatal Exposure to Selective Serotonin Reuptake Inhibitors: overview and design of a Finnish Register-Based Study (FinESSI) (submitted)

- Artama M, Gissler M, Malm H, Ritvanen A and the Drug and Pregnancy Group. Effects of maternal epilepsy and antiepileptic drug use during pregnancy on perinatal health in offspring– nationwide, retrospective cohort study in Finland. Drug Saf 2012 in press.

- Kieler H, Artama M, Engeland A, Ericsson O, Furu K, Gissler M et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension of the newborn; population based cohort study from the five Nordic countries. BMJ 2012;344:d8012.
- Malm H, Artama M, Gissler M, Ritvanen A. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. Obstet Gynecol 2011;118:111-20.

- Artama M, Gissler M, Malm H, Ritvanen A; Drugs and Pregnancy Study Group. Nationwide register-based surveillance system on drugs and pregnancy in Finland 1996-2006. Pharmacoepidemiol Drug Saf 2011;20:729-38.

- Gissler M, Artama M, Ritvanen A, Wahlbeck K. Use of psychotropic drugs before pregnancy and the risk of induced abortion: population-based register data from Finland. BMC Public Health 2010;10:383.

Antiepileptic drug use during pregnancy and the risk for major malformations

***Table 2** Number and prevalence of congenital malformations in the offspring of mothers with antiepileptic medication during the first trimester of pregnancy, and OR with 95% CI for congenital malformation in relation to the offspring of epileptic mothers without antiepileptic medication during the first trimester of pregnancy by type of antiepileptic medication, Finland 1991 to 2000*

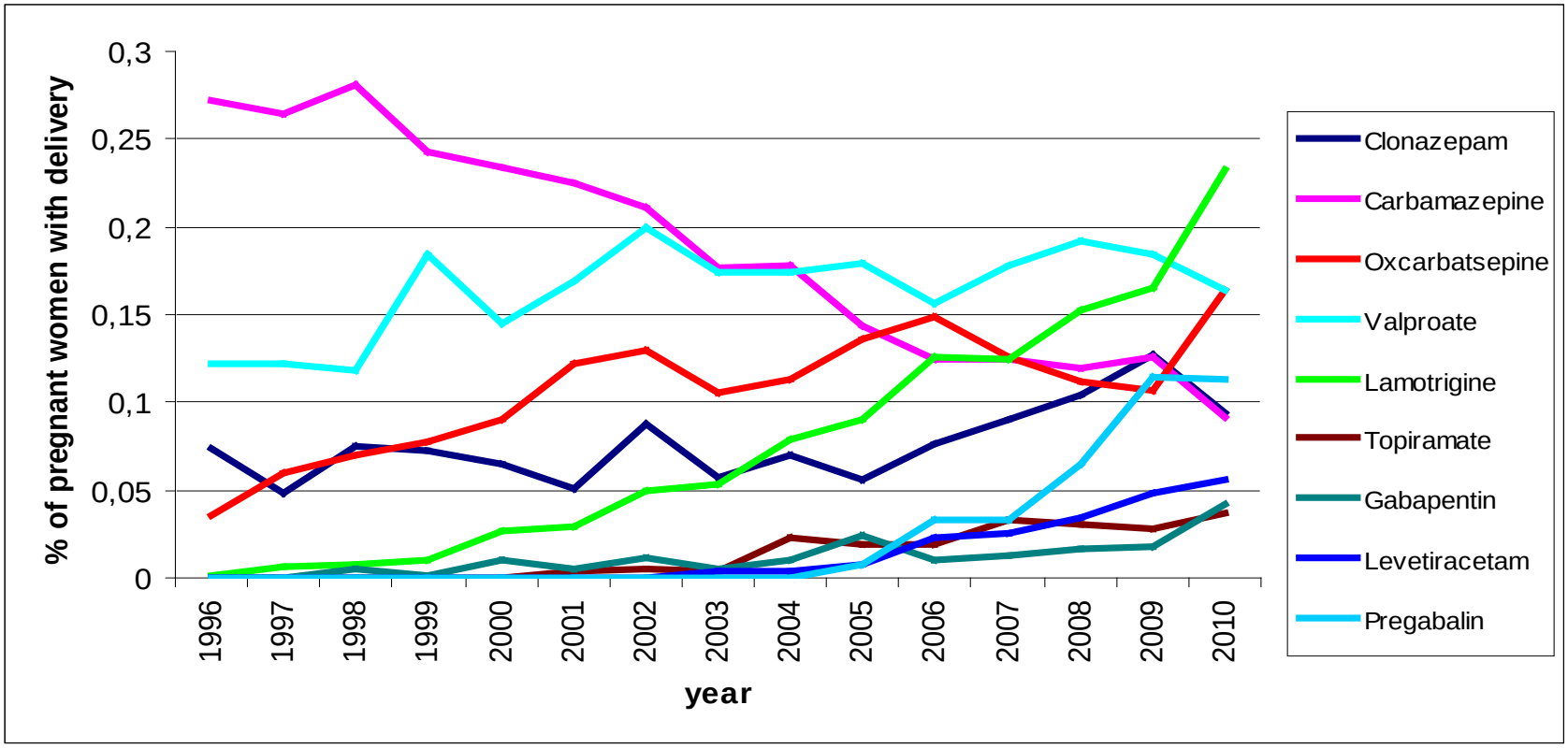
	No. of births with malformation	Prevalence per 1,000 births	OR*	95% CI*
No AED	26	28	1.00	Reference
Carbamazepine	32	35	1.27	0.72, 2.23
Polytherapy	10	88	3.43	1.44, 7.61
Excluding VPA	4	69	2.60	0.64, 7.88
Oxcarbazepine	3	23	0.83	0.16, 2.77
Polytherapy	2	65	2.42	0.27, 10.5
Excluding VPA	1	59	2.19	0.05, 15.2
Valproate	37	102	4.01	2.32, 7.01
Monotherapy	28	107	4.18	2.31, 7.57
Polytherapy	9	92	3.54	1.42, 8.11
Other medication*	5	38	1.37	0.40, 3.72
Polytherapy	5	47	1.75	0.51, 4.77
Excluding VPA	3	41	1.48	0.28, 5.02
Total therapy	65	46	1.70	1.05, 2.81
Excluding VPA	38	36	0.96	0.54, 1.72
Total monotherapy	52	42	1.55	0.94, 2.60
Excluding VPA	24	25	0.89	0.49, 1.63
Total polytherapy	13	72	2.73	1.26, 5.64
Excluding VPA	4	49	1.80	0.45, 5.38

* Other medication: acetazolamide, clobazam, clonazepam, ethosuximide, gabapentin, lamotrigine, phenobarbital, primidone, tiagabine, topiramate, or vigabatrin.

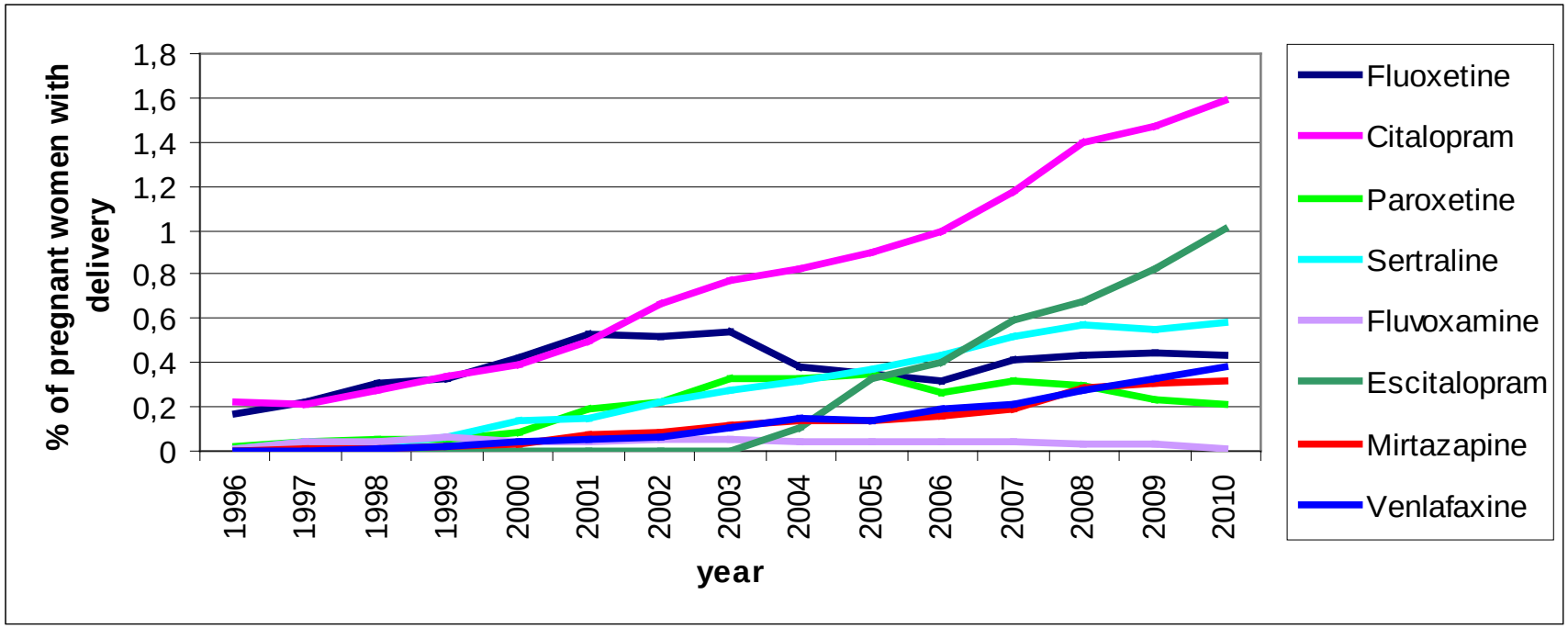
AED = antiepileptic drug; VPA = valproate.

Artama et al. Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. Neurology 2005;64:1874-1878

Use of antiepileptics during pregnancy in Finland 1996-2010, pregnancies ending in delivery



Use of antidepressants during pregnancy in Finland 1996-2010, pregnancies ending in delivery



Selective Serotonin Reuptake Inhibitors and Risk for Major Congenital Anomalies

Heli Malm, MD, PhD, Miia Artama, MSc, PhD, Mika Gissler, MSocSc, PhD, and Annukka Ritvanen, MD

Table 3. Prevalence of Major Cardiovascular Anomalies in Offspring of Pregnant Women Exposed to Selective Serotonin Reuptake Inhibitors

	Major Cardiovascular Anomalies			
	No. Exposed	No. Unexposed	Crude OR	Adjusted OR
Fluoxetine (1,818)				
All major cardiovascular anomalies	37 (204 of 10,000)		1.58 (1.14–2.19)	1.40 (1.01–1.95)
Atrial septal defects	7 (39 of 10,000)		1.90 (0.90–4.00)	1.52 (0.71–3.24)
Ventricular septal defects[†]	26 (143 of 10,000)		1.65 (1.12–2.43)	1.49 (1.00–2.20)
Isolated ventricular septal defects	19 (105 of 10,000)	3,113 (49 of 10,000)	2.14 (1.36–3.37)	2.03 (1.28–3.21) ←
Excluding offspring in neonatal care unit treatment (1,516)	16 (106 of 10,000)	2,423 (43 of 10,000)	2.50 (1.52–4.09)	2.47 (1.50–4.07)
Right ventricular outflow tract defects[‡¶]	3 (17 of 10,000)		2.49 (0.80–7.76)	2.68 (0.85–8.49)
Transposition of great arteries	—		—	—
Conotruncal heart defects[§]	—		—	—
Left ventricular outflow tract defects[‖]	2		1.48 (0.37–5.91)	1.21 (0.30–4.94)
Paroxetine (968)				
All major cardiovascular anomalies	16 (165 of 10,000)		1.28 (0.78–2.10)	1.09 (0.66–1.79)
Atrial septal defects	3 (31 of 10,000)		1.53 (0.49–4.74)	1.28 (0.41–4.00)
Ventricular septal defects[†]	10 (103 of 10,000)		1.19 (0.64–2.21)	1.01 (0.54–1.88)
Right ventricular outflow tract defects[‡¶]	3 (31 of 10,000)		4.70 (1.51–14.65)	4.68 (1.48–14.74) ←
Major chromosomal anomalies excluded (959)	3 (31 of 10,000)	392 (6 of 10,000)	5.06 (1.63–15.78)	5.18 (1.64–16.34)
Transposition of great arteries	—		—	—
Conotruncal heart defects[§]	2 (21 of 10,000)		3.02 (0.75–12.13)	2.46 (0.60–10.03)
Left ventricular outflow tract defects[‖]	—		—	—

Malm et al. Obstet Gynecol 2011;118:111-120

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Table 4. Adjusted Odds Ratios and 95% Confidence Intervals for Organ System-Specific and Some Previously Reported Major Congenital Anomalies in Relation to Selective Serotonin Reuptake Inhibitor Use

Organ System	Any Selective Serotonin Reuptake Inhibitor	Citalopram	Fluoxetine	Paroxetine	Sertraline	Escitalopram	Fluvoxamine
n	6,976	2,799	1,818	968	869	441	240
Central nervous system	1.03 (0.68–1.57)	1.20 (0.66–2.19)	0.95 (0.42–2.15)	0.32 (0.05–2.27)	1.35 (0.50–3.64)	—	2.34 (0.58–9.49)
Neural tube defects*	1.85 (1.07–3.20)	2.46 (1.20–5.07)	1.69 (0.62–4.63)	—	1.77 (0.43–7.21)	—	2.86 (0.39–20.73)
Respiratory tract	0.61 (0.28–1.30)	0.44 (0.11–1.80)	1.03 (0.33–3.25)	0.67 (0.09–4.78)	0.69 (0.10–4.93)	—	—
Cleft lip with or without cleft palate	0.62 (0.25–1.51)	0.62 (0.15–2.52)	0.48 (0.07–3.42)	0.91 (0.13–6.52)	1.01 (0.14–7.20)	—	—
Cleft palate	1.18 (0.67–2.08)	0.89 (0.33–2.41)	1.03 (0.33–3.25)	2.65 (0.98–7.14)	1.42 (0.35–5.76)	—	—
Digestive system	0.87 (0.54–1.38)	0.92 (0.46–1.85)	0.90 (0.37–2.17)	0.67 (0.17–2.69)	1.09 (0.35–3.41)	—	1.35 (0.19–9.64)
Urogenital	1.09 (0.80–1.50)	0.91 (0.53–1.54)	1.43 (0.84–2.44)	1.51 (0.75–3.04)	1.22 (0.55–2.74)	0.37 (0.05–2.66)	—
Musculoskeletal†	0.96 (0.75–1.23)	1.04 (0.72–1.50)	0.69 (0.40–1.12)	1.11 (0.61–2.02)	0.97 (0.50–1.88)	1.22 (0.54–2.75)	0.79 (0.20–3.19)
Omphalocele	0.47 (0.11–1.94)	—	0.97 (0.13–7.04)	1.83 (0.25–13.25)	—	—	—
Craniosynostosis	1.53 (0.61–3.87)	1.49 (0.36–6.15)	1.12 (0.15–8.16)	2.16 (0.30–15.64)	2.42 (0.33–17.60)	—	—

—, no cases.

Data are adjusted odds ratio (95% confidence interval).

Logistic regression analyses adjusted to maternal age at the end of pregnancy, parity, year of pregnancy ending, marital status, smoking any time during pregnancy, other reimbursed psychiatric medicine purchases, and entitlement for special reimbursement for prepregnancy diabetes. "Exposed" are offspring of pregnant women with one or more selective serotonin reuptake inhibitor drug purchases during the period of 1 month before pregnancy until 12 completed gestational weeks. Comparisons made with unexposed referent offspring of pregnant women with no purchases of selective serotonin reuptake inhibitors or the individual selective serotonin reuptake inhibitor drug analyzed during the same study period.

* Including anencephaly, encephalocele, and spina bifida.

† Also including limb defects.

Miia Artama

Source Malm et al. Obstet Gynecol 2011;118:111-120

Gissler et al. BMC Public Health 2010, 10:383
http://www.biomedcentral.com/1471-2458/10/383

BMC Public Health

RESEARCH ARTICLE Open Access

Use of psychotropic drugs before pregnancy and the risk for induced abortion: population-based register-data from Finland 1996-2006

Mika Gissler[1,2*], Miia Artama[1], Annukka Ritvanen[1], Kristian Wahlbeck[1,3]

Table 4 The proportion of terminated pregnancies among primigravidas using psychotropic medicine 0-3 months before pregnancy, Finland 1996-2006

ATC code	N05/N06	N05A	N05B	N05C	N06A	N06C
Terminated pregnancies per 100	30.1	36.0	25.7	29.1	32.1	17.9
Crude OR	1.88	2.42	1.49	1.76	2.07	0.94
95% CI	1.78-2.00	2.05-2.86	1.31-1.69	1.47-2.12	1.94-2.20	0.60-1.46
Adjusted OR[1)]	1.53	1.73	1.46	1.74	1.57	1.40
95% CI	1.42-1.65	1.39-2.16	1.25-1.75	1.36-2.22	1.44-1.71	0.79-2.53
Explanation, %	40	49	1	4	47	< 0

Excluding 704 induced abortions due to fetal reasons.
1) Adjusted by year, age, region, marital status and socioeconomic position.

BMJ

BMJ 2011;344:d8012 doi: 10.1136/bmj.d8012 (Published 12 January 2012)

RESEARCH

Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries

Table 3| Exposure to selective serotonin reuptake inhibitors (SSRIs) in gestational week 20 or later and risk for persistent pulmonary hypertension of the newborn

	No of infants with persistent pulmonary hypertension of the newborn (per 1000)		Odds ratio (95% CI)	
Drugs	Not exposed	Exposed	Unadjusted	Adjusted*
Any SSRI	1899 (1.2)	33 (3.0)	2.5 (1.8 to 3.6)	2.1 (1.5 to 3.0)
Fluoxetine	1952 (1.2)	9 (2.7)	2.3 (1.2 to 4.3)	2.0 (1.0 to 3.8)
Citalopram	1936 (1.2)	11 (3.3)	2.8 (1.5 to 5.0)	2.3 (1.2 to 4.1)
Paroxetine	1959 (1.2)	5 (3.9)	3.2 (1.3 to 7.8)	2.8 (1.2 to 6.7)
Sertraline	1949 (1.2)	10 (3.5)	2.9 (1.6 to 5.4)	2.3 (1.3 to 4.4)
Escitalopram	1966 (1.2)	1 (1.8)	1.5 (0.2 to 10.5)	1.3 (0.2 to 9.5)

*Adjusted for maternal age, dispensed non-steroidal anti-inflammatory drugs and antidiabetes drugs, pre-eclampsia, chronic diseases during pregnancy, country of birth, birth year, level of delivery hospital, and birth order.

Source: Kieler et al. BMJ 2011;344:d8012.

Strenghts of register-based data on maternal medication during pregnancy

- Excellent possibilities for research and follow-up
  - Drug use during pregnancy
  - Detailed and large information on
    - Maternal background factors
    - pregnancy course and outcomes
  - Possibilities for long-term follow-up of mothers and children
  - Possibilities for both cohort and case-control settings

Limitations

- No information on use of drugs outside the reimbursement system
  - Over the counter medicines
  - Drugs given for institutionalised persons or in hospitals
  - Use of medicines prescribed for other persons

Limitations

- No certain information on use of the drug, or timing of drug use
- Later effects (i.e. cancer, infertility) can be evaluated only with further linkages

Conclusions

- Half of parturients had drug purchases during pregnancy
- 6.7 percent of parturients had at least one chronic disease during pregnancy
- Most common maternal chronic diseases were asthma, hypothyreosis and epilepsy

THANK YOU!